Chestnut's OBSTETRIC ANESTHESIA

PRINCIPLES AND PRACTICE

FIFTH EDITION

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To my wife, ***Janet****; our children,* ***Stephen****,* ***Annie****,* ***Mary Beth****,* ***Michael*** *and* ***Jordan****, and* ***John Mark*** *and* ***Catherine****; and our grandchildren,* ***Caleb****,* ***Emily****,* ***Hannah****, and* ***Jackson***
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YB

To my husband, ***Keith****, and our children,* ***Fiona*** *and* ***Rhys***
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Preface

The first edition of this text was published exactly 20 years ago. In the preface to the first edition, I identified two goals: (1) to collate the most important information that anesthesia providers should know about obstetrics, and (2) to prepare a thorough and user-friendly review of anesthesia care for obstetric patients. I asked each contributor to write a thorough, scholarly discussion of the subject and also to provide clear, practical recommendations for clinical practice. Those goals remain intact in the fifth edition, and the result is a comprehensive resource for all anesthesia providers (and obstetricians) who provide care for pregnant women.

The fifth edition is an extensive revision with much new **content**. A new chapter discusses psychiatric disorders, 14 chapters have been rewritten from start to finish, and most other chapters have undergone substantial revision. The trauma chapter now includes a focused review of critical care medicine, and other chapters have been expanded to include discussions of obstetric pharmacology and chronic pain. The chapters on fetal physiology and fetal and neurologic injury have undergone extensive revision, as have the chapters on problems of early pregnancy, preterm labor, hemorrhage, embolic disorders, obesity, and airway management. The chapter on cardiovascular disease was rewritten by a cardiologist who is also an anesthesiologist. The chapter on hypertensive disorders not only underwent comprehensive revision, but also was moved so that it is now grouped with other obstetric complications. And the keystone chapters on neuraxial labor analgesia and cesarean delivery underwent extensive revision to include abundant new information that is highly relevant for clinical practice.

The fifth edition includes 26 new **contributors**. I am also happy to welcome three outstanding new editors: **Warwick D. Ngan Kee, BHB, MBChB, MD, FANZCA, FHKCA, FHKAM** (our first international editor), **Yaakov (Jake) Beilin, MD**, and **Jill M. Mhyre, MD**. Both **Cynthia A. Wong, MD**, and **Lawrence C. Tsen, MD**, have continued their work as editors, and Dr. Wong has assumed editorial responsibility equal to my own. Each chapter has been carefully reviewed by at least two editors, and we sought the input of all six editors for resolution of difficult issues. Altogether, the fifth edition reflects the collective wisdom of a diverse group of prominent anesthesiologists and obstetricians from 20 states and 7 countries.

The fifth edition **cover** again features a striking maternal-fetal image, which draws attention to the fact that the anesthesia provider and the obstetrician provide simultaneous care for two (or more) patients—both the mother and her unborn child(ren). The new cover image was created by an extraordinarily talented anesthesiologist and artist, **Naveen Nathan, MD**, who prepared abundant new illustrations (and revised existing illustrations) throughout the text. We are indebted to Dr. Nathan for his invaluable contributions as graphics editor for the fifth edition.

It remains gratifying to receive positive feedback on this text. At the risk of sounding self-congratulatory, I should like to summarize the three most common comments about the first four editions: The content is **comprehensive**, the material is both **current** and **relevant**, and the writing is **clear**. Indeed, the other editors and I place high value on clarity. I trust that you will conclude that the fifth edition meets and perhaps exceeds the standards set by the previous four editions.

The other editors and I would like to acknowledge the important roles of four groups of special people. First, we express our heartfelt thanks to the 79 distinguished and talented contributors to the fifth edition (including **Linda S. Polley, MD**, who helped edit the fourth edition), as well as the contributors to previous editions of this text. Second, we gratefully acknowledge the invaluable help provided by our competent and loyal assistants, including Jennifer Lee and Jodi Vogel. Third, we acknowledge the encouragement, expertise, and attention to detail provided by the professional production team at Elsevier. And finally, we should like to thank *you*, the readers, not only for your continued confidence in this text, but especially for your ongoing commitment to the provision of safe and compassionate care for pregnant women and their unborn children.

David H. Chestnut, MD

Micah 6:8

CHAPTER 1

The History of Obstetric Anesthesia

Donald Caton, MD

CHAPTER OUTLINE

For I heard a cry as of a woman in travail, anguish as of one bringing forth her first child, the cry of the daughter of Zion gasping for breath, stretching out her hands, "Woe is me!"

—JEREMIAH 4:31

"The position of woman in any civilization is an index of the advancement of that civilization; the position of woman is gauged best by the care given her at the birth of her child." So wrote Haggard[1] in 1929. If his thesis is true, Western civilization made a giant leap on January 19, 1847, when James Young Simpson used diethyl ether to anesthetize a woman with a deformed pelvis for delivery. This first use of a modern anesthetic for childbirth occurred a scant 3 months after Morton's historic demonstration of the anesthetic properties of ether at the Massachusetts General Hospital in Boston. Strangely enough, Simpson's innovation evoked strong criticism from contemporary obstetricians, who questioned its safety, and from many segments of the lay public, who questioned its wisdom. The debate over these issues lasted more than 5 years and influenced the future of obstetric anesthesia.[2]

JAMES YOUNG SIMPSON

Few people were better equipped than Simpson to deal with controversy. Just 36 years old, Simpson already had 7 years' tenure as Professor of Midwifery at the University of Edinburgh, one of the most prestigious medical schools of its day (Figure 1-1). By that time, he had established a reputation as one of the foremost obstetricians in Great Britain, if not the world. On the day he first used ether for childbirth, he also received a letter of appointment as Queen's Physician in Scotland. Etherization for childbirth was only one of Simpson's contributions. He also designed obstetric forceps (which still bear his name), discovered the anesthetic properties of chloroform, made important innovations in hospital architecture, and wrote a textbook on the practice of witchcraft in Scotland that was used by several generations of anthropologists.[3]

An imposing man, Simpson had a large head, a massive mane of hair, and the pudgy body of an adolescent. Contemporaries described his voice as "commanding," with a wide range of volume and intonation. Clearly Simpson had "presence" and "charisma." These attributes were indispensable to someone in his profession, because in the mid-nineteenth century, the role of science in the development of medical theory and practice was minimal; rhetoric resolved more issues than facts. The medical climate in Edinburgh was particularly contentious and vituperative. In this milieu, Simpson had trained, competed for advancement and recognition, and succeeded. The rigor of this preparation served him well. Initially, virtually every prominent obstetrician, including Montgomery of Dublin, Ramsbotham of London, Dubois of Paris, and Meigs of Philadelphia, opposed etherization for childbirth. Simpson called on all of his professional and personal finesse to sway opinion in the ensuing controversy.

MEDICAL OBJECTIONS TO THE USE OF ETHER FOR CHILDBIRTH

Shortly after Simpson administered the first obstetric anesthetic, he wrote, "It will be necessary to ascertain anesthesia's precise effect, both upon the action of the uterus and on the assistant abdominal muscles; its influence, if any, upon the child; whether it has a tendency to hemorrhage or other complications."[4] With this

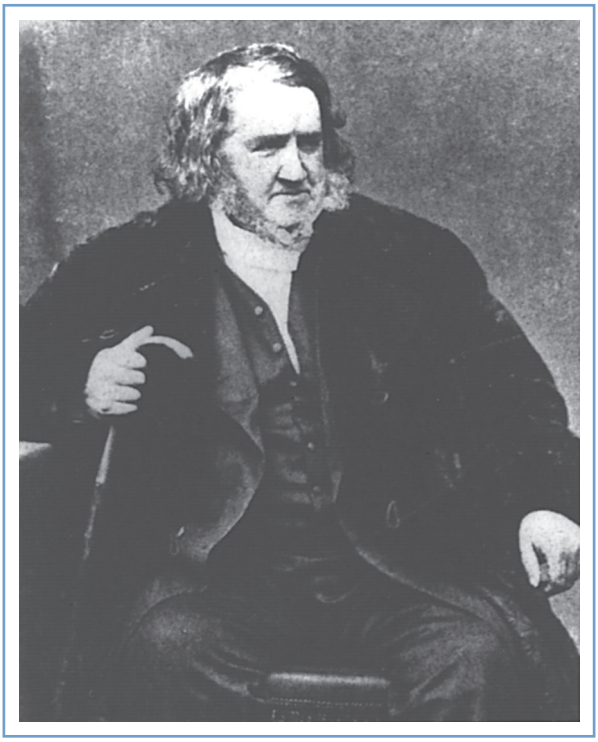


FIGURE 1-1 ■ James Young Simpson, the obstetrician who first administered a modern anesthetic for childbirth. He also discovered the anesthetic properties of chloroform. Many believe that he was the most prominent and influential physician of his day. (Courtesy Yale Medical History Library.)

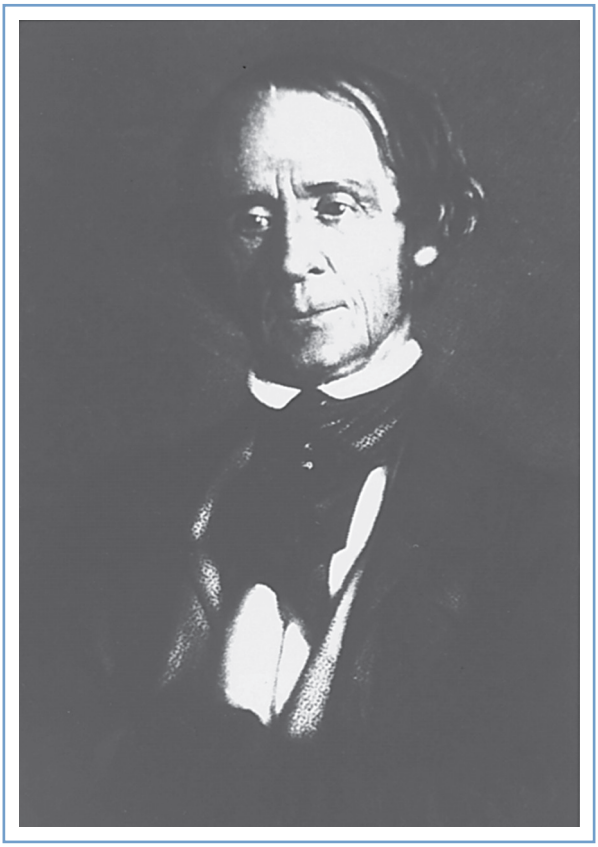


FIGURE 1-2 ■ Charles D. Meigs, the American obstetrician who opposed the use of anesthesia for obstetrics. He questioned the safety of anesthesia and said that there was no demonstrated need for it during a normal delivery. (Courtesy Wood-Library Museum.)

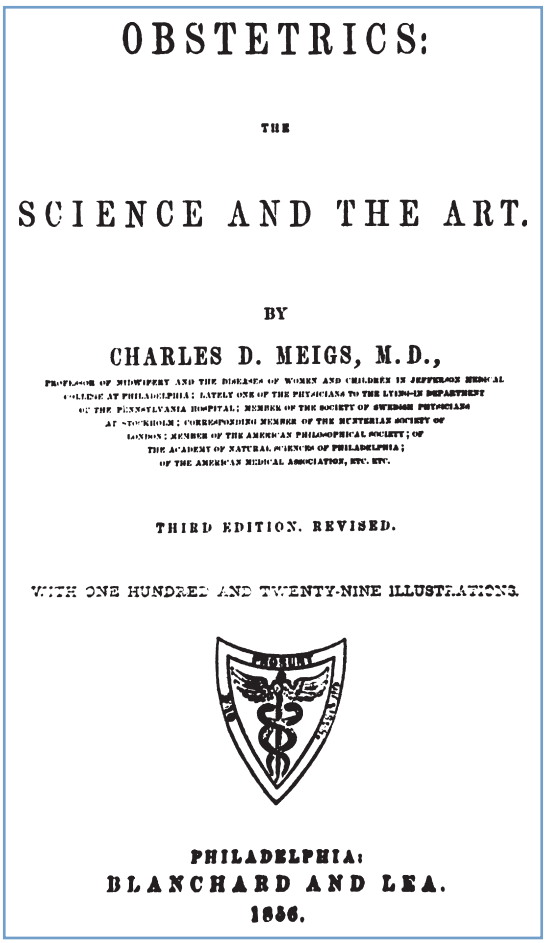
statement he identified the issues that would most concern obstetricians who succeeded him and thus shaped the subsequent development of the specialty.

Simpson's most articulate, persistent, and persuasive critic was Charles D. Meigs, Professor of Midwifery at Jefferson Medical College in Philadelphia (Figure 1-2). In character and stature, Meigs equaled Simpson. Born to a prominent New England family, Meigs' forebears included heroes of the American revolutionary war, the first governor of the state of Ohio, and the founder of the University of Georgia. His descendants included a prominent pediatrician, an obstetrician, and one son who served the Union Army as Quartermaster General during the Civil War.[5]

At the heart of the dispute between Meigs and Simpson was a difference in their interpretation of the nature of labor and the significance of labor pain. Simpson maintained that all pain, labor pain included, is without physiologic value. He said that pain only degrades and destroys those who experience it. In contrast, Meigs argued that labor pain has purpose, that uterine pain is inseparable from contractions, and that any drug that abolishes pain will alter contractions. Meigs also believed that pregnancy and labor are normal processes that usually end quite well. He said that physicians should therefore not intervene with powerful, potentially disruptive drugs (Figure 1-3). We must accept the statements of both men as expressions of natural philosophy, because neither had facts to buttress his position. Indeed, in 1847, physicians had little information of any sort about uterine function, pain, or the relationship between them. Studies of the anatomy and physiology of pain had just begun. It was only during the preceding 20 years that investigators had recognized that specific nerves and areas of the brain have different functions and that specialized peripheral receptors for painful stimuli exist.[2]

In 1850, more physicians expressed support for Meigs's views than for Simpson's. For example, Baron Paul Dubois[6] of the Faculty of Paris wondered whether ether, "after having exerted a stupefying action over the cerebrospinal nerves, could not induce paralysis of the muscular element of the uterus?" Similarly, Ramsbotham[7] of London Hospital said that he believed the "treatment of rendering a patient in labor completely insensible through the agency of anesthetic remedies … is fraught with extreme danger." These physicians' fears gained credence from the report by a special committee of the Royal Medical and Chirurgical Society documenting 123 deaths that "could be positively assigned to the inhalation of chloroform."[8] Although none involved obstetric patients, safety was on the minds of obstetricians.

The reaction to the delivery of Queen Victoria's eighth child in 1853 illustrated the aversion of the medical community to obstetric anesthesia. According to private records, John Snow anesthetized the Queen for the delivery of Prince Leopold at the request of her personal physicians. Although no one made a formal


OBSTETRICS:

THE

SCIENCE AND THE ART.

BY

CHARLES D. MEIGS, M.D.,

PROFESSOR OF MIDWIFERY AND THE DISEASES OF WOMEN AND CHILDREN IN JEFFERSON MEDICAL COLLEGE AT PHILADELPHIA; LATELY ONE OF THE PHYSICIANS TO THE LYING-IN DEPARTMENT OF THE PENNSYLVANIA HOSPITAL; MEMBER OF THE SOCIETY OF SWEDISH PHYSICIANS AT STOCKHOLM; CORRESPONDING MEMBER OF THE HUNTERIAN SOCIETY OF LONDON; MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY; OF THE ACADEMY OF NATURAL SCIENCES OF PHILADELPHIA; OF THE AMERICAN MEDICAL ASSOCIATION, ETC. ETC.

THIRD EDITION. REVISED.

WITH ONE HUNDRED AND TWENTY-NINE ILLUSTRATIONS.

PHILADELPHIA:
BLANCHARD AND LEA.
1856.

FIGURE 1-3 ■ Frontispiece from Meigs's textbook of obstetrics.

announcement of this fact, rumors surfaced and provoked strong public criticism. Thomas Wakley, the irascible founding editor of *The Lancet*, was particularly incensed. He "could not imagine that anyone had incurred the awful responsibility of advising the administration of chloroform to her Majesty during a perfectly natural labour with a seventh child."[9] (It was her eighth child, but Wakley had apparently lost count—a forgivable error considering the propensity of the Queen to bear children.) Court physicians did not defend their decision to use ether. Perhaps not wanting a public confrontation, they simply denied that the Queen had received an anesthetic. In fact, they first acknowledged a royal anesthetic 4 years later when the Queen delivered her ninth and last child, Princess Beatrice. By that time, however, the issue was no longer controversial.[9]

PUBLIC REACTION TO ETHERIZATION FOR CHILDBIRTH

The controversy surrounding obstetric anesthesia was not resolved by the medical community. Physicians remained skeptical, but public opinion changed. Women lost their reservations, decided they wanted anesthesia, and virtually forced physicians to offer it to them. The change in the public's attitude in favor of obstetric anesthesia marked the culmination of a more general change in social attitudes that had been developing over several centuries.

Before the nineteenth century, pain meant something quite different from what it does today. Since antiquity, people had believed that all manner of calamities—disease, drought, poverty, and pain—signified divine retribution inflicted as punishment for sin. According to Scripture, childbirth pain originated when God punished Eve and her descendants for Eve's disobedience in the Garden of Eden. Many believed that it was wrong to avoid the pain of divine punishment. This belief was sufficiently prevalent and strong to retard acceptance of even the idea of anesthesia, especially for obstetric patients. Only when this tradition weakened did people seek ways to free themselves from disease and pain. In most Western countries, the transition occurred during the nineteenth century. Disease and pain lost their theologic connotations for many people and became biologic processes subject to study and control by new methods of science and technology. This evolution of thought facilitated the development of modern medicine and stimulated public acceptance of obstetric anesthesia.[10]

The reluctance that physicians felt about the administration of anesthesia for childbirth pain stands in stark contrast to the enthusiasm expressed by early obstetric patients. In 1847, Fanny Longfellow, wife of the American poet Henry Wadsworth Longfellow and the first woman in the United States anesthetized for childbirth, wrote:

> *I am very sorry you all thought me so rash and naughty in trying the ether. Henry's faith gave me courage, and I had heard such a thing had succeeded abroad, where the surgeons extend this great blessing more boldly and universally than our timid doctors.... This is certainly the greatest blessing of this age.*[11]

Queen Victoria, responding to news of the birth of her first grandchild in 1860 and perhaps remembering her own recent confinement, wrote, "What a blessing she [Victoria, her oldest daughter] had chloroform. Perhaps without it her strength would have suffered very much."[9] The new understanding of pain as a controllable biologic process left no room for Meigs's idea that pain might have physiologic value. The eminent nineteenth-century social philosopher John Stuart Mill stated that the "hurtful agencies of nature" promote good only by "inciting rational creatures to rise up and struggle against them."[12]

Simpson prophesied the role of public opinion in the acceptance of obstetric anesthesia, a fact not lost on his adversaries. Early in the controversy he predicted, "Medical men may oppose for a time the superinduction of anaesthesia in parturition but they will oppose it in vain; for certainly our patients themselves will force use of it upon the profession. The whole question is, even now, one merely of time."[13] By 1860, Simpson's prophecy came true; anesthesia for childbirth became part of medical practice by public acclaim, in large part in response to the demands of women.

OPIOIDS AND OBSTETRICS

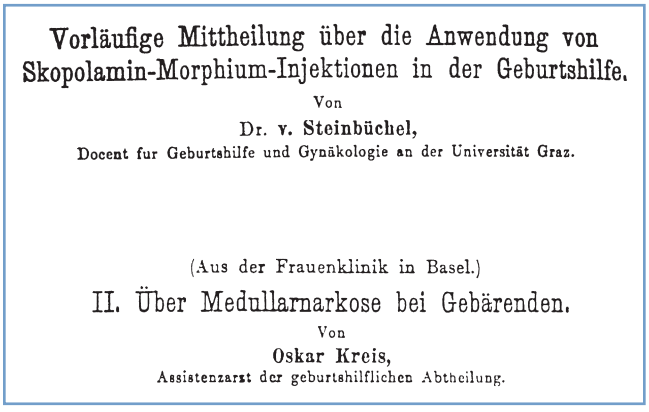
The next major innovation in obstetric anesthesia came approximately 50 years later. *Dämmerschlaff*, which means "twilight sleep," was a technique developed by von Steinbüchel[14] of Graz and popularized by Gauss[15] of Freiberg. It combined opioids with scopolamine to make women amnestic and somewhat comfortable during labor (Figure 1-4). Until that time, opioids had been used sparingly for obstetrics. Although opium had been part of the medical armamentarium since the Roman Empire, it was not used extensively, in part because of the difficulty of obtaining consistent results with the crude extracts available at that time. Therapeutics made a substantial advance in 1809 when Sertürner, a German pharmacologist, isolated codeine and morphine from a crude extract of the poppy seed. Methods for administering the drugs remained unsophisticated. Physicians gave morphine orally or by a method resembling vaccination, in which they placed a drop of solution on the skin and then made multiple small puncture holes with a sharp instrument to facilitate absorption. In 1853, the year Queen Victoria delivered her eighth child, the syringe and hollow metal needle were developed. This technical advance simplified the administration of opioids and facilitated the development of twilight sleep approximately 50 years later.[16]

Although reports of labor pain relief with hypodermic morphine appeared as early as 1868, few physicians favored its use. For example, in an article published in *Transactions of the Obstetrical Society of London*, Sansom[17] listed the following four agents for relief of labor pain: (1) carbon tetrachloride, the use of which he favored; (2) bichloride of methylene, which was under evaluation; (3) nitrous oxide, which had been introduced recently by Klikgowich of Russia; and (4) chloroform. He did not mention opioids, but neither did he mention diethyl ether, which many physicians still favored. Similarly, Gusserow,[18] a prominent German obstetrician, described using salicylic acid but not morphine for labor pain. (Von Baeyer did not introduce acetylsalicylic acid to medical practice until 1899.) In retrospect, von Steinbüchel's and Gauss's descriptions of twilight sleep in the first decade of the century may have been important more for popularizing morphine than for suggesting that scopolamine be given with morphine.

Physicians reacted to twilight sleep as they had reacted to diethyl ether several years earlier. They resisted it, questioning whether the benefits justified the risks. Patients also reacted as they had before. Not aware of, or perhaps not concerned with, the technical considerations that confronted physicians, patients harbored few doubts and persuaded physicians to use it, sometimes against the physicians' better judgment. The confrontation between physicians and patients was particularly strident in the United States. Champions of twilight sleep lectured throughout the country and published articles in popular magazines. Public enthusiasm for the therapy subsided slightly after 1920, when a prominent advocate of the method died during childbirth. She was given twilight sleep, but her physicians said that her death was unrelated to any complication from its use. Whatever anxiety this incident may have created in the minds of patients, it did not seriously diminish their resolve. Confronted by such firm insistence, physicians acquiesced and used twilight sleep with increasing frequency.[19,20]

Although the reaction of physicians to twilight sleep resembled their reaction to etherization, the medical milieu in which the debate over twilight sleep developed was quite different from that in which etherization was deliberated. Between 1850 and 1900, medicine had changed, particularly in Europe. Physiology, chemistry, anatomy, and bacteriology became part of medical theory and practice. Bright students from America traveled to leading clinics in Germany, England, and France. They returned with new facts and methods that they used to examine problems and critique ideas. These developments became the basis for the revolution in American medical education and practice launched by the Flexner report published in 1914.[21]

Obstetrics also changed. During the years preceding World War I, it had earned a reputation as one of the most exciting and scientifically advanced specialties. Obstetricians experimented with new drugs and techniques. They recognized that change entails risk, and they examined each innovation more critically. In addition, they turned to science for information and methods to help them solve problems of medical management. Developments in obstetric anesthesia reflected this change in strategy. New methods introduced during this time stimulated physicians to reexamine two important but unresolved issues, the effects of drugs on the child, and the relationship between pain and labor.



Vorläufige Mittheilung über die Anwendung von Skopolamin-Morphium-Injektionen in der Geburtshilfe.

Von

Dr. v. Steinbüchel,

Docent fur Geburtshilfe und Gynäkologie an der Universität Graz.

(Aus der Frauenklinik in Basel.)

II. Über Medullarnarkose bei Gebärenden.

Von

Oskar Kreis,

Assistenzarzt der geburtshilflichen Abtheilung.

FIGURE 1-4 ■ Title pages from two important papers published in the first years of the twentieth century. The paper by von Steinbüchel introduced twilight sleep. The paper by Kreis described the first use of spinal anesthesia for obstetrics.

THE EFFECTS OF ANESTHESIA ON THE NEWBORN

Many physicians, Simpson included, worried that anesthetic drugs might cross the placenta and harm the newborn. Available information justified their concern. The idea that gases cross the placenta appeared long before the discovery of oxygen and carbon dioxide. In the sixteenth century, English physiologist John Mayow[22]

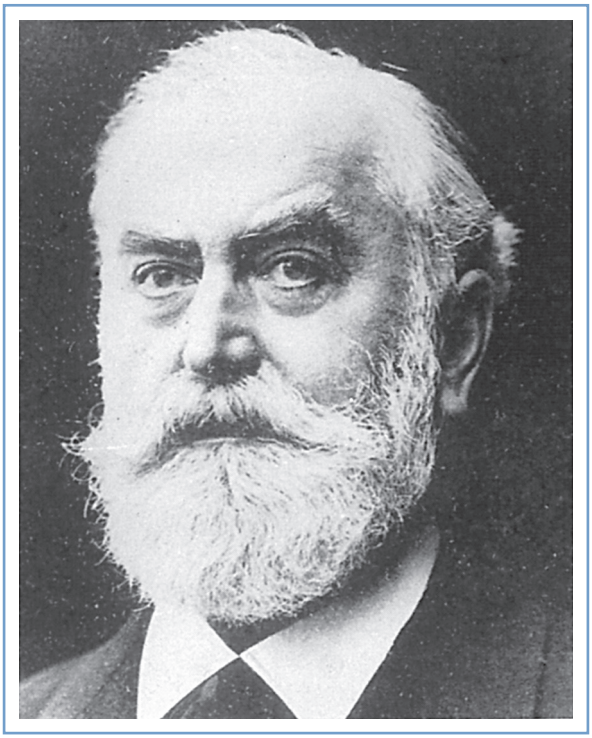


FIGURE 1-5 ■ Paul Zweifel, the Swiss-born obstetrician who performed the first experiments that chemically demonstrated the presence of chloroform in the umbilical blood and urine of infants delivered by women who had been anesthetized during labor. (Courtesy J.F. Bergmann-Verlag, München, Germany.)

suggested that "nitro aerial" particles from the mother nourish the fetus. By 1847, physiologists had corroborative evidence. Clinical experience gave more support. John Snow[23] observed depressed neonatal breathing and motor activity and smelled ether on the breath of neonates delivered from mothers who had been given ether. In an early paper, he surmised that anesthetic gases cross the placenta. Regardless, some advocates of obstetric anesthesia discounted the possibility. For example, Harvard professor Walter Channing denied that ether crossed the placenta because he could not detect its odor in the cut ends of the umbilical cord. Oddly enough, he did not attempt to smell ether on the child's exhalations as John Snow had done.[24]

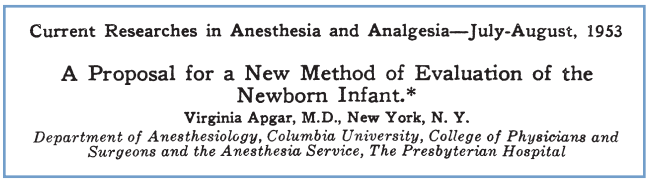
In 1874, Swiss obstetrician Paul Zweifel[25] published an account of work that finally resolved the debate about the placental transfer of drugs (Figure 1-5). He used a chemical reaction to demonstrate the presence of chloroform in the umbilical blood of neonates. In a separate paper, Zweifel[26] used a light-absorption technique to demonstrate a difference in oxygen content between umbilical arterial and venous blood, thereby establishing the placental transfer of oxygen. Although clinicians recognized the importance of these data, they accepted the implications slowly. Some clinicians pointed to several decades of clinical use "without problems." For example, Otto Spiegelberg,[27] Professor of Obstetrics at the University of Breslau, wrote in 1887, "As far as the fetus is concerned, no unimpeachable clinical observation has yet been published in which a fetus was injured by chloroform administered to its mother." Experience lulled them into complacency, which may explain their failure to appreciate the threat posed by twilight sleep.

Dangers from twilight sleep probably developed insidiously. The originators of the method, von Steinbüchel and Gauss, recommended conservative doses of drugs. They suggested that 0.3 mg of scopolamine be given every 2 to 3 hours to induce amnesia and that no more than 10 mg of morphine be administered subcutaneously for the whole labor. Gauss, who was especially meticulous, even advised physicians to administer a "memory test" to women in labor to evaluate the need for additional scopolamine. However, as other physicians used the technique, they changed it. Some gave larger doses of opioid—as much as 40 or 50 mg of morphine during labor. Others gave additional drugs (e.g., as much as 600 mg of pentobarbital during labor as well as inhalation agents for delivery). Despite administering these large doses to their patients, some physicians said they had seen no adverse effects on the infants.[28] They probably spoke the truth, but this probability says more about their powers of observation than the safety of the method.

Two situations eventually made physicians confront problems associated with placental transmission of anesthetic drugs. The first was the changing use of morphine.[29] In the latter part of the nineteenth century (before the enactment of laws governing the use of addictive drugs), morphine was a popular ingredient of patent medicines and a drug frequently prescribed by physicians. As addiction became more common, obstetricians saw many pregnant women who were taking large amounts of morphine daily. When they tried to decrease their patients' opioid use, several obstetricians noted unexpected problems (e.g., violent fetal movements, sudden fetal death), which they correctly identified as signs of withdrawal. Second, physiologists and anatomists began extensive studies of placental structure and function. By the turn of the century, they had identified many of the physical and chemical factors that affect rates of drug transfer. Thus, even before twilight sleep became popular, physicians had clinical and laboratory evidence to justify caution. As early as 1877, Gillette[30] described 15 instances of neonatal depression that he attributed to morphine given during labor. Similarly, in a review article published in 1914, Knipe[31] identified stillbirths and neonatal oligopnea and asphyxia as complications of twilight sleep and gave the incidence of each problem as reported by other writers.

When the studies of obstetric anesthesia published between 1880 and 1950 are considered, four characteristics stand out. First, few of them described effects of anesthesia on the newborn. Second, those that did report newborn apnea, oligopnea, or asphyxia seldom defined these words. Third, few used controls or compared one mode of treatment with another. Finally, few writers used their data to evaluate the safety of the practice that they described. In other words, by today's standards, even the best of these papers lacked substance. They did, however, demonstrate a growing concern among physicians about the effects of anesthetic drugs on neonates. Perhaps even more important, their work prepared clinicians for the work of Virginia Apgar (Figure 1-6).

FIGURE 1-6 ■ Virginia Apgar, whose scoring system revolutionized the practice of obstetrics and anesthesia. Her work made the well-being of the infant the major criterion for the evaluation of medical management of pregnant women. (Courtesy Wood-Library Museum.)



Current Researches in Anesthesia and Analgesia—July-August, 1953

A Proposal for a New Method of Evaluation of the Newborn Infant.*

Virginia Apgar, M.D., New York, N. Y.

Department of Anesthesiology, Columbia University, College of Physicians and Surgeons and the Anesthesia Service, The Presbyterian Hospital

FIGURE 1-7 ■ Title page from the paper in which Virginia Apgar described her new scoring system for evaluating the well-being of a newborn.

Apgar became an anesthesiologist when the chairman of the Department of Surgery at the Columbia University College of Physicians and Surgeons dissuaded her from becoming a surgeon. After training in anesthesia with Ralph Waters at the University of Wisconsin and with E. A. Rovenstine at Bellevue Hospital, she returned to Columbia Presbyterian Hospital as Director of the Division of Anesthesia. In 1949, she was appointed professor, the first woman to attain that rank at Columbia University.[32]

In 1953, Apgar[33] described a simple, reliable system for evaluating newborns and showed that it was sufficiently sensitive to detect differences among neonates whose mothers had been anesthetized for cesarean delivery by different techniques (Figure 1-7). Infants delivered of women with spinal anesthesia had higher scores than those delivered with general anesthesia. The Apgar score had three important effects. First, it replaced simple observation of neonates with a reproducible measurement—that is, it substituted a numerical score for the ambiguities of words such as oligopnea and asphyxia. Thus it established the possibility of the systematic comparison of different treatments. Second, it provided objective criteria for the initiation of neonatal resuscitation. Third, and most important, it helped change the focus of obstetric care. Until that time the primary criterion for success or failure had been the survival and well-being of the mother, a natural goal considering the maternal risks of childbirth until that time. After 1900, as maternal risks diminished, the well-being of the mother no longer served as a sensitive measure of outcome. The Apgar score called attention to the child and made its condition the new standard for evaluating obstetric management.

THE EFFECTS OF ANESTHESIA ON LABOR

The effects of anesthesia on labor also worried physicians. Again, their fears were well-founded. Diethyl ether and chloroform depress uterine contractions. If given in sufficient amounts, they also abolish reflex pushing with the abdominal muscles during the second stage of labor. These effects are not difficult to detect, even with moderate doses of either inhalation agent.

Simpson's method of obstetric anesthesia used significant amounts of drugs. He started the anesthetic early, and sometimes he rendered patients unconscious during the first stage of labor. In addition, he increased the depth of anesthesia for the delivery.[34] As many people copied his technique, they presumably had ample opportunity to observe uterine atony and postpartum hemorrhage.

Some physicians noticed the effects of anesthetics on uterine function. For example, Meigs[35] said unequivocally that etherization suppressed uterine function, and he described occasions in which he had had to suspend etherization to allow labor to resume. Other physicians waffled, however. For example, Walter Channing,[36] Professor of Midwifery and Medical Jurisprudence at Harvard (seemingly a strange combination of disciplines, but at that time neither of the two was thought sufficiently important to warrant a separate chair), published a book about the use of ether for obstetrics (Figure 1-8). He endorsed etherization and influenced many others to use it. However, his book contained blatant contradictions. On different pages Channing contended that ether had no effect, that it increased uterine contractility, and that it suspended contractions entirely. Then, in a pronouncement smacking more of panache than reason, Channing swept aside his inconsistencies and said that whatever effect ether may have on the uterus he "welcomes it." Noting similar contradictions among other writers, W. F. H. Montgomery,[37] Professor of Midwifery at the King and Queen's College of Physicians in Ireland, wrote, "By one writer we are told that, if uterine action is excessive, chloroform will abate it; by another that if feeble, it will strengthen it and add new vigor to each parturient effort."

A TREATISE

ON

ETHERIZATION IN CHILDBIRTH.

ILLUSTRATED BY

FIVE HUNDRED AND EIGHTY-ONE CASES.

BY WALTER CHANNING, M.D.

PROFESSOR OF MIDWIFERY AND MEDICAL JURISPRUDENCE IN THE UNIVERSITY AT CAMBRIDGE.

"Give me the facts, said my Lord Judge: your reasonings are the mere guess-work of the imagination." — Old Play.

BOSTON:

WILLIAM D. TICKNOR AND COMPANY,

CORNER OF WASHINGTON AND SCHOOL STREETS.

M.DCCC.XLVIII.

FIGURE 1-8 ■ Frontispiece from Walter Channing's book on the use of etherization for childbirth. Channing favored the use of etherization, and he persuaded others to use it, although evidence ensuring its safety was scant.

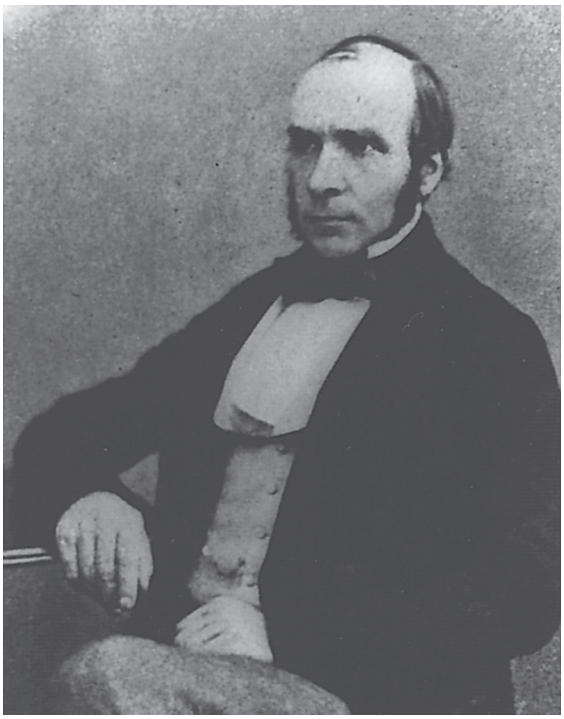


FIGURE 1-9 ■ John Snow, a London surgeon who gave up his surgical practice to become the first physician to devote all his time to anesthesia. He wrote many monographs and papers, some of which accurately describe the effects of anesthesia on infant and mother. (Courtesy Wood-Library Museum.)

John Snow[23] gave a more balanced review of the effects of anesthesia on labor. Originally a surgeon, Snow became the first physician to restrict his practice to anesthesia. He experimented with ether and chloroform and wrote many insightful papers and books describing his work (Figure 1-9). Snow's technique differed from Simpson's. Snow withheld anesthesia until the second stage of labor, limited administration to brief periods during contractions, and attempted to keep his patients comfortable but responsive. To achieve better control of the depth of anesthesia, he recommended using the vaporizing apparatus that he had developed for surgical cases. Snow[23] spoke disparagingly of Simpson's technique and the tendency of people to use it simply because of Simpson's reputation:

> *The high position of Dr. Simpson and his previous services in this department, more particularly in being the first to administer ether in labour, gave his recommendations very great influence; the consequence of which is that the practice of anesthesia is presently probably in a much less satisfactory state than it would have been if chloroform had never been introduced.*

Snow's method, which was the same one he had used to anesthetize Queen Victoria, eventually prevailed over Simpson's. Physicians became more cautious with anesthesia, reserving it for special problems such as cephalic version, the application of forceps, abnormal presentation, and eclampsia. They also became more conservative with dosage, often giving anesthesia only during the second stage of labor. Snow's methods were applied to each new inhalation agent—including nitrous oxide, ethylene, cyclopropane, trichloroethylene, and methoxyflurane—as it was introduced to obstetric anesthesia.

Early physicians modified their use of anesthesia from experience, not from study of normal labor or from learning more about the pharmacology of the drugs. Moreover, they had not yet defined the relationship between uterine pain and contractions. As physicians turned more to science during the latter part of the century, however, their strategies began to change. For example, in 1893 the English physiologist Henry Head[38] published his classic studies of the innervation of abdominal viscera. His work stimulated others to investigate the role of the nervous system in the control of labor. Subsequently, clinical and laboratory studies of pregnancy after spinal cord transection established the independence of labor from nervous control.[39] When regional anesthesia appeared during the first decades of the twentieth century, physicians therefore had a conceptual basis from which to explore its effects on labor.

Carl Koller[40] introduced regional anesthesia when he used cocaine for eye surgery in 1884. Recognizing the potential of Koller's innovation, surgeons developed techniques for other procedures. Obstetricians quickly adopted many of these techniques for their own use. The first papers describing obstetric applications of spinal, lumbar epidural, caudal, paravertebral, parasacral, and pudendal nerve blocks appeared between 1900 and 1930 (see Figure 1-4).[41-43] Recognition of the potential effects of regional anesthesia on labor developed more slowly, primarily because obstetricians seldom used it. They continued to rely on inhalation agents and opioids, partly because few drugs and materials were available for regional anesthesia at that time, but also because obstetricians did not appreciate the chief advantage of regional over general anesthesia—the relative absence of drug effects on the infant. Moreover, they rarely used regional anesthesia except for delivery, and then they often used elective forceps anyway. This set of circumstances limited their opportunity and motivation to study the effects of regional anesthesia on labor.

Among early papers dealing with regional anesthesia, one written by Cleland[44] stands out. He described his experience with paravertebral anesthesia, but he also wrote a thoughtful analysis of the nerve pathways mediating labor pain, an analysis he based on information he had gleaned from clinical and laboratory studies. Few investigators were as meticulous or insightful as Cleland. Most of those who studied the effects of anesthesia simply timed the length of the first and second stages of labor. Some timed the duration of individual contractions or estimated changes in the strength of contractions by palpation. None of the investigators measured the intrauterine pressures, even though a German physician had described such a method in 1898 and had used it to evaluate the effects of morphine and ether on the contractions of laboring women.[45]

More detailed and accurate studies of the effects of anesthesia started to appear after 1944. Part of the stimulus was a method for continuous caudal anesthesia introduced by Hingson and Edwards,[46] in which a malleable needle remained in the sacral canal throughout labor. Small, flexible plastic catheters eventually replaced malleable needles and made continuous epidural anesthesia even more popular. With the help of these innovations, obstetricians began using anesthesia earlier in labor. Ensuing problems, real and imagined, stimulated more studies. Although good studies were scarce, the strong interest in the problem represented a marked change from the early days of obstetric anesthesia.

Ironically, "natural childbirth" appeared just as regional anesthesia started to become popular and as clinicians began to understand how to use it without disrupting labor. Dick-Read,[47] the originator of the natural method, recognized "no physiological function in the body which gives rise to pain in the normal course of health." He attributed pain in an otherwise uncomplicated labor to an "activation of the sympathetic nervous system by the emotion of fear." He argued that fear made the uterus contract and become ischemic and therefore painful. He said that women could avoid the pain if they simply learned to abolish their fear of labor. Dick-Read never explained why uterine ischemia that results from fear causes pain, whereas ischemia that results from a normal contraction does not. In other words, Dick-Read, like Simpson a century earlier, claimed no necessary or physiologic relationship between labor pain and contractions. Dick-Read's book, written more for the public than for the medical profession, represented a regression of almost a century in medical thought and practice. It is important to note that contemporary methods of childbirth preparation do not maintain that fear alone causes labor pain. However, they do attempt to reduce fear by education and to help patients manage pain by teaching techniques of self-control. This represents a significant difference from and an important advance over Dick-Read's original theory.

SOME LESSONS

History is important in proportion to the lessons it teaches. With respect to obstetric anesthesia, four lessons stand out. First, every new drug and method entails risks. Physicians who first used obstetric anesthesia seemed reluctant to accept this fact, perhaps because of their inexperience with potent drugs (pharmacology was in its infancy) or because they acceded too quickly to patients, who wanted relief from pain and had little understanding of the technical issues confronting physicians. Whatever the reason, this period of denial lasted almost half a century, until 1900. Almost another half-century passed before obstetricians learned to modify their practice to limit the effects of anesthetics on the child and the labor process.

Second, new drugs or therapies often cause problems in completely unexpected ways. For example, in 1900, physicians noted a rising rate of puerperal fever.[48] The timing was odd. Several decades had passed since Robert Koch had suggested the germ theory of disease and since Semmelweis had recognized that physicians often transmit infection from one woman to the next with their unclean hands. With the adoption of aseptic methods, deaths from puerperal fever had diminished dramatically. During the waning years of the nineteenth century, however, they increased again. Some physicians attributed this resurgence of puerperal fever to anesthesia. In a presidential address to the Obstetrical Society of Edinburgh in 1900, Murray[49] stated the following:

> *I feel sure that an explanation of much of the increase of maternal mortality from 1847 onwards will be found in, first the misuse of anaesthesia and second in the ridiculous parody which, in many hands, stands for the use of antiseptics.…Before the days of anaesthesia, interference was limited and obstetric operations were at a minimum because interference of all kinds increased the conscious suffering of the patient.…When anaesthesia became possible, and interference became more frequent because it involved no additional suffering, operations were undertaken when really unnecessary … and so complications arose and the dangers of the labor increased.*

Although it was not a direct complication of the use of anesthesia in obstetric practice, puerperal fever appeared to be an indirect consequence of it.

Changes in obstetric practice also had unexpected effects on anesthetic complications. During the first decades of the twentieth century, when cesarean deliveries were rare and obstetricians used only inhalation analgesia for delivery, few women were exposed to the risk of aspiration during deep anesthesia. As obstetric practice changed and cesarean deliveries became more common, this risk rose. The syndrome of aspiration was not identified and labeled until 1946, when obstetrician Curtis Mendelson[50] described and named it. The pathophysiology of the syndrome had already been described by Winternitz et al.,[51] who instilled hydrochloric acid into the lungs of dogs to simulate the lesions found in veterans poisoned by gas during the trench warfare of World War I. Unfortunately, the reports of these studies, although excellent, did not initiate any change in practice. Change occurred only after several deaths of obstetric patients were highly publicized in lay, legal, and medical publications. Of course, rapid-sequence induction, currently recommended to reduce the risk of aspiration, creates another set of risks—those associated with a failed intubation.

The third lesson offered by the history of obstetric anesthesia concerns the role of basic science. Modern medicine developed during the nineteenth century after physicians learned to apply principles of anatomy, physiology, and chemistry to the study and treatment of disease. Obstetric anesthesia underwent a similar pattern of development. Studies of placental structure and function called physicians' attention to the transmission of drugs and the potential effects of drugs on the infant. Similarly, studies of the physiology and anatomy of the uterus helped elucidate potential effects of anesthesia on labor. In each instance, lessons from basic science helped improve patient care.

The fourth and perhaps the most important lesson is the role that patients have played in the use of anesthesia for obstetrics. During the nineteenth century it was women who pressured cautious physicians to incorporate routine use of anesthesia into their obstetric practice. A century later, it was women again who altered patterns of practice, this time questioning the overuse of anesthesia for routine deliveries. In both instances the pressure on physicians emanated from prevailing social values regarding pain. In 1900 the public believed that pain, and in particular obstetric pain, was destructive and something that should be avoided. Half a century later, with the advent of the natural childbirth movement, many people began to suggest that the experience of pain during childbirth, perhaps even in other situations, might have some physiologic if not social value. Physicians must recognize and acknowledge the extent to which social values may shape medical "science" and practice.[52,53]

During the past 60 years, scientists have accumulated a wealth of information about many processes integral to normal labor: the processes that initiate and control lactation; neuroendocrine events that initiate and maintain labor; the biochemical maturation of the fetal lung and liver; the metabolic requirements of the normal fetus and the protective mechanisms that it may invoke in times of stress; and the normal mechanisms that regulate the amount and distribution of blood flow to the uterus and placenta. At this point, we have only the most rudimentary understanding of the interaction of anesthesia with any of these processes. Only a fraction of the information available from basic science has been used to improve obstetric anesthesia care. Realizing the rewards from the clinical use of such information may be the most important lesson from the past and the greatest challenge for the future of obstetric anesthesia.

KEY POINTS

- Physicians have debated the safety of obstetric anesthesia since 1847, when James Young Simpson first administered anesthesia for delivery. Two issues have dominated the debate: the effects of anesthesia on labor and the effects of anesthesia on the newborn.
- Despite controversy, physicians quickly incorporated anesthesia into clinical practice, largely because of their patients' desire to avoid childbirth pain.
- Only after obstetric anesthesia was in use for many years did problems become apparent.
- Important milestones in obstetric anesthesia are the introduction of inhalation agents in 1847, the expanded use of opioids in the early decades of the twentieth century, and the refinement of regional anesthesia starting in the mid-twentieth century.
- Outstanding conceptual developments are (1) Zweifel's idea that drugs given to the mother cross the placenta and affect the fetus and (2) Apgar's idea that the condition of the newborn is the most sensitive assay of the quality of anesthetic care of the mother.
- The history of obstetric anesthesia suggests that the major improvements in patient care have followed the application of principles of basic science.

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PART II

MATERNAL AND FETAL PHYSIOLOGY

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Metabolism was among the first areas of physiology to influence clinical practice. By the beginning of the twentieth century, physiologists had established many of the principles that we recognize today, including normal rates of oxygen consumption and carbon dioxide production, the relationship between oxygen consumption and heat production, and the relationship between metabolic rate, body weight, and surface area among individuals and species. Almost simultaneously, clinicians began to apply these principles to their studies of patients in different states of health and disease.

In one early study, physiologist Magnus-Levy[1] found an exception to the rule that basal metabolic rate varied in proportion to body surface area. As he measured a woman's oxygen consumption during pregnancy, he observed that her metabolic rate increased out of proportion to increments in her body weight and surface area. Subsequent studies by other investigators established the basis of this phenomenon. Per unit of weight, the fetus, placenta, and uterus together consumed oxygen (and released carbon dioxide and heat) at a higher rate than the mother. In effect, the metabolism of a pregnant woman represented the sum of two independent organisms, each metabolizing at its own rate in proportion to its own surface area. Thus, each kilogram of maternal tissue consumed oxygen at a rate of approximately 4 mL/min, whereas the average rate for the fetus, placenta, and uterus was approximately 12 mL/min, although it could rise as high as 20 mL/min. Therefore, during pregnancy, the mother's metabolism was the sum of her metabolic rate plus that of the fetus, placenta, and uterus.[1-4] Subsequent studies established that the highest rates of fetal metabolism occurred during the periods of most rapid growth, thereby reaffirming another physiologic principle—the high metabolic cost of synthesizing new tissue.[5]

The aforementioned studies gave clinicians estimates of the stress imposed by pregnancy. To maintain homeostasis during pregnancy, a pregnant woman had to make an appropriate adjustment in each of the physiologic mechanisms involved in the delivery of substrates to the fetal placental unit and in the excretion of metabolic wastes. Thus, for every increment in fetal weight, clinicians could expect to find a proportional change in all the mechanisms involved in the delivery of substrate to the fetus and in the excretion of all byproducts. In fact, subsequent clinical studies established predictable changes in uterine blood flow, cardiac output, blood volume, minute ventilation, the dissipation of body heat, and the renal excretion of nitrogenous waste and other materials.

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CHAPTER 2

Physiologic Changes of Pregnancy

Robert Gaiser, MD

CHAPTER OUTLINE

Marked anatomic and physiologic changes occur during pregnancy that allow the woman to adapt to the developing fetus and its metabolic demands. The enlarging uterus places mechanical strain on the woman's body. Greater hormonal production by the ovaries and the placenta further alters maternal physiology. The hallmark of successful anesthetic management of the pregnant woman is recognition of these anatomic and physiologic changes and appropriate adaptation of anesthetic techniques to account for them. The physiologic alterations of normal pregnancy and their anesthetic implications are reviewed in this chapter.

BODY WEIGHT AND COMPOSITION

The mean maternal weight increase during pregnancy is 17% of the prepregnancy weight or approximately 12 kg.[1] It results from an increase in the size of the uterus and its contents (uterus, 1 kg; amniotic fluid, 1 kg; fetus and placenta, 4 kg), increases in blood volume and interstitial fluid (approximately 1 kg each), and deposition of new fat and protein (approximately 4 kg). The weight gain during pregnancy recommended by the Institute of Medicine reflects the increased incidence of obesity[2] and depends on the prepregnancy body mass index (BMI; Table 2-1).

TABLE 2-1 Recommended Weight Gain during Pregnancy

Prepregnancy Body Mass Index (kg/m²)	Total Weight Gain in kg (lb)	Rate of Weight Gain during 2nd and 3rd Trimester in kg/wk (lb/wk)
< 18.5	12.7-18.2 (28-40)	0.45 (1)
18.5-24.9	11.4-15.9 (25-35)	0.45 (1)
25.0-29.9	6.8-11.4 (15-25)	0.27 (0.6)
≥ 30	5.0-9.1 (11-20)	0.23 (0.5)

Modified from Institute of Medicine (U.S.) Committee to Reexamine IOM Pregnancy Weight Guidelines, Rasmussen KM, Yaktine AL, editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC, National Academies Press, 2009.

BOX 2-1 Changes in the Cardiac Examination in the Pregnant Patient

- Accentuation of first heart sound (S1) and exaggerated splitting of the mitral and tricuspid components
- Typical systolic ejection murmur
- Possible presence of third heart sound (S3) and fourth heart sound (S4); no clinical significance
- Leftward displacement of point of maximal cardiac impulse

The expected weight increase during the first trimester in a nonobese individual is 1 to 2 kg, and there is a 5- to 6-kg increase in each of the last two trimesters. The recommended gain is less in obese individuals. Obesity is a major problem in the United States and has many implications for obstetric anesthesia (see Chapter 50). Excessive weight gain during pregnancy is a risk factor for a long-term increase in BMI.[3]

CARDIOVASCULAR CHANGES

Physical Examination and Cardiac Studies

Pregnancy causes the heart to increase in size, a result of both greater blood volume and increased stretch and force of contraction.[4] These changes, coupled with the elevation of the diaphragm from the expanding uterus, cause several changes in the physical examination and in cardiac studies.

Changes in heart sounds include accentuation of the first heart sound with exaggerated splitting of the mitral and tricuspid components (Box 2-1).[5] The second heart sound changes little, although the aortic-pulmonic interval tends to vary less with respiration during the third trimester, a finding without clinical significance. A fourth heart sound may be heard in 16% of pregnant women, although typically it disappears at term. A grade II systolic ejection murmur is commonly heard at the left sternal border[6]; the murmur is considered a benign flow murmur, attributable to cardiac enlargement from increased intravascular volume, which causes dilation of the tricuspid annulus and regurgitation. Elevation of the diaphragm by the growing uterus shifts the heart anteriorly and to the left. The point of maximal cardiac impulse is displaced cephalad to the fourth intercostal space and also to the left to at least the midclavicular line.

The electrocardiogram typically changes, especially during the third trimester. Heart rate steadily increases during the first and second trimesters, and both the PR interval and the uncorrected QT interval are shortened. This has clinical implications for women with *long QT syndrome* (see Chapter 42). The QRS axis shifts to the right during the first trimester but may shift to the left during the third trimester.[7] Depressed ST segments and isoelectric low-voltage T waves in the left-sided precordial and limb leads are commonly observed.[8]

Echocardiography demonstrates left ventricular hypertrophy by 12 weeks' gestation with a 50% increase in mass at term.[9] This hypertrophy results from an increase in the size of the preexisting cardiomyocytes rather than an increase in the number of cells. The hypertrophy is eccentric, resembling that occurring from exercise.[1] The annular diameters of the mitral, tricuspid, and pulmonic valves increase; 94% of term pregnant women exhibit tricuspid and pulmonic regurgitation, and 27% exhibit mitral regurgitation.[10] The aortic annulus is not dilated.

Central Hemodynamics

For accurate determination of central hemodynamic changes during pregnancy, measurements should be made with the patient in a resting position, tilted to the left, to minimize aortic and vena caval compression. Comparisons must be made with an appropriate control, such as prepregnancy values or a matched group of nonpregnant women. If control measurements are made during the postpartum period, a sufficient interval must have elapsed for hemodynamic parameters to have returned to prepregnancy values; this may take 24 weeks or more.[11]

Cardiac output begins to increase by 5 weeks' gestation and is 35% to 40% above baseline by the end of the first trimester.[9,12] It continues to increase throughout the second trimester until it is approximately 50% greater than nonpregnant values (Figures 2-1 and 2-2).[9,11,13-15] Cardiac output does not change from this level during the third trimester. Some studies have reported a decrease in cardiac output during the third trimester; typically this is when measurements are made in the supine position and thus reflects aortocaval compression rather than a true gestational decline.

The initial increase in cardiac output results from an increase in heart rate, which occurs by the fourth to fifth week of pregnancy.[9] The heart rate increases 15% to 25% above baseline by the end of the first trimester and remains relatively unchanged from that level for the remainder of the pregnancy.[9,11-16] Cardiac output continues to increase during the second trimester because of an increase in stroke volume. Stroke volume increases by approximately 20% during the first trimester and by 25%

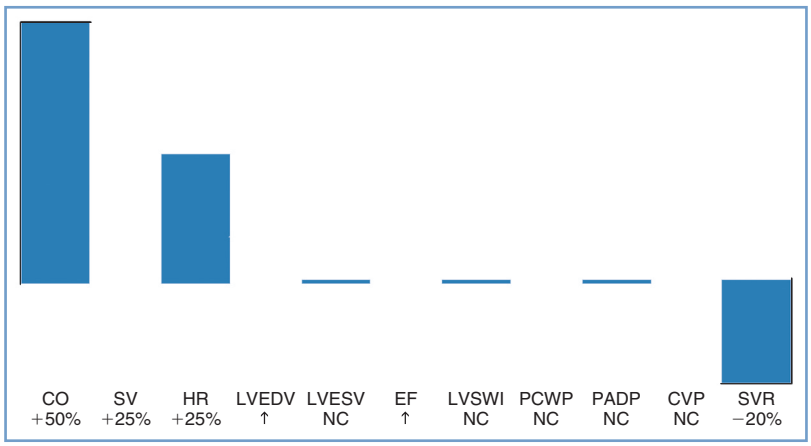

FIGURE 2-1 ■ Central hemodynamic changes at term gestation. Changes are relative to the nonpregnant state. *CO*, cardiac output; *SV*, stroke volume; *HR*, heart rate; *LVEDV*, left ventricular end-diastolic volume; *LVESV*, left ventricular end-systolic volume; *EF*, ejection fraction; *LVSWI*, left ventricular stroke work index; *PCWP*, pulmonary capillary wedge pressure; *PADP*, pulmonary artery diastolic pressure; *CVP*, central venous pressure; *SVR*, systemic vascular resistance; *NC*, no change. (Data from Conklin KA. Maternal physiological adaptations during gestation, labor, and puerperium. Semin Anesth 1991; 10:221-34.)

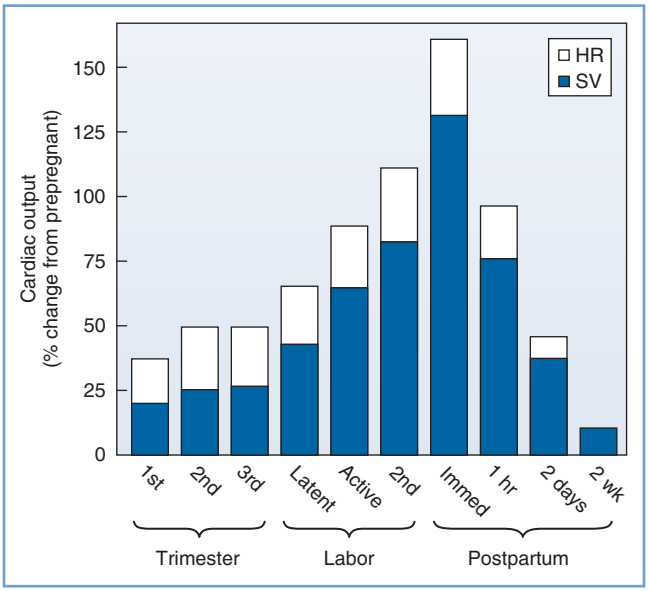

FIGURE 2-2 ■ Cardiac output during pregnancy, labor, and the puerperium. Values during pregnancy are measured at the end of the first, second, and third trimesters. Values during labor are measured between contractions. For each measurement, the relative contributions of heart rate (*HR*) and stroke volume (*SV*) to the change in cardiac output are illustrated.

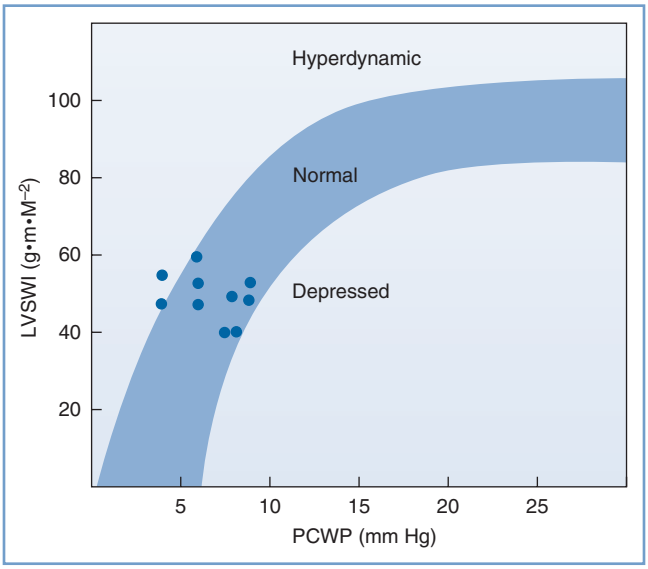

FIGURE 2-3 ■ Left ventricular function in late phase of third-trimester normotensive pregnant patients. *LVSWI*, left ventricular stroke work index; *PCWP*, pulmonary capillary wedge pressure. (Modified from Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of cardiac function. Am J Obstet Gynecol 1989; 161:439-42.)

to 30% above baseline during the second trimester.[9,11,12,16] The increase in stroke volume correlates with increasing estrogen levels.[1] Left ventricular mass increases by 23% from the first to the third trimester.[17] Cardiac output increases to meet the demands of the developing fetus, and the distribution of cardiac output to the uterine circulation increases from 5% to 12% during the second half of pregnancy.[18]

Left ventricular end-diastolic volume increases during pregnancy, whereas end-systolic volume remains unchanged, resulting in a larger ejection fraction.[9,11-14,16] Central venous, pulmonary artery diastolic, and pulmonary capillary wedge pressures are within the normal nonpregnant range.[15] The apparent discrepancy between left ventricular filling pressure and end-diastolic volume is explained by hypertrophy and dilation, with the dilated ventricle accommodating a greater volume without an increase in pressure.

Myocardial contractility increases, as demonstrated by higher velocity of left ventricular circumferential fiber shortening (Figure 2-3).[9,13,16] Tissue Doppler imaging, which is relatively independent of preload, has been used to assess diastolic function.[19] Left ventricular diastolic function is not impaired during pregnancy, whereas systolic function is increased during the second trimester.

The increase in cardiac output during pregnancy results in increased perfusion to the uterus, kidneys, and extremities. Uterine blood flow increases from a baseline value of approximately 50 mL/min to a level at term of 700 to 900 mL/min.[20-24] Approximately 90% of this flow perfuses the intervillous space, with the balance perfusing

the myometrium.[22] At term, skin blood flow is approximately three to four times the nonpregnant level, resulting in higher skin temperature.[25] Renal plasma flow is increased by 80% at 16 to 26 weeks' gestation but declines to 50% above the nonpregnant baseline at term.[26]

The U.S. Department of Health and Human Services recommends that pregnant women have at least 150 minutes of moderate-intensity aerobic activity every week[27]; however, most women do not achieve this goal. Pregnant women are less active, with only half as many meeting guidelines for vigorous activity compared with nonpregnant women.[28] For every two women who exercise before pregnancy, one will not do so during pregnancy. Failure to exercise results in greater gestational weight gain.[29] Exercise is safe for the fetus[29,30]; in a study of 45 women, exercise on a treadmill of moderate intensity (40% to 59% of heart rate reserve) did not affect fetal heart or umbilical artery Doppler indices.[30]

During exercise, maximal oxygen consumption is greater in pregnancy,[31] especially during cardiovascular exercise. The rate of increase in minute ventilation is greater with exercise during pregnancy.[32] Cardiac output is also greater, primarily from increased stroke volume[33] and increased oxygen delivery to the fetus.

Blood Pressure

Positioning, gestational age, and parity affect blood pressure measurements. Brachial sphygmomanometry yields the highest measurements in the supine position and the lowest measurements in the lateral position.[14,34] Blood pressure increases with maternal age, and for a given age, nulliparous women have a higher mean pressure than parous women.[35] Systolic, diastolic, and mean blood pressure decrease during midpregnancy and return toward baseline as the pregnancy approaches term.[36] Diastolic blood pressure decreases more than systolic blood pressure, with early to mid-gestational decreases of approximately 20%.[37] The changes in blood pressure are consistent with changes in systemic vascular resistance, which decreases during early gestation, reaches its nadir (35% decline) at 20 weeks' gestation, and increases during late gestation. Unlike blood pressure, systemic vascular resistance remains approximately 20% below the nonpregnant level at term.[11,15] A postulated explanation for the decreased systemic vascular resistance is the development of a low-resistance vascular bed (the intervillous space) as well as vasodilation caused by prostacyclin, estrogen, and progesterone. The lower blood pressure persists beyond the pregnancy. A longitudinal study of 2304 initially normotensive women over 20 years showed that nulliparous women at baseline who subsequently delivered one or more infants had a blood pressure that was 1 to 2 mm Hg lower than corresponding women who did not have children. This finding demonstrates that pregnancy may create long-lasting vascular changes.[37]

Aortocaval Compression

The extent of compression of the aorta and inferior vena cava by the gravid uterus depends on positioning and gestational age. At term, partial vena caval compression occurs when the woman is in the lateral position, as documented by angiography.[38] This finding is consistent with the 75% elevation above baseline of femoral venous and lower inferior vena cava pressures.[39] Despite caval compression, collateral circulation maintains venous return, as reflected by the right ventricular filling pressure, which is unaltered in the lateral position.[15]

In the supine position, nearly complete obstruction of the inferior vena cava is evident at term.[40] Blood returns from the lower extremities through the intraosseous, vertebral, paravertebral, and epidural veins.[41] However, this collateral venous return is less than would occur through the inferior vena cava, resulting in a decrease in right atrial pressure.[42] Compression of the inferior vena cava occurs as early as 13 to 16 weeks' gestation and is evident from the 50% increase in femoral venous pressure observed when these women assume the supine position (Figure 2-4).[43] By term, femoral venous and lower inferior vena caval pressures are approximately 2.5 times the nonpregnant measurements in the supine position.[39,43]

In the supine position, the aorta may be compressed by the term gravid uterus. This compression accounts for lower pressure in the femoral versus the brachial artery in the supine position.[44,45] These findings are consistent with angiographic studies in supine pregnant women, which show partial obstruction of the aorta at the level of the lumbar lordosis and enhanced compression during periods of maternal hypotension.[46]

At term, the left lateral decubitus position results in less enhancement of cardiac sympathetic nervous system activity and less suppression of cardiac vagal activity than the supine or right lateral decubitus position.[47] Women who assume the supine position at term gestation experience a 10% to 20% decline in stroke volume and cardiac output,[48,49] consistent with the fall in right atrial filling pressure. Blood flow in the upper extremities is normal, whereas uterine blood flow decreases by 20% and lower extremity blood flow decreases by 50%.[50] Perfusion of the uterus is less affected than that of the lower extremities because compression of the vena cava does not obstruct venous outflow via the ovarian veins.[51] The adverse hemodynamic effects of aortocaval compression are reduced once the fetal head is engaged.[44,45] The sitting position has also been shown to result in aortocaval compression, with a decrease in cardiac output of 10%.[52] Flexing the legs rotates the uterus to compress against the vena cava. Short intervals in the sitting position, such as occurs during epidural catheter placement, have no impact on uteroplacental blood flow.

Some term pregnant women exhibit an increase in brachial artery blood pressure when they assume the supine position, which is caused by higher systemic vascular resistance from compression of the aorta. Up to 15% of women at term experience bradycardia and a substantial drop in blood pressure when supine, the so-called *supine hypotension syndrome*.[53] It may take several minutes for the bradycardia and hypotension to develop, and the bradycardia is usually preceded by a period of tachycardia. The syndrome results from a profound drop in venous return for which the cardiovascular system is not able to compensate.

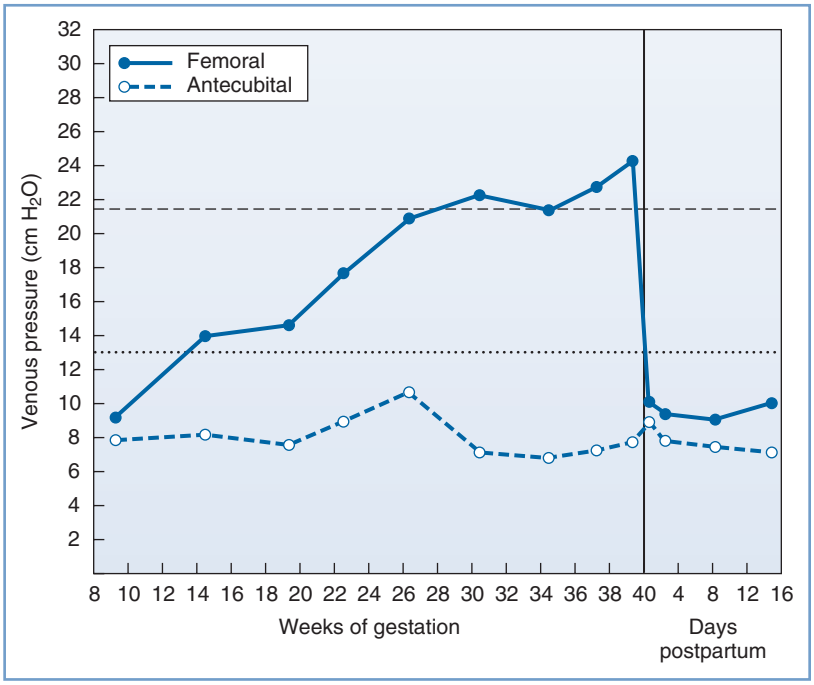

FIGURE 2-4 ■ Femoral and antecubital venous pressures in the supine position throughout normal pregnancy and the puerperium. (Modified from McLennan CE. Antecubital and femoral venous pressure in normal and toxemic pregnancy. Am J Obstet Gynecol 1943; 45:568-91.)

Hemodynamic Changes during Labor and the Puerperium

Cardiac output during labor (but between uterine contractions) increases from pre-labor values by approximately 10% in the early first stage, by 25% in the late first stage, and by 40% in the second stage of labor.[54-56] In the immediate postpartum period, cardiac output may be as much as 75% above pre-delivery measurements.[55] These changes result from an increase in stroke volume due to greater venous return and to alterations in sympathetic nervous system activity. During uterine contractions, 300 to 500 mL of blood is displaced from the intervillous space into the central circulation ("autotransfusion").[57-59] Increased intrauterine pressure forces blood from the intervillous space through the relatively unimpeded ovarian venous outflow system. The postpartum increase in cardiac output results from relief of vena caval compression, diminished lower extremity venous pressure, and a reduction of maternal vascular capacitance.[56] Cardiac output decreases to just below pre-labor values at 24 hours postpartum[57] and returns to prepregnancy levels between 12 and 24 weeks postpartum.[11] Heart rate decreases rapidly after delivery, reaches prepregnancy levels by 2 weeks postpartum, and is slightly below the prepregnancy rate for the next several months.[11,60] Other anatomic and functional changes of the heart are also fully reversible.[18,61]

THE RESPIRATORY SYSTEM

Despite the multiple anatomic and physiologic changes that occur during pregnancy, it is remarkable that pregnancy has a relatively minor impact on lung function.

Anatomy

The thorax undergoes both mechanical and hormonal changes during pregnancy.[62,63] Relaxin (the hormone responsible for relaxation of the pelvic ligaments) causes relaxation of the ligamentous attachments to the lower ribs.[62,63] The subcostal angle progressively widens from 68.5 to 103.5 degrees. The anteroposterior and transverse diameters of the chest wall each increase by 2 cm, resulting in an increase of 5 to 7 cm in the circumference of the lower rib cage. These changes peak at 37 weeks' gestation. The subcostal angle remains about 20% wider than the baseline value after delivery.[64] The vertical measurement of the chest cavity decreases by as much as 4 cm as a result of the elevated position of the diaphragm.

Capillary engorgement of the larynx and the nasal and oropharyngeal mucosa begins early in the first trimester and increases progressively throughout pregnancy.[65] The effect of estrogen on the nasal mucosa leads to symptoms of rhinitis and nosebleeds. Nasal breathing commonly becomes difficult, and epistaxis may occur. Nasal congestion may contribute to the perceived shortness of breath of pregnancy.[66] Throughout the first and second trimesters, the voice has been described as rounded and well carried with good vibration. During the third trimester, vocal cord fatigue is more prevalent with a decrease in the maximum time of phonation. Both of these changes resolve in the immediate postpartum period.[67]

Airflow Mechanics

Inspiration in the term pregnant woman is almost totally attributable to diaphragmatic excursion[68] because of greater descent of the diaphragm from its elevated resting position and limitation of thoracic cage expansion because of its expanded resting position (Table 2-2). Both

TABLE 2-2 Effects of Pregnancy on Respiratory Mechanics

Parameter	Change*
Diaphragm excursion	Increased
Chest wall excursion	Decreased
Pulmonary resistance	Decreased 50%
FEV_1	No change
FEV_1/FVC	No change
Flow-volume loop	No change
Closing capacity	No change

FEV_1, Forced expiratory volume in 1 second; FVC, forced vital capacity.
*Relative to nonpregnant state.
Adapted from Conklin KA. Maternal physiological adaptations during gestation, labor, and the puerperium. Semin Anesth 1991; 10:221-34.

TABLE 2-3 Changes in Respiratory Physiology at Term Gestation

Parameter	Change*
Lung Volumes	
Inspiratory reserve volume	+5%
Tidal volume	+45%
Expiratory reserve volume	–25%
Residual volume	–15%
Lung Capacities	
Inspiratory capacity	+15%
Functional residual capacity	–20%
Vital capacity	No change
Total lung capacity	–5%
Ventilation	
Minute ventilation	+45%
Alveolar ventilation	+45%

*Relative to nonpregnant state.
From Conklin KA. Maternal physiological adaptations during gestation, labor and the puerperium. Semin Anesth 1991; 10:221-34.

large- and small-airway function are minimally altered during pregnancy. The shape of flow-volume loops, the absolute flow rates at normal lung volumes,[69] forced expiratory volume in one second (FEV_1), the ratio of FEV_1 to forced vital capacity (FVC), and closing capacity are unchanged during pregnancy.[70] There is no significant change in respiratory muscle strength during pregnancy despite the cephalad displacement of the diaphragm. Furthermore, despite the upward displacement of the diaphragm by the gravid uterus, diaphragm excursion actually increases by 2 cm.[71]

The peak expiratory flow rate achieved with a maximal effort after a maximal inspiration is often considered a surrogate for the FEV_1 and is often used to monitor asthma therapy. Studies of changes in peak expiratory flow rate during pregnancy have had conflicting results, most likely reflecting differences in measurement devices and patient position during measurements. Nonetheless, Harirah et al.[72] found that peak expiratory flow rate declined throughout gestation in all positions and that flow rates in the supine position were lower than those during standing and sitting. The mean rate of decline was 0.65 L/min per week, and peak expiratory flow rate remained below normal at 6 weeks postpartum. By contrast, Grindheim et al.[73] reported that peak expiratory flow rate increased in 100 pregnant women followed longitudinally, starting at an average of 6.7 L/s in the early second trimester and peaking at 7.2 L/s at term (Figure 2-5). These authors also reported that the FVC increased by 100 mL after 14 to 16 weeks' gestation, with the change being greater in parous than in primigravid women.[73] The changes in functional residual capacity (FRC) that occur during pregnancy may persist postpartum.

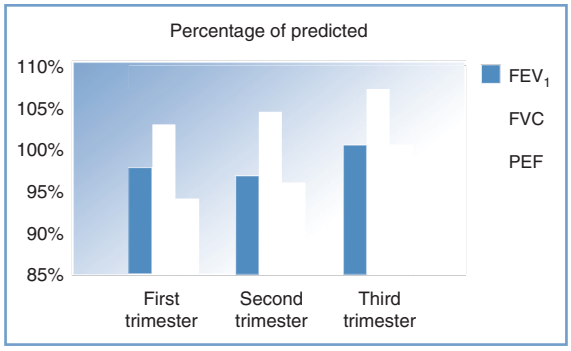

FIGURE 2-5 Changes in airflow mechanics during pregnancy. The magnitude of the increase in flow rates is small. The forced expiratory volume in one second (*FEV_1*) is within the normal range of predictive values for nonpregnant individuals. *FVC,* forced vital capacity; *PEF,* peak expiratory flow. (Based on data from Grindheim G, Toska K, Estensen ME, Rosseland LA. Changes in pulmonary function during pregnancy: a longitudinal study. BJOG 2012; 119:94-101.)

Lung Volumes and Capacities

Lung volumes can be measured using body plethysmography or by inert gas techniques with slightly differing results.[74] During pregnancy, total lung capacity is slightly reduced,[75] whereas tidal volume increases by 45%, with approximately half the change occurring during the first trimester (Table 2-3 and Figure 2-6). The early change in tidal volume is associated with a reduction in inspiratory reserve volume. Residual volume tends to drop slightly, a change that maintains vital capacity. Inspiratory capacity increases by 15% during the third trimester because of increases in tidal volume and inspiratory reserve volume.[76,77] There is a corresponding decrease in expiratory reserve volume.[76,77] The FRC begins to decrease by the fifth month of pregnancy and decreases by 400 to 700 mL to 80% of the prepregnancy value at term.[76,77] This change is caused by elevation of the diaphragm as the enlarging uterus enters the abdominal cavity and is accounted for by a 25% reduction in expiratory reserve volume (200 to 300 mL) and a 15% reduction in residual volume (200 to 400 mL). Assumption of the supine position causes the FRC to decrease further to 70% of the prepregnancy value. The supine FRC can

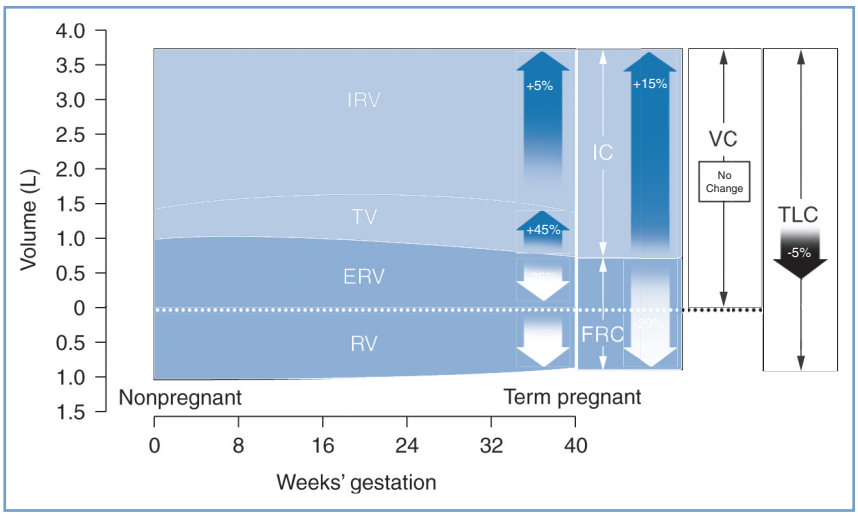

FIGURE 2-6 ■ Lung volumes and capacities during pregnancy. *ERV,* expiratory reserve volume; *FRC,* functional residual capacity; *IC,* inspiratory capacity; *IRV,* inspiratory reserve volume; *RV,* residual volume; *TLC,* total lung capacity; *TV,* tidal volume; *VC,* vital capacity.

TABLE 2-4 Blood Gas Measurements during Pregnancy

Parameter	Nonpregnant	Trimester		
		FIRST	SECOND	THIRD
$Paco_2$ in mm Hg (kPa)	40 (5.3)	30 (4.0)	30 (4.0)	30 (4.0)
Pao_2 in mm Hg (kPa)	100 (13.3)	107 (14.3)	105 (14.0)	103 (13.7)
pH	7.40	7.44	7.44	7.44
$[HCO_3^-]$ (mEq/L)	24	21	20	20

be increased by 10% (approximately 188 mL) by placing the patient in a 30-degree head-up position.[78]

Ventilation and Blood Gases

During pregnancy, respiratory rate and pattern remain relatively unchanged. Minute ventilation increases via an increase in tidal volume from 450 to 600 mL and a small increase in respiratory rate of 1 to 2 breaths/min.[79] This occurs primarily during the first 12 weeks of gestation with a minimal increase thereafter. The ratio of total dead space to tidal volume remains constant during pregnancy, resulting in an increase in alveolar ventilation of 30% to 50% above baseline. The increase in minute ventilation results from hormonal changes and from an increase in CO_2 production at rest by approximately 30% to 300 mL/min. The latter is closely related to the blood level of progesterone,[80] which acts as a direct respiratory stimulant. The progesterone-induced increase in chemosensitivity results in a steeper slope and a leftward shift of the CO_2-ventilatory response curve. This change occurs early in pregnancy and remains constant until delivery.[69]

Dyspnea is a common complaint during pregnancy, affecting up to 75% of women.[81] Contributing factors include increased respiratory drive, decreased $Paco_2$, the enlarging uterus, larger pulmonary blood volume, anemia, and nasal congestion. Dyspnea typically begins in the first or second trimester but improves as the pregnancy progresses. In a study in which 35 women were observed closely during pregnancy and postpartum, dyspnea was not due to alterations in central ventilatory control or respiratory mechanical factors but rather to the awareness of the increased ventilation.[82] Exercise has no effect on pregnancy-induced changes in ventilation or alveolar gas exchange.[83] The hypoxic ventilatory response is increased during pregnancy to twice the normal level, secondary to elevations in estrogen and progesterone levels.[84] This increase occurs despite blood and cerebrospinal fluid (CSF) alkalosis.

During pregnancy, Pao_2 increases to 100 to 105 mm Hg (13.3 to 14.0 kPa) as a result of greater alveolar ventilation (Table 2-4).[85] The higher Pao_2 results from the decline in $Paco_2$ and a lower arteriovenous oxygen difference, which reduces the impact of venous admixture on Pao_2.[86,87] As pregnancy progresses, oxygen consumption continues to increase, and cardiac output increases to a lesser extent, resulting in a reduced mixed venous oxygen content and increased arteriovenous oxygen difference. After mid gestation, pregnant women in the supine position frequently have a Pao_2 less than 100 mm Hg (13.3 kPa). This occurs because the FRC may be less than closing capacity, resulting in closure of small airways during normal tidal volume ventilation.[85] Moving a pregnant woman from the supine to the erect or lateral decubitus position improves arterial oxygenation and reduces the alveolar-to-arterial oxygen gradient. The increased oxygen tension facilitates the transfer of oxygen across the placenta to the fetus.

$Paco_2$ declines to approximately 30 mm Hg (4.0 kPa) by 12 weeks' gestation but does not change further during the remainder of pregnancy. Although a gradient exists between the end-tidal CO_2 tension and $Paco_2$ in nonpregnant women, the two measurements are equivalent during early pregnancy,[88] at term gestation,[89] and in the postpartum period.[90] This is attributable to a reduction in alveolar dead space, which results from an increase in cardiac output during pregnancy. The mixed venous Pco_2 is 6 to 8 mm Hg (0.8 to 1.1 kPa) below the nonpregnant level from the later first trimester until term.[1]

Metabolic compensation for the respiratory alkalosis of pregnancy reduces serum bicarbonate concentration to approximately 20 mEq/L, the base excess by 2 to 3 mEq/L, and the total buffer base by approximately 5 mEq/L.[91] This compensation is incomplete, as demonstrated by the elevation of venous,[92] capillary,[93] and arterial[85] blood pH by 0.02 to 0.06 units.

Metabolism and Respiration during Labor and the Puerperium

Minute ventilation in the unmedicated parturient increases by 70% to 140% in the first stage of labor and by 120% to 200% in the second stage of labor compared with prepregnancy values.[94] Pain, anxiety, and coached breathing techniques increase minute ventilation. $Paco_2$ may decrease to as low as 10 to 15 mm Hg (1.3 to 2.0 kPa). Oxygen consumption increases above the prelabor value by 40% in the first stage and by 75% in the second stage, secondary to the increased metabolic demands of hyperventilation, uterine activity, and maternal expulsive efforts.[94,95] The maternal aerobic requirement for oxygen exceeds oxygen consumption during labor, as is evident from the progressive elevation of blood lactate concentration, an index of anaerobic metabolism.[95-98] Provision of effective neuraxial analgesia prevents these changes during the first stage of labor and mitigates the changes during the second stage of labor.[95,98]

FRC increases after delivery but remains below the prepregnancy volume for 1 to 2 weeks. Although minute ventilation decreases halfway toward nonpregnant values by 72 hours, oxygen consumption, tidal volume, and minute ventilation remain elevated until at least 6 to 8 weeks after delivery. The alveolar and mixed venous Pco_2 values increase slowly after delivery and are still slightly below prepregnancy levels at 6 to 8 weeks postpartum.[1]

HEMATOLOGY

Blood Volume

Maternal plasma volume expansion begins as early as 6 weeks' gestation and continues until it reaches a net increase of approximately 50% by 34 weeks' gestation (Table 2-5, Figure 2-7).[99-102] After 34 weeks' gestation, the plasma volume stabilizes or decreases slightly. Red blood cell volume decreases during the first 8 weeks of pregnancy, increases to the prepregnancy level by 16 weeks, and undergoes a further rise to 30% above the prepregnancy level at term.[100,102,103] The increase in plasma volume exceeds the increase in red blood cell volume, resulting in the **physiologic anemia of pregnancy.** Hemoglobin concentration, which typically ranges from 12 to 15.8 g/dL in the nonpregnant woman, decreases to 11.6 to 13.9 g/dL in the first trimester, 9.7 to 14.8 g/dL in the second trimester, and 9.5 to 15.0 g/dL in the third trimester.[104] Hematocrit, which ranges from 35.4% to 44.4% in the nonpregnant woman, decreases to 31% to 41% in the first trimester, 30% to 39% in the second trimester, and 28% to 40% in the third trimester.[100] There is an increase in plasma volume from 49 to 67 mL/kg, an increase in total blood volume from 76 to 94 mL/kg, and little change in red cell volume (27 mL/kg) (Figure 2-8).[100] Blood volume is positively correlated with the size of the fetus in singleton pregnancies and is greater in multiple gestations.[101] The

TABLE 2-5 Hematologic Parameters at Term Gestation

Parameter	Change* or Actual Measurement
Blood volume	+45%*
Plasma volume	+55%*
Red blood cell volume	+30%*
Hemoglobin concentration (g/dL)	11.6
Hematocrit	35.5%

*Relative to nonpregnant state.

Adapted from Conklin KA. Maternal physiological adaptations during gestation, labor, and puerperium. Semin Anesth 1991; 10:221-34.

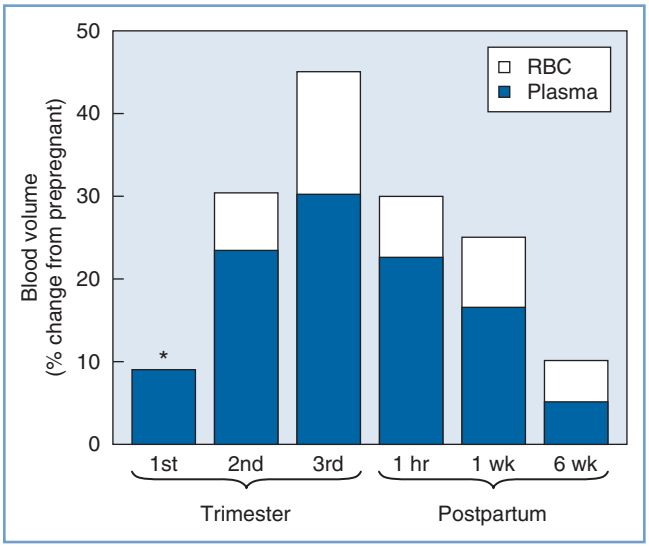

FIGURE 2-7 ■ Blood volume during pregnancy and the puerperium. Values during pregnancy measured at the end of the first, second, and third trimesters. Postpartum values measured after a vaginal delivery. The values for red blood cell volume (*RBC*) and plasma volume (*Plasma*) do not represent the actual percentage of change in these parameters but rather reflect the relative contribution of each to the change in blood volume. The *asterisk* indicates that RBC volume is below the prepregnancy volume at the end of the first trimester.

physiologic hypervolemia facilitates delivery of nutrients to the fetus, protects the mother from hypotension, and reduces the risks associated with hemorrhage at delivery. The decrease in blood viscosity from the lower hematocrit creates lower resistance to blood flow, which may be an essential component of maintaining the patency of the uteroplacental vascular bed.

The increase in plasma volume results from fetal and maternal hormone production, and several systems may play a role. Additionally, the expansion of plasma volume may help to maintain blood pressure in the presence of decreased vascular tone.[103,105] The maternal concentrations of estrogen and progesterone increase nearly 100-fold during pregnancy. Estrogens increase plasma renin activity, enhancing renal sodium absorption and water retention via the renin-angiotensin-aldosterone system. Fetal adrenal production of the estrogen precursor dehydroepiandrosterone may be the underlying control mechanism. Progesterone also enhances aldosterone production. These changes result in marked increases in plasma renin activity and aldosterone level as well as in retention of approximately 900 mEq of sodium and 7000 mL of total body water. The concentration of plasma adrenomedullin, a potent vasodilating peptide, increases during pregnancy and correlates significantly with blood volume.[106]

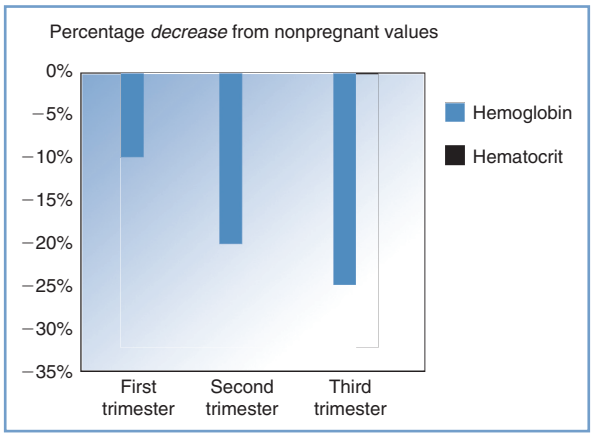

FIGURE 2-8 ■ The decrease in both hemoglobin concentration and hematocrit during pregnancy underlies the physiologic anemia of pregnancy. The decrease is greater for hematocrit and the greatest decreases occur during the third trimester. (Based on data from Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol 2009; 114:1326-31.)

Red blood cell volume increases in response to elevated erythropoietin concentration[107] and the erythropoietic effects of progesterone, prolactin, and placental lactogen. Both hemoglobin concentration and hematocrit decrease after conception to approximately 11.2 g/dL and 34%, respectively, by mid gestation,[102,103] which is a 15% decrease from prepregnancy levels. During the late third trimester, the hemoglobin concentration and hematocrit increase to approximately 11.6 g/dL and 35.5%, respectively, because red blood cell volume increases more than plasma volume. Women who do not receive iron supplements during pregnancy have greater decreases in hemoglobin concentration and hematocrit.[102]

Plasma Proteins

Plasma albumin concentration decreases from a nonpregnant range of 4.1-5.3 g/dL to 3.1-5.1 g/dL in the first trimester, 2.6-4.5 g/dL in the second trimester, and 2.3-4.2 g/dL in the third trimester (Table 2-6).[104,108,109] The globulin level decreases by 10% in the first trimester and then increases throughout the remainder of pregnancy to 10% above the prepregnancy value at term.[108] The albumin-globulin ratio decreases during pregnancy from 1.4 to 0.9, and the total plasma protein concentration decreases from 7.8 to 7.0 g/dL.[109] Maternal colloid osmotic pressure decreases by approximately 5 mm Hg during pregnancy.[15,110,111] The plasma cholinesterase concentration falls by approximately 25% during the first trimester and remains at that level until the end of pregnancy.[112,113]

Coagulation

Pregnancy is associated with enhanced platelet turnover, clotting, and fibrinolysis (Box 2-2). Thus, pregnancy represents a state of accelerated but compensated intravascular coagulation.

Increases in platelet factor 4 and beta-thromboglobulin signal elevated platelet activation, and the progressive increase in platelet distribution width and platelet volume are consistent with greater platelet consumption during pregnancy.[114-116] Platelet aggregation in response to collagen, epinephrine, adenosine diphosphate, and arachidonic acid is increased.[117] Despite changes in platelet

TABLE 2-6 **Plasma Protein Values during Pregnancy**

Protein	Nonpregnant	Trimester		
		FIRST	SECOND	THIRD
Total protein (g/dL)	7.8	6.9	6.9	7.0
Albumin (g/dL)	4.5	3.9	3.6	3.3
Globulin (g/dL)	3.3	3.0	3.3	3.7
Albumin/globulin ratio	1.4	1.3	1.1	0.9
Plasma cholinesterase		−25%	−25%	−25%
Colloid osmotic pressure (mm Hg)	27	25	23	22

BOX 2-2 Changes in Coagulation and Fibrinolytic Parameters at Term Gestation*

Increased Factor Concentrations

- Factor I (fibrinogen)
- Factor VII (proconvertin)
- Factor VIII (antihemophilic factor)
- Factor IX (Christmas factor
- Factor X (Stuart-Prower factor)
- Factor XII (Hageman factor)

Unchanged Factor Concentrations

- Factor II (prothrombin
- Factor V (proaccelerin)

Decreased Factor Concentrations

- Factor XI (thromboplastin antecedent)
- Factor XIII (fibrin-stabilizing factor)

Other Parameters

- Prothrombin time: shortened 20%
- Partial thromboplastin time: shortened 20%
- Thromboelastography: hypercoagulable
- Fibrinopeptide A: increased
- Antithrombin III: decreased
- Platelet count: no change or decreased
- Fibrin degradation products: increased
- Plasminogen: increased

*Relative to nonpregnant state.

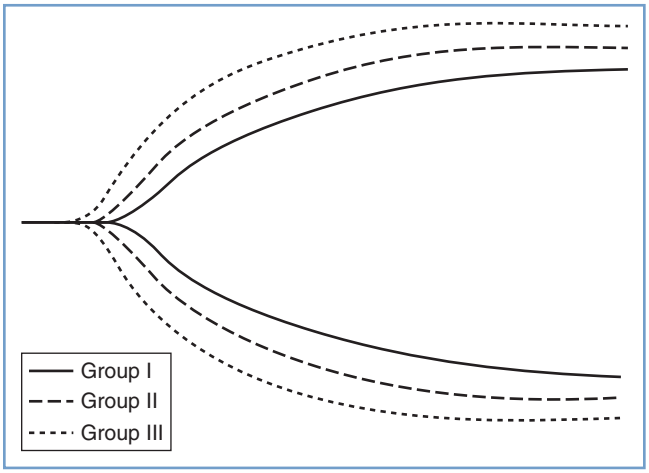

FIGURE 2-9 ■ **Comparative thromboelastographs in nonpregnant (Group I), nonlaboring term pregnant (Group II), and laboring (Group III) women.** (From Steer PL, Krantz HB. Thromboelastrography and Sonoclot analysis in the healthy parturient. J Clin Anesth 1993; 5:419-24.)

count and/or function, the bleeding time measurement is not altered during normal gestation.[118] Some investigators have noted a decrease in platelet count,[116,119] whereas others have noted no change,[114,115] suggesting that increased platelet production compensates for greater activation. The platelet count usually decreases during the third trimester, with an estimated 8% of pregnant women having a platelet count less than 150,000/mm^3 and 0.9% of pregnant women having a platelet count less than 100,000/mm^3.[115,120] The most common causes of thrombocytopenia are gestational thrombocytopenia, hypertensive disorders of pregnancy, and idiopathic thrombocytopenia. The decrease in platelet count in the third trimester is due to increased destruction and hemodilution.[121] Gestational thrombocytopenia is an exaggerated normal response.

The concentrations of most coagulation factors, including fibrinogen (factor I), proconvertin (factor VII), antihemophilic factor (factor VIII), Christmas factor (factor IX), Stuart-Prower factor (factor X), and Hageman factor (factor XII), increase during pregnancy. The increase in factor VIII is generally more marked in the third trimester. The concentrations of some factors increase by more than 100% (factors VII, VIII, IX, and fibrinogen).[121-124] Prothrombin (factor II) and proaccelerin (factor V) concentrations do not change, whereas the concentrations of thromboplastin antecedent (factor XI) and fibrin-stabilizing factor (factor XIII) decrease.[123-125] An increase in most factor concentrations, shortening of the prothrombin time (PT) and activated partial thromboplastin time (aPTT),[122] an increase in fibrinopeptide A concentration, and a decrease in antithrombin III concentration suggest activation of the clotting system (PT decreases from 12.7 to 15.4 seconds in nonpregnant women to 9.6 to 12.9 seconds in the third trimester, and aPTT decreases from 26.3 to 39.4 seconds in nonpregnant women to 24.7 to 35 seconds in the third trimester).[126] Protein S activity decreases steadily during pregnancy, reaching the lowest values at delivery.[127]

Thromboelastrography demonstrates evidence of hypercoagulability in pregnancy. These changes (decrease in R and K values, increase in the α angle and maximum amplitude [MA], and decrease in lysis) are observed as early as 10 to 12 weeks' gestation and are even greater during labor (Figure 2-9).[128-130] *In vitro*, exogenous oxytocin decreases R and K values, while increasing the α angle, thus resulting in an even more hypercoagulable state.[131] The *in vivo* effects of exogenous oxytocin are not known.

The greater concentration of fibrin degradation products signals increased fibrinolytic activity during gestation.[114] The marked elevation in the plasminogen concentration also is consistent with enhanced fibrinolysis.[132]

Hematology and Coagulation during the Puerperium

Blood loss during normal vaginal delivery and the early puerperium is approximately 600 mL.[133] The normal physiologic changes of pregnancy allow the healthy parturient to compensate for this loss. However, blood loss after either vaginal or cesarean delivery is often underestimated and the discrepancy between actual and estimated blood loss is greater with increasing blood loss.[134]

Blood volume decreases to 125% of the prepregnancy level during the first postpartum week,[133] followed by a more gradual decline to 110% of the prepregnancy level

at 6 to 9 weeks postpartum. The hemoglobin concentration and hematocrit decrease during the first 3 postpartum days, increase gradually during the next 3 days (because of a reduction in plasma volume), and continue to increase to prepregnancy measurements by 3 weeks postpartum.[135]

Cesarean delivery results in a blood loss of approximately 1000 mL within the first few hours of delivery.[133] The hematocrit in the immediate postpartum period is lower after cesarean delivery than after vaginal delivery because of the greater blood loss during cesarean delivery.[133]

Albumin and total protein concentrations and colloid osmotic pressure decline after delivery and gradually return to prepregnancy levels by 6 weeks postpartum.[110] The plasma cholinesterase value decreases below the predelivery level by the first postpartum day and remains at that decreased level during the next week.[112,113] Globulin concentrations are elevated throughout the first postpartum week.[108]

Beginning with delivery and during the first postpartum day, there is a rapid decrease in the platelet count and in the concentrations of fibrinogen, factor VIII, and plasminogen and an increase in antifibrinolytic activity.[136] Clotting times remain shortened during the first postpartum day,[137] and thromboelastography remains consistent with a hypercoagulable state.[131] During the first 3 to 5 days postpartum, increases are noted in the fibrinogen concentration and platelet count, changes that may account for the greater incidence of thrombotic complications during the puerperium.[137] The coagulation profile returns to the nonpregnant state by 2 weeks postpartum.[136]

THE IMMUNE SYSTEM

The blood leukocyte count increases progressively during pregnancy from the prepregnancy level of approximately 6,000/mm^3 to between 9,000 and 11,000/mm^3.[119] This change reflects an increase in the number of polymorphonuclear cells, with the appearance of immature granulocytic forms (myelocytes and metamyelocytes) in most pregnant women. The proportion of immature forms decreases during the last 2 months of pregnancy. The lymphocyte, eosinophil, and basophil counts decrease, whereas the monocyte count does not change. The leukocyte count increases to approximately 13,000/mm^3 during labor and increases further to an average of 15,000/mm^3 on the first postpartum day.[135] By the sixth postpartum day, the leukocyte count decreases to an average of 9,250/mm^3, although the count is still above normal at 6 weeks postpartum.

Polymorphonuclear leukocyte function is impaired during pregnancy, as evidenced by depressed neutrophil chemotaxis and adherence.[138] This impairment may account for the greater incidence of infection during pregnancy and improved symptoms in some pregnant women with autoimmune diseases (e.g., rheumatoid arthritis). Levels of immunoglobulins A, G, and M are unchanged during gestation, but humoral antibody titers to certain viruses (e.g., herpes simplex, measles, influenza type A) are decreased.[139]

During pregnancy, the uterine mucosa is characterized by a large number of maternal immune cells found in close contact with the trophoblast. The fetal expression of paternal antigens requires adaptations in the maternal immune system so that the fetus is not perceived by the mother as "foreign."[140,141] This "immune tolerance" occurs because of a lack of fetal antigen expression, because of separation of the mother from the fetus, or from a functional suppression of the maternal lymphocytes.[142] During the first trimester of pregnancy, T lymphocytes express granulysin, a novel cytolytic protein, which provides a protective role at the maternal-fetal interface.[143] Human T cells may be classified into T-helper cells types 1 and 2 (Th1 and Th2) on the basis of their cytokine production. Successful pregnancy is associated with a predominant Th2 cytokine profile. Th1 cytokines are detrimental to pregnancy. These cells also produce natural antimicrobial agents within the uterus, which are important for prevention of uterine infection during pregnancy.[144]

THE GASTROINTESTINAL SYSTEM

Anatomy, Barrier Pressure, and Gastroesophageal Reflux

The stomach is displaced upward toward the left side of the diaphragm during pregnancy, and its axis is rotated approximately 45 degrees to the right from its normal vertical position. This altered position displaces the intra-abdominal segment of the esophagus into the thorax in most women, causing a reduction in tone of the lower esophageal high-pressure zone (LEHPZ), which normally prevents the reflux of gastric contents. Progestins also may contribute to a relaxation of the LEHPZ.[145]

Approximately 30% to 50% of women experience **gastroesophageal reflux disease (GERD)** during pregnancy,[146] with the majority (80%) experiencing regurgitation not heartburn (pyrosis) (20%).[147] The prevalence of GERD is approximately 10% in the first trimester, 40% in the second trimester, and 55% in the third trimester. In the first trimester of pregnancy, basal LEHPZ pressure may not change, but the sphincter is less responsive to physiologic stimuli that usually increase pressure.[148] In the second and third trimesters, LEHPZ pressure gradually decreases to approximately 50% of basal values, reaching a nadir at 36 weeks' gestation and returning to prepregnancy values at 1 to 4 weeks postpartum (Table 2-7). Risk factors for GERD in pregnancy include gestational age, heartburn antecedent to pregnancy, and multiparity. Gravidity, prepregnancy BMI, and weight gain during pregnancy do not correlate with the occurrence of reflux, whereas maternal age has an inverse correlation.[147,149]

Gastrointestinal Motility

Gastric emptying is not altered during pregnancy. This has been demonstrated by studies that measured the absorption of orally administered acetaminophen[150-152] and by studies that assessed the emptying of a test meal

TABLE 2-7 **Changes in Gastrointestinal Physiology during Pregnancy***

Parameter	Trimester			Labor	Postpartum (18 h)
	FIRST	SECOND	THIRD		
Barrier pressure†	Decreased	Decreased	Decreased	Decreased	?
Gastric emptying	No change	No change	No change	Delayed	No change
Gastric acid secretion	No change	No change	No change	?	?
Proportion of women with gastric volume > 25 mL	No change	No change	No change	Increased	No change
Proportion of women with gastric pH < 2.5	No change	No change	No change	No change	No change

*Relative to nonpregnant state.
†Difference between intragastric pressure and tone of the lower esophageal high-pressure zone.

by radiographic,[153] ultrasonographic,[152,154] dye dilution,[155] epigastric impedance,[156] and applied potential tomographic[157] techniques. In a study of morbidly obese women at term, no difference was noted between gastric emptying of 300 mL and 50 mL of water, suggesting that fasting guidelines should not differ for obese versus lean parturients.[158]

Esophageal peristalsis and intestinal transit are slowed during pregnancy,[154,159] which has been attributed to the inhibition of gastrointestinal contractile activity by progesterone. However, this inhibition may be an indirect action that results from a negative effect of progesterone on the plasma concentration of motilin, which declines during pregnancy.[154] Up to 40% of women suffer from constipation at some time during their pregnancy.[160] The prevalence of constipation is greatest in the first two trimesters of gestation and declines in the third trimester.

Gastric Acid Secretion

Early work suggested that both basal and maximal gastric acid secretion decline in mid gestation, reaching a nadir at 20 to 30 weeks' gestation.[161] Van Thiel et al.[162] demonstrated no difference in basal or peak gastric acid secretion in four pregnant women studied in each trimester and at 1 to 4 weeks postpartum, although a plasma gastrin level significantly lower than postpartum levels was observed during the first trimester. Levels of gastric pH and serum gastrin concentration were compared in 100 women who were not in labor but were scheduled for elective cesarean delivery and in 100 nonpregnant women undergoing gynecologic surgery.[163] The pH was lower in the pregnant group (2.4 versus 3.0), but serum gastrin levels were not different despite the fact that gastrin is secreted by the placenta from 15 weeks' gestation onward.[164] Other studies that have examined stomach contents have shown that approximately 80% of both pregnant and nonpregnant women have a gastric pH of 2.5 or less, approximately 50% have gastric volumes of 25 mL or greater, and 40% to 50% exhibit both low pH and gastric volume greater than 25 mL. These results are similar to those obtained from studies of women at a mean gestation of 15 weeks.[165]

Nausea and Vomiting

Approximately 80% of pregnant women will experience nausea and vomiting during pregnancy.[166] The symptoms typically start between 4 to 9 weeks' gestation and may last until 12 to 16 weeks' gestation.[167] Of these women, 1% to 5% will develop symptoms that persist throughout the pregnancy, known as **hyperemesis gravidarum** (see Chapter 16).

Gastric Function during Labor and the Puerperium

Gastric emptying is slowed during labor, as shown by ultrasonographic imaging, emptying of a test meal, and the rate of absorption of oral acetaminophen.[168,169] Direct measurements show that the mean gastric volume increases.[170] However, in one study, postpartum gastric volume was found to be no different in parturients who consumed water in labor compared with those who consumed an isotonic sports drink composed of mixed carbohydrates and electrolytes.[171] Gastric acid secretion may decrease during labor because only 25% of parturients who are in labor have gastric pH of 2.5 or less.[172] Gastric emptying is delayed during the early postpartum period but returns to prepregnancy levels by 18 hours postpartum.[173] Gastric volume and pH values are similar in fasting women more than 18 hours after delivery and in nonpregnant individuals who have fasted before elective surgery.[174-176] The effects of opioids and neuraxial analgesia on gastric emptying are discussed in Chapters 23 and 29.

THE LIVER AND GALLBLADDER

Liver size, morphology, and blood flow do not change during pregnancy, although the liver is displaced upward, posterior, and to the right during late pregnancy.

Serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase increase to the upper limits of the normal range during pregnancy.[177] The total alkaline phosphatase activity increases twofold to fourfold, mostly from production by the placenta. Excretion of sulfobromophthalein into bile decreases, whereas the hepatic extraction and retention of this compound increases.[178]

Biliary stasis and greater secretion of bile with cholesterol increase the risk of gallbladder disease during pregnancy.[179] The incidence of gallstones is 5% to 12% in pregnant women.[180] One in 1,600 to 1 in 10,000 women undergo cholecystectomy during pregnancy. Progesterone inhibits the contractility of gastrointestinal smooth muscle, leading to gallbladder hypomotility.[181] The size

of the total bile acid pool increases by about 50% during pregnancy, and the relative proportions of the various bile acids change.[182] The changes in the composition of bile revert rapidly after delivery, even in patients with gallstones.

THE KIDNEYS

Owing to an increase in total intravascular volume, both renal vascular and interstitial volume increase during pregnancy. These increases are reflected in enlarged kidneys, with renal volume increased by as much as 30%.[183] Vasodilation of the kidneys contributes to the overall decline in systemic vascular resistance during the first trimester. The collecting system, including the renal calyces, pelvis, and ureters, dilates. Hydronephrosis may occur in 80% of women by mid pregnancy.[184]

Both the glomerular filtration rate (GFR) and the renal plasma flow increase markedly during pregnancy secondary to reduced renal vascular resistance.[26] The renal plasma flow is 75% greater than nonpregnant values by 16 weeks' gestation and is maintained until 34 weeks, when a slight decline occurs. By the end of the first trimester, the GFR is 50% greater than baseline, and this rate is maintained until the end of pregnancy. The GFR does not return to prepregnancy levels until 3 months postpartum. Because the GFR does not increase as rapidly or as much as the renal plasma flow, the filtration fraction decreases from nonpregnant levels until the third trimester.[185] The potential role of nitric oxide in the renal vasodilation was tested and confirmed in a rat model.[186]

Creatinine clearance is increased to 150 to 200 mL/min from the normal baseline values of 120 mL/min.[187] The increase occurs early in pregnancy, reaches a maximum by the end of the first trimester, decreases slightly near term, and returns to the prepregnancy level by 8 to 12 weeks postpartum.[185] These renal hemodynamic alterations are among the earliest and most dramatic maternal adaptations to pregnancy. The increased GFR results in reduced blood concentrations of nitrogenous metabolites. The blood urea nitrogen concentration decreases to 8 to 9 mg/dL by the end of the first trimester and remains at that level until term.[187] Serum creatinine concentration is a reflection of skeletal muscle production and urinary excretion. In pregnancy, skeletal muscle production of creatinine remains relatively constant but the GFR is increased, resulting in a reduced serum creatinine concentration. The serum creatinine concentration decreases progressively to 0.5 to 0.6 mg/dL by the end of pregnancy. The serum uric acid level declines in early pregnancy because of the rise in GFR, to 2.0 to 3.0 mg/dL by 24 weeks' gestation.[188] Subsequently, the uric acid level begins to increase, reaching the prepregnancy level by the end of pregnancy. Tubular reabsorption of urate accounts for this elevated uric acid level during the third trimester.

Total protein excretion and urinary albumin excretion are higher than nonpregnant levels. Average 24-hour total protein and albumin excretion are 200 mg and 12 mg, respectively (upper limits are 300 mg and 20 mg, respectively).[189,190] Proteinuria (> 300 mg/24 h) has been described without the diagnosis of preeclampsia.[191] However, women with isolated proteinuria are more likely to progress to preeclampsia than women with isolated hypertension. The protein-to-creatinine ratio in a random urine sample correlates well with a 24-hour urine protein measurement, and a value of greater than 0.18 has been estimated as indicating significant proteinuria[192]; this test may be an alternative method if time is lacking for a 24-hour urine collection. The degree of proteinuria in normal pregnancy also correlates with gestation. Women with twin pregnancies have greater protein excretion compared with those with singleton pregnancies.[193]

Glucose is filtered and almost completely absorbed in the proximal tubule. In the nonpregnant state, a small amount of glucose is excreted. Pregnancy imposes a change in the glucose resorptive capacity of the proximal tubules, so all pregnant women exhibit an elevation of glucose excretion. Of pregnant women who have normal glucose tolerance to an oral load and normal glucose excretion when not pregnant, approximately half will exhibit a doubling of glucose excretion. Most of the remainder have increases of 3 to 10 times the nonpregnant amount, and a small proportion (< 10%) excrete as much as 20 times the nonpregnant amount.[194] Overall, the amount of glucose excreted in the third trimester is several times greater than that in the nonpregnant state. The normal nonpregnant pattern of glucose excretion is reestablished within a week after delivery.

The kidney is also involved in maintenance of acid-base status during pregnancy. An increase in alveolar ventilation results in respiratory alkalosis. A compensatory response occurs in the kidney, with greater bicarbonate excretion and a decline in serum bicarbonate levels. The decrease in serum bicarbonate affects the pregnant woman's ability to buffer an acid load.

NONPLACENTAL ENDOCRINOLOGY

Thyroid Function

The thyroid gland enlarges by 50% to 70% during pregnancy because of follicular hyperplasia and greater vascularity. The estrogen-induced increase in thyroid-binding globulin results in a 50% increase in total triiodothyronine (T3) and thyroxine (T4) concentrations during the first trimester, which are maintained until term.[195] The concentrations of free T3 and T4 do not change. The concentration of thyroid-stimulating hormone (TSH) decreases during the first trimester but returns to the nonpregnant level shortly thereafter and undergoes no further change during the remainder of pregnancy. The fetal thyroid gland cannot produce thyroid hormone until the end of the first trimester and relies solely on maternal T4 production during this critical time of development and organogenesis.

Approximately 4% to 7% of women of childbearing age are either hypothyroid or at risk of hypothyroidism during pregnancy.[196] Only 20% to 30% of affected women demonstrate symptoms of hypothyroidism, likely because

symptoms of hypothyroidism mimic features of pregnancy.[197] In a large study of 502,036 pregnant women, 15% of tested women had gestational hypothyroidism, with 33% of these women demonstrating symptoms.[198] Based on these results, many physicians advocate universal screening, which appears to be cost effective, given the risk of decreased intelligence in the offspring, miscarriage, and postpartum bleeding if hypothyroidism is left untreated.[199]

Glucose Metabolism

Mean blood glucose concentration remains within the normal range during pregnancy, although the concentration may be lower in some women during the third trimester compared with nonpregnant individuals.[200] This finding is explained by the greater glucose demand of the fetus and the placenta. The relative hypoglycemic state results in fasting hypoinsulinemia. Pregnant women also exhibit exaggerated starvation ketosis.

Pregnant women are insulin resistant because of hormones such as placental lactogen secreted by the placenta.[201] The blood glucose levels after a carbohydrate load are greater in pregnant women than in nonpregnant women, despite a hyperinsulinemic response. These changes resolve within 24 hours of delivery.

Adrenal Cortical Function

The concentration of corticosteroid-binding globulin (CBG) doubles during gestation as a result of an estrogen-induced enhancement of hepatic synthesis.[202] The elevated CBG value results in a 100% increase in the plasma cortisol concentration at the end of the first trimester and a 200% increase at term. The concentration of unbound, metabolically active cortisol at the end of the third trimester is two and one-half times the nonpregnant level. The increase in free cortisol results from greater production and reduced clearance. Protein binding of corticosteroids is affected by an increase in the CBG concentration and a decrease in the serum albumin level. CBG binding capacity usually saturates at low concentrations of glucocorticoids. Clearance of betamethasone is greater during pregnancy, possibly because the drug is metabolized by placental enzymes.[203]

THE MUSCULOSKELETAL SYSTEM

Back pain during pregnancy is common. A cohort of 200 consecutive women without back pain at the start of pregnancy were observed throughout their pregnancy.[204] At 12 weeks' gestation, 19% of the study population complained of backache. The incidence increased to 47% at 24 weeks' gestation and peaked at 49% at 36 weeks' gestation. After delivery, the prevalence of back pain declined to 9.4%. Despite a relatively high prevalence, only 32% of women with low back pain during pregnancy reported this problem to their physicians and only 25% of providers recommended specific therapy.[205]

The etiology of the back pain is multifactorial. One theory is that the enlarging uterus results in exaggerated lumbar lordosis, placing mechanical strain on the lower back. The hormonal changes of pregnancy may also play a role. Relaxin, a polypeptide hormone of the insulin-like growth factor family, is associated with remodeling of collagen fibers and pelvic connective tissue. The primary source of circulating relaxin is the corpus luteum; the placenta is a secondary source. Serum relaxin levels in early pregnancy are positively correlated with the presence of back pain.[206]

Women who develop low back pain during pregnancy may avoid subsequent pregnancy to prevent recurrence. These women have a very high risk of a new episode during a subsequent pregnancy.[207] In the majority of patients, low back pain during pregnancy responds to activity and postural modification. Exercises to increase the strength of the abdominal and back muscles are helpful. Scheduled rest periods with elevation of the feet to flex the hips and decrease the lumbar lordosis help relieve muscle spasm and pain.[208]

The enhancement of the lumbar lordosis during pregnancy alters the center of gravity over the lower extremities (Figure 2-10) and may lead to other mechanical problems. Exaggerated lumbar lordosis tends to stretch the lateral femoral cutaneous nerve, possibly resulting in **meralgia paresthetica,** with paresthesia or sensory loss over the anterolateral thigh. Anterior flexion of the neck and slumping of the shoulders usually accompany the enhanced lordosis, sometimes leading to a brachial plexus neuropathy.

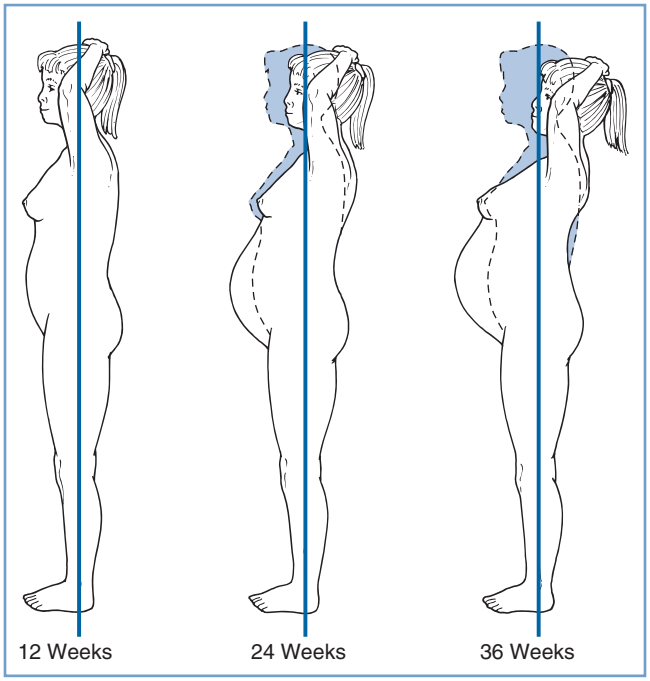

FIGURE 2-10 ■ Changes in posture during pregnancy. The first and the subsequent dotted-line figures represent a woman's posture before growth of the uterus and its contents have affected the center of gravity. The second and third solid figures show that as the uterus enlarges and the abdomen protrudes, the lumbar lordosis is enhanced and the shoulders slump and move posteriorly. (Modified from Beck AC, Rosenthal AH. Obstetrical Practice. Baltimore, Williams & Wilkins, 1955;146.)

Mobility of the sacroiliac, sacrococcygeal, and pubic joints increases during pregnancy in preparation for passage of the fetus. A widening of the pubic symphysis is evident by 30 weeks' gestation. These changes are attributable to relaxin and the biomechanical strain of pregnancy on the ligaments.[209] Relaxin may also contribute to the greater incidence of carpal tunnel syndrome during pregnancy by changing the nature of the connective tissue so that more fluid is absorbed.[210]

The human fetus requires approximately 30 g of calcium for skeletal development by the time of term delivery.[211] Although intestinal absorption of calcium by the mother increases from as early as 12 weeks' gestation to meet this increased demand, it is insufficient to meet fetal demand and thus the maternal skeleton undergoes resorption.[212] This does not cause long-term changes in skeletal calcium content or strength. Pregnant women with a twin gestation have a much higher calcium requirement. Compared with singleton pregnancies, there is a larger increase in bone resorption in twin gestation.[213]

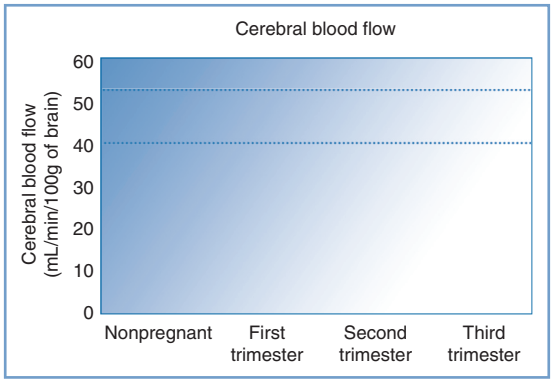

FIGURE 2-11 ■ Cerebral blood flow during pregnancy. Cerebral blood flow increases as pregnancy progresses and is attributable to vasodilation from the hormonal changes of pregnancy. This increase in cerebral blood flow explains the increased risk of complications in patients with intracranial pathology as pregnancy progresses. (Based on data from Nevo O, Soustiel JF, Thaler I. Maternal cerebral blood flow during normal pregnancy: a cross-sectional study. Am J Obstet Gynecol 2010; 203:475.e1-6.)

THE NERVOUS SYSTEM

Sleep

Sleep disturbances from mechanical and hormonal factors occur commonly during pregnancy. Latency and duration of rapid eye movement (REM) sleep are influenced by changes in progesterone and estrogen concentrations. Pregnant women have more complaints of insomnia and daytime sleepiness. The American Academy of Sleep Medicine defined **pregnancy-associated sleep disorder** as the occurrence of insomnia or excessive sleepiness that develops in the course of pregnancy.[214] Progesterone has a strong sedating effect, and cortisol, levels of which are higher in pregnancy, is associated with an increase in REM sleep.[215] In a cohort study of 189 healthy nulliparous women, Facco et al. reported that mean (± SD) sleep duration was shorter in the third trimester (7.0 ± 1.2 hours) compared with the baseline period between 6 and 20 weeks' gestation (7.4 ± 1.2 hours).[216]

The Pittsburgh Sleep Quality Index, a sum of seven components assessing sleep quality, sleep latency, sleep duration, and daytime drowsiness, indicated poor sleep quality as the pregnancy progressed. Polysomnography reveals reduced slow-wave and REM phases of sleep, decreased total sleep time, and increased rate of wakening after sleep onset.[217] Sleep may be poor for up to 3 months postpartum.[218] Upper airway changes lead to increased airflow resistance and snoring. Although only 4% of nonpregnant women snore, as many as 23% of pregnant women snore by the third trimester. Snoring is more common in women with preeclampsia.

Pregnancy is associated with **transient restless leg syndrome,** a disorder in which the patient experiences the need to move her legs. The incidence ranges from 15% in the first trimester to 23% in the third trimester.[219]

Central Nervous System

Cerebral blood flow increases in pregnancy. Nevo et al.[220] measured cerebral blood flow in 210 women at different gestational ages and found that it increased from 44.4 mL/min/100 g during the first trimester to 51.8 mL/min/100 g during the third trimester (Figure 2-11). The increase was secondary to a decrease in cerebrovascular resistance and an increase in internal carotid artery diameter. Two other changes in the brain that occur during pregnancy include (1) an increase in permeability of the blood-brain barrier owing to decreased cerebrovascular resistance with an increase in hydrostatic pressure and (2) an increase in capillary density in the posterior cerebral cortex.[221]

Women experience an elevation in the threshold to pain and discomfort near the end of pregnancy and during labor.[222] The mechanism, although unclear, may be related to the effects of progesterone and endorphins. Elevated concentrations of endorphins and enkephalins are found in the plasma and CSF of parturients,[223] and opioid antagonists abolish pregnancy-induced analgesia to visceral stimulation in experimental animals.[224]

Vertebral Column

Anatomic and mechanical changes occur to the vertebral column during pregnancy. The epidural space can be regarded as a rigid tube that contains two fluid-filled distensible tubes, the dural sac, and epidural veins. The volume of epidural fat and the epidural veins enlarge during pregnancy; spinal CSF volume is reduced.[40]

In the lateral position, lumbar epidural pressure is positive in term pregnant women but negative in more than 90% of nonpregnant women.[225] Turning a parturient from the lateral to the supine position increases the epidural pressure. Epidural pressure also increases during labor because of increased diversion of venous blood through the vertebral plexus secondary to either enhanced compression of the inferior vena cava in the supine position or greater intra-abdominal pressure during pain and pushing. The epidural pressure returns to the nonpregnant level by 6 to 12 hours postpartum.

Despite compression of the dural sac by the epidural veins, the CSF pressure in pregnant women is the same as in nonpregnant women.[226] Uterine contractions and pushing result in an increase in CSF pressure that is secondary to acute increases in epidural vein distention.

Sympathetic Nervous System

Dependence on the sympathetic nervous system for maintenance of hemodynamic stability increases progressively throughout pregnancy and reaches a peak at term.[227-229] The dependence on the sympathetic nervous system returns to that of the nonpregnant state by 36 to 48 hours postpartum.

ANESTHETIC IMPLICATIONS

Positioning

Aortocaval compression, decreased blood pressure and cardiac output, and impairment of uteroplacental blood flow occur when a pregnant woman is placed in the supine position. This may compromise fetal well-being and neonatal outcome during labor or cesarean delivery.[230-232] Therefore, after 20 weeks' gestation, the supine position should be avoided and the uterus should be displaced to the left by placement of a wedge underneath the right hip or by tilting the operating table to the left (Figure 2-12). Anesthetic drugs or techniques that cause venodilation further reduce venous return with caval obstruction. Studies performed with pregnant women placed in the lateral position have not shown major decreases in cardiac output.[233,234]

Blood Replacement

At delivery, maternal vascular capacitance is reduced by the volume of the intervillous space (at least 500 mL). Therefore, during vaginal or cesarean delivery, this volume of blood does not need to be replaced and should not be considered in the estimation of blood loss for replacing red blood cells. Hemoconcentration occurs as maternal blood volume declines from 94 mL/kg at term to 76 mL/kg during the postpartum period; this should be considered in the decision as to whether a parturient should receive crystalloid, colloid, or blood for volume replacement.[100]

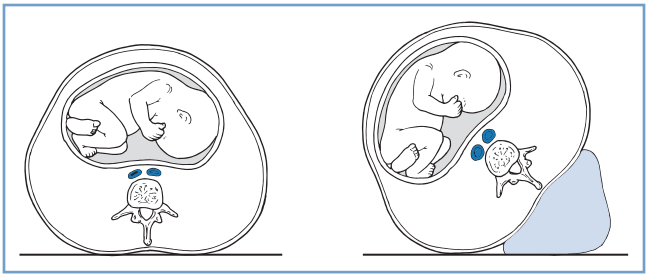

FIGURE 2-12 ■ Compression of the aorta and inferior vena cava in the supine (*left*) and lateral tilt (*right*) positions. (Redrawn from Camann WR, Ostheimer GW. Physiologic adaptations during pregnancy. Int Anesthesiol Clin 1990; 28:2-10.)

General Anesthesia

Airway Management, Oxygenation, and Ventilation

Changes in the maternal airway and respiratory physiology mandate modification of airway management during pregnancy (Box 2-3) (see Chapter 30). The proportion of pregnant women with a Mallampati IV classification increases by 34% between 12 and 38 weeks' gestation.[235] Vascular engorgement of the airway results in edema of the oral and nasal pharynx, larynx, and trachea,[236] which may lead to difficult tracheal intubation and difficult mask ventilation. Airway edema may be exacerbated in patients with upper respiratory tract infection or preeclampsia and in those who have been pushing for a long time during the second stage of labor. Management of the difficult obstetric airway is discussed in Chapter 30.

Because FRC is reduced, oxygen consumption is increased, and FRC is less than closing capacity in up to 50% of supine individuals.[70] Pregnant women become hypoxemic more rapidly than nonpregnant women during episodes of apnea. During apnea accompanying rapid-sequence induction of general anesthesia, Pao_2 decreases twice as rapidly (139 versus 58 mm Hg/min) in pregnant versus nonpregnant women.[237] Denitrogenation is achieved faster in pregnant versus nonpregnant women because of elevated minute ventilation and decreased FRC. However, after

BOX 2-3 Considerations for General Anesthesia during Pregnancy

Drugs

- Propofol
  - Induction dose decreased
  - Elimination half-life unaltered
- Thiopental
  - Induction dose decreased
  - Elimination half-life prolonged
- Volatile anesthetic agents
  - Minimum alveolar concentration (MAC) decreased, but unclear whether hypnotic dose requirement differs from that in nonpregnant women
  - Speed of induction increased
- Succinylcholine
  - Duration of blockade unaltered
- Rocuronium
  - Increased sensitivity
- Chronotropic agents and vasopressors
  - Decreased sensitivity

Tracheal Intubation

- Increased rate of decline of Pao_2 during apnea
- Smaller endotracheal tube required (6.5 or 7.0 mm)
- Increased risk of failed intubation with traditional laryngoscopy
- Increased risk of bleeding with nasal instrumentation

complete denitrogenation via inhalation of 100% oxygen, parturients tolerate only 2 to 3 minutes of apnea, versus 9 minutes in nonpregnant patients, before oxygen saturation decreases to less than 90%.

Ventilation should be adjusted to maintain $Paco_2$ at approximately 30 mm (4 kPa). This can be achieved with minute ventilation of 121 mL/kg/min; in comparison, 77 mL/kg/min is required to maintain a comparable $Paco_2$ in nonpregnant women.[238] Decreased plasma bicarbonate concentration reduces buffering capacity in pregnancy. Allowing the $Paco_2$ to increase to the normal level for nonpregnant women results in respiratory acidosis.

Intravenous and Inhalation Anesthetics

Propofol requirement decreases 10% during the first trimester[239]; this decrease is not accounted for by progesterone because the dose reduction does not correlate with progesterone levels. The elimination half-life of propofol is unaffected by pregnancy, although clearance may be higher.[240] The average induction dose of **thiopental** in pregnant women is 18% lower in the first trimester and 35% lower at term compared with that in nonpregnant women.[241,242] The elimination half-life of thiopental in pregnant women is 26.1 hours, compared with 11.5 hours in nonpregnant women[243]; this is explained by a marked increase in volume of distribution despite increased clearance. Plasma protein binding of thiopental is similar in term pregnant and nonpregnant women.[243]

The rate of rise of alveolar versus inspired anesthetic concentration (F_A/F_I) of **volatile anesthetics**, and thus the speed of induction, is increased during pregnancy because of greater minute ventilation and reduced FRC, despite higher cardiac output.

The minimum alveolar concentration (MAC) for volatile anesthetics is up to 40% lower in pregnancy.[244-246] Although MAC is a spinal nociceptive reflex that involves both sensory and motor components,[247] practitioners have interpreted this decrease in MAC as indicating that pregnant patients have a decreased requirement for inhaled anesthetics. However, this interpretation has been questioned. Ueyama et al.[248] compared bispectral index values in 15 patients undergoing cesarean delivery with sevoflurane general anesthesia versus 15 patients undergoing elective gynecologic surgery and found no difference between groups. This finding suggests that the hypnotic effect of sevoflurane was not enhanced by pregnancy. The investigators concluded that although pregnancy may decrease MAC, it does not decrease volatile anesthetic requirements, and suggested that parturients should be given the same dose of volatile anesthetics as nonpregnant patients. Further work is required to confirm these findings.

Muscle Relaxants

Pseudocholinesterase activity is decreased by 24% before delivery and by 33% on the third postpartum day.[249] It returns to normal 2 to 6 weeks postpartum. The reduced activity does not usually result in clinically relevant prolongation of paralysis after a single dose of **succinylcholine**. Twitch height recovery after administration of succinylcholine is similar between pregnant and nonpregnant women, and recovery may even be faster because the larger volume of distribution results in a lower initial drug concentration and a shorter time before the threshold for recovery is attained. Pregnant women may be less sensitive than nonpregnant women to comparable plasma concentrations of succinylcholine, a feature that also may contribute to more rapid recovery during pregnancy.

Pregnant and postpartum women exhibit enhanced sensitivity to the aminosteroid muscle relaxants **vecuronium** and **rocuronium**.[250,251] The greater sensitivity to vecuronium is not explained by altered pharmacokinetics because the drug exhibits increased clearance and a shortened elimination half-life in pregnant women.[252] The mean onset time and clinical duration of **cisatracurium** are significantly shorter in women immediately after delivery than in nonpregnant women.[253]

Chronotropic Agents and Vasopressors

Pregnancy reduces the chronotropic response to **isoproterenol** and **epinephrine** because of down-regulation of beta-adrenergic receptors.[254] These agents are less-sensitive markers of intravascular injection during administration of an epidural test dose in pregnant patients than in nonpregnant patients. Because of down-regulation of adrenergic receptors, treatment of hypotension requires higher doses of vasopressors such as **phenylephrine** in pregnant women than in nonpregnant women.

Neuraxial Analgesia and Anesthesia

Technical Considerations and Positioning

Increased lumbar lordosis during pregnancy may reduce the vertebral interspinous gap, thus creating technical difficulty in administering neuraxial anesthesia (Box 2-4 and Figure 2-13) (see Chapter 12). Widening of the

BOX 2-4 Neuraxial Anesthesia:

ANESTHETIC IMPLICATIONS OF MATERNAL PHYSIOLOGIC CHANGES

Technical Considerations

- Lumbar lordosis increased
- Apex of thoracic kyphosis at higher level
- Head-down tilt when in lateral position

Treatment of Hypotension

- Decreased sensitivity to vasopressors*

Local Anesthetic Dose Requirements†

- Subarachnoid dose reduced 25%
- Epidural dose unaltered or slightly reduced

*Compared with nonpregnant women.
†Change in the segmental dose requirement compared with nonpregnant women.
Modified from Conklin KA. Maternal physiologic adaptations during gestation, labor, and the puerperium. Semin Anesth 1991; 10:221-34.

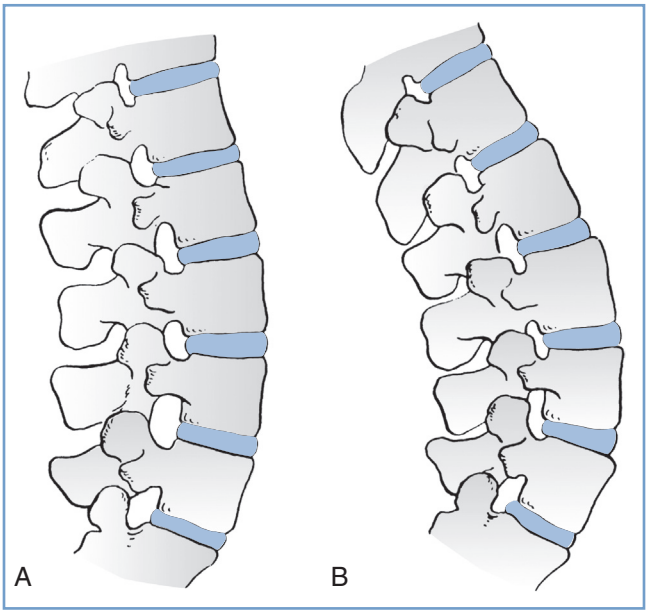

FIGURE 2-13 ■ Effects of pregnancy on the lumbar spine. **A,** Nonpregnant. **B,** Pregnant. There is a marked increase in lumbar lordosis and a narrowing of the interspinous spaces during pregnancy. (Modified from Bonica JJ. Principles and Practice of Obstetric Analgesia and Anesthesia, Volume 1. Philadelphia, FA Davis, 1967:35.)

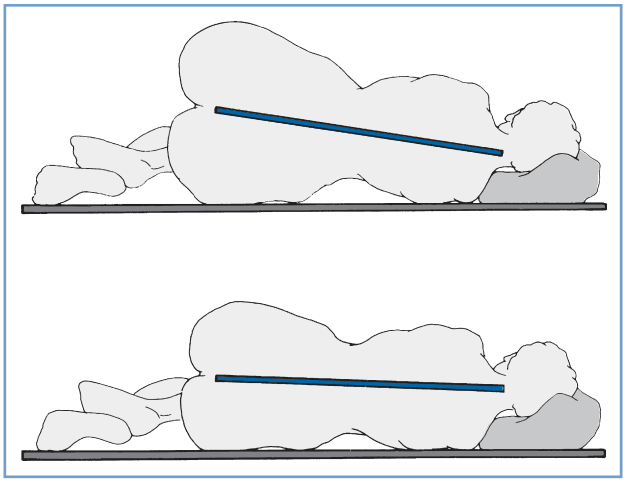

FIGURE 2-14 ■ Pelvic widening and resultant head-down tilt in the lateral position during pregnancy. *Upper panel,* pregnant; *lower panel,* nonpregnant. (Modified from Camann WR, Ostheimer GW. Physiological adaptations during pregnancy. Int Anesthesiol Clin 1990; 28:2-10.)

pelvis results in a head-down tilt when a pregnant woman is in the lateral position (Figure 2-14). This may increase the rostral spread of hyperbaric local anesthetics when injected intrathecally with patients in the lateral position. The flow of CSF from a spinal needle is unchanged throughout gestation because pregnancy does not alter CSF pressure.[226] However, flow rate may increase during a uterine contraction because of increased CSF pressure.

Local Anesthetic Dose Requirements

Pregnant patients show decreased local anesthetic dose requirement in the first trimester. This change occurs well before significant mechanical changes have occurred in the vertebral canal,[255] suggesting that there are pregnancy-induced alterations in nerve tissue sensitivity, either directly or indirectly from changes in hormone concentrations.[256]

Pregnant women exhibit a more rapid onset and a longer duration of spinal anesthesia than nonpregnant women who receive the same dose of local anesthetic. These results are consistent with enhanced neural sensitivity to local anesthetics; pregnancy-associated elevation in CSF pH may contribute to these effects.[257-259] The dose of hyperbaric local anesthetic required in term pregnant women is 25% lower than that in nonpregnant women.[260,261] This is attributed to the following factors: (1) reduction of spinal CSF volume, which accompanies distention of the vertebral venous plexus[40]; (2) enhanced neural sensitivity to local anesthetics; (3) increased rostral spread when injections are made with the patient in the lateral position; (4) inward displacement of intervertebral foraminal soft tissue, resulting from increased abdominal pressure[262]; and (5) a higher level of the apex of the thoracic kyphosis (the lowest point of the thoracic spinal canal in the supine position) during late pregnancy.[263] Spinal dose requirements change rapidly in the postpartum period, with segmental dose requirements returning to those of nonpregnant women within 24 to 48 hours[264] as spinal CSF volume expands with the relief of vena caval compression. In contrast to spinal anesthesia, pregnancy appears to have less effect on the spread of epidural anesthesia.[265,266]

Pregnancy does not enhance the susceptibility of ewes to the neurotoxicity of lidocaine or to the cardiac toxicity of bupivacaine (see Chapter 13). The incidence of lethal ventricular arrhythmias is no greater in pregnant than in nonpregnant ewes treated with bupivacaine, ropivacaine, or levobupivacaine.[267]

Hypotension during Neuraxial Analgesia and Anesthesia

Pregnancy increases dependence on the sympathetic nervous system for the maintenance of venous return and systemic vascular resistance.[228] This, together with the effects of aortocaval compression, means that pregnant patients are particularly prone to hypotension and hemodynamic instability from sympathetic block induced by neuraxial anesthesia. Management of hypotension is discussed in Chapter 26.

Effects of Neuraxial Anesthesia on Respiratory Function

FRC diminishes during neuraxial anesthesia, resulting in an increase in respiratory dead space and ventilation-perfusion mismatch. Abdominal muscles are important for forced expiration and coughing, and paralysis of these muscles during neuraxial anesthesia decreases peak expiratory flow rate, maximum expiratory pressure, and the ability to increase intra-abdominal and intrathoracic pressures during coughing.[268-270]

KEY POINTS

- Pregnancy results in various anatomic and physiologic changes that allow the mother to adapt to the growing fetus and that allow the fetus to develop.
- Cardiac output increases during pregnancy as a result of an increase in stroke volume and heart rate. A pregnant woman with cardiovascular disease may not be able to meet this greater demand.
- Beginning at mid pregnancy, assumption of the supine position may result in compression of the inferior vena cava and aorta by the gravid uterus, which may result in decreases in both cardiac output and uteroplacental perfusion. Severe hypotension and bradycardia in the supine position is called the *supine hypotension syndrome.*
- Pregnant women should not lie supine after 20 weeks' gestation. The uterus should be displaced to the left by placement of a wedge underneath the right hip or by tilting the operating table, or the pregnant women should assume the full lateral position.
- The greater blood volume of pregnancy allows the parturient to tolerate the blood loss of delivery, within limits, with minimal hemodynamic perturbation. Maternal vascular capacitance is reduced at the time of delivery.
- Oxygen demand and delivery are greater during pregnancy.
- Minute ventilation increases whereas functional residual capacity decreases during pregnancy. It is not uncommon for the pregnant women to experience dyspnea.
- Pregnancy is a state of partially compensated respiratory alkalosis.
- Gastric volume, emptying, and pH are unaltered during pregnancy, but lower esophageal sphincter tone may be reduced with possible increased risk of gastroesophageal reflux.
- Mechanical changes in the vertebral column influence neuraxial analgesia and anesthesia.
- Pregnant women have greater sympathetic tone than nonpregnant women.
- Minimum alveolar concentration (MAC) values for the volatile anesthetics are decreased during pregnancy. However, it is unclear whether hypnotic dose requirement is altered during pregnancy.
- Pregnant women have a rapid decrease in Pa_{O_2} during periods of apnea.
- Pregnant women are at increased risk for failed tracheal intubation.
- Pregnant women are less responsive to vasopressors than nonpregnant women.

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CHAPTER 3

Uteroplacental Blood Flow

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CHAPTER OUTLINE

Uteroplacental blood flow is responsible for the delivery of oxygen and nutrients to the fetus. A normal uteroplacental circulation is essential for healthy fetal growth and development. Acute reduction in uteroplacental blood flow may rapidly threaten fetal viability. Chronic reduction in uteroplacental blood flow, as may occur from abnormal development of the placental vasculature, leads to gestational pathologic processes such as preeclampsia and fetal growth restriction (also known as intrauterine growth restriction) and may even predispose the fetus to developing cardiovascular disease during subsequent adulthood.[1] The uteroplacental circulation undergoes circadian changes[2] and may be affected by parturition, disease, and anesthetic techniques and drugs. An understanding of the regulation of uteroplacental circulation is an important foundation for the safe provision of obstetric anesthesia and assists in the management of many pregnancy-related diseases. Research in this area is active but complicated by ethical considerations. Much of the available knowledge comes from studies in animals, particularly sheep but also nonhuman primates and other species. It is important to consider possible interspecies differences and to critically examine the methodology and context of animal research when extrapolating findings into recommendations for clinical care.

ANATOMY AND STRUCTURE

The blood supply to the uterus is derived mainly from the uterine arteries (Figure 3-1) with a smaller, variable contribution from the ovarian arteries. Although the pelvic vasculature shows anatomic variation,[3] the uterine artery arises bilaterally from the anterior division of the internal iliac (hypogastric) artery, whereas the ovarian artery arises from the anterolateral abdominal aorta below the renal arteries. The uterine artery passes medially to the side of the uterus, where it supplies branches to the cervix and vagina and ascends between the two layers of the broad ligament, yielding arcuate arteries that supply the body of the uterus to the junction with the fallopian tubes. During pregnancy, flow may differ between the right and left uterine arteries; Konje et al.[4] estimated that vessel diameter was approximately 11% greater and blood flow was approximately 18% greater in the uterine artery on the same side as the placenta compared with the contralateral artery. Anastomoses are formed with the contralateral uterine artery, the vaginal arteries, and the ovarian arteries. The arcuate arteries give rise to small branches that supply the myometrium and large radial arteries that branch deeply and enter the endometrium to form the convoluted spiral arteries.

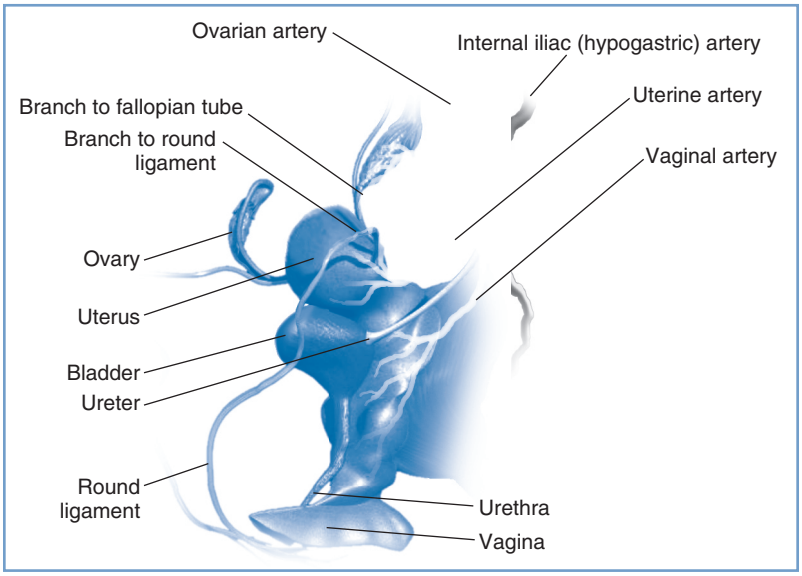

FIGURE 3-1 ■ Arterial supply to the female reproductive tract. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

During gestation, trophoblastic invasion of the spiral arteries results in loss of smooth muscle and loss of contractile ability, leading to vasodilation with decreased resistance and increased blood flow. Abnormal or inadequate trophoblastic invasion is integral to the pathophysiology of preeclampsia (see Chapter 36).[5]

From the spiral arteries, oxygenated maternal blood enters the intervillous space in fountain-like jets. Blood traveling toward the chorionic plate bathes the villi, permitting the exchange of oxygen, nutrients, and wastes between maternal and fetal blood. Maternal blood then returns to the basal plate and drains into multiple collecting veins. Venous drainage of the uterus occurs via the uterine veins to the internal iliac veins and also via the ovarian veins (utero-ovarian plexus) to the inferior vena cava on the right and the renal vein on the left.[6] The uterine artery and other branches of the anterior division of the internal iliac artery, as well as the ovarian artery, may be targeted during angiographic embolization procedures for treatment of obstetric and gynecologic hemorrhage[3] and for the treatment of uterine fibroids.[7]

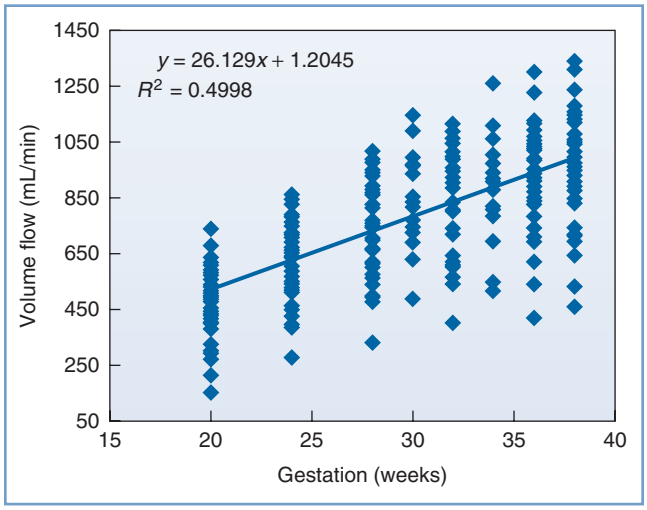

FIGURE 3-2 ■ Changes in uterine artery blood flow with gestation. (From Konje JC, Kaufmann P, Bell SC, Taylor DJ. A longitudinal study of quantitative uterine blood flow with the use of color power angiography in appropriate for gestational age pregnancies. Am J Obstet Gynecol 2001; 185:608-13.)

CHANGES AND FUNCTION DURING PREGNANCY

Pregnancy-Induced Changes

Uterine blood flow increases dramatically during pregnancy, rising from 50 to 100 mL/min before pregnancy to 700 to 900 mL/min at term, depending on the method of measurement (Figure 3-2). Studies in sheep have shown that increases in uterine blood flow can be divided into three phases.[8] An initial phase, most likely controlled by the ovarian hormones estrogen and progesterone, occurs before and during implantation and early placentation. A second phase results from the growth and remodeling of the uteroplacental vasculature to support further placental development. A third and final phase results from progressive uterine artery vasodilation to meet the markedly increased nutrient requirements of the rapidly growing fetus. When expressed in terms of uterine weight, however, uterine flow per gram of tissue is particularly high in early gestation, and this ratio decreases as pregnancy progresses.[8] In comparison, umbilical blood flow, expressed as a function of fetal weight, is relatively constant throughout most of pregnancy and is estimated to be 110 to 120 mL/min/kg.[9] Uterine blood flow is increased in twin pregnancy, but the flow per unit of estimated fetal weight is similar to that in a singleton pregnancy.[10] The progressive increase in uteroplacental blood flow during pregnancy is matched by a concurrent increase in blood flow on the fetal side (fetoplacental blood flow). However, despite suggestions

of the possibility of intrinsic flow matching, it is believed that these circulations are independently regulated.[11]

Distribution of Blood Flow

Uterine blood flow at term represents a greater proportion of cardiac output (approximately 12%) than in early pregnancy (approximately 3.5%).[12] Regional distribution of blood flow within the pelvis also changes during gestation. Palmer et al.[13] observed that increases in common iliac artery blood flow during pregnancy were associated with corresponding increases in uterine artery blood flow but also with decreases in external iliac artery blood flow. This pattern effectively constitutes a "steal" phenomenon, in which blood flow in the pelvis is preferentially redistributed toward the uterus (Figure 3-3).

Primate studies have shown that 80% to 90% of total uterine blood flow perfuses the placenta at term, with the remainder supplying the myometrium and nonplacental endometrium.[14] The placental and nonplacental vasculatures are anatomically and functionally distinct, and regulation of perfusion through these vascular beds differs.[14] Therefore, it is important to differentiate studies that measure total uteroplacental blood flow versus placental blood flow.

Functional Classification

Placental vascular function varies among species. The human multivillous model is commonly believed to function as a "venous equilibrator," in which oxygen tension in the umbilical vein approximates that in the uterine veins. In contrast, the placenta in some species (e.g., rodents) functions as a countercurrent exchanger. The more efficient function of the latter is reflected by the higher fetoplacental weight ratio in rodents (20:1) than in humans (6:1).[15]

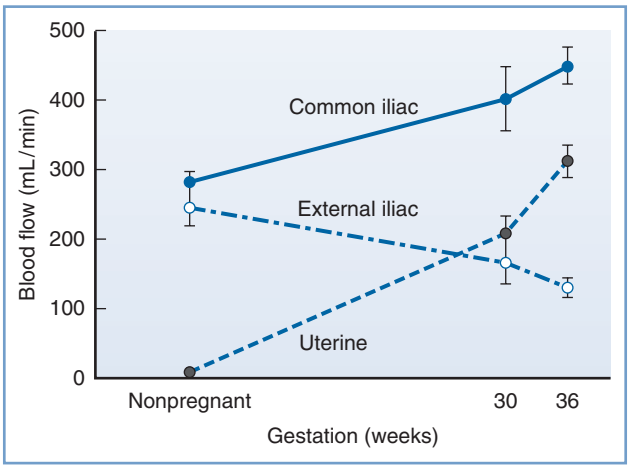

FIGURE 3-3 ■ Redistribution of blood flow in pelvic blood vessels during pregnancy determined unilaterally by Doppler ultrasonography. Blood flow increased in the common iliac and uterine arteries but decreased in the external iliac artery, indicating that redistribution of flow favors uterine perfusion. Data are mean ± SEM. (Adapted from Palmer SK, Zamudio S, Coffin C, et al. Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol 1992; 80:1000-6.)

Autoregulation

Studies of pressure-flow relationships suggest that the nonpregnant uterine circulation exhibits autoregulation, alternately vasoconstricting or vasodilating in response to a number of different stimuli.[16] In contrast, the pregnant uterine circulation is complicated by the properties of both the placental and nonplacental circulations. Animal studies have demonstrated that the uteroplacental circulation is a widely dilated, low-resistance system with perfusion that is largely pressure dependent.[17,18] However, a study in pregnant rabbits found that uteroplacental blood flow was relatively constant over a wide range of perfusion pressures.[19] During hemorrhage in pregnant rats, uterine vascular resistance *increased* as systemic blood pressure and uterine blood flow decreased, thereby demonstrating an absence of autoregulation. Moreover, although the uteroplacental circulation is often considered to be maximally vasodilated with little or no ability for autoregulation,[17] further vasodilation has been observed in response to systemically administered estrogen, prostacyclin, bradykinin, and acetylcholine.[20-22] These discrepancies may be explained by changes in the nonplacental uterine vasculature, which accounts for a small fraction of total uteroplacental blood flow but appears to have similar autoregulatory responses during pregnant and nonpregnant states; this feature contrasts with the limited autoregulatory ability of the placental circulation.[23] Laird et al.[18] found that reducing arterial pressure by 22% with an inflatable aortic occluder in pregnant rabbits produced a reduction in total uteroplacental and placental blood flow but no significant change in myoendometrial blood flow. Clinically, limited autoregulation means that placental blood flow may diminish with reductions in maternal blood pressure (e.g., during neuraxial anesthesia).

Margin of Safety

Studies in animals have demonstrated that, in normal physiologic conditions, uterine blood flow exceeds the minimum required to satisfy fetal oxygen demand.[24] Although this feature confers a margin of safety that protects the fetus from fluctuations in uterine blood flow,[25] decreases in fetal Po_2 and progressive metabolic acidosis can occur with reductions in uteroplacental blood flow, depending on the magnitude and duration.[26] However, the relationship between uterine blood flow and oxygen transfer appears nonlinear and suggests that uteroplacental blood flow can decrease by as much as 50% for limited periods before fetal oxygen uptake decreases and metabolic acidosis occurs.[24]

Studies in sheep have shown that although uterine blood flow varies over a wide range, fetal oxygen uptake remains relatively constant, suggesting that the efficiency of oxygen extraction is greater when perfusion decreases.[27] Using an inflatable balloon occluder around the terminal aorta to reduce uterine blood flow in sheep, Wilkening and Meschia[24] found that at high levels of oxygen

delivery, fetal oxygen uptake was not significantly affected by variations in uterine blood flow; moreover, fetal oxygen uptake became flow dependent only when uterine oxygen delivery was reduced to less than half the baseline value. Boyle et al.,[28] investigating the effects of acute uterine arterial embolization with microspheres in sheep, found a linear decrease in fetal aortic oxygen tension as uterine blood flow decreased. However, uterine oxygen consumption did not decrease and fetal hydrogen ion concentration did not increase until uterine blood flow had decreased to approximately 50% of the baseline value. As uterine blood flow diminished, a reduction in uterine venous oxygen content and a greater arteriovenous oxygen content difference were observed, indicating an increase in oxygen extraction. Gu et al.[29] reported comparable findings with the compression of the common uterine artery by an inflatable occluder in sheep.

Although the preceding experiments were conducted in sheep, the same principles may apply to humans. The human placenta, like the sheep placenta, is a relatively inefficient oxygen exchanger. Thus, in humans and sheep, the transfer rate of oxygen is affected less by decreases in placental perfusion than the transfer rate in animals with more efficient placentas, such as the rabbit and guinea pig. Of interest, this difference may afford some protection in humans, because alterations in placental perfusion in animals with more efficient placentas frequently result in spontaneous abortion.[30] Animal data would also suggest the presence of a significant physiologic buffer that protects the fetus during transient fluctuations in uteroplacental perfusion (e.g., changes in endogenous vasoconstrictor levels, uterine contractions, and parturition).[31] This may partially explain why clinical studies have failed to demonstrate fetal acidosis when alpha-adrenergic agonists are used to maintain maternal blood pressure during neuraxial anesthesia,[32] despite experimental data showing that these agents reduce uteroplacental perfusion in laboratory animals.[33] These observations are based on an assumption of normal physiology; the presence of pathology likely diminishes any margin of safety.

Changes during Parturition

With the onset of the uterine contractions of labor, uteroplacental perfusion undergoes cyclical changes. During uterine contractions, a decrease in perfusion occurs that is inversely related to the strength of the contraction and the increase in intrauterine pressure.[31] Conversely, during uterine relaxation, there is a period of hyperemia when perfusion is increased. Placental perfusion is believed to be more sensitive to these contraction-induced changes than myometrial or endometrial blood flow.[34] Within the first few hours of parturition, uterine blood flow in sheep decreases on average by 50% or more, although there is notable inter-individual variation.[35]

Clinical Determinants of Uterine Blood Flow

In the acute setting, uterine blood flow is related to perfusion pressure (the difference between uterine arterial pressure and uterine venous pressure) and vascular resistance, as represented in the following equation:

$$\text{Uterine blood flow} = \frac{\text{Uterine perfusion pressure}}{\text{Uterine vascular resistance}} \quad (1)$$

Thus, there are several ways that uterine blood flow can decrease (Box 3-1). First, uterine blood flow may decline with reductions in perfusion pressure because of decreased uterine arterial pressure—for example, during systemic hypotension from hemorrhage, aortocaval compression, or sympathetic blockade during neuraxial anesthesia. Second, uterine blood flow may decline with reductions in perfusion pressure caused by increased uterine venous pressure—for example, with vena caval compression, increased intrauterine pressure during uterine contractions, drug effects (e.g., oxytocin, cocaine), and Valsalva maneuvers that accompany maternal expulsive efforts during the second stage of labor. Third, uterine blood flow may decline because of increased uterine vascular resistance, which may be caused by a number of factors, including endogenous vasoconstrictors that are released in response to stress, exogenous vasoconstrictors, and compression of endometrial spiral arterioles with uterine contractions.[34]

BOX 3-1 Causes of Decreased Uterine Blood Flow

Decreased Perfusion Pressure

Decreased uterine arterial pressure:
- Supine position (aortocaval compression)
- Hemorrhage/hypovolemia
- Drug-induced hypotension
- Hypotension during sympathetic blockade

Increased uterine venous pressure:
- Vena caval compression
- Uterine contractions
- Drug-induced uterine tachysystole (oxytocin, local anesthetics)
- Skeletal muscle hypertonus (seizures, Valsalva maneuver)

Increased Uterine Vascular Resistance

Endogenous vasoconstrictors:
- Catecholamines (stress)
- Vasopressin (in response to hypovolemia)

Exogenous vasoconstrictors:
- Epinephrine
- Vasopressors (phenylephrine > ephedrine)
- Local anesthetics (in high concentrations)

MECHANISMS OF VASCULAR CHANGES AND REGULATION

Vascular Changes during Pregnancy

Because mean arterial pressure decreases slightly during pregnancy, the increase in uteroplacental blood flow is

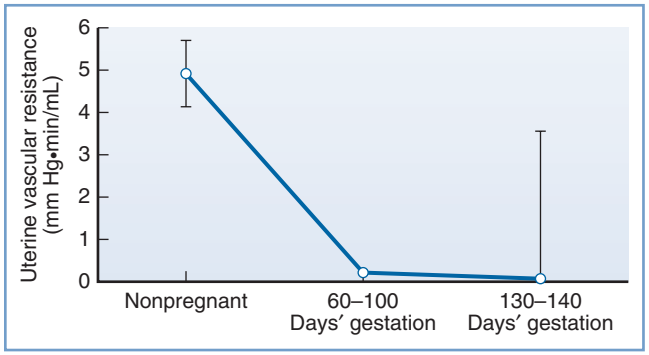

FIGURE 3-4 ■ Changes in uterine vascular resistance with gestation. Data are mean ± SE. (Adapted from Rosenfeld CR. Distribution of cardiac output in ovine pregnancy. Am J Physiol 1977; 232:H231-5.)

dependent on a substantial decrease in uterine vascular resistance (Figure 3-4), together with increased cardiac output and intravascular volume. The main factors contributing to the decrease in vascular resistance include vascular remodeling, changes in vascular reactivity, and the development of the widely dilated placental circulation.

Vascular remodeling of arteries in the uterus during pregnancy is believed to include increases in both vessel diameter and vessel length. In humans, both vessel lengthening and straightening of coiled vessels may occur.[12] According to Poiseuille's law, vascular resistance is decreased in proportion to the fourth power of the radius, whereas resistance is increased in proportion to the first power of vessel length; as such, the effects of changes in vessel diameter dominate, resulting in an overall decrease in resistance. Palmer et al.,[13] using serial Doppler studies during pregnancy, observed that uterine artery diameter is doubled by 21 weeks' gestation, whereas there is no change in the diameter of the common iliac or external iliac arteries. These investigators also showed that uterine artery mean flow velocity increased progressively during pregnancy to values eight times greater than those of nonpregnancy. In parallel with arterial changes, there is also structural remodeling of uterine veins in pregnancy. This includes increases in diameter and distensibility and decreases in elastin content.[36] Although blood viscosity decreases during pregnancy and also contributes to reduced uterine vascular resistance, this is considered a relatively minor effect compared with vascular changes.[37]

Changes in vascular reactivity during pregnancy include a vasodilatory response that is meditated at endothelial and vascular smooth muscle levels.[38] The growth of the placenta creates a low-resistance vascular pathway by eliminating the intramyometrial microcirculation and creating an intervillous space.[39] This has functional characteristics of an arteriovenous shunt.[15]

The mechanisms underlying the vascular changes during pregnancy are incompletely understood. Contributing factors include steroid hormones, decreased response to vasoconstrictors, endothelium-derived vasodilators, increased shear stress, and venoarterial exchange.

Steroid Hormones

Steroids play an integral role in the development and regulation of the uteroplacental circulation. Estrogen and progesterone are especially important, and there is evidence that cortisol may also contribute.

Estrogen has a fundamental role in the short- and long-term uterine vascular changes during pregnancy. Plasma concentrations of estrogen, initially derived from the ovaries and later predominantly from the placenta, rise concomitantly with the increase in uterine blood flow during pregnancy. Exogenously administered estrogen causes uterine vasodilation and a marked rise in uterine blood flow, independent of systemic effects.[40] Angiogenic and vasodilatory effects of estrogen are meditated via estrogen receptors ER-α and ER-β, which are structurally and functionally distinct. The majority of these receptors are located in the nucleus and mediate genomic effects by regulating transcription of genes that are particularly responsible for the longer-term uterine angiogenic responses. There are also membrane receptors that mediate nongenomic effects by up-regulating endothelial production of nitric oxide through the activation of endothelial nitric oxide synthase (eNOS) and the augmentation of eNOS protein expression.[41]

Progesterone modulates the effect of estrogen on uterine blood flow. In a nonpregnant sheep model, exogenous progesterone administered alone had no uterine vasodilatory effect but had an inhibitory effect when combined with estrogen.[38] Progesterone down-regulates expression of estrogen receptors.[42] An increase in the estrogen-progesterone ratio parallels the increase in uterine blood flow in late pregnancy in many species.[43]

Plasma **cortisol** levels approximately double during pregnancy. Cortisol has both systemic and local effects on uterine blood flow. Systemically, cortisol contributes to regulation of uterine blood flow by increasing plasma volume. Although cortisol is believed to decrease eNOS protein expression and decrease nitric oxide release, it potentiates the response to vasoconstrictor agents including angiotensin II, vasopressin, and norepinephrine. Attenuation of these effects occurs during pregnancy.[38]

Decreased Response to Vasoconstrictors

In pregnancy, there is a generalized reduction in response to endogenous and exogenous vasoconstrictors, including angiotensin II, endothelin, thromboxane, epinephrine, norepinephrine, phenylephrine, serotonin, thromboxane, and arginine vasopressin.[44-46] The relative refractoriness of the systemic and uterine circulations varies for different agents, which has important implications for the regulation and maintenance of uteroplacental blood flow.

During pregnancy, concentrations of **angiotensin II** in maternal blood are increased twofold to threefold[47]; however, the vasopressor response to angiotensin II is attenuated.[48] This refractoriness is diminished in patients in whom preeclampsia develops.[48] The uterine circulation is less responsive to angiotensin II than the systemic circulation. Thus, infusion of physiologic doses of

angiotensin II has been shown to have minimal effect on uteroplacental blood flow while increasing systemic blood pressure.[49] The difference in sensitivity of the uterine and systemic circulations to angiotensin II is considered an important physiologic adaptation during pregnancy that contributes to the redistribution of cardiac output, the increase in uterine blood flow, and possibly the maintenance of uterine blood flow during normal fluctuations in blood pressure.[50]

Sensitivity to vasoconstrictors such as **epinephrine**, **norepinephrine**, and **phenylephrine** is attenuated during pregnancy.[51] However, in contrast to the responses to angiotensin II, the uterine circulation is *more* responsive to these agents than the systemic circulation.[51] Thus, during hemorrhage or other major stresses that result in large catecholamine release, it is unlikely that uteroplacental perfusion will be preferentially preserved above essential maternal perfusion.[52]

The mechanism underlying the difference in vascular sensitivity between the uterine and systemic circulations is unclear, but distribution of receptor subtypes is believed to be important.[53] There are two distinct subtypes of angiotensin II receptors: AT_1R and AT_2R. In most tissues, including systemic vascular smooth muscle, AT_1R receptors are predominant and mediate vasoconstriction. However, AT_2R receptors, which do not mediate smooth muscle contraction, account for 75% to 90% of angiotensin II binding in uterine artery and myometrium.[54,55]

Vasodilators

The greater synthesis and higher circulating concentrations of endothelial-derived vasodilators during pregnancy are believed to modulate systemic and uterine vascular responses to angiotensin II and other vasoconstrictors.[56] Uterine vascular production of **prostacyclin** is greater than systemic vascular production, which probably contributes to maintaining uteroplacental blood flow in opposition to the effects of circulating vasoconstrictors.[57] An enhanced response to angiotensin II during pregnancy has been demonstrated with the systemic and local infusion of indomethacin (which blocks prostacyclin production).[58] However, inhibition of prostaglandin synthesis by an infusion of indomethacin induces only a transient decrease in uteroplacental blood flow, indicating that uteroplacental blood flow is not solely dependent on the continued production of prostacyclin.[56]

Nitric oxide is synthesized from arginine in vascular endothelial cells and stimulates soluble guanylate cyclase in vascular smooth muscle, resulting in vascular relaxation through increases in cyclic guanosine monophosphate. Synthesis of nitric oxide is an important mechanism underlying changes in systemic and uterine vascular resistance, attenuated responses to vasoconstrictors, and vascular effects of estrogen during pregnancy.[59] During pregnancy, uterine arteries have increased eNOS activity, higher levels of eNOS messenger ribonucleic acid and eNOS protein, and increased biosynthesis of nitric oxide and cyclic guanosine monophosphate.[59,60] Removal of the vascular endothelium diminishes or eliminates the refractoriness of the uterine artery to vasoconstrictors[45] and inhibition of nitric oxide synthesis by *N*-nitro-L-arginine methyl ester (L-NAME) decreases uterine blood flow and also reverses refractoriness to vasoconstrictors.[61] Long-term inhibition of nitric oxide synthase causes hypertension and fetal growth restriction in rats.[62]

Other Vasoactive Substances

Atrial and brain natriuretic peptides attenuate the response to angiotensin II, and intravenous infusion of atrial natriuretic peptide reduces blood pressure while increasing uterine blood flow in preeclamptic women.[63] **Protein kinase C** activity is decreased in uterine, but not systemic, arteries of pregnant sheep and may cause vasodilation and an increase in uterine blood flow; this may have a regulatory effect on local ovarian and placental estrogen production.[43] Studies in rats have shown a decrease in endogenous endothelin-dependent vasoconstrictor tone in uteroplacental vessels, which may contribute to the increase in placental blood flow in late gestation.[64] Uterine vascular resistance in early pregnancy may be increased by **relaxin,** which may have a role in modulating the effects of estrogen and progesterone.[65]

Shear Stress

Shear stress, the frictional forces on the vessel wall from blood flow, is believed to be an important stimulus for uteroplacental vasodilation and remodeling.[66] The reduction in downstream resistance resulting from the formation of the placenta would be expected to increase the upstream flow velocity and thus shear stress.[39] Nitric oxide is considered an important mediator of this effect because increases in eNOS expression and nitric oxide production are witnessed with shear stress and because stripping the endothelium or pretreatment with L-NAME reduces or abolishes flow-induced vasodilation.[66] Studies *in vitro* have shown that shear stress also increases endothelial production of prostacyclin.

Venoarterial Signaling

It has been postulated that growth factors or signal substances secreted by the placenta and/or myometrium could pass from uterine veins to adjacent uterine arteries; this may provide a system whereby the uterus and placenta regulate their own perfusion.[39] Possible candidates for signal substances include vascular endothelial growth factor and placental growth factor. Confirmation of whether this mechanism is important in humans is awaited.

METHODS OF MEASUREMENT OF UTEROPLACENTAL BLOOD FLOW

Many techniques have been used to measure uteroplacental blood flow in animals and humans. The approaches used in different studies have varied according to the nature of the experimental question, the existing state of technology, and ethical considerations and limitations. All methods have an inherent potential for error.

Many past studies of uterine artery flow have measured flow in only one uterine artery, which may not be an accurate representation of total flow, depending on the location of the placenta (see earlier discussion). The parameter of greatest clinical interest is placental perfusion, but this is not always differentiated from total uterine blood flow, from which it may vary independently. However, in most circumstances, the measurement of intervillous blood flow provides a close approximation of functional placental blood flow. Ovarian arterial blood flow is generally not measured, although studies in primates suggest it may contribute as much as one sixth of placental perfusion.[67]

Early studies of uteroplacental blood flow involved a number of substances that could affect maternal hemodynamics (e.g., nitrous oxide) or myometrial activity (e.g., 4-amino-antipyrine) and relied on the Fick principle. This principle, which calculates blood flow by the measurement of a marker substance entering and leaving an organ, is subject to error in the uterus, where a number of veins are responsible for collecting venous effluent.[68] In animals, placental perfusion can also be measured by the injection of radioactive microspheres. This method allows for the separate calculation of placental and myometrial blood flows but only provides information from a single point in time. Total uterine arterial blood flow can also be measured (or estimated) with the use of surgically implanted electromagnetic or Doppler flow probes.

In humans, placental perfusion can be measured by the injection of trace amounts of radioactive substances, typically xenon-133.[69] During the washout phase, the rapid decrease in measured radioactivity over the placenta is calculated as a biexponential or triexponential process. The most rapid decay constant is ascribed to intervillous perfusion. Alternatively, radioactively tagged proteins (e.g., albumin) can be injected and measured by scintigraphy over the placenta.[70] Although the accuracy of these methods for determining absolute flow is limited, their ability to measure relative change over time is adequate in most cases.

In humans, the most common method of clinically assessing uterine blood flow is Doppler ultrasonography.[71] The uterine artery is identified after it crosses the external iliac artery, before it divides into branches. Color flow aids vessel identification. Blood flow can be quantified by measuring the mean flow velocity and vessel cross-sectional area.

Flow velocity is calculated by applying the principle of Doppler shift. A pulsed ultrasound signal from a stationery transducer is directed toward the vessel with an angle of insonation (θ) less than 60 degrees. Reflections scattered from the red blood cells are received. Because the red blood cells are moving, the frequency of the received signal differs from the transmitted frequency (f_0) by an amount known as the Doppler shift (Δf). This shift is proportional to the red blood cell flow velocity (V_{RBC}) according to the following equation:

$$\Delta f = \frac{2 \times f_0 \times V_{REL}}{c} \quad (2)$$

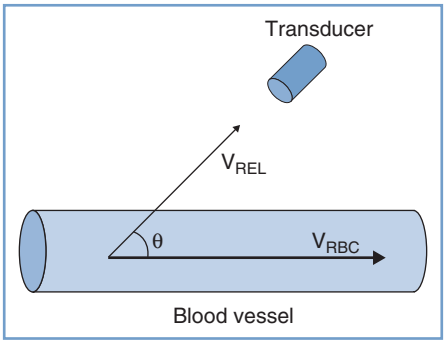

FIGURE 3-5 ■ Principles of use of Doppler ultrasonography to estimate blood flow. Blood flow is calculated as the product of blood vessel cross-sectional area and mean flow velocity in the vessel (V_{RBC}). The latter is derived from the measured flow velocity relative to the direction of the probe (V_{REL}) and requires precise determination of the angle of insonation (θ).

where c is the speed of sound propagation in tissue and V_{REL} is the vector component of the velocity of flow relative to the direction of the transducer. The latter takes into account the difference between the direction of the ultrasound signal from the direction of flow according to θ (Figure 3-5). With the use of basic trigonometry, V_{RBC} is related to the relative velocity of flow in the direction of the probe (V_{REL}) according to the following equation:

$$V_{RBC} = \frac{V_{REL}}{\cos\theta} \quad (3)$$

Combining equations 2 and 3 gives the following equation:

$$V_{RBC} = \frac{\Delta f}{f_0} \times \frac{c}{2 \times \cos\theta} \quad (4)$$

Thus, the flow velocity is estimated from the ratio of the Doppler shift frequency to the transmitted frequency, multiplied by the speed of sound propagation, and divided by two times the cosine of the insonation angle.

An estimation of the volume of blood flow (Q) can be made by multiplying mean velocity by the vessel cross-sectional area (A), which is estimated with two-dimensional (B-mode) ultrasonography:

$$Q = V_{RBC} \times A \quad (5)$$

However, measurement of absolute flow using this technique is prone to difficulty and error, both from inaccurate measurement of vessel cross-sectional area (e.g., arteries pulsate during the cardiac cycle) and from inaccurate measurement of flow (e.g., from inaccuracies in measurement of θ). Therefore, for diagnostic purposes, a number of indices related to vascular impedance can be derived from the flow velocity waveform that are independent of θ.[72] These rely on the fact that the uterine vascular bed normally has low resistance with flow

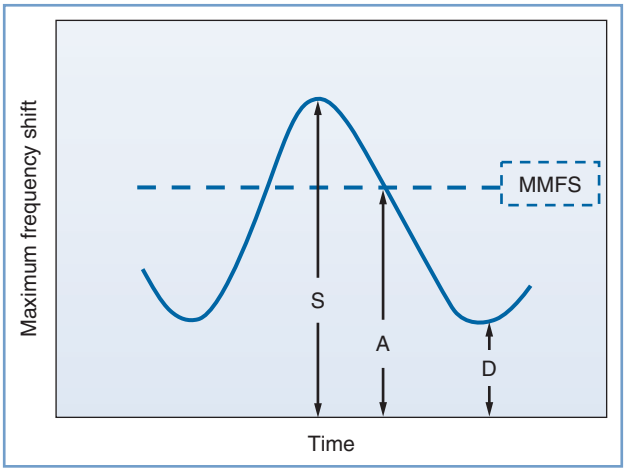

FIGURE 3-6 ■ Schematic diagram showing elements of typical Doppler waveform of the uterine artery. *S,* peak systolic frequency shift (maximum velocity); *D,* end-diastolic frequency shift (minimum velocity); *A,* temporal averaged frequency shift (mean velocity) averaged over one cardiac cycle; *MMFS,* mean maximum frequency shift. Derived indices include systolic/diastolic (S/D) ratio = S/D, pulsatility index (PI) = (S – D)/A, and resistance index (RI) = (S – D)/S.

continuing during diastole. If distal resistance is increased, for example during the development of preeclampsia or fetal growth restriction, diastolic velocity decreases relative to systolic velocity resulting in a waveform showing greater pulsatility. Commonly derived indices (Figure 3-6) are:

$$\text{Systolic} - \text{diastolic}\left(\frac{\text{S}}{\text{D}}\right)\text{ratio} = \frac{\text{Systolic (maximal) velocity}}{\text{Diastolic (minimal) velocity}} \quad (6)$$

$$\text{Pulsatility index (PI)} = \frac{\text{(Systolic [maximum] velocity} - \text{Diastolic [minimum] velocity)}}{\text{Mean velocity}} \quad (7)$$

$$\text{Resistance index (RI)} = \frac{\text{(Systolic [maximum] velocity} - \text{Diastolic [minimum] velocity)}}{\text{Systolic [maximum] velocity}} \quad (8)$$

In addition, the waveform can be described or categorized according to features such as the absence of end-diastolic flow and the presence of post-diastolic notches. Examples of normal and abnormal uterine artery Doppler tracings are shown in Figure 3-7.[73] Doppler velocimetry can be applied to the umbilical vessels for antepartum fetal assessment (see Chapter 6).

There are several potential sources of error in Doppler measurements of absolute flow with regard to both accuracy and reproducibility of measurements. For example, small errors in the estimation of θ can result in blood flow measurement errors as large as 30%.[13] Thus, the methods used in any clinical study that employs Doppler ultrasonography to assess uterine artery blood flow should be examined critically.

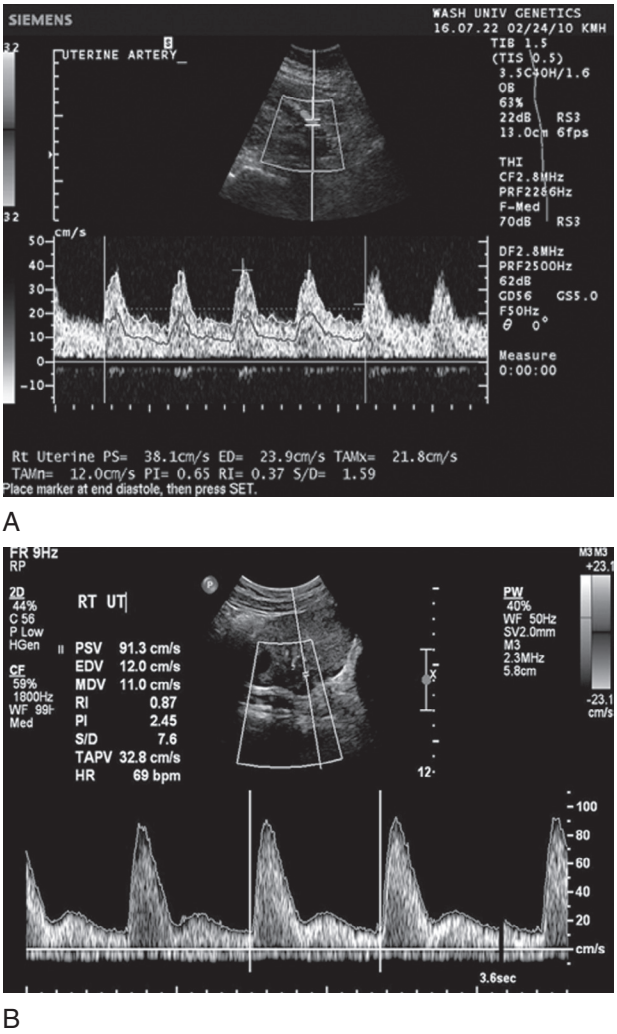

FIGURE 3-7 ■ Normal (**A**) and abnormal (**B**) uterine artery Doppler waveforms. The normal waveform has no notching and normal pulsatility. The abnormal waveform shows notching and increased pulsatility. (From Tuuli M, Odibo AO. The role of serum markers and uterine artery Doppler in identifying at-risk pregnancies. Clin Perinatol 2001; 38:1-19.)

NEURAXIAL ANESTHESIA

The effect of neuraxial anesthesia on uteroplacental blood flow depends on the complex interaction of many factors (Box 3-2). Pain and stress during labor may reduce uteroplacental blood flow through sympathetic stimulation and the release of circulating catecholamines. Shnider et al.[74] observed that acute stress increased plasma norepinephrine concentrations by 25% and decreased uterine blood flow by 50% in gravid ewes. In laboring women, stress is associated with increased plasma epinephrine concentrations and abnormal fetal heart rate patterns. Effective pain relief with neuraxial analgesia decreases circulating concentrations of catecholamines[75] and reduces hyperventilation and therefore may help protect uteroplacental blood flow. In the absence of hypotension, epidural anesthesia does not change uteroplacental blood flow in pregnant sheep.[76] Results from human studies are

BOX 3-2 Effects of Neuraxial Anesthesia on Uterine Blood Flow

Increased uterine blood flow as a result of:
- Pain relief
- Decreased sympathetic activity
- Decreased maternal hyperventilation

Decreased uterine blood flow as a result of:
- Hypotension
- Unintentional intravenous injection of local anesthetic and/or epinephrine
- Absorbed local anesthetic (little effect)

variable, partly because of differences in study design, techniques used, and clinical circumstances. However, most studies have shown no change or an increase in uteroplacental blood flow after administration of epidural analgesia.[77-80] Some studies have shown an increase in uterine vascular resistance indices,[81,82] but with no effect on neonatal outcomes. There is evidence that in women with preeclampsia, epidural analgesia using a plain local anesthetic may reduce uterine artery resistance[78] and increase intervillous blood flow.[83] Ginosar et al.[84] reported that antenatal continuous epidural infusion of ropivacaine in preterm patients with preeclampsia reduced uterine artery resistance. Further work is required to determine whether this might have therapeutic potential for short-term prolongation of pregnancy.

Fetal bradycardia is sometimes observed after combined spinal-epidural techniques and has been attributed to decreases in uteroplacental blood flow; the mechanism for this association is unclear. Although alterations in uteroplacental blood flow have been primarily attributed to maternal hypotension and respiratory depression,[85] another postulated mechanism is uterine tachysystole (hypertonus) caused by a rapid decrease in circulating catecholamine concentrations (see Chapter 23).[86] Additional studies are needed to evaluate the relationship between neuraxial anesthetic techniques, uteroplacental blood flow, and fetal bradycardia.

Hypotension

Hypotension occurring during neuraxial blockade, depending on its magnitude and duration, may decrease uteroplacental blood flow for several reasons—reduction in perfusion pressure,[17] reflex release of endogenous vasoconstrictors, diversion (steal) of blood to the lower limbs,[87] and response to administered vasopressors.[33] The rapid and extensive sympathetic blockade during spinal anesthesia, and some of the methods used to treat hypotension, may account for the observation that umbilical arterial blood pH is lower with spinal anesthesia than with epidural or general anesthesia for cesarean delivery.[88]

Intravenous Fluid Loading

Studies of the effect of intravenous fluid boluses used in conjunction with assessment of the uteroplacental circulation have had mixed results. Most Doppler studies have shown that fluid preload before the initiation of neuraxial analgesia does not change vascular resistance indices,[89] although a decrease has been reported.[90]

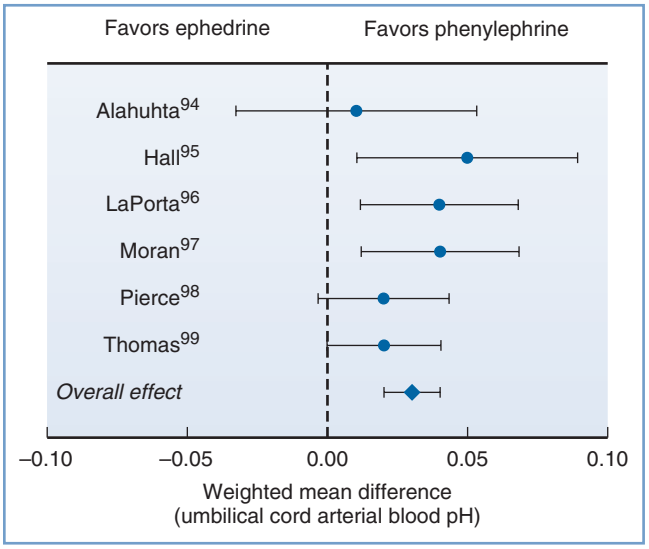

FIGURE 3-8 ■ Results from a meta-analysis of trials comparing phenylephrine and ephedrine for the management of hypotension during spinal anesthesia for cesarean delivery. The chart shows the effect of choice of vasopressor on umbilical cord arterial pH. Data are mean difference with 95% confidence intervals. (Modified from Lee A, Ngan Kee WD, Gin T. A quantitative systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002; 94:920-6.)

Vasopressors

The effects of vasopressors on uteroplacental blood flow and the resulting implications for clinical drug selection are controversial. Animal and *in vitro* studies have observed that uteroplacental blood flow was better maintained using ephedrine versus alpha-adrenergic agonists such as phenylephrine, metaraminol, and methoxamine,[33] which likely reflects the predominant beta-adrenergic effects of ephedrine. In addition, *in vitro* studies in pregnant sheep evaluating the effects of ephedrine on blood vessels have demonstrated enhanced vasoconstrictor activity on the femoral versus uterine vessels and decreased uterine vasoconstriction as a result of nitric oxide release.[91] In contrast, an increase in the uterine arteriolar vasoconstrictor response to phenylephrine has been observed during pregnancy.[92] However, in clinical studies, umbilical arterial blood pH and base excess have been observed to be greater with the use of alpha-adrenergic agonists in comparison to ephedrine to maintain maternal blood pressure during spinal anesthesia for cesarean delivery (Figure 3-8).[93-100] A comparison of different infusion regimens of phenylephrine, titrated to keep maternal systolic blood pressure near baseline, observed no depression of fetal pH and base excess despite very large total doses (up to 2500 µg) before delivery.[32] In contrast, large doses of ephedrine administered to maintain blood pressure during spinal

anesthesia for cesarean delivery depressed umbilical arterial blood pH and base excess in a dose-dependent manner.[101]

The explanation for the discrepancy between experimental and clinical data is complex and incompletely determined. Animal studies are not always appropriate models for clinical situations. Under clinical conditions, Doppler studies have shown some evidence that uterine vascular resistance is increased by alpha-adrenergic agonists,[94] but this finding has not been consistent.[100] Although data suggest that alpha-adrenergic agonists increase uterine vascular resistance more than systemic vascular resistance, the difference may be primarily due to an effect in the myometrium, with relative sparing of the vessels that perfuse the placenta.[102] In addition, uteroplacental blood flow in humans has a margin of safety that appears to allow modest decreases in uterine blood flow (caused by clinically appropriate doses of alpha-adrenergic agonists) to occur without compromising oxygen transfer. Finally, the propensity of ephedrine to worsen fetal acid-base status may be related less to its effects on uteroplacental blood flow and more to direct beta-adrenergic receptor–mediated fetal metabolic effects. When compared with phenylephrine, ephedrine has been observed to cross the placenta to a greater extent and be associated with higher fetal levels of lactate, glucose, epinephrine, and norepinephrine.[103]

Thus, when considering the choice of vasopressor for clinical use, the anesthesiologist should take into account the sum effect on fetal oxygen supply and demand balance rather than the isolated effects on uteroplacental blood flow. In this respect, clinical studies do not favor the use of ephedrine. In addition, the slow onset and long duration of action of ephedrine make it more difficult to titrate than phenylephrine. Conversely, the use of phenylephrine is commonly associated with a reflex slowing of heart rate and a corresponding decrease in cardiac output. At modest doses, this decrease reflects a normalization of the cardiac output that is elevated secondary to decreased afterload after the initiation of spinal anesthesia; at larger doses, alpha-adrenergic agents can cause cardiac output to decrease below baseline.[104] The implications of these findings on uteroplacental blood flow are controversial because the relative importance of maintaining cardiac output versus maintaining uterine perfusion pressure is unknown. Overall, to date, studies comparing ephedrine and other vasopressors in humans have not demonstrated differences in clinical neonatal outcome.

Limited data are available for the comparison of vasopressors in the presence of fetal compromise or placental insufficiency. Erkinaro et al.[105,106] developed a sheep model to compare the effects of phenylephrine and ephedrine after a period of experimental fetal hypoxia. Hypotension was induced by epidural anesthesia and then corrected with either phenylephrine or ephedrine. In an initial study, ephedrine was associated with better restoration of uterine artery blood flow, but no differences in fetal acid-base measurements or lactate concentration were observed.[105] However, in a second study, these investigators embolized the placenta with microspheres to model placental insufficiency and found that phenylephrine and ephedrine had similar effects on uterine blood flow, fetal pH, and base excess as found in the initial study, with the exception that fetal lactate concentration was greater in the phenylephrine group.[106] Although the investigators speculated that this exception might reflect impaired fetal clearance of lactate, the placental embolization may have narrowed the margin of safety for uteroplacental blood flow and increased fetal lactate production in the phenylephrine group. Ngan Kee et al.[107] compared phenylephrine and ephedrine for maintaining blood pressure in patients receiving spinal anesthesia for nonelective cesarean delivery, 24% of whom had evidence of fetal compromise. The results showed that although umbilical arterial and venous blood lactate concentrations were lower in the phenylephrine group, umbilical arterial blood pH and base excess values were similar in the two groups. However, umbilical arterial and venous blood Po_2 measurements were lower in the phenylephrine group, suggesting that although phenylephrine may have caused some reduction in uteroplacental perfusion, adequate oxygen supply was likely maintained by increased oxygen extraction.

In summary, ephedrine and phenylephrine both continue to be used clinically for maintaining maternal blood pressure during the administration of neuraxial anesthesia. Although most experimental data suggest that uteroplacental perfusion is likely to be better maintained with ephedrine than with alpha-adrenergic agonists, this advantage may be outweighed by other considerations, such as differences in efficacy for maintaining blood pressure and direct fetal effects that occur from the placental transfer of the drug.

Local Anesthetics

Studies *in vitro* have shown that local anesthetics constrict arteries directly and inhibit endothelium-mediated vasodilation.[108] High concentrations of local anesthetic can decrease uteroplacental blood flow by stimulating vasoconstriction and myometrial contractility.[109,110] A comparative study in pregnant sheep showed that bupivacaine was more potent than either lidocaine or 2-chloroprocaine in decreasing uterine blood flow.[110] However, the adverse effects of local anesthetics were seen only at concentrations in excess of those observed clinically, with two possible exceptions: (1) the unintentional intravenous injection of local anesthetic and (2) the use of local anesthetics for a paracervical block. At clinically relevant doses, no adverse effect on uteroplacental blood flow was reported.[111] Although initially the inherent vasoconstrictor properties of ropivacaine were a matter of concern, studies in animals[111] and humans[112] have not shown that administration of ropivacaine results in a reduction in uterine blood flow.

Epinephrine and α_2-Adrenergic Agonists

Epinephrine is often combined with local anesthetic agents in obstetric anesthesia. Wallis et al.[76] found that the epidural injection of 1.5% 2-chloroprocaine with epinephrine (10 μg/mL) produced a small, brief reduction

in uterine blood flow in pregnant sheep. In contrast, Alahuhta et al.[113] reported that epidural bupivacaine with epinephrine (5 μg/mL) had no effect on intervillous blood flow in women undergoing cesarean delivery. Studies have not shown a reduction in uteroplacental blood flow as a result of the absorption of epinephrine from local anesthetic solutions given epidurally to healthy women during labor.[114] However, one study observed that the addition of epinephrine (85 to 100 μg) to epidural bupivacaine increased Doppler indices of uteroplacental vascular resistance in hypertensive parturients with chronic fetal asphyxia.[115] Therefore, some anesthesia providers avoid epidural administration of epinephrine-containing local anesthetic solutions to women with preeclampsia. Commonly, epinephrine (10 to 15 μg) is included in the epidural test dose. Marcus et al.[116] reported that repeated epidural injections of epinephrine (10 to 15 μg) did not decrease uterine blood flow in pregnant sheep; however, the same dose injected intravenously reduced uterine blood flow, with a maximum decrease of 43% observed at 1 minute.

The epidural and intrathecal administration of α_2-adrenergic agonists (e.g., clonidine, dexmedetomidine) has been a subject of clinical investigations. Intravenous, but not epidural, administration of clonidine decreased uterine blood flow in gravid ewes.[117,118]

Opioids

Opioids are often combined with local anesthetic agents for epidural and intrathecal analgesia during labor and the peripartum period. Intrathecal opioids have been implicated as contributing to a greater risk for fetal bradycardia when used for labor analgesia compared with non-intrathecal opioid neuraxial analgesic techniques.[119] The mechanism for this effect has been postulated as an increase in uterine tone and a resulting decrease in uteroplacental blood flow, although further research is needed. Craft et al.[120,121] observed that neither epidural fentanyl nor morphine had a significant effect on uterine blood flow in gravid ewes. Alahuhta et al.[122] reported that epidural sufentanil 50 μg did not alter uterine artery blood flow velocity waveform indices in laboring women. Intrathecal meperidine and sufentanil, however, may be associated with hypotension that may potentially decrease uterine blood flow.[123,124]

GENERAL ANESTHESIA

Induction Agents

Available data suggest that the commonly used induction agents have minimal or no direct adverse effect on uteroplacental blood flow. Allen et al.[125] found that thiopental inhibited the response of human myometrial arteries to contractile agents *in vitro* but had no effect on relaxation induced by prostacyclin. Alon et al.[126] reported that uterine blood flow did not change significantly during induction and maintenance of propofol anesthesia in pregnant sheep. Craft et al.[127] reported that uterine tone increased but uterine blood flow remained constant after an intravenous bolus of ketamine in pregnant sheep. Similarly, Strümper et al.[128] reported that neither racemic nor S^+-ketamine affected uterine perfusion in pregnant sheep. Few data are available on the direct effects of etomidate on uteroplacental blood flow.

During the intravenous induction of general anesthesia, uteroplacental perfusion may be affected by indirect mechanisms such as blood pressure changes and the sympathetic response to laryngoscopy and endotracheal intubation. Jouppila et al.[129] reported that intervillous blood flow decreased by 22% to 50% during induction of general anesthesia for cesarean delivery with thiopental 4 mg/kg, succinylcholine 1 mg/kg, and endotracheal intubation. Gin et al.[130] compared thiopental 4 mg/kg and propofol 2 mg/kg in patients undergoing elective cesarean delivery. These investigators found that venous plasma concentrations of epinephrine and norepinephrine increased after endotracheal intubation in both groups, but maximum norepinephrine concentrations were lower in the propofol group. No differences in neonatal outcomes were observed. Levinson et al.[131] found that intravenous ketamine increased blood pressure with a concomitant rise in uterine blood flow in pregnant sheep. Addition of a rapid-acting opioid (e.g., alfentanil, remifentanil) during induction of general anesthesia may minimize the increase in circulating catecholamines that occurs after laryngoscopy and endotracheal intubation.[132,133] Although the use of such opioids might attenuate any decrease in uterine blood flow, the potential for neonatal respiratory depression should be considered.

Inhalational Agents

Studies in pregnant sheep have shown that usual clinical doses (i.e., 0.5 to 1.5 minimum alveolar concentration) of the volatile anesthetic agents, including isoflurane, desflurane, and sevoflurane, have little or no effect on uterine blood flow, although deeper planes of anesthesia are associated with reductions in cardiac output, maternal blood pressure, and uterine blood flow.[134,135] Nonetheless, high concentrations of inhalational agents (approximately 2 minimum alveolar concentration) have been used during *ex utero* intrapartum treatment procedures without evidence of impaired fetal gas exchange.[136] A dose-dependent reduction in uterine tone caused by inhalational agents would be expected to increase uterine blood flow in clinical circumstances in which tone is increased (e.g., hyperstimulation with oxytocin, cocaine overdose, placental abruption). Overall, there is little reason to choose one inhalational agent over another on the basis of an agent's effects on uterine blood flow.

Ventilation

Although moderate levels of hypoxemia and hypercapnia do not affect uteroplacental blood flow,[137] marked alterations may reduce blood flow indirectly by mechanisms most likely involving sympathetic activation and catecholamine release. The effect of hypocapnia on uteroplacental blood flow is controversial. Some investigators have noted that hyperventilation with hypocapnia caused

fetal hypoxia and metabolic acidosis in animals,[138] whereas others have found no effect.[139] Levinson et al.[140] observed that positive-pressure ventilation decreased uterine blood flow in pregnant sheep; however, because the addition of carbon dioxide did not improve uterine blood flow, the reduction in blood flow was attributed to the mechanical hyperventilation rather than the hypocapnia. In general, most authorities recommend that hyperventilation be avoided in pregnancy, in part because of concerns about uterine blood flow.

EFFECTS OF OTHER DRUGS

Magnesium Sulfate

Magnesium sulfate increases uterine blood flow in normotensive and hypertensive pregnant sheep.[141,142] Although hypermagnesemia was found to exacerbate maternal hypotension during epidural anesthesia in pregnant sheep, no reduction in uterine blood flow was observed.[141] In women in preterm labor[143] and with severe preeclampsia,[144] magnesium sulfate caused a modest decrease in Doppler indices of uterine vascular resistance. Infusion of magnesium caused an increase in uterine blood flow, which was associated with an improvement in red blood cell deformability in women with preeclampsia or fetal growth restriction.[145]

Antihypertensive Agents

In patients with pregnancy-induced hypertension, the effects of antihypertensive drugs on uteroplacental perfusion depend on the interaction of their effects on uterine vascular resistance and systemic maternal blood pressure. In animal models of pharmacologically induced hypertension, hydralazine reduced maternal blood pressure but increased uteroplacental blood flow, reflecting a decrease in uterine vascular resistance.[146,147] Similar studies with labetalol have had varying results, showing increased,[148] decreased,[149] and no change[150] in uteroplacental blood flow. A study in preeclamptic women observed an increase in uterine artery resistance indices after hydralazine but not labetalol.[151] However, previous studies have generally demonstrated no significant change in uteroplacental blood flow with either drug,[152-155] indicating that other considerations are probably more important for guiding drug selection. Studies of methyldopa in patients with preeclampsia have found either a reduction[156] or no change[157] in indices of uterine and placental vascular resistance.

Calcium Entry–Blocking Agents

Verapamil 0.2 mg/kg was shown to decrease maternal blood pressure and uterine blood flow in pregnant sheep.[158] Studies with nifedipine have yielded conflicting results. Some animal studies have shown that nifedipine decreases uteroplacental blood flow and worsens the fetal condition, whereas human studies have shown either no change in uteroplacental blood flow or vascular resistance[159] or a decrease in vascular resistance.[160]

Vasodilators

Nitroglycerin was shown to relax human uterine arteries *in vitro*.[161] In women with abnormal uterine artery blood flow at 24 to 26 weeks' gestation, infusion of intravenous nitroglycerin decreased uterine resistance indices.[162] Similarly, transdermal nitroglycerin administered for 3 days to patients with preeclampsia and fetal growth restriction decreased uterine resistance indices.[163] However, Grunewald et al.[164] reported that an infusion of nitroglycerin in women with severe preeclampsia did not change the pulsatility index of the uterine artery. When interpreting such studies, clinicians should remember that increases in total uterine blood flow do not necessarily result in enhanced placental perfusion.[165] Further work is required to define the utility of systemic vasodilators for improving uteroplacental blood flow in clinical practice.

Inotropic Drugs

Positive inotropic drugs are rarely indicated in obstetric patients. On the basis of studies of normal pregnant sheep, milrinone and amrinone may increase uterine blood flow, whereas dopamine and epinephrine may diminish it.[166,167] The choice of an inotropic agent should be based primarily on the desired efficacy (i.e., maternal considerations) rather than the potential direct effects on uterine blood flow. This is especially important during maternal resuscitation or cardiac arrest, when maternal welfare is the overriding priority and standard resuscitation drugs should be given. Restoration of spontaneous circulation and adequate uterine perfusion pressure is far more important than avoidance of uterine vasoconstriction.

KEY POINTS

- Growth and development of the uteroplacental vasculature and progressive vasodilation allow uteroplacental blood flow to increase during pregnancy. Uteroplacental blood flow constitutes approximately 12% of maternal cardiac output at term.
- Many factors modulate the maintenance and regulation of uteroplacental blood flow, including altered responses to vasoconstrictors, increases in endothelium-derived vasodilators, and the effects of steroid hormones and shear stress.
- The uteroplacental circulation is a dilated, low-resistance vascular bed with limited ability for autoregulation. Flow may be reduced by a decrease in uterine arterial pressure, an increase in uterine venous pressure, or an increase in uterine vascular resistance.
- The uteroplacental circulation is composed of placental and nonplacental circulations that are anatomically and functionally dissimilar.
- Acute or chronic reductions in uteroplacental blood flow may threaten fetal viability and

predispose to disorders such as preeclampsia and fetal growth restriction. In situations of acute reduction in uteroplacental perfusion, there is a limited margin of safety; exceeding this limit may decrease fetal oxygen uptake with resultant metabolic acidosis.

- Animal studies are the principal source of uteroplacental blood flow data; thus, clinicians should carefully consider interspecies differences and study methodology when extrapolating experimental findings to clinical practice.
- Doppler ultrasonography is the method most commonly used to estimate uterine blood flow in humans. Estimates of absolute flow and indices of resistance can be derived, but there are many potential sources of inaccuracy.
- Neuraxial anesthesia can increase uterine blood flow by reducing pain and stress or can decrease uterine blood flow by causing hypotension.
- Although animal studies show that ephedrine protects uteroplacental blood flow better than alpha-adrenergic agonists such as phenylephrine, umbilical arterial blood pH and base excess are lower after administration of ephedrine. This effect may be related to a greater propensity of ephedrine to cross the placenta and have direct metabolic effects on the fetus. Thus, a growing number of obstetric anesthesia providers recommend phenylephrine as a first-line vasopressor for treatment of hypotension associated with neuraxial anesthesia in obstetric patients.
- The doses of general anesthetic agents used clinically have minimal direct effects on uterine blood flow. General anesthesia may reduce uterine blood flow by causing decreased cardiac output as well as hypotension. Conversely, noxious stimulation during light anesthesia may precipitate the release of catecholamines, which results in decreased uterine blood flow.
- For cardiovascular emergencies in pregnant women, the choice of inotropic drug should depend primarily on the efficacy of the drugs to optimize the maternal condition, rather than on minor differences in uterine blood flow. Standard resuscitation drugs should be used in an emergency.

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CHAPTER 4

The Placenta: Anatomy, Physiology, and Transfer of Drugs

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CHAPTER OUTLINE

The placenta is a critical organ of great importance to obstetric anesthesia. Revered by ancient cultures as "the seat of the external soul" or "the bundle of life," the placenta is involved in many cultural rituals.[1] However, understanding of the indispensable role of the placenta in the development of the fetus did not start to evolve until the 17th century and continues today via microanatomic, biochemical, and molecular biologic techniques. The concept of the placenta as a passive sieve (acting only as a conduit for oxygen, nutrients, and waste) has been dispelled with the realization that the placenta is a complex and dynamic organ. Indeed, new studies show the critical importance of placental function in the metabolism, nutrition, and hormonal maintenance of pregnancy. Maternal-placental conditions can affect the fetus not only during pregnancy but also in adulthood and beyond into the next generation via epigenetic mechanisms.[2]

The placenta brings the maternal and fetal circulations into close apposition without substantial interchange of maternal and fetal blood for the physiologic transfer of gases, nutrients, and wastes. This important exchange is accomplished within a complex structure that is almost entirely of fetal origin.

ANATOMY

Embryology

The blastocyst initially attaches to endometrial pinopodes (uterodomes), which express markers of endometrial receptivity (e.g., galectin-9).[3] The remodeling of uterine extracellular matrix starts with serine proteases and metalloproteinases (e.g., MMP-2 and MMP-9). The developing blastocyst erodes the surrounding decidua, leaving the cellular debris on which it survives. The syncytiotrophoblasts (invasive cells located at the margin of the growing conceptus) continue to erode the surrounding decidua and its associated capillaries and arterioles until the blastocyst is surrounded by a sea of circulating maternal blood (trophoblastic lacunae). The vitelline vein system develops in the yolk sac of the embryo to enhance the transport of nutrients, which diffuse from the maternal blood through the trophoblast layer and chorionic plate into the chorionic cavity. The embryo undergoes a dramatic acceleration in growth as its dependence on simple diffusion diminishes.[4]

At 2 weeks of development, the primitive extraembryonic mesoderm (cytotrophoblast layer) begins to

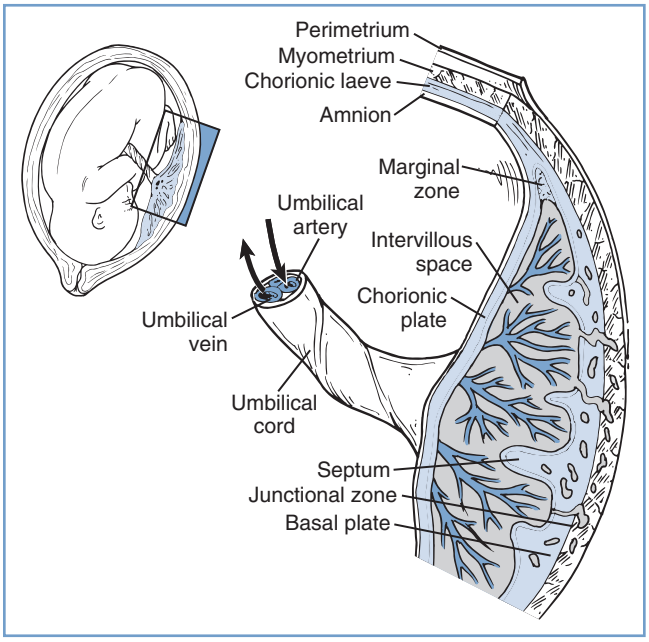

FIGURE 4-1 ■ The placenta is a complex structure that brings the maternal and fetal circulations into close apposition for exchange of substances. (Redrawn from Kaufmann P, Hans-Georg F. Placental development. In Polin RA, Fox WW, Abman SH, editors. Fetal and Neonatal Physiology. 3rd edition. Philadelphia, Saunders, 2004:85-96.)

proliferate as cellular columns into the syncytiotrophoblast. These columns with their syncytiotrophoblast covering extend into the maternal blood lacunae and represent *primary* villi. Further mesodermal invasion into the core of these primary villi marks the metamorphosis into *secondary* villi. Cellular differentiation of the villi mesoderm results in the formation of a network of blood cells and vessels; this transition allows their classification as *tertiary* villi. The vascular components of each villus develop connections within the chorionic plate and into the stalk that connects the developing embryo and primitive placenta. Penetration of the cytotrophoblast continues through the syncytiotrophoblastic layer until many of the villi reach the decidua and form *anchoring* villi (Figure 4-1).[4,5]

Villi continue to develop and undergo extensive branching into treelike structures; the branches, which extend into the lacunar (or intervillous) spaces, enlarge the surface area available for exchange. Further villous maturation results in a marked reduction in the cytotrophoblastic component and a shortening of the distance between the fetal villi and maternal intervillous blood.[4]

The growing embryo within the blastocyst attaches to the chorion through a connecting or body stalk. Mesodermal components of this stalk coalesce to form the allantoic (or rudimentary umbilical) vessels. As the embryo continues its exponential growth phase, the connecting stalk shifts ventrally from its initial posterior attachment. The expansive open region at the ventral surface of the embryo constricts as the body wall grows and closes. By so doing, the body wall surrounds the yolk stalk, allantois, and developing vessels within the connecting stalk to form the primitive umbilicus. As the expanding amnion surrounds and applies itself over the connecting stalk and yolk sac, the cylindrical umbilical cord takes on its mature form.[4]

Placental development is a dynamic process influenced by many factors. **Nitric oxide** plays an important role in embryo development, implantation, and trophoblast invasion in diverse species.[6] Human endothelial nitric oxide synthase (eNOS) expression in the syncytiotrophoblast and early endothelium occurs in the first trimester. Later in pregnancy, eNOS increases and becomes more prominent in the syncytiotrophoblast and endothelial cells. Vasculogenesis and angiogenesis depend on vascular endothelial growth factor (VEGF) and its receptors VEGFR-1 (Flt-1) and VEGFR-2 (Flk-2), transforming growth factor-β_1 (TGF-β_1), and angiopoietin 1 and 2, which exert their effects in part through nitric oxide. Hypoxia also plays an important role in placental development and angiogenesis by stimulating trophoblast invasion and differentiation via hypoxia-inducible factor-alpha, which activates VEGF and eNOS. Relative hypoxia must be maintained in early placental development because the placental-fetal unit cannot tolerate the oxidative stress of reactive oxygen species during organogenesis.[7] Oxygen levels influence the placental vascular sensitivity to vasodilators and constrictors. *In vitro* studies have shown that NOS inhibition and hypoxia independently increase placental perfusion pressure. Both of these effects are prevented by nitric oxide donors, suggesting a common pathway with the effect of hypoxia mediated partly by low NOS activity.[6]

The development of preeclampsia is related, at least in part, to abnormal placental growth and implantation at this early stage of development (see Chapter 36). In patients with preeclampsia, the villous tree has longer capillaries with fewer branches.[6] Vascular dysfunction occurs mainly from changes in vascular structure and activation of nitric oxide synthesis rather than from altered responses to nitric oxide and vasoconstrictors.

DNA, gene expression, and manipulation of gene expression control placental development, fetal development, adult phenotype expression, and clinical diseases, even into subsequent generations.[2,8] The evolving field of epigenetics explores the prolonged effect of maternal and paternal environmental influences; gene expression becomes altered by DNA methylation, histone modification, and noncoding RNA. At fertilization, global DNA methylation is erased so at the blastocyst stage (implantation) the genome is hypomethylated.[8] DNA methylation occurs in a specific manner so the trophectoderm (which becomes the placenta) remains relatively hypomethylated (50% to 70%) compared with the inner cell mass tissue (which becomes somatic human tissue). Genomic imprinting causes the silencing of one allele-specific copy of a gene. DNA methylation of imprinted genes occurs at the germ cell stage but is not involved in the methylation remodeling. Indeed, the human placenta exhibits extensive intraplacental mosaicism in an X-chromosome inactivation pattern. Individual placental cotyledons are derived from only a few cells, leading to cotyledon mosaicism. Even the process of *in vitro* fertilization produces an altered imprinted gene methylation pattern in the placenta.

Altered gene methylation has been linked to clinical disease states.[8] Increased long interspersed nuclear element-1 (*LINE1*) gene methylation is associated with early-onset preeclampsia. Compared with disease-free matched tissue, early-onset preeclampsia is associated with hypomethylation of 34 specific genes, whereas only 4 hypomethylated genes were associated with late-onset preeclampsia.[9] Thus, DNA and DNA regulatory changes influence not only early placental development but also the occurrence of pregnancy-associated disease.

Human studies have demonstrated fetal programming of childhood and adult disease. For example, a study showed that adults who were exposed *in utero* to episodes of malnutrition developed reduced glucose tolerance, atherogenic lipid profiles, and a doubled rate of cardiovascular diseases; these disease states were associated with hypomethylation of regulatory areas for insulin-like growth factor-2 and other genes.[2] *In utero* exposure to a high-fat diet can lead to an increased incidence of diabetes in offspring. Maternal stress during pregnancy can lead to infant neurodevelopmental disorders.[2]

The placenta grows dramatically from the third month of gestation until term, with a direct correlation between placental growth and fetal growth. By term, the mature placenta is oval and flat, with an average diameter of 18.5 cm, weight of 500 g, and thickness of 23 mm. At term, the human fetal-placental weight constitutes 6% of maternal weight. Placental weight increases 0.7% per day, with active fetal growth contributing up to 1.5% of fetal body mass per day.[10] The allocation of nutrient and metabolic resources for fetal growth potentially come at the expense of the mother. The growth of the placenta and fetus is influenced by maternal anabolic status, placental growth hormone, insulin-like growth factor-1, leptin, and glucocorticoids.[11] Whether maternal or fetal in origin, increased glucocorticoids signal adverse environmental conditions and result in reduced glucose and amino acid transfer to the fetus. Indeed, competition between mother and fetus for resource allocation has been termed the *kinship theory*, in which imprinted genes influence the balance of nutrient allocation in a context-specific manner.[11]

Comparative Anatomy

The placentas of different species differ greatly, beginning with their method of uterine attachment, which can include adhesion, interdigitation, and fusion. In addition, the number of tissue layers between the maternal and fetal circulations differ. The most commonly used placental categorization system, the Grossner classification, uses the number of tissue layers in the placental barrier to help differentiate species (Figure 4-2).[12]

The ability of the placenta to transfer various substances differs among species. The markedly thicker epitheliochorial placenta found in sheep, a species commonly used for placental transfer studies, has three maternal layers (epithelium, connective tissue, and endothelium) that separate maternal from fetal blood. By contrast, the human hemochorial placenta lacks these maternal layers, which allows maternal blood to bathe fetal tissues directly (see Figure 4-2). As a result, species

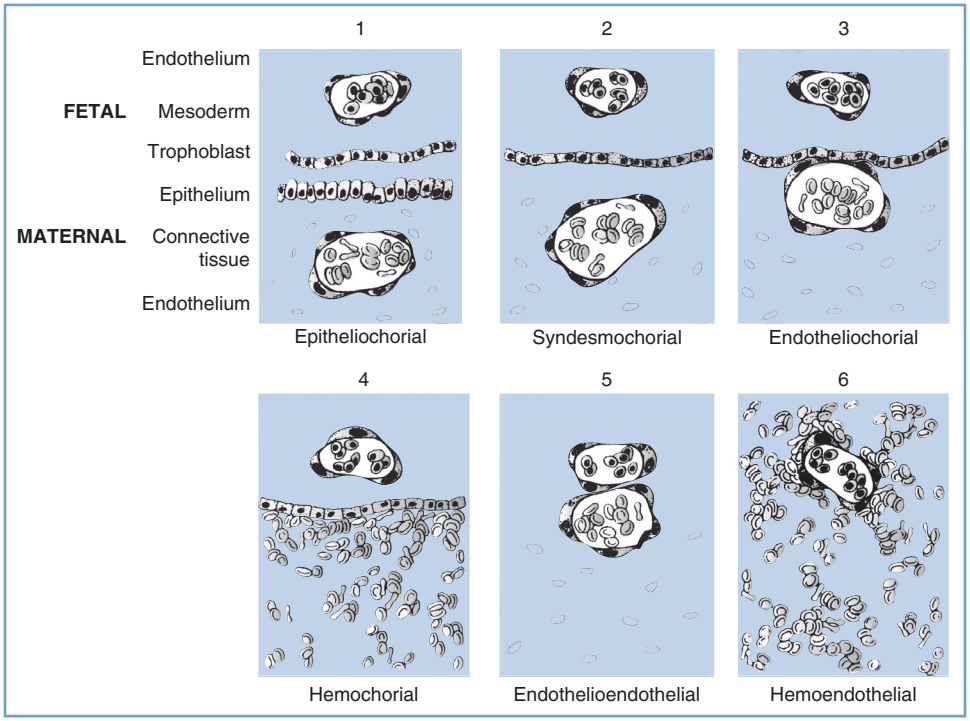

FIGURE 4-2 ■ Modification of Grossner's original classification scheme, showing the number and types of tissue layers between the fetal and maternal circulations. Examples of each are as follows: (1) epitheliochorial, sheep; (2) syndesmochorial, no known examples; (3) endotheliochorial, dogs and cats; (4) hemochorial, human and hamster; (5) endothelioendothelial, bandicoot (Australian opossum); and (6) hemoendothelial, Rocky Mountain pika. (Modified from Ramsey EM. The Placenta: Human and Animal. New York, Praeger Publishers, 1982.)

differ in the transfer of substances through the placenta; for example, fatty acids cannot cross through the placenta in sheep as they do in humans.[13] This wide diversity in placental structure and function among species makes extrapolation from animal investigations to clinical medicine tenuous.

Vascular Architecture

Maternal

Under the initial hormonal influences of the corpus luteum, the spiral arteries of the uterus become elongated and more extensively coiled. In the area beneath the developing conceptus, the compression and erosion of the decidua induces lateral looping of the already convoluted spiral arteries,[14] accessing the intervillous spaces. In late pregnancy, the growing demands of the developing fetus use approximately 200 spiral arteries that directly feed the placenta to handle a blood flow of approximately 600 mL/min.[14] The vasodilation required to accommodate this flow is the result of the replacement of the elastic and muscle components of the artery, initially by cytotrophoblast cells and later by fibroid cells. This replacement reduces the vasoconstrictor activity of these arteries and exposes the vessels to the dilating forces of the greater blood volume of pregnancy, especially at the terminal segments, where they form funnel-shaped sacs that enter the intervillous space.[14] The increased diameter of the vessels decreases blood velocity and reduces blood pressure.

The **intervillous space** is a large cavernous expanse that develops from the fusion of the trophoblastic lacunae and the erosion of the decidua by the expanding blastocyst, forming a huge blood sinus bounded by the chorionic plate and the decidua basalis (i.e., the maternal or basal plate). Folds in the basal plate form septa that separate the space into 13 to 30 anatomic compartments known as *lobules*. Each lobule contains numerous villous trees that are also known as *cotyledons* or *placentomes*. Although tightly packed with highly branched villous trees, the intervillous space of the mature placenta can accommodate approximately 350 mL of maternal blood.

Maternal arterial blood leaves the funnel-shaped spiral arteries and enters the intervillous space. The blood moves into the nearly hollow, low-resistance area, where villi are very loosely packed (the intercotyledonary space), before entering another region of densely packed intermittent and *terminal* villi (Figure 4-3).[15] The terminal villi represent the areas where placental exchange predominates. After passing through this dense region, maternal venous blood collects between neighboring villous trees in an area called the *perilobular zone*.[16] Collecting veins penetrate the maternal plate at the periphery of the villous trees to drain perilobular blood from the intervillous space.

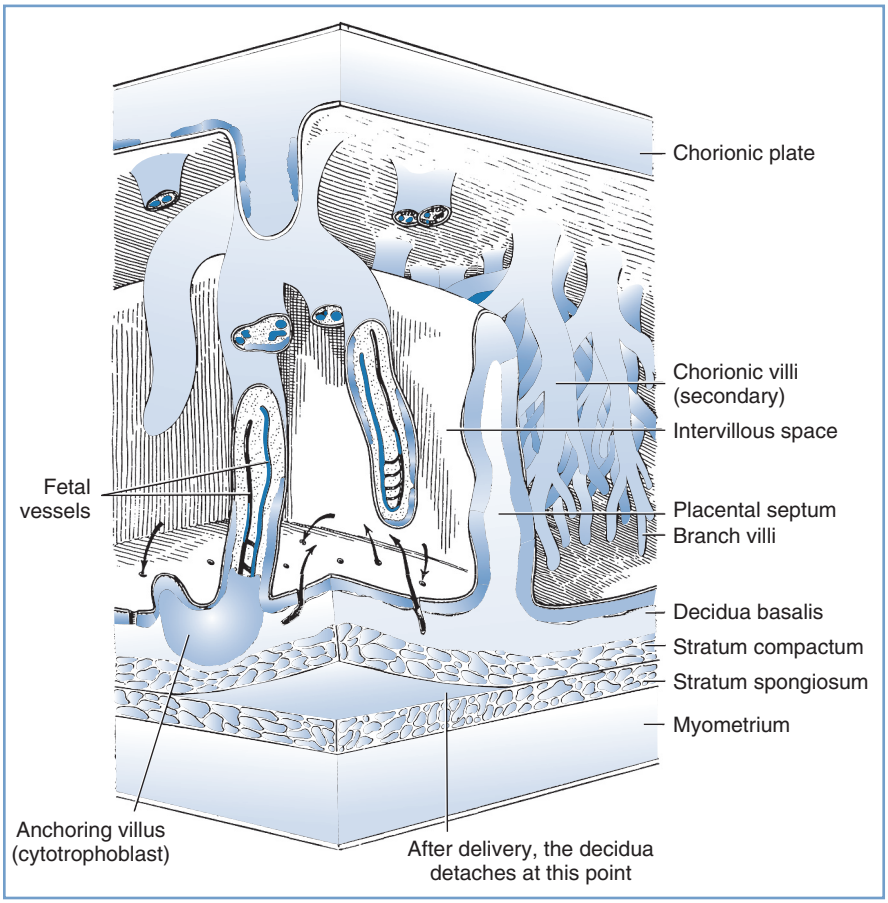

FIGURE 4-3 ■ The relationship between the villous tree and maternal blood flow. *Arrows* indicate the maternal blood flow from the spiral arteries into the intervillous space and out through the spiral veins. (Modified from Tuchmann-Duplessis H, David G, Haegel P. Illustrated Human Embryology. Volume 1. Embryogenesis. New York, Springer Verlag, 1972:73.)

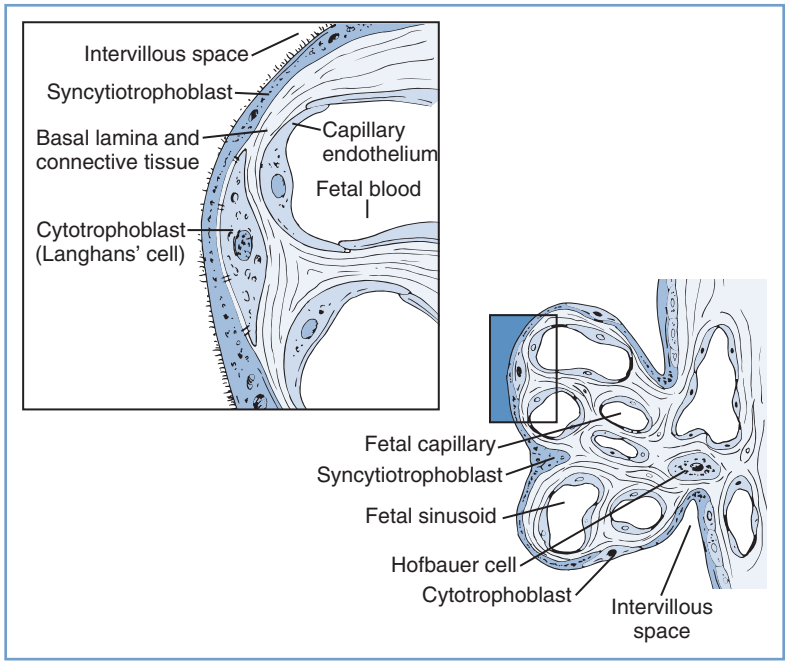

FIGURE 4-4 ■ *Left,* Cellular morphology of two terminal villi. *Right,* Higher magnification of the boxed region exhibiting the placental barrier between fetal and maternal blood. (Redrawn from Kaufmann P. Basic morphology of the fetal and maternal circuits in the human placenta. Contrib Gynecol Obstet 1985; 13:5-17.)

Fetal

Two coiled arteries bring fetal blood within the umbilical cord toward the placenta. On the placental surface, these arteries divide into **chorionic arteries** that supply the 50 villous trees located in the placental lobules. At the base of each villous tree, the chorionic arteries are considered the *main villous stem* or *truncal arteries* (first-order vessels), which in turn branch into four to eight *ramal* or *cotyledonary arteries* (second-order vessels); as they pass toward the maternal plate, they further subdivide into *ramulus chorii* (third-order vessels) and, finally, *terminal arterioles.* The terminal arterioles lead through a neck region into a bulbous enlargement where they form two to four narrow capillary loops. Here the large endothelial surface area and the near-absence of connective tissue allow optimal maternal-fetal exchange (Figure 4-4).[16,17]

The **venous end of the capillaries** loops, narrows, and returns through the neck region to the collecting venules, which coalesce to form the larger veins in the stem of the villous trees. Each villous tree drains into a large vein, which, as it perforates the chorionic plate, becomes a **chorionic vein.** All of the venous tributaries course toward the umbilical cord attachment site, where they empty into the one umbilical vein that delivers blood back to the fetus.

PHYSIOLOGY

Barrier Function

The placenta is an imperfect barrier that allows many substances to cross from the maternal to the fetal circulation and from the fetal to the maternal circulation. The rate and amount of placental transfer depend on the permeability and the ability of various mechanisms to restrict movement. A vast array of cytochrome P450 isoenzymes and transporters are found within the placenta; some of these are inducible, whereas others are constitutive. In addition, a number of substances undergo specific or nonspecific binding within the placental tissues, thereby minimizing fetal exposure to and accumulation of the substances. Finally, the thickness of the placental membranes, which diminishes as gestation progresses, may influence the rate of diffusion.[18] Of interest, the rate of transfer of certain substances (e.g., glucose, water) differs very little among species, even though the placental thickness varies greatly.[19]

Fetal cells have been detected in maternal circulation, before organogenesis and full maternal arterial perfusion of the placenta, and maternal cells have also been shown to enter the fetal circulation.[20] Maternal-fetal cell transfer may occur by disruption of the trophoblastic layer or by active adhesion and transmigration (similar mechanism to blood-brain barrier migration). Fetal cells may be pluripotent, and the DNA may be found in maternal organs for decades. Murine fetal progenitor cells have been found to migrate and assist with maternal wound healing.[21] These microchimeric fetal cells may contribute to maternal immunomodulation, development or worsening of autoimmune diseases (e.g., thyroiditis, lupus, and asthma), and healing of wounds, including neuronal tissue.[22] Indeed, placental exosomes, nanovesicles 30 to 100 nm in size found in maternal circulation that contain proteins and transcription-related materials, exert a maternal immunosuppressive effect. Placental microparticles, vesicular products of syncytiotrophoblast greater than 100 nm, also contain RNA and DNA fragments and affect fetal and maternal apoptosis, angiogenesis, and inflammation. An excess of microparticles has been observed in early-onset preeclampsia. The placenta and fetal-maternal interactions are certainly complex and worthy of further study.

Cell-free fetal DNA has been shown to be present in the plasma of pregnant women.[23] This discovery has facilitated the development of a range of noninvasive diagnostic investigations, including tests for fetal sex assessment, fetal rhesus D blood group genotyping, fetal chromosomal aneuploidy detection, and other genetic abnormalities.[24]

Hormonal Function

A sophisticated transfer of precursor and intermediate compounds in the maternal-fetal-placental unit allows placental enzymes to convert steroid precursors into estrogen and progesterone. This steroidogenic function of the placenta begins very early in pregnancy; by 35 to 47 days after ovulation, the placental production of estrogen and progesterone exceeds that of the corpus luteum (i.e., the ovarian-placental shift).[25]

The placenta also produces a wide array of enzymes, binding proteins, and polypeptide hormones. For example, the placenta produces human chorionic gonadotropin, human placental lactogen (a growth hormone also known as human chorionic somatomammotropin), and factors that control hypothalamic function.[25] This ability to produce proteins and steroid hormones allows the placenta to influence and control the fetal environment.[26]

Regulation of Placental Blood Flow

Maternal Blood Flow

The trophoblastic invasion and functional denervation of the musculoelastic lining of the spiral arteries may represent adaptive mechanisms to decrease vascular reactivity and promote vasodilation. These alterations allow the spiral arteries to vasodilate as much as 10 times their normal diameter, thereby lowering resistance for the passage of blood through the intervillous spaces.[27]

Maternal blood enters the intervillous cotyledon space at a pressure of 70 to 80 mm Hg in an area that has relatively few villi.[14] The pressure and velocity of blood flow rapidly diminishes to approximately 10 mm Hg as the blood passes into an area of higher resistance created by the densely packed villi of the placentome.[18]

Fetal Blood Flow

In contrast to maternoplacental blood flow, the gestational increases in fetoplacental blood flow primarily results from vascular growth rather than vasodilation of the villous beds. Fetal perfusion of the placenta is not classically autoregulated; the placental vasculature has no innervation by the sympathetic nervous system. However, the fetus can modulate fetoplacental perfusion in a number of ways: (1) via endocrine effects of adrenomedullin, (2) via net efflux/influx of water regulated by fetal blood pressure, and (3) via local autoregulatory effects mediated by the paracrine vasodilators nitric oxide and acetylcholine.[28,29] Adrenomedullin release by the fetal adrenal glands assists in maintenance of tone in placental vessels. Fetal blood pressure changes cause net influx/efflux of water across the placenta that affects fetal intravascular volume and perfusion. Maternal hyperglycemia[30] and hypoxemia[31] are examples of derangements that can alter regional fetal blood flow, probably through vascular mediators. Endothelium-derived relaxing factors, especially prostacyclin[32] and nitric oxide,[33] are important in the control of fetoplacental circulation. Hypoxia-induced fetoplacental vasoconstriction is mediated by a reduction in the basal release of nitric oxide.[34] This vasoconstrictor activity is functionally similar to that found in the lung (i.e., hypoxic pulmonary vasoconstriction) and allows optimal fetal oxygenation through redistribution of fetal blood flow to better-perfused lobules.[31] The placental vasculature constricts in response to graded hypoxia.[35]

Transport Mechanisms

Substances are transferred across the placenta by one of several mechanisms.

Passive Transport

The passive transfer of molecules across a membrane depends on (1) concentration and electrochemical differences across the membrane, (2) molecular weight, (3) lipid solubility, (4) degree of ionization, and (5) membrane surface area and thickness. This process requires no expenditure of cellular energy, with transfer driven principally by the concentration gradient across a membrane. Simple transmembrane diffusion can occur either through the lipid membrane (e.g., lipophilic molecules and water) or within protein channels that traverse the lipid bilayer (e.g., charged substances such as ions) (Figure 4-5).[36,37] Drugs with a molecular weight less than 600 daltons cross the placenta by passive diffusion.[38]

Facilitated Transport

Carrier-mediated adenosine triphosphate (ATP)–independent transport of relatively lipid-insoluble molecules down their concentration gradient is called *facilitated diffusion*.[36] Facilitated diffusion differs from simple diffusion in several ways. Specifically, this mode of transfer exhibits (1) saturation kinetics, (2) competitive and noncompetitive inhibition, (3) stereospecificity, and (4) temperature influences (e.g., a higher temperature results in greater transfer). With *simple diffusion*, the net rate of diffusion is proportional to the difference in concentration between the two sides of the membrane. This rate limitation is valid for facilitated diffusion only when transmembrane concentration differences are small. At higher concentration gradients, a maximum rate of transfer (V_{max}) is reached; thereafter, further increases in the concentration gradient do not affect the rate of transfer. The rate of transfer is determined by the number of membranous carrier protein complexes and the extent of interaction between the carrier and the substance undergoing transport.[37] An example of facilitated diffusion is the transplacental transfer of glucose.

A special type of facilitated diffusion involves the "uphill" transport of a molecule linked to another substance traveling down its own concentration gradient. As

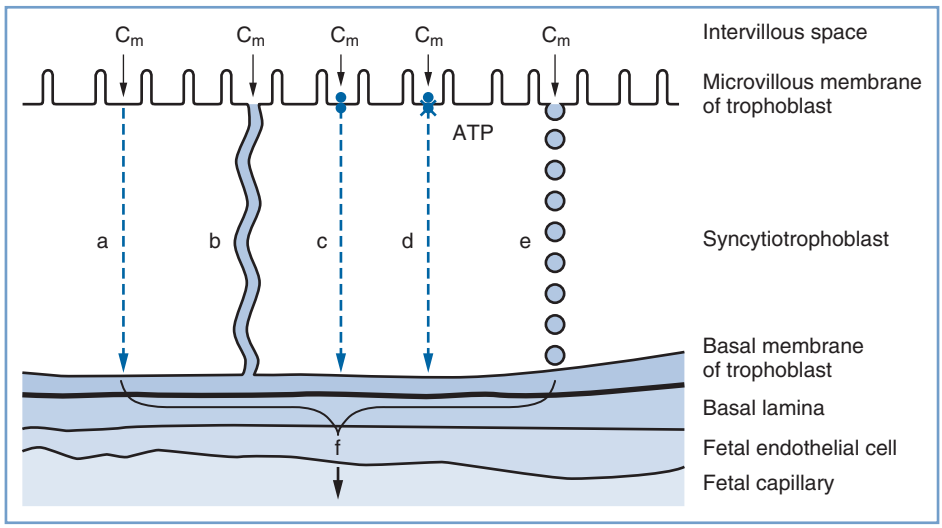

FIGURE 4-5 ■ The transfer mechanisms used for the transfer of substances across the placental barrier: *a*, simple diffusion; *b*, simple diffusion through channels; *c*, facilitated diffusion; *d*, active transport; *e*, endocytosis; *f*, substance available for transfer into fetal circulation; C_m, intervillous concentration of substance at the trophoblastic membrane. (Modified from Atkinson DE, Boyd RDH, Sibley CP. Placental transfer. In Neill JD, Plant TM, Pfaff DW, et al., editors. Knobil and Neill's Physiology of Reproduction. 3rd edition. St. Louis, Academic Press, 2006:2787-846.)

such, the transfer is not directly driven by cellular energy expenditure. In most cases, sodium is the molecule that facilitates transport. For the membrane-bound carrier to transfer these molecules, both molecules must be bound to the carrier. This hybrid system is called *secondary active transport* or *co-transport*.[37] The transplacental transport of amino acids appears to occur principally through secondary active transport. Transporters may be affected by disease states (e.g., preeclampsia) or signaling molecules (e.g., elevated steroid levels).[39]

Active Transport

Active transport involves the movement of any substance across a cell membrane; the process requires cellular energy. In general, active transport occurs against a concentration, electrical, or pressure gradient.

Like facilitated diffusion, active transport requires a protein membrane carrier that exhibits saturation kinetics and competitive inhibition.[36] However, unlike secondary active transport, the movement of a substance against its concentration gradient is directly linked to the hydrolysis of high-energy phosphate bonds of ATP. The best known example of primary active transport is the translocation of sodium and potassium through the sodium-potassium adenosine triphosphatase (Na^+/K^+ ATPase) pump.

Active transport proteins include P-glycoprotein, breast cancer resistance protein, multidrug resistance protein, and the sodium/multivitamin transporter, as well as the many proteins involved in monoamine transport and xenobiotics.[39] These transport proteins play an important role in protecting the fetus from foreign and potentially teratogenic compounds. Drugs may compete with endogenous compounds of similar shape and charge for active transport.[39] P-glycoprotein transports many lipophilic drugs and antibiotics and removes cytotoxic compounds from the fetus; it exists on the maternal side of the trophoblastic cell membrane of the placenta and prevents compounds such as methadone and saquinavir (a protease inhibitor) from leaving the maternal blood, thus limiting fetal exposure.[40] Inhibition of these transporter proteins (e.g., inhibition of P-glycoprotein by verapamil) can significantly increase the fetal transfer of certain drugs, including midazolam, which is a substrate for P-glycoprotein. DNA transcription of transporters may be induced by drugs or disease states. Expression of transporters may change with gestational age.[41]

Pinocytosis

Large macromolecules (e.g., proteins that exhibit negligible diffusion properties) can cross cell membranes via the process of pinocytosis (a type of endocytosis). Pinocytosis is an energy-requiring process in which the cell membrane invaginates around the macromolecule. Although the contents of pinocytotic vesicles are subject to intracellular digestion, electron microscopic studies have demonstrated that vesicles can move across the cytoplasm and fuse with the membrane at the opposite pole. This appears to be the mechanism by which immunoglobulin G is transferred from the maternal to the fetal circulation.[36]

Other Factors That Influence Placental Transport

Other factors that affect maternal-fetal exchange include (1) maternal and fetal blood flow, (2) placental binding, (3) placental metabolism, (4) diffusion capacity, (5) maternal and fetal plasma protein binding, and (6) gestational age (the placenta is more permeable in early pregnancy).[42] Lipid solubility, pH gradients between the maternal and fetal environments for certain basic drugs ("ion trapping"), and alterations in maternal or fetal plasma protein

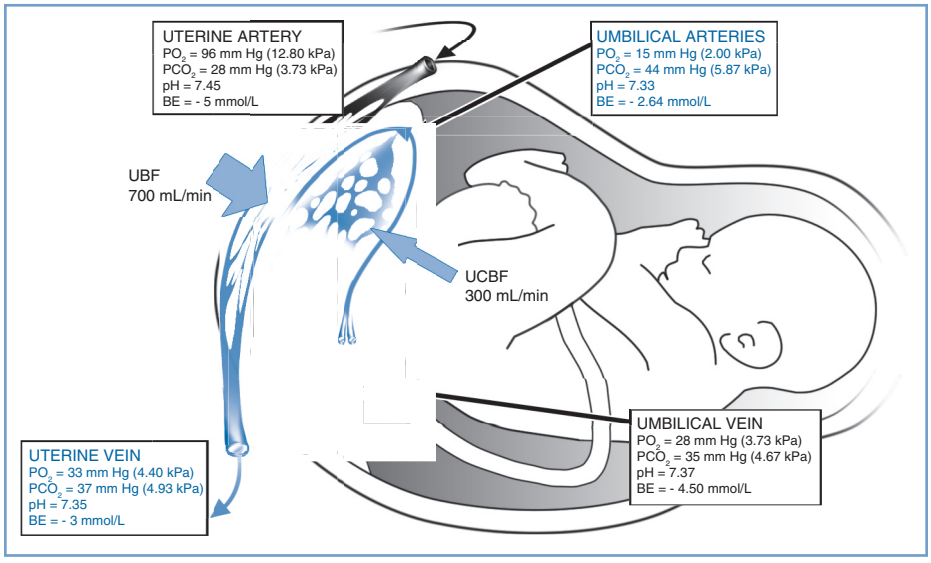

FIGURE 4-6 ■ The concurrent relationship between the maternal and fetal circulations within the placenta and the way this arrangement affects gas transfer. These values were obtained from patients' breathing room air during elective cesarean delivery. *BE,* base excess; *Po_2,* partial pressure of oxygen; *Pco_2,* partial pressure of carbon dioxide; *UBF,* uterine blood flow; *UCBF,* umbilical cord blood flow. (Blood gas data from Ramanathan S. Obstetric Anesthesia. Philadelphia, Lea & Febiger, 1988:27. Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

concentrations found in normal pregnancy[43] and other disease states (e.g., preeclampsia) may also alter placental transport.

Transfer of Respiratory Gases and Nutrients

Oxygen

Our knowledge of oxygen transfer physiology in the placenta is largely derived from the lung. The placenta must provide approximately 8 mL O_2/min/kg fetal body weight for fetal growth and development, while adults only require 3 to 4 mL O_2/min/kg at rest.[44] As the "lung" for the fetus, the placenta has only one fifth the oxygen transfer efficiency of the adult lung.[45] The human lung, with a surface area of 50 to 60 m^2 and a thickness of only 0.5 µm, has a very large oxygen diffusion capacity; in comparison, the placenta has a lower diffusion capacity because of its smaller surface area of 16 m^2 and a thicker membrane of 3.5 µm. Furthermore, 16% of uterine blood flow and 6% of umbilical blood flow are shunted through the placenta.[18]

Oxygen transfer across the placenta depends on the membrane surface area, membrane thickness, oxygen partial pressure gradient between maternal blood and fetal blood, affinity of maternal and fetal hemoglobin, and relative maternal and fetal blood flows. As physically dissolved oxygen diffuses across the villous membranes, bound oxygen is released by maternal hemoglobin in the intervillous space and diffuses across the placenta. Several factors affect the fetal blood Po_2 once it reaches equilibration in the villi end-capillaries. First, the concurrent and countercurrent arrangements of maternal and fetal blood flow play a key role for placental oxygen transfer in various species. The almost complete equilibration of maternal and fetal Po_2 values suggests that a concurrent (or parallel) relationship between maternal blood and fetal blood exists within the human placenta (Figure 4-6),[18,46] although others have described a multivillous, cross-current flow pattern.

Much of the literature in this area is based on animal studies. Because the functional anatomy of the placenta in many mammals involves more layers than the human placenta (e.g., the epitheliochorial placenta of the sheep has three layers), results of animal models can only provide evidence for trends, not values, in humans.

In humans, oxygen solubility is 10^{-4} M in plasma and 10^{-2} M in hemoglobin; thus, 99% of the oxygen content in blood is bound to hemoglobin. With an inspired oxygen fraction of 1.0, the maximum maternal arterial Po_2 was 425 mm Hg, but the fetal umbilical venous Po_2 was only 47 mm Hg, indicating a low diffusion capacity of oxygen across the placenta.[47] In addition, the placenta receives less than 50% of the fetal cardiac output, and blood returning from the placenta admixes with the nonoxygenated blood in the fetal inferior vena cava, thus limiting fetal arterial Po_2.

Although some have called the human placenta "diffusion limited" because of the decreased ability of oxygen to cross the intervillous membrane, the delivery of oxygen to the fetus is predominantly flow limited. Maternal delivery of blood (i.e., oxygen) to the uterus is the predominant factor controlling fetal oxygen transfer. The high fetal hemoglobin concentration (17 mg/dL) accounts for the large oxygen content and the net delivery of large quantities of oxygen to the fetus. Fetal hemoglobin has a higher oxygen affinity and therefore a lower partial pressure at which it is 50% saturated (P_{50}: 18 mm Hg) than maternal hemoglobin (P_{50}: 27 mm Hg). This gradient produces a "sink" effect that enhances oxygen uptake by

fetal red blood cells, keeping fetal Po_2 lower and promoting the transfer of additional oxygen across the placenta (see Figure 5-7). The **Bohr effect** also augments the transfer of oxygen across the placenta. Specifically, fetal-maternal transfer of carbon dioxide makes maternal blood more acidic and fetal blood more alkalotic. These alterations of pH cause shifts in the maternal and fetal oxyhemoglobin dissociation curves, further enhancing the maternal oxygen transfer to the fetus in what is termed the "double" Bohr effect. This accounts for 2% to 8% of the transplacental transfer of oxygen.[48]

The placenta normally has a 50% reserve for changes in maternal or fetal blood flow by increasing venous extraction, a mechanism similar to that in adults. Based on umbilical venoarterial difference, human fetal oxygen uptake at term is 0.25 mmol/kg/min.[49] The metabolic activity of the placenta itself consumes up to 40% of the oxygen uptake. Placental oxygen consumption is stable even with changes in maternal blood pressure and Po_2; 30% of placental oxygen is used for protein synthesis and almost 30% for Na^+/K^+ ATPase. The human placenta has a villous structure, which may be an adaptation for greater maternal flow and thus oxygen delivery, but at the expense of a smaller surface area and cross-current exchange mechanism.[50] However, the placenta does change in response to chronic hypoxia found at high altitudes, with an increased capillary volume and decreased capillary thickness providing a near-doubling of the oxygen diffusion capacity.[51]

Carbon Dioxide

The transfer of CO_2 occurs through a number of different forms, including dissolved CO_2, carbonic acid (H_2CO_3), bicarbonate ion (HCO_3^-), carbonate ion (CO_3^{2-}), and carbaminohemoglobin. Equilibrium between CO_2 and HCO_3^- is maintained by a reaction catalyzed by carbonic anhydrase in red blood cells. The Pco_2 gradient between fetal and maternal blood (i.e., 40 versus 34 mm Hg, respectively) drives fetal-maternal transfer. Carbon dioxide is 20 times more diffusible than oxygen and readily crosses the placenta,[52] although dissolved CO_2 is the form that actually crosses. The rapid movement of CO_2 from fetal capillary to maternal blood invokes a shift in the equilibrium of the carbonic anhydrase reaction **(La Chatelier's principle)** that produces more CO_2 for diffusion. The transfer of CO_2 is augmented further by the production of deoxyhemoglobin in the maternal blood, which has a higher affinity for CO_2 than oxyhemoglobin (the **Haldane effect**). The resulting affinity may account for as much as 46% of the transplacental transfer of carbon dioxide.[46] Although a significant fetal-maternal concentration gradient exists for HCO_3^-, its charged nature impedes its transfer and contribution to CO_2 transport except as a source for CO_2 production through the carbonic anhydrase reaction.[53]

Glucose

Simple diffusion alone cannot account for the amount of glucose required to meet the demands of the placenta and fetus. To assist the movement of glucose down its concentration gradient, stereospecific-facilitated diffusion systems have been described with glucose transporters such as GLUT1 and GLUT3; the system is independent of insulin, a sodium gradient, or cellular energy.[54] Insulin does not cross the placenta; however, insulin receptors in the maternal side of the syncytiotrophoblast regulate nutrient transport through a signaling cascade involving the mammalian target of rapamycin complex (mTORC). Nutrient sensors for glucose, amino acids, oxygen, cytokines, growth factors, and energy levels stimulate mTORC1, a key sensing and signaling protein in the syncytiotrophoblast that regulates nutrient transport and growth.[55]

Amino Acids

Concentrations of amino acids are highest in the placenta, followed by umbilical venous blood and then maternal blood. The maternal-fetal transplacental transfer of amino acids is an active process that occurs principally through a linked translocation with sodium. The energy required for this transfer comes from the large sodium gradient established by the Na^+/K^+ ATPase pump, resulting in increased intracellular concentrations of amino acids, which then "leak" down their gradients into the fetal circulation. This transport mechanism may not apply to all amino acids and may be susceptible to inhibitors. Transport also occurs via transport exchangers of amino acids on both maternal and fetal sides of the placenta as well as facilitated diffusion. Pregnancies with fetal growth restriction (also known as intrauterine growth restriction) have reduced amino acid transport with an inability to increase transport in spite of higher maternal levels of essential amino acids than occur in healthy pregnancies.[56]

Fatty Acids

Free fatty acids readily cross the human, but not ovine, placenta. The essential fatty acids, linoleic and alpha-linolenic acid, must be transferred across the placenta. Lipid transfer to the fetus reaches a peak of 7 g/day at term. The placental basal membrane has specific binding sites for very low-density, low-density, and high-density lipoproteins. Lipase activity in the placenta is responsible for converting triglycerides to nonessential fatty acids. The placenta does not elongate fatty acid chains, whereas the fetus does. Fatty acid transport occurs primarily by simple diffusion; however, fatty acid–binding proteins (FABPpm, FAT/CD36, and FATP), which facilitate transport, have been discovered. Nonessential fatty acids are albumin bound and may displace other protein-bound substances.[57]

DRUG TRANSFER

Placental permeability and pharmacokinetics determine the fetal exposure to maternal drugs. Animal models (e.g., pregnant ewes, guinea pigs) have been used to assess the placental transport of drugs; however, interspecies differences in placental anatomy and physiology limit the

application of these data to humans.[58] Human placental transport mechanisms have been studied in placental slices, isolated villi, membrane vesicles, homogenates, and tissue culture cells. The direct application of these data, however, is in question because these methods do not account for the dual (i.e., maternal and fetal) perfusion of the intact placenta *in situ*.[58]

The inaccessibility of the placenta *in situ* and concerns for maternal and fetal safety have limited direct studies of the placenta in humans. Data regarding the transplacental transfer of anesthetic agents have been extrapolated primarily from single measurements of drug concentrations in maternal and umbilical cord blood samples obtained at delivery. Most studies have reported fetal-to-maternal (F/M) ratios of drug concentration. In these studies, the umbilical vein blood concentration represents the fetal blood concentration of the drug. Maternal and fetal concentrations of a drug are influenced by drug metabolism in the mother, the placenta, and the fetus and also by changes during delivery (e.g., altered uteroplacental blood flow).[58]

A dual-perfused, *in vitro* human placental model has been developed to allow for the independent perfusion of the maternal and fetal sides of the placenta and thereby investigate maternal-fetal (or fetal-maternal) transport.[58] Equilibration studies (i.e., recirculating maternal and fetal perfusates) using this model are not directly applicable to the placenta *in vivo*. However, when a nonrecirculating design is used, steady-state drug clearance can be determined for either direction (maternal to fetal *or* fetal to maternal) and may have direct clinical application. This method has been used to assess the placental transfer of anesthetic agents (e.g., thiopental,[59] methohexital,[60] propofol,[61] bupivacaine,[62] ropivacaine,[63] alfentanil,[64] and sufentanil[65,66]). Transfer across the placenta may be reported as drug clearance or as a ratio referred to as the **transfer index** (i.e., drug clearance/reference compound clearance). The use of a transfer index allows for interplacental comparisons by accounting for differences between placentas (e.g., lobule sizes). Commonly used reference compounds are either flow limited (e.g., antipyrine, tritiated water) or membrane limited (e.g., creatinine). These studies have enhanced our understanding of the placental transfer of anesthetic drugs (Box 4-1).

BOX 4-1 Transplacental Transfer of Anesthetic Drugs

Drugs That Readily Cross the Placenta

- Anticholinergic agents
  - Atropine
  - Scopolamine
- Antihypertensive agents
  - Beta-adrenergic receptor antagonists
  - Nitroprusside
  - Nitroglycerin
- Benzodiazepines
  - Diazepam
  - Midazolam
- Induction agents
  - Propofol
  - Ketamine
  - Etomidate
  - Thiopental
- Inhalation anesthetic agents
  - Halothane
  - Isoflurane
  - Sevoflurane
  - Desflurane*
  - Nitrous oxide
- Local anesthetics
- Opioids
- Vasopressor
  - Ephedrine

Drugs That Do Not Readily Cross the Placenta

- Anticholinergic agent
  - Glycopyrrolate
- Anticoagulants
  - Heparin
- Muscle relaxants
  - Depolarizing: succinylcholine
  - Nondepolarizing agents
- Vasopressor
  - Phenylephrine

*Experimental data for desflurane are lacking but, based on physical characteristics similar to other halogenated anesthetics, placental transfer is assumed.

Pharmacokinetic Principles

Factors affecting drug transfer across the human placenta include lipid solubility, protein binding, tissue binding, pKa, pH, and blood flow (Table 4-1). High lipid solubility may readily enable cell membrane (lipid bilayer) penetration but may also cause the drug (e.g., sufentanil) to be trapped within the placental tissue.[66] Highly protein-bound drugs are affected by the concentration of maternal and fetal plasma proteins, which varies with gestational age and disease. Some drugs (e.g., diazepam) bind to albumin, whereas others (e.g., sufentanil, cocaine) bind predominantly to α_1-acid glycoprotein (AAG) (Table 4-2). Although the free, unbound fraction of drug equilibrates across the placenta, the total drug concentration is greatly affected by both the extent of protein binding and the quantity of maternal and fetal proteins; fetal blood typically contains less than half the concentration of AAG than maternal blood.[67] One study of the placental transfer of sufentanil *in vitro* noted different results when fresh frozen plasma, rather than albumin, was used as a perfusate. Albumin binds primarily acidic and lipophilic compounds, whereas AAG binds more basic compounds. Indeed, the fetal levels of both albumin and AAG increase from first trimester to term.[68]

The pKa of a drug determines the fraction of drug that is non-ionized at physiologic pH. Thus, fetal acidemia greatly enhances the maternal-fetal transfer (i.e., "ion trapping") of many basic drugs, such as local anesthetics and opioids (Figure 4-7) (see Chapter 13).[69] Most anesthetic drugs are passively transferred, with the rate of blood flow (hence drug delivery) affecting the amount of drug that crosses the placenta.[70] One of the authors (M.I.Z.) has used the *in vitro* perfused human placenta model to perform a number of studies of the placental transfer of opioids (Table 4-3).

TABLE 4-1 Factors Affecting Placental Transfer of Drug (Maternal to Fetal)

	Increased Transfer	Decreased Transfer
Size: molecular weight (Da)	<1000	>1000
Charge of molecule	Uncharged	Charged
Lipid solubility	Lipophilic	Hydrophilic
pH versus drug pKa*	Higher proportion of un-ionized drug in maternal plasma	Higher proportion of ionized drug in maternal plasma
Placental efflux transporter† proteins (e.g., P-glycoprotein)	Absent	Present
Binding protein type	Albumin (lower binding affinity)‡	α_1-Acid glycoprotein (AAG) (higher binding affinity)
Free (unbound) drug fraction	High	Low

Da, dalton.
*The pH relative to the pKa determines the amount of drug that is ionized and un-ionized in both maternal and fetal plasma. Fetal acidemia enhances the maternal-to-fetal transfer (i.e., "ion trapping") of basic drugs such as local anesthetics and opioids.
†The efflux transporter pumps substances in a fetal-to-maternal direction.
‡*Note:* albumin concentration is higher in the fetus, and AAG concentration is higher in the maternal circulation.

TABLE 4-2 Concentrations of Proteins That Bind Drugs

	Maternal	Umbilical Cord
Albumin	33.1 g/L	37.1 g/L*
Alpha$_1$-acid glycoprotein (AAG)	0.77 g/L	0.26 g/L*

*$P < .05$.
Data from Sudhakaran S, Rayner CR, Li J, et al. Differential protein binding of indinavir and saquinavir in matched maternal and umbilical cord plasma. Br J Clin Pharmacol 2006; 63:315-21.

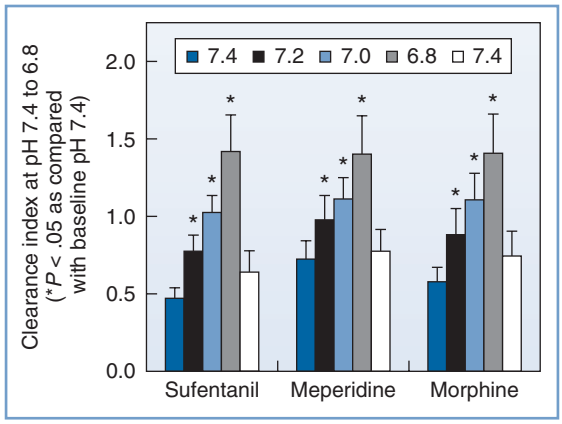

FIGURE 4-7 ■ The effects of changes in fetal pH on the transfer of opioids during *in vitro* perfusion of the human placenta. This figure demonstrates the "ion trapping" of opioids, which is similar to that of local anesthetics. Clearance index = clearance drug/clearance creatinine (a reference compound). (Modified from Zakowski MI, Krishna R, Grant GJ, Turndorf H. Effect of pH on transfer of narcotics in human placenta during in vitro perfusion. Anesthesiology 1995; 85:A890.)

TABLE 4-3 Opioid Transfer during *In Vitro* Perfusion of the Human Placenta

	Morphine	Meperidine	Alfentanil	Fentanyl	Sufentanil
Lipid solubility	1.4	39	129	816	1727
Percent non-ionized at pH 7.4	23%	7.4%	89%	8.5%	20%
Percent protein binding	30%	70%	93%	84%	93%
Placenta drug ratio	0.1	0.7	0.53	3.4	7.2
F/M ratio, MTF	0.08	0.27	0.22	0.19	0.14
F/M ratio, FTM	0.08	0.13	0.11	0.08	0.18
Minutes to steady state	30	20	20	40-60	40-60
Clearance index, MTF	0.4	0.95	0.75	0.76	0.41
Clearance index, FTM	0.5	0.91	0.78	0.61	0.76

Clearance index, clearance drug/clearance antipyrine (a flow-limited reference compound); *FTM,* fetal-to-maternal (direction); *MTF,* maternal-to-fetal (direction); *placenta drug ratio,* placenta drug concentration/g placental tissue/maternal drug concentration.
Data from non-recirculated experiments, using perfusate Media 199 without protein, with maternal flow 12 mL/min and fetal flow 6 mL/min.[64,66,102,105,110]

Inhalation Anesthetic Agents

The lipid solubility and low molecular weight of inhalation anesthetic agents facilitate rapid transfer across the placenta. A prolonged induction-to-delivery interval results in lower Apgar scores.[71]

When administered during cesarean delivery, **halothane** is detectable in both umbilical venous blood and arterial blood within 1 minute. Even with a relatively short induction-to-delivery time, an F/M ratio of 0.71 to 0.87 is established.[72,73] **Isoflurane** distributes rapidly across the placenta during cesarean delivery, resulting in an F/M ratio of approximately 0.71.[73] **Sevoflurane** has an F/M ratio of 0.38, similar to that of other inhaled agents.[74] Sevoflurane causes a dose-dependent vasodilation of the placental vessels that is not mediated by nitric oxide.[75] To our knowledge, there are no published data regarding the placental transfer of **desflurane.**

Nitrous oxide also rapidly crosses the placenta, with an F/M ratio of 0.83 within 3 minutes.[76] Maternal administration of nitrous oxide decreases fetal central vascular resistance by 30%,[77] and a prolonged induction to delivery interval may cause neonatal depression. Diffusion hypoxia may occur during the rapid elimination of nitrous oxide from the neonate; supplemental oxygen for any neonate exposed to nitrous oxide immediately before delivery appears prudent.

Induction Agents

The lipophilic characteristics that make anesthetic agents ideal for the induction of anesthesia also enhance their transfer across the placenta. The understanding of the transplacental transfer of these drugs is better than for any other group of anesthetic agents.

Propofol

A 2- to 2.5-mg/kg bolus dose of propofol, the most widely used induction agent for general anesthesia, results in a mean F/M ratio between 0.65 and 0.85.[78-80] A bolus dose of 2 mg/kg followed by a continuous infusion of 6 mg/kg/h or 9 mg/kg/h of propofol resulted in mean F/M ratios of 0.50 and 0.54, respectively.[81] These F/M ratios are similar to those found when propofol is given in early gestation (at 12 to 18 weeks).[82] Propofol may have sedative effects on the neonate; in a randomized trial of propofol compared with thiopental for the induction of anesthesia for elective cesarean delivery, the maternal administration of propofol (2.8 mg/kg) resulted in lower 1- and 5-minute Apgar scores than thiopental (5 mg/kg).[83] Plasma levels of propofol in the neonate depend on the maternal dose and the time elapsed between drug administration and delivery of the neonate. In one study, when delivered within 10 minutes of induction, neonates whose mothers were given propofol (2 mg/kg) had an average umbilical vein propofol concentration of 0.32 μg/mL.[84]

Several factors that affect propofol transfer have been investigated with *in vitro* human placental perfusion models.[85-87] Increased maternal blood flow and reduced protein binding increase both placental tissue uptake and transplacental transfer of propofol.[81] Propofol is highly protein bound to albumin. Thus, altered albumin concentrations in mother or fetus will affect transplacental transfer and the total, but not free, concentration in umbilical vein.[87] Propofol causes calcium channel-dependent vasodilation of human placental vessels *in vitro.*[88]

Ketamine

Ketamine, a phencyclidine derivative, rapidly crosses the placenta. Ketamine 2 mg/kg reached a mean F/M ratio of 1.26 in as little as 97 seconds when administered to the mother for vaginal delivery.[89] In a sheep study, fetal concentration was 25% less than maternal concentration at 10 minutes.[90]

Etomidate

Etomidate, a carboxylated imidazole, has long been used for the induction of general anesthesia in obstetric patients. A dose of 0.3 to 0.4 mg/kg administered for cesarean delivery resulted in an F/M ratio of approximately 0.5,[91] which is similar to the ratio found in sheep.[92]

Barbiturates

Previously a popular agent for the induction of general anesthesia in parturients, **thiopental** is the most extensively studied barbiturate. An extremely short-acting agent, it quickly appears in umbilical venous blood after maternal injection, with a mean F/M ratio between 0.4 and 1.1.[93,94] The high F/M ratios suggest that thiopental is freely diffusible; however, there is wide intersubject variability in umbilical cord blood concentration at delivery. Both maternal-fetal and fetal-maternal transfer of thiopental are strongly influenced by maternal and fetal protein concentrations.[59]

The rapid transfer of the oxybarbiturate **methohexital** into the fetal circulation, with simultaneous peak concentrations in maternal blood and fetal blood, has been demonstrated by *in vivo* studies.[95] Human *in vitro* placental perfusion studies in which the concentration of albumin was equal in the maternal and fetal perfusates confirm that methohexital rapidly crosses the placenta in both maternal-to-fetal and fetal-to-maternal directions, with transfer indices of less than 0.5 at 30 minutes.[60]

Dexmedetomidine

In humans, **dexmedetomidine**, an α_2-adrenergic agonist, has an F/M ratio of 0.12, with evidence of significant placental tissue binding due to high lipophilicity.[96] At 10 minutes, fetal concentration of medetomidine was about 28% less than maternal concentration in the sheep model.[90]

Benzodiazepines

Highly un-ionized, lipophilic, and 95% protein-bound **diazepam** is associated with an F/M ratio of 1 within

minutes of maternal administration and a ratio of 2 at 60 minutes after maternal administration.[97] Less lipophilic, **lorazepam** requires almost 3 hours after administration for the F/M ratio to reach unity.[98] **Midazolam** is more polar, with an F/M ratio of 0.76 at 20 minutes after administration. The F/M ratio of midazolam, unlike that of other benzodiazepines, decreases rapidly; by 200 minutes it is only 0.3.[99]

Opioids

Meperidine has been associated with neonatal central nervous system and respiratory depression. Intravenous administration results in rapid transfer across the human placenta within 90 seconds after maternal administration.[100] F/M ratios for meperidine may exceed 1.0 after 2 to 3 hours; maternal levels fall more rapidly than fetal levels because of the mother's greater capacity for metabolism of the drug.[101] This same time interval is associated with the greatest likelihood of neonatal depression, in part because of the active drug metabolite normeperidine. Human placental perfusion studies *in vitro* have demonstrated rapid placental transfer in both maternal-to-fetal and fetal-to-maternal directions with equal clearance profiles, minimal placental tissue binding, and no placental drug metabolism.[102] As maternal levels fall, the meperidine and normeperidine will transfer from the fetus back to the mother, correlating with the clinically observed decrease in neonatal sedation 4 hours after maternal administration.

Morphine also rapidly crosses the placenta. One study demonstrated a mean F/M ratio of 0.61, a mean umbilical venous blood concentration of 25 ng/mL, and a significant reduction in the biophysical profile score (primarily as a result of decreased fetal breathing movements and fewer fetal heart rate accelerations) within 20 to 30 minutes of maternal administration.[103] Intrathecal administration of morphine results in a high F/M ratio (0.92), although the absolute fetal concentrations are less than those associated with fetal and neonatal side effects.[104] Human placental perfusion studies *in vitro* have demonstrated that morphine, which is a hydrophilic compound, exhibits membrane-limited transfer with a low placental tissue content and a fast washout.[105] Concurrent naloxone administration does not affect the placental transfer of morphine.[106]

Fentanyl and its analogues are administered via the epidural, intrathecal, and intravenous routes. Fentanyl has a high lipophilicity and albumin binding (74%).[107] Maternal epidural administration results in an F/M ratio between 0.37 and 0.57.[108] During early pregnancy, fentanyl is rapidly transferred and may be detected not only in the placenta but also in the fetal brain.[109] Perfusion of the human placenta *in vitro* results in rapid transfer in both maternal-to-fetal and fetal-to-maternal directions, with the placenta acting as a moderate drug depot.[110,111]

Despite a relatively low F/M ratio (0.30),[112] maternal administration of **alfentanil** has been associated with a reduction of 1-minute Apgar scores when administered to the mother immediately before the induction of anesthesia.[113] Perfusion of the human placenta *in vitro* shows rapid and symmetric maternal-fetal and fetal-maternal transfers of alfentanil, with low placental drug uptake and rapid washout.[64]

Maternal administration of **sufentanil** results in a high F/M ratio, 0.81. Compared with fentanyl, sufentanil has higher lipid solubility and more rapid uptake by the central nervous system, resulting in less systemic absorption from the epidural space; lower maternal and umbilical vein concentrations reduce fetal exposure and the associated potential risk for neonatal respiratory depression.[108] Human placental perfusion studies *in vitro* have confirmed the rapid transplacental transfer of sufentanil, which is influenced by differences in maternal and fetal plasma protein binding and fetal pH. High placental tissue uptake suggests that the placenta serves as a drug depot.[65,66]

Remifentanil undergoes rapid placental transfer. During cesarean delivery, average F/M ratios were 0.88 when remifentanil was administered by intravenous infusion (0.1 μg/kg/min) during epidural anesthesia[114] and 0.73 when it was given as a single bolus (1 μg/kg) at induction of general anesthesia.[115] Excessive maternal sedation without adverse neonatal effects has been reported with the use of remifentanil during labor; presumably, the rapid metabolism of remifentanil by nonspecific esterases (context-sensitive half-time of 3 minutes) results in minimal fetal exposure.[116] When remifentanil was used for patient-controlled analgesia during labor, bolus doses of 0.5 μg/kg resulted in an F/M ratio of approximately 0.5 and a 20% incidence of fetal heart rate changes.[117] With continuous infusion of 0.33 μg/kg/min, the F/M ratio in plasma rapidly reached 0.1 to 0.3 in sheep.[116]

The systemic administration of an opioid agonist/antagonist for labor analgesia has been associated with few maternal, fetal, and neonatal side effects. Both **butorphanol** and **nalbuphine** rapidly cross the placenta, with mean F/M ratios of 0.84 and 0.74 to 0.97, respectively.[118,119] In one study, maternal administration of nalbuphine resulted in "flattening" of the fetal heart rate tracing in 54% of cases.[119]

Local Anesthetics

Local anesthetic agents readily cross the placenta (see Chapter 13). The enantiomers of bupivacaine cross the placenta at the same rate as racemic bupivacaine.[120]

Muscle Relaxants

As fully ionized, quaternary ammonium salts, muscle relaxants do not readily cross the placenta; however, single doses of muscle relaxants can result in detectable fetal blood concentrations. Maternal administration of muscle relaxants for the induction of general anesthesia for cesarean delivery rarely affects neonatal muscle tone at delivery.

After a standard induction dose, **succinylcholine** is not detectable in umbilical venous blood at delivery; maternal doses larger than 300 mg are required before the drug can be detected.[121] Neonatal neuromuscular blockade can occur when high doses are given repeatedly

or when both the parturient and fetus are homozygous for atypical pseudocholinesterase deficiency.[122]

The administration of nondepolarizing muscle relaxants results in low F/M ratios: 0.19 to 0.26 for **pancuronium,**[123-125] 0.06 to 0.11 for **vecuronium,**[125,126] 0.16 for **rocuronium,**[127] and 0.07 for **atracurium.**[128] The F/M ratio may be the result of expedient fetal/neonatal blood sampling; in a study in rats, the F/M ratio of vecuronium nearly doubled as the induction-to-delivery interval increased from 180 to 420 seconds.[126] No published study has investigated the placental transfer of the atracurium isomer **cisatracurium.** However, laudanosine, a metabolite of atracurium and cisatracurium, has an F/M ratio of 0.14.[129]

Although nondepolarizing muscle relaxant transfer rates are low, the fetal blood concentrations increase over time.[126] Fetal blood concentrations of nondepolarizing muscle relaxants can be minimized by giving succinylcholine to facilitate intubation, followed by a nondepolarizing muscle relaxant to maintain paralysis.[124]

Anticholinergic Agents

The placental transfer rate of anticholinergic agents directly correlates with their ability to cross the blood-brain barrier. **Atropine** is detected in the umbilical circulation within 1 to 2 minutes of maternal administration, and an F/M ratio of 0.93 is attained at 5 minutes.[130] **Scopolamine** also crosses the placenta easily; intramuscular administration results in an F/M ratio of 1.0 within 55 minutes.[131] By contrast, **glycopyrrolate** is poorly transferred across the placenta, with maternal intramuscular administration resulting in a mean F/M ratio of only 0.22.[132] Maternal intravenous administration of glycopyrrolate does not result in a detectable fetal hemodynamic response, whereas atropine and scopolamine may directly increase fetal heart rate.

Anticholinesterase Agents

Neostigmine, **pyridostigmine**, and **edrophonium** are quaternary ammonium compounds that are ionized at physiologic pH and consequently undergo limited transplacental transfer.[133] For example, maternal administration of neostigmine does not reverse atropine-induced fetal tachycardia. However, small amounts of these agents do cross the placenta, and fetal bradycardia after maternal administration of neostigmine and glycopyrrolate has been reported.[134] Because neostigmine may cross the placenta to a greater extent than glycopyrrolate, the combination of neostigmine and atropine should be considered for the reversal of nondepolarizing muscle relaxants in pregnant patients.[134] **Physostigmine** crossed the placenta in 9 minutes and reversed the fetal heart rate effect of scopolamine.[135]

Antihypertensive Agents

Beta-adrenergic receptor antagonists have been commonly used as antihypertensive agents in pregnancy, despite early investigations noting an association with fetal growth restriction and neonatal bradycardia, hypoglycemia, and respiratory depression.[136] Although a single dose of **propranolol** administered 3 hours before cesarean delivery has been shown to lead to an F/M ratio of 0.26,[137] long-term administration during pregnancy results in F/M ratios greater than 1.0.[138] Maternal administration of **atenolol** and **metoprolol** leads to mean F/M ratios of 0.94 and 1.0, respectively.[139,140]

Labetalol, the most commonly used antihypertensive during pregnancy, has a low F/M ratio of 0.38 with long-term oral administration, despite reports of mild neonatal bradycardia.[141,142] National data from Denmark showed that use of beta-adrenergic receptor antagonists during pregnancy, including labetalol, approximately doubles the risk for small-for-gestational-age preterm births and for perinatal mortality, even after adjusting for preeclampsia.[143] Preterm hypertensive women receiving labetalol had no acute change in umbilical artery or fetal middle cerebral resistance indices of flow.[144]

The ultra-short-acting beta-adrenergic receptor antagonist **esmolol** has been used to attenuate the hypertensive response to laryngoscopy and intubation. A mean F/M ratio of 0.2 after maternal administration of esmolol was observed in gravid ewes.[145] However, a few cases of significant and prolonged fetal bradycardia requiring the performance of emergency cesarean delivery have been reported.[146]

Clonidine and **methyldopa** act through the central stimulation of α_2-adrenergic receptors; studies have reported mean F/M ratios of 0.89[147] and 1.17,[148] respectively, for these agents. In concentrations likely to be present in maternal blood during clinical use, **magnesium** and **nifedipine**, but not clonidine, produce fetal vasodilation in human placental perfusion studies *in vitro*.[149] **Phenoxybenzamine**, an alpha-adrenergic receptor antagonist, is commonly used to treat hypertension in patients with pheochromocytoma and has an F/M ratio of 1.6 with long-term maternal administration.[150]

Direct-acting vasodilators are used for short-term management of severe hypertension in pregnant women. Administration of **hydralazine**, which is often given to lower blood pressure in preeclampsia, results in an F/M ratio of 1.0[151] and causes fetal vasodilation in *in vitro* studies.[152] Hydralazine increased the umbilical artery resistance index, indicating vasodilation, in hypertensive women.[144]

Sodium nitroprusside is lipid soluble, rapidly crosses the placenta, and can produce cyanide as a byproduct.[153] Sodium thiosulfate, the agent used to treat cyanide toxicity, does not cross the placenta in gravid ewes; it can be used to treat fetal cyanide toxicity by lowering maternal cyanide levels, thereby enhancing fetal-maternal transfer of cyanide.[154]

Glyceryl trinitrate (nitroglycerin) crosses the placenta to a limited extent, with an F/M ratio of 0.18, and results in minimal changes in fetal umbilical blood flow, blood pressure, heart rate, and blood gas measurements in gravid ewes.[155] However, dinitrate metabolites found in both maternal and fetal venous blood indicate the capacity for placental biotransformation.[156] Indeed, placental tissue production of nitric oxide enhances the uterine relaxation caused by nitroglycerin *in vivo*.[157] In one *in vitro* study, in which prostaglandin $F_{2\alpha}$ was used to

create fetal vasoconstriction, the following order of nitrovasodilator compound potency was observed: glyceryl trinitrate ≥ sodium nitroprusside ≥ sodium nitrite ($NaNO_2$) ≥ S-nitroso-*N*-acetylpenicillamine (SNAP) = S-nitroso-*N*-glutathione (SNG).[158] SNG and $NaNO_2$ were significantly more potent under conditions of low oxygen tension. The antioxidants cysteine, glutathione, and superoxide dismutase significantly enhanced the vasodilatory effects of $NaNO_2$ only.[158]

Placental transfer of angiotensin-converting enzyme inhibitors may adversely affect fetal renal function. **Enalaprilat** rapidly crosses the placenta, and its maternal administration in high doses resulted in a 20% reduction in fetal arterial pressure in rhesus monkeys.[159]

Vasopressor Agents

Vasopressor agents are often administered to prevent or treat hypotension during the administration of neuraxial anesthesia in obstetric patients. **Ephedrine** readily crosses the placenta and results in an F/M ratio of approximately 0.7.[160] In an *in vitro* human perfusion model that required supraphysiologic doses to obtain any effect, **phenylephrine** increased placental arterial pressure, but less so than ephedrine, whereas **epinephrine**, **norepinephrine**, and **methoxamine** had no effect.[161]

Ephedrine possesses 10 times greater lipid solubility than phenylephrine, with F/M ratios of 1.1 versus 0.17, respectively, in humans.[162] Indeed, when either ephedrine or phenylephrine was given during spinal anesthesia for cesarean delivery, the ephedrine group had lower pH and base excess, higher Pco_2, and higher glucose, lactate, epinephrine, and norepinephrine concentrations in umbilical arterial blood than the phenylephrine group.[162] These differences may be due to the beta-adrenergic agonist effects of ephedrine in the fetus.[162,163]

Cocaine, a common drug of abuse during pregnancy (see Chapter 54), has potent vasoconstrictor activity. Human placenta perfusion studies *in vitro* have demonstrated the rapid transfer of cocaine in both maternal-to-fetal and fetal-to-maternal directions; transfer is constant over a wide range of concentrations.[164] The active cocaine metabolites norcocaine and cocaethylene, but not the inactive metabolite benzoylecgonine, are also rapidly transferred across the placenta.[165] Chronic maternal exposure to cocaine increases fetal concentrations; however, they remain lower than maternal peak levels.[166]

In a study using the *in vitro* dually perfused human placental lobule, fetal-side administration of vasoconstrictors was found to raise fetal placental perfusion pressure, thus causing a shift of fluid from the fetus to the maternal circulation.[167]

Anticoagulants

Anticoagulation therapy is often necessary during pregnancy. Maternal administration of **warfarin** in the first trimester results in placental transfer to the fetus, causing a higher rate of fetal loss and congenital anomalies.[168] After the first trimester, warfarin may be used in the setting of stroke or mechanical heart valves.[169] In contrast, **heparin** does not appear to cross the placenta, as measured by neonatal coagulation studies and the measurement of radiolabeled heparin in fetal lambs.[170] **Low-molecular-weight heparin** appears to have limited placental transfer; maternal administration of enoxaparin does not alter fetal anti-IIa or anti-Xa activity.[171] Even when **enoxaparin** or **fondaparinux** (a pentasaccharide that selectively inhibits factor Xa) was given at doses used for acute thromboembolic therapy, human placental perfusion studies *in vitro* demonstrated no placental transfer.[172,173] Several case reports discussed use of direct thrombin inhibitors as early as 9 weeks' gestation with successful delivery of normal neonates.[174,175] Antiplatelet therapy (e.g., **aspirin**, **clopidogrel**) has been used successfully in the first trimester in dual therapy for coronary artery disease in the setting of drug-eluting stents.[176] **Abciximab,** a glycoprotein IIb/IIIa platelet inhibitor, did not transfer across the *in vitro* perfused human placenta but did bind to the trophoblastic layer of the placenta.[177]

Drug Delivery Systems

New drug delivery systems may influence drug transfer and distribution across the human placenta. Liposome encapsulation, depending on the type and ionic charge, can affect placental transfer; anionic and neutral liposomes increase placental transfer, whereas cationic liposomes decrease placental transfer and placental tissue uptake.[178] Liposome encapsulation of valproic acid significantly reduces drug transfer and placental uptake.[179]

Disease States

Disease states, such as diabetes, may affect the placental transfer of drugs. **Glyburide**, a second-generation sulfonylurea, is partially dependent on a P-glycoprotein active transport mechanism and demonstrates a lower F/M ratio (0.3) than the first-generation agents, even in the presence of a P-glycoprotein inhibitor.[180] A high level of protein binding (99.8%) may also contribute to the low transplacental transfer of glyburide; when protein levels are reduced *in vitro*, higher transfer rates are observed.[181,182] Some investigators have speculated that the thickened placenta found in diabetic patients is a cause of low transfer rates; however, no difference in maternal-fetal transfer of **metformin** has been observed between placentas from parturients with gestational diabetes and those from healthy parturients.[183]

Gestational age may alter placental transfer, although the direction of the alteration requires further evaluation. Although traditional belief holds that placentas from younger fetuses are more likely to transfer substances, one study has demonstrated that **methadone** transfer is 30% lower in human preterm placentas than in term placentas.[184] **Dexamethasone** and **betamethasone**, corticosteroids that are often given to accelerate fetal lung maturity, increase *ABCB1* gene expression fourfold. ABCB1 is an efflux transporter protein; hence increased gene expression may increase fetal-maternal transfer of substrate molecules.[185]

Oxidative stress increases in preeclampsia, fetal growth restriction, and diabetes. New studies have shown that

nitrative stress, the covalent modification of proteins and DNA by peroxynitrite (formed by nitric oxide reacting with superoxide), also occurs.[186] Peroxynitrite reacts with tyrosine to form nitro-tyrosine, a negatively charged group, which may mimic phosphorylation. Nitration may result in loss or gain of protein function.

Vitamin D helps modulate cytokines, inflammation, and insulin sensitivity, and a deficiency leads to increased risk for gestational diabetes and preeclampsia.[187]

PLACENTAL PATHOLOGY

There has been a growing interest in the clinicopathologic correlation between placental abnormalities and adverse obstetric outcomes. In some cases, a skilled and systematic examination of the umbilical cord, fetal membranes, and placenta may provide insight into antepartum pathophysiology; in most of these cases, examination of the placenta confirms the clinical diagnosis (e.g., chorioamnionitis). When adverse outcomes occur, often the "disorder that was not suspected clinically may be revealed by placental pathology."[188] Drugs may produce placental abnormalities (e.g., cocaine causes chorionic villus hemorrhage and villous edema).[189] The significance of many findings (e.g., villous edema, hemorrhagic endovasculitis, chronic villitis), however, is unclear.

The following factors limit the assessment of placental pathology: (1) "the paucity of properly designed studies of adequate size with appropriate outcome parameters,"[188] which impairs the correlation of placental abnormalities with adverse clinical outcomes; (2) the limited number of pathologists with expertise in the recognition and interpretation of subtle abnormalities of the placenta; and (3) the cost associated with a routine assessment of placental pathology.

KEY POINTS

- The placenta is a dynamic organ with a complex structure. It brings two circulations close together for the exchange of blood gases, nutrients, and other substances (e.g., drugs).
- During pregnancy, anatomic adaptations result in substantial (near-maximal) vasodilation of the uterine spiral arteries; this leads to a low-resistance pathway for the delivery of blood to the placenta. Therefore, adequate uteroplacental blood flow depends on the maintenance of a normal maternal perfusion pressure.
- The marked diversity in placental structure and function among various animal species limits clinicians' ability to extrapolate the results of animal investigations to human pregnancy and clinical practice.
- Placental transfer involves all of the physiologic transport mechanisms that exist in other organ systems.
- Physical factors (e.g., molecular weight, lipid solubility, level of ionization) affect the placental transfer of drugs and other substances. In addition, other factors affect maternal-fetal exchange, including changes in maternal and fetal blood flow, placental binding, placental metabolism, diffusion capacity, and extent of maternal and fetal plasma protein binding.
- Lipophilicity, which enhances the central nervous system uptake of general anesthetic agents, also heightens the transfer of these drugs across the placenta. However, the placenta itself may take up highly lipophilic drugs, thereby creating a placental drug depot that limits the initial transfer of drug.
- Fetal acidemia can result in the "ion trapping" of both local anesthetics and opioids.
- Vasoactive drugs cross the placenta and may affect the fetal circulation and may have effects on fetal metabolism.

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CHAPTER 5

Fetal Physiology

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CHAPTER OUTLINE

Fetal life *in utero* differs significantly from postnatal life. The fetus relies completely on the mother and the placenta for basic metabolic needs such as nutrient delivery, gas exchange, acid-base balance, and electrolyte homeostasis. During gestation, the fetus gradually assumes the responsibility for many of the vital physiologic functions that must be assumed after the abrupt transition to physiologic independence at birth. Knowledge of fetal physiology, and the timing associated with these developmental changes, is necessary for the optimal provision of analgesia and anesthesia during pregnancy and childbirth.

FETAL ENVIRONMENT

Amniotic Fluid

The fetus is surrounded by amniotic fluid, a complex fluid that changes as the pregnancy progresses. Amniotic fluid serves a number of vital roles, including the facilitation of fetal growth, the provision of a microgravity environment that cushions the fetus, and the generation of a defense mechanism against invading microbes.[1,2] The formation and maintenance of amniotic fluid is an intricate process that depends on fetal maturation and maternal hydration, hormonal status, and uteroplacental perfusion.

Amniotic fluid during early embryogenesis is principally derived from maternal plasma by the passage of water and solutes through fetal membranous and placental layers. Between 10 and 20 weeks' gestation, the volume of amniotic fluid increases in a predictable and linear manner from approximately 25 mL to 400 mL. During this period, the composition of amniotic fluid is similar to fetal extracellular fluid, owing to the absence of keratin in the fetal skin. After this period, the volume of amniotic fluid is a function of production, from fetal urine (600 to 1200 mL/day near term) and respiratory tract secretions (60 to 100 mL/kg fetal body weight/day), and removal through fetal swallowing (200 to 250 mL/kg fetal body weight/day).[3] Amniotic fluid volume is also influenced by intramembranous (between amniotic fluid and fetal blood within the placenta) and transmembranous (between amniotic fluid and maternal blood within the uterus) pathways in both physiologic and pathophysiologic states.[4] Finally, the status of maternal hydration and the amount of decidual prolactin may alter the transfer of amniotic fluid through fetal and maternal tissues.

The *composition* of amniotic fluid undergoes more marked variation than its volume.[5,6] Keratinization of the fetal skin is complete by 25 weeks' gestation and decreases the permeability of fetal tissues to water and solutes. The impact of this process, coupled with the ability of the fetal kidneys to produce urine, results in increased amniotic fluid concentrations of urea and creatinine, decreased concentrations of sodium and chloride, and reduced osmolality. A variety of carbohydrates, proteins, lipids, electrolytes, enzymes, and hormones, which vary in concentration depending on the gestational age, are also present; some of these elements, particularly the amino acids taurine, glutamine, and arginine, serve a nutritive function for mitotic cells involved in trophoblastic growth and placental angiogenesis.[1] An abundance of growth factors are found in amniotic fluid, including epidermal growth factor, transforming growth factor-alpha, transforming growth factor-beta 1, insulin-like growth

factor-1, erythropoietin, and granulocyte colony-stimulating factor; many of these growth factors play an important role in fetal intestinal development.[1,7]

Antimicrobial defenses within the amniotic fluid are primarily composed of humoral mediators such as alpha-defensins, which are released from neutrophils, especially in the setting of preterm labor and/or chorioamnionitis. Other humoral mediators include lactoferrin, calprotectin, leukocyte protease inhibitor, and cathelicidin, which have significant activity against bacteria, viruses, and fungi.[8-10] Cellular mediators of the immune response are poorly characterized in amniotic fluid, and it remains unclear if the macrophages that are present serve a scavenging or an antimicrobial role. Neutrophils are usually absent from the amniotic fluid of a healthy fetus, and their presence typically signifies an inflammatory or infectious process.[1]

Biochemical and cellular analyses of amniotic fluid provide valuable information on chromosomal abnormalities, neural tube defects, prenatal infections, and most inborn errors of metabolism.[11,12] Several amniotic fluid–based indices, including the lecithin-sphingomyelin ratio, the phosphatidylglycerol level, and the lamellar body count, are commonly used to assess fetal lung maturity.[13,14] Bilirubin levels can be determined by measuring the optical density of amniotic fluid, which assists in the monitoring of fetal hemolysis. Estimation of the amniotic fluid levels of S100-β (a protein released from injured astrocytes) and cell-free fetal nucleic acids may serve as early screening tests for perinatal neurologic damage and fetal development, respectively.[15,16] Finally, amniotic fluid is a valuable reservoir for cell types of multiple lineages at different maturational ages; approximately 1% of these cells are pluripotent, thereby representing a novel source of stem cells.[17,18]

Oxygen Supply and Transport

The fetus has almost no oxygen reserve and thus depends on maternal sources of oxygen delivery. Oxygen is an essential substrate for cell survival, because it is the final electron acceptor in the electron transport chain. When oxygen is scarce, the electron transport chain is compromised, resulting in decreased oxidative phosphorylation and adenosine triphosphate (ATP) production.[19] Hypoxia ensues when the demand for oxygen exceeds the available supply, and it occurs more frequently in the presence of low oxygen tensions. In adult tissues, hypoxia occurs at oxygen tensions less than 20 mm Hg (normal, 40 mm Hg). By contrast, in fetal tissues, hypoxia occurs at oxygen tensions less than 17 mm Hg (normal, 20 to 25 mm Hg).[20,21] This implies that fetal development occurs in an environment that exhibits a smaller margin of safety before reaching a state of oxygen insufficiency and highlights the importance of ensuring fetal oxygen delivery through the maintenance of adequate uteroplacental perfusion and fetal cardiac output. Ultimately, oxygenation of fetal tissues depends principally on the partial pressure of oxygen gradient between maternal and fetal blood as well as on the difference in the types of hemoglobin that exist in maternal and fetal blood.

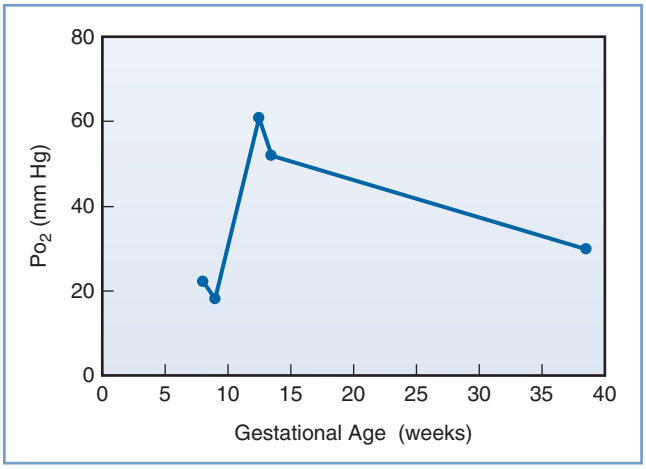

FIGURE 5-1 ■ **The mean oxygen partial pressure (Po_2) throughout gestation in the human intervillous space.** (Data from Jauniaux E, Kiserud T, Ozturk O, et al. Amniotic gas values and acid-base status during acute maternal hyperoxemia and hypoxemia in the early fetal sheep. Am J Obstet Gynecol 2000; 182:661-5; Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. Obstet Gynecol 1992; 80:283-5; and Schaaps JP, Tsatsaris V, Goffin F, et al. Shunting the intervillous space: new concepts in human uteroplacental vascularization. Am J Obstet Gynecol 2005; 192:323-32.)

Placental oxygen concentrations change with gestation. In early pregnancy, the placental intervillous space is free of maternal blood cells, thereby requiring the embryo to rely on endometrial secretions and maternal plasma for its energy requirements.[22,23] The first trimester placenta has (1) an oxygen partial pressure (Po_2) of approximately 20 mm Hg; (2) only a few capillaries, which are located mainly in the center of the mesenchymal core; and (3) a trophoblastic layer that is twice the thickness of that in the second trimester.[24] Moreover, the fetal red blood cells are nucleated and the exocoelomic cavity does not contain an oxygen transport system, but rather it contains antioxidant molecules. These anatomic features, which limit the transfer of oxygen and the creation of free radicals, protect the highly sensitive embryo from the effects of oxidative stress.[25] At the end of the first trimester, an exponential increase in fetal growth creates significant demands for oxygen and nutrients (Figure 5-1). In response, cytotrophoblastic cells interact with the smooth muscle of maternal spiral arteries, resulting in vessel dilation (Figure 5-2). This allows oxygen-rich maternal blood to flow to the placenta.[26]

The placenta acts as both a conduit and consumer of oxygen. The placenta is metabolically active and performs important roles in carbohydrate and amino acid metabolism, protein synthesis, and substrate transport. Almost 40% of the oxygen delivered to the pregnant uterus is needed to support the metabolic processes of the placenta.[27] During periods of hypoxia, the placenta appears to alter its metabolism to diminish its consumption of oxygen, most likely by increasing glycolysis.[28,29] This process can maintain fetal oxygen supply but, if ongoing, may result in fetal growth restriction (also known as intrauterine growth restriction). When the oxygen supply is compromised, the fetus shunts blood flow from peripheral tissues to vital organs (see later discussion), converts

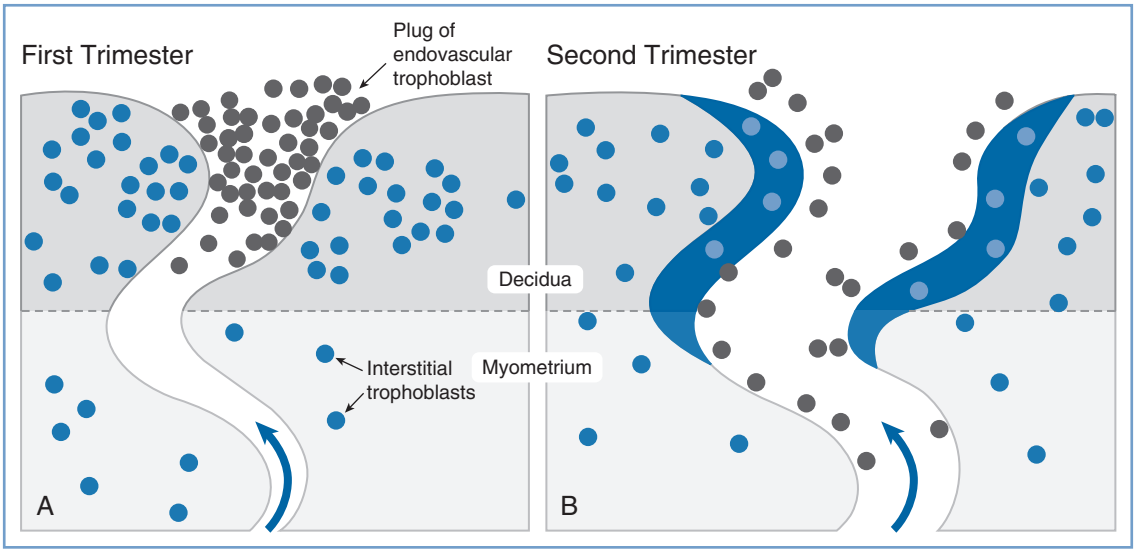

FIGURE 5-2 ■ Invasion and remodeling of the spiral arteries by endovascular and interstitial extravillous trophoblasts. **A,** In the first trimester, the terminal portion of the spiral artery is blocked by a plug of endovascular trophoblast. Early placental and embryonic development occurs in a state of low oxygen tension, and nutrition at this early stage is derived from secretions from maternal endometrial glands. **B,** After 10 to 12 weeks' gestation, the endovascular trophoblast plug dissolves and the endovascular trophoblast migrates into the myometrium, replacing endothelial cells, which undergo apoptosis. Maternal blood is now able to enter the intervillous space, the oxygen tension increases to 60 mm Hg, and nutrition changes from histotrophic to hemotrophic. (Modified from Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006; 27:939-58.)

to greater use of anaerobic pathways, and undergoes an induction of gene expression that enables improved survival in a low-oxygen environment.[19] The presence of fetal hemoglobin (hemoglobin F), with its greater affinity for oxygen than adult hemoglobin (see later discussion), and a hemoglobin concentration higher than that of adults (approximately 18 g/dL) result in a fetal arterial blood oxygen content that is only marginally lower than that in the adult, despite a lower oxygen tension.[30]

Glucose and Lactate Metabolism

Under normal conditions, gluconeogenesis does not occur to any significant extent in mammalian fetuses; the only source of glucose is that which is transferred across the placenta.[31] Fetal glucose concentrations are linearly related to maternal concentrations over a range of 3 to 5 mmol/L (54 to 90 mg/dL; Figure 5-3); studies in isolated placentas suggest that this relationship continues up to a glucose concentration of 20 mmol/L (360 mg/dL).[32] The placenta uses the majority of glucose delivered to the uterus for oxidation, glycogen storage, and conversion to lactate, with the remainder being transferred to the umbilical venous blood by facilitated, carrier-mediated diffusion. The amount of glucose supplied to the fetus appears more than adequate during normal conditions; ovine uterine blood flow must be reduced by greater than 50% before a decrease in fetal glucose uptake or fetal arterial glucose concentration is observed.[33,34]

The umbilical cord blood glucose uptake is approximately 5 mg/kg/min at normal maternal arterial plasma glucose concentrations.[35] Because the umbilical glucose/oxygen quotient varies from approximately 0.5 in sheep[36] to 0.8 in human fetuses during labor,[37] it is assumed that

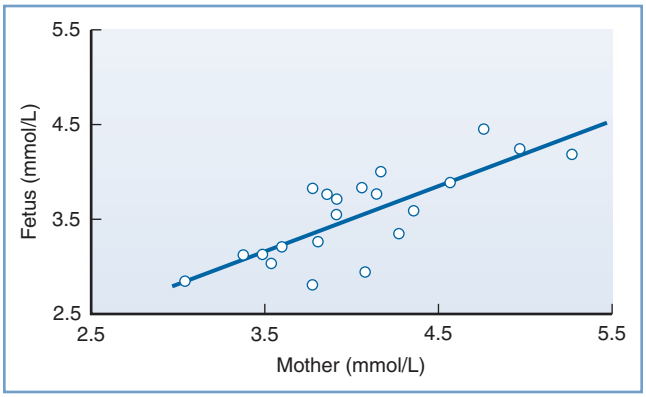

FIGURE 5-3 ■ The linear relationship between maternal and fetal blood glucose concentrations during the third trimester. Fetal blood was obtained by percutaneous umbilical cord blood sampling. (From Kalhan SC. Metabolism of glucose and methods of investigation in the fetus and newborn. In Polin RA, Fox WW, editors. Fetal and Neonatal Physiology. Vol I. Philadelphia, WB Saunders, 1992:477-88.)

substrates other than glucose are used to support fetal oxidative metabolism; it is estimated that lactate and amino acids each provides approximately 25% of the total fetal energy requirements.[38,39]

Lactate is produced even in well-oxygenated fetal lambs, with total lactate production being approximately 4 mg/kg/min.[40] Although the exact origin of fetal lactate is unclear, skeletal muscles and bones have been identified as sources of lactate production under resting conditions. Lactate production increases during episodes of acute hypoxemia, although this response may be blunted in fetuses previously exposed to oxidative stress.[41] Lactate

consumption occurs in the fetal myocardium and liver.[42] Short-term exogenous lactate infusion in fetal lambs (sufficient to lower the pH to 7.20) results in transient fetal bradycardia and increased fetal breathing movements but no other adverse effects.[43]

Amino Acid and Lipid Metabolism

The fetus uses amino acids for protein synthesis, growth, and oxidation. Most maternal-to-fetal amino acid transfer occurs against a concentration gradient and involves energy-dependent transfer mechanisms. Under conditions in which fetal aerobic metabolism is decreased, amino acid uptake by the placenta and fetus may be reduced because it involves an expenditure of energy. Hypoxia results in a large reduction in nitrogen uptake in fetal lambs.[44] During maternal fasting, fetal amino acid uptake does not change; however, enhanced fetal proteolysis may occur, which subsequently results in amino acid oxidation or gluconeogenesis.

Lipid products are transferred from the mother to the fetus. The fetus requires free fatty acids for growth, brain development, and the deposition of body fat for postnatal life. Fatty acids are transferred across the placenta by simple diffusion. Ketones are also transferred by simple diffusion; in humans, the maternal/fetal ketone ratio is approximately 2.0.[45] The fetus can use ketones as lipogenic substrates or as energy substrates in the brain, kidney, heart, liver, and placenta.[46] Beta-hydroxybutyrate (fatty acid) metabolism can occur in the placenta, brain, and liver during episodes of fetal hypoglycemia that result from maternal fasting.[46] Cholesterol synthesis or free cholesterol diffusion does not appear to occur in the placenta.[47] However, there is a significant correlation between maternal and fetal concentrations of lipoprotein(a), implying that diffusion of lipoprotein(a) may occur.[47]

Thermoregulation

Intrauterine fetal temperature largely depends on maternal temperature. However, owing to the high metabolic rate in the fetus, the net flow of heat is from the fetus to the mother. When compared with the mother during the third trimester, the fetus produces approximately twice as much heat (on a weight-adjusted basis) and maintains a temperature 0.5° C higher.[48,49] This maternal-fetal difference in temperature remains relatively constant and is referred to as the "heat clamp."[50]

The placental circulation is responsible for approximately 85% of the heat exchange between the mother and fetus. The remaining 15% is dissipated through the fetal skin and transferred through the amniotic fluid and the uterine wall to the maternal abdomen.[51] As a consequence, fetal temperature may be rapidly affected by changes in umbilical blood flow; fetal temperatures rise quickly on occlusion of umbilical blood flow in both baboons and sheep.[52,53] In humans, fetal temperatures increase during uterine contractions, which may be a result of intermittent obstruction of umbilical cord blood flow.[54] Whether this rise in fetal temperature contributes to acute hypoxic-ischemic brain damage in the setting of umbilical cord prolapse is currently unknown. However, relatively small increases in temperature increase the sensitivity of the fetal brain to hypoxic injury (see Chapter 10).[55]

Although the fetus generates heat through high metabolic activity, the ability of the fetus to generate heat through thermogenic mechanisms is not developed until the end of gestation and is largely inactive *in utero*. Newborns are at high risk for rapid heat loss due to amniotic fluid evaporation and a sudden decrease in ambient temperature.[49] They are not capable of significant heat production through shivering owing to their small muscle mass. As a consequence, nonshivering thermogenesis plays an important role in maintaining neonatal temperature. Nonshivering thermogenesis occurs in brown adipose tissue, which is unique from other adipocytes owing to the significant presence of mitochondria, fat vacuoles, sympathetic innervation, and blood vessels. In the mitochondria of brown adipose tissue, ATP production is uncoupled from the oxidative process, resulting in an increase in heat production and oxygen consumption.[56] Nonshivering thermogenesis is inhibited *in utero*, most likely owing to the presence of adenosine and prostaglandin E_2, which have strong antilipolytic actions on brown tissue.[57-59] Inadequate oxygen levels and low levels of intrauterine catecholamines and thyroid hormones may also inhibit nonshivering thermogenesis. The inhibition of nonshivering thermogenesis is believed to be beneficial to the health of the fetus, in that it allows for conservation of fetal oxygenation and accumulation of brown adipose tissue.[50]

FETAL CARDIOVASCULAR SYSTEM

The cardiovascular system is one of the first functional organ systems in the developing fetus. The morphologic development of the human heart, from its first appearance as a heart tube to its development as a four-chambered structure, occurs between 20 and 44 days' gestation. Even before the development of the four-chambered heart, the valveless heart tube generates unidirectional flow, typically around 21 days' gestation.

Circulatory Pattern

Fetal circulation differs significantly from the postnatal circulation. The fetal cardiovascular system is anatomically arranged in such a way as to allow blood to bypass the lungs and provide maximal perfusion of the placenta, where gas and nutrient exchange occur. The fetal systemic circulation receives cardiac output from both the left and the right ventricle, with the ventricles working in *parallel*. In contrast, during postnatal life, the left and right circulations are separated and the ventricles work in *series*.

Fetal blood flow is characterized by three anatomic communications between the left and right circulations: the **ductus venosus**, the **foramen ovale**, and the **ductus arteriosus** (Figure 5-4). Oxygenated blood travels from the placenta through the umbilical vein to the **ductus venosus**, which connects the umbilical vein with the inferior vena cava, thus bypassing the portal circulation and the liver. At mid gestation, approximately 30% of the

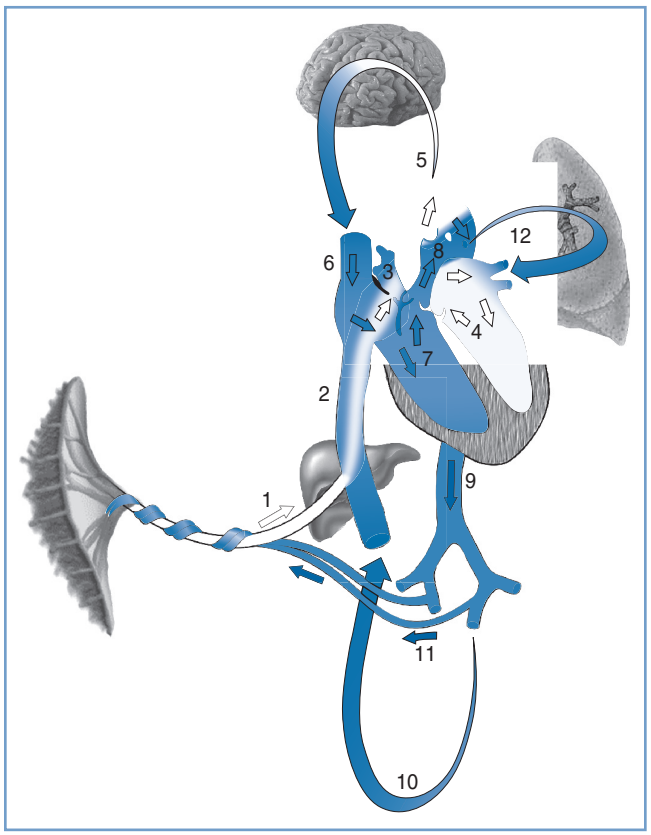

FIGURE 5-4 ■ Oxygenated blood leaves the placenta via the fetal umbilical vein (*1*), enters the liver where flow divides between the portal sinus and the ductus venosus, and then empties into the inferior vena cava (*2*). Inside the fetal heart, blood enters the right atrium, where most of the blood is directed through the foramen ovale (*3*) into the left atrium and ventricle (*4*), and then enters the aorta. Blood is then sent to the brain (*5*) and myocardium, ensuring that these cells receive the highest oxygen content available. Deoxygenated blood returning from the lower extremities and the superior vena cava (*6*) is preferentially directed into the right ventricle (*7*) and pulmonary trunk. The majority of blood passes through the ductus arteriosus (*8*) into the descending aorta (*9*), which in turn supplies the lower extremities (*10*) and the hypogastric arteries (*11*). Blood returns to the placenta via the umbilical arteries for gas and nutrient exchange. A small amount of blood from the pulmonary trunk travels through the pulmonary arteries (*12*) to perfuse the lungs. *Arrows* in this figure depict the direction and oxygen content [*white* (oxygenated), *blue* (deoxygenated)] of the blood in circulation. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

umbilical venous blood is shunted through the ductus venosus; from 30 to 40 weeks' gestation, this fraction decreases to approximately 20%, although a significant increase can occur in response to hypoxia (see later discussion).[60] Once in the right atrium, oxygenated blood preferentially flows through the **foramen ovale** to the left atrium and left ventricle, before entering the aorta and the systemic circulation. This mechanism ensures the delivery of well-oxygenated blood to the brain and the heart, which are the two organs with the highest oxygen requirements. The preferential shunting of ductus venosus blood through the foramen ovale into the left atrium is related to the umbilical venous pressure and the portocaval pressure gradient.

Deoxygenated blood from the head and upper extremities enters the right atrium through the superior vena cava and is preferentially directed into the right ventricle and the pulmonary artery. Because fetal pulmonary vascular resistance is higher than systemic vascular resistance, the majority of pulmonary artery blood flow crosses the **ductus arteriosus** into the descending aorta, which in turn supplies the lower extremities and hypogastric arteries. Deoxygenated blood returns to the placenta via the umbilical arteries for gas and nutrient exchange; only a small percentage travels through the lungs into the left atrium, the left ventricle, and the ascending aorta.

At birth, the fetus undergoes a significant and abrupt transition to a state of physiologic independence (see Chapter 9). Clamping of the umbilical cord results in a sudden increase in systemic vascular resistance, whereas expansion of the lungs and an increased alveolar oxygen tension result in decreased pulmonary vascular resistance. This allows for greater blood flow through the lungs, resulting in a decrease in right atrial pressure and an increase in left atrial pressure, ultimately leading to the functional closure of both the foramen ovale and the ductus arteriosus.

Blood Volume

Human fetal intravascular volume is approximately 110 mL/kg, which is higher than that in postnatal life. However, approximately 25% of this blood volume is contained within the placenta; the blood volume within the fetal body is estimated to be approximately 80 mL/kg.[61,62] Fetal intravascular volume is regulated through a complex interplay between the fetal heart, kidneys, and circulation and the placenta.[63] The fetus can adapt more quickly to changes in intravascular volume than the adult, owing to higher diffusion rates between fetal compartments.[64]

Transplacental transfer of water from mother to fetus depends on hydrostatic and osmotic pressures. The hydrostatic pressure is determined by the difference in pressures between the maternal intervillous space or capillaries and the fetal capillaries. The osmotic pressure is mainly determined by the presence of plasma proteins (i.e., colloid osmotic pressure). Transplacental water transfer is further regulated by angiotensin II. Adamson et al.[65,66] found that angiotensin II lowered the pressures in fetal placental exchange vessels, thereby promoting fluid transfer from the maternal to the fetal circulation. The production of angiotensin II is under control of the renin-angiotensin-aldosterone system in the fetal kidneys. A reduction in fetal arterial pressure results in an increase in fetal plasma renin activity, which results in subsequent increases in angiotensin I and II. The resulting expansion of intravascular volume augments fetal cardiac output and arterial pressure.

Cardiac Development

During gestation the fetal heart grows quickly and adapts to the continuously changing demands. The fetal myocardium grows primarily through cell division, whereas

after delivery, cardiac mass increases as a result of cell enlargement.[67] This growth correlates with a pre-birth transition from mononucleated cardiomyocytes, which contribute to heart growth by hyper*plasia*, to binucleated cardiomyocytes, which contribute to heart growth by hyper*trophy*.

The number of cardiac myofibrils and the transition in the type of cardiac troponins that are present during prenatal development can alter fetal heart contractility.[68] The change from fetal to adult troponin is associated with decreased sensitivity of the contractile apparatus to calcium. A heightened calcium sensitivity is important in the early development of the fetal heart, when the sarcoplasmic reticulum is immature.[69] With advancing gestational age, ejection fraction declines but cardiac output (per unit of fetal weight) does not change owing to increasing ventricular volume. The fetal heart rate decreases over the course of gestation from 140 to 150 beats per minute at 18 weeks' gestation to 120 to 140 beats per minute at term.[70,71]

Ventricular Responses to Changes in Preload and Afterload

It is unclear whether fetal and adult hearts possess similar responses to preload and afterload. The adult heart responds in accordance to the Frank-Starling curve, which indicates that ventricular distention lengthens the diastolic fibers and results in augmented contractility. A number of studies have indicated that the fetal heart has a limited capacity to increase its stroke volume in response to an increase in preload (e.g., intravenous fluid infusion).[72,73] By contrast, other studies have observed that the fetal heart can accommodate increases in preload and afterload in a manner consistent with the Frank-Starling curve.[74,75] These seemingly contradictory findings may be partially explained if the fetal heart functions *in vivo* near the peak of the Frank-Starling curve. However, the left ventricular stroke volume is known to double at birth, which would not be in agreement with this hypothesis. A more plausible explanation is that ventricular constraint, arising from tissues that surround the heart (chest wall, pericardium, and lungs), limits fetal ventricular preload and overall cardiac function *in utero*. Relief of this constraint at birth, as a result of lung aeration and clearance of liquid from the lungs, may then allow for an increase in left ventricular preload and subsequent stroke volume in the newborn.[76]

Studies investigating the effects of afterload on fetal ventricular function have observed a significant decrease in right ventricular stroke volume in response to increases in arterial pressure.[72] The same phenomenon occurs in the left ventricle, although to a lesser degree. In a study of fetal lambs, in which gradual constriction of the descending aorta was applied, stroke volume was maintained until high mean arterial pressures were achieved, after which decreases were observed. This decrease in stroke volume in the presence of high mean arterial pressure may represent the exhaustion of "preload reserve," which will typically allow the maintenance of stroke volume in the setting of increased afterload.[77]

Cardiac Output and Distribution

In postnatal life, the right and left ventricles operate in series and their output is approximately equal; as a consequence, cardiac output is defined through measurements of output from either ventricle. However, in the fetus, the systemic circulation receives blood from both the left and right ventricle in parallel (i.e., the sum of the right and left ventricular outputs, with the exception of a proportion of the right ventricular output that is delivered to the fetal lungs). At mid gestation, the combined ventricular output (CVO) is approximately 210 mL, and it increases to approximately 1900 mL at 38 weeks' gestation (500 mL/min/kg).[73,78,79] During fetal life, the right ventricular volume is greater than the left ventricular volume during both systole and diastole, but stroke volume does not differ significantly between the two ventricles.[70]

Fetal cardiac output is sensitive to changes in fetal heart rate. As heart rate increases, cardiac output increases. As fetal heart rate decreases, fetal stroke volume increases only slightly, in part because of low fetal myocardial compliance. Although fetal bradycardia results in an extended diastolic filling time, the stiff fetal cardiac ventricles have limited ability to distend. Therefore, fetal bradycardia is associated with a marked drop in fetal cardiac output.

The distribution of the CVO in near-term fetal lambs and resting adult humans is shown in Figure 5-5. The fetal lamb CVO is distributed to the placenta (41%), the bone and skeletal muscle (38%), the gastrointestinal system (6%), the heart (4%), the brain (3%), and the kidneys (2%). In both fetal and adult animals, approximately equal volumes of blood are delivered to

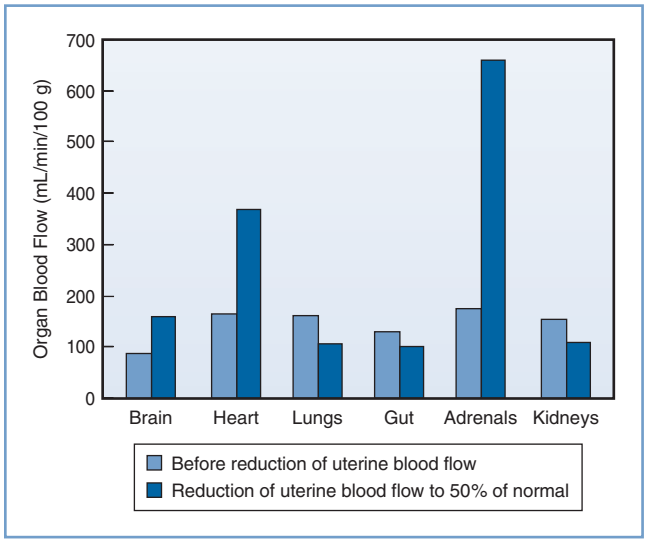

FIGURE 5-5 ■ **Redistribution of combined ventricular output in fetal lambs during hypoxemia caused by reduced uterine blood flow.** (Modified from Jensen A, Roman C, Rudolph AM. Effects of reducing uterine blood flow on fetal blood flow distribution and oxygen delivery. J Dev Physiol 1991; 15: 309-23.)

oxygen-uptake organs (i.e., the placenta before delivery, the lungs after delivery) and the oxygen-consuming organs.

The distribution of the CVO changes over the course of gestation and in certain conditions, such as hypoxia and hypovolemia. Interpretation of CVO data should be evaluated with the understanding that significant interspecies differences exist. For example, in humans the fetal lungs receive approximately 20% of CVO, whereas in the fetal lamb the lungs receive 10% or less of CVO. In human fetuses at 10 to 20 weeks' gestation, the brain receives approximately 15% of CVO,[80] but this fraction may be increased during circumstances of decreased placental perfusion, acidosis, and increased Pco_2. In the rhesus monkey, the fraction of CVO devoted to cerebral blood flow was observed to increase from 16% to 31% during a hypoxic challenge.[81]

Fetal Blood Pressure

Fetal blood pressure increases with gestational age. Intracardiac (intraventricular) pressure recordings in the human fetus suggest that systolic pressure increases from 15 to 20 mm Hg at 16 weeks' gestation to 30 to 40 mm Hg at 28 weeks' gestation.[67] Substantial variation in blood pressure may be observed. The diastolic ventricular pressures undergo similar, albeit slower and smaller increases, from 5 mm Hg or less at 16 to 18 weeks' gestation to 5 to 15 mm Hg at 19 to 26 weeks' gestation.[67]

Regulation of Fetal Circulation

Fetal cardiovascular function continuously adapts to varying metabolic and environmental conditions through regulation by the neurologic and endocrine systems. The predominant form of neuroregulation occurs in response to baroreceptor and chemoreceptor afferent input to the autonomic nervous system and through modulation of myocardial adrenergic receptor activity. Thus, the autonomic nervous system functions to reversibly redirect blood flow and oxygen delivery as required.

Arterial baroreceptor function has been demonstrated in several different fetal animal models. The predominant baroreceptors are located within the vessel walls of the aortic arch and at the bifurcation of the common carotid arteries. These receptors project signals to the vasomotor center in the medulla, from which autonomic responses emanate. The baroreceptors are functional early in fetal development and undergo continuous adaptation to the increases in blood pressure observed over time.[82] A sudden increase in fetal mean arterial pressure—as occurs with partial or complete occlusion of the umbilical arteries—results in cholinergic stimulation and subsequent fetal bradycardia.

Peripheral chemoreceptors are present within the vessel walls of the aortic arch and at the bifurcation of the common carotid arteries. In some animal species, peripheral chemoreceptors are transiently present in the adrenal gland but disappear after birth.[83] The fetal aortic chemoreceptors are responsive to even small changes in arterial oxygenation,[84,85] which contrasts to the less active fetal carotid chemoreceptors. Dawes et al.[86] concluded that the carotid chemoreceptors are important for postnatal respiratory control, whereas the aortic chemoreceptors are more involved in the control of cardiovascular responses and the regulation of oxygen delivery. Central chemoreceptors, located in the medullar oblongata, appear to play little if any role in fetal circulatory responses.

The neural control of the fetal circulation is far more dependent on chemoreceptor-mediated responses than neural control of the adult circulation.[87] Acute fetal hypotension often stimulates a reflex response, which can include both bradycardia and vasoconstriction. Vasoconstriction is dependent on increases in both sympathetic autonomic activity and the rate of secretion of several vasoactive hormones, including arginine vasopressin, renin, angiotensin, and aldosterone. Fetal bradycardia is most likely caused by activation of peripheral chemoreceptors.[87]

Autonomic Nervous System

The autonomic nervous system is present early in gestation and plays a critical role in maintaining cardiovascular homeostasis. In the fetal chick heart, evidence of cholinergic innervation occurs as early as 3 days after fertilization (average incubation, 22 days). In the mammalian heart, inotropic and chronotropic responses to adrenergic agents have been measured as early as 4 to 5 weeks' gestation,[88] and the fetal myocardial pacemaker can be inhibited at this time by the cholinergic agonists carbamylcholine and acetylcholine.[89]

In comparing the parasympathetic cholinergic and sympathetic adrenergic nervous systems during gestation, the majority of studies indicate that the parasympathetic system appears earlier (8 weeks' gestation versus 9 to 10 weeks' gestation),[88,90,91] becomes more dominant as pregnancy progresses, and is more functionally complete at birth (Figure 5-6). As a result, the baseline fetal heart rate is slower at term than at 26 weeks' gestation. The administration of atropine can result in fetal tachycardia by 15 to 17 weeks' gestation, which occurs before fetal bradycardia can be demonstrated with the administration of a beta-adrenergic receptor antagonist.[88]

Both parasympathetic and sympathetic systems undergo significant maturation during postnatal life, and full maturation of the vagal response is not observed until 1 to 2 months after delivery.[92-94] Similarly, although the contractile response of the fetal vasculature is less functional than the adult response, the fetal administration of an alpha-adrenergic agonist can result in the redistribution of blood flow away from the kidneys, skin, and splanchnic organs and toward the heart, brain, placenta, and adrenal glands.[95] At birth, the autonomic nervous system can mediate a number of hemodynamic adjustments, including changes in heart rate and peripheral vascular resistance, as well as a redistribution of blood flow.[88]

FETAL PULMONARY SYSTEM

The lungs begin as small, saccular outgrowths of the ventral wall foregut. Although sacculi with type I and II

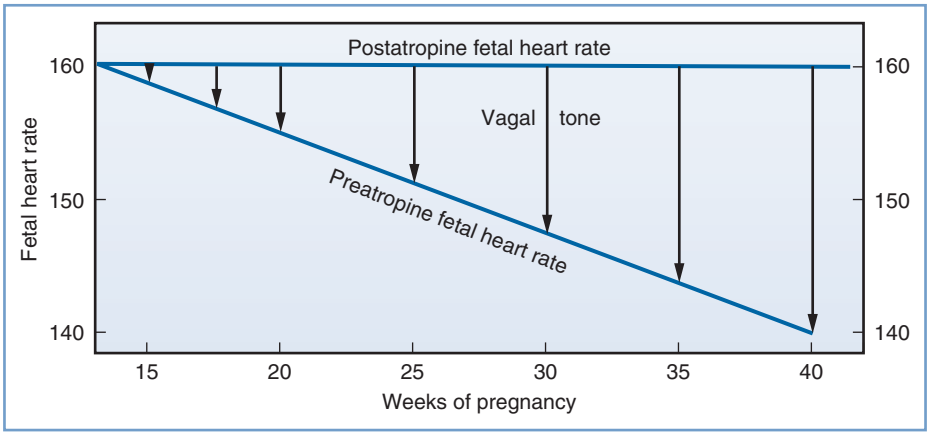

FIGURE 5-6 ■ The growing influence of the parasympathetic nervous system on fetal heart rate as gestation progresses. This parasympathetic activity is reversible with administration of atropine. (From Schifferli P, Caldeyro-Barcia R. Effects of atropine and beta-adrenergic drugs on the heart rate of the human fetus. In Boréus LO, editor. Fetal Pharmacology. New York, Raven Press, 1973:264.)

pneumocytes and ventilatory capacity are present during the last trimester, true alveoli develop at approximately 36 weeks' gestation. The majority of alveolar development occurs postnatally, within the first 6 to 18 months of life, when further maturation of the microvasculature and the air-blood barrier occurs.[96]

The pulmonary vasculature develops early in gestation, with continuous circulation being documented at 34 days' gestation.[97,98] The size and number of pulmonary arteries and veins increases over time; however, vessel reactivity to local and hormonal influences is not detectable until after 20 weeks' gestation.[99,100] From 20 to 30 weeks' gestation, an increase in the size of the pulmonary vascular bed combined with a decrease in the pulmonary vascular resistance results in an increase in pulmonary blood flow (i.e., from 10% to 15% of the CVO to 25% of the CVO). During this time, alterations in maternal oxygenation have no effect on the fetal pulmonary vasculature.[80,99] However, after 30 weeks' gestation, blood flow to the lung decreases slightly owing to a significant increase in pulmonary vascular resistance, diminishing the fraction of CVO to approximately 20%. Contemporaneously, the vasomotor tone and reactivity of the fetal circulation begins to respond to maternal hyperoxygenation with a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow.[80,99] A study in near-term fetal lambs observed a 10-fold increase in pulmonary blood flow when fetal oxygen tension was increased from 24 to 46 mm Hg[101]; this finding emphasizes the importance of ventilation and oxygenation in the newborn to assist in the transition to postnatal circulation.

The reduction in pulmonary vascular resistance at birth is also attributed to a number of mechanical and molecular processes. *In utero*, the fetal lungs are filled with fluid to maintain an appropriate level of expansion for normal pulmonary development.[102] The expulsion of lung liquid, particularly with a vaginal birth, likely decreases extraluminal pressure on the pulmonary vasculature and leads to a decrease in pulmonary vascular resistance.[103] Breathing movements, shear stress created by an abrupt surge in pulmonary blood flow, and the creation of alveolar surface tension are other mechanical factors that can decrease pulmonary vascular resistance.[104] Finally, the relative predominance of vasodilators (e.g., endothelium-derived nitric oxide, prostacyclin) versus vasoconstrictors (e.g., platelet activating factor) at birth may also significantly decrease pulmonary vascular resistance.[105-109]

The pulmonary **surfactant system** is one of the last systems to develop before birth.[110] Surfactant is a lipoprotein complex (phospholipoprotein) that reduces and regulates the surface tension at the air-liquid interface to prevent alveolar collapse and reduces the work associated with breathing.[111] Pulmonary surfactant is composed predominantly (> 90%) of lipids (i.e., phospholipids and neutral lipids [primarily cholesterol]), with the remaining fraction being proteins.[112,113] Surfactant assembly occurs in the endoplasmic reticulum and the Golgi apparatus of the type II alveolar cells, and it is stored in the lamellar bodies. The primary stimuli for surfactant secretion (i.e., exocytosis from the lamellar bodies) are signals from the autonomic nervous system (β_2-adrenergic receptor mediated) and mechanical factors (e.g., stretching of the basement membrane of alveolar type II cells with ventilation).[114] Dipalmitoylphosphatidylcholine, an important component of surfactant, is present in amniotic fluid and can be found in alveolar lavage samples from human fetuses between 24 and 28 weeks' gestation.

The amount and composition of surfactant changes over the course of gestation. For example, the ratio of phosphatidylglycerol to phosphatidylinositol, as well as the ratio of lecithin to sphingomyelin, increases with gestation and may be used as markers of fetal lung maturity.[115-117] Fetal surfactant production can be accelerated by a number of factors, including glucocorticoids, thyroid hormones, and autonomic neurotransmitters. The maternal administration of glucocorticoids such as betamethasone or dexamethasone has been associated with a 35% to 40% reduction in respiratory distress syndrome in preterm infants.[118]

FETAL RENAL SYSTEM

Although fluid and electrolyte balance, as well as acid-base homeostasis, are primarily regulated and maintained by the placenta, the fetal kidneys play an important role in fetal development through amniotic fluid production. Fetal glomeruli begin to develop at 8 to 9 weeks' gestation and start producing urine at 10 weeks' gestation, which contributes significantly to amniotic fluid production.[119,120] By 20 weeks' gestation, greater than 90% of amniotic fluid is provided by the kidneys. Fetal oliguria and anuria can lead to lung hypoplasia and skeletal and tissue deformities (e.g., Potter sequence).[121] Glomerular filtration rate (GFR) increases over the course of gestation but remains low during fetal and early neonatal life. At birth, term newborns have a GFR of approximately 20 mL/min/1.73m^2,[122,123] which increases to approximately 50 mL/min/1.73 m^2 by 1 month of age.[123] This early increase in GFR is believed to result from a large increase in the glomerular capillary surface area and the ultrafiltration coefficient, together with a small increase in the filtration pressure.[124,125] Thereafter, the GFR undergoes progressive increases and reaches adult levels between 1 and 2 years of age.[126]

The ability of the fetal kidneys to perform filtration, reabsorption, and secretion (i.e., tubular function) begins by 14 weeks' gestation and continues to develop postnatally. Immaturity of tubular function in preterm infants can lead to acidosis and salt wasting.[127,128] Renal function *in utero* is regulated by a variety of factors that control renal blood flow, glomerular filtration, and tubular function. The renin-angiotensin system is particularly important for normal fetal renal growth and development[129]; angiotensin II helps regulate blood pressure as well as the volume of fluid in the extravascular space.[130]

FETAL HEMATOLOGIC SYSTEM

Red blood cells, platelets, neutrophils, monocytes, and macrophages are all derived from a common progenitor cell.[131] In the developing embryo, hematopoiesis occurs at several anatomic sites in multiple waves. The first wave occurs in the yolk sac and produces mostly primitive erythroid cells, but also macrophages and megakaryocytes. The second wave also arises in the yolk sac but creates the same cells found in the adult human (i.e., erythroid, megakaryocyte, and several myeloid lineages). The third wave emerges from hematopoietic stem cells located within the major arteries of the embryo, yolk sac, and placenta. Hematopoietic stem cells migrate to the fetal liver and eventually seed the bone marrow. The final wave of hematopoiesis produces all hematopoietic cell lineages, including B- and T-lymphocyte progenitor cells.[132,133]

Erythroid (red blood cells) are the first blood cells to develop. There are two developmentally and morphologically distinct erythroid lineages: primitive (embryonic) and definitive (adult). Cells of the primitive lineage support the transition from the rapidly growing embryo to fetus; primitive megaloblastic erythrocytes are much larger than definitive erythrocytes, express different globin genes, and differ in their oxygen-carrying capacity and response to low oxygen tension. By contrast, definitive erythrocytes function during the transition from fetal to extrauterine life at birth are produced continuously from hematopoietic stem cells in the bone marrow and participate in a variety of normal physiologic processes throughout postnatal life.[131,134]

Fetal and adult human erythrocytes can be distinguished by their hemoglobin (hemoglobin F and A, respectively). The tetramer for hemoglobin F consists of two alpha (α) chains and two gamma (γ) chains (α2γ2), whereas the tetramer for hemoglobin A includes two alpha (α) chains and two beta (β) chains ($\alpha_2\beta_2$). The gamma chain and the beta chain contain the same number of amino acids (146), but their sequences differ by a total of 39 amino acids.[135] The change in expression from fetal to adult beta-globin genes begins at approximately 32 weeks' gestation and is completed after birth.[136]

Hemoglobin F has a greater affinity for oxygen and a lower affinity for 2,3-disphosphoglycerate (DPG) and exhibits a leftward shift in the oxyhemoglobin dissociation curve compared with hemoglobin A (Figure 5-7).[137-139] These differences result in greater arterial oxygen saturation in fetal versus maternal blood for any given arterial oxygen pressure. This difference in oxygen affinity can be explained by a decreased interaction between the gamma chains of hemoglobin F and intraerythrocyte 2,3-DPG, which acts to lower oxygen affinity by binding and stabilizing the deoxygenated hemoglobin tetramer. As a consequence, 2,3-DPG decreases the oxygen affinity of hemoglobin F less than that of hemoglobin A.[140,141] Although fetuses and adults have similar intraerythrocyte

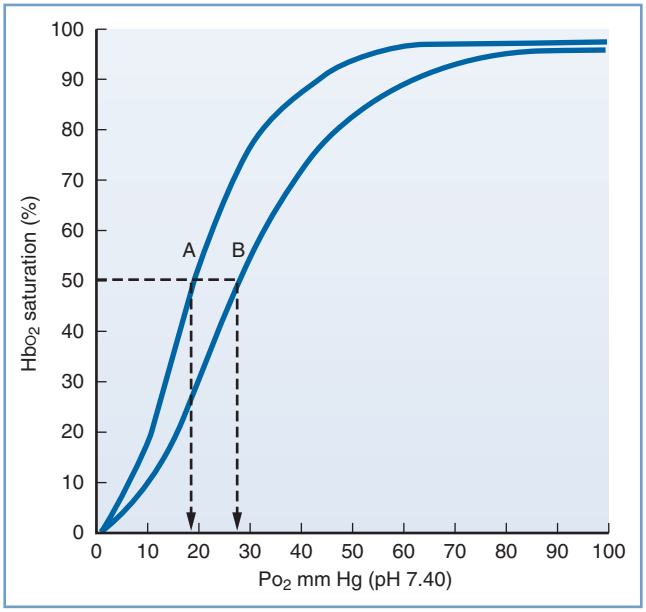

FIGURE 5-7 ■ Oxyhemoglobin saturation curves for fetal (**A**) and adult (**B**) human blood. The P_{50} is indicated by the *dashed vertical line.* (Modified from Delivoria-Papadopoulos M, DiGiacomo JE. Oxygen transport. In Polin RA, Fox WW, editors. Fetal and Neonatal Physiology. Vol 1. Philadelphia, WB Saunders, 1992:807.)

2,3-DPG concentrations, fetal blood exhibits a lower oxygen tension at which hemoglobin is 50% saturated (P_{50}). Hemoglobin F levels begin to decrease toward the end of pregnancy, resulting in a corresponding increase in the P_{50}. At term, hemoglobin A accounts for approximately 25% of total hemoglobin and the P_{50} is approximately 19 mm Hg.[142,143]

Hemoglobin A levels begin to increase and 2,3-DPG concentrations transiently increase above usual fetal and adult levels during the first few months of life. During this time, the affinity of neonatal blood for oxygen is equivalent to that of the adult despite the persistence of 25% fetal hemoglobin.[137,142,143]

FETAL GASTROINTESTINAL SYSTEM

The gastrointestinal tract develops from the primitive digestive tube, which includes the foregut, midgut, and hindgut. The foregut receives its vascular supply from the celiac axis and gives origin to the oral cavity, pharynx, esophagus, stomach, and upper duodenum. The midgut, which receives its vascular supply from the superior mesenteric artery, develops into the distal duodenum, jejunum, ileum, cecum, appendix, and transverse colon. The hindgut receives its vascular supply from the inferior mesenteric artery, and it differentiates into the descending colon, the sigmoid colon, and the upper two thirds of the rectum.[144] Intestinal villi appear by 7 weeks' gestation, and active absorption of glucose and amino acids occurs by 10 and 12 weeks' gestation, respectively.[145] Peristaltic waves and gastrointestinal motility are initiated by 8 weeks' gestation. Teniae, the three longitudinal ribbons of smooth muscle on the outside of the colon, appear by 12 weeks' gestation and contract to produce the haustra (bulges) in the colon.[146] In the small intestine, Auerbach's and Meissner's plexuses of parasympathetic nerves provide motor and secretomotor innervation, respectively; the two plexuses are present as early as 8 weeks' gestation.[145] Aggregations of lymphoid nodules (i.e., Peyer patches) develop by 20 weeks' gestation in the ileum.[147]

Swallowing

The fetus starts swallowing at approximately 15 weeks' gestation, and at term the fetus ingests 500 to 750 mL of amniotic fluid per day.[148] Fetal swallowing plays an important role in amniotic fluid homeostasis,[148] and the swallowed fluid appears to provide nutritional support for mucosal development within the gastrointestinal tract.[149] Avila et al.[150] found that surgical obstruction of ingested fluid within the upper gastrointestinal tract resulted in restricted development of the gastrointestinal tract, liver, and pancreas. In addition, the ingestion and intestinal absorption of nutrient-rich amniotic fluid appears to play an important role in general fetal growth and development. In the fetal rabbit model, disorders of the upper gastrointestinal tract (e.g., esophageal obstruction, gastroschisis) lead to decreased intestinal nutrient absorption and decreased birth weight and crown-rump length.[151,152] Similar findings have been reported in human neonates with congenital esophageal atresia.[153]

Meconium

Meconium, which consists of water, intestinal secretions, squamous cells, lanugo hair, bile pigments, and blood, first appears in the fetal intestine between 10 and 12 weeks' gestation.[154] By 16 weeks' gestation, meconium moves into the colon.[155] Between 14 and 22 weeks' gestation, fetal colonic contents, as indicated by the presence of high levels of intestinal enzymes (disaccharidases, alkaline phosphatase), appear in the amniotic fluid.[156] After 22 weeks' gestation, a subsequent decline in the concentration of these gastrointestinal enzymes within the amniotic fluid is observed, which coincides with the development of anal sphincter tone.[156,157]

Meconium is continually cleared by fetal swallowing, leading to relatively clear amniotic fluid in the majority of pregnancies. The presence of meconium-stained amniotic fluid may therefore represent either decreased meconium clearance or increased meconium passage, which is observed in the presence of fetomaternal stress factors such as hypoxia and infection, independent of fetal maturation.[154] Meconium-stained amniotic fluid occurs more frequently with advanced gestational age and is common in post-term pregnancies.[158]

Although many fetuses with meconium-stained amniotic fluid are born without adverse sequelae, meconium can have detrimental effects on fetal organs and the placenta. Meconium may cause umbilical cord vessel constriction, vessel necrosis, and the production of thrombi, which can lead to altered coagulation, cerebral palsy, and neonatal seizures.[159] In addition, meconium may reduce the antibacterial properties of amniotic fluid by altering zinc levels.[154] Fetal aspiration of meconium also may neutralize the action of surfactant, promote lung tissue inflammation through the activation of neutrophils, and possibly result in meconium aspiration syndrome (see Chapter 9). Finally, in the presence of perinatal hypoxia, meconium also may contribute to vascular hypertrophy and possible pulmonary hypertension.[154]

FETAL NERVOUS SYSTEM

Over the course of gestation, the human brain and central nervous system begin to develop from a few embryonic cells to a complex system in which billions of neurons are arranged and interconnected; small, seemingly minor changes may have profound implications. For example, animal studies suggest that intrauterine exposure to a variety of anesthetic agents at specific time intervals appears to result in anatomic, functional, and behavioral changes following birth (see Chapter 10).

Structural and Functional Brain Development

Primary neuromodulation and neural tube formation occur by 4 weeks' gestation. Between 8 and 12 weeks' gestation, prosencephalon development is initiated, which

is accompanied by neuronal proliferation and migration. Simultaneously, the subplate layer is created to fulfill a critical, albeit transient, role as a location for synapses with cortical and thalamic projections; the subplate layer disintegrates between 24 and 28 weeks' gestation. A significant increase in cortical development, organization, and synapse formation begins by 20 weeks' gestation and continues postnatally; during the third trimester alone, the cerebral cortex volume increases fourfold.[160-163]

The first fetal movements are witnessed near the end of the first trimester. These initial movements have simple patterns and originate from spontaneous discharges within the spine and brainstem. The fetal movements become more organized and complex as the pregnancy progresses, with higher brain centers modulating the activity of the brainstem and spine.

The exact onset of electrocortical activity is unknown, but electroencephalographic (EEG) activity can be recorded in preterm infants as early as 24 weeks' gestation. Fetal EEG activity differs from that in the adult and is characterized by the presence of intermittent bursts of activity separated by periods of complete suppression. With maturation, these suppressed episodes become shorter and less frequent before completely disappearing in postnatal life. The early electrical activity within the nervous system controls several developmental processes, such as neuronal differentiation, migration, synaptogenesis, and formation of neuronal networks. For example, the initial spontaneous spinal and subcortical discharges are believed necessary for somatosensory development. As they elicit movements in the periphery, afferent signals establish topographic representation on the sensory cortex.[164-166]

Cerebral Metabolism

The immature brain, similar to the adult brain, relies mostly on oxidative metabolism for the production of energy. However, owing to the limited capacity for mitochondrial oxidative phosphorylation and the lower partial pressures of oxygen observed *in utero*, anaerobic glycolysis exhibits a greater role during this developmental period than after delivery.[167,168] In the presence of aerobic conditions, glucose is converted to pyruvic acid (glycolysis), which enters the Krebs cycle and the mitochondrial cytochrome system to create chemical energy; this process converts 1 mole of glucose into 36 moles of ATP. By contrast, during anaerobic conditions, glycolysis is much less efficient, yielding only 2 moles of ATP for each mole of glucose.[169]

Although glucose represents the primary and predominant source of cerebral energy, the perinatal brain is uniquely capable of metabolizing other substrates, such as lactic acid and ketone bodies (β-hydroxybutyrate and acetoacetate). Lactic acid concentrations in the peripartum period are significantly elevated and may support over 50% of total cerebral oxidative metabolism in certain conditions such as hypoglycemia and hypoxia.[170,171] During hypoxic conditions, the fetal brain will also significantly decrease its energy consumption, as evidenced by fewer fetal movements and a slower EEG wave pattern.[172]

Cerebral Blood Flow

The development of the neural tube begins with formation of endothelium-lined vascular channels; by 10 weeks' gestation, an extensive network of leptomeningeal arteries covers the fetal brain, allowing vessels to sprout and penetrate the brain parenchyma. Subsequent vascular growth is most pronounced in rapidly developing areas of the brain.[167]

The fetal systemic circulation has unique features that ensure optimal oxygen delivery to the brain. Well-oxygenated blood from the umbilical vein and ductus venosus is preferentially shunted through the foramen ovale to the left side of the heart and the ascending aorta to supply the cerebral and coronary circulations. Hypoxia results in acute changes in fetal and placental vascular resistance, which leads to intense peripheral vasoconstriction (likely mediated by stimulation of chemoreceptors) and further shunting of umbilical venous blood through the ductus venosus. The fetal circulatory system is much more sensitive to hypoxemia than that in the adult, which helps maintain oxygen delivery to the developing brain and myocardium (Figure 5-8).[173-175]

The redistribution of blood flow to the most actively developing regions of the fetal brain is at least partially the result of an adenosine-mediated mechanism. Adenosine, the breakdown product of ATP, accumulates during failure of ATP resynthesis and causes vasodilation of blood vessels and suppression of neuronal activity.[172] Other substances (e.g., nitric oxide, endogenous opioids, adrenomedullin) may also play a role in cerebral blood redistribution, but the exact mechanisms are incompletely understood.[176]

Nociception

Cutaneous sensory receptors are present in the human fetus at approximately 7 weeks' gestation, and a widespread network is established by 20 weeks. At term gestation, the density of cutaneous nociceptive receptors in the fetus is comparable to, and may even exceed, that of the adult. Although the development of sensory fiber-to-dorsal horn interneuron synapses has been reported to occur as early as 6 weeks' gestation,[177] differentiation of dorsal horn neurons begins at approximately 13 weeks' gestation; the laminar arrangement of dorsal horn neurons, replete with synaptic interconnections and neurotransmitter vesicles, is present in some regions of the spinal cord by 30 weeks' gestation.[178] At this time, the A-delta and C fibers make connections at the spinal cord level and with the surrounding dermatomes.

The neurons of the cerebral cortex develop by 20 weeks' gestation, and synaptogenesis of the thalamocortical connections is established between 20 and 24 weeks' gestation. Thalamocortical axons reach the somatosensory cortex at 24 to 26 weeks' gestation. Myelination of the pain pathways of the spinal cord and brainstem is completed during the second and third trimesters of gestation[179]; however, the process continues postnatally in other areas of the brain and in peripheral

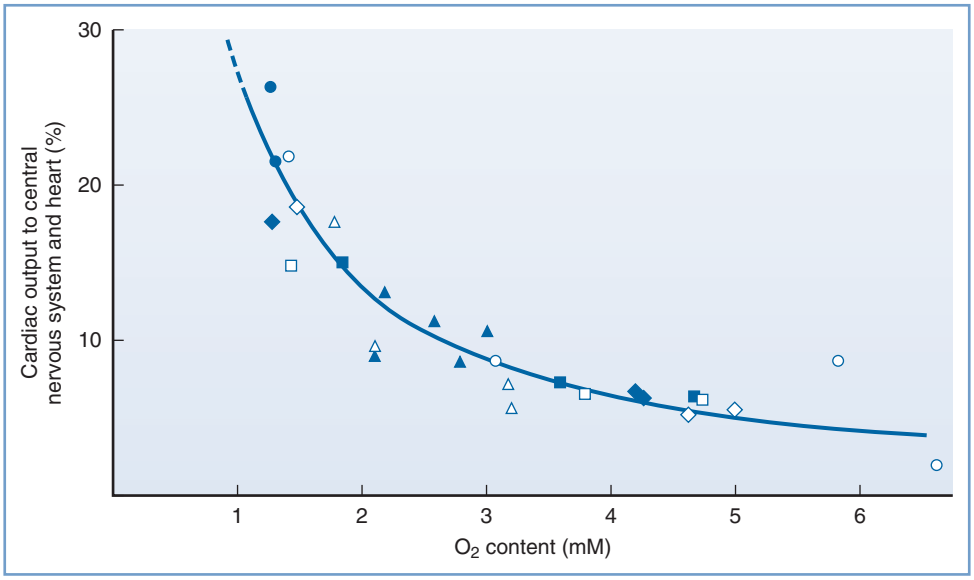

FIGURE 5-8 ■ The redistribution of cardiac output to the heart and central nervous system during hypoxemia in fetal lambs. Each symbol represents a measurement from an individual fetal lamb. (Modified from Sheldon RE, Peeters LLH, Jones MD Jr, et al. Redistribution of cardiac output and oxygen delivery in the hypoxic fetal lamb. Am J Obstet Gynecol 1979; 135:1071-8.)

nerve fibers. Although optimal pain processing requires myelination of pain pathways, cortical maturation, dendritic arborization, and thalamocortical fiber synaptogenesis, it is unclear when nociception, the capacity to feel pain, develops within the fetus. As early as 18 weeks' gestation, human fetuses demonstrate pituitary-adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli.[180-182] In studies of intrauterine blood transfusion in the human fetus, surgical needling of the intrahepatic vein (compared with needling of the insensate umbilical cord) is associated with evidence of a stress response, including increases in plasma beta-endorphin and cortisol levels and a diminution in the middle cerebral artery pulsatility index.[183] Administration of fentanyl 10 μg/kg blunts this stress response to intrahepatic needling.[184]

Near-infrared spectroscopy has demonstrated cortical activity in response to noxious stimuli in preterm neonates born and studied as early as 25 weeks' postmenstrual age.[185,186] Similarly, facial responses to painful stimuli (similar to those seen in adults) can be provoked in preterm neonates born and assessed as early as 25 weeks' gestation, which suggests the development of functional pathways from the spinal cord to the brain.[187,188] However, the withdrawal from noxious stimuli or an increased release of stress hormones does not necessarily reflect an *awareness* of pain, because local spinal reflexes and hormonal release can occur without cortical involvement.[189] The experience of pain is a conscious subjective experience with emotional and affective components that requires higher-level cortical processing. Nociceptive processing begins in the peripheral neurons, which relay signals through the spinothalamic tract, the thalamus, and ultimately the cerebral cortex, where conscious perception of pain occurs.[190]

After birth, neonates appear to be more sensitive to pain, with lower pain thresholds, poor discriminative abilities, and a greater tendency to exhibit central sensitization in response to later noxious stimuli than adults. Early sensory experiences in the neonate can influence the development of nociceptive pathways.[191] Neonates and especially preterm infants who undergo numerous procedures in the neonatal intensive care unit and/or surgery have been observed to demonstrate altered pain perceptions later in life.[192] In the rodent model, tissue injury in early neonatal life results in an increased magnitude and duration of hyperalgesia after reinjury in later life, compared with those with no early life pain experience.[191] Collectively, these observations have prompted some investigators to conclude that noxious events in neonates, when pain pathways are still undergoing a learning or "tuning process," may result in structural functional and behavioral alterations in adult pain processing. Some of these long-term consequences may be attenuated by preemptive analgesia.[193]

The foregoing neuroanatomic and neurochemical evidence, in addition to the well-characterized behavioral and physiologic responses to pain, indicate that both the fetus and newborn infant have nociceptive pathways capable of communicating nociceptive stimuli from the periphery to the cerebral cortex and regulating the response via efferent inhibitory pathways. Current evidence suggests that fetal nociception at the level of the cortex occurs after the midpoint of pregnancy (i.e., between 24 and 30 weeks' gestation). Of note, maternal administration of general anesthesia does not guarantee the presence of fetal anesthesia or analgesia (see Chapter 7). For example, most infants are clearly awake and cry loudly immediately after cesarean delivery during maternal administration of general anesthesia.

KEY POINTS

- Amniotic fluid serves a number of vital roles, including the facilitation of fetal growth, the provision of a microgravity environment that cushions the fetus, and the generation of a defense mechanism against invading microbes.
- The fetus depends on the mother and the placenta for its basic metabolic needs, such as nutrient delivery, gas exchange, and electrolyte and acid-base homeostasis.
- Fetal arterial blood P_{O_2} ranges from 20 to 30 mm Hg, and fetal development exists in a state of relative hypoxia compared with adult oxygen tension.
- Despite a lower fetal oxygen tension, the fetal arterial blood oxygen content is not much lower than that of the adult. This results from a higher oxygen-carrying capacity (hemoglobin concentration of 18 g/dL) and a higher affinity of hemoglobin F for oxygen, when compared with hemoglobin A.
- The fetus produces approximately twice as much heat (on a weight-adjusted basis) and maintains a temperature 0.5°C higher than the mother during the third trimester.
- The fetal circulation receives output from both the left and the right ventricle, with the ventricles working in parallel. Systemic blood flow consists of the sum of the right and left ventricular outputs, with the exception of the small amount of blood delivered to the fetal lungs by the right ventricle.
- Fetal blood flow is characterized by three important communications between the left and right circulation: the ductus venosus, the foramen ovale, and the ductus arteriosus.
- Acute hypotension in the fetus stimulates a reflex response, which includes both bradycardia and vasoconstriction.
- The sympathetic nervous system at birth is not as well developed as the parasympathetic nervous system; however, it plays an important role in the hemodynamic adjustments at birth.
- Although fetal fluid and electrolyte balance, as well as acid-base homeostasis, are primarily regulated and maintained by the placenta, the fetal kidneys play an important role in fetal development through amniotic fluid production.
- The pulmonary surfactant system is one of the last systems to develop before birth. Surfactant assembly occurs in the type II alveolar cells, and components of surfactant are first detected between 24 and 28 weeks' gestation.
- Fetal hemoglobin has a greater oxygen affinity than adult hemoglobin, owing to a decreased interaction between hemoglobin F and 2,3-DPG. The P_{50} of fetal blood is significantly lower than that of adult blood.
- Fetal hypoxemia leads to a significant redistribution of cardiac output to the heart and the brain. This results in both a global increase in cerebral blood flow and a redistribution of blood flow within the fetal brain.
- Fetal swallowing plays an important role in amniotic fluid homeostasis, and the swallowed fluid appears to provide nutritional support for mucosal development within the gastrointestinal tract.
- The fetus has nociceptive pathways capable of communicating painful stimuli from the periphery to the cerebral cortex. Current evidence suggests that fetal nociception at the level of the cortex occurs after the midpoint of pregnancy (i.e., between 24 and 30 weeks' gestation).

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PART III

FETAL AND NEONATAL ASSESSMENT AND THERAPY

Donald Caton, MD

Ostensibly, concern for the neonate began in 1861, when London physician W. J. Little published a paper entitled "On the influence of abnormal parturition, difficult labors, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities."[1] Hailed as "an original field of observation," Little's paper was among the first to identify antepartum asphyxia as the cause of problems in the neonate.

Almost half a century passed, however, before clinicians developed a sustained interest in fetal oxygenation. This development came through the influence of Sir Joseph Barcroft and his book *Researches on Prenatal Life*.[2] A professor of physiology at Cambridge University, Barcroft was already highly respected for his studies of respiration when this book was published.

From his laboratory studies, Barcroft discovered a progressive decrease in fetal oxygen saturation during the last half of pregnancy. He attributed this finding to the fetal demands for oxygen, which slowly increased until the capacity of the placenta was exhausted. Barcroft compared the fetus to a mountaineer climbing Mt. Everest, in that the oxygen environment of the fetus became progressively less dense. He suggested that the term fetus faced either asphyxia *in utero* or escape through the initiation of labor. Barcroft's depiction of the fetal environment disturbed clinicians who were already well aware of the additional stress imposed by labor.

Ironically, one of Barcroft's own students proved him wrong. D. H. Barron, professor of physiology at Yale, suggested that Barcroft's data had been skewed by the conditions of his experiments, all of which had been conducted on animals anesthetized for immediate surgery. Barron and his colleagues developed methods to sample fetal blood in awake, unstressed animals. Under these circumstances, they observed no deterioration in the fetal environment until the onset of labor. Oxygen saturation, hemoglobin concentration, and pH remained stable and normal.[3]

Barcroft's data have had the greatest impact on clinical practice. Virtually all current methods of fetal monitoring grew out of the belief that oxygen availability is the single most important factor influencing the well-being of the newborn. However, Barron's studies affected physiologists, who began to study the mechanisms that maintained the stability of the intrauterine environment in the presence of increasing fetal demands.

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CHAPTER 6

Antepartum Fetal Assessment and Therapy

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CHAPTER OUTLINE

Obstetric care providers have two patients, the mother and the fetus. Although assessment of maternal health is relatively straightforward, assessment of fetal well-being is far more challenging. Several tests have been developed to assess the fetus during pregnancy, including some that are recommended for all pregnancies (e.g., ultrasonography for pregnancy dating) and others that are reserved only for women with pregnancy complications (e.g., middle cerebral artery Doppler velocimetry in pregnancies with isoimmunization). In addition, a limited number of fetal interventions are employed to improve fetal outcome, including some that are used frequently, such as maternal corticosteroid administration, and others that are used much more rarely, such as intrauterine fetal procedures. A review is presented here of the tests available to assess fetal well-being in both low- and high-risk pregnancies and of the fetal therapies used during the antepartum period.

PRENATAL CARE IN LOW-RISK PREGNANCIES

Determination of Gestational Age

The mean duration of a singleton pregnancy is 280 days (40 weeks) from the first day of the last normal menstrual period in women with regular 28-day menstrual cycles. *Term*, defined as the period from 37 weeks' (259 days') to 42 weeks' (294 days') gestation, is the optimal time for delivery. Both preterm births (defined as delivery before 37 weeks' gestation) and post-term births (delivery after 42 weeks' gestation) are associated with increased perinatal and neonatal morbidity and mortality. Evaluation of fetal growth, efficient use of screening and diagnostic tests, appropriate initiation of fetal surveillance, and optimal timing of delivery all depend on accurate dating of the pregnancy.

A number of clinical, biochemical, and radiologic tests are available to determine gestational age (Box 6-1).[1,2] Determination of gestational age is most accurate in early pregnancy, and the estimated date of delivery (EDD) should be established at the first prenatal visit. Embryo transfer dating in women undergoing *in vitro* fertilization (IVF) is the most accurate clinical dating criterion. Among women with regular menstrual cycles who conceive spontaneously, if the first day of the last menstrual period (LMP) is known and if uterine size is consistent with dates by clinical examination, then Naegele's rule (subtract 3 months and add 7 days to the LMP) can be used to determine the EDD. Menstrual dating is known to be inaccurate in women taking oral contraceptives, in women who conceive in the immediate postpartum period, and in women who have irregular menstrual cycles or a history of intermenstrual bleeding. Moreover, clinical examination of uterine size can be inaccurate in

BOX 6-1 Clinical Criteria Commonly Used to Confirm Gestational Age

- Reported date of last menstrual period (estimated due date can be calculated by subtracting 3 months and adding 7 days to the first day of the last normal menstrual period [Naegele's rule]) or date of assisted reproductive technology (intrauterine insemination or embryo transfer)
- The size of the uterus as estimated on bimanual examination in the first trimester, which should be consistent with dates
- The perception of fetal movement ("quickening"), which usually occurs at 18 to 20 weeks in nulliparous women and at 16 to 18 weeks in parous women
- Fetal heart activity, which can be detected with a nonelectronic fetal stethoscope by 18 to 20 weeks and with Doppler ultrasonography by 10 to 12 weeks
- Fundal height; at 20 weeks, the fundal height in a singleton pregnancy should be approximately 20 cm above the pubic symphysis (usually corresponding to the umbilicus)
- Ultrasonography, involving crown-rump length measurement of the fetus during the first trimester, or fetal biometry (biparietal diameter, head circumference, and/or femur length) during the second trimester

Data from American College of Obstetricians and Gynecologists. Antepartum fetal surveillance. ACOG Practice Bulletin No. 9. Washington, DC, 1999 (reaffirmed 2009); and American College of Obstetricians and Gynecologists. Management of postterm pregnancy. ACOG Practice Bulletin No. 55. Washington, DC, 2004 (reaffirmed 2009).

women with a high body mass index (BMI), uterine fibroids, or a multifetal pregnancy. For these reasons, reliance on standard clinical criteria alone to determine the EDD will lead to an inaccurate diagnosis, with a tendency to overestimate gestational age.[3-6] One study reported that reliance on LMP alone leads to a false diagnosis of preterm birth and post-term pregnancy in one fourth and one eighth of cases, respectively.[7] Use of other historic factors (e.g., the date of the first positive pregnancy test result or the first perceived fetal movements ["quickening"]) and physical findings (e.g., the date when fetal heart sounds are first audible) may help obstetric providers determine the EDD more accurately (see Box 6-1).

Most early pregnancy tests involve the identification and quantification of human chorionic gonadotropin (hCG), a hormone produced by the syncytiotrophoblast of the fetoplacental unit.[8,9] Levels in the maternal circulation increase exponentially to a peak of 80,000 to 100,000 mIU/mL at 8 to 10 weeks' gestation and then decrease to a level of 20,000 to 30,000 mIU/mL for the remainder of the pregnancy. Commercially available hCG test kits can detect concentrations as low as 25 to 50 mIU/mL in serum or urine, which are typically evident 8 to 9 days after conception.

Uncertainty in dating parameters should prompt ultrasonographic assessment of gestational age. Transabdominal ultrasonography can identify an intrauterine sac in 94% of eutopic (intrauterine) pregnancies once the serum hCG concentration is 6000 mIU/mL or higher.[10] With the use of transvaginal ultrasonography, an intrauterine pregnancy can typically be confirmed at a serum hCG level of 1500 to 2000 mIU/mL.[11] Failure to confirm an intrauterine sac at these hCG levels should raise concerns about an abnormal pregnancy (e.g., ectopic pregnancy, missed abortion) and requires further evaluation. A fetal pole and cardiac activity should be visible at a serum hCG concentration of approximately 1700 mIU/mL (5 to 6 weeks) and 5400 mIU/mL (6 to 8 weeks), respectively. The EDD derived from ultrasonographic evaluation should be used when there is a 5- to 7-day discrepancy from LMP dating in the first trimester.[11]

In the first trimester, the fetal crown-rump length (CRL) is the most accurate determinant of gestational age (± 3 to 5 days). In the second trimester, the biparietal diameter (BPD) and length of the long bones (especially femur length) are the ultrasonographic measurements used most often to determine gestational age. Of these, the BPD is the more accurate indicator with a variation of ± 7 to 10 days.[12] Two large clinical studies of approximately 50,000 pregnancies demonstrated that a second-trimester BPD measurement, when used instead of menstrual dating to establish the EDD, resulted in a significant increase in the number of women who delivered within 7 days of their due dates and a 60% to 70% reduction in the number of pregnancies continuing post term.[13,14] After 26 weeks' gestation, the variation in the BPD measurement is greater (± 14 to 21 days), thereby making it less valuable in estimating gestational age.[12] Both femur length and humerus length correlate strongly with the BPD and gestational age and are sometimes used for additional confirmation.[15] By contrast, because abdominal circumference (AC) reflects fetal nutritional status and growth, it is less accurate than either BPD or femur length. All fetal biometric measurements are subject to some degree of error, so a number of techniques have been used to predict gestational age more accurately. Serial determinations of gestational age at 2- to 3-week intervals may be more accurate than a single determination in the third trimester to confirm dating and eliminate the possibility of fetal growth restriction.

Routine Ultrasonography

Routine early ultrasonography significantly improves the accuracy of gestational age dating.[3-6,16-19] Early ultrasonography can also detect pregnancy abnormalities (e.g., molar pregnancy), major fetal structural abnormalities (e.g., anencephaly), and multiple pregnancy. Although recommended in Europe, the practice of routine ultrasonography for pregnancy dating has not been recommended as a standard of prenatal care in the United States.[20,21]

The usefulness of routine second-trimester ultrasonography in all pregnant women remains a subject of debate. Early studies suggested an improvement in perinatal outcome with its use.[17,22-25] For example, one prospective clinical trial in Helsinki, Finland, randomly assigned 9310 low-risk women either to a single screening ultrasonographic examination at 16 to 20 weeks' gestation or to ultrasonography for obstetric indications only; a significantly lower perinatal mortality rate was

found in the screening ultrasonography group (4.6 versus 9.0 per 1000 births, respectively).[18] This difference was due in part to earlier detection of major fetal malformations (which prompted elective abortion) and multiple pregnancies (which resulted in more appropriate antenatal care) with the screening examination. As expected, routine ultrasonography also led to improved pregnancy dating and a lower rate of induction of labor for postterm pregnancy.[18]

In contrast, a subsequent large multicenter randomized clinical trial involving 15,151 low-risk women in the United States (designated as the RADIUS study) concluded that screening ultrasonography did *not* improve perinatal outcomes and had no impact on the management of the anomalous fetus.[19,26,27] Although this trial was adequately powered, it has been criticized for the highly selective entry criteria (by one estimate, less than 1% of pregnant women in the United States would have been eligible[28]) and the selection of primary outcomes (perinatal morbidity and mortality) that were inappropriate for the low-risk population studied. In addition, only 17% of major congenital anomalies were detected before 24 weeks' gestation in the routine ultrasonography group, so the rate of elective pregnancy termination for fetal anomalies was significantly lower than that in the Helsinki study. The skill and experience of the ultrasonographer is also an important variable in these studies.

Evaluation of Fetal Growth

Normal fetal growth is a critical component of a healthy pregnancy and the subsequent long-term health of the child. Maternal weight gain during pregnancy is at best an indirect measure of fetal growth, because much of the weight gain during pregnancy is the result of fluid (water) retention. Earlier recommendations for weight gain in pregnancy were based on the Institute of Medicine (IOM) guidelines published in 1990.[29] In 2009, the IOM revised their 1990 recommendations to include an upper limit of weight gain for obese women (9 kg [20 lb]), and they altered the lower limit of weight gain from 6.8 kg (15 lb) to 5 kg (11 lb) (Table 6-1); they also recommended that all women try to be within the normal BMI range when they conceive.[30]

The size, presentation, and lie of the fetus can be assessed with abdominal palpation. A systematic method of examination of the gravid abdomen was first described by Leopold and Sporlin in 1894.[31] Although the abdominal examination has several limitations (especially in the setting of a small fetus, maternal obesity, multiple pregnancy, uterine fibroids, or polyhydramnios), it is safe, is well tolerated, and may add valuable information to assist in antepartum management. Palpation is divided into four separate Leopold's maneuvers (Figure 6-1). Each maneuver is designed to identify specific fetal landmarks or to reveal a specific relationship between the fetus and mother. The first maneuver, for example, involves measurement of the fundal height. The uterus can be palpated above the pelvic brim at approximately 12 weeks' gestation. Thereafter, fundal height should increase by approximately 1 cm per week, reaching the level of the umbilicus at 20 to 22 weeks' gestation (Figure 6-2). Between 20 and 32 weeks' gestation, the fundal height (in centimeters) is approximately equal to the gestational age (in weeks) in healthy women of average weight with an appropriately growing fetus. However, there is a wide range of normal fundal height measurements. In one study, a 6-cm difference was noted between the 10th and 90th percentiles at each week of gestation after 20 weeks.[32] Moreover, maximal fundal height occurs at approximately 36 weeks' gestation, after which time the fetus drops into the pelvis in preparation for labor. For all of these reasons, reliance on fundal height measurements alone fails to identify more than 50% of fetuses with fetal growth restriction (also known as intrauterine growth restriction).[33] Serial fundal height measurements by an experienced obstetric care provider are more accurate than a single measurement and will lead to better diagnosis of fetal growth restriction, with reported sensitivities as high as 86%.[34]

If clinical findings are not consistent with the stated gestational age, ultrasonography is indicated to confirm gestational age and provide a more objective measure of fetal growth. Ultrasonography may also identify an

TABLE 6-1 Recommendations for Weight Gain in Pregnancy

Mother's Body Mass Index	Recommended Weight Gain
18.5 to 24.9 kg/m^2 (normal weight)	11.2 to 15.9 kg (25 to 35 lb)
25 to 29.9 kg/m^2 (overweight)	6.8 to 11.2 kg (15 to 25 lb)
>30 kg/m^2 (obesity)	5.0 to 9.0 kg (11 to 20 lb)

Data from the Institute of Medicine. Nutritional status and weight gain. In Nutrition during Pregnancy. Available at http://iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx.

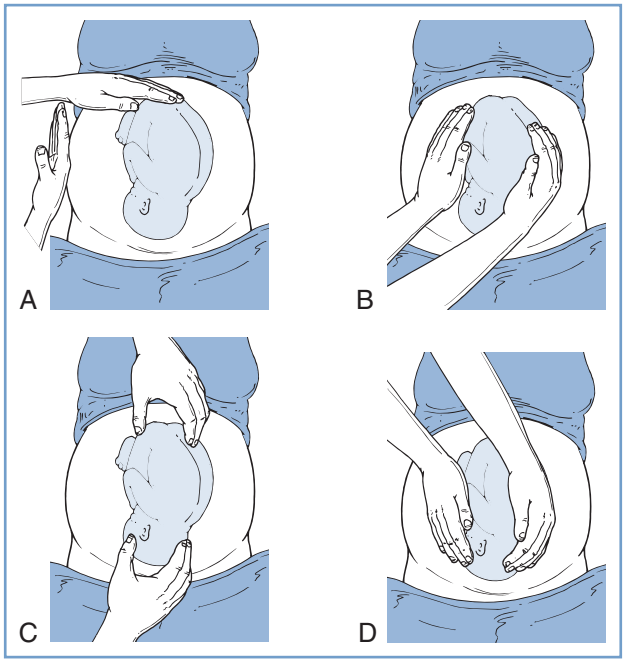

FIGURE 6-1 ■ Leopold's maneuvers for palpation of the gravid abdomen.

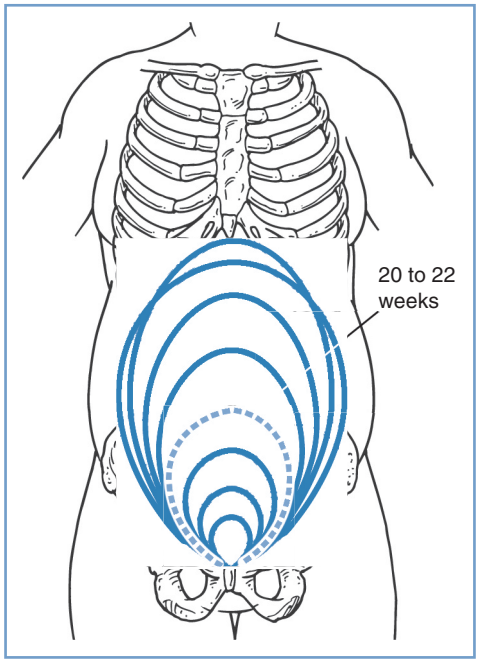

FIGURE 6-2 ■ Fundal height measurements in a singleton pregnancy with normal fetal growth.

alternative explanation for the discrepancy, such as multifetal pregnancy, polyhydramnios, fetal demise, and uterine fibroids. For many years, obstetric ultrasonography has used fetal biometry to define fetal size by weight estimations. This approach has a number of limitations. First, regression equations used to create weight estimation formulas are derived primarily from cross-sectional data for infants being delivered within an arbitrary period after the ultrasonographic examination. Second, these equations assume that body proportions (fat, muscle, bone) are the same for all fetuses.[34-45] Finally, growth curves for "normal" infants between 24 and 37 weeks' gestation rely on data collected from pregnancies delivered preterm, which are abnormal and probably complicated by some element of uteroplacental insufficiency, regardless of whether the delivery was spontaneous or iatrogenic. Despite these limitations, if the gestational age is well validated, the prevailing data suggest that prenatal ultrasonography can be used to verify an alteration in fetal growth in 80% of cases and to exclude abnormal growth in 90% of cases.[46]

Ultrasonographic estimates of fetal weight are commonly derived from mathematical formulas that use a combination of fetal measurements, especially the BPD, AC, and femur length.[47] The AC is the single most important measurement and is weighted more heavily in these formulas. Unfortunately, the AC is also the most difficult measurement to acquire, and small differences in the measured value result in large changes in the estimated fetal weight (EFW). The accuracy of the EFW depends on a number of variables, including gestational age (in absolute terms, EFW is more accurate in preterm or growth-restricted fetuses than in term or macrosomic fetuses), operator experience, maternal body habitus, and amniotic fluid volume (measurements are more difficult to acquire if the amniotic fluid volume is low). Objective ultrasonographic EFW estimations have an error of 15% to 20%, even in experienced hands.[48] Indeed, an ultrasonographic EFW at term is no more accurate than a clinical estimate of fetal weight made by an experienced obstetric care provider or the mother's estimate of fetal weight if she has delivered before.[49] Ultrasonographic estimates of fetal weight must therefore be evaluated within the context of the clinical situation and balanced against the clinical estimate. Serial ultrasonographic evaluations of fetal weight are more useful than a single measurement in diagnosing abnormal fetal growth. The ideal interval for fetal growth evaluations is every 3 to 4 weeks, because more frequent determinations may be misleading. Similarly, the use of population-specific growth curves, if available, improves the ability of the obstetric care provider to identify abnormal fetal growth. For example, growth curves derived from a population that lives at high altitude, where the fetus is exposed to lower oxygen tension, will be different from those derived from a population at sea level. Abnormal fetal growth can be classified as insufficient (fetal growth restriction) or excessive (fetal macrosomia).

Fetal Growth Restriction

The definition of *fetal growth restriction* has been a subject of long-standing debate. Distinguishing the healthy, constitutionally small-for-gestational-age (SGA) fetus, defined as having an EFW below the 10th percentile for a given week of gestation, from the nutritionally deprived, truly growth-restricted fetus has been particularly difficult. Fetuses with an EFW less than the 10th percentile are not necessarily pathologically growth restricted. Conversely, an EFW above the 10th percentile does not necessarily mean that an individual fetus has achieved its growth potential, and such a fetus may still be at risk for perinatal mortality and morbidity. Therefore, fetal growth restriction is best defined as either (1) an EFW less than the 5th percentile for gestational age in a well-dated pregnancy or (2) an EFW less than the 10th percentile for gestational age in a well-dated pregnancy with evidence of fetal compromise, such as oligohydramnios or abnormal umbilical artery Doppler velocimetry.

Fetal growth restriction has traditionally been classified as either asymmetric or symmetric fetal growth restriction. **Asymmetric fetal growth restriction,** characterized by normal head growth but suboptimal body growth, is seen most commonly in the third trimester. It is believed to result from a late pathologic event (e.g., chronic placental abruption leading to uteroplacental insufficiency) in an otherwise uncomplicated pregnancy and normal fetus. In cases of **symmetric fetal growth restriction,** both the fetal head size and body weight are reduced, indicating a global insult that likely occurred early in gestation. Symmetric fetal growth restriction may reflect an inherent fetal abnormality (e.g., fetal chromosomal anomaly, inherited metabolic disorder, early congenital infection) or long-standing severe placental insufficiency due to an underlying maternal disease (e.g., hypertension, pregestational diabetes mellitus, or

collagen vascular disorder). In practice, the distinction between asymmetric and symmetric fetal growth restriction is not particularly useful.

Early and accurate diagnosis of fetal growth restriction coupled with appropriate intervention leads to an improvement in perinatal outcome. If fetal growth restriction is suspected clinically and on the basis of ultrasonography, a thorough evaluation of the mother and fetus is indicated. Referral to a maternal-fetal medicine specialist should be considered. Every effort should be made to identify the cause of the fetal growth restriction and to modify or eliminate contributing factors. Up to 20% of cases of severe fetal growth restriction are associated with fetal chromosomal abnormalities or congenital malformations, 25% to 30% are related to maternal conditions characterized by vascular disease, and a smaller proportion are the result of abnormal placentation. Other causes of fetal growth restriction include exposure to teratogens, alcohol, and substance abuse. In a substantial number of cases (>50% in some studies), the etiology of the fetal growth restriction remains unclear even after a thorough investigation.[50]

Fetal Macrosomia

Fetal macrosomia is defined as an EFW (not birth weight) of 4500 g or greater measured either clinically or by ultrasonography and is independent of gestational age, diabetic status, and actual birth weight.[51] Fetal macrosomia should be differentiated from the large-for-gestational age (LGA) fetus, in whom the EFW is greater than the 90th percentile for gestational age. By definition, 10% of all fetuses are LGA at any given gestational age. Fetal macrosomia is associated with an increased risk for cesarean delivery, instrumental vaginal delivery, and birth injury to both the mother (including vaginal, perineal, and rectal trauma) and the infant (orthopedic and neurologic injury).[52-56] Shoulder dystocia with resultant brachial plexus injury (Erb's palsy) is a serious consequence of fetal macrosomia; it is more likely in the setting of diabetes because of the larger diameters of the fetal upper thorax and neck.

Fetal macrosomia can be determined clinically (e.g., Leopold's maneuvers) or with ultrasonography, and these two techniques appear to be equally accurate.[57] Estimated fetal weight measurements are less accurate in macrosomic fetuses than in normally grown fetuses, and factors such as low amniotic fluid volume, advancing gestational age, maternal obesity, and fetal position can compound these inaccuracies. Indeed, clinical examination has been shown to underestimate the birth weight by more than 0.5 kg in almost 80% of macrosomic fetuses.[58] For all these reasons, prediction of fetal macrosomia is not particularly accurate, with a false-positive rate of 35% and a false-negative rate of 10%.[57,58] A number of alternative ultrasonographic measurements have therefore been proposed in an attempt to better identify the macrosomic fetus, including fetal AC alone,[59] umbilical cord circumference,[60] cheek-to-cheek diameter,[61] and subcutaneous fat in the mid humerus, thigh, abdominal wall, and shoulder.[62] However, these measurements remain investigational.

Despite the inaccuracy in the prediction of fetal macrosomia, an EFW should be documented by either clinical estimation or ultrasonography in all high-risk women at approximately 38 weeks' gestation. Suspected fetal macrosomia is not an indication for induction of labor, because induction does not improve maternal or fetal outcomes and may increase the risk for cesarean delivery.[51] The American College of Obstetricians and Gynecologists (ACOG) recommends performance of an elective cesarean delivery when the suspected birth weight exceeds 4500 g in a diabetic woman or 5000 g in a nondiabetic woman.[51,52,63]

Assessment of Fetal Well-Being

All pregnant women should receive regular antenatal care throughout their pregnancy, and fetal well-being should be evaluated at every visit. Fetal heart activity should be assessed and the fetal heart rate (FHR) estimated. A low FHR (<100 bpm) is associated with an increased risk for pregnancy loss, although congenital complete heart block should be excluded. In the latter half of pregnancy, physical examination of the abdomen should be performed to document fetal lie and presentation.

Fetal movements ("quickening") are typically reported at 18 to 20 weeks' gestation by nulliparous women and at 16 to 18 weeks' gestation by parous women; the presence of fetal movements is strongly correlated with fetal health. Although the mother appreciates only 10% to 20% of total fetal movements,[64-67] such movements are almost always present when she does report them.[67] Factors associated with a diminution in perceived fetal movements include increasing gestational age, smoking, decreased amniotic fluid volume, anterior placentation, and antenatal corticosteroid therapy. Decreased fetal movements may also be a harbinger of an adverse pregnancy event (e.g., stillbirth) that can be averted if detected early. For these reasons, a subjective decrease in perceived fetal movements in the third trimester should prompt an immediate investigation.

Published studies support the value of **fetal movement** charts ("kick counts") in the detection and prevention of fetal complications (including stillbirth) in both high- and low-risk populations.[68-73] The normal fetus exhibits an average of 20 to 50 (range of 0 to 130) gross body movements per hour, with fewer movements during the day and increased activity between 9:00 PM and 1:00 AM.[74] Several different schemes have been proposed to determine the baseline fetal activity pattern for an individual fetus after 28 weeks' gestation and to evaluate activity patterns that may represent fetal compromise. One commonly used scheme ("count-to-10") instructs the mother to rest quietly on her left side once each day in the evening (between 7:00 PM and 11:00 PM) and to record the time interval required to feel 10 fetal movements. Most patients with a healthy fetus will feel 10 movements in approximately 20 minutes; 99.5% of women with a healthy fetus feel this amount of activity within 90 minutes.[75] Under this scheme, failure to appreciate 10 fetal movements in 2 hours should prompt immediate fetal assessment. In one large clinical trial, institution of this fetal activity monitoring scheme

BOX 6-2 High-Risk Pregnancies

Maternal Factors

- Preeclampsia (gestational proteinuric hypertension)
- Chronic hypertension
- Diabetes mellitus (including gestational diabetes)
- Maternal cardiac disease
- Chronic renal disease
- Chronic pulmonary disease
- Active thromboembolic disease

Fetal Factors

- Nonreassuring fetal testing (fetal compromise)
- Fetal growth restriction
- Isoimmunization
- Intra-amniotic infection
- Known fetal structural anomaly
- Prior unexplained stillbirth
- Multiple pregnancy

Uteroplacental Factors

- Premature rupture of fetal membranes
- Unexplained oligohydramnios
- Prior classic (high vertical) hysterotomy
- Placenta previa
- Placental abruption
- Vasa previa

resulted in a significant increase in hospital visits, labor induction, and cesarean deliveries, but also in a reduction in perinatal mortality from 44.5 to 10.3 per 1000 births.[75] Taken together, these data suggest that daily or twice-daily fetal "kick counts" should be performed after 32 weeks' gestation in high-risk pregnancies. Currently there is insufficient evidence to recommend this practice in low-risk pregnancies.

PRENATAL CARE IN HIGH-RISK PREGNANCIES

Approximately 20% of all pregnancies should be regarded as high risk (Box 6-2). Because of the attendant risks to both the mother and fetus, additional efforts should be made to confirm fetal well-being throughout such pregnancies. In addition to the testing outlined previously, high-risk pregnancies should be monitored closely and regularly by a multidisciplinary team, including subspecialists in maternal-fetal medicine and neonatology, if indicated.

Goals of Antepartum Fetal Testing

The goal of antepartum fetal surveillance is the early identification of a fetus at risk for preventable neurologic injury or death. Numerous causes of neonatal cerebral injury exist, including congenital abnormalities, chromosomal abnormalities, intracerebral hemorrhage, hypoxia, infection, drugs, trauma, hypotension, and metabolic derangements (e.g., hypoglycemia, thyroid dysfunction). Antenatal fetal testing cannot reliably predict or detect all of these causes; however, those specifically associated with uteroplacental vascular insufficiency should be identified when possible. Antenatal fetal testing makes the following assumptions: (1) pregnancies may be complicated by progressive fetal asphyxia that can lead to fetal death or permanent neurologic handicap; (2) current antenatal tests can adequately discriminate between asphyxiated and nonasphyxiated fetuses; and (3) detection of asphyxia at an early stage can lead to an intervention that is capable of reducing the likelihood of an adverse perinatal outcome.

Of interest, it is not clear whether any of these assumptions are true, and nonreassuring fetal test results may reflect existing but not ongoing neurologic injury. At most, 15% of cases of cerebral palsy are thought to result from antepartum or intrapartum hypoxic-ischemic injury.[75-78] Despite these limitations, a number of antepartum tests have been developed in an attempt to identify fetuses at risk. These include the nonstress test (NST), biophysical profile (BPP), and contraction stress test (CST). Such tests can be used either individually or in combination. There is no consensus as to which of these modalities is preferred, and no single method has been shown to be superior.[1]

Antepartum Fetal Tests

All antepartum fetal tests should be interpreted in relation to the gestational age, the presence or absence of congenital anomalies, and underlying clinical risk factors.[79] For example, a nonreassuring NST in a pregnancy complicated by severe fetal growth restriction and heavy vaginal bleeding at 32 weeks' gestation has a much higher predictive value in identifying a fetus at risk for subsequent neurologic injury than an identical tracing in a well-grown fetus at 40 weeks, because of the higher prevalence of this condition in the former situation. It should be remembered that, in many cases, the efficacy of antenatal fetal testing in preventing long-term neurologic injury has not been validated by prospective randomized clinical trials. Indeed, because of ethical and medicolegal concerns, there are no studies of pregnancies at risk that include a nonmonitored control group, and it is highly unlikely that such trials will ever be performed.

Nonstress Test

The fetal nonstress test, also known as fetal cardiotocography, investigates changes in the FHR pattern with time and reflects the maturity of the fetal autonomic nervous system. For this reason, it is less useful in the extremely premature fetus (< 28 weeks) before the autonomic nervous system has matured sufficiently to influence the FHR. The NST is noninvasive, simple to perform, inexpensive, and readily available in all obstetric units. However, interpretation of the NST is largely subjective. Although a number of different criteria have been used to evaluate these tracings, most obstetric care providers have used the definitions for FHR interpretation established in 1997 by the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop (Table 6-2).[80] A 2008 NIH report summarized

TABLE 6-2 Interpretation of Antepartum Nonstress Test Results

Criterion	Definition
Baseline fetal heart rate (FHR)	Defined as the approximate mean FHR during a 10-min segment and lasting at least 2 min. The normal FHR is defined as 110 to 160 bpm.
Baseline FHR variability	Described as fluctuations in the baseline FHR of ≥ 2 cycles/min. It is quantified visually as the amplitude of peak-to-trough in bpm. Variability is classified as follows: • Absent: amplitude range undetectable • Minimal: amplitude range detectable but ≤ 5 bpm • Moderate: amplitude range 6 to 25 bpm • Marked: amplitude range > 25 bpm The normal baseline FHR variability is defined as moderate variability.
Accelerations	Defined as an abrupt increase in FHR above baseline. • At and after 32 weeks' gestation, an acceleration is defined as ≥ 15 bpm above baseline for ≥ 15 sec but < 2 min. • Before 32 weeks' gestation, an acceleration is defined as ≥ 10 bpm above baseline for ≥ 10 sec but < 2 min. A **prolonged acceleration** is defined as an acceleration lasting ≥ 2 min but < 10 min. If the duration is longer than 10 min, it is referred to as a "change in baseline" and not a prolonged acceleration.
Decelerations	Decelerations are not normal. However, some decelerations are a more serious sign of fetal compromise than others. The following three types of decelerations are recognized: • **Early decelerations** are characterized by a gradual decrease and return to baseline FHR associated with a uterine contraction. The onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the uterine contraction. • **Variable decelerations** are characterized by an abrupt decrease in the FHR to ≥ 15 bpm below the baseline and lasting for ≥ 15 sec but < 2 min. Abrupt is defined as < 30 sec from baseline to the nadir of the deceleration. When variable decelerations are associated with uterine activity, their onset, depth, and duration commonly vary with successive contractions. • **Late decelerations** are characterized by a gradual decrease and return to baseline FHR associated with a uterine contraction. Importantly, the deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction. Onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the uterine contraction. A **prolonged deceleration** is defined as a deceleration lasting ≥ 2 min but < 10 min. If the duration is longer than 10 min, it is referred to as a "change in baseline" and not a prolonged deceleration. **Recurrent decelerations** describe the presence of decelerations with more than 50% of uterine contractions in any 20-min period.

Data from the National Institute of Child Health and Human Development Research Planning Workshop. Electronic fetal heart rate monitoring: research guidelines for interpretation. Am J Obstet Gynecol 1997; 177:1385-90.

terminology and nomenclature used in contemporary clinical practice. This report described a three-tier system for FHR tracing interpretation: category I (normal), category II (indeterminate), and category III (abnormal).[81]

By definition, an NST is performed before the onset of labor and does not involve invasive (intrauterine) monitoring. The test is performed by recording the FHR for a period of 20 to 40 minutes; the recording is then evaluated for the presence of periodic changes. The FHR is determined externally with use of Doppler ultrasonography, in which sound waves emitted from the transducer are deflected by movements of the heart and heart valves. The shift in frequency of these deflected waves is detected by a sensor and converted into heart rate. The FHR is printed on a strip-chart recorder running at 3 cm/min. A single mark on the FHR tracing therefore represents the average rate in beats per minute (bpm) of 6 fetal heart beats. The presence or absence of uterine contractions is typically recorded at the same time with an external tonometer. This tonometer records myometrial tone and provides information about the timing and duration of contractions, but it does not measure intrauterine pressure or the intensity of the contractions. Results of the NST are interpreted as reactive or nonreactive. An FHR tracing is designated *reactive* if there are two or more accelerations of at least 15 bpm for 15 seconds in a 20-minute period (Figure 6-3).[80-82] For preterm fetuses (<32 weeks' gestation), an FHR tracing is designated as reactive if there are two or more accelerations of at least 10 bpm for 10 seconds.

An NST is performed when formal documentation of the fetal condition is necessary. Because most healthy fetuses move within a 75-minute period, the testing period for an NST should not exceed 80 minutes.[83] The NST is most useful in cases of suspected uteroplacental insufficiency. A reactive NST is regarded as evidence of fetal health,[84,85] but the interpretation of a nonreactive NST remains controversial. Determination of a nonreactive NST must consider the gestational age, the underlying clinical circumstance, and the results of previous FHR tracings. Only 65% of fetuses have a reactive NST by 28 weeks' gestation, whereas 95% do so by 32 weeks.[79,86] However, once a reactive NST has been documented in a given pregnancy, the NST should remain reactive throughout the remainder of the pregnancy. A nonreactive NST at term is associated with poor

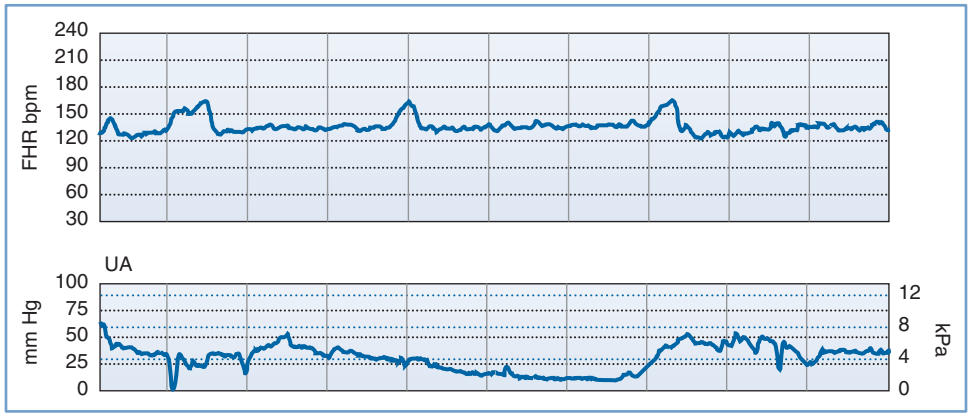

FIGURE 6-3 ■ A normal (reactive) fetal heart rate (FHR) tracing. The baseline FHR is normal (between 110 and 160 bpm), there is moderate variability (defined as 6 to 25 bpm from peak to trough), there are no decelerations, and there are two or more accelerations (defined as an increase in FHR of ≥ 15 bpm above baseline lasting at least 15 seconds) in a 20-minute period.

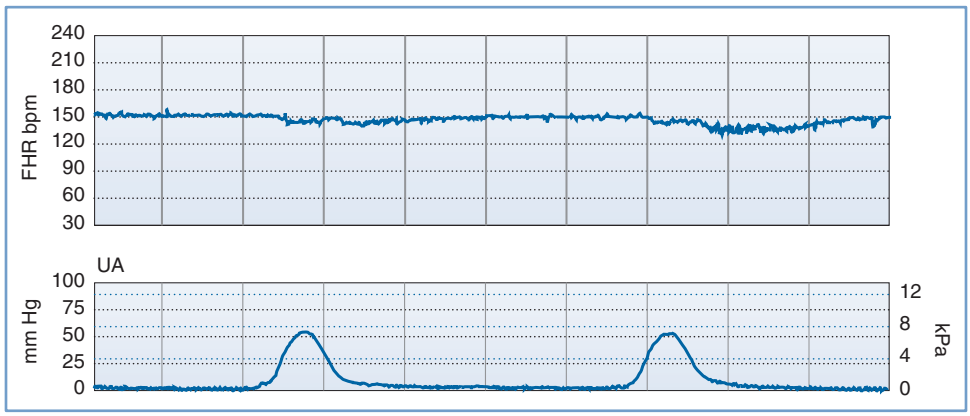

FIGURE 6-4 ■ An "at risk" fetal heart rate (FHR) tracing. The baseline FHR is normal (between 110 and 160 bpm), but the following abnormalities can be seen: minimal baseline FHR variability (defined as 0 to 5 bpm from peak to trough), no accelerations, and decelerations that are late in character (start after the peak of the contraction) and repetitive (occur with more than half of the contractions).

perinatal outcome in only 20% of cases. The significance of such a result at term depends on the clinical endpoint under investigation. If the clinical endpoint of interest is a 5-minute Apgar score less than 7, a nonreactive NST at term has a sensitivity of 57%, a positive predictive value of 13%, and a negative predictive value of 98% (assuming a prevalence of 4%). If the clinical endpoint is permanent neurologic injury, a nonreactive NST at term has a 99.8% false-positive rate.[87]

Visual interpretation of the FHR tracing involves the following components: (1) baseline FHR, (2) baseline FHR variability, (3) presence of accelerations, (4) presence of periodic or episodic decelerations, and (5) changes of FHR pattern over time. The definitions of each of these variables are summarized in Table 6-2.[80,81] The patterns are categorized as baseline, periodic (i.e., associated with uterine contractions), or episodic (i.e., not associated with uterine contractions). Periodic changes are described as *abrupt* or *gradual* (defined as onset-to-nadir time < 30 seconds or > 30 seconds, respectively). In contrast to earlier classifications, this classification makes no distinction between short-term and long-term variability, and certain characteristics (e.g., the definition of an acceleration) depend on gestational age (see Table 6-2).[80,81]

A normal FHR tracing is defined as having a normal baseline rate (110 to 160 bpm), normal baseline variability (i.e., moderate variability, defined as 6 to 25 bpm from peak to trough), presence of accelerations, and absence of decelerations. The FHR typically accelerates in response to fetal movement. Therefore, FHR accelerations usually indicate fetal health and adequate oxygenation.[80-82] At-risk FHR patterns demonstrate recurrent late decelerations with absence of baseline variability, recurrent variable decelerations with absence of baseline variability, or substantial bradycardia with absence of baseline variability (Figure 6-4). Intermediate FHR patterns have characteristics between the two extremes of normal and at risk already described.[80,81]

Persistent fetal tachycardia (defined as an FHR > 160 bpm) may be associated with fetal hypoxia, maternal fever, chorioamnionitis (intrauterine infection), administration of an anticholinergic or beta-adrenergic receptor agonist, fetal anemia, or tachyarrhythmia. Persistent fetal bradycardia (FHR < 110 bpm) may be a result of congenital heart block, administration of a beta-adrenergic receptor antagonist, hypoglycemia, or hypothermia (Table 6-3). However, it may also indicate fetal hypoxia.[80,81] Both tachyarrhythmias and bradyarrhythmias require immediate evaluation.

TABLE 6-3 Drugs That Affect the Fetal Heart Rate Tracing

Effect on the Fetus	Drug
Fetal tachycardia	Atropine
	Epinephrine (adrenaline)
	Beta-adrenergic agonists (ritodrine, terbutaline)
Fetal bradycardia	Antithyroid medications (including propylthiouracil)
	Beta-adrenergic antagonists (e.g., propranolol)
	Intrathecal or epidural analgesia
	Methylergonovine (contraindicated prior to delivery)
	Oxytocin (if associated with excessive uterine activity)
Sinusoidal fetal heart rate pattern	Systemic opioid analgesia
Diminished variability	Atropine
	Anticonvulsants (but not phenytoin)
	Beta-adrenergic antagonists
	Antenatal corticosteroids (betamethasone, dexamethasone)
	Ethanol
	General anesthesia
	Hypnotics (including diazepam)
	Insulin (if associated with hypoglycemia)
	Magnesium sulfate
	Systemic opioid analgesia
	Promethazine

Baseline FHR variability, perhaps the most important component of the NST, is determined on a beat-to-beat basis by the competing influences of the sympathetic and parasympathetic nervous systems on the fetal sinoatrial node. A variable FHR, characterized by fluctuations that are irregular in both amplitude and frequency,[80,81] indicates that the autonomic nervous system is functioning and that the fetus has normal acid-base status. *Variability* is defined as absent, minimal, moderate, or marked (see Table 6-2) (Figure 6-5).[80,81] The older terms *short-term variability* and *long-term variability* are no longer used.[81] Normal (moderate) variability indicates the absence of cerebral hypoxia. With acute hypoxia, variability may be minimal or marked. Persistent or chronic hypoxia is typically associated with loss of variability. Reduced variability also may be the result of other factors, including maternal drug administration (see Table 6-3), fetal arrhythmia, and neurologic abnormality (e.g., anencephaly).[1,80,81]

Vibroacoustic Stimulation

Fetal vibroacoustic stimulation (VAS) refers to the response of the FHR to a vibroacoustic stimulus (82 to 95 dB) applied to the maternal abdomen for 1 to 2 seconds in the region of the fetal head. An FHR acceleration in response to VAS represents a positive result and is suggestive of fetal health. VAS is a useful adjunct to shorten the time needed to achieve a reactive NST and to decrease the proportion of nonreactive NSTs at term, thereby precluding the need for further testing. In one study of low-risk women at term, VAS reduced the proportion of nonreactive NSTs over a 30-minute period by 50% (from 14% to 9%) and shortened the time needed to achieve a reactive NST by an average of 4.5 minutes.[88] VAS has no adverse effect on fetal hearing. The absence of an FHR acceleration in response to VAS at term is associated with an 18-fold higher risk for nonreassuring fetal testing in labor[89] and a 6-fold higher risk for cesarean delivery.[90]

Biophysical Profile

An NST alone may not be sufficient to confirm fetal well-being. In such cases, a biophysical profile (BPP) may be performed. The BPP is an ultrasonographic scoring system performed over a 30- to 40-minute period designed to assess fetal well-being. Initially described for testing of the post-term fetus, the BPP has since been validated for use in both term and preterm fetuses, but not during active labor.[91-97] The five variables described in the original BPP were (1) gross fetal body movements, (2) fetal tone (i.e., flexion and extension of limbs), (3) amniotic fluid volume, (4) fetal breathing movements, and (5) the NST.[97] More recently, the BPP has been interpreted without the NST (Table 6-4).

The individual variables of the BPP become apparent in the normal fetus in a predictable sequence: fetal tone appears at 7.5 to 8.5 weeks' gestation, fetal movement at 9 weeks, fetal breathing at 20 to 22 weeks, and FHR reactivity at 24 to 28 weeks. In the setting of antepartum hypoxia, these characteristics typically disappear in the reverse order of their appearance (i.e., FHR reactivity is lost first, followed by fetal breathing, fetal movements, and finally fetal tone).[93] The amniotic fluid volume, which is composed almost entirely of fetal urine in the second and third trimesters, is not influenced by acute fetal hypoxia or acute fetal central nervous system dysfunction. Rather, oligohydramnios (decreased amniotic fluid volume) in the latter half of pregnancy and in the absence of ruptured membranes is a reflection of chronic uteroplacental insufficiency and/or increased renal artery resistance leading to diminished urine output.[98] It predisposes to umbilical cord compression, thus leading to intermittent fetal hypoxemia, meconium passage, or meconium aspiration. Adverse pregnancy outcome (including a nonreassuring FHR tracing, low Apgar scores, and/or admission to the neonatal intensive care unit) is more common when oligohydramnios is present.[98-101] Weekly or twice-weekly screening of high-risk pregnancies for oligohydramnios is important because amniotic fluid can become drastically reduced within 24 to 48 hours.[102]

Although each of the five features of the BPP are scored equally (2 points if the variable is present or normal and 0 points if absent or abnormal, for a total of 10 points), they are not equally predictive of adverse

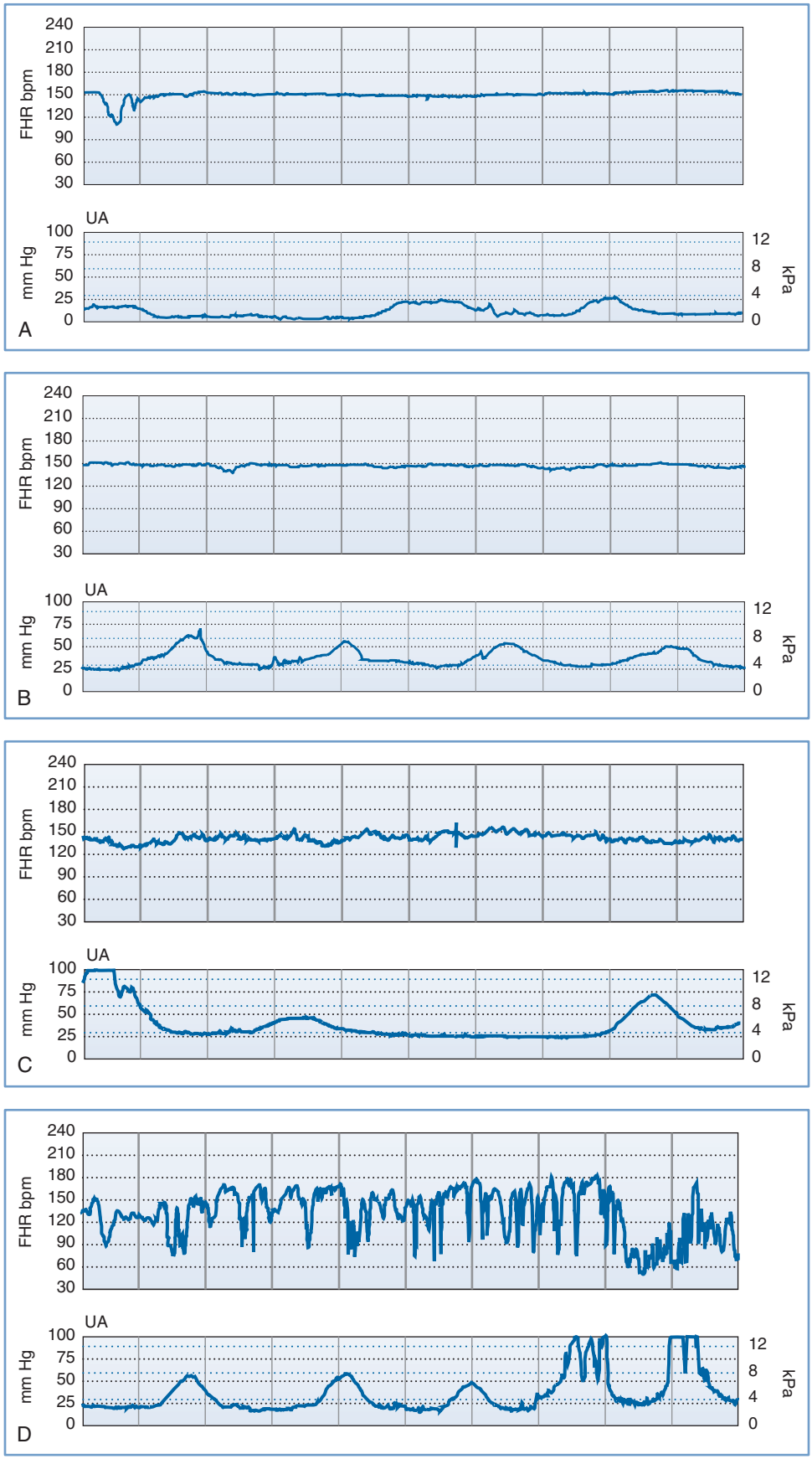

FIGURE 6-5 ■ Components of baseline fetal heart rate (FHR) variability. **A,** Absence of variability. **B,** Minimal variability (0 to 5 bpm from peak to nadir). **C,** Moderate variability (6 to 25 bpm from peak to nadir). **D,** Marked variability (> 25 bpm from peak to nadir).

TABLE 6-4 Characteristics of the Biophysical Profile

Biophysical Variable	Normal Score (Score = 2)	Abnormal Score (Score = 0)
Fetal breathing movements (FBMs)	At least one episode of FBM lasting at least 30 sec	Absence of FBM altogether or no episode of FBM lasting ≥ 30 sec
Gross body movements	At least three discrete body/limb movements in 30 min (episodes of active continuous movements should be regarded as a single movement)	Fewer than three episodes of body/limb movements over a 30-min period
Fetal tone	At least one episode of active extension with return to flexion of fetal limbs or trunk; opening and closing of hand are considered normal tone	Slow extension with return to partial flexion, movement of limb in full extension, or absence of fetal movements
Qualitative amniotic fluid (AF) volume	At least one pocket of AF that measures ≥ 1 cm in two perpendicular planes	No AF pockets or an AF pocket measuring < 1 cm in two perpendicular planes
Reactive nonstress test	At least two episodes of FHR acceleration of ≥ 15 bpm lasting ≥ 15 sec associated with fetal movements over 30 min of observation	Fewer than two episodes of FHR accelerations or accelerations of < 15 bpm over 30 min of observation

Data from Manning FA. Fetal biophysical assessment by ultrasound. In Creasy RK, Resnik R, editors. Maternal-Fetal Medicine: Principles and Practice. 2nd edition. Philadelphia, WB Saunders, 1989:359.

TABLE 6-5 Recommended Management Based on Biophysical Profile

Score	Interpretation	Recommended Management
8 or 10	Normal	No intervention
6	Suspect asphyxia	Repeat in 4 to 6 h Consider delivery for oligohydramnios
4	Suspect asphyxia	If ≥ 36 weeks' gestation or mature pulmonary indices, deliver immediately If < 36 weeks' gestation, repeat BPP in 4 to 6 h versus delivery with mature pulmonary indices If score persistently ≤ 4, deliver immediately
0 or 2	High suspicion of asphyxia	Evaluate for immediate delivery

Data from Manning FA. Fetal biophysical assessment by ultrasound. In Creasy RK, Resnik R, editors. Maternal-Fetal Medicine: Principles and Practice. 2nd edition. Philadelphia, WB Saunders, 1989:359.

pregnancy outcome. For example, amniotic fluid volume is the variable that correlates most strongly with adverse pregnancy events. The management recommended on the basis of the BPP score is summarized in Table 6-5.[97] A score of 8 or 10 is regarded as reassuring; a score of 4 or 6 is suspicious and requires reevaluation; and a score of 0 or 2 suggests nonreassuring fetal status (previously referred to as "fetal distress").[91,92] Evidence of nonreassuring fetal status should prompt evaluation for immediate delivery.[93,94]

Contraction Stress Test

Also known as the oxytocin challenge test (OCT), the contraction stress test is an older test of uteroplacental function. It assesses the response of the FHR to uterine contractions induced by either intravenous oxytocin administration or nipple stimulation (which causes release of endogenous oxytocin from the maternal neurohypophysis). A minimum of three contractions of minimal-to-moderate strength in 10 minutes is required to interpret the test. A negative CST (no decelerations with contractions) is reassuring and suggestive of a healthy, well-oxygenated fetus. A positive CST (repetitive late or severe variable decelerations with contractions with at least 50% of the contractions) is suggestive of a fetus suffering from impaired maternal-to-fetal oxygen exchange during uterine contractions and is associated with adverse perinatal outcome in 35% to 40% of cases (Figure 6-6). The combination of a positive CST and absence of FHR variability is especially ominous. Consideration should be given to immediate and urgent delivery of a fetus with a positive CST, with or without FHR variability. It should be noted, however, that the false-positive rate of this test exceeds 50%.[84] If the CST is uninterpretable or equivocal, the test should be repeated in 24 to 72 hours. Studies suggest that more than 80% of results of repeated tests are negative. The rate of antepartum intrauterine fetal demise within 1 week of a negative CST is 0.04%.[84,97]

Because this test is time consuming, requires skilled nursing care, and necessitates an inpatient setting owing to the possibility of precipitating fetal compromise requiring emergency cesarean delivery, the CST is reserved for specific clinical indications. Moreover, there are a number of contraindications to its use, including placenta previa, placental abruption, prior classic (high-vertical) cesarean delivery, and risk for preterm labor. Despite these limitations, the CST allows for indirect evaluation of fetal oxygenation during periods of uterine contractions and diminished uteroplacental perfusion and may therefore provide a better assessment of fetal well-being and fetal reserve than either the NST or the BPP (Table 6-6).[1,84,95,103]

Umbilical Artery Doppler Velocimetry

Doppler velocimetry shows the direction and characteristics of blood flow and can be used to examine the maternal, uteroplacental, or fetal circulation. The umbilical artery is one of the few arteries that normally has diastolic flow and consequently is one of the vessels most frequently evaluated during pregnancy. Umbilical artery

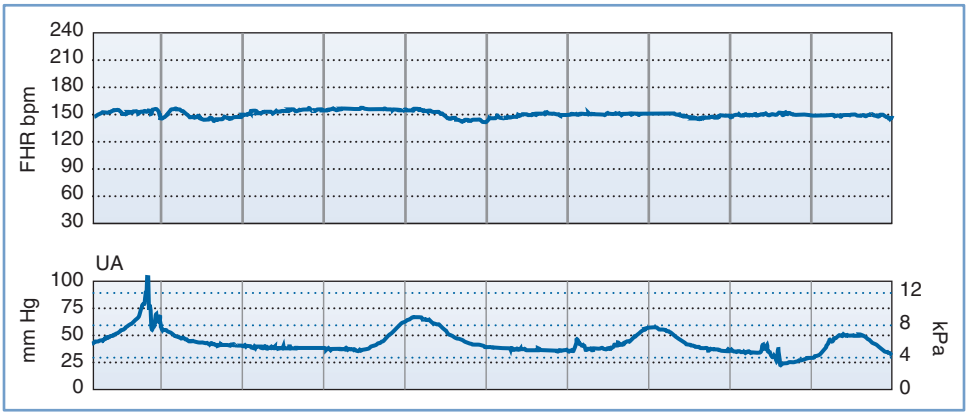

FIGURE 6-6 ■ A positive contraction stress test (CST) result. There are at least three contractions in a 10-minute period. The baseline fetal heart rate (FHR) is 130 bpm, there is minimal baseline FHR variability (defined as 0 to 5 bpm from peak to trough), and there are decelerations that are late in character (start after the peak of the contraction) and repetitive (occur with more than half of the contractions).

TABLE 6-6 False-Positive and False-Negative Rates for the Nonstress Test, Biophysical Profile, and Contraction Stress Test

Test	False-Positive Rate (%)	False-Negative Rate (per 1000 live births)*
Nonstress test (NST)	58	1.4 to 6.2
Biophysical profile (BPP):		0.7 to 1.2
• Score 6/10	45	
• Score 0/10	0	
Contraction stress test (CST)	30	0.4 to 0.6

*Data are presented as perinatal mortality rate within 1 wk of a reactive NST, a BPP score of 8 or 10, or a negative CST after adjustments for congenital anomalies and known causes.

Data from references 1, 84, 95, and 103.

Doppler velocimetry measurements reflect resistance to blood flow from the fetus to the placenta. Normally, umbilical artery resistance falls progressively throughout pregnancy, reflecting the increase in number of tertiary stem vessels. Factors that affect placental vascular resistance include gestational age, placental location, pregnancy complications (e.g., placental abruption, preeclampsia), and underlying maternal disease (chronic hypertension).

Doppler velocimetry of umbilical artery blood flow provides an indirect measure of fetal status. Decreased diastolic flow with a resultant increase in the systolic-to-diastolic (S/D) ratio suggests an increase in placental vascular resistance and fetal compromise. Severely abnormal umbilical artery Doppler velocimetry (defined as absence of or reversed diastolic flow) is an especially ominous observation and is associated with poor perinatal outcome in the setting of fetal growth restriction (Figure 6-7).[104-108] The role of ductus venosus and/or middle cerebral artery (MCA) Doppler velocimetry in the management of fetal growth restriction pregnancies is not well defined. Preparation for delivery—including administration of corticosteroids for fetal lung maturity and transfer to a tertiary delivery center—should be considered when Doppler findings are severely abnormal in the setting of fetal growth restriction, regardless of gestational age. However, in the presence of a normally grown fetus, it is unclear how to interpret such findings. For these reasons, umbilical artery Doppler velocimetry should not be performed routinely in women at low risk for fetal abnormalities. Appropriate indications include fetal growth restriction, cord malformations, unexplained oligohydramnios, suspected or established preeclampsia, and, possibly, fetal cardiac anomalies.

Umbilical artery Doppler velocimetry has not been shown to be useful in the evaluation of some high-risk pregnancies, including diabetic and post-term pregnancies, primarily owing to a high false-positive rate.[2,109-112] Thus, in the absence of fetal growth restriction, obstetric management decisions are not usually made on the basis of Doppler velocimetry findings alone. New applications for Doppler technology include the use of MCA peak systolic velocity for the noninvasive evaluation of fetal anemia resulting from isoimmunization. When severe anemia develops in a fetus, blood is preferentially shunted to the vital organs, such as the brain, and the shunt can be demonstrated by an increase in MCA peak systolic flow velocity.[113] This finding can help the perinatologist counsel affected patients about the need for cordocentesis and fetal blood transfusion. Doppler studies of other vessels (including the uterine artery, fetal aorta, ductus venosus, and fetal carotid arteries) have contributed to our knowledge of maternal-fetal physiology but as yet have resulted in few clinical applications.

Multiple Modalities to Assess Fetal Well-Being

All standard tests to assess antepartum fetal well-being (i.e., NST, BPP, CST) are evaluated according to their ability to predict the absence of fetal death during the 1-week period after the test. The false-negative rate (defined as a reassuring test result with a subsequent bad outcome) and false-positive rate (an abnormal result with a subsequent normal outcome) for each of these tests are listed in Table 6-6.[1,84,95,103] The false-negative rates for all

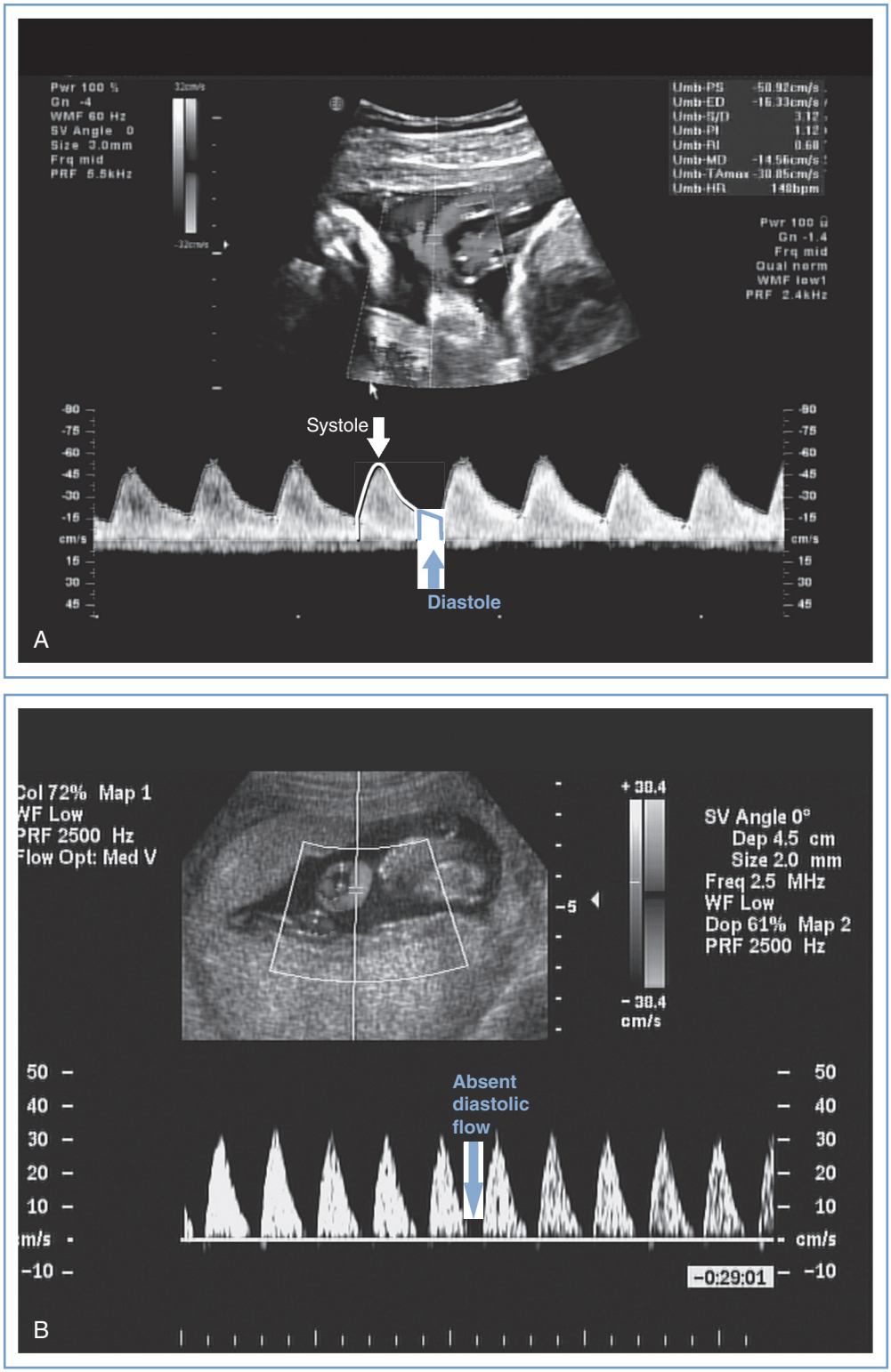

FIGURE 6-7 ■ Umbilical artery Doppler velocimetry. **A,** Normal waveform in the umbilical artery as shown on Doppler velocimetry. Forward flow can be seen during both fetal systole and diastole. **B,** Absent end-diastolic flow. Forward flow can be seen during systole, but there is no flow during diastole.

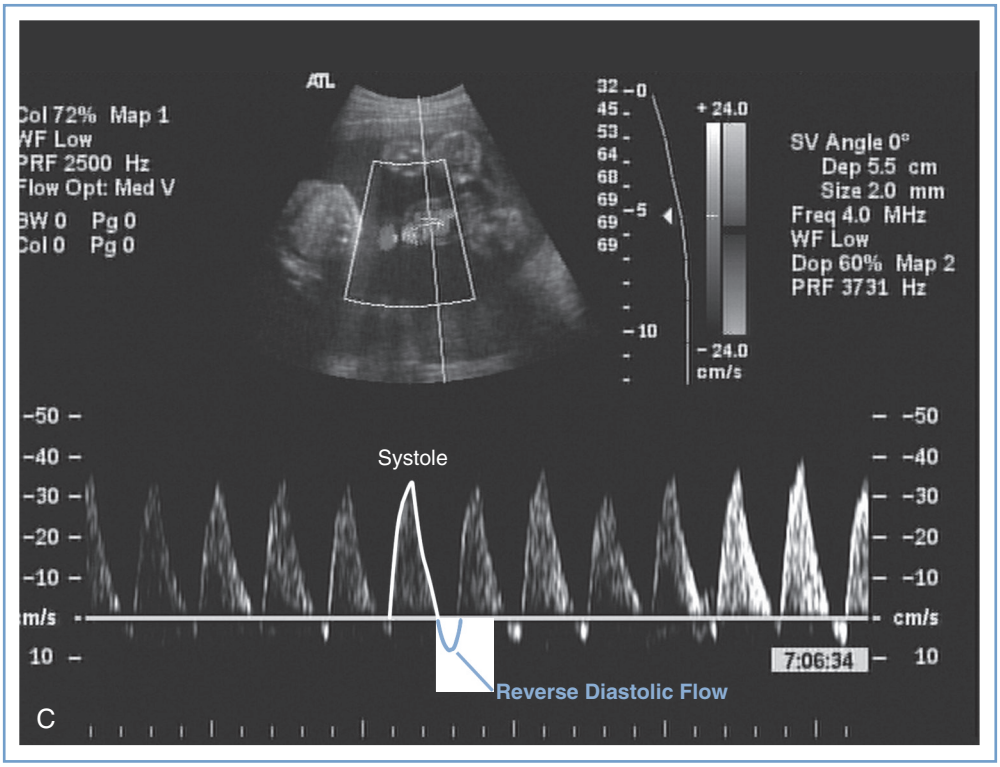

FIGURE 6-7, cont'd ■ C, Reverse diastolic flow. Forward flow can be seen during systole, but there is reverse flow in the umbilical artery during diastole, which is suggestive of high resistance to blood flow in the placenta.

three tests are relatively low. Because the NST has a high false-positive rate, some authorities consider it a screening test to identify fetuses requiring further assessment with either a BPP or a CST. No method of fetal assessment is perfect, and clinical judgment plays a large role in any management decision.

SPECIAL TECHNIQUES FOR ANTEPARTUM FETAL SURVEILLANCE

Perinatal Ultrasonography

Ultrasonography uses high-frequency sound waves (3.5 to 5 MHz for transabdominal transducers and 5 to 7.5 MHz for transvaginal transducers) that are directed into the body by a transducer, reflected by maternal and fetal tissue, detected by a receiver, processed, and displayed on a screen. Increasing the wave frequency results in greater display resolution at the expense of diminished tissue penetration. Interpretation of images requires operator experience. Widespread clinical application of two-dimensional ultrasonography began in the 1960s after pioneering work by researchers in the United States and Great Britain.[114] Although no deleterious biologic effects have been associated with obstetric ultrasonography, the rates of false-positive and false-negative diagnoses based on the images are a major limitation.

Perinatal ultrasonography can be classified broadly into three types of examinations: basic, targeted (comprehensive), and limited. The **basic examination** (level I) involves determination of fetal number, viability, position, gestational age, and gross malformations. Placental location, amniotic fluid volume, and the presence of abnormal maternal pelvic masses can be evaluated as well.[20] Most pregnancies can be evaluated adequately with this type of examination alone. If the patient's history, physical findings, or basic ultrasonographic results suggest the presence of a fetal malformation, an ultrasonographer who is skilled in fetal evaluation should perform a **targeted** or **comprehensive examination** (level II). During a targeted ultrasonographic examination, which is best performed at 18 to 20 weeks' gestation, fetal structures are examined in detail to identify and characterize any fetal malformation. Ultrasonographic markers of fetal aneuploidy (see later discussion) can be evaluated as well. In some situations, a **limited examination** may be appropriate to answer a specific clinical question (e.g., fetal viability, amniotic fluid volume, fetal presentation, placental location, cervical length) or to provide ultrasonographic guidance for an invasive procedure (e.g., amniocentesis).

Current debate centers on identifying those patients who would benefit from an ultrasonographic evaluation and determining what type of evaluation would be optimal. Advocates of the universal application of ultrasonography cite the advantages of more accurate dating of pregnancy (see earlier discussion) and earlier and more accurate diagnosis of multiple gestation, structural malformations, and fetal aneuploidy (see later discussion). Opponents of routine ultrasonographic examination view it as an expensive screening test ($100 to $250 for a basic

examination) that is not justified by published research, which suggests that routine ultrasonography does not change perinatal outcome significantly.[19,26,27] Although routine ultrasonography for all low-risk pregnant women is controversial, few would disagree that the benefits far outweigh the costs for selected patients. The ACOG[20] has recommended that the benefits and limitations of ultrasonography should be discussed with all pregnant women.

First-trimester ultrasonography is indicated to confirm an intrauterine pregnancy (i.e., exclude ectopic pregnancy), confirm fetal viability, document fetal number, estimate gestational age, and evaluate the maternal pelvis and ovaries.

Second-trimester ultrasonography is indicated in patients with an uncertain LMP date, uterine size larger or smaller than expected for the estimated gestational age, a medical disorder that can affect fetal growth and development (e.g., diabetes, hypertension, collagen vascular disorders), a family history of an inherited genetic abnormality, and suspected fetal malformation or growth disturbance.[20] Most patients undergo a detailed fetal anatomic survey at 18 to 20 weeks' gestation to screen for structural defects. An understanding of normal fetal physiology is critical to the diagnosis of fetal structural anomalies. Placental location should be documented with the maternal bladder empty, because overdistention of the bladder or a lower uterine contraction can give a false impression of placenta previa. If placenta previa is identified at 18 to 22 weeks' gestation, serial ultrasonographic examinations should be performed to follow placental location. Only 5% of cases of placenta previa identified in the second trimester persist to term.[115] The umbilical cord should also be imaged and the number of vessels, placental insertion, and fetal insertion should be noted. Evaluation of the amniotic fluid volume should also be done. In pregnancies at high risk for fetal cardiac anomalies or preterm birth, fetal echocardiography and cervical length measurements, respectively, should be performed.

The indications for **third-trimester ultrasonography** are similar to those for second-trimester ultrasonography. Fetal anatomic surveys and EFW become less accurate with greater gestational age, especially in obese women or pregnancies complicated by oligohydramnios. Fetal biometry and detailed anatomic surveys are still performed in late gestation, because certain fetal anomalies (e.g., achondroplasia, duodenal atresia) may become evident for the first time during this period. Transvaginal ultrasonographic measurement of cervical length (performed to identify women at risk for preterm birth) is of little use after 30 to 32 weeks' gestation.[116]

Screening for Fetal Chromosomal Abnormalities

Fetal chromosomal abnormalities are a major cause of perinatal morbidity and mortality, accounting for 50% of first-trimester spontaneous abortions, 6% to 12% of all stillbirths and neonatal deaths, and 10% to 15% of structural anomalies in live-born infants.[117] The most common aneuploidy encountered during pregnancy (autosomal trisomy) results primarily from nondisjunction during meiosis I, an event that occurs with growing frequency in older women. Women of advanced maternal age (> 35 years or older at EDD) are at higher risk for having a pregnancy complicated by fetal aneuploidy and are routinely offered noninvasive prenatal screening as well as an invasive diagnostic procedure, either amniocentesis or chorionic villus sampling (CVS). However, because only 8% to 12% of all births occur in women age 35 and older, at most 20% to 25% of all cases of trisomy 21 (Down syndrome) would be identified if all women of advanced maternal age agreed to amniocentesis.[118] Many older women are now opting for serum analyte screening for fetal aneuploidy, which is equally accurate in older women.[119] All women, regardless of age, should be offered aneuploidy screening during early gestation.[117]

Second-Trimester Fetal Aneuploidy Screening

Methods have been developed to help identify women at high risk for fetal aneuploidy. The major focus of attention has been the detection of Down syndrome, because it is the most common chromosomal abnormality manifesting at term and because, unlike the less common disorders trisomy 13 and 18, its diagnosis can be very difficult to make with ultrasonography. In all of these screening tests, one or more serum analytes are used to adjust the *a priori* risk for fetal aneuploidy in a given pregnancy, which depends primarily on maternal age. The maternal serum analytes used most commonly in second-trimester aneuploidy screening protocols are maternal serum alpha-fetoprotein (MS-AFP), total or free β-subunit hCG (β-hCG), unconjugated estriol, and dimeric inhibin A (collectively known as the quadruple or "quad" screen). Screening results are reported as positive or negative. If the adjusted risk for fetal aneuploidy exceeds the age-related risk at age 35 or the rate of amniocentesis procedure-related pregnancy loss, which is currently defined as 1 in 300 to 500 (i.e., if the chance of finding a chromosomal abnormality on fetal karyotype is higher than the risk of the invasive procedure), then genetic amniocentesis is recommended.[120] If all screen-positive women undergo amniocentesis and if the fetal karyotype analysis is successful in all cases, this protocol can identify 60% of all Down syndrome cases with a screen-positive (amniocentesis) rate of approximately 5%. Older women are more likely to be screen positive but also have higher detection rates. In women older than 35 years, this protocol identifies 75% of aneuploid fetuses with a screen-positive rate of approximately 25%.[118,121,122]

Second-Trimester Ultrasonographic Screening for Fetal Aneuploidy

Second-trimester ultrasonographic markers, such as intracardiac echogenic focus and echogenic bowel (Table 6-7), are not generally incorporated into standard algorithms to predict risk for fetal aneuploidy; however, a risk adjustment based on ultrasonographic markers can be made. Multiple major structural abnormalities, such as those often found in fetuses with trisomy 13 or 18,

TABLE 6-7 **Accuracy Measurements of Second-Trimester Ultrasonographic "Soft Markers" for Trisomy 21 (Down Syndrome) When Identified as Isolated Anomalies**

Ultrasonographic Marker	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Thickened nuchal fold	0.04 (0.02-0.10)	0.99 (0.99-0.99)	17 (8.0-38.0)	0.97 (0.94-1.00)
Choroid plexus cyst	0.01 (0.00-0.03)	0.99 (0.97-1.00)	1.00 (0.12-9.40)	1.00 (0.97-1.00)
Short femur length	0.16 (0.05-0.40)	0.96 (0.94-0.98)	2.7 (1.2-6.0)	0.87 (0.75-1.00)
Short humeral length	0.09 (0.00-0.60)	0.97 (0.91-0.99)	7.5 (4.7-12.0)	0.87 (0.67-1.10)
Echogenic bowel	0.04 (0.01-0.24)	0.99 (0.97-1.00)	6.1 (3.0-12.6)	1.00 (0.98-1.00)
Echogenic intracardiac focus	0.11 (0.06-0.18)	0.96 (0.94-0.97)	2.8 (1.5-5.5)	0.95 (0.89-1.00)
Renal pyelectasis (pelviceal dilation)	0.02 (0.01-0.06)	0.99 (0.98-1.00)	1.9 (0.7-5.1)	1.00 (1.00-1.00)

CI, confidence interval; LR, likelihood ratio.
Data from Smith-Bindman P, Hosmer W, Feldstein VA, et al. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA 2001; 285:1044-55; and Vintzeleos AM, Campbell WA, Rodis JF, et al. The use of second-trimester genetic sonogram in guiding clinical management of patients at increased risk for fetal trisomy 21. Obstet Gynecol 1996; 87:948-52.

can be detected reliably by perinatal ultrasonography. Approximately 50% of fetuses with Down syndrome appear structurally normal on ultrasonography.[123] Several major structural ultrasonographic abnormalities (e.g., endocardial cushion defect) may be associated with trisomy 21 in more than 30% of cases.[123-125] The clinical significance of an isolated "soft" ultrasonographic marker for Down syndrome in a low-risk population is unclear.

First-Trimester Fetal Aneuploidy Screening

First-trimester fetal aneuploidy screening is a more recent development. The screening protocol involves the following three steps undertaken at 11 to 14 weeks' gestation: (1) maternal serum analyte screening for pregnancy-associated placental protein-A (PAPP-A) and total or free β-hCG, (2) ultrasonographic assessment of nuchal translucency, and (3) genetic counseling.[126] The measurement of free rather than total β-hCG provides a small statistical advantage without apparent clinical benefit.[127] First-trimester aneuploidy screening appears to be as good as second-trimester serum analyte screening in identifying fetuses with Down syndrome.[128,129] The serum analytes in the first trimester associated with an increased risk for Down syndrome include a decrease in PAPP-A (< 0.4 multiples of the median [MoM]) and an increase in free hCG (> 1.8 MoM). *Nuchal translucency* is defined as the fluid-filled space between the back of the fetal neck and the overlying skin. Proper training and technique are needed to obtain this measurement. There is a correlation between an increased nuchal translucency measurement and a risk for Down syndrome.

The advantage of first-trimester aneuploidy screening is that it is performed early in pregnancy, allowing for more counseling, the option of CVS, and early pregnancy termination if desired. The screening test most commonly used in Europe for identifying pregnancies at risk for Down syndrome is the "integrated" test, which combines first-trimester aneuploidy screening with second-trimester serum analyte screening into a single adjusted risk in the mid to late second trimester. The integrated test can identify 85% to 90% of fetuses with Down syndrome with a false-positive rate of 2% (Table 6-8).[129-135] However, the true application of the integrated screening test requires that the first-trimester test results, *even if abnormal*, be withheld from the patient until combined with the second-trimester test results; this practice of withholding information has generated controversy, particularly in the United States. To overcome this objection, *sequential* and *contingent* integrated screening tests have been developed, whereby the second-trimester test is performed after disclosure of the first-trimester screening result or if the first test result is abnormal, respectively. It remains unclear, however, whether the detection rates for these integrated tests are any better than those of the first-trimester screening test alone (see Table 6-8).[129-132] Indeed, if the first-trimester aneuploidy screen result is negative (indicating low risk), the sensitivity of second-trimester serum analyte screening is reduced fivefold.[136] For this reason, many authorities suggest that no further aneuploidy screening be done if the first-trimester screen result is negative, with the exception of the second-trimester fetal anatomic survey and possibly isolated MS-AFP serum screening for open neural tube defects at 15 to 20 weeks' gestation.

In addition to the nuchal translucency measurement, absence of the nasal bone on first-trimester ultrasonography has been correlated with Down syndrome. However, whether this ultrasonographic marker adds to the predictive value of first-trimester risk assessment in either low- or high-risk populations has been questioned.[137,138] At this time, the presence or absence of the nasal bone is not included in the first-trimester screening test.

Risk assessment for Down syndrome can be performed in twin pregnancies using either first- or second-trimester serum analyte measurements but is less accurate than in singleton pregnancies.[132] Such screening has not been validated for use in higher-order multiple pregnancies (triplets and up) or in multiple pregnancies with a nonviable fetus (either due to spontaneous demise or following a multifetal pregnancy reduction). In such cases, Down syndrome risk assessment can be achieved using first-trimester nuchal translucency measurements only, although this is not a particularly good screening test and has a lower sensitivity even than nuchal translucency alone in singleton pregnancies.[132]

TABLE 6-8 **Detection Rate of Down Syndrome Screening Tests**

Screening Test	Detection Rate (%)*	False-Positive Rate (%)†
Maternal age > 35 yr	30-40	10-15
First Trimester		
NT assessment	64-70	5-10
NT assessment, PAPP-A, and total or free β-hCG measurements	82-87	5-6
Second Trimester		
Triple screen (measurements of MS-AFP, total or free β-hCG, unconjugated estriol)	69-77	9
Quadruple screen (measurements of MS-AFP, total or free β-hCG, unconjugated estriol, inhibin A)	79-83	6
Combined First and Second Trimesters		
Integrated (NT assessment, PAPP-A measurement, quadruple screen)	93-96	1-2
Serum integrated (APP-A measurement, quadruple screen)	84-88	2-3
Stepwise sequential: • If first-trimester test result positive, diagnostic test offered • If first-trimester test result negative, second-trimester test offered, and final risk assessment incorporates both first- and second-trimester results	84-95	1
Contingent sequential: • If first-trimester test result positive, diagnostic test offered • If first-trimester test result negative, no further testing • If first-trimester test result intermediate, second-trimester test offered, and final risk assessment incorporates both first- and second-trimester results	88-94	1

β-hCG, beta-human chorionic gonadotropin; *MS-AFP,* maternal serum level of alpha-fetoprotein; *NT,* nuchal translucency; *PAPP-A,* pregnancy-associated placental protein-A.
*Assuming a 5% false-positive rate.
†Assuming an 85% detection rate.
Data from references 128 and 130-132.

Definitive Diagnosis of Fetal Chromosomal Abnormalities

Although an abnormal screening test result or the presence of ultrasonographic abnormalities may signal an increased risk for Down syndrome or other chromosomal abnormality, the majority of fetuses with such findings are chromosomally normal. To provide a definitive diagnosis, an invasive procedure is needed to obtain the fetal karyotype; generally amniocentesis or CVS is used, although in rare cases a cordocentesis is performed.

All invasive procedures are associated with risks to the pregnancy. Risks common to all invasive procedures include the chance of bleeding, isoimmunization (especially in women who are Rh negative), and infection. All women who are Rh negative should receive Rh_0(D) immune globulin before or after the procedure. Although the risk for vertical transmission of viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus) with invasive procedures is believed to be low,[139] every effort should be made to avoid invasive procedures in such patients, especially if there is a high viral load in the maternal circulation.

Amniocentesis

Amniotic fluid is composed of fetal urine, lung fluid, skin transudate, and water that is filtered across the amniotic membranes. It contains electrolytes, proteins, and desquamated fetal cells (amniocytes). Sampling of amniotic fluid **(amniocentesis)** can be used to measure various substances such as lecithin and sphingomyelin for assessing fetal lung maturity, to look for pathogenic bacteria for confirmation of an intra-amniotic infection, and to obtain fetal cells for determination of fetal karyotype or performance of specific genetic analyses.

Cell culture with karyotype analysis typically takes 10 to 14 days, although a small chance exists that the cells will fail to grow, resulting in an inconclusive result. Fluorescence *in situ* hybridization (FISH) does not require that the cells be cultured for any length of time, and its results can be obtained within a few days. This technique uses a series of chromosome-specific fluorescent probes to analyze the metaphase spread in fetal cells to determine fetal gender and detect common trisomies (21, 18, 13, X, and Y). It can also be used to identify chromosome deletions or duplications in pregnancies at risk for a specific genetic disorder because of a family history or suspicious ultrasonographic findings, such as the 22q11 deletion in DiGeorge's syndrome.[140-142] Although FISH is highly sensitive (trisomy present on FISH testing is invariably present in the fetus), it is not particularly specific, with a false-negative rate of approximately 15%. For this reason, the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) recommend that all FISH results be confirmed by complete karyotype analysis.[142]

The most common indication for second-trimester amniocentesis is cytogenetic analysis of fetal cells, although on occasion it is performed to determine amniotic fluid AFP levels and acetylcholinesterase activity for the diagnosis of fetal open neural tube defects. Amniocentesis later in pregnancy is usually performed for nongenetic indications, such as (1) documentation of fetal

pulmonary maturity prior to elective delivery before 39 weeks' gestation, (2) for amnioreduction in pregnancies complicated by severe polyhydramnios, (3) to confirm preterm premature rupture of membranes (PROM) (amniodye test), or (4) to exclude intra-amniotic infection.

Genetic amniocentesis typically involves the insertion of a 22-gauge spinal needle through the maternal abdominal wall and into the uterine cavity at 15 to 20 weeks' gestation. The procedure is now commonly performed under ultrasonographic guidance, which allows the operator to choose the safest site, preferably away from the fetal face and umbilical cord and when possible without passage of the needle through the placenta. The greatest risk of amniocentesis is spontaneous abortion; however, the procedure-related pregnancy loss rate for genetic amniocentesis appears to be only 1 in 300 to 500.[120,143-145] Of interest, the pregnancy loss rate is not influenced by operator experience or needle placement through the placenta[145,146] but is higher in the presence of first-trimester bleeding or recurrent miscarriage, ultrasonographic demonstration of chorioamniotic separation, discolored amniotic fluid at the time of the procedure, and an unexplained elevation in MS-AFP.[144,147] Whether this risk is higher in twin pregnancies is not clear. Transient leakage of amniotic fluid can be seen in 1% to 2% of procedures. This leakage usually stops after 48 to 72 hours, infection is extremely rare (< 0.1% of cases), and the perinatal survival rate after mid-trimester fluid leakage may be as high as 90%.[117,148-152]

Compared with late second-trimester amniocentesis, early amniocentesis (before 15 weeks' gestation) is associated with significantly higher procedure-related pregnancy loss rates, ranging from 2.2% to 4.8%.[148-151] This rate is fourfold higher than that of late amniocentesis and twice as high as that of CVS. Early amniocentesis has also been shown to be associated with higher rates of rupture of membranes, club foot, and amniocyte culture failures (2% to 5%) than late amniocentesis.[148-153] For these reasons, amniocentesis before 15 weeks' gestation is not recommended.

If early karyotyping is desired, CVS is preferred over early amniocentesis (see later discussion). Amniocentesis in the third trimester is technically easier and is associated with fewer complications. If a late amniocentesis is being performed for any reason (e.g., to confirm fetal pulmonary maturity), consideration should be given to obtaining the karyotype if indicated, even though the pregnancy is too far along to be ended electively.

Amniocentesis in multiple gestations can be performed safely. Care must be taken to carefully map the fetal sacs so that the amniotic fluid for each fetus is sampled separately. A small amount of indigo carmine (3 to 5 mL) is typically inserted into the first sac after the fluid is sampled to ensure that the same sac is not sampled twice.

Chorionic Villus Sampling

Like that of amniocentesis, the goal of CVS is to provide fetal cells for genetic analysis, although in this case the cells are trophectoderm (placental) cells rather than amniocytes. The technique entails ultrasound-guided aspiration of chorionic villi by means of a 16-gauge catheter inserted transcervically or a 20-gauge spinal needle inserted transabdominally into the placenta. The 15 to 30 mg of villous material collected can be examined in two ways: (1) by direct cytogenetic analysis after an overnight incubation, which yields results in 2 to 3 days; and (2) by longer-term culture followed by cytogenetic analysis, which yields results in 6 to 8 days.[154] To provide rapid and accurate results, many centers report the results of both methods. The main advantage of CVS over amniocentesis is that it allows for fetal karyotyping results in the first trimester, thereby allowing decisions about pregnancy termination to be made earlier if chromosomal abnormalities are detected. Moreover, although rare, certain genetic disorders (e.g., osteogenesis imperfecta) can be diagnosed antenatally only through analysis of placental tissue.

CVS is best performed between 10 and 12 weeks' gestation. CVS performed before 10 weeks' gestation has been associated with limb reduction defects,[155,156] whereas no such association exists if the procedure is performed after 66 days' gestation.[157] Transabdominal CVS can also be performed in the second or third trimester and is a reasonable alternative to cordocentesis for obtaining tissue for an urgent fetal karyotype.[158]

The most common complication of CVS is vaginal spotting, which occurs in 10% to 25% of patients within the first few days after the procedure. Fortunately, the bleeding is usually mild and resolves spontaneously with no long-term sequelae. The incidences of amnionitis (0.3%) and rupture of membranes (0.3%) after CVS do not differ significantly from those seen with late amniocentesis and are significantly lower than those reported after early amniocentesis.[157] As with amniocentesis, the most serious complication of CVS is spontaneous abortion. CVS appears to be associated with a higher risk for pregnancy loss than late amniocentesis; the procedure-related loss rate in CVS is reported as 1.0% to 1.5%.[157,159-164] This rate is significantly higher (0.6% to 0.8%) than that seen after late amniocentesis, with an adjusted odds ratio of 1.30 (95% confidence interval [CI], 1.17 to 1.52).[163] Factors that increase the procedure-related loss rate are operator inexperience, number of needle passes, and a history of bleeding prior to the procedure.[163] By contrast, the risk does not appear to be increased in twin gestations or with the anatomic approach used (i.e., transabdominal versus transcervical catheter placement).[162,165] Some investigators have suggested that the apparently higher pregnancy loss related to CVS (compared with amniocentesis) is a function of the earlier gestational age at which the procedure is performed.[120]

One complication unique to CVS involves the interpretation of the genetic test results. Because the fetus and placenta both arise from the same cell, it is assumed that the genetic complements of these two tissues are identical, but this is not always the case. **Confined placental mosaicism** refers to the situation in which the karyotype of the chorionic villus is a mosaic (i.e., it contains two or more populations of cells with different karyotypes, usually one normal and one trisomic) but the karyotype of the fetus is normal. The incidence of confined placental mosaicism may be as high as 1% to 2% with the direct

cytogenetic analysis method, but most cases are not confirmed by the long-term tissue-culture method,[157,161] suggesting a methodologic error. For this reason, many centers report only the long-term culture results. On occasion, it may be necessary to repeat the fetal karyotype, either with a second CVS or with amniocentesis, to resolve the dilemma. The reverse situation, in which the CVS result is normal but the fetus has aneuploidy (a false-negative result), has also been reported[166] but is rare. It may occur from contamination with maternal cells or from inadvertent sampling of a twin placenta.

Cordocentesis

In cases in which pregnancy complications or fetal abnormalities are discovered late in gestation, **cordocentesis** (also known as percutaneous umbilical blood sampling) is an option for rapid evaluation of the fetal karyotype. Cordocentesis involves the insertion of a 22-gauge spinal needle through the maternal abdominal and uterine walls and into the umbilical vein, preferably at the insertion site on the placenta, under direct ultrasonographic guidance. Considerable training and expertise are needed to perform this procedure. Karyotype analysis results can be obtained in 24 to 48 hours.

The first cordocentesis was reported in 1983.[167] Although this procedure was originally considered superior to amniocentesis for a number of diagnostic indications, advances in laboratory analysis have allowed more information to be obtained through amniocentesis.[168] For example, cordocentesis was commonly used to obtain a sample of fetal blood for rapid karyotyping when a major structural anomaly or severe fetal growth restriction was identified late in pregnancy; however, this sample can be obtained as rapidly from amniocentesis or CVS samples using FISH analysis. Similarly, DNA analysis of amniocytes can rapidly and accurately determine the fetal Rh status as well as the presence of other red cell and platelet antigens,[169] which in the past was an absolute indication for cordocentesis. Now employed primarily for therapeutic indications, cordocentesis is most commonly used to transfuse fetuses with severe anemia from isoimmunization, parvovirus infection, or fetal-maternal hemorrhage (spilling of fetal blood cells into the maternal circulation). This intravascular route of fetal transfusion is preferred to the older technique of intraperitoneal transfusion.[170] Other rare indications for cordocentesis are to measure drug concentrations in the fetal circulation, to document response to pharmacologic therapy, and to administer drugs directly to the fetus (e.g., adenosine to treat resistant fetal tachydysrhythmia).[171]

When skilled operators perform cordocentesis, complications are infrequent and similar to those encountered with amniocentesis. Specifically, there is risk for bleeding, cord hematoma, infection, and preterm PROM. The risk for pregnancy loss as a result of the procedure is estimated to be 1.2% to 4.9%,[172] although fetuses with severe fetal growth restriction, hydrops or major structural anomalies may be at higher risk compared with well-grown, structurally normal fetuses. Operator experience is an important determinant of success, as are logistical issues (e.g., volume of amniotic fluid, placental position, location of the cord insertion site within the placenta). A transient fetal bradycardia may occur during the procedure, often resulting from unintentional placement of the needle into one of the umbilical arteries and leading to arterial vasospasm. Although this bradycardia invariably resolves, if the fetus is at a favorable gestational age (> 24 weeks), the procedure should be performed at a facility with the capacity to perform an emergency cesarean delivery. No consistent data or recommendations exist regarding the use of prophylactic antibiotics, tocolysis, and maternal sedation during cordocentesis.

Other Tests

Three-Dimensional Ultrasonography

Compared with standard two-dimensional ultrasonography, three-dimensional (3D) ultrasonography (or four-dimensional, if fetal movements are included) allows for concurrent visualization of fetal structures in all three dimensions for improved characterization of complex fetal structural anomalies. Unlike two-dimensional ultrasonographic images, 3D images are greatly influenced by fetal movements and are subject to more interference from structures such as fetal limbs, umbilical cord, and placental tissue. Because of movement interference, visualization of the fetal heart with 3D ultrasonography is suboptimal.

In addition to rapid acquisition of images that can be later reconstructed and manipulated, 3D ultrasonography has the following potential advantages:

1. The ability to provide clearer images of soft tissue structures through surface rendering. Such images may improve the diagnosis of certain fetal malformations, especially craniofacial anomalies (e.g., cleft lip and palate, micrognathia, ear anomaly, facial dysmorphism, intracranial lesions), club foot, finger and toe anomalies, spinal anomalies, ventral wall defects, and fetal tumors.
2. The ability to provide more accurate measurements of the gestational sac, yolk sac, and crown-rump length and to obtain a midsagittal view for measuring nuchal translucency.
3. The ability to measure tissue volume. Preliminary data suggest that assessment of cervical volume may identify women at risk for cervical insufficiency,[173] and measurement of placental volume in the first trimester may determine fetuses at risk for fetal growth restriction.[174]

Despite these advantages, 3D ultrasonography has been used primarily as a complementary technique rather than the standard technique for ultrasonographic imaging. In the future, technical improvements should provide higher-quality images, perhaps similar to those offered by computed tomography and magnetic resonance imaging (MRI).

Complementary Radiographic Imaging

Ultrasonography remains the first-line imaging modality during pregnancy. In certain situations, however, enhanced imaging may be required to better define a

particular fetal anomaly. For example, radiographic imaging is superior to ultrasonography in evaluating the fetal skeleton and may provide valuable information in the evaluation of a fetus with a suspected bony dystrophy. At least 25 different forms of skeletal dysplasias are identifiable at birth, 11 of which are lethal in the peripartum period.[175] Although some of these forms can be identified from their unusual appearance on ultrasonography (e.g., cloverleaf skull and small thorax in thanatophoric dysplasia), the majority are difficult to identify. Timely radiographic imaging may allow an experienced pediatric radiologist to more thoroughly evaluate the fetal skeleton and determine the correct diagnosis. A simple maternal abdominal radiograph may be all that is required, because ossification is sufficient by 20 weeks' gestation to allow good visualization of the fetal bones.

Although computed tomography is best avoided in pregnancy because it exposes the fetus to ionizing radiation (albeit at small doses), MRI is regarded as safe. This latter technology relies on the interaction between an applied magnetic field and the inherent nuclear magnetism of atomic nuclei within the patient's tissues to generate a high-resolution anatomic image. Because MRI is particularly good at visualizing soft tissue rather than bony structures, it is uniquely suited to the evaluation of fetal intracranial defects and the soft tissues of the maternal pelvis (Figure 6-8).[176,177] Although fetal motion artifact has previously been a major limitation in the use of MRI, new ultrafast technology allows for rapid image acquisition and has largely overcome this problem.

Fetal Echocardiography

Cardiac anomalies are the most common major congenital defects encountered in the antepartum period. A four-chamber ultrasonographic view of the heart during the fetal anatomic survey at 18 to 20 weeks' gestation detects only 30% of congenital cardiac anomalies, although the detection rate can be increased to 60% to 70% if the outflow tracts are adequately visualized.[178] Owing to the number of congenital cardiac anomalies that would be missed, however, fetal echocardiography should be performed by a skilled and experienced sonologist at 20 to 22 weeks' gestation in all pregnancies at high risk for a fetal cardiac anomaly. Indications for fetal echocardiography include (1) pregnancies complicated by pregestational diabetes mellitus, (2) a personal or family history of congenital cardiac disease (regardless of the nature of the lesion or whether it has been repaired), (3) maternal exposure to certain drugs (e.g., lithium, paroxetine),[179] and (4) conception by *in vitro* fertilization (but not if the pregnancy was conceived through the use of clomiphene citrate or ovarian stimulation/intrauterine insemination alone).[180]

Fetal Cells or DNA in the Maternal Circulation

To minimize the risks associated with invasive prenatal diagnosis (amniocentesis and CVS), improved noninvasive tests are being developed for fetal aneuploidy genetic testing. Fetal cells are known to be present in the maternal circulation throughout pregnancy at a concentration of approximately 1 fetal cell for every 10,000 to 1 million maternal cells.[181] However, we do not currently have the technology to isolate these cells with sufficient purity to develop a reliable prenatal test. Recent efforts have focused on genetic analysis of cell-free DNA in the maternal circulation. It is now apparent that fetal DNA (most of which comes from the placenta) accounts for 3% to 10% of all cell-free DNA in maternal serum, and it may account for as much as 20% of cell-free DNA in women with preeclampsia or after major fetal-maternal hemorrhage. Because of its relative abundance, purity, and short half-life (precluding contamination from a prior pregnancy), high-throughput sequencing of cell-free DNA provides new opportunities for noninvasive prenatal testing.[182] Several commercial tests are now available that rely on analysis of cell-free DNA in the maternal circulation to screen for fetal aneuploidy as early as 10 weeks' gestation. Recent publications have shown that such noninvasive prenatal testing can increase the detection rate for trisomy 21 (Down syndrome) to approximately 99.8% with a 0.2% false-positive rate in high-risk pregnancies [183-186]; these results have not yet

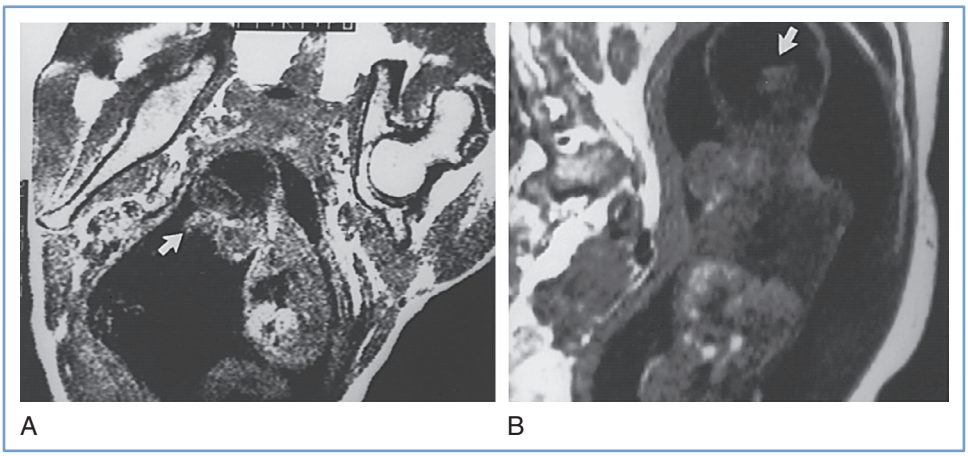

FIGURE 6-8 ■ Magnetic resonance images of a fetus with holoprosencephaly. **A,** Sagittal view showing the proboscis (*arrow*). **B,** Coronal view showing the single ventricle and fused thalami (*arrow*). (Reprinted from Wenstrom KD, Williamson RA, Weiner CP, et al. Magnetic resonance imaging of fetuses with intracranial defects. Obstet Gynecol 1991; 77:529-32.)

been validated in low-risk pregnancies. Because of the small but finite false-positive rate, these tests should be considered screening and not diagnostic tests, and confirmatory CVS or amniocentesis is still recommended before acting on a positive test. The detection of trisomy 18 (98%) and trisomy 13 (65%) is also possible using this technology.[184,186]

An alternative approach under investigation for definitive genetic testing is the isolation of trophoblast cells from the cervicovaginal discharge of women in early pregnancy.[187,188] Provisional studies have isolated these cells from the maternal cervix with cervical canal lavage at 7 to 10 weeks' gestation[187] or with the use of a brush-type collection device at 5 to 12 weeks (the "genetic Pap smear").[188] With this technique, such cells have been isolated in 86% (195/227) of samples by immunocytochemistry with trophoblast-specific antibodies, and results agreed with those of placental tissue karyotyping via CVS in 95% (186/195) of cases.[188] The ability to successfully collect trophoblast cells from the cervicovaginal discharge of women in early pregnancy may provide a simple, reliable, noninvasive, yet definitive genetic test for fetal aneuploidy in a singleton pregnancy with no risk to the mother or fetus.

SPECIAL CIRCUMSTANCES REQUIRING ADDITIONAL FETAL SURVEILLANCE

Under certain circumstances, additional antenatal fetal surveillance may be required (see Box 6-2). If appropriate, early consultation with a specialist (e.g., a maternal-fetal medicine specialist, medical geneticist, pediatric surgeon, pediatric urologist, pediatric cardiologist, or infectious disease specialist) and delivery at a tertiary care center should be considered.

Abnormal Serum Analyte and Nuchal Translucency Screening with Normal Fetal Karyotype

Pregnancies with abnormal serum analyte screening in the first or second trimester are at increased risk for adverse outcomes, including preterm birth, preeclampsia, and stillbirth, *even if the karyotype is normal* (Tables 6-9 and 6-10).[189-191] Such pregnancies therefore require more intensive fetal monitoring (Table 6-11), including serial growth evaluation and NST. Fetuses with a nuchal translucency measurement of 3.0 mm or more in the first trimester have a higher risk for congenital heart defects and other chest abnormalities, even with a negative aneuploidy screening test result and normal fetal chromosomes.[132,192] Women with such pregnancies should be offered a fetal echocardiogram at 20 to 22 weeks' gestation in addition to a routine targeted fetal anatomic survey at 18 to 20 weeks.

Hydrops Fetalis

Hydrops fetalis ("edema of the fetus") is a rare pathologic condition that complicates approximately 0.05% of all pregnancies. It is an ultrasonographic diagnosis requiring the presence of an abnormal accumulation of fluid in more than one fetal extravascular compartment, including ascites, pericardial effusion, pleural effusion, subcutaneous edema, and/or placental edema. Polyhydramnios is seen in 50% to 75% of cases. Although classically seen in fetuses with severe anemia resulting from Rh isoimmunization, the introduction of Rh_0(D) immune globulin has led to a substantial decrease in the incidence of immune hydrops. Indeed, 90% of hydrops fetalis cases

TABLE 6-9 Relationship between First-Trimester PAPP-A Level at or below Fifth Percentile (0.42 MoM) and Risks of Adverse Pregnancy Outcomes

Adverse Outcome	Adjusted Odds Ratio	95% Confidence Interval
Spontaneous loss < 24 weeks	2.50	1.76-3.56
Fetal death ≥ 24 weeks	2.15	1.11-4.15
Preterm birth ≤ 37 weeks	1.87	1.61-2.17
Preterm birth ≤ 32 weeks	2.10	1.59-2.76
Preeclampsia	1.54	1.16-2.03
Gestational hypertension	1.47	1.20-1.82
Placental abruption	1.80	1.15-2.84
Fetal growth restriction	3.22	2.38-4.36

MoM, multiple of the median; *PAPP-A,* pregnancy-associated placental protein-A test.

Data from Dugoff L, Hobbins JS, Malone FD, et al. First-trimester maternal serum PAPP-A and free beta-subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004; 191:1446-51.

TABLE 6-10 Second-Trimester Serum Analyte (Marker) Screening and Adverse Pregnancy Outcome

Adverse Outcome	Marker	Odds Ratio
Spontaneous loss < 24 weeks	MS-AFP	7.8
Fetal death ≥ 24 weeks	Inhibin A	3.7
Preterm birth ≤ 32 weeks	Inhibin A	5.0
Preterm premature rupture of membranes	MS-AFP	1.9
Preeclampsia	Inhibin A	3.8
Gestational hypertension	Inhibin A	1.7
Placental abruption	MS-AFP	1.9
Placenta previa (confirmed at delivery)	MS-AFP	3.1
Fetal growth restriction	Inhibin A	3.0
Birth weight ≤ 5th percentile	Inhibin A	2.3
• Delivery < 37 weeks	Inhibin A	8.0
• Delivery < 32 weeks	Inhibin A	18.6

MS-AFP, maternal serum level of alpha-fetoprotein.

Data from Dugoff L, Hobbins JS, Malone FD, et al; FASTER Trial Research Consortium. Quad screen as a predictor of adverse pregnancy outcome. Obstet Gynecol 2005; 106:260-7.

TABLE 6-11 **Special Circumstances Requiring Additional Fetal Surveillance during Pregnancy**

Pregnancy-Related Condition	Additional Testing Recommended	Gestational Age at Which Testing Should Be Started
Maternal Conditions		
Chronic hypertension	Growth scans q3-4 wk	24 weeks
	Weekly NST ± AFV	32 weeks
Diabetes mellitus:		
Pregestational diabetes	Growth scans q3-4 wk	24 weeks
	Weekly NST ± AFV	32 weeks
Gestational diabetes	Growth scans q3-4 wk	From diagnosis
	Weekly NST ± AFV	36 weeks
Maternal obesity (body mass index > 30 kg/m^2)	Weekly NST ± AFV	36 weeks
Advanced maternal age	Weekly NST ± AFV	38 weeks
Abnormal serum analyte screening result (maternal serum level of alpha-fetoprotein [MS-AFP] > 2.0 MoM; pregnancy-associated placental protein-A [PAPP-A] < 0.4 MoM) with normal fetal karyotype	Growth scans q3-4 wk	24 weeks
	Weekly NST ± AFV	36 weeks
Prior unexplained preterm birth < 35 weeks	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	24 weeks to 32-34 weeks
Prior cervical cone biopsy	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	24 weeks to 32-34 weeks
Post-term pregnancy	Twice-weekly NST and AFV	41-42 weeks
Isoimmunization	Weekly middle cerebral artery Doppler velocimetry	18-20 weeks
Uteroplacental Conditions		
Chronic abruption	Growth scans q3-4 wk	From diagnosis
	Weekly NST ± AFV	28-32 weeks
Uterus didelphys	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
Preterm premature rupture of membranes	Daily NST	From diagnosis
	Growth scans q3-4 wk	From diagnosis
	Weekly AFV	From diagnosis
Unexplained oligohydramnios	Growth scans q3-4 wk	From diagnosis
	Weekly AFV	From diagnosis
	Weekly NST with AFV	32 weeks
	Weekly UA Doppler velocimetry	From diagnosis
Fetal Conditions		
Twin pregnancy:		
Dichorionic, diamniotic twin pregnancy	Biweekly AFV	18-20 weeks
	Growth scans q3-4 wk	24 weeks
	Weekly NST with AFV	32 weeks
	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	22-24 weeks to 30-32 weeks
Monochorionic, diamniotic twin pregnancy	Weekly AFV	16-18 weeks
	Growth scans q3-4 wk	24 weeks
	Weekly NST with AFV	28-32 weeks
	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	22-24 weeks to 30-32 weeks
Monochorionic, monoamniotic twin pregnancy	Weekly AFV	16-18 weeks
	Growth scans q3-4 wk	24 weeks
	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	22-24 weeks to 30-32 weeks
	± Continuous fetal heart rate monitoring	24-26 weeks to delivery
Twin pregnancy complicated by demise of one twin	Weekly NST with AFV	From diagnosis
	Growth scans q3-4 wk	From diagnosis
Higher-order multiple pregnancy (≥ triplets)	Weekly AFV	16-18 weeks
	Growth scans q3-4 wk	24 weeks
	Weekly NST with AFV	28-32 weeks
	Weekly to biweekly cervical length measurements	16-18 weeks to 30-32 weeks
	± Weekly to biweekly fFN	22-24 weeks to 30-32 weeks

TABLE 6-11 **Special Circumstances Requiring Additional Fetal Surveillance during Pregnancy** (Continued)

Pregnancy-Related Condition	Additional Testing Recommended	Gestational Age at Which Testing Should Be Started
Fetal growth restriction:		
< 10th percentile	Growth scans q3-4 wk	From diagnosis
	Weekly NST with AFV	From diagnosis
< 5th percentile	Growth scans q3-4 wk	From diagnosis
	Weekly to twice weekly NST with AFV	From diagnosis
	Weekly to twice weekly UA Doppler velocimetry	From diagnosis
Major fetal structural anomaly	Growth scans q3-4 wk	24 weeks
	Weekly NST with AFV	32 weeks
	± Weekly UA Doppler velocimetry	32 weeks

AFV, amniotic fluid volume; *biweekly,* every 2 weeks; *fFN,* fetal fibronectin; *MoM,* multiple of median; *NST,* nonstress test; *UA,* umbilical artery.

are due to nonimmune causes, such as maternal infection (e.g., with parvovirus B19, cytomegalovirus, syphilis), massive fetal-maternal hemorrhage, and fetal abnormalities (e.g., congenital cardiac defects, fetal thalassemia, twin-to-twin transfusion syndrome). Although the overall perinatal mortality rate in the setting of hydrops fetalis exceeds 50%, the prognosis depends on the underlying cause, severity, and gestational age.

Immune hydrops occurs when fetal erythrocytes express a protein that is not present on maternal erythrocytes. The maternal immune system can become sensitized and produce antibodies against these "foreign" proteins. These immunoglobulin (Ig) G antibodies can cross the placenta and destroy fetal erythrocytes, leading to fetal anemia and high-output cardiac failure. Immune hydrops is typically associated with a fetal hematocrit less than 15% (normal fetal hematocrit is 50%). The most antigenic protein on the surface of fetal erythrocytes is the D antigen of the Rhesus protein complex, also known as Rh(D). Other antigens that can cause severe immune hydrops are Kell ("Kell kills"), Rh(E), Rh(c), and Duffy ("Duffy dies"). Antigens causing less severe hydrops are ABO, Rh(e), Rh(C), Ce, k, and s. Lewis a and b (Le^a, Le^b) incompatibility can cause mild anemia but not hydrops, because this condition primarily results in production of IgM antibodies, which do not cross the placenta ("Lewis lives"). For identification of women at risk for isoimmunization, every pregnant woman should undergo blood type and antibody screening at the first prenatal visit and again in the third trimester.

Sixty percent of cases of immune hydrops result from ABO incompatibility; however, only Rh(D) isoimmunization can be prevented. The Rh(D) antigen is expressed only on primate erythrocytes and becomes evident by 38 days of intrauterine life. A mutation in the Rh(D) gene on chromosome 1 results in lack of expression of Rh(D) antigen on circulating erythrocytes (Rh[D] negative). This mutation arose in the Basque region of Spain, and the difference in prevalence of Rh(D)-negative individuals between the races likely reflects the amount of Spanish blood in their ancestry: Caucasian, 15%; African-American, 8%; African, 4%; Native American, 1%; and Asian, less than 1%.[193] If the fetus of an Rh(D)-negative woman is Rh(D) negative, Rh(D) sensitization will not occur. However, 60% of Rh(D)-negative women have Rh(D)-positive fetuses, and exposure of these women to as little as 0.25 mL of Rh(D)-positive blood may induce an antibody response. Because the initial immune response is production of IgM, the index pregnancy is rarely affected. However, immunization in subsequent pregnancies triggers an IgG response that crosses the placenta and causes hemolysis. Risk factors for Rh(D) sensitization include a mismatched blood transfusion (95% sensitization rate), ectopic pregnancy (< 1%), abortion (3% to 6%), amniocentesis (1% to 3%), and pregnancy itself. Indeed, the sensitization rate is 16% to 18% after a normal pregnancy without Rh_0(D) immune globulin administration, 1.3% with Rh_0(D) immune globulin at delivery only, and 0.13% with anti-Rh_0(D) immune globulin at 28 weeks and again after delivery.[193,194] The risk for isoimmunization depends on the volume of fetal-maternal hemorrhage (Table 6-12). Passive immunization with Rh_0(D) immune globulin can destroy fetal erythrocytes before they evoke a maternal immune response, thereby preventing sensitization. Therefore, Rh_0(D) immune globulin should be given within 72 hours of potential exposure; 300 µg given intramuscularly is

TABLE 6-12 **Fetal-Maternal Transfusion Volume and Risk for Rh(D) Isoimmunization in an Rh(D)-Negative Woman**

Transfusion Volume	Incidence at Delivery (%)	Risk for Isoimmunization (%)*
Unmeasurable	50	Minimal
< 0.1 mL	45-50	3
> 5.0 mL	1	20-40
> 30 mL	0.25	60-80

*Without Rh_0(D) immune globulin.

Data from American College of Obstetricians and Gynecologists. Prevention of Rh D alloimmunization. ACOG Practice Bulletin No. 4. Int J Gynaecol Obstet 1999; 66:63-70 (reaffirmed 2009); and Moise KJ. Red blood cell alloimmunization in pregnancy. Semin Hematol 2005; 42:169-78.

adequate for exposure to as much as 30 mL of fetal whole blood or 15 mL of fetal red blood cells.

Once isoimmunization has occurred, passive immunoglobulin is not useful. Such pregnancies should be observed closely for evidence of fetal compromise. Fetal hemolysis results in release of bile pigment into the amniotic fluid, which can be quantified as a change in optical density measured at wavelength 450 nm. Traditionally, the extent of hemolysis had been measured with serial amniocenteses, with amniotic fluid optical density plotted against gestational age; increased density (upper 80% of zone 2 or zone 3 of the Liley curve) is associated with a poor prognosis,[195,196] and prompt intervention is indicated. Measurements of peak systolic velocity in the fetal MCA by means of noninvasive Doppler velocimetry have now emerged as the best tool to accurately identify fetuses with severe anemia requiring urgent intervention, regardless of the cause of the anemia.[113,194,197] The sensitivity of an elevated MCA peak systolic velocity (i.e., >1.5 MoM for a given gestational age) for predicting moderate to severe anemia approaches 100%.[113] Depending on gestational age, these interventions may include immediate delivery or intrauterine blood transfusion.

Post-Term Pregnancy

Post-term (prolonged) pregnancy is defined as any pregnancy that continues to or beyond 42 weeks (294 days) from the first day of the last normal menstrual period or 14 days beyond the best obstetric estimate of the EDD.[2,198] The prevalence of post-term pregnancy depends on the patient population (e.g., percentage of primigravidas, incidence of pregnancy complications, frequency of spontaneous preterm births) and the local practice patterns (e.g., use of ultrasonographic assessment of gestational age, cesarean delivery rates, use of labor induction). Approximately 10% (range, 3% to 14%) of all pregnancies continue beyond 42 weeks, and 4% (range, 2% to 7%) continue beyond 43 weeks in the absence of obstetric intervention.[2] Compared with delivery at 40 weeks, post-term pregnancies pose significant risks to both the mother (including higher risk for cesarean delivery, severe perineal injury, and postpartum hemorrhage) and the fetus (including stillbirth, fetal macrosomia, birth injury, and meconium aspiration syndrome).[2,198-201] The risks to the fetus can be largely prevented by routine induction of labor for all low-risk pregnancies at 40 to 41 weeks' gestation.[2,199]

Post-term pregnancy is a universally accepted indication for antenatal fetal surveillance,[2] although the efficacy of this approach has not been validated by prospective randomized trials. Options for evaluating fetal well-being include NST with or without amniotic fluid volume assessment, BPP, CST, and a combination of these modalities. There is no consensus as to which of these modalities is preferred, and no single method has been shown to be superior.[2] The ACOG has recommended that antepartum fetal surveillance be initiated by 42 weeks' gestation at the latest, without making a specific recommendation about the type of test or frequency.[2] Many investigators would advise twice-weekly testing with some evaluation of amniotic fluid volume at least weekly. Doppler ultrasonography has no benefit in monitoring the post-term fetus and is not recommended for this indication.[109,110] Although the data are inconsistent, there is a suggestion that antenatal testing at 40 to 42 weeks' gestation may be associated with improvements in perinatal outcome. In one retrospective study, women with routine antenatal testing beginning at 41 weeks had lower rates of cesarean delivery for nonreassuring fetal test results than women in whom testing was started at 42 weeks (2.3% versus 5.6%, respectively; $P < .01$).[202] In addition, the group with delayed antenatal testing experienced three stillbirths and seven other neonatal major morbidity events, compared with none in the group who had antenatal testing from 41 weeks ($P < .05$).[202]

In the post-term period, evidence of fetal compromise (nonreassuring fetal test results) or **oligohydramnios** (e.g., low amniotic fluid volume) should prompt delivery.[2] Oligohydramnios may result from uteroplacental insufficiency or increased renal artery resistance and may predispose to umbilical cord compression, thus leading to intermittent fetal hypoxemia, meconium passage, and meconium aspiration. A uniform definition for oligohydramnios has not been established; however, options are as follows: (1) a depth of less than 2 cm for the maximum vertical fluid pocket; (2) amniotic fluid index less than 5 cm (i.e., < 5 cm for the sum of the depths in cm of the largest vertical pocket in each of four uterine quadrants); and (3) product of length times width times depth of the largest pocket (in cm) less than 60. Adverse pregnancy outcomes (nonreassuring FHR tracing, low Apgar score, and neonatal intensive care unit admission) are more common when oligohydramnios is present. Frequent (twice-weekly) screening of post-term patients for oligohydramnios is important, because amniotic fluid can become dramatically reduced within 24 to 48 hours. One prospective double-blind cohort study of 1584 women after 40 weeks' gestation found that an amniotic fluid index less than 5 cm with no largest vertical fluid pocket depth greater than 2 cm was associated with birth asphyxia and meconium aspiration, although the sensitivity for adverse outcomes was low.[203]

Intrauterine Fetal Demise

Intrauterine fetal demise (IUFD), also known as stillbirth, is defined in the United States as demise of the fetus after 20 weeks' gestation and prior to delivery.[204-206] In Europe, only fetuses more than 24 weeks' gestation are included. The stillbirth rate in the United States diminished from 15.8 per 1000 total births in 1960 to 7.5 per 1000 births in 1990.[205,206] However, it remains a vastly underappreciated clinical problem, with antepartum stillbirths accounting for more perinatal deaths than either complications of prematurity or sudden infant death syndrome.[207] Risk factors for stillbirth include extremes of maternal age, chromosomal disorders, congenital malformations, antenatal infection, multiple pregnancy, prior unexplained IUFD, post-term pregnancy, fetal macrosomia, male fetus, umbilical cord and placental abnormalities, and underlying maternal medical conditions (e.g., chronic hypertension, pregestational or gestational diabetes mellitus, autoimmune disorders, inherited or acquired thrombophilia).[204,208,209]

Although older studies observed that approximately 50% of cases of IUFD were unexplained, an aggressive

TABLE 6-13 Causes of Intrauterine Fetal Demise

Maternal causes	Underlying medical conditions (diabetes mellitus, thyroid disease, antiphospholipid antibody syndrome)
	Preeclampsia
	Isoimmunization
	Illicit drug use (cocaine)
	Antepartum drug/toxin exposure
Uteroplacental causes	Placental abruption
	Placenta previa
	Vasa previa
	Fetomaternal hemorrhage
	Cord accident
Fetal causes	Fetal chromosomal/genetic anomalies
	Fetal structural abnormalities
	Intra-amniotic infection
	Complications of multiple pregnancies (including twin-to-twin transfusion syndrome)

approach may identify the cause in up to 80% to 90% of cases (Table 6-13).[209-212] Pathologic examination of the fetus and the placenta/fetal membranes is the single most useful means of identifying a cause for the IUFD.[210,211] Early detection and appropriate management of underlying maternal disorders (e.g., diabetes, preeclampsia) may also reduce the risk. Fetal karyotyping should be considered in all cases of fetal death to identify chromosomal abnormalities, particularly in cases with documented fetal structural abnormalities. Six to 10 percent of stillborn fetuses have an abnormal karyotype.[212] On occasion, amniocentesis may be recommended to salvage viable amniocytes for cytogenetic analysis before delivery. Fetal-maternal hemorrhage occurs in all pregnancies but is usually minimal (< 0.1 mL total volume). In rare instances, this hemorrhage may be massive, leading to fetal demise. The Kleihauer-Betke (acid elution) test allows an estimate of the volume of fetal blood in the maternal circulation, and a maternal blood sample should be drawn within 6 to 8 hours of the purported bleeding episode because of rapid clearance of fetal cells from the maternal circulation.[213] Intra-amniotic infection resulting in fetal death is usually evident on clinical examination. Placental membrane culture and autopsy examination of the fetus, placenta/fetal membranes, and umbilical cord may be useful. Fetal radiographic or MRI may sometimes be valuable if autopsy is declined.[214,215]

The inability to identify fetal heart activity or the absence of uterine growth may suggest the diagnosis. Ultrasonography is the "gold standard" for confirming IUFD by documenting the absence of fetal cardiac activity. Other ultrasonographic findings in late pregnancy include Spalding's sign (overlapping of the cranial sutures), scalp edema, and soft tissue maceration, although these usually take a few days to develop. Every effort should be made to avoid cesarean delivery in the setting of IUFD. Thus, in the absence of a contraindication, expectant management is often recommended. Latency (the period from fetal demise to delivery) varies according to the underlying cause and gestational age. In general, the earlier the gestational age, the longer the latency period. Overall, more than 90% of women go into spontaneous labor within 2 weeks of fetal death. However, many women find the prospect of carrying a dead fetus distressing and want the pregnancy terminated as soon as possible. Management options include surgical dilation and evacuation or induction of labor with cervical ripening, if indicated. Disseminated intravascular coagulation develops in 20% to 25% of women who retain a dead singleton fetus for longer than 3 weeks because of excessive consumption of clotting factors.[216,217] Therefore, delivery should be effected within this period. Induction of labor with prostaglandins or oxytocin has been shown to be safe in the setting of an IUFD.

The death of one twin in a monochorionic twin gestation poses a particular challenge. In this setting, the surviving twin is at significant risk for major morbidity, including IUFD, neurologic injury, multiorgan system failure, thromboembolic events, placental abruption, and preterm birth.[218-220] The prognosis for the surviving twin depends on the cause of death, gestational age, chorionicity, and the time between death of the first twin and delivery of the second. Dizygous twin pregnancies do not share a circulation, and death of one twin may have little impact on the surviving twin. The dead twin may be resorbed completely or may become compressed and incorporated into the membranes (*fetus papyraceus*). Disseminated intravascular coagulation in the surviving fetus and/or mother is rare.[221] On the other hand, some level of shared circulation can be demonstrated in almost all monozygous twin pregnancies, and death of one fetus in this setting raises the risk for death of its co-twin owing to profound hypotension and/or purported transfer of thromboplastic proteins from the dead fetus to the live fetus.[222] If it survives, the co-twin has a 20% risk for development of permanent neurologic injury (multicystic encephalomalacia), which may not be prevented by immediate delivery.[223,224] Therefore, management of a surviving twin depends on chorionicity and gestational age. Regular fetal surveillance (kick counts, NST, BPP) should be instituted (see Table 6-11), and delivery considered in the setting of nonreassuring fetal test results or at a favorable gestational age.

FETAL THERAPY

Continued assessment of the fetus throughout pregnancy is critical to optimizing pregnancy outcomes. In most cases, evidence of fetal compromise prompts delivery. However, in certain situations, treatment may be available to improve or even correct the underlying problem *in utero*. These interventions can be noninvasive (e.g., administration of digoxin to the mother to treat a fetal supraventricular tachycardia) or invasive (e.g., placement of a vesicoamniotic shunt) and are summarized in Tables 6-14 and 6-15, respectively.[225-260] Some of these interventions have been subjected to rigorous clinical trials and have been shown to be effective, whereas others remain investigational. The intervention that has perhaps had the greatest effect on perinatal outcome is antenatal maternal administration of corticosteroids.

TABLE 6-14 Noninvasive Treatment Options to Improve Perinatal Outcome

Clinical Condition	Treatment	Efficacy
Imminent risk for preterm birth < 34 weeks	Antenatal corticosteroids	Effective in decreasing respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis[225]
Pregestational diabetes mellitus	Strict glycemic control	Effective in decreasing rate of stillbirths and birth defects[226]
Phenylketonuria (autosomal recessive disorder due to phenylalanine hydroxylase deficiency)	Dietary manipulation (low-phenylalanine diet)	Effective in decreasing birth defects and brain damage in affected fetuses[227]
Alloimmune thrombocytopenia	Maternal intravenous immunoglobulin ± corticosteroids	Data conflicting on effect of intravenous immunoglobulin on fetal platelets; steroids probably of no benefit[228,229]
Fetal thyrotoxicosis	Maternal propylthiouracil	Effective in decreasing fetal growth restriction and subsequent neurodevelopmental defects[230,231]
Congenital adrenal hyperplasia (due usually to 21-hydroxylase deficiency)	Maternal dexamethasone	Effective in preventing virilization of female fetus if given prior to 8 to 9 weeks' gestation[232]
Fetal supraventricular tachycardia (SVT)	Maternal digoxin	Data conflicting on effect of digoxin to correct fetal SVT

TABLE 6-15 Invasive Treatment Options to Improve Perinatal Outcome

Clinical Condition	Treatment	Efficacy
Severe fetal anemia with or without hydrops fetalis	Intrauterine transfusion	Effective[233,234]
Fetal supraventricular tachycardia	Digoxin given directly to fetus by intramuscular injection	Effective
Severe obstructive uropathy	Vesicoamniotic shunt	Effective in preventing renal injury and improving survival[235]
Isolated fluid collection in the fetus (severe ascites, hydrothorax)	Fetoamniotic shunting	Effective[236]
Severe valvular stenosis	Fetal surgery (*in utero* valvuloplasty)	Investigational[237]
Fetal lung masses (congenital cystic adenomatous malformation, pulmonary sequestration)	Fetal surgery (*in utero* resection of lesion)	Investigational[238,239]
Congenital hydrocephalus	Fetal surgery (*in utero* shunting)	Investigational[240]
Congenital diaphragmatic hernia	Fetal surgery (*in utero* repair; tracheal occlusion)	Investigational[241,242]
Fetal neural tube defect	Fetal surgery (*in utero* repair)	Investigational[243-245]
Higher-order multiple pregnancy (≥ triplets)	Multifetal pregnancy reduction	Effective in improving perinatal outcomes with reduction to twins[246-249]
Twin-to-twin transfusion syndrome (TTTS)	Serial amnioreduction versus septostomy versus fetal surgery (endoscopic laser ablation, cord ligation)	Effective Laser ablation appears to give the best chance of intact survival in severe TTTS[250-255]
Preterm premature rupture of membranes	Serial amnioinfusion versus fetal surgery (laser coagulation, intra-amniotic amniopatch)	Investigational[256-258]
Ex utero intrapartum therapy (EXIT)	To facilitate oxygenation at delivery prior to ligation of the umbilical cord when the infant's airway is obstructed; may facilitate transition to extracorporeal membrane oxygenation (ECMO) in infants with severe pulmonary or cardiac malformations	Case reports of success[259,260]

Antenatal Corticosteroids

Respiratory distress syndrome (RDS) refers to respiratory compromise presenting at or shortly after delivery due to a deficiency of pulmonary surfactant, an endogenous detergent that serves to decrease the surface tension within alveoli, thereby preventing alveolar collapse. Overall, neonatal RDS affects approximately 1% of live births, but not all infants are at equal risk. The pulmonary system is among the last of the fetal organ systems to become functionally mature. Thus, RDS is primarily, although not exclusively, a disease of preterm infants, with the incidence and severity highly dependent on gestational age. For example, RDS affects more than 80% of infants younger than 28 weeks' gestation and 10% to 15% of all infants weighing less than 2500 g.[261,262] RDS

remains a major cause of perinatal morbidity and mortality in extremely preterm infants. In addition to gestational age, a number of other factors influence the risk for RDS in a given fetus. For reasons that are not clear, African-American ethnicity, female gender, preeclampsia, and intrauterine exposure to cigarette smoke are protective against the development of RDS.

In 1972, Liggins and Howie[263] demonstrated that the administration of a single course of two antenatal doses of a corticosteroid (betamethasone) reduced the incidence of RDS by 50%. This original observation has since been confirmed by a number of investigators.[225,264-267] A meta-analysis of 12 randomized controlled trials with more than 3000 participants concluded that antenatal administration of corticosteroids to women in preterm labor reduced the incidence of neonatal RDS by 40% to 60% and resulted in an improvement in overall survival.[225] In one study, a single course of antenatal corticosteroids resulted in a threefold rise in the chance of unaffected survival in neonates with a birth weight less than 1500 g.[264] Certain steroids cross the placenta and induce cellular differentiation at the expense of growth. Type II pneumocytes in the lungs differentiate and begin making pulmonary surfactant, which accounts for the decrease in risk for RDS, and endothelial cells lining the vasculature undergo cellular maturation and stabilization, which explains the concomitant drop in incidence of bleeding into the brain (intraventricular hemorrhage) or gastrointestinal tract (necrotizing enterocolitis).[265] Prednisone does not cross the placenta and therefore does not have a similar protective effect.

The National Institutes of Health and the ACOG have recommended that a single course of antenatal corticosteroids, defined as either betamethasone (12 mg intramuscularly q24 h × two doses) or dexamethasone (6 mg intramuscularly q12 h × four doses), be given after 23 to 24 weeks' gestation to any pregnant woman in whom delivery before 34 weeks' gestation is threatening.[266,267] There is as yet no proven benefit to antenatal administration of corticosteroids after 34 weeks' gestation[266,267] or between 32 to 34 weeks in the setting of preterm PROM,[268] but this situation is largely due to the absence of data in these subgroups. Although the maximum benefit of antenatal corticosteroids is achieved 24 to 48 hours after the first injection, as little as 4 hours of treatment exerts some protective effect. This protective effect lasts for 7 days, after which further benefit is unclear. Multiple (three or more) courses of antenatal corticosteroids have been associated with fetal growth restriction, smaller head circumference, and (in animals) abnormal myelination of the optic nerves; consequently, multiple courses are not routinely recommended. If a threat of preterm delivery occurs more than 2 weeks after the initial course was completed, a rescue course of corticosteroids is recommended.[269-273]

Fetal Surgery

Fetal surgery has been proposed in selected cases to prevent progressive organ damage or to restore normal anatomy and fetal development (see Chapter 7). The ideal case for fetal surgery consists of a singleton pregnancy prior to fetal viability (i.e., before 23 to 24 weeks' gestation) in which the fetus has a normal karyotype and an isolated malformation that, if untreated, will result in fetal or neonatal demise. A detailed understanding of the natural history of the malformation is essential when one is considering whether to recommend surgery. Fetal surgery should not be attempted if the natural history of the disorder is unknown or if the chances of survival without *in utero* treatment are equal to or greater than the risks of the procedure. The only two randomized controlled trials published to date in fetal surgery—one on tracheal occlusion for the management of congenital diaphragmatic hernia[274] and the other on prenatal versus postnatal repair of myelomeningocele[275]—found little significant benefit to *in utero* surgery. Repair of lesions that are not believed to be life threatening (e.g., cleft lip and palate) should be deferred until after delivery to minimize risks to the mother.

Before *in utero* surgery can be recommended, a thorough evaluation must be performed to (1) precisely characterize the defect, (2) exclude associated malformations, (3) perform a fetal karyotype analysis, and (4) eliminate the possibility that the condition can be treated using less aggressive technologies. Detailed counseling about the risks and benefits of the proposed procedure is required, and written informed consent is mandatory. Such a discussion must include a detailed review of the risks to both the fetus and the mother, including preterm PROM (28% to 100%), preterm labor and delivery (> 50%), maternal pulmonary edema (20% to 30%), placental abruption (5% to 10%), chorioamnionitis and sepsis (< 5%), and maternal death (rare).[242,244] Specific examples of fetal surgical procedures are summarized in Table 6-15.

KEY POINTS

- Accurate determination of gestational age is essential for the management of pregnancy complications and the effective use of antepartum fetal testing.
- Ultrasonography can be used to estimate gestational age, assess fetal growth, monitor amniotic fluid volume, and detect and characterize fetal anomalies.
- Appropriate fetal growth is strongly correlated with fetal health and can be assessed either clinically or with ultrasonography. Inappropriate fetal growth requires further evaluation.
- Fetal movement charts ("kick counts") can be used to confirm fetal well-being in both high- and low-risk populations. High-risk pregnancies may require additional fetal monitoring such as the nonstress test (NST), biophysical profile (BPP), or contraction stress test (CST).
- A fetal karyotype can be obtained by chorionic villus sampling, amniocentesis, or fetal blood sampling (cordocentesis).

- Doppler velocimetry has advanced our understanding of maternal-fetal physiology, but its role in confirming fetal well-being is unclear.
- Additional radiologic imaging (especially magnetic resonance imaging) may be used in selected cases to better define fetal malformations.
- A number of intrauterine therapies have been shown to improve perinatal outcome in selected cases, including antenatal corticosteroid administration, intrauterine transfusion, and fetal surgery (e.g., laser photocoagulation for twin-to-twin transfusion syndrome).
- The appropriate timing of delivery is a critical determinant of perinatal outcome. In general, delivery is indicated when the benefits of delivery to the fetus or mother outweigh the risks of continuing the pregnancy. Simply stated, delivery is indicated when the fetus is better off outside the uterus than inside. A number of variables should be considered in such a decision, the most important of which are gestational age and fetal well-being.

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CHAPTER 7

Anesthesia for Fetal Surgery and Other Intrauterine Procedures

Mark D. Rollins, MD, PhD • Mark A. Rosen, MD

CHAPTER OUTLINE

Fetal therapy originated in 1963 with Sir William Liley's successful intraperitoneal blood transfusion to a fetus with erythroblastosis fetalis.[1] This was followed by many years of discouraging attempts to transfuse blood via direct cannulation of fetal vessels through a small uterine incision.[2] In 1981, after careful experimentation and practice in sheep[3,4] and rhesus monkeys,[5] the first successful human fetal surgery, a vesicostomy, was performed in a fetus with bilateral hydronephrosis due to a lower urinary tract obstruction.[6]

Advances in prenatal diagnostic technology, particularly in the resolution of imaging, contribute to increasing sophistication in diagnosis of fetal disorders, principally anatomic anomalies. Fetal therapy is largely nonsurgical (e.g., administration of medications, nutrients, blood, stem cells) (see Chapter 6). Some identified disorders are amenable to intrauterine fetal surgery, but most anatomic malformations diagnosed *in utero* remain unsuitable for antenatal intervention. Prenatal diagnosis of serious malformations (e.g., those that are uncorrectable and incompatible with normal postnatal life) allows the choice of pregnancy termination. Most correctable malformations are best managed after delivery at term gestation, but antepartum recognition allows time for the coordination of appropriate prenatal and postnatal care, including transfer of peripartum care to an appropriate medical center while the fetus is *in utero* rather than as a newly delivered, fragile neonate. Some defects, especially those that cause airway obstruction, can be treated with an intrapartum intervention, in which the fetus undergoes repair of the defect and/or the airway is secured during birth, while the uteroplacental unit remains functional.

Fetal surgery is reasonable only with informed consent and only if (1) the lesion is diagnosed accurately, (2) the lesion's severity is assessed correctly, (3) the associated anomalies that contraindicate intervention are excluded, (4) the maternal risk is acceptably low, and (5) the neonatal outcome would be better with *in utero* surgery than with surgery performed after delivery. With all fetal surgical procedures, an emphasis also must be placed on maternal welfare to guard against undue maternal risk.[7,8]

Fetal surgical interventions can be broadly categorized into three kinds of procedures, namely, open surgical procedures, minimally invasive procedures, and intrapartum procedures. **Open surgical procedures** involve both maternal laparotomy and hysterotomy with use of pharmacologic agents to maintain uterine relaxation. These procedures are typically performed near mid gestation and entail greater maternal and fetal risks compared with the minimally invasive techniques, including a significant risk for preterm premature rupture of membranes (PROM), preterm labor and delivery, uterine dehiscence, oligohydramnios, hemorrhage, pulmonary edema, and fetal mortality.[9,10] In addition, after an open surgical procedure, a cesarean delivery is required for the subsequent delivery and all future deliveries owing to the location of the hysterotomy and the associated risks for uterine dehiscence or rupture. Open fetal surgical procedures have been used to repair fetal myelomeningoceles, resect congenital pulmonary airway abnormalities, and debulk sacrococcygeal teratomas.

Minimally invasive procedures involve either endoscopic or percutaneous procedures guided by ultrasonography, typically performed at mid gestation (e.g., intrauterine blood transfusion, fetoscopic laser coagulation for twin-to-twin transfusion syndrome [TTTS]). They include a significantly lower risk for preterm labor and delivery than open procedures because they do not require a hysterotomy, yet the risk for preterm PROM remains.

The third kind of procedure involves a modification of cesarean delivery to allow intrapartum fetal therapy while the fetus remains supported by placental gas exchange. These delivery techniques are termed **EXIT procedures,** for *ex utero* intrapartum therapy.[11] EXIT procedures are most often employed (1) to secure the airway by endotracheal intubation, bronchoscopy, or tracheostomy or (2) to perform other fetal procedures while gas exchange continues in the placenta (placental bypass). The EXIT procedure enables the prevention of postnatal asphyxia in newborns with lesions such as cystic hygroma, lymphangioma, cervical teratoma, and congenital syndromes, in whom securing an airway after birth can be problematic. The procedure is also used as a bridge to extracorporeal membrane oxygenation (ECMO) for a fetus with cardiopulmonary disease at risk for postnatal cardiac failure or failure of adequate gas exchange in the lungs.

Fetal surgery is a reasonable therapeutic intervention for certain correctable fetal anomalies with predictable, life-threatening, or serious developmental consequences. If untreated, these lesions can interfere with fetal organ development or result in cardiac failure; if corrected *in utero*, irreversible organ damage and fetal demise may be prevented.

INDICATIONS AND RATIONALE FOR FETAL SURGERY

Bilateral Hydronephrosis–Obstructive Uropathy

Congenital obstructive uropathy occurs in approximately 0.1% of pregnancies.[12] Congenital bilateral hydronephrosis results from fetal urethral obstruction at the bladder outlet, most often by posterior urethral valves in male fetuses or urethral obstruction in females. Other causes of fetal obstructive uropathy include obstruction at the ureteropelvic or vesicoureteric junction and a number of complex disorders in females (e.g., cloacal plate anomalies). These uropathies are easily detected by ultrasonography, which is often performed to investigate oligohydramnios from diminished fetal urine output. Severe obstructive lesions may lead to progressive renal dysplasia and dysfunction, bladder distention, and oligohydramnios and ultimately result in devastating developmental consequences, such as limb and facial deformities and pulmonary hypoplasia (Figure 7-1).[13] Preterm delivery allows early urinary tract decompression *ex utero*, but fetal pulmonary immaturity limits the efficacy of this approach. Early intrauterine intervention with placement of a vesicoamniotic shunt allows drainage of urine from the fetal bladder into the amniotic cavity, thereby decompressing the urinary tract. In animal models, *in utero* relief of obstructive uropathy improves dysplastic renal histology, restores normal urine flow and amniotic fluid volume, and results in improved lung growth and development.[14] The applicability of these findings to human fetal obstructive uropathy remains unclear and controversial.[15]

Vesicoamniotic catheter shunts have been used for intrauterine treatment of bilateral hydronephrosis since the early 1980s.[16] These valveless, double-coiled catheters are placed percutaneously with ultrasonographic guidance, with one coil being left in the urinary bladder and the other in the amniotic space. Common problems associated with these catheters include (1) difficult placement, occlusion, and displacement; (2) fetal trauma, iatrogenic abdominal wall defects, and amnioperitoneal leaking; and (3) preterm PROM, preterm labor, and infection.[17] Neonatal survival rates after fetal vesicoamniotic shunting (performed from the 1980s to 2001) varied from 50% to 90%, with approximately half of the survivors having normal renal function.[15,18,19] Currently a multicenter, randomized controlled trial is underway comparing the perinatal mortality and renal function of fetuses with lower urinary tract obstruction treated by either vesicoamniotic shunting or conservative noninterventional care.[20]

Fetal cystoscopy is a more recent treatment option that allows direct visualization of the fetal urethra.

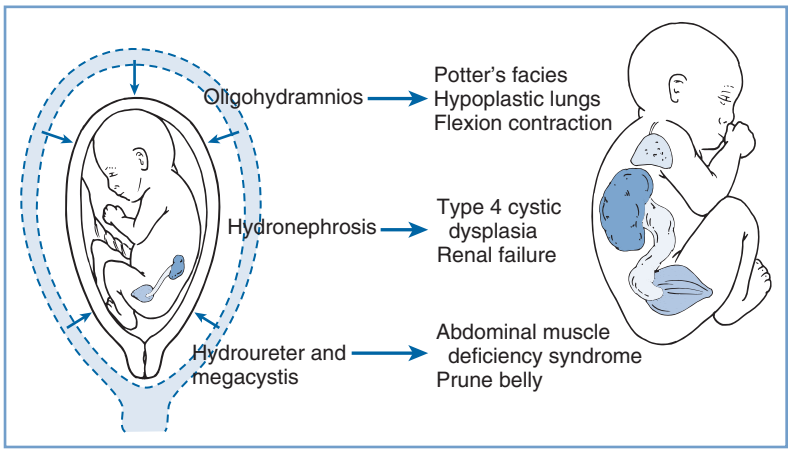

FIGURE 7-1 ■ Developmental consequences of fetal urethral obstruction. Obstructed fetal urinary flow results in hydronephrosis, hydroureter, megacystis, oligohydramnios, and pulmonary hypoplasia. (Redrawn from Harrison MR, Filly RA, Parer JT, et al. Management of the fetus with a urinary tract malformation. JAMA 1981; 246:635-9.)

Although not a viable treatment for urethral atresia, fetal cystoscopy facilitates diagnosis and treatment of lower urinary tract obstruction due to posterior urethral valves.[21] Fetal cystoscopy with ablation of posterior urethral valves appears to provide a survival advantage over conservative therapy but has not been demonstrated to improve perinatal survival over vesicoamniotic shunting.[22]

Current evidence supports fetal surgery for the correction of obstructive uropathy in selected fetuses in an effort to restore amniotic fluid volume, prevent pulmonary hypoplasia, and decrease perinatal mortality. However, the effects on long-term renal function and other morbidities remain unclear, and additional evidence is needed.

Congenital Diaphragmatic Hernia

Approximately 1 of 2500 live newborns has a congenital diaphragmatic hernia (CDH).[23] Without fetal intervention, this anomaly causes significant mortality from pulmonary hypoplasia and insufficiency. Survival rates have improved to between 60% and 85% over the past 20 years[24-27] and are closely associated with the degree of pulmonary hypertension and dysfunction.[24] Significant mortality occurs despite optimal postnatal surgical management at tertiary care medical centers (i.e., procedures involving removal of the herniated viscera from the chest, administration of surfactant, ventilation techniques that minimize lung trauma, use of ECMO, and closure of the diaphragm). Intrauterine correction of CDH has the potential to prevent the development of pulmonary hypoplasia and allow the fetal lung to develop before delivery.

The use of a fetal lamb model demonstrates that parenchymal hypoplasia and associated pulmonary vascular changes can be reversed by correction *in utero*.[3] Primary repairs of human CDH *in utero* have been undertaken only for fetuses with severe disease, with limited success but many lessons learned, including the development of minimally invasive approaches.[28,29]

Fetal lungs contribute to amniotic fluid volume by secreting more than 100 mL/kg/day of fluid that exits the trachea and mouth. Tracheal occlusion impedes the normal egress of fetal lung fluid and results in expansion of the hypoplastic lung, thereby inducing lung growth and cellular maturation in fetuses with CDH.[30,31] This occlusion technique, termed "*p*lug the *l*ung *u*ntil it *g*rows" (i.e., PLUG),[32,33] replaced primary repair *in utero* for the correction of the pulmonary hypoplasia associated with CDH. It is a less extensive, palliative fetal surgical procedure that enhances lung growth to improve postnatal survival, with postponement of the definitive repair until after birth.[30,34] Once the trachea is occluded, fetal pulmonary fluid slowly accumulates and expands the lung, pushing the viscera out of the thorax. A small detachable balloon for endoluminal tracheal occlusion is placed in the trachea via percutaneous endoscopic endotracheal intubation and is either left in place until delivery or deflated and removed earlier (Figure 7-2).[35,36]

A prospective randomized trial (1999-2001) evaluated fetal tracheal occlusion for intrauterine treatment of severe CDH.[37] Inclusion criteria included (1) a gestational age of 22 to 28 weeks, (2) left-sided herniation of the liver into the hemithorax, and (3) a low lung-to-head ratio (LHR) (i.e., < 1.4). The LHR is a ratio of the contralateral lung size compared with head circumference and is correlated with the severity of pulmonary hypoplasia and survival for a given gestational age.[38] The trial was closed early (n = 11); fetal tracheal occlusion resulted in no improvement in survival compared with control (77% versus 73%) and no reduction in morbidity at 90 days. The rates of preterm PROM and preterm delivery were higher in the fetal intervention group.[37] However, the survival rate was unexpectedly high in the control group. It is possible that the LHR criterion of less than 1.4 was not sufficiently restrictive and allowed inclusion of fetuses in the study that were likely to survive with standard postnatal tertiary medical care. Table 7-1 notes outcomes of left-sided CDH fetuses treated *in utero* or with standard postnatal care.

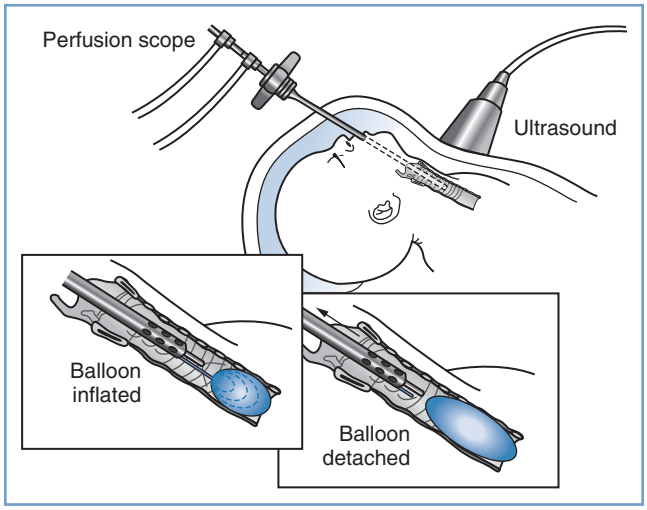

FIGURE 7-2 ■ Schematic of fetal tracheal occlusion using a balloon. (From Harrison MR, Albanese CT, Hawgood SB, et al. Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. Am J Obstet Gynecol 2001; 185:730-3.)

More recently in Europe, the Fetal Endoscopic Tracheal Occlusion (FETO) Task Force began a collaboration among three medical centers for treatment of severe cases of CDH with a high risk for death.[39] FETO intervention criteria for fetuses at high risk included both LHR less than 1.0 and liver herniation into the hemithorax.[40] Use of smaller-gauge endoscopes and reversal of the tracheal occlusion before birth appear to show great promise for reduction in the risk for preterm delivery due to preterm PROM.[41,42] Owing to concern for tracheal damage by very early tracheal balloon placement,[43] the tracheal balloon is placed between 26 and 28 weeks' gestation and removed before birth by a second fetoscopic procedure near 34 weeks (if the fetus is still *in utero*).[44] This second procedure is performed to minimize the risk of preterm labor, avoid the need for the EXIT procedure, and potentially improve lung growth and minimize the reduction of type II alveolar cells associated with prolonged tracheal occlusion. Outcomes for 210 cases (through 2008) of fetuses with a mean gestational age of 27 weeks, LHR less than 1.0, and primarily left-sided

TABLE 7-1 Postnatal Survival in Fetuses with Left-Sided Congenital Diaphragmatic Hernia and Intrathoracic Liver Herniation Based on Fetal Lung-to-Head Ratio (LHR)

	Postnatal Management		*Fetoscopic Tracheal Occlusion*	
LHR (mm)*	NO. FETUSES	SURVIVAL NO. (%)	NO. FETUSES	SURVIVAL NO. (%)
0.4-0.5	2	0	6	1 (16.7)
0.6-0.7	6	0	13	8 (61.5)
0.8-0.9	19	3 (15.8)	9	7 (77.8)
1.0-1.1	23	14 (60.8)		
1.2-1.3	19	13 (68.4)		
1.4-1.5	11	8 (72.7)		
≥1.6	6	5 (83.3)		
TOTAL	86	43 (50)	28	16 (57.1)

*LHR measurements in the table were obtained at 23 to 29 weeks' gestation.

Modified from Jani JC, Nicolaides KH, Gratacos E, et al. Fetal lung-to-head ratio in the prediction of survival in severe left-sided diaphragmatic hernia treated by fetal endoscopic tracheal occlusion (FETO). Am J Obstet Gynecol 2006; 195:1646-50.

CDH (84%) were compared with those for historic postnatal treatment controls (1995-2004). Use of FETO significantly improved the survival rate (47% versus 20%), and delivery occurred at a median gestational age of 35.3 weeks.[39] However, the comparative results may represent selection bias or improvement in technique and clinical care over time. A more recent (2008-2010) randomized, controlled, single-institution trial compared cases of severe CDH (LHR < 1.0 with liver herniation) randomized to either FETO (n = 21) at 26 to 30 weeks' gestation or standard postnatal care (n = 20).[45] The overall survival rate with severe CDH was significantly greater in the FETO intervention group than in the expectant management group (52.6% versus 5.3%). In 2009, a randomized Tracheal Occlusion To Accelerate Lung growth trial (TOTAL) was started.[46] It compared postnatal management to late (30 to 32 weeks' gestation) FETO intervention for moderate lung hypoplasia and earlier FETO intervention (27 to 30 weeks' gestation) for severe lung hypoplasia. In addition, it is now understood that LHR depends on gestational age[47] and that a ratio of observed to expected LHR is a better expression of CDH severity and likelihood of survival.[48,49] This ratio is used as part of the ongoing TOTAL trial. Results of this trial will help determine if and when FETO should be offered for cases of severe CDH.

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformations (CPAM) are pulmonary tumors with cystic and solid components; these malformations were previously described as congenital cystic adenomatoid malformations (CCAM).[50] The incidence is approximately 1 in 25,000 pregnancies.[51] The classification scheme for CPAM includes five subtypes, based on cyst size, characteristics of the epithelial lining, cyst wall thickness, and the presence of mucous cells, cartilage, and skeletal muscle.[50,52] Lesions are assessed by ultrasonography and described as containing cysts larger (macrocystic) and smaller (microcystic) than 5 mm in diameter. Lesions can either regress with minimal associated morbidity or progressively enlarge, often resulting in hydrops fetalis (fetal heart failure). Small lesions detected *in utero* or in the newborn are treated after birth by surgical excision of the affected pulmonary lobe. Large lesions can cause mediastinal shift, hydrops, and pulmonary hypoplasia and can interfere with fetal or neonatal survival; fetuses with untreated lesions associated with hydrops fetalis have a survival rate of less than 5%.[53] In a retrospective single-institution review of 71 cases, the initial antenatal ultrasonographic ratio of CPAM volume to fetal head circumference (CVR) was evaluated for the formation of hydrops fetalis and postnatal outcomes.[54] Fetuses with a CVR less than 0.56 were noted to have no adverse postnatal outcomes, whereas a CVR greater than 0.56 had a positive predictive value for adverse postnatal outcome of 33%. In addition, a CVR greater than 1.6 was associated with a greater risk for hydrops fetalis.[55]

Depending on lesion size, location, and characteristics, CPAMs can be managed with either fetal intervention or postnatal resection. Macrocystic lesions have been decompressed *in utero* by placement of shunt catheters between the cysts and the amniotic cavity, resulting in sustained decompression and resolution of hydrops[56]; these procedures are followed by postnatal surgery. However, not all lesions can be decompressed successfully because the cysts are not always contiguous (i.e., in communication with each other) and can refill rapidly. In addition, these thoracoamniotic shunts have associated risks, including malfunction, displacement, fetal hemorrhage, and chorioamnionitis.[57] CPAMs inappropriate for drainage can be resected with open fetal surgery. Fetal pulmonary lobectomy for lesions associated with hydrops fetalis has resulted in a 30-day postnatal survival rate of 50%, with tumor resection allowing for compensatory lung growth and resolution of hydrops fetalis.[58] Maternal administration of betamethasone also has been noted to improve hydrops fetalis and overall outcome in selected fetuses with CPAM.[59,60] A retrospective review of 24 fetuses with predominantly microcystic CPAM and the presence of hydrops fetalis found that corticosteroid treatment resulted in better survival than resection with open fetal surgery.[61]

Intralobar and extralobar pulmonary sequestrations (bronchopulmonary sequestrations) are rarer congenital lung anomalies than CPAM and involve nonfunctional lung tissue (disconnected from the bronchial tree). As with CPAM, therapeutic options depend on fetal morbidities including hydrops fetalis and pulmonary hypoplasia. Thoracoamniotic shunts have been successfully placed to decompress massive congenital pleural effusions caused by fetal chylothorax that otherwise result in

hydrops fetalis, pulmonary compression, and fetal or neonatal death.[62]

Sacrococcygeal Teratoma

The prevalence of sacrococcygeal teratoma (SCT) is approximately 1 in 20,000 to 40,000.[63] Some fetuses with SCT undergo massive tumor enlargement, experience hydrops fetalis and placentomegaly, and die *in utero*. These tumors function as large arteriovenous fistulas, and fetal demise results from high-output cardiac failure. Management of these tumors requires close surveillance because they can grow rapidly and reach a size as large as 1000 cubic centimeters.[63] Fetuses with large lesions are at risk for intrapartum dystocia or tumor rupture and hemorrhage; these fetuses may require cesarean delivery. Fetuses with lesions diagnosed before 30 weeks' gestation have a poor prognosis but may benefit from surgical debulking *in utero;* surgical techniques have not reached the necessary level of sophistication to allow complete resection of lesions that deeply invade the pelvis. *In utero* radiofrequency ablation and thermocoagulation have been used to reduce the tumor blood supply, but the benefit remains unclear.[64] Catheterization of a fetal hand or umbilical cord vein for blood and crystalloid transfusion during tumor resection may be needed. To date, there has been no significant improvement in outcome with intervention in cases of SCT with hydropic fetalis.

Some SCT cases are accompanied by "maternal mirror syndrome" or Ballantyne syndrome, a hyperdynamic state (i.e., hypertension, peripheral and pulmonary edema) in which the maternal physiology mirrors the abnormal circulatory physiology of the hydropic fetus.[65] This syndrome is associated with a substantial increase in fetal mortality and maternal morbidity and requires aggressive management similar to that used for severe preeclampsia, a disease from which it must be distinguished. Platelet count, aspartate aminotransferase, alanine aminotransferase, and haptoglobin are typically unaffected in maternal mirror syndrome and may serve as diagnostic clues to rule out severe preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelets). Unfortunately, maternal mirror syndrome typically does not resolve quickly, even with rapid correction of the fetal pathophysiology, and severe maternal complications including pulmonary edema occur in about 20% of cases.[65]

Myelomeningocele

Although not lethal, a myelomeningocele is a protrusion of the meninges and spinal cord through a congenital defect in the vertebrae and overlying muscles and skin. It can result in lifelong morbidity and disability, including paraplegia, bowel and bladder incontinence, hydrocephalus, Arnold-Chiari II malformation, and impaired cognition.[66] Myelomeningocele has an incidence of about 1 in 2000 live births but is becoming less common owing to folate supplementation in the maternal diet. In addition, detection by ultrasonography and alpha-fetoprotein screening of maternal blood has allowed for earlier diagnosis (i.e., second trimester) and consideration of pregnancy termination.

The specific cause of myelomeningocele remains unknown. Animal models have demonstrated improved neonatal neurologic function with fetal closure of the defect *in utero*.[67,68] The results associated with defect closure support a "two-hit" disease model in which the pathology is produced by failure of the fetal neural tube to form combined with prolonged exposure to the uterine amniotic fluid.[69] Mutations of the *PAX3* gene and direct cord trauma may also play a role in the pathophysiology associated with a myelomeningocele.[70]

The 5-year mortality of myelomeningocele is approximately 8% for live births; if it is not corrected *in utero*, surgical closure must be performed within a few days after birth.[71] Ventriculoperitoneal shunting is required in 85% to 90% of uncorrected cases; however, despite successful shunting, permanent deficits such as central hypoventilation, vocal cord dysfunction, and oromotor and swallowing dysfunction can still occur from the associated Arnold-Chiari malformation.[72] The average intelligence quotient in myelomeningocele patients who require ventriculoperitoneal shunting is 80 (low normal).[73]

The purpose of fetal surgery for myelomeningocele is to improve function later in life.[69] Fetal surgery is primarily performed through an open fetal surgical technique. Preliminary results suggest that *in utero* repair successfully reverses the hindbrain herniation of the Arnold-Chiari II malformation, probably through normalization of cerebrospinal fluid flow, and decreases the need for ventriculoperitoneal shunt placement before 1 year of age.[74] More recently, a randomized, prospective, multicenter clinical trial completed between 2003 and 2010 examined the risks and benefits of open fetal surgery for myelomeningocele repair compared with standard postnatal repair in 183 patients.[75] Open fetal repair reduced the need for ventriculoperitoneal shunting and improved motor function at 30 months of age, but increased the risk for preterm birth and a partial or complete uterine dehiscence. Two perinatal deaths occurred in each group. Table 7-2 displays a subset of outcome measures that were significantly different between the prenatal and postnatal repair groups. Further data from the trial will include assessment of the long-term benefit from the prenatal intervention.

A recent study of endoscopic intrauterine myelomeningocele repair resulted in an extraordinarily high complication rate for both mothers and fetuses.[76] Of the 19 study patients, three fetuses died intraoperatively and another three procedures were stopped owing to severe hemorrhage from the procedure. Although this intervention was associated with spinal segmental neuroprotection, it resulted in significantly more complications; the authors concluded that, pending further advances, this technique is unsuitable as standard care.[76]

Twin-to-Twin Transfusion Syndrome

An abnormal connection of chorionic blood vessels in the placenta between two monochorionic twins can result in twin-to-twin transfusion syndrome (TTTS). TTTS complicates 10% to 15% of monochorionic pregnancies, usually manifests at 15 to 26 weeks' gestation, and is typically recognized at 20 to 21 weeks' gestation.[77,78]

TABLE 7-2 **Maternal and Fetal or Neonatal Complications for MOMS Trial Patients***

	Prenatal (n = 78)	Postnatal (n = 80)	*P*
Maternal Outcomes			
Chorioamniotic membrane separation	20 (26%)	0	< .001
Pulmonary edema	5 (6%)	0	.03
Oligohydramnios	16 (21%)	3 (4%)	.001
Placental abruption	5 (6%)	0	.03
Spontaneous rupture of membranes	36 (46%)	6 (8%)	< .001
Spontaneous labor	30 (38%)	11 (14%)	< .001
Blood transfusion at delivery	7 (9%)	1 (1%)	.03
Hysterotomy site thin, or partial or complete dehiscence noted at delivery	27 (36%)	N/A	
Fetal Outcomes			
Fetal bradycardia during repair	8 (10%)	0	.003
Mean gestational age at birth (weeks)	34.1 ± 3.1	37.3 ± 1.1	< .001
Mean birth weight (g)	2383 ± 688	3039 ± 469	< .001
Respiratory distress syndrome	16 (21%)	5 (6%)	.008

*The table lists maternal and fetal/neonatal complications that were significantly different ($P < .05$) between the prenatal and postnatal repair groups in the Management of Myelomeningocele Study (MOMS). Other outcomes were evaluated, but only those that were different between the two groups are included. Data for each group are shown as both an absolute number and as a percentage.

Modified from Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011; 364:993-1004.

Intertwin transfusion is common between monochorionic twins and is usually balanced by the presence of arterioarterial (AA) and venovenous (VV) connections; the presence of AA connections is associated with a ninefold reduction in TTTS.[79] By contrast, unidirectional and imbalanced blood flow through arteriovenous (AV) chorionic vessels results in TTTS. In normal fetoplacental vasculature, the umbilical artery branches at the placenta surface and traverses and then descends into the tissue, where it further branches into capillary divisions for gas and nutrient exchange. The arterial system is "paired" with venous vasculature, which returns blood to the umbilical cord. In TTTS, the umbilical artery similarly descends into the placenta and cotyledon, but rather than connecting with a paired vein it connects with a vein that transports blood to the other twin.[80]

The twin serving as the recipient demonstrates polycythemia, polyuria, polyhydramnios, and hypertrophic cardiomyopathy; this twin is at risk for hydrops fetalis and fetal death. The twin serving as the donor is typically hypovolemic, growth restricted, and pressed against the endometrium in an oligohydramniotic sac (hence the designation "stuck" or "pump" twin) and often has a velamentous cord insertion; this twin is at risk for neonatal renal failure, tubular dysgenesis and dysfunction, and high cardiac output hydrops fetalis. Diagnosis is currently based on ultrasonographic findings that focus on differences in fetal size or amniotic sac fluid volume, presence of cardiac dysfunction in the recipient twin, umbilical cord size, and abnormal umbilical arterial flow velocity.[77,81] Twin size discordance is not always present and is no longer considered necessary to confirm the diagnosis. For unclear reasons, fetuses with TTTS are at risk for neurologic injury with white-matter lesions and long term disability; poor neurodevelopmental outcomes are associated with increased TTTS severity, delayed therapeutic interventions, and preterm delivery.[82] If TTTS is untreated, it carries a greater than 80% mortality with 15% to 50% risk for significant morbidity in surviving neonates.[83]

A variety of therapeutic management techniques have been developed, including (1) serial amnioreduction to control polyhydramnios and reduce the risk for preterm labor, (2) surgical septostomy to equalize amniotic pressures, (3) selective feticide to allow the other fetus to survive, and (4) selective fetoscopic laser photocoagulation (SFLP) of the vascular anastomoses between the two twins. Serial amnioreduction was demonstrated to improve placental perfusion and decrease the occurrence of preterm delivery.[84] In a retrospective review of 223 twin sets with TTTS, amnioreduction resulted in an overall birth survival rate of 78%, with 65% of recipient twins and 55% of donor twins alive at 1 month of age.[85] In a prospective randomized trial comparing serial amnioreduction to septostomy, there was no difference in the rate of survival between the two techniques.[86] Septostomy is rarely used for treatment because the creation of a single amniotic sac can increase the risk for umbilical cord entanglement.

The laser used for SFLP is typically inserted percutaneously through an endoscope (≤ 2.0 mm diameter) into the recipient twin's amniotic sac. Maternal anesthesia is commonly managed with either neuraxial blockade or local anesthetic infiltration from skin to myometrium. Fetoscope placement is determined by placental location and is guided by ultrasonography. Vessels that cross the dividing membrane separating the amniotic sacs are visualized, and abnormal connecting vessels are selectively coagulated with the laser.[77,80] On occasion, based on anatomic constraints created by the location of the fetuses and placenta, nonselective laser ablation is performed; however, this type of ablation is associated with higher rates of intrauterine fetal demise.[77,87] Ablation of all abnormal connecting vasculature is not needed for success of

the procedure.[88] After completion of the SFLP, amniotic fluid may be removed to reduce the degree of polyhydramnios and possibly decrease the risk for preterm labor.

A 2004 randomized multicenter trial compared laser therapy to amnioreduction for treatment of severe TTTS diagnosed between 15 and 26 weeks' gestation.[89] Rates of at least one twin survival were significantly higher in the laser treatment group at both 28 days (76% versus 56%, $P < .01$) and 6 months of life (76% versus 51%, $P < .01$). In addition, neurologic outcomes were better in the laser treatment group. A subsequent prospective study of a large subgroup of survivors from this trial observed these children for 6 years and found no additional change in survival or long-term neurologic outcome from the original 6-month data.[90] A meta-analysis of studies published between 1997 and 2007 noted that treatment of TTTS with laser ablation resulted in a higher overall rate of fetal survival than amnioreduction[91]; similar findings were demonstrated in a Cochrane review of treatment for TTTS.[92]

A more recent variation of the SFLP technique requires vascular laser ablation in a specific sequence. First, ablation occurs at the donor-to-recipient AV anastomoses, then at the recipient- to-donor AV anastomoses, then at the AA superficial anastomoses, and finally at the VV superficial anastomoses. The order of the procedure is designed to reduce the chance of hemodynamic compromise and hypotension during the procedure in the donor twin[93]; however, it is associated with longer operative times and increased case difficulty, particularly with an anterior placenta. In a single-institution study of consecutive SFLP for treatment of TTTS, twins treated with this sequence had better survival rates than twins whose SFLP procedure was performed without a specific sequence.[93] A prospective multicenter trial found a significantly improved 30-day survival of both fetuses and improved donor survival with this sequential technique when compared with a cohort control group.[94]

The most common complication of SFLP is preterm PROM with subsequent preterm labor and delivery. Other possible complications include placement of the trocar through the placenta, hemorrhage, and possible membrane perforation resulting in limb entrapment and ischemia.[77] In conclusion, trial results and meta-analyses provide evidence that SFLP results in superior outcomes than amnioreduction for the treatment of TTTS. Further research is needed to determine optimal techniques and timing of interventions for the treatment of TTTS.

Twin Reversed Arterial Perfusion Sequence

In monozygotic twins, one twin can also perfuse the other by retrograde blood flow though AA anastomoses. Twin reversed arterial perfusion (TRAP) sequence affects 1% of monozygotic twins and 1 in 30 triplets. Inadequate perfusion of the recipient twin via retrograde flow results in the development of a lethal set of anomalies that include acardia and acephalus. The normal ("pump") twin perfuses both itself and the nonviable twin and is at risk for high-output congestive heart failure, polyhydramnios, and preterm birth. If untreated, TRAP sequence is associated with a risk for intrauterine death of the pump twin exceeding 50%.[95] Diagnosis is confirmed with ultrasonographic demonstration of reverse flow to the acardiac twin via the umbilical artery. Cardiovascular failure in the pump twin is the indication for intervention, and early diagnosis is beneficial for optimal treatment.

The goal of therapy is to interrupt the vascular communication between the two twins. In contrast to the treatment of TTTS, treatment of TRAP sequence results in the death of the anomalous nonviable fetus. Percutaneous endoscopic laser or radiofrequency coagulation of the umbilical cord and/or placental vascular anastomoses is the most viable therapeutic option.[96,97] Alternative therapies include *sectio parva* (selective cesarean delivery of one of multiple fetuses), percutaneous thrombosis of the acardiac twin's umbilical cord with coils or other thrombogenic material, and alcohol-impregnated suture cord ligation. A retrospective review of 60 TRAP sequence cases from multiple European centers using endoscopic laser coagulation noted overall survival rates approaching 80% and a median gestational age of 37.4 weeks at delivery.[98] An additional study, using radiofrequency coagulation in 26 TRAP sequence cases at a single U.S. medical center, demonstrated a 92% survival rate of the viable twin with a mean gestational age of 35.6 weeks at delivery.[96] Both procedures are typically performed with infiltration of local anesthesia at the insertion site of the ablation device, although neuraxial anesthesia has also been used. The procedures are guided by ultrasonography, and absence of flow to the nonviable acardiac twin is confirmed with Doppler imaging at the end of the procedure and again 12 to 24 hours later.

Congenital Heart Defects

The most commonly performed closed fetal cardiac intervention for a congenital heart defect is an aortic valvuloplasty for mid-gestational aortic stenosis with evolving hypoplastic left heart syndrome. Technical success as high as 75% has been reported using an angioplasty balloon over a guidewire inserted percutaneously through an access cannula.[99] Approximately 40% of successful cases result in aortic regurgitation and minimal subsequent left ventricular growth; however, the physiology of the left ventricle improves and leads to improved aortic and mitral valvular growth. In about 30% of the successful cases, biventricular circulation is present at birth. Other congenital heart defects that may benefit from antepartum closed fetal cardiac intervention include (1) hypoplastic left heart syndrome with an intact or highly restrictive atrial septum and (2) evolving hypoplastic right heart syndrome with pulmonary atresia or stenosis without a ventricular septal defect.[100,101]

More complex congenital cardiac defects that might benefit from open repair have only been repaired in animal models and require fetal extracorporeal circulatory bypass; the use of fetal cardiac bypass induces a catecholamine-mediated fetal stress response that increases vascular resistance and cardiac afterload and is poorly tolerated by the immature fetal myocardium. Fetal cardiac bypass can also result in severe placental

dysfunction when the high-capacitance, low-resistance placenta is incorporated as the oxygenator, resulting in endothelial dysfunction and leukocyte and complement activation. After fetal cardiac bypass, increases in placental vascular resistance, reduced blood flow, impaired gas exchange, and fetal acidosis are frequently observed.[102,103] Correction of complex congenital cardiac defects, either open or closed, requires careful anesthetic and pharmacologic strategies for myocardial protection.

SURGICAL BENEFITS AND RISKS

The primary goal of intrauterine fetal surgery is to improve neonatal outcomes over that of surgery performed after a preterm or term delivery. The intrauterine environment supports rapid wound healing (i.e., without scarring before mid gestation),[104] and the umbilical circulation meets nutritional and respiratory needs without outside assistance. The poorly developed fetal immune surveillance system may facilitate certain invasive procedures. However, continued refinement of surgical and anesthetic techniques, reduction of maternal and fetal risk, and appropriate clinical trials for each intervention must occur before fetal surgery can be performed on a more routine basis for a given congenital anomaly.

Serious maternal complications from intrauterine fetal surgery are relatively uncommon. Maternal risks include blood loss, infection, placental abruption, and pulmonary edema secondary to tocolytic therapy and fluid overload from absorption of significant amounts of pressurized crystalloid uterine irrigation during fetoscopic techniques.[105,106] Open fetal surgery involves a hysterotomy that is not in the lower uterine segment, and therefore all future deliveries must occur via a cesarean procedure. Maternal welfare must always be emphasized.[7]

The fetal risks of intrauterine surgery remain relatively high. The most common postoperative complications are fetal central nervous system injuries, postoperative amniotic fluid leaks, membrane separation, preterm PROM, and preterm labor and delivery. Preterm delivery accounts for significant morbidity and mortality among fetuses that might otherwise have benefited from the therapeutic interventions. Chorioamniotic membrane separation can cause amniotic bands, umbilical cord strangulation, and fetal demise.[107] Improved techniques for sealing the membranes are being devised, including different surgical techniques, fibrin glue, and intra-amniotic injection of platelets and cryoprecipitate.[108,109]

ANESTHETIC MANAGEMENT

Fundamental considerations for the anesthetic management of fetal surgery are similar to those for nonobstetric surgery during pregnancy (see Chapter 17). Maternal safety is paramount. Anesthesiologists must participate in preoperative maternal assessment and exclude women when their perioperative risk is not acceptably low given the potential fetal benefit. To ensure both maternal and fetal safety, the anesthesiologist must understand the physiologic impact of pregnancy on anesthetic management (see Chapter 2) and must take an active role as a member of the multidisciplinary team. Imaging studies should be reviewed for placental location, anatomic information about the congenital lesion, and estimated fetal weight.

Unlike other surgical procedures performed during pregnancy in which the fetus is an innocent bystander (e.g., maternal appendectomy), fetal surgery involves two surgical patients. This requires the anesthesiologist to balance the anesthetic needs of both patients, as well as control uterine tone throughout the perioperative period. Complete uterine relaxation is necessary during open fetal surgical procedures.

Maternal analgesia and anesthesia can involve local infiltration, intravenous sedation, neuraxial anesthesia, general anesthesia, or a combination of these techniques, depending on the procedure, location of the placenta, and maternal co-morbidities. Fetal analgesia and anesthesia can be achieved via placental transfer of anesthetic agents given to the mother, via direct fetal intravenous or intramuscular administration of agents, or by a combination of these methods. An appropriate method of fetal monitoring and the potential requirement for fetal intravenous access or fluid resuscitation should be determined preoperatively. The operative team should be prepared for emergency situations such as maternal hemorrhage, fetal deterioration requiring aggressive intrauterine resuscitation (e.g., fetal epinephrine administration), and/or delivery and resuscitation of the viable newborn infant.[110]

Anesthesia for Minimally Invasive and Percutaneous Procedures

Local anesthetic infiltration of the abdominal wall is sufficient to reduce maternal discomfort for many percutaneous procedures (e.g., amniocentesis, cordocentesis, intrauterine blood transfusion, needle aspiration of cysts, shunt placement into the fetal bladder or thorax, SFLP for TTTS). Supplemental maternal analgesia and anxiolysis can be achieved by maternal administration of an opioid, a benzodiazepine, or a low-dose propofol infusion, which may confer some fetal immobility and analgesia via placental transfer.[111] However, when larger needles or multiple attempts are necessary for percutaneous procedures or a minilaparotomy, maternal comfort can be difficult to achieve with local infiltration, even when supplemented with sedation. In these circumstances, neuraxial anesthesia is recommended.[77,91] General anesthesia is rarely necessary for percutaneous procedures unless placental location makes the procedure significantly challenging or uterine exteriorization is needed.

Fetal movement may be hazardous for the fetus in cases of intrauterine transfusion, cord blood sampling, or thoracic shunt placement, because displacement of the needle or catheter may lead to trauma, bleeding, or compromise of the umbilical circulation. Placental transfer of maternally administered opioids and benzodiazepines can reduce fetal movement[89] but cannot ensure fetal immobility for more stimulating procedures. A randomized controlled trial of the use of a maternal remifentanil infusion (0.1 μg/kg/min) demonstrated improved fetal immobility

and operating conditions during fetoscopic surgery, when compared with maternal administration of diazepam.[112] Fetal immobility can be safely achieved with direct fetal intramuscular or umbilical venous administration of pancuronium or vecuronium (0.3 mg/kg intramuscularly or 0.1 to 0.25 mg/kg intravenously) using ultrasonographic guidance. The onset of fetal paralysis occurs in 2 to 5 minutes, with an approximate duration of 1 to 2 hours.[113] For procedures that can cause noxious stimulation to the fetus, such as shunt catheter placement or cardiac septoplasty, an opioid (e.g., fentanyl 10 to 20 µg/kg) can be administered to the fetus intramuscularly or intravenously.[114,115] When general anesthesia is employed, placental transfer of a volatile halogenated agent is usually sufficient to immobilize and anesthetize the fetus.

The fetal surgical team should be prepared for treatment of fetal compromise with immediate availability of appropriate doses of atropine and epinephrine. The obstetric team should be prepared to perform an emergency cesarean delivery if the gestational age is compatible with extrauterine viability. The anesthesiologist should be prepared to emergently provide general anesthesia if required.

Tocolysis typically is unnecessary after cordocentesis or intrauterine transfusion. For more invasive percutaneous procedures (e.g., shunt catheter placement, endoscopic techniques), some fetal surgery groups administer prophylactic tocolytic agents.

Anesthesia for Open Fetal Surgery

When corrective fetal surgery or an intrauterine procedure requires surgical access through a hysterotomy, general anesthesia is typically administered. Unique considerations for open fetal procedures include the need for profound uterine relaxation, intraoperative fetal monitoring, fetal anesthesia or analgesia, and postoperative maternal analgesia and uterine tocolysis (Table 7-3). In addition, significant maternal and fetal blood loss may occur, and the anesthesiologist must be prepared to achieve maternal and fetal resuscitation. A high concentration of a volatile halogenated agent is typically

TABLE 7-3 **Perioperative Considerations for Open Fetal Surgery**

Preoperative Considerations
- Complete maternal history and physical examination
- Fetal work-up to exclude other anomalies and imaging studies to determine fetal lesion, placental location, and estimated fetal weight
- Maternal counseling by multidisciplinary team and preoperative team meeting
- Lumbar epidural catheter placed and tested
- Prophylactic premedications for aspiration and tocolysis
- Blood products available for potential maternal and fetal transfusion
- Sequential compression devices on lower extremities for thrombosis prophylaxis

Induction and Intraoperative Considerations
- Left uterine displacement and standard monitors
- Preoxygenation for 3 minutes prior to induction
- Rapid-sequence induction and intubation
- Maintain maternal F_{IO_2} > 50% and end-tidal CO_2 28-30 mm Hg
- Ultrasonography to determine fetal and placental positioning
- Urinary catheter placed; additional large-bore IV access placed ± arterial line
- Prophylactic antibiotics administered
- Fetal resuscitation drugs and fluid transferred to scrub nurse in unit doses
- Following skin incision, high concentration of volatile anesthetic administered
- Blood pressure maintained (± 10% baseline with IV phenylephrine, ephedrine, and/or glycopyrrolate)
- Consider IV nitroglycerin if uterine relaxation not adequate
- IM administration of fetal opioid and neuromuscular blocking agent by surgeons
- Fluid restriction to < 2 L to reduce risk for maternal pulmonary edema
- IV loading dose of magnesium sulfate once uterine closure begins
- Discontinue volatile agent once magnesium sulfate load is complete
- Administer propofol, opioids, nitrous oxide as needed
- Activate epidural catheter for postoperative analgesia
- Monitor neuromuscular blockade carefully due to magnesium sulfate administration
- Extubate trachea when patient is fully awake

Early Postoperative Considerations
- Continue tocolytic therapy
- Patient-controlled epidural analgesia
- Monitor uterine activity and fetal heart rate
- Ongoing fetal evaluation

CO_2, carbon dioxide; *F_{IO_2},* fraction of inspired oxygen; *IM,* intramuscular; *IV,* intravenous.

administered to provide both maternal and fetal anesthesia as well as uterine relaxation; adequate uterine relaxation may require greater than twice the minimum alveolar concentration (MAC) of a volatile halogenated agent.[116]

Preoperatively, the mother receives agents for aspiration prophylaxis and uterine tocolysis (e.g., rectal indomethacin) and an epidural catheter is placed for postoperative analgesia. Minimal doses of preanesthetic and adjuvant anesthetic agents are given to allow significant doses of a volatile halogenated agent to be administered to achieve effective uterine relaxation; this approach may also reduce the occurrence of hypotension. The patient is placed in the supine position with left uterine displacement. After administration of 100% oxygen and denitrogenation of the lungs, a rapid-sequence induction of general anesthesia with cricoid pressure and endotracheal intubation is performed. Fetal heart rate (FHR) and umbilical cord blood flow are often monitored with ultrasonography during induction.

Initially, anesthesia is maintained with a low concentration of a volatile halogenated agent while further preparations for surgery are undertaken, including (1) obtaining additional maternal vascular access, (2) prophylactic antibiotic administration, (3) urinary bladder catheterization, and (4) ultrasonographic assessment of fetal presentation and placental location. Medications to provide fetal analgesia (e.g., fentanyl 10 to 20 μg/kg), immobility (e.g., vecuronium 0.3 mg/kg), and resuscitation (atropine 0.02 mg/kg, epinephrine 1 and 10 μg/kg, and crystalloid 10 mL/kg) are prepared in sterile labeled syringes; each syringe should contain a single weight-based unit dose. Crossmatched blood should be available for maternal transfusion. In addition, O-negative, cytomegalovirus (CMV)-negative, irradiated, leukocyte-depleted, maternally crossmatched blood should be available for fetal transfusion. For open procedures that have a high risk for significant fetal blood loss (e.g., mass resection), an intravenous catheter should be placed in the fetus to provide access for blood and fluid transfusions. An arterial catheter should be placed for maternal blood pressure monitoring if uterine tocolysis with a nitroglycerin infusion is planned. Intraoperative maternal intravenous fluids are restricted (< 2 L) to reduce the risk for postoperative pulmonary edema; some fetal surgery centers choose to limit fluids even further (< 500 mL), although no clinical trials have proven a benefit of fluid restriction in this setting.[117] The use of tocolytic agents such as magnesium sulfate and nitroglycerin has been associated with maternal pulmonary edema in patients undergoing fetal surgery.

A final discussion (i.e., surgical time-out), prophylactic antibiotic administration, and an increase in the concentration of the volatile halogenated agent should occur before skin incision. Maternal blood pressure is maintained with a mean arterial pressure within 10% of baseline values and greater than 65 mm Hg; a phenylephrine infusion provides titratable blood pressure control with minimal changes in the fetal acid-base status.[118,119] Ephedrine or glycopyrrolate boluses also can be administered to maintain maternal heart rate and improve cardiac output.[120] Maternal administration of a nondepolarizing muscle relaxant is usually not needed owing to the profound depth of anesthesia but may be used to improve operative conditions. The intrauterine location and position of the fetus is confirmed with ultrasonography just before hysterotomy to optimize the incision location.

Before uterine incision, it is important to achieve an increased end-tidal concentration of the volatile halogenated agent to provide both fetal anesthesia and uterine relaxation (typically ≥ 2 MAC). Fetal well-being can be assessed with pulse oximetry, ultrasonography for FHR monitoring, echocardiography to assess fetal ventricular contractility, and electrocardiography (ECG).

The uterus is assessed both visually and by palpation for contractions or increased tone; further tocolysis can be achieved with the administration of additional halogenated agent (≤ 3 MAC) or intravenous nitroglycerin as an infusion or in small boluses (50 to 200 μg).[121] Use of desflurane at 1.5 MAC with supplemental intravenous propofol and remifentanil has provided adequate uterine relaxation in one retrospective study.[122] For circumstances in which volatile halogenated agents or general anesthesia must be avoided (e.g., family history of malignant hyperthermia), a spinal or epidural anesthetic can be used with an intravenous infusion of nitroglycerin in doses up to 20 μg/kg/min.[121] This technique does not have a clear advantage for fetal outcome and may be associated with more morbidity. Nitroglycerin administration during open fetal surgery has been associated with maternal pulmonary edema.[117,123] Fetal intraventricular and periventricular hemorrhage and cerebral ischemia can result from changes in fetal cerebral blood flow, and concern has been raised regarding the use of tocolytic agents, which may affect vascular tone.[124]

An opioid and a muscle relaxant are administered to the fetus intramuscularly, either before uterine incision with ultrasonographic guidance or after uterine incision with direct vision. Some anesthesiologists administer atropine at this time in an effort to prevent opioid-induced fetal bradycardia; a muscle relaxant with vagolytic effects also can be chosen to minimize this type of bradycardia. Further studies are needed to determine the optimal anesthetic technique for ensuring maternal and fetal cardiovascular stability, optimal uteroplacental perfusion, and adequate fetal anesthesia to cause immobility and blockade of the fetal stress response.

A small uterine incision is created remote from the location of the placenta. A stapling device with absorbable synthetic copolymer (Lactomer) staples is used to extend the incision to seal the membranes to the endometrium and prevent excessive bleeding.[125] During surgery, the exposed fetus and uterus are bathed with warmed fluids. The intrauterine temperature is closely monitored to prevent fetal circulatory compromise associated with hypothermia.[126]

When uterine closure is initiated at the conclusion of the procedure, a loading dose of magnesium sulfate is administered (4 to 6 g intravenously over 20 minutes), followed by an intravenous infusion of 1 to 2 g per hour. As magnesium potentiates neuromuscular relaxation, close monitoring of twitch recovery is needed if a nondepolarizing muscle relaxant was administered. The volatile halogenated agent can be significantly decreased or

discontinued after the magnesium sulfate bolus has been administered. The epidural analgesia can be initiated and maternal anesthesia is maintained with additional fentanyl, nitrous oxide, and/or propofol.

Postoperative concerns include maternal and fetal pain, preterm PROM, preterm labor, infection, and a variety of potential fetal complications, including heart failure, intracranial hemorrhage, constriction of the ductus arteriosus from indomethacin, and fetal demise. Postoperative maternal analgesia can be maintained with a continuous epidural infusion of a dilute solution of local anesthetic and opioid for several days. Effective analgesia may help prevent postoperative preterm labor.[127,128] Intravenous opioids can also be used for analgesia; however, decreased FHR variability may occur.[129]

Management of postoperative preterm labor has been the "Achilles heel" of fetal surgery.[7] Tocolysis is typically provided by an infusion of magnesium sulfate for at least 24 hours; however, supplemental agents may include indomethacin, terbutaline, or nifedipine. Magnesium most likely competes with calcium at voltage-operated calcium channels, indomethacin blocks the synthesis of prostaglandins, and beta-adrenergic agonists activate adenylate cyclase in the uterine muscle, thereby reducing intracellular calcium levels. Frequently two tocolytic agents are required to create uterine quiescence. Uterine activity and FHR are monitored closely during the first 2 to 3 postoperative days. The fetus is evaluated postoperatively by ultrasonography, and if indomethacin is used, periodic fetal echocardiography is conducted to determine whether premature closure of the ductus arteriosis has occurred.

Patients recovering from open fetal surgery should remain near the fetal treatment center after being discharged. These patients are at high risk for preterm PROM, preterm labor, infection, and uterine rupture. Unless preterm labor occurs, cesarean delivery is typically planned at 37 weeks' gestation.

Anesthesia for the *Ex Utero* Intrapartum Treatment Procedure

Initially described as a method to remove the iatrogenic airway obstruction created for intrauterine treatment of CDH, the EXIT procedure has evolved into a technique useful for a number of fetal disorders that compress the airway and/or render neonatal tracheal intubation difficult or impossible. It is also useful when resuscitation and surgical intervention are required immediately before birth, while the fetus is still supported by the placentofetal circulation. Cases appropriate for an EXIT procedure include (1) thoracotomy for congenital pulmonary airway malformations and (2) tracheostomy and the removal of neck masses such as fetal teratoma. The use of an EXIT procedure may also assist the transition to ECMO for pulmonary insufficiency or the stabilization of conjoined twins prior to separation.[11,130,131] Similar to open fetal surgery procedures, sustained uterine relaxation and delay of placental separation are necessary for a successful EXIT procedure.

Anesthesia for EXIT procedures is most commonly performed with the use of general anesthesia, although neuraxial anesthesia, typically combined with intravenous nitroglycerin infusion to achieve uterine relaxation, may also be used. Multiple reviews of the surgical and obstetric considerations associated with the EXIT procedure have been published.[132-134]

The conventional anesthetic approach is a modification of the general anesthetic technique used for cesarean delivery. Preparation for fetal monitoring, airway management, fetal/neonatal resuscitation, and postdelivery care should be completed before entering the operating room. A sterile pulse oximeter probe and an end-tidal carbon dioxide indicator or gas analyzer are used for fetal monitoring during the procedure; basic ultrasonography can be added to assess the fetal heart. Unit doses of atropine, epinephrine, and calcium for intramuscular fetal injection are transferred sterilely to the scrub nurse for possible emergency intraoperative resuscitation. Supplemental fetal anesthetic agents for intramuscular injection are also prepared and transferred to the scrub nurse (see later discussion). A sterile ventilation bag with an air/oxygen source and manometer is available for the fetus, along with multiple endotracheal tube sizes and devices for fetal tracheal intubation. Catheters for intravenous access as well as crystalloid and blood (O-negative, CMV-negative, leukocyte depleted, irradiated, maternally crossmatched) should be available for fetal volume resuscitation if needed.

A maternal epidural catheter may be placed preoperatively for postoperative analgesia. Anesthetic considerations for the mother are similar to those for cesarean delivery but should also include large-bore intravenous access, availability of uterotonic agents and crossmatched blood, and the ability to quickly obtain invasive maternal monitoring if needed.

Techniques of induction and tracheal intubation do not differ from those typically used for cesarean delivery. Although techniques for maintenance of anesthesia vary between medical centers, administration of 2 to 3 MAC of a volatile halogenated agent is often needed to achieve and maintain adequate uterine relaxation. Occasionally, nitroglycerin administered intravenously as a bolus dose (50 to 200 μg) or as an infusion is required to obtain appropriate uterine relaxation. Fetal anesthesia from the halogenated agent transferred across the placenta can be supplemented by direct fetal (intramuscular) administration of an opioid (fentanyl 5 to 15 μg/kg) and a paralytic agent (rocuronium 1 to 3 mg/kg or pancuronium 0.1 to 0.3 mg/kg); some practitioners also administer intramuscular atropine (20 μg/kg) to prevent fetal bradycardia.[132,134] Intramuscular agents can be administered to the fetus either before uterine incision with ultrasonographic guidance or after incision with direct visualization. Significant variability in serum fentanyl concentrations among fetuses has been documented in umbilical cord blood during EXIT procedures,[135] and similar variability may exist with muscle relaxants and other agents.

When adequate uterine relaxation has been achieved, the placental location and edges are confirmed by intraoperative ultrasonography. Similar to open fetal procedures, the uterine incision is extended with a stapling device to minimize blood loss. The fetal head and shoulders are delivered in preparation for tracheal intubation.

For more extensive procedures, such as fetal thoracotomy, or when there is fetal bradycardia suggestive of umbilical cord compression, the fetus can be completely delivered and placed on the maternal chest and abdomen. In an effort to maintain fetoplacental circulation, warmed fluids are continuously irrigated into the uterine cavity and care is taken to avoid manipulation of the umbilical cord. The warmed irrigant maintains fetal euthermia and helps prevent decreased uterine volume, placental separation, and spasm of the cord vessels. The fetus is initially monitored with (1) a pulse oximeter probe placed on the fetal hand, (2) periodic ultrasonography, and (3) direct visualization.

The duration of the fetal procedure can range from a few minutes (e.g., bronchoscopy or intubation) to several hours (e.g., neck or thoracic mass resection, tracheostomy, or central intravascular access). Although the majority of procedures require less than an hour, the anesthetic technique should be capable of providing maternal, fetal, and uteroplacental stability over several hours.[136,137] Once surgery is completed and the trachea secured, surfactant is given if indicated. Fetal oxygen saturation is typically 40% to 60% at this time[138] but increases significantly to above 90% with ventilation of the fetal lungs. Failure to achieve a fetal saturation of at least 90% is an indication for the use of ECMO before clamping the umbilical cord and delivering the fetus.[139]

After the umbilical cord is clamped, the maternal anesthetic technique is altered to help achieve uterine tone and diminish the risk for postpartum hemorrhage.[132,140] This is accomplished by (1) substantially reducing the inspired concentration of the volatile halogenated agent; (2) adding nitrous oxide, propofol, and/or an opioid to maintain anesthesia; (3) administering oxytocin and other uterotonic agents, if needed; and (4) initiating epidural analgesia via the epidural catheter that was placed before surgery.

An alternative technique for EXIT procedures involves the use of neuraxial anesthesia.[141-143] Although this approach avoids many of the risks associated with general anesthesia, large doses of intravenous nitroglycerin (1 to 10 μg/kg/min) are often required to achieve adequate uterine relaxation. Nitroglycerin can cross the placenta; however, a significant amount is metabolized at the placental interface, resulting in minimal fetal effects.[121,143] If nitroglycerin is to be used at significant doses for a prolonged period, an arterial catheter is recommended and the patient should be observed for evidence of pulmonary edema. Fetal analgesia and immobility can be achieved with fetal administration of intramuscular drugs (see earlier discussion); maternally administered intravenous remifentanil undergoes significant transfer across the placenta and may serve as an adjuvant for fetal analgesia and immobility.[144,145] Prospective trials are necessary to delineate the advantages and disadvantages of these various anesthetic techniques for the EXIT procedure.

Fetal Response to Surgical Stimulation

The subjective phenomenon of pain has not been, and perhaps cannot be, assessed adequately in human fetuses. Pain is a multidimensional, subjective, psychological construct that can exist in the absence of physical stimuli (e.g., phantom limb pain), and it includes emotional and affective components that require higher-level cortical processing. As such, although pain is commonly associated with physical noxious stimuli, it is more than nociception or a simple reflex activity associated with a withdrawal response.[146] Attempts have been made to correlate pain with surgical stress; however, the physiologic responses are not equivalent and reductions in stress hormones should not be interpreted as an indicator of adequate analgesia.[147] The stress response is mediated primarily in the spinal cord, brainstem, and/or basal ganglia, without involvement of the cortex. This distinction acknowledged, pioneering studies of preterm neonates undergoing surgery with minimal anesthesia have revealed circulatory, sympathoadrenal, and pituitary adrenal responses characteristic of stress (e.g., increased release of catecholamines, growth hormone, glucagon, cortisol, aldosterone, and other corticosteroids; decreased secretion of insulin).[148,149] Administration of adequate anesthesia in neonates blunts this stress response,[150] and attenuation of the stress response in preterm neonates has been associated with improved outcomes.[151]

In studies of intrauterine blood transfusion in the human fetus, surgical needling of the intrahepatic vein (in contrast to the insensate umbilical cord) is associated with evidence of a stress response, including increases in plasma beta-endorphin and cortisol concentrations and decreases in the middle cerebral artery pulsatility index (determined by Doppler imaging). These responses, which may redistribute blood flow to vital organs, including the brain,[152] can be blunted by the administration of fentanyl 10 μg/kg.[114] Human fetuses elaborate pituitary-adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli as early as 18 weeks' gestation.[153-156] During late gestation, fetuses can respond to environmental stimuli such as noise, light, music, pressure, touch, and cold.[157]

Nerve terminals for the detection of touch, temperature, and vibration (not pain) are present deep within the human skin at 6 weeks' gestation and become more numerous and superficial (e.g., toward the skin surface) by 10 weeks' gestation.[158] Immature skin nociceptors likely begin to emerge at 10 weeks' gestation and are present by 17 weeks' gestation[159]; in internal organs, nociceptors develop slightly later.

Peripheral nerve fibers that control movement grow into the spinal cord at about 8 weeks' gestation. When these fibers connect with nociceptors is unknown, but the timing of these connections is delayed when compared with other sensory inputs in nonhuman, mammalian models. One human study suggested that nociceptive nerve fibers do not enter the spinal cord before about 19 weeks' gestation.[160] The cerebral cortex develops after the fetal spinal cord and brainstem. Thalamocortical axons reach the somatosensory cortex at 24 to 26 weeks' gestation.[146]

The developing cerebral cortex consists of transient fetal zones where neuronal proliferation, cell migration, apoptosis, axonal outgrowth, and synaptogenesis occur according to a highly specific timetable (see Chapter 10). Originating as a smooth layer without sulci and gyri, the

cerebral cortex, like the thalamus, has no internal cellular organization.[158] The cortical subplate is a temporary structure that serves as a waiting and organizing zone for various afferents destined for the cortex; it develops about 13 weeks' gestation and recedes after 32 to 34 weeks' gestation. The insular cortex starts developing in humans at approximately 15 weeks' gestation, with the cortical plate eventually developing into the six layers of the cerebral cortex.[161-163]

The first fibers from the thalamus reach the subplate between 12 and 18 weeks' gestation and remain until the maturation of the cortical plate. The gestational age at which thalamic pain fibers reach the human cortex only can be estimated from histologic studies of other thalamocortical circuits. Thalamic projections reach the visual subplate at 20 to 22 weeks' gestation,[162,164] the visual cortex at 23 to 27 weeks' gestation,[165] and the auditory cortical plate at 26 to 28 weeks' gestation.[166] The subplate becomes thinner in the insula and in areas of the brain where early cortical folding occurs. Extensive brain growth and maturation occur after 34 weeks' gestation, resulting in cortical sulci and gyri and an extensive network of pathways within the cortex and to the thalamus, midbrain, and spinal cord. Prior to the completion of the thalamocortical system, the midbrain reticular system is possibly responsible for pain awareness, as it is for consciousness.[162,167]

Studies of fetal electroencephalograms (EEGs) at 24 weeks' gestation demonstrate electrical activity only 2% of the time, predominantly in 20-second bursts with periods of inactivity lasting up to 8 minutes. At 30 weeks' gestation, EEGs begin showing patterns of wakefulness and sleep, but these are not concordant with fetal behavior. By 34 weeks' gestation, electrical activity is present 80% of the time, with more distinct wakefulness and sleep cycles similar to adult patterns.

Low levels of oxygenation *in utero* and endogenous neural inhibitors such as adenosine and pregnenolone may preclude optimal functioning of neural tissues and networks.[168] However, two studies using near-infrared spectroscopy in preterm infants demonstrated differences in cerebral oxygenation over the somatosensory cortex with noxious and non-noxious stimulation. This appears to indicate that noxious information is at least transmitted to the infant cortex by 25 weeks' gestation[169,170]; similarly, preterm neonates also have demonstrated cortical evoked potentials after a heel lance.[171]

Although initial fetal reactions to nociceptive stimulation are purely reflexive, and cortical processes can occur only after thalamocortical connections have been completed, nociceptive stimuli can activate a number of subcortical mechanisms; moreover, stress responses may influence the maturation of both the thalamocortical pathways and the cerebral cortex. Although the data on the consequences of fetal exposure to stressful stimuli are incomplete, recognition should be given to the possibility that noxious stimuli, which can be attenuated or blocked by anesthesia, may be associated with adverse long-term neurodevelopmental consequences.[172] For example, circumcision in nonanesthetized neonates has been associated with increased pain responses to injections performed 6 months later[173]; in addition, fetal stress has been associated with long-term adverse hormonal effects in young monkeys.[174]

The exact onset of fetal *sentience*, the capacity to feel pain, is unknown (see Chapter 5). Because of this uncertainty, it seems best to err on the side of administering adequate fetal anesthesia.[175] Altogether, clinical observations of fetal and neonatal behavior, information about the development of mechanisms of pain perception, and studies of fetal and neonatal responses to noxious stimuli provide a compelling physiologic and philosophic rationale for the provision of adequate fetal anesthesia, especially after 24 to 26 weeks' gestation. Noxious stimulation during fetal life causes a stress response, which could have both short- and long-term adverse effects on the developing central nervous system. Although the link between the stress response and pain is not always predictable, the threshold for pain relief is typically below that for stress response ablation, and the stress response to noxious stimulation is clear evidence that the fetal nervous system is reactive.[176] Administration of fetal anesthesia has been the standard practice worldwide since the inception of fetal surgery more than 30 years ago.[5,6,177,178] The importance of fetal immobility, cardiovascular homeostasis, analgesia, and perhaps amnesia have always been emphasized in fetal surgery practice.

Effects of Anesthesia on the Fetus

In fetal lambs, the concentration of halothane required to prevent movement in response to painful stimuli (1.0 MAC) is less than 40% of the concentration required in adult sheep.[179] Despite rapid placental transfer of volatile halogenated agents, experiments in sheep models have shown that fetal concentrations of these agents remain lower than maternal concentrations for significant periods after maternal administration (Figure 7-3).[180]

Experimental studies of the fetal effects of maternal administration of a volatile halogenated agent in sheep have not produced uniform results.[180-183] Maternal administration of isoflurane and halothane resulted in variable changes in fetal blood pressure, heart rate, oxygen saturation, cardiac output, and acid-base status. A retrospective analysis of cardiac imaging from both open fetal cases and EXIT procedures noted severe left ventricular systolic dysfunction in the fetus with use of high concentrations of desflurane.[122]

Maternal-fetal sheep studies, with no surgical stimulus to either the mother or fetus, show that deep maternal inhalation anesthesia (> 2.0 MAC) results in progressive fetal acidosis. By contrast, lower maternal inhalation anesthesia (1.0 MAC) also may be undesirable because it does not adequately block the fetal response to a painful stimulus, which includes increased fetal catecholamines, vasoconstriction, and redistribution of fetal blood flow.[184] However, the combined effect of adequate fetal anesthesia with a halogenated agent, intrauterine manipulation, and fetal stress on fetal cardiovascular stability and regional blood flow remains unknown. Brief fetal exposure to deep maternal inhalation anesthesia (i.e., 2.0 to 3.0 MAC) does not appear significantly detrimental to the fetus, with no fetal hypoxia, hypercarbia, or acidosis observed even after exposures of 2 hours if maternal

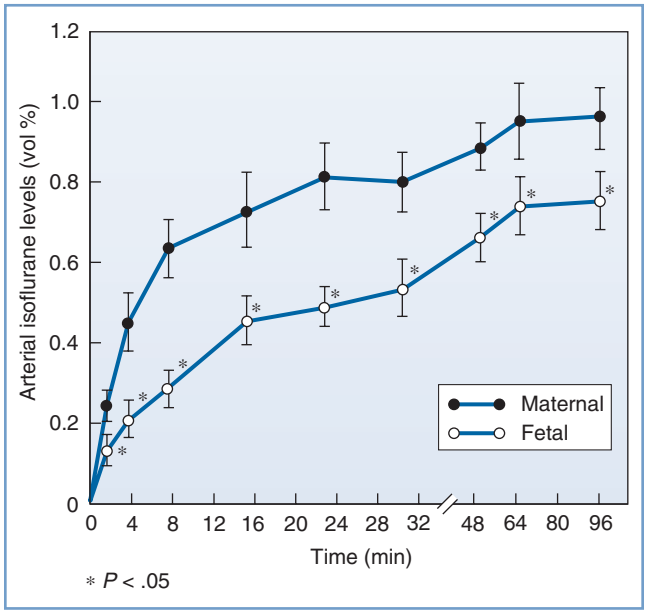

FIGURE 7-3 ■ Maternal and fetal arterial isoflurane concentrations in sheep during maternal administration of 2.0% isoflurane (mean ± SE). (From Biehl DR, Yarnell R, Wade JG, Sitar D. The uptake of isoflurane by the foetal lamb *in utero*: effect on regional blood flow. Can Anaesth Soc J 1983; 30:581-6.)

arterial pressure is maintained.[136] However, others have seen acidosis after 45 minutes of fetal exposure to anesthesia.[185]

Another concern is that anesthetic agents may result in neuronal apoptosis in the developing fetal brain (see Chapter 10). Initial evidence was found in 2003, when an anesthetic consisting of midazolam, nitrous oxide, and isoflurane was shown to alter neurons in the developing brain of 7-day-old rats and to cause long-term impairment of brain function.[186] Additional *in utero* rat studies noted that fetal exposure to isoflurane for 4 hours near mid gestation resulted in abnormal spatial memory acquisition.[187] Primate studies have demonstrated significant neurodegeneration in the neonatal period after exposure to isoflurane.[188] It is not currently known if anesthetic agents similarly affect human fetuses or newborns. Several retrospective human studies have produced inconclusive results. One retrospective cohort trial noted that a single short anesthetic exposure in children younger than age 2 years did not have long-term cognitive implications; however, exposure to multiple anesthetics was a significant risk factor for development of learning disabilities.[189] Another retrospective study examined anesthetic exposure among twins and found no causal relationship between early anesthetic exposure and learning disabilities.[190] Although there is concern for neurotoxicity in human fetuses or children exposed to anesthetic drugs, current findings remain inconclusive about the long-term effects of anesthetic agents on brain function in humans. A 2007 U.S. Food and Drug Administration advisory committee concluded that no change in clinical practice is justifiable based on current data.[191,192] The neurocognitive effect of anesthetic exposure on fetuses during fetal surgery remains unknown.

Fetal Monitoring

Maternal and fetal anesthesia, uterine incision, fetal manipulation, and surgical stress may adversely affect uteroplacental and fetoplacental circulation by several mechanisms. Maternal hypotension, increased uterine activity, and maternal hyperventilation and hypocarbia impair uteroplacental and/or umbilical blood flow. Fetal manipulation may affect fetal cardiac output, regional distribution of cardiac output, and umbilical blood flow. Direct compression of the umbilical cord, inferior vena cava, and mediastinum adversely affects fetal circulation. Current methods of intraoperative fetal monitoring include FHR monitoring, pulse oximetry, ultrasonography (including echocardiography and Doppler assessment of umbilical cord blood flow), and blood gas and acid-base analysis.

Intraoperative monitoring of the FHR during open fetal surgery was initially attempted with a standard fetal corkscrew electrode processed by a standard FHR cardiotachometer, but signal failure was frequent, secondary to low signal amplitude and movement artifact. With use of atrial pacing wires sutured to the fetus, proximal wire shielding, increased gain to allow signal amplification, and filter modification, a more reliable display of fetal ECG with visible P waves and QRS complexes was possible. Unfortunately, this technique did not eliminate motion artifact. Analysis of the fetal ECG using ST waveform analysis may prove beneficial for fetal surgery.[193] A fetal scalp electrode has been used successfully as part of an EXIT procedure to monitor FHR after the head was exposed.[194]

Plethysmography combined with pulse oximetry has proved to be very useful, particularly for the EXIT procedure. The predictive value of pulse oximetry may be superior to FHR monitoring; bradycardia has been found to be a late sign of fetal compromise in fetal lambs subjected to umbilical cord compression (Figure 7-4).[195] However, bradycardia can also precede oxyhemoglobin desaturation during human fetal surgery (Figure 7-5).[196]

Ultrasonography is a crucial intraoperative fetal monitoring device. The FHR can be determined with visualization of the heart or with Doppler assessment of umbilical cord blood flow. Fetal cardiac contractility and volume also can be assessed qualitatively by echocardiography. Unfortunately, the sterile transducer often cannot be positioned continuously because its location interferes with surgery.

New devices may allow monitoring of (1) fetal blood pressure and EEG; (2) fetal arterial blood oxygen saturation, Po_2, and Pco_2; and (3) fetal cerebral oxygenation, blood volume, and blood flow with near-infrared spectroscopy.

THE FUTURE OF FETAL THERAPY

Successful diagnosis and management of complex congenital anomalies and other fetal conditions amenable to prenatal intervention relies on a multidisciplinary team whose members communicate and work together to

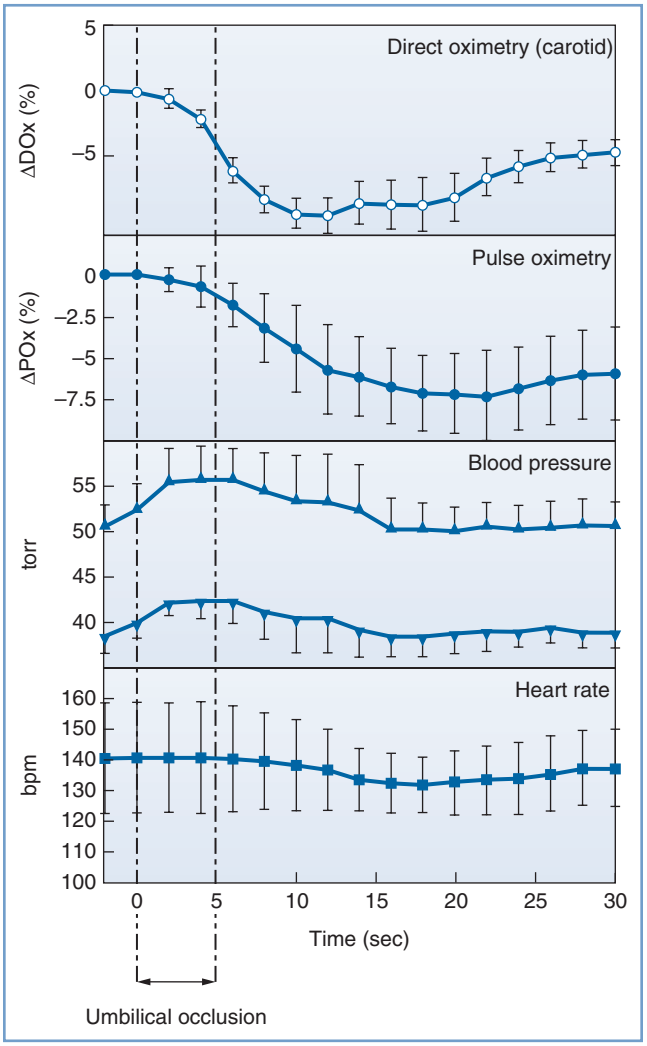

FIGURE 7-4 ■ Response to 5 seconds of umbilical cord occlusion in the fetal lamb. Direct oximetry and pulse oximetry are expressed as delta saturation ($T_x - T_0$). (From Luks FI, Johnson BD, Papadakis K, et al. Predictive value of monitoring parameters in fetal surgery. J Pediatr Surg 1998; 33:1297-1301.)

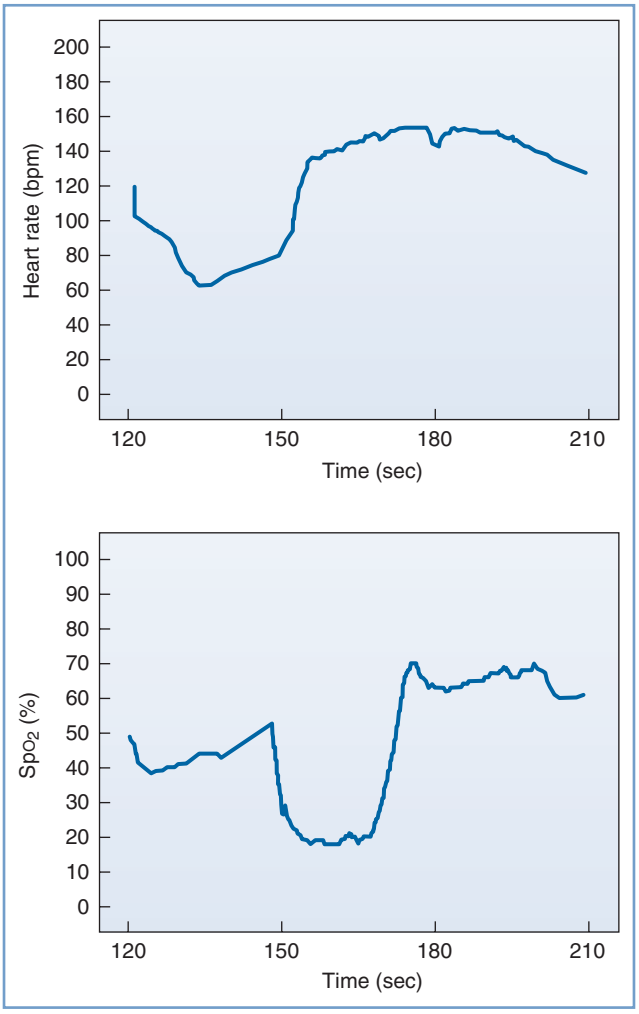

FIGURE 7-5 ■ Graphic representation of monitoring data from a fetus at 24 weeks' gestation undergoing open diaphragmatic hernia repair. Top graph shows fetal heart rate (bpm) and bottom graph shows oxygen saturation (Spo_2) detailed over a 2-minute period. The tracings demonstrate an acute decrease in fetal heart rate (FHR) with an associated decrease in fetal Spo_2. The onset of the desaturation detected in the fetal hand is delayed in relation to the onset of the bradycardia. Similarly, the recovery in FHR precedes the onset of the rapid increase in saturation. This pattern most likely represents a transport delay of the blood from the heart to the fetal hand. (From Rosen MA. Anesthesia for fetal surgery. In Hughes SC, Levinson G, Rosen MA, editors. Shnider and Levinson's Anesthesia for Obstetrics. 4th edition. Philadelphia, Lippincott Williams & Wilkins, 2002.)

improve fetal outcome without incurring substantive maternal risk. Well-organized, multidisciplinary, professional, and comprehensive fetal treatment programs at academic medical centers facilitate the sustained effort to innovate new techniques, challenge dogma, and ensure ongoing success. More collaborative clinical investigation among international research centers will benefit these efforts and guide the evolution of prenatal fetal therapy. Advances in technology will continue to drive improvement and availability of fetal intervention. For example, dynamic tracheal occlusion for CDH rather than complete occlusion, using devices that have pressure-sensitive valves to allow egress of fetal lung fluid, may improve outcome by more closely imitating normal developmental physiology and result in more normal lung function than that seen with current techniques.

With continued advances and miniaturization of invasive techniques and decreases in maternal and fetal risk, fetal intervention for a wider variety of procedures is the likely future for fetal therapy. Endoscopic repair of myelomeningocele has already been attempted. Other procedures with future potential include (1) placement of a cardiac pacemaker to restore sinus rhythm and improve survival in fetuses with complete heart block or a cardiac arrhythmia, when treatment is refractory to transplacental administration of medication; (2) repair of craniofacial anomalies, gastroschisis, and cleft lip and palate; and (3) corrections of skeletal anomalies by allogenic bone grafting. Innovations focused on tissue engineering, using stem cells and gene therapies, are exciting possibilities for future fetal therapy.

Although the rationale for prenatal fetal therapy seems straightforward, many issues remain problematic. Questions remain regarding the manner in which fetal development is modulated by intrauterine intervention. Other questions revolve around maternal and fetal rights, safety, efficacy, long-term outcomes, cost-effectiveness, and societal resource allocation. Societal expectations and the availability of therapy must be balanced against the budgetary constraints in contemporary health care. In addition, there is concern about the sensitivity, specificity, and appropriate use of diagnostic testing. Fetal therapy raises complex social, ethical, and legal issues that go beyond those customary for therapeutic intervention.[197] In some cases, distinguishing innovative therapy from experimentation is difficult. The ethical framework for the transition from innovation to clinical trials to offering fetal surgery as a standard of care must be managed thoughtfully and responsibly. A bioethics committee with representatives from both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists has provided recommendations for medical institutions offering fetal surgery.[198]

Fetal therapy must be evaluated carefully in properly conducted trials and undertaken only with great caution and informed maternal consent. Publication in scientific journals and open communication with colleagues nationally and internationally facilitates the moral obligation of researchers to report all results to allow peer review of the merits and liabilities of fetal surgery. The principal concept of *primum non nocere* argues that it is unethical to undertake human trials until a procedure is appropriately tested in animals.[199,200]

Training programs are necessary to safely expand access and services from academic medical centers to local units. There is debate whether results of trials from tertiary academic centers such as the MOMS trial[75] are applicable to institutions that did not participate. Outcomes from new fetal centers with little experience and patients outside strict inclusion criteria may have less favorable outcomes with greater morbidity.[201] Fetuses that may benefit from invasive therapy must be carefully distinguished from those that will not. Intervention should be undertaken only when there is a reasonable probability of long-term benefit and minimal maternal risk. Despite more than 3 decades of experience, there remains much to study, a great deal to learn, and, it is hoped, a lot to achieve.

KEY POINTS

- Most malformations diagnosed *in utero* are not suitable for antenatal intervention. Fetal surgery is a reasonable option for anomalies that cause harm to the fetus before adequate development necessary for extrauterine survival (particularly lung maturity).
- Local or neuraxial anesthesia is often suitable for percutaneous or minimally invasive procedures. Open intrauterine procedures typically require administration of general anesthesia.
- Anesthetic considerations for intrauterine fetal surgery are similar to those for nonobstetric surgery in pregnant women. However, fetal surgery typically requires (1) provision of analgesia for the fetus, (2) more intensive intraoperative fetal monitoring, and (3) intraoperative uterine relaxation.
- Preterm premature rupture of membranes and preterm labor after surgery are significant barriers to optimal outcomes with fetal surgery.
- There are many medical, social, ethical, and legal questions regarding the efficacy and safety of intrauterine fetal surgery. Careful evaluation of fetal benefits and maternal risks is fundamental to the decision as to when and whether fetal intervention is appropriate.

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CHAPTER 8

Intrapartum Fetal Assessment and Therapy

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CHAPTER OUTLINE

The value of intrapartum obstetric interventions to assess and maintain fetal well-being has been scrutinized in recent years. Old technologies have been reassessed, and new ones have been introduced. A rising cesarean delivery rate, renewed interest in home birth, persistent cases of fetal/neonatal neurologic injury, and excessive litigation have prompted an ongoing search for methods to identify and intervene on behalf of the fetus at risk during labor and delivery.

FETAL RISK DURING LABOR

Historical epidemiologic data suggest that the fetus is at increased risk for morbidity and mortality during labor and delivery. In 1963, the British Perinatal Mortality Survey reviewed autopsy data for 1400 stillborn infants and concluded that slightly more than 30% of these losses resulted from intrapartum asphyxia.[1] Neonatal outcomes in the industrialized world have improved over the past 40 years. A Canadian database identified approximately 80 intrapartum stillbirths per 120,000 live births from 1981 to 2002, a rate of 0.67/1000; some 11 of the infants were considered viable (i.e., not severely preterm or anomalous), which indicated a preventable death rate of 0.09/1000.[2] A Scottish study indicated that perinatal deaths due to intrapartum anoxia in term, singleton, cephalic infants declined significantly from 5.7 to 3.0/10,000 births between 1988 and 2007.[3] Intrapartum stillbirths are rare in developed countries, constituting less than 10% of all stillbirths. By contrast, in some developing countries, as many as 50% of stillbirths occur intrapartum.[4] According to a World Health Organization report, intrapartum-related neonatal deaths account for almost 10% of deaths in children younger than 5 years of age.[5,6]

Experimental models lend support to the hypothesis that intrapartum events can have long-term neurologic sequelae. Fetal monkeys subjected to hypoxia *in utero* suffer neurologic injuries similar to those seen in children who presumably suffered asphyxia *in utero*.[7-9] Work with rodent models has shown similar patterns of damage.[10] Hankins et al.[11] suggested that performance of elective cesarean delivery at 39 weeks' gestation (and avoidance of a trial of labor) might result in an 83% reduction in risk for moderate or severe neonatal encephalopathy. Altogether, epidemiologic and experimental data suggest that the fetus is at significant risk during labor and delivery.

Some fetuses appear to be at greater risk for adverse intrapartum events than others. Older studies report that high-risk mothers constitute 20% of the pregnant population, but their offspring represent 50% of the cases of perinatal morbidity and mortality.[12] Various schemes to identify high-risk pregnancies have been published.[13,14] High-risk pregnancies include, but are not limited to, women with (1) **medical complications** (e.g., hypertension, preeclampsia, diabetes, autoimmune disease, hemoglobinopathy); (2) **fetal complications** (e.g., fetal growth restriction [also known as intrauterine growth restriction], nonlethal anomalies, prematurity, multiple gestation, postdatism, hydrops); and (3) **intrapartum complications** (e.g., abnormal vaginal bleeding, maternal fever, meconium-stained amniotic fluid, oxytocin augmentation of labor). Owing to inadequate sensitivity, poor positive predictive values, and the inability to modify outcomes related to risk factors, scoring systems for identifying high-risk fetuses have not been shown to improve pregnancy outcomes.[15] Lo et al.[16] indicated that more than half of infants with asphyxia had no clinical risk factors. However, for low-risk parturients who wish to avoid continuous monitoring during labor, scoring systems may demonstrate some benefit.[15] One strategy used in European centers for identifying high-risk parturients is fetal heart rate (FHR) tracing analysis at the time of admission to the labor and delivery suite; if the FHR

tracing is abnormal, patients receive more intensive monitoring.[17] A meta-analysis of this approach observed an increase in cesarean delivery rates but failed to demonstrate improvements in fetal and neonatal outcomes.[18]

The magnitude of risk for intrapartum fetal neurologic injury is a matter of some dispute. In 2003, the American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy and Cerebral Palsy concluded that 70% of these types of fetal neurologic injuries result from events that occur before the onset of labor.[19-21] Examples of antepartum events that may cause fetal neurologic injury include congenital anomalies, chemical exposure, infection, and fetal thrombosis/coagulopathy. Only 4% of cases of neonatal encephalopathy result solely from intrapartum hypoxia, an incidence of approximately 1.6/1000.[19,20,22] The Task Force identified criteria that define an acute intrapartum hypoxic event sufficient to cause cerebral palsy (Box 8-1).[19,20,23] A recent study found that fetuses that underwent a sudden and sustained deterioration of the FHR and that subsequently had a diagnosis of cerebral palsy demonstrated characteristics consistent with the criteria developed by the ACOG Task Force.[24] An additional case series of sentinel events during labor (e.g., uterine rupture, cord prolapse, placental abruption, amniotic fluid embolus) resulted in a high rate of hypoxic-ischemic encephalopathy in surviving infants.[25] Approximately 25% of fetuses may have antepartum and intrapartum risk factors for neurologic injury.

BOX 8-1 Criteria That Define an Acute Intrapartum Hypoxic Event as Sufficient to Cause Cerebral Palsy

Essential Criteria

1. Evidence of metabolic acidosis in umbilical cord arterial blood obtained at delivery (i.e., pH < 7.00, base deficit > 12 mmol/L)
2. Early onset of encephalopathy in an infant delivered at > 34 weeks' gestation
3. Cerebral palsy of the spastic quadriplegia or dyskinetic type
4. Exclusion of other identifiable causes

Criteria That Suggest Intrapartum Timing of Insult

1. Sentinel hypoxic event occurring immediately before or during labor
2. Sudden, sustained bradycardia or absence of fetal heart rate variability with persistent late or variable decelerations
3. Apgar scores of 0-3 beyond 5 minutes of life
4. Evidence of multisystem involvement within 72 hours of delivery
5. Early imaging study that shows evidence of acute, nonfocal cerebral abnormality

Modified from the American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy. Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Washington, DC, American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, January 2003; and MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. Br Med J 1999; 319:1054-9.

The ability of contemporary obstetricians to recognize and treat pregnancies at risk for hypoxia during labor is an evolving science. With the current understanding of pathophysiology and the technology in current clinical use, the extent to which obstetricians can prevent intrapartum injury is unclear.[26] It is hoped that the development of standardized, clearer definitions of intrapartum injury, and new strategies and interventions that can correct reversible pathophysiology, will lead to more precise identification and optimization of fetuses at risk.

Efforts to understand placental physiology and pathophysiology are central to the efforts to support the health of the pregnant woman and her fetus, both antepartum and intrapartum. The fetus depends on the placenta for the diffusion of nutrients and for respiratory gas exchange. Many factors affect placental transfer, including concentration gradients, villus surface area, placental permeability, and placental metabolism (see Chapter 4). Maternal hypertensive disease, congenital anomalies, and intrauterine infection are examples of conditions that may impair placental transfer.

One of the most important determinants of placental function is uterine blood flow.[27] A uterine contraction results in a transient decrease in uteroplacental blood flow. A placenta with borderline function before labor may be unable to maintain gas exchange adequate to prevent fetal asphyxia during labor. The healthy fetus may compensate for the effects of hypoxia during labor.[28,29] The compensatory response includes (1) decreased oxygen consumption, (2) vasoconstriction of nonessential vascular beds, and (3) redistribution of blood flow to the vital organs (e.g., brain, heart, adrenal glands, placenta).[30,31] Humoral responses (e.g., release of epinephrine from the adrenal medulla, release of vasopressin and endogenous opioids) may enhance fetal cardiac function during hypoxia.[27] Prolonged or severe hypoxia overwhelms these compensatory mechanisms, resulting in fetal injury or death.

INTRAPARTUM FETAL ASSESSMENT

Electronic Fetal Heart Rate Monitoring

An optimal, yet practical method for assessing fetal health during labor and delivery has not been developed. Most contemporary methods include assessment of the FHR. The FHR can be monitored intermittently with a simple DeLee stethoscope. Alternatively, either Doppler ultrasonography or a fetal electrocardiographic (ECG) electrode can be used to monitor the FHR intermittently or continuously.

Experimental models have provided insight into the regulation of the FHR. Both neuronal and humoral factors affect the intrinsic FHR. Parasympathetic outflow by means of the vagus nerve decreases the FHR, whereas sympathetic activity increases FHR and cardiac output.[27] Baroreceptors respond to increased blood pressure and chemoreceptors respond to decreased Pao_2 and increased $Paco_2$ to modulate the FHR through the autonomic

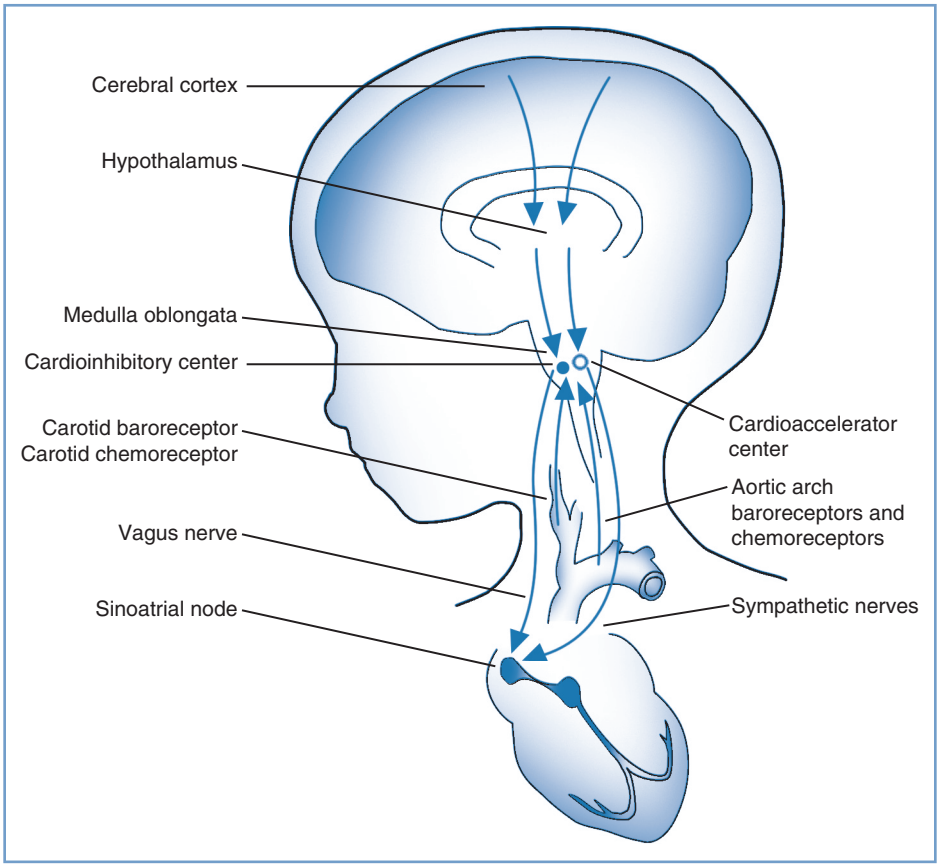

FIGURE 8-1 ■ Regulation of fetal heart rate. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

nervous system. Cerebral cortical activity and hypothalamic activity affect the FHR through their effects on integrative centers in the medulla oblongata (Figure 8-1).[27] Both animal studies and clinical observations have helped establish a correlation between FHR and perinatal outcome.

An electronic monitor simultaneously records the FHR and uterine contractions. Use of an electronic monitor allows determination of the **baseline rate** and **patterns** of the FHR and their relationship to uterine contractions. External or internal techniques can assess the FHR and uterine contractions (Figure 8-2). Doppler ultrasonography detects the changes in ventricular wall motion and blood flow in major vessels during each cardiac cycle. The monitor calculates the FHR by measuring the intervals between fetal myocardial contractions. Alternatively, an ECG lead attached to the fetal scalp enables the cardiotachometer to calculate the FHR by measuring each successive RR interval. Both external and internal methods allow continuous assessment of the FHR.

The FHR is superimposed over the uterine contraction pattern. Uterine contractions can be monitored externally with a tocodynamometer or internally with an intrauterine pressure catheter. The tocodynamometer allows determination of the approximate onset, duration, and offset of each uterine contraction. A normal pattern of uterine contractions in labor is five or less in a 10-minute period averaged over 30 minutes; tachysystole is defined as more than five uterine contractions within a 10-minute period.[32] An intrauterine pressure catheter may be used to measure the strength of uterine contractions. In some cases, an intrauterine pressure catheter is placed to determine the precise onset and offset of each uterine contraction. Such information may be used to distinguish among early, variable, and late FHR decelerations. In a nonblinded, randomized controlled trial, Bakker et al.[33] observed no significant differences in adverse neonatal outcomes with internal tocodynamometry as compared with external monitoring of uterine contractions in women in whom oxytocin was used for induction or augmentation of labor.

The following features of the FHR pattern can be assessed: (1) **baseline measurements,** (2) **variability** (the extent to which the rate changes both instantaneously and over longer periods), (3) **accelerations**, and (4) **decelerations** and their association with uterine contractions.

Baseline Fetal Heart Rate

A normal baseline FHR is defined as 110 to 160 beats per minute (bpm) and is determined by assessing the mean heart rate over a 10-minute period rounded to increments of 5 bpm.[32,34] In general, term fetuses have a lower baseline FHR than preterm fetuses because of greater parasympathetic nervous system activity. Laboratory

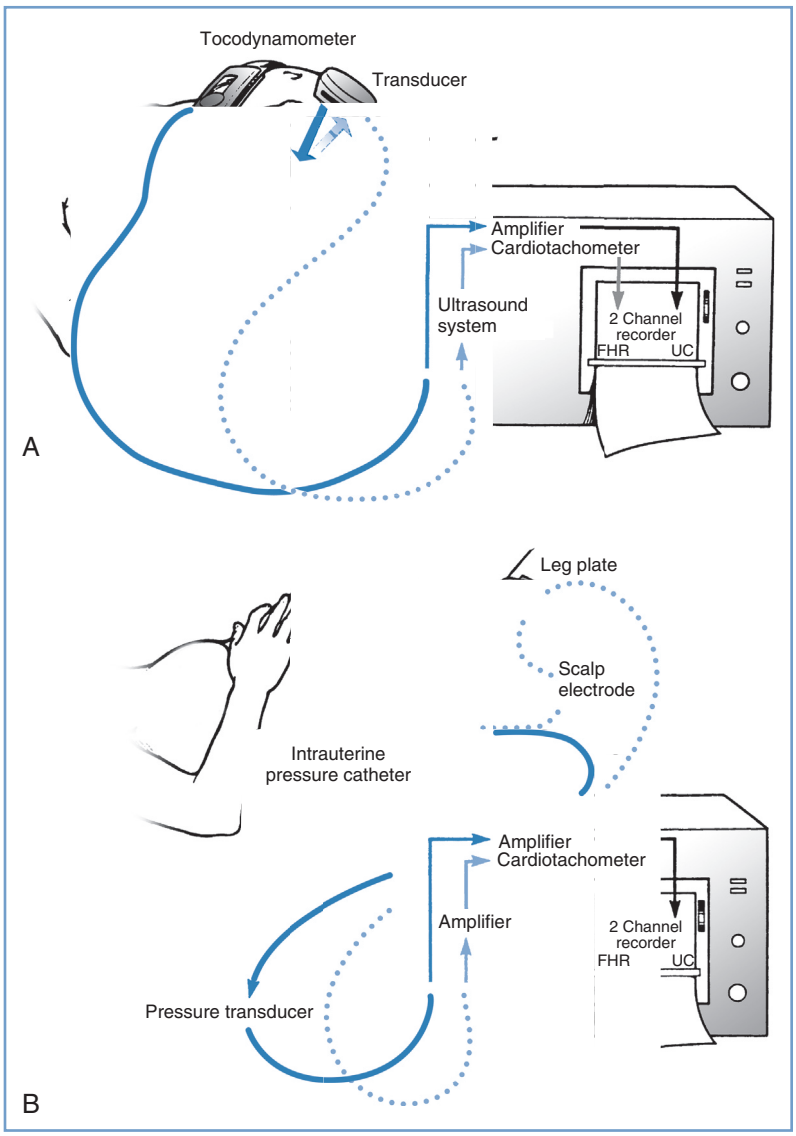

FIGURE 8-2 ■ Electronic fetal monitoring apparatus. **A,** Instrumentation for external monitoring. Contractions are detected by the pressure-sensitive tocodynamometer, amplified, and then recorded. The fetal heart rate (FHR) is monitored with the Doppler ultrasound transducer, which emits and receives the reflected ultrasound signal that is then counted and recorded. **B,** Techniques used for direct monitoring of FHR and uterine contractions (UC). Uterine contractions are assessed with an intrauterine pressure catheter connected to a pressure transducer. This signal is then amplified and recorded. The fetal electrocardiogram (ECG) is obtained by direct application of the scalp electrode, which is then attached to a leg plate on the mother's thigh. The signal is transmitted to the monitor, where it is amplified, counted by the cardiotachometer, and recorded. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

studies suggest that bradycardia (caused by increased vagal activity) is the initial fetal response to acute hypoxemia. After prolonged hypoxemia, the fetus may experience tachycardia as a result of catecholamine secretion and sympathetic nervous system activity.[28] Changes in baseline FHR may also be caused by fetal anatomic or functional heart pathology, maternal fever and/or intrauterine infections, or maternally administered medications, such as beta-adrenergic receptor agonists (e.g., terbutaline) or the anticholinergic agent atropine.

Fetal Heart Rate Variability

Fetal heart rate variability is the fluctuation in the FHR of 2 cycles or greater per minute.[32,34] Previously, FHR variability was divided into *short term* (from one beat, or R wave, to the next) and *long term* (occurring over the course of 1 minute), but this distinction is no longer made because in clinical practice variability is visually assessed as a unit (Figure 8-3). The presence of normal FHR variability reflects the presence of normal, intact pathways from—and within—the fetal cerebral cortex, midbrain, vagus nerve, and cardiac conduction system (see Figure 8-1).[27] Variability is greatly influenced by the parasympathetic tone, by means of the vagus nerve; maternal administration of atropine, which readily crosses the placenta, can eliminate some variability. In humans, the sympathetic nervous system appears to have a lesser role in influencing variability.[27] Maternal administration of the beta-adrenergic receptor antagonist propranolol has little effect on FHR variability.[27]

During hypoxemia, myocardial and cerebral blood flows increase to maintain oxygen delivery.[35,36] However, in severe hypoxemia, blood flow cannot increase sufficiently to maintain oxygen delivery and a loss of FHR variability is observed.[27] The absence of FHR variability in an anencephalic fetus indicates the influence of an intact central nervous system (CNS) in producing these patterns. In animal models, perfusion of the CNS with calcium results in depolarization of

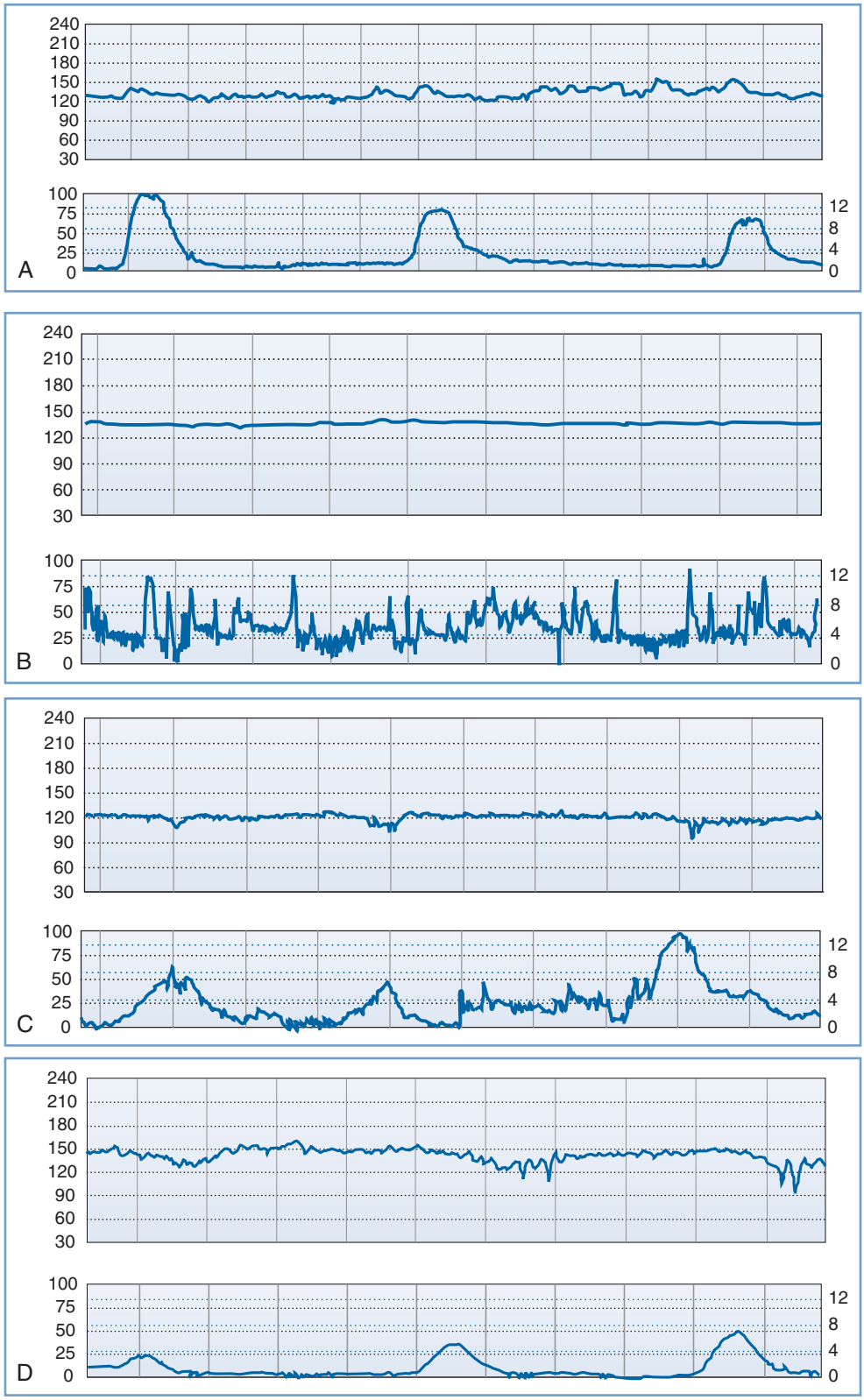

FIGURE 8-3 ■ **A,** Normal intrapartum fetal heart rate (FHR) tracing. The infant had Apgar scores of 8 and 8 at 1 and 5 minutes, respectively. **B,** Absence of variability in a FHR tracing. Placental abruption was noted at cesarean delivery. The infant had an umbilical arterial blood pH of 6.75 and Apgar scores of 1 and 4, respectively. **C,** Early FHR decelerations. After a normal spontaneous vaginal delivery, the infant had Apgar scores of 8 and 8, respectively. **D,** Late FHR decelerations. The amniotic fluid surrounding this fetus was meconium stained. Despite the late FHR decelerations, the variability remained acceptable. The infant was delivered by cesarean delivery and had an umbilical venous blood pH of 7.30. Apgar scores were 9 and 9, respectively.

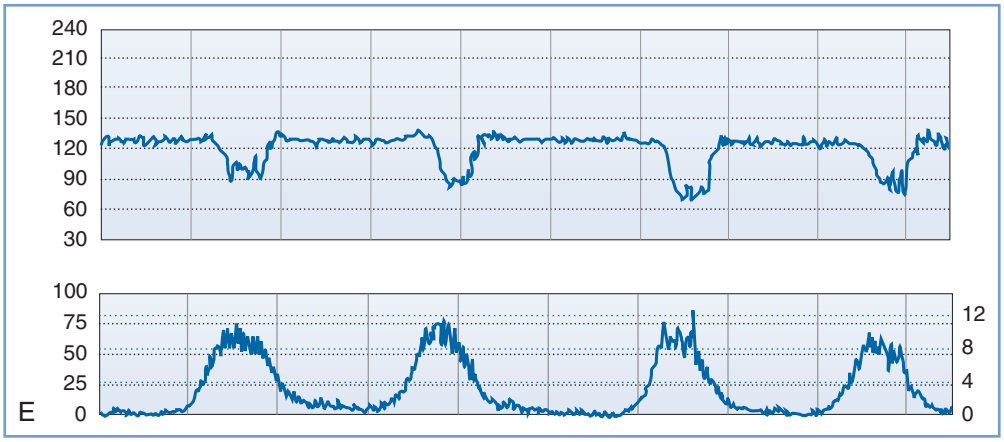

FIGURE 8-3, cont'd ■ **E,** Variable FHR decelerations. A tight nuchal cord was noted at low-forceps vaginal delivery. The infant had Apgar scores of 6 and 9, respectively. Numerical scales: *Left upper panel margin,* FHR in beats per minute; *left lower panel margin,* uterine pressure in mm Hg; *right lower panel margin,* uterine pressure in kilopascal (kPa).

electroencephalographic (EEG) activity, which abolishes FHR variability.

Clinically, the presence of normal FHR variability predicts early neonatal health, as defined by an Apgar score of greater than 7 at 5 minutes.[37,38] In a case series of monitored fetal deaths, no fetus had normal variability immediately before demise.[27] The differential diagnosis of decreased variability includes fetal hypoxia, fetal sleep state, fetal neurologic abnormality, and decreased CNS activity that results from exposure to drugs such as opioids.

Accelerations

Accelerations are abrupt changes in the FHR above the baseline. Beyond 32 weeks' gestation, an acceleration is defined by a peak of at least 15 bpm above the baseline, lasting at least 15 seconds. (Before 32 weeks' gestation, a peak of 10 bpm above the baseline, lasting at least 10 seconds, is required.[34]) A prolonged acceleration extends for at least 2 minutes; however, when greater than 10 minutes in duration, it is considered a change in baseline.[34] Antepartum FHR accelerations can occur in response to fetal movement and typically are a sign of fetal well-being; their presence indicates a reactive nonstress test. During the intrapartum period, the significance of FHR accelerations is less clear.[28,38] Although the presence of accelerations generally precludes the existence of significant fetal metabolic acidosis, in some cases intrapartum accelerations may indicate a vulnerable umbilical cord.

Decelerations

Decelerations are typically classified as early, late, or variable. **Early decelerations** occur simultaneously with uterine contractions and usually are less than 20 bpm below baseline. The onset and offset of each deceleration coincides with the onset and offset of the uterine contraction (see Figure 8-3). In animal models, head compression can precipitate early decelerations.[28] In humans, early decelerations are believed to result from reflex vagal activity secondary to mild hypoxia. Early decelerations are not ominous.

Late decelerations begin 10 to 30 seconds after the beginning of uterine contractions and end 10 to 30 seconds after the end of uterine contractions. Late decelerations are smooth and repetitive (i.e., they occur with each uterine contraction). Animal studies suggest that late decelerations represent a response to hypoxemia. The delayed onset of the deceleration reflects the time needed for the chemoreceptors to detect decreased oxygen tension and mediate the change in FHR by means of the vagus nerve.[28,39] Late decelerations may also result from decompensation of the myocardial circulation and myocardial failure. Unfortunately, clinical and animal studies suggest that late decelerations may be an oversensitive indication of fetal asphyxia.[28] However, the combination of late decelerations and decreased or absent FHR variability is an accurate, ominous signal of fetal compromise.[29,40,41]

Variable decelerations vary in depth, shape, and duration. They often are abrupt in onset and offset. Variable decelerations result from baroreceptor- or chemoreceptor-mediated vagal activity. Experimental models and clinical studies suggest that **umbilical cord occlusion,** either partial or complete, results in variable decelerations. During the second stage of labor, variable decelerations may result from compression of the fetal head. In this situation, dural stimulation leads to increased vagal discharge.[42] The healthy fetus can typically tolerate mild to moderate variable decelerations (not below 80 bpm) without decompensation. With prolonged, severe variable decelerations (< 60 bpm) or persistent fetal bradycardia, it is difficult for the fetus to maintain cardiac output and umbilical blood flow.[42]

Sinusoidal and **saltatory** patterns are two unusual FHR tracing results that may indicate fetal compromise. The sinusoidal FHR pattern is a regular, smooth, wavelike pattern that may signal fetal anemia.[27] Occasionally, maternal administration of an opioid can lead to a sinusoidal FHR pattern. The saltatory pattern consists of excessive alterations in variability (> 25 bpm) and may signal the occurrence of acute fetal hypoxia; there is a

weak association between this pattern and low Apgar scores.[27]

Limitations of Electronic Fetal Heart Rate Monitoring

Despite laboratory and clinical data suggesting that FHR monitoring accurately reflects fetal health, controversy exists regarding the ability of this assessment tool to improve fetal and neonatal outcomes. First described more than 40 years ago, the use of continuous electronic FHR monitoring increased dramatically to encompass 45% and 85% of the monitored deliveries by 1980 and 2002, respectively.[32] Retrospective reports of continuous FHR monitoring associate its use with a lower incidence of intrauterine fetal demise, neonatal seizures, and neonatal death.[43-45] By contrast, the only consistent finding from multiple case-control studies and more than a dozen prospective, randomized trials of electronic FHR monitoring (with control arms that employed intermittent FHR auscultation[46-48]) is an increased rate of operative delivery. In a meta-analysis of these trials, which included more than 50,000 women from several continents, the incidence of 1-minute Apgar scores less than 4 and neonatal seizures was decreased with the use of continuous FHR monitoring.[46-49] These results appear to suggest a correlation between abnormal FHR tracings and fetal acidemia.[41,50] An evaluation of the 2004 United States birth cohort data suggested that the use of electronic FHR monitoring was associated with a significant decrease in early neonatal and infant mortality, a decreased risk for 5-minute APGAR scores less than 4 in low-risk pregnancies, and a lower rate of neonatal seizures in high-risk pregnancies.[51]

It remains unclear why prospective studies have not confirmed greater benefit of the use of continuous electronic FHR monitoring during labor; the intensity of intrapartum assessment and care may be partially responsible. In prospective trials, women randomly assigned to receive intermittent FHR auscultation were monitored by dedicated nursing staff who provided intensive intrapartum care. By contrast, the historical cohort studies compared patients who received continuous electronic FHR monitoring and intensive intrapartum care with patients who had intermittent FHR auscultation with *nonintensive* nursing care. There are no published studies that randomly assigned a group of patients to receive no FHR monitoring; however, the continued high rate of intrapartum stillbirth in unmonitored births in the developing world suggests that FHR assessment may be beneficial.

Consistent with the findings of the prospective trials, the ACOG endorses the use of either intermittent auscultation or continuous electronic FHR monitoring during labor. In high-risk patients, the ACOG guidelines recommend that the obstetrician or nurse review the electronic FHR tracing every 15 minutes during the first stage of labor and every 5 minutes during the second stage. For low-risk patients, the intervals may be lengthened to 30 minutes for the first stage and 15 minutes for the second stage.[52] The optimal interval for intermittent FHR monitoring has not been studied, but the intervals suggested within the ACOG guidelines have some indirect support.[53] Adherence to these standards for intermittent auscultation may be difficult to achieve in the clinical setting; in one study, only 3% of parturients met these standards.[54]

Several hypotheses to account for the apparent failure of intrapartum FHR monitoring to reduce the incidence of cerebral palsy have been proposed and include (1) a large proportion of the asphyxial damage begins before the onset of labor; (2) catastrophic events (e.g., cord prolapse, placental abruption, uterine rupture) may not allow sufficient time for intervention before neurologic damage occurs; (3) a larger proportion of very low-birth-weight infants survive and thus contribute to the numbers with cerebral palsy; (4) infection is associated with abnormal FHR patterns and the subsequent development of cerebral palsy, and it is unclear that early intervention offers any benefit in such cases; and (5) the amount of asphyxia required to cause permanent neurologic damage approximates the amount that causes fetal death, leaving a narrow window for intervention.[55] The number of patients in whom cerebral palsy develops from intrapartum asphyxia is probably quite small.[55]

Limitations of FHR monitoring include a poor positive predictive value in distinguishing between abnormal FHR tracings and abnormal outcomes. Because of this imprecision, the ACOG recommended that abnormal FHR tracings be described with the term *nonreassuring fetal status* rather than *fetal distress* or *birth asphyxia*.[56] In one population-based study of California children with cerebral palsy, FHR tracings were retrospectively reviewed and compared with those of neurologically normal children (i.e., control subjects). A markedly higher incidence of tracings with late decelerations and decreased variability was found in children with cerebral palsy than in the control subjects. However, of the estimated 10,791 monitored infants weighing 2500 g or more who had these FHR abnormalities, only 21 (0.19%) had cerebral palsy, representing a false-positive rate of 99.8%.[57] Later case-control studies have yielded similar results.[16,58] A 2006 meta-analysis of 12 trials including 37,000 women suggested that electronic FHR monitoring has resulted in a decrease in the occurrence of seizures but no change in the incidence of neonatal mortality or cerebral palsy.[49] The authors suggested that electronic FHR monitoring resulted in one cesarean delivery for every 58 women monitored and that 661 women would need to be monitored to prevent one neonatal seizure.[49] Therefore, use of electronic FHR monitoring in combination with clinical and laboratory assessments has been proposed to enhance the prediction and perhaps the prevention of severe asphyxia, but with poor specificity.[16]

Further limitations of continuous FHR monitoring include (1) the poor intra-observer and inter-observer agreement despite the use of trained observers, (2) the required continual presence of a nurse or physician to assess the FHR tracing, (3) the inconvenience for the patient (e.g., confinement to bed and the application of monitor belts or a scalp electrode), and (4) the need to archive the FHR tracings as legal documents.[59-61]

Despite little evidence for its efficacy, Parer and King[62] have noted that obstetricians continue to rely heavily on

BOX 8-2 Three-Tier Fetal Heart Rate (FHR) Interpretation System

Category I tracings include all of the following:
- Baseline rate: 110-160 beats per minute (bpm)
- Baseline FHR variability: moderate
- Accelerations: present or absent
- Late or variable decelerations: absent
- Early decelerations: present or absent

Category II tracings include:
- All tracings not categorized as category I or category III
- Baseline FHR
  - Bradycardia not accompanied by absent baseline variability
  - Tachycardia
- Baseline FHR variability
  - Minimal baseline variability
  - Absent baseline variability not accompanied by recurrent decelerations
  - Marked baseline variability
- Accelerations
  - Absence of induced accelerations after fetal stimulation
- Periodic or episodic decelerations
  - Recurrent variable decelerations accompanied by minimal or moderate variability
  - Prolonged deceleration > 2 minutes but < 10 minutes
  - Recurrent late decelerations with moderate baseline variability
  - Variable decelerations with other characteristics such as slow return to baseline, overshoots, or shoulders

Category III tracings include either:
- Absent baseline FHR variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Modified from Macones GA, Hankins GDV, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. Obstet Gynecol 2008; 112:661-6.

FHR monitoring for at least the following three reasons: (1) professional obstetric organizations (e.g., the ACOG) advise some form of monitoring during labor, (2) electronic FHR monitoring is logistically easier and less expensive than one-on-one nursing care during labor, and (3) individual (often anecdotal) experiences cause "many obstetricians [to] believe that in their own hands FHR monitoring is … efficacious."[62]

In 2008 the National Institute of Child Health and Human Development sponsored a workshop that resulted in the publication of updated definitions, interpretation, and research guidelines for intrapartum electronic FHR monitoring.[34] The published report proposed a three-tier system for the categorization of FHR patterns (Box 8-2).[34] The ACOG described this system in subsequent 2009 practice bulletins with suggested options for management[32,63]:

Category I (normal): Strongly predictive of *normal* fetal acid-base status at the time of observation.

Category II (indeterminate): Not predictive of *abnormal* fetal acid-base status, but without adequate evidence to classify as normal or abnormal.

Category III (abnormal): Predictive of *abnormal* fetal acid-base status at the time of observation and thus requiring prompt evaluation.

In a multicenter review of 48,444 patients, Jackson et al.[64] observed that category I, II, and III FHR tracings were present 78%, 22%, and 0.004% of the time, respectively. Only 0.2% of newborns of women whose last 2 hours of labor had exclusively category I FHR tracings had low 5-minute Apgar scores followed by admission to a neonatal intensive care unit (NICU); in contrast, when more than 75% of the last 2 hours of labor showed category II FHR tracings, the incidence of low 5-minute Apgar scores with NICU admission increased to 0.7%.

A significant difficulty with the current three-tier system is the number and heterogeneity of fetuses with category II tracings.[65] A five-tier system has been proposed.[66,67] However, Elliott et al.[68] used specialized computer software to distinguish the five tiers among 2472 FHR tracings of near-term fetuses with and without known neonatal encephalopathy and blood gas abnormalities, and they found that a lack of specificity still occurred. A correlation between the frequency and duration of FHR abnormalities with worse neonatal outcome was observed; however, the electronic FHR patterns that identified 75% of the neonatal encephalopathy group also included 29% of the normal neonates.[68]

Methods for Improving the Efficacy of Electronic Fetal Heart Rate Monitoring

Several technologies have been employed to enhance the value of electronic FHR monitoring. To facilitate continual FHR assessment, many labor-and-delivery units transmit the tracings from the bedside to the nurses' station. Presumably, this practice facilitates a rapid response to worrisome FHR tracings.

Computerized algorithms may assist in the interpretation of FHR tracings. Although some studies have suggested that computerized analysis may be more accurate than traditional methods in identifying pregnancies with a pathologic neonatal outcome, others have not confirmed this finding.[69-73] As a result, none of these computerized methods has achieved widespread use.

Continuous FHR monitoring requires the patient to wear FHR and uterine contraction monitoring devices and remain within several feet of the monitor. An alternative is the use of telemetry, which transmits the FHR from the patient to the monitor and consequently allows ambulation. The low-risk patient who wishes to ambulate probably does not require continuous electronic FHR monitoring.

Electronic archiving allows for the electronic storage and retrieval of FHR tracings and eliminates the need for long-term storage of the paper record. The FHR tracing is a medicolegal document, and if it is lost, the plaintiff's lawyer may allege that the tracing was discarded intentionally because it was detrimental to the defendant.[74]

Supplemental Methods of Fetal Assessment

Electronic FHR monitoring is more than 99% accurate in predicting a 5-minute Apgar score greater than 7. Unfortunately, this monitoring also suffers from a lack of specificity; an abnormal FHR tracing has a false-positive rate of more than 99%.[52] As a consequence, clinicians have sought additional fetal assessment tools to assist in the identification of the compromised fetus with greater specificity.

Fetal scalp blood pH determination is an older method used to confirm or exclude the presence of fetal acidosis when FHR monitoring suggests the presence of fetal compromise. Suggested indications include the presence of decreased or absent FHR variability or persistent late or variable FHR decelerations.[27] The obstetrician inserts an endoscope into the vagina, makes a small laceration in the fetal scalp (or buttock), and uses a capillary tube to collect a sample of fetal capillary blood (Figure 8-4). The technical challenges of obtaining the sample and having readily available instrumentation to conduct the test have led most U.S. centers to abandon this technique. Although early studies suggested that fetal scalp sampling may decrease the cesarean delivery rate,[75] a 1994 study reported that there was no change in the rate of cesarean delivery or perinatal asphyxia when the technique was abandoned.[76] A similar, alternative method used in Europe evaluates the fetal blood sample for the presence of lactate. When compared with pH determination, an interpretable result is obtained more frequently with lactate determination primarily owing to a smaller volume of blood required; however, no differences in fetal/neonatal/infant outcomes have been observed in trials comparing the two methods.[77]

Fetal scalp stimulation can be performed during a vaginal examination either digitally or with an Allis clamp. The heart rate of a healthy, nonacidotic fetus accelerates in response to scalp stimulation; FHR acceleration is associated with a fetal pH of at least 7.19.[78,79]

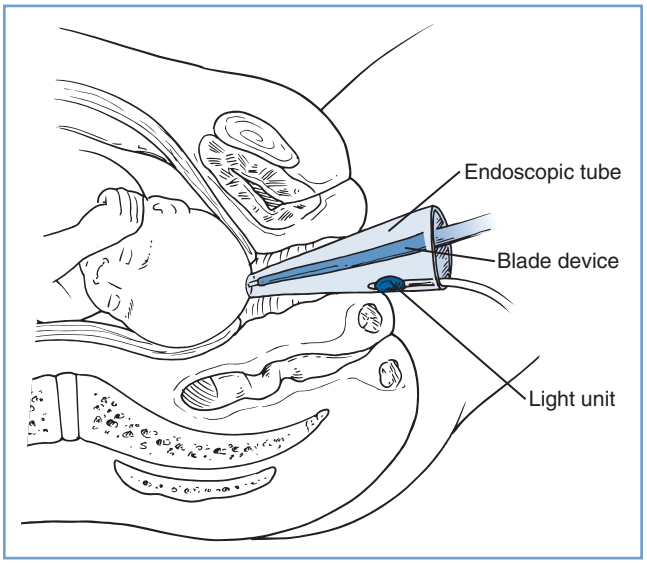

FIGURE 8-4 ■ Technique of obtaining fetal scalp blood during labor. (Redrawn from Creasy RK, Parer JT. Perinatal care and diagnosis. In Rudolph AM, editor. Pediatrics. 16th edition. New York, Appleton-Century-Crofts, 1977:121.)

Advocates of **vibroacoustic stimulation** contend that the application of an artificial larynx to the maternal abdomen results in an FHR acceleration in a healthy fetus and improves the specificity of FHR monitoring.[80] Vibroacoustic stimulation is used primarily for antepartum fetal assessment. A 2005 Cochrane review concluded that there is insufficient evidence from randomized clinical trials on which to make conclusions and recommendations regarding the use of vibroacoustic stimulation for the evaluation of fetal well-being during labor in the presence of a nonreassuring FHR tracing.[81] Nonetheless, direct fetal scalp stimulation and/or vibroacoustic stimulation have largely replaced the use of fetal scalp blood pH determination in most centers. A meta-analysis of intrapartum stimulation tests (i.e., fetal scalp blood pH determination, Allis clamp and digital fetal scalp stimulation, and vibroacoustic stimulation) found the tests to be equivalent in predicting fetal acidemia, with digital fetal scalp stimulation having the greatest ease of use.[82]

The intrapartum use of **umbilical artery velocimetry** has been used as an adjunct to FHR monitoring to assess fetal well-being, with mixed results (see Chapter 6).[83,84] The **biophysical profile (BPP),** which is composed of four ultrasonographic assessments and a nonstress test, has been observed antenatally to decrease the false-positive rate of a positive nonstress test (see Chapter 6); however, its value during intrapartum management is still under investigation.[85,86]

The presence of **meconium-stained amniotic fluid** has long been associated with an increased risk for depression at birth. Moderate to thick meconium is associated with lower Apgar scores, lower umbilical arterial blood pH, an increased incidence of neonatal seizures, and higher rates of cesarean delivery and admission to an intensive care nursery.[87-89] Although 5% to 20% of all deliveries are complicated by meconium-stained amniotic fluid, few of these infants experience neonatal depression. The odds ratio for complications is increased with meconium, but the majority of infants with neonatal complications have clear fluid.[87] Meconium-stained fluid has a poor positive predictive value and poor sensitivity in predicting adverse neonatal outcomes.[87] The physiology associated with the passage of meconium is incompletely understood. Ultrasonographic imaging suggests that the fetus regularly passes rectal contents into the amniotic fluid throughout gestation.[87] However, meconium-stained amniotic fluid is more common in pregnancies complicated by postdatism or fetal growth restriction. Putative triggers for the passage of meconium include umbilical cord compression and hypoxia. The presence of meconium combined with an abnormal FHR tracing or another risk factor (e.g., fetal growth restriction, postdatism) appears to be associated with an increased likelihood of neonatal depression.[88,89]

Among the pregnancies with meconium-stained amniotic fluid, approximately 5% develop significant neonatal respiratory compromise termed **meconium aspiration syndrome.**[90-92] Antenatal risk factors for this syndrome

include moderate or thick meconium (suggesting recent passage and lower amniotic fluid volume) and abnormal FHR tracings.[91] The lung injury likely originates from intrapartum fetal hypoxia.[91,93,94] Oropharyngeal suctioning at delivery has not proved beneficial; randomized controlled trials have suggested that vigorous newborns do not need aggressive airway cleansing with tracheal intubation (see Chapter 9).[91,95] Aggressive obstetric management of postdate pregnancies (i.e., avoidance of postdatism) has led to a substantial decrease in the incidence of meconium-stained amniotic fluid and meconium aspiration syndrome.[92]

New Technologies for Fetal Assessment

Because FHR monitoring provides only an *indirect* measure of fetal oxygenation and acid-base status, alternative technologies, such as transcutaneous Po_2, Pco_2, and pH monitors have been developed to provide a more direct assessment.[96-98] However, the use of these monitors has been limited by technical difficulties in the application of the probe(s), drift in the baseline readings, artifactual measurements, and difficulties in establishing diagnostic criteria for intervention.

ST waveform analysis of fetal electrocardiography is a technique proposed to enhance intrapartum fetal assessment. Fetal hypoxia induces changes in the ECG morphology of the ST segment and T wave. ST waveform analysis enhances the specificity of FHR tracings,[99,100] but not the sensitivity.[101] A 2006 meta-analysis of randomized controlled trials, accounting for almost 10,000 deliveries, of automatic ST waveform analysis (the STAN S21 system, Neoventa Medical, Göteborg, Sweden) demonstrated that a combination of FHR monitoring and ST waveform analysis reduced the risk for severe fetal acidosis and the incidence of neonates with encephalopathy.[102-104] No differences in the rates of cesarean delivery, 5-minute Apgar scores less than 7, or admission to the NICU were observed.[100,102,103,105,106] In a recent trial of 5600 parturients randomized to fetal observation with and without ST waveform analysis, Westerhuis et al.[107] observed a lower rate of acidosis in the ST waveform analysis group but no other differences in outcome (e.g., operative deliveries or hypoxic ischemic encephalopathy). An unmasked, randomized controlled trial of ST waveform analysis is currently being conducted to assess neonatal outcomes in 11,000 parturients within the U.S. Maternal-Fetal Medicine Network.

Reflectance pulse oximetry has been adapted for assessment of fetal oxygenation. The U.S. Food and Drug Administration (FDA) approved the Nellcor N-400 fetal pulse oximeter (Nellcor, Puritan Bennett, Pleasanton, CA) for use in the setting of a term, singleton fetus at more than 36 weeks' gestation with a vertex presentation and a nonreassuring FHR pattern after rupture of membranes.[108,109] The most commonly used probes are held in place against the fetal head or cheek with pressure from the cervix. A reliable pulse oximetry signal can be obtained in 60% to 70% of cases; however, environmental factors and physiologic events (e.g., fetal scalp congestion, thick fetal hair, vernix caseosa, uterine activity, movement artifacts) may affect the accuracy.[109] The saturation measurements are averaged every 45 seconds,[108] and the human fetus typically demonstrates an oxygen saturation of 35% to 65%. Animal and human data suggest that metabolic acidosis does not occur until the oxygen saturation has fallen below 30% for at least 10 minutes when measured with this device.[110,111] Pulse oximetry does not predict acidosis accurately in fetuses with severe variable decelerations during the second stage of labor.[112] Moreover, the accuracy of fetal pulse oximetry readings lower than 30% in human fetuses has been challenged.[108,113] Fetal pulse oximetry used in conjunction with FHR monitoring appears to reduce the rate of cesarean delivery for a nonreassuring FHR tracing; however, this reduction is offset by an increased rate of cesarean delivery for dystocia.[114-116] The absence of an effect on the overall cesarean delivery rate prompted the ACOG to withhold an endorsement of fetal pulse oximetry pending further investigation of its use.[109] A Spanish trial randomly allocated 180 women with nonreassuring intrapartum FHR tracings to receive further evaluation with either ST waveform analysis or pulse oximetry; the investigators observed a lower cesarean delivery rate in the ST waveform analysis group, with fewer low 1-minute APGAR scores and improved umbilical cord venous blood pH measurements.[117]

Proton magnetic resonance spectroscopy (^{1}H MRS) can obtain metabolic information from human and animal brains, and early investigations suggest an ability to assess fetal brain oxygenation.[118-120] ^{1}H MRS has proved useful in the evaluation of hypoxic-ischemic encephalopathy and metabolic disorders in pediatric patients. This technique can also measure levels of the metabolites lactate, *N*-acetylaspartate, creatine, choline, and inositol in fetal and neonatal neural tissue. It has been applied experimentally in a case series of fetuses with fetal growth restriction.[121] Although these measurements can be correlated with the level of tissue oxygenation, the clinical use of this technique as a means of fetal assessment remains unclear.[122]

Near-infrared spectroscopy (NIRS) has the potential to directly measure fetal tissue oxygenation.[123] Transabdominal NIRS has been used in research settings to assess placental oxygenation.[124] NIRS has gained some acceptance in assessing the effects of clinical interventions on neonatal organ oxygenation at the bedside. NIRS can detect changes in the ratio of reduced to oxygenated cytochrome-*c* oxidase in the brain and in the ratio of oxygenated to deoxygenated hemoglobin in the blood perfusing the brain; the technique can also measure the total amount of hemoglobin in the tissue, thereby allowing an estimation of tissue blood perfusion.[123] In theory, NIRS offers the opportunity to determine whether neurons are at risk for hypoxic damage; currently, the technique is being correlated with other measures of fetal well-being, such as periodic FHR changes and umbilical cord blood pH measurements at delivery. However, similar to fetal pulse oximetry, NIRS technology is limited by a frequent (approximately 20%) inability to obtain interpretable measurements and the need to correlate the measurements with long-term neurodevelopmental outcomes. As a consequence, NIRS remains a research rather than a clinical tool at this time.[123]

TABLE 8-1 Various Intrauterine Resuscitative Measures for Category II or Category III Fetal Heart Rate (FHR) Tracings or Both

Goal	Associated Fetal Heart Rate Abnormality*	Potential Intervention(s)†
Promote fetal oxygenation and improve uteroplacental blood flow	Recurrent late decelerations Prolonged decelerations or bradycardia Minimal or absent FHR variability	Initiate lateral positioning (either left or right) Administer supplemental maternal oxygen Administer intravenous fluid bolus Reduce uterine contraction frequency
Reduce uterine activity	Tachysystole with category II or III tracing	Discontinue oxytocin or cervical ripening agents Administer tocolytic medication (e.g., terbutaline)
Alleviate umbilical cord compression	Recurrent variable decelerations Prolonged decelerations or bradycardia	Initiate maternal repositioning Initiate amnioinfusion If prolapsed umbilical cord is noted, elevate the presenting fetal part while preparations are underway for operative delivery

*Evaluation for the underlying suspected cause(s) is also an important step in management of abnormal FHR tracings.
†Depending on the suspected underlying cause(s) of FHR abnormality, combining multiple interventions simultaneously may be appropriate and potentially more effective than doing individually or serially (Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. Obstet Gynecol 2005;105:1362-8).
From American College of Obstetricians and Gynecologists. Management of intrapartum fetal heart rate tracings. ACOG Practice Bulletin No. 116, November 2010. (Obstet Gynecol 2010; 116:1232-40.)

INTRAPARTUM FETAL THERAPY

The ACOG has suggested intrapartum management be based on the three-tier evaluation framework.[63] A category I tracing requires only periodic reevaluation, whereas a category III tracing should prompt preparation for delivery if intrauterine resuscitative measures do not result in improvement of the FHR in a timely manner (Table 8-1). Category II tracings should be evaluated for the presence of moderate variability and spontaneous or provoked accelerations, which suggest a nonacidotic fetus (see earlier discussion). The identification of potential intrapartum fetal compromise with a category II or III tracing should prompt a careful assessment of maternal, placental, and fetal factors. Clinical history, physical findings, laboratory findings, and fetal monitoring (e.g., FHR, ultrasonography) should be evaluated in an attempt to identify an etiology for poor tracings. If intrauterine resuscitative measures do not result in an improved category II tracing, or if the FHR tracing progresses to category III, then the obstetrician should consider prompt delivery.[63]

Correctable **maternal factors** that may contribute to fetal compromise include pathologic states that result in hypoxemia or decreased oxygen delivery to the placenta. **Respiratory failure** due to long-standing diseases (e.g., asthma) can be determined from the history and physical findings, whereas additional laboratory measurements may be necessary to diagnose pneumonia or pulmonary edema as an underlying cause. **Decreased oxygen delivery** to the placenta may result from acute (e.g., sepsis, hypotension) or chronic conditions. **Decreased uteroplacental perfusion** can result from reduced maternal cardiac output (e.g., cardiovascular disease) or chronic vascular disease (e.g., chronic hypertension, diabetes). Dehydration from prolonged labor is a more subtle cause of diminished uteroplacental perfusion.

Attention to the etiology of fetal hypoxemia and institution of appropriate treatments may mitigate fetal compromise. Administration of supplemental oxygen may enhance fetal oxygenation, even in the previously normoxemic mother; however, whether maternal oxygen therapy improves fetal outcome remains unclear.[125-128]

Uterine hypertonus or frequent uterine contractions (tachysystole), which may result in decreased uteroplacental perfusion, are known risks of oxytocin or prostaglandin compounds used for the induction of labor. Uterine contractions constrict the uterine spiral arteries, decreasing oxygen delivery to the placenta. A rare cause of fetal compromise is **uterine rupture,** which may result from uterine hyperstimulation, particularly in the setting of a uterine scar. **Placental abruption,** which may result in a partial or complete cessation of oxygen transfer to the fetus, can be associated with chronic or acute diseases. Long-standing vascular diseases produced by chronic hypertension or smoking, as well as acute factors such as cocaine abuse and abdominal trauma, can precipitate a placental abruption.

The treatment of uteroplacental causes of fetal compromise includes correction of uterine hypertonus or tachysystole by cessation of oxytocin infusion and the removal of cervical ripening agents (see Table 8-1). Oxytocin has a plasma half-life of 1 to 6 minutes; consequently, it may take several minutes for the hypertonus to be relieved. Alternatively, a tocolytic agent (e.g., terbutaline, nitroglycerin) may be administered. Normal maternal circulation should be maintained by avoiding aortocaval compression, expanding intravascular volume, and giving a vasopressor (e.g., phenylephrine, ephedrine) for treatment of hypotension.[129]

Fetal factors may contribute to fetal hypoxemia and acidosis. **Umbilical cord prolapse** through the cervix causes cord compression and often results in sudden fetal bradycardia. In the vast majority of circumstances, treatment of a prolapsed cord consists of manual elevation of the fetal head until emergency cesarean delivery can be accomplished. Only rarely should the umbilical cord be returned into the uterus and expectant care attempted.[130]

Reports from the developing world indicate that, in some cases, expeditious vaginal delivery may produce acceptable neonatal outcome.[131] Alternative methods to decompress a prolapsed umbilical cord include the use of the Trendelenburg position or an infusion of 500 to 700 mL of 0.9% saline into the maternal bladder until an expedited delivery can occur.[130,132,133]

Uterine contractions represent a much more common cause of **umbilical cord compression** and can manifest as variable FHR decelerations or bradycardia. **Oligohydramnios** is a risk factor for this type of cord compression, and a **change in maternal position** or the use of **saline amnioinfusion** may be therapeutic. Amnioinfusion has been observed to reduce the frequency of severe variable FHR decelerations and the incidence of cesarean delivery and to increase the umbilical cord blood pH in women with preterm premature rupture of membranes, oligohydramnios, or variable FHR decelerations during labor.[134,135] Systematic reviews have produced different conclusions as to whether *prophylactic* intrapartum amnioinfusion in patients with oligohydramnios is superior to *therapeutic* amnioinfusion in patients with both oligohydramnios and FHR abnormalities.[136,137]

Initial studies suggested that in patients with thick, meconium-stained amniotic fluid, amnioinfusion might decrease the incidence of meconium aspiration syndrome and fetal acidosis.[138-140] However, meta-analyses of studies suggest no benefit of amnioinfusion in the setting of meconium unless decelerations due to oligohydramnios are present.[141-145]

Saline amnioinfusion requires a dilated cervix, ruptured membranes, and the placement of an intrauterine catheter. Equipment that allows simultaneous saline amnioinfusion and measurement of intrauterine pressure is preferred. Either normal saline or lactated Ringer's solution may be infused as a bolus or as a continuous infusion.[146] The ideal rate of infusion has not been determined, but a commonly used regimen consists of a bolus of as much as 800 mL (infused at a rate of 10 to 15 mL/min) followed by either a continuous infusion at a rate of 3 mL/min or repeated boluses of 250 mL, as needed.[146] The necessity of either an infusion pump or a fluid warmer has not been demonstrated.[146] Alleviation of abnormal FHR patterns generally requires 20 to 30 minutes.[146]

Although most studies suggest that amnioinfusion is safe for the mother and fetus, some complications have been reported. Overdistention of the uterus and a higher rate of maternal infections and maternal respiratory distress, including cases of fatal amniotic fluid embolism, have occurred.[143,147-149] A causal relationship between amniotic fluid embolism and amnioinfusion has yet to be determined. Overdistention of the uterus may be controlled with proper documentation of fluid loss from the uterus during infusion, the provision of amnioinfusion by gravity instead of an infusion pump, and the use of ultrasonography to evaluate the fluid volume.[147]

Maternal fever may increase fetal oxygen consumption. Obstetricians should treat maternal fever with acetaminophen, a cooling blanket, and antibiotics as indicated to maintain maternal and fetal euthermia. **Hyperglycemia** also increases fetal oxygen consumption, so administration of a large bolus of a glucose-containing solution is contraindicated.

Fetal cardiac failure results in inadequate umbilical blood flow and fetal hypoxemia and acidosis. **Fetal anemia** due to maternal isoimmunization, fetal hemoglobinopathy, or fetal hemorrhage results in diminished fetal oxygen-carrying capacity. There are few options for the treatment of fetal cardiac failure or anemia during labor.

Standardization of FHR tracing interpretation and staged levels of intervention based on likely etiology will assist obstetric management. If intrapartum assessment suggests the presence of fetal compromise and fetal therapy is unsuccessful, the obstetrician should effect an expeditious, atraumatic delivery.

KEY POINTS

- A normal FHR tracing accurately predicts fetal well-being. An abnormal tracing is not very specific in the prediction of fetal compromise. Exceptions include the fetus with a prolonged bradycardia or the fetus with late FHR decelerations and absence of variability; both suggest a high likelihood of fetal compromise.
- Large, prospective, randomized studies have not confirmed that continuous electronic FHR monitoring confers substantial clinical benefit over intermittent FHR auscultation as performed by dedicated labor nurses.
- The specificity of FHR monitoring may be augmented by the use of fetal scalp stimulation, fetal vibroacoustic stimulation, and fetal scalp blood sampling. Pulse oximetry increases the specificity of FHR monitoring but does not reduce the rate of cesarean delivery.
- When possible, FHR resuscitation *in utero* is preferable to emergency delivery of an acidotic fetus.
- Saline amnioinfusion effectively prevents or relieves variable decelerations caused by umbilical cord compression and may improve perinatal outcomes in patients with oligohydramnios.

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CHAPTER 9

Neonatal Assessment and Resuscitation

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CHAPTER OUTLINE

The transition from intrauterine to extrauterine life represents the most important adjustment that a neonate will make. Occurring uneventfully after most deliveries, this transition is dependent on the anatomic and physiologic condition of the infant, the ease or difficulty of the delivery, and the extrauterine environmental conditions. When the transition is unsuccessful, prompt assessment and supportive care must be initiated immediately.

At least one person skilled in neonatal resuscitation should be present at every delivery.[1] The resuscitation team may include personnel from the pediatrics, anesthesiology, obstetrics, respiratory therapy, and nursing services. The composition of the team varies among institutions, but some form of 24-hour coverage should be present within all hospitals that provide labor and delivery services.[1] A multidisciplinary team should participate in the process of ensuring that appropriate personnel and equipment are available for neonatal resuscitation.[1]

All personnel working in the delivery area should receive basic training in neonatal resuscitation to ensure prompt initiation of care before the arrival of the designated resuscitation team. The 2010 American Heart Association (AHA) Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care led to the publication of updated guidelines for neonatal resuscitation.[2] Changes in these guidelines reflected a review of scientific evidence by members of the American Academy of Pediatrics (AAP), the AHA, and the International Liaison Committee on Resuscitation. These guidelines have been incorporated into the Neonatal Resuscitation Program (NRP), which is the standardized training and certification program administered by the AAP. The NRP, which was originally sponsored by the AAP and the AHA in 1987, is designed to be appropriate for all personnel who attend deliveries. To ensure the implementation of current guidelines for neonatal resuscitation, the AAP recommends that at least one NRP-certified practitioner attend every delivery.[3,4]

Both the American Society of Anesthesiologists (ASA) and the American College of Obstetricians and Gynecologists (ACOG) have published specific goals and guidelines for neonatal resuscitation (Box 9-1).[5] The ASA has emphasized that a single anesthesiologist should not be expected to assume responsibility for the concurrent care of both the mother and her child. Rather, a second anesthesia provider or a qualified individual from another service should assume responsibility for the care of the neonate, except in an unforeseen emergency.

In clinical practice, anesthesiologists often are involved in neonatal resuscitation.[6,7] Heyman et al.[7] observed that anesthesia personnel were involved in neonatal resuscitation in 99 (31%) of 320 selected Midwestern community hospitals. In 13.4% of these hospitals, the individual who administered anesthesia to the mother was also responsible for the care of the neonate; in 6.8% of these institutions, a second anesthesia provider typically assumed primary responsibility for the neonate. In a larger survey of obstetric anesthesia workforce patterns within the United States, Bucklin et al.[6] found that fewer anesthesiologists were involved in neonatal resuscitation in 2001 than in 1981, with this practice occurring in less than 5% of cesarean deliveries.

BOX 9-1 Optimal Goals for Anesthesia Care in Obstetrics:

NEONATAL RESUSCITATION

Personnel other than the surgical team should be immediately available to assume responsibility for resuscitation of the depressed neonate. The surgeon and anesthesiologist are responsible for the mother and may not be able to leave her to care for the neonate, even when a neuraxial anesthetic is functioning adequately. Individuals qualified to perform neonatal resuscitation should demonstrate:

- Proficiency in rapid and accurate evaluation of the neonate's condition, including Apgar scoring
- Knowledge of the pathogenesis of a depressed neonate (acidosis, drugs, hypovolemia, trauma, anomalies, and infection) as well as specific indications for resuscitation
- Proficiency in neonatal airway management, laryngoscopy, endotracheal intubations, suctioning of airways, artificial ventilation, cardiac massage, and maintenance of thermal stability

In larger maternity units and those functioning as high-risk centers, 24-hour in-house anesthesia, obstetric, and neonatal specialists are usually necessary.

Modified from a joint statement from the American College of Obstetricians and Gynecologists and the American Society of Anesthesiologists. Optimal goals for anesthesia case in obstetrics. Approved by the American Society of Anesthesiologists in October 2008. (See Appendix C for full document.)

Despite this relatively low incidence of primary involvement, the anesthesiologist is often asked to provide assistance in cases of difficult airway management or when members of the neonatal resuscitation team have not yet arrived. The anesthesiologist should be prepared to provide assistance, provided that such care does not compromise the care of the mother. A study of University of Pennsylvania anesthesiology residency program graduates from 1989 to 1999 revealed that, despite a desire to be certified in neonatal resuscitation, most anesthesiologists were not.[8]

In a 1991 review of the ASA Closed-Claims Database, 13% of obstetric anesthesia malpractice claims were related to neonatal resuscitation, including delayed or failed tracheal intubation and an unrecognized esophageal intubation.[9] Another review of obstetric anesthesia–related lawsuits from 1985 to 1993 demonstrated that 12 (17%) of the 69 cases involved claims of inadequate neonatal resuscitation by anesthesia personnel[7]; 10 of these 12 cases resulted in payment to the plaintiff. Written hospital policies should identify the personnel responsible for neonatal resuscitation; obstetric anesthesia providers should also maintain a high level of skill in neonatal resuscitation.

TRANSITION FROM INTRAUTERINE TO EXTRAUTERINE LIFE

Circulation

At birth, the circulatory system changes from a fetal circulation pattern (which is in parallel), through a transitional circulation, to an adult circulation pattern (which is in series) (Figure 9-1).[10] In the fetus, blood from the placenta travels through the umbilical vein and the ductus venosus to the inferior vena cava and the right side of the heart. The anatomic orientation of the inferior vena caval–right atrial junction favors the shunting (i.e., streaming) of this well-oxygenated blood through the foramen ovale to the left side of the heart. This well-oxygenated blood is pumped through the ascending aorta, where branches that perfuse the upper part of the body (e.g., heart, brain) exit proximal to the entrance of the ductus arteriosus.[11] Desaturated blood returns to the heart from the upper part of the body by means of the superior vena cava. The anatomic orientation of the superior vena caval–right atrial junction favors the streaming of blood into the right ventricle. Because fetal pulmonary vascular resistance is higher than systemic vascular resistance (SVR), approximately 90% of the right ventricular output passes through the ductus arteriosus and enters the aorta distal to the branches of the ascending aorta and aortic arch; therefore, less well-oxygenated blood perfuses the lower body, which consumes less oxygen than the heart and brain.

At the time of birth and during the resulting circulatory transition, the amount of blood that shunts through the foramen ovale and ductus arteriosus diminishes and the flow becomes bidirectional. Clamping the umbilical cord (or exposing the umbilical cord to room air) results in increased SVR. Meanwhile, expansion of the lungs and increased alveolar oxygen tension and pH result in decreased pulmonary vascular resistance and subsequently greater flow of pulmonary artery blood through the lungs.[12,13] Increased pulmonary artery blood flow results in improved oxygenation and higher left atrial pressure; the latter leads to a diminished shunt across the foramen ovale. Increased Pao_2 and SVR and decreased pulmonary vascular resistance result in a constriction of the ductus arteriosus.[14,15] Together, these changes in vascular resistance result in functional closure of the foramen ovale and the ductus arteriosus. This process does not occur instantaneously, and arterial oxygen saturation (Sao_2) remains higher in the right upper extremity (which is preductal) than in the left upper extremity and the lower extremities until blood flow through the ductus arteriosus is minimal.[16] Differences in Sao_2 are usually minimal by 10 minutes and absent by 24 hours after birth. Provided that there is no interference with the normal drop in pulmonary vascular resistance, both the foramen ovale and the ductus arteriosus close functionally, and the infant develops an adult circulation (which is in series).

Persistent fetal circulation—more correctly called **persistent pulmonary hypertension of the newborn—** can occur when the pulmonary vascular resistance remains elevated at the time of birth. Factors that may contribute to this problem include hypoxia, acidosis, hypovolemia, and hypothermia.[13,17] Maternal use of nonsteroidal anti-inflammatory drugs may also cause premature constriction of the ductus arteriosus in the fetus and thus predispose to persistent pulmonary hypertension of the newborn.[18]

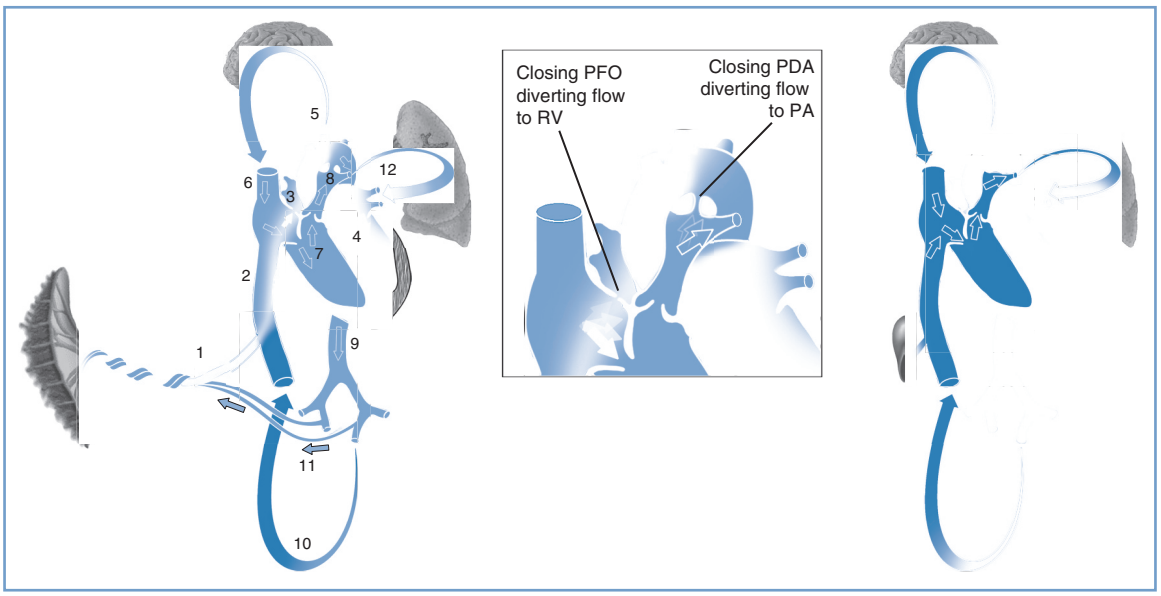

FIGURE 9-1 ■ Modification of blood flow patterns from the fetal (*left*), via the transitional (*center*), to the neonatal (*right*) circulation. In the fetal circulation, oxygenated blood (*white*) from the placenta travels through the umbilical vein (*1*) into the ductus venosus and the inferior vena cava (*2*). The majority of oxygenated blood passes through the patent foramen ovale (PFO) from the right atrium to the left atrium (*3*) and ventricle (*4*), and distributes this blood to the brain (*5*). The deoxygenated blood (*blue*) from the brain and upper extremities enters the superior vena cava, mixing with a small portion of the oxygenated blood in the right atrium, before entering the right ventricle (RV, *7*). The mostly deoxygenated blood is transported into the pulmonary artery where the majority is diverted through the patent ductus arteriosus (PDA, *8*) into the descending aorta (*9*), thereby bypassing the lungs. Some blood enters the lower body (*10*), but the majority returns to the placenta via the umbilical arteries (*11*). A small amount of blood from the pulmonary artery enters the lungs (*12*). During the transitional circulation, which occurs over a few days, the PFO closes, diverting blood from the right atrium to the right ventricle. Closure of the PDA diverts deoxygenated blood through the pulmonary arteries to the lungs. The neonatal circulation separates the oxygenated and deoxygenated blood flow pathways. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Respiration

Fetal breathing movements have been observed *in utero* as early as 11 weeks' gestation. These movements increase with advancing gestational age but undergo a marked reduction within days of the onset of labor. They are stimulated by hypercapnia and maternal smoking and are inhibited by hypoxia and central nervous system (CNS) depressants (e.g., barbiturates). Under normal conditions, this fetal breathing activity results only in the movement of pulmonary dead space.[19]

The fetal lung contains a liquid composed of an ultrafiltrate of plasma, which is secreted by the lungs in utero[20]; the volume of this lung liquid is approximately 30 mL/kg. Partial reabsorption of this liquid occurs during labor and delivery, and approximately two thirds is expelled from the lungs of the term neonate by the time of delivery.[21] Small preterm infants and those requiring cesarean delivery may have a greater amount of residual lung liquid after delivery. These infants experience less chest compression at delivery than infants who are larger or delivered vaginally; this difference can lead to difficulty in the initiation and maintenance of a normal breathing pattern. Retained fetal lung liquid is the presumed cause of **transient tachypnea of the newborn (TTN).**[22]

The first breath occurs approximately 9 seconds after delivery. Air enters the lungs as soon as the intrathoracic pressure begins to fall. This air movement during the first breath is important, because it establishes the neonate's functional residual capacity (Figure 9-2).

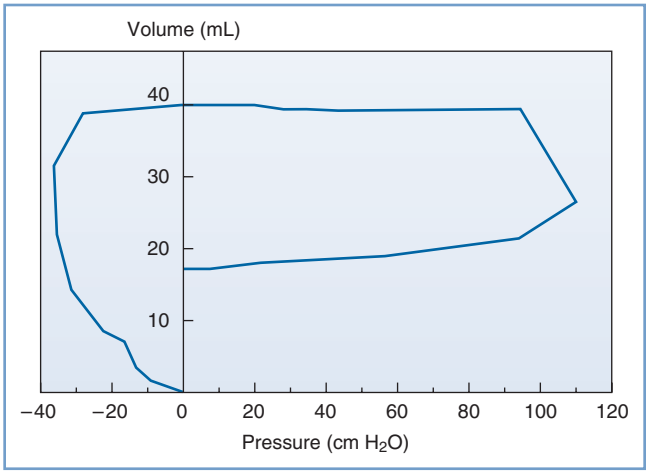

FIGURE 9-2 ■ Typical pressure-volume loop of the first breath. The intrathoracic pressure falls to −30 to −40 cm H_2O, drawing air into the lungs. The expiratory pressure is much greater than the inspiratory pressure. (Modified from Milner AD, Vyas H. Lung expansion at birth. J Pediatr 1982; 101:881.)

Lung inflation is a major physiologic stimulus for the release of lung surfactant into the alveoli.[23] Surfactant, which is necessary for normal breathing, is present within the alveolar lining cells by 20 weeks' gestation[24] and within the lumen of the airways by 28 to 32 weeks' gestation. However, significant amounts of surfactant do not appear in terminal airways until 34 to 38 weeks'

gestation unless surfactant production has been stimulated by chronic stress or maternal corticosteroid administration.[25]

Stress during labor and delivery can lead to gasping efforts by the fetus, which may result in the inhalation of amniotic fluid into the lungs.[26] This event can produce problems if the stress causes the fetus to pass meconium into the amniotic fluid before gasping.

Catecholamines

Transition to extrauterine life is associated with a catecholamine surge, which may be necessary for the process to be successful. In chronically catheterized sheep, catecholamine levels begin to rise a few hours before delivery and may be higher at the time of delivery than at any other time during life.[27] Catecholamines have an important role in the following areas: (1) the production and release of surfactant, (2) the mediation of preferential blood flow to vital organs during the period of stress that occurs during every delivery, and (3) thermoregulation of the neonate.

Thermal Regulation

Thermal stress challenges the neonate in the extrauterine environment. Neonates raise their metabolic rates and release norepinephrine in response to cold; this response facilitates the oxidation of brown fat, which contains numerous mitochondria. The oxidation results in **nonshivering thermogenesis,** the major mechanism for neonatal heat regulation.[28] This process may lead to significant oxygen consumption, especially if the neonate has not been dried off and kept in an appropriate thermoneutral environment, such as a radiant warmer. Thermal stress is an even greater problem in infants with low fat stores, such as preterm infants or infants who are small for gestational age. An alternative method to eliminate heat loss from evaporation is to provide an occlusive wrap rather than drying the infant. For infants born at less than 28 weeks' gestation, the use of polythene wraps or bags is recommended to minimize heat loss.[29,30] The maintenance of a neutral thermal environment (i.e., 34° to 35° C) is recommended. However, in the neonate with a perinatal brain injury, mild hypothermia therapy through selective head or whole body cooling is initiated in the first 6 hours of life and may be neuroprotective in the setting of hypoxia-ischemia.[31,32] Hyperthermia may worsen neurologic outcomes and should be avoided.[2,33] Hypothermia therapy, via selective head cooling or whole body hypothermia, is continued for 72 hours after initiation. Consequently, if an infant is delivered at a center where hypothermia therapy is unavailable, passive cooling can be initiated by turning the radiant warmer off while awaiting infant transfer.

Administration of epidural analgesia during labor is associated with an increase in maternal and fetal temperature.[34] Concern has been expressed that the temperature elevation associated with intrapartum epidural analgesia might result in an increase in the frequency of neonatal sepsis evaluations.[34,35] However, a number of variables (e.g., preeclampsia/hypertension, gestational age, birth weight, meconium aspiration, respiratory distress at birth, hypothermia at birth, and group B beta-hemolytic streptococcal colonization of the maternal birth canal) have been observed to be strong predictors of the performance of neonatal sepsis evaluations, whereas maternal fever and epidural analgesia have not.[36] Confounding variables may influence the findings of these types of association studies; patients who choose either to receive or not receive epidural analgesia may be inherently different. The incidence of actual neonatal sepsis is not different in term infants whose mothers either did or did not receive epidural analgesia.

ANTENATAL ASSESSMENT

Approximately 10% of neonates require some level of resuscitation.[7] The need for resuscitation can be predicted before labor and delivery with approximately 80% accuracy on the basis of a number of antepartum factors (Box 9-2).

Preterm delivery increases the likelihood that the neonate will require resuscitation. When a mother is admitted with either preterm labor or premature rupture of membranes, plans should be made for neonatal care in the event of delivery. The antenatal assessment of gestational age is based on the presumed date of the last menstrual period, the fundal height, and ultrasonographic measurements of the fetus. Unfortunately, it may be difficult to assess gestational age accurately, because menstrual dates may be unknown or incorrect, the fundal height may be affected by abnormalities of fetal growth or amniotic fluid volume, and ultrasonographic assessment of fetal age is less precise after mid pregnancy. The assessment of gestational age is most accurate in patients who receive prenatal care in early pregnancy. An accurate approximation of gestational age enables the health care team to plan for the needs of the neonate and to counsel the parents regarding neonatal morbidity and mortality. These plans and expectations must be formulated with caution and flexibility, because the antenatal assessment may not accurately predict neonatal size, maturity, and/or condition at delivery.

A variety of **intrauterine insults** can impair the fetal transition to extrauterine life. For example, neonatal depression at birth can result from acute or chronic uteroplacental insufficiency or acute umbilical cord compression. Chronic uteroplacental insufficiency, regardless of its etiology, may result in fetal growth restriction. Fetal hemorrhage, viral or bacterial infection, meconium aspiration, and exposure to opioids or other CNS depressants also can result in neonatal depression. Although randomized trials have not confirmed that fetal heart rate (FHR) monitoring improves neonatal outcome, a nonreassuring FHR tracing is considered a predictor of the need for neonatal resuscitation.[37]

Studies have evaluated the use of fetal pulse oximetry for the evaluation of fetal well-being during labor. This technique involves the transcervical insertion of a flexible fetal oxygen sensor until it rests against the fetal cheek. A randomized trial found that use of the fetal pulse oximeter in conjunction with FHR monitoring led to a

BOX 9-2 Risk Factors Suggesting a Greater Need for Neonatal Resuscitation

Antepartum Risk Factors

- Maternal diabetes
- Hypertensive disorder of pregnancy
- Chronic hypertension
- Fetal anemia or isoimmunization
- Previous fetal or neonatal death
- Bleeding in second or third trimester
- Maternal infection
- Maternal cardiac, pulmonary, renal, thyroid, or neurologic disease
- Polyhydramnios
- Oligohydramnios
- Premature rupture of membranes
- Fetal hydrops
- Post-term gestation
- Multiple gestation
- Discrepancy between fetal size and dates (i.e., last menstrual period)
- Drug therapy (e.g., lithium carbonate, magnesium, adrenergic-blocking drugs)
- Maternal substance abuse
- Fetal malformation
- Diminished fetal activity
- No prenatal care
- Maternal age > 35 years

Intrapartum Risk Factors

- Emergency cesarean delivery
- Forceps or vacuum-assisted delivery
- Breech or other abnormal presentation
- Preterm labor
- Precipitous labor
- Chorioamnionitis
- Prolonged rupture of membranes (> 18 hours before delivery)
- Prolonged labor (> 24 hours)
- Macrosomia
- Category II or III fetal heart rate patterns
- Use of general anesthesia
- Uterine tachysystole with fetal heart rate changes
- Maternal administration of opioids within 4 hours of delivery
- Meconium-stained amniotic fluid
- Prolapsed umbilical cord
- Placental abruption
- Placenta previa
- Significant intrapartum bleeding

Modified from Textbook of Neonatal Resuscitation. 6th edition. Elk Grove Village, IL, American Academy of Pediatrics and American Heart Association, 2011:216.

reduction in the number of cesarean deliveries performed due to a nonreassuring FHR tracing.[38] However, this decrease was offset by an increased number of cesarean deliveries performed due to dystocia, raising the concern that the presence of the probe might predispose to dystocia. As a consequence, the ACOG has recommended further study before fetal pulse oximetry is used routinely in clinical practice.[39] A meta-analysis of five trials concluded that there was some benefit to fetal pulse oximetry in the presence of a nonreassuring FHR tracing, but the use of fetal pulse oximetry did not lead to an overall reduction in the cesarean delivery rate.[40]

Infants with **congenital anomalies** (e.g., tracheoesophageal fistula, diaphragmatic hernia, CNS and cardiac malformations) may need resuscitation and cardiorespiratory support. Improved ultrasonography allows for the antenatal diagnosis of many congenital anomalies and other fetal abnormalities (e.g., nonimmune hydrops). Obstetricians should communicate knowledge or suspicions regarding these entities to those who will provide care for the neonate in the delivery room to allow the resuscitation team to make specific resuscitation plans.

In the past, infants born by either elective or emergency cesarean delivery were considered more likely to require resuscitation than infants delivered vaginally. Evidence suggests that repeat cesarean deliveries and those performed for dystocia—in patients without FHR abnormalities—result in the delivery of infants at low risk for neonatal resuscitation, especially when the cesarean deliveries are performed with neuraxial anesthesia.[3,4,41] Of interest, infants born by elective repeat cesarean delivery are at higher risk for subsequent respiratory problems (e.g., transient tachypnea of the newborn) than similar infants born vaginally. In addition, infants born by cesarean delivery after a failed trial of labor are at a higher risk for neonatal sepsis than similar infants born vaginally.[42] Emergency cesarean delivery is considered a risk factor for the need for neonatal resuscitation.

NEONATAL ASSESSMENT

Apgar Score

Resuscitative efforts typically precede the performance of a thorough physical examination of the neonate. Because NRP instructions require simultaneous assessment and treatment, it is important that the neonatal assessment be both simple and sensitive. In 1953, Dr. Virginia Apgar, an anesthesiologist, described a simple method for neonatal assessment that could be performed while care was being delivered.[43] She suggested that this standardized and relatively objective scoring system would differentiate between infants who require resuscitation and those who need only routine care.[44]

The Apgar score is based on five parameters that are assessed at 1 and 5 minutes after birth. Further scoring at 5- or 10-minute intervals may be done if initial scores are low. The parameters are heart rate, respiratory effort, muscle tone, reflex irritability, and color. A score of 0, 1, or 2 is assigned for each of these five entities (Table 9-1). A total score of 8 to 10 is normal; a score of 4 to 7 indicates moderate impairment; and a score of 0 to 3 signals the need for immediate resuscitation. Dr. Apgar emphasized that this system does not replace a complete physical examination and serial observations of the neonate for several hours after birth.[45]

The Apgar score is widely used to assess neonates, although its value has been questioned. The scoring system may help predict mortality and neurologic morbidity in *populations* of infants, but Dr. Apgar cautioned against the use of the Apgar score to make these

TABLE 9-1 **Apgar Scoring System**

Parameter	Score		
	0	1	2
Heart rate (bpm)	Absent	< 100	> 100
Respiratory effort	Absent	Irregular, slow, shallow, or gasping respirations	Robust, crying
Muscle tone	Absent, limp	Some flexion of extremities	Active movement
Reflex irritability (nasal catheter, oropharyngeal suctioning)	No response	Grimace	Active coughing and sneezing
Color	Cyanotic	Acrocyanotic (trunk pink, extremities blue)	Pink

bpm, beats per minute.
Modified from Tabata BK. Neonatal resuscitation. In Rogers MC, editor. Current Practice in Anesthesiology. 2nd edition. St. Louis, Mosby, 1990:368.

predictions in an *individual* infant. She noted that the risk for neonatal mortality was inversely proportional to the 1-minute score.[45] In addition, the 1-minute Apgar score was a better predictor of mortality within the first 2 days of life than within 2 to 28 days of life.

Several studies have challenged the notion that a low Apgar score signals perinatal asphyxia. In a prospective study of 1210 deliveries, Sykes et al.[46] noted a poor correlation between the Apgar score and the umbilical cord blood pH. Other studies, including those of low-birthweight infants, have found that a low Apgar score is a poor predictor of neonatal acidosis, although a high score is reasonably specific for excluding the presence of severe acidosis.[47-53] By contrast, the fetal biophysical profile has a good correlation with the acid-base status of the fetus and the neonate (see Chapter 6).[54] The biophysical profile includes performance of a nonstress test and ultrasonographic assessment of fetal tone, fetal movement, fetal breathing movements, and amniotic fluid volume.[54]

Additional studies have suggested that Apgar scores are poor predictors of long-term neurologic impairment.[55,56] The Apgar score is more likely to predict a poor neurologic outcome when the score remains 3 or less at 10, 15, and 20 minutes. However, when a child has cerebral palsy, low Apgar scores alone are not adequate evidence that perinatal hypoxia was responsible for the neurologic injury.

The ACOG Task Force on Neonatal Encephalopathy and Cerebral Palsy published criteria for defining an intrapartum event sufficient to cause cerebral palsy.[57] An Apgar score of 0 to 3 beyond 5 minutes of age is not included in the list of "essential criteria"; rather, it is one of five criteria that "collectively suggest an intrapartum timing (within close proximity to labor and delivery…) but are nonspecific to asphyxial insults."[57-62]

In a retrospective analysis of 151,891 singleton infants born at 26 weeks' gestation or later between 1988 and 1998, Casey et al.[63] examined the relationship between Apgar scores and neonatal death rates during the first 28 days of life. The highest relative risk for neonatal death was observed in infants with an Apgar score of 3 or less at 5 minutes of age. The 5-minute Apgar score was a better predictor of neonatal death than the umbilical arterial blood pH. In term infants, the relative risk for neonatal death was eight times higher in infants with a 5-minute Apgar score of 3 or less than in those with an umbilical arterial blood pH of 7.0 or less.[63,64] In preterm infants, lower 5-minute Apgar scores were associated with younger gestational ages (i.e., mean score 6.6 ± 2.1 for infants born at 26 to 27 weeks' and 8.7 ± 0.8 for infants born at 34 to 36 weeks' gestation).[63,64] Similarly, earlier studies found that preterm infants were more likely than term infants to have low 1- and 5-minute Apgar scores, independent of neonatal oxygenation and acid-base status. Respiratory effort, muscle tone, and reflex irritability are the components of the score that are most influenced by gestational age.[65]

The earlier the gestational age, the greater the likelihood of a low Apgar score, even in the presence of a normal umbilical cord blood pH. Preterm infants often require active resuscitation efforts immediately after delivery, and these manipulations may affect the components of the Apgar score. For example, pharyngeal and tracheal stimulation may cause a reflex bradycardia, which affects the heart rate score.[49] In addition, it is difficult to judge respiratory effort during suctioning or endotracheal intubation.

During cases of active neonatal resuscitation, the Apgar scores often are not assigned at the appropriate times; rather, these scores may be assigned retrospectively. In these situations, the individual must rely on recall of the infant's condition at earlier times, introducing inaccuracy. Even if the scores are assigned at the appropriate times, there may be disagreement among the several individuals who are providing care for the infant. To avoid bias, Dr. Apgar recommended that someone not involved in the care of the mother assign the score.

Although there is some appeal to the use of objective measurements (i.e., Sao_2, heart rate) rather than subjective observations, it should not be inferred that the subjective components of the Apgar score (e.g., muscle tone) are less important. There are some practical limitations that may make objective measurements difficult to obtain (e.g., movement artifact with pulse oximetry).[16] However, newer-generation pulse oximeters provide more accurate estimations of Sao_2 (see later discussion).[66]

In summary, the usefulness of the Apgar score is still being debated more than 50 years after its inception.[63,64]

The Apgar scoring system is used throughout the world, but its limitations must be kept in mind. Low Apgar scores alone do not provide sufficient evidence of perinatal asphyxia; rather, Apgar scores can be low for a variety of reasons. Preterm delivery, congenital anomalies, neuromuscular diseases, antenatal drug exposure, manipulation at delivery, and subjectivity and error may influence the Apgar score.

Umbilical Cord Blood Gas and pH Analysis

Umbilical cord blood gas and pH measurements reflect the fetal condition immediately before delivery and can be obtained routinely after delivery or measured only in cases of neonatal depression. These measurements may be a more objective indication of a neonate's condition than the Apgar score. However, there is a delay between obtaining the samples and completing the analysis; during this interval, decisions must be made on the basis of clinical assessment. The ACOG[67] has recommended that cord blood gas measurements be obtained in circumstances of cesarean delivery for fetal compromise, low 5-minute Apgar score, severe growth restriction, abnormal FHR tracing, maternal thyroid disease, intrapartum fever, and/or multiple gestations.

The fetus produces carbonic acid (from oxidative metabolism) and lactic and beta-hydroxybutyric acids (primarily from anaerobic metabolism). Carbonic acid, which is often called *respiratory acid*, is cleared rapidly by the placenta as carbon dioxide when placental blood flow is normal. However, metabolic clearance of lactic and beta-hydroxybutyric acids requires hours; thus, these acids are called *metabolic* or *fixed acids*. In the fetus, metabolic acidemia is more ominous than respiratory acidemia because the former reflects a significant amount of anaerobic metabolism.

The measured components of umbilical cord blood gas analysis are pH, Pco_2, Po_2, and HCO_3^-. Bicarbonate (HCO_3^-) is a major buffer in fetal blood. The measure of change in the buffering capacity of umbilical cord blood is reflected in the delta base, which is also known as the base excess or deficit; this value can be calculated from the pH, Pco_2, and HCO_3^-. Ideally, blood samples from both the umbilical artery and vein are collected. Umbilical artery blood gas measurements represent the fetal condition, whereas umbilical vein measurements reflect the maternal condition and uteroplacental gas exchange. Unfortunately, it may be difficult to obtain blood from the umbilical artery, especially when it is small, as it is in very low-birth-weight (VLBW) infants. Caution should be used in the interpretation of an isolated umbilical venous blood pH measurement, which can be normal despite the presence of arterial acidemia.

Proper blood sampling and handling are necessary. The measurements should be accurate, provided that (1) the umbilical cord is double clamped immediately after delivery[68-70]; (2) the samples are drawn, within 15 minutes of delivery,[71] into a syringe containing the proper amount of heparin[72]; and (3) the samples are analyzed within 30 to 60 minutes.[71,73] The Po_2 measurement is more accurate if residual air bubbles are removed from the syringe.

Historically, a normal umbilical cord blood pH measurement was believed to be 7.2 or higher.[74] However, investigators have challenged the validity of this number, given its lack of distinction between umbilical arterial and venous blood despite clear differences in their normal measurements.[75] One study noted that the median umbilical arterial blood pH in vigorous infants (those with 5-minute Apgar scores of 7 or higher) was 7.26, with a measurement of 7.10 representing the 2.5th percentile.[76] Published studies suggest that the lower limit of normal umbilical arterial blood pH measurements may range from 7.02 to 7.18 (Table 9-2).[46,77-86] A number of factors may also influence the umbilical arterial blood pH measurement. A fetus subjected to the stress of labor has lower pH measurements than one born by cesarean delivery without labor.[83] Offspring of nulliparous women tend to have a lower pH than offspring of parous women, a difference that is likely related to a difference in the duration of labor.[87]

Some studies have suggested that preterm infants have a higher incidence of acidemia; however, later studies have observed that term and preterm infants have similar umbilical cord blood gas and pH measurements.[78,79,87] Preterm infants often receive low Apgar scores despite the presence of normal umbilical cord blood gas and pH measurements; therefore, the assessment of umbilical cord blood may be especially helpful in the evaluation of preterm neonates.

Physicians should use strict definitions when interpreting umbilical cord blood gas and pH measurements. Terms such as *birth asphyxia* should be avoided in most cases.[57] *Acidemia* refers to an increase in the hydrogen ion concentration in the blood. *Acidosis* occurs when there is an increased hydrogen ion concentration in tissue. *Asphyxia* is a clinical situation that involves hypoxia (i.e., a decreased level of oxygen in tissue), damaging acidemia, and metabolic acidosis.

When acidemia is present, the type—respiratory, metabolic, or mixed—must be identified (Table 9-3). Metabolic acidemia is more likely to be associated with acidosis than respiratory acidemia and is clinically more significant. Similarly, mixed acidemia with a high Pco_2, an extremely low HCO_3^-, and a high base deficit is more ominous than a mixed acidemia with a high Pco_2 but only a slightly reduced HCO_3^- and a low base deficit. Mixed or metabolic acidemia (but not respiratory acidemia) is associated with an increased incidence of neonatal complications and death.[87] In their study of 3506 term neonates, Goldaber et al.[88] noted that an umbilical arterial blood pH measurement less than 7.00 was associated with a significantly higher incidence of neonatal death. All neonatal seizures in their study occurred in infants with an umbilical arterial blood pH less than 7.05. By contrast, a short-term outcome study failed to show a good correlation between arterial blood pH and the subsequent health of an infant.[53] In the previously discussed large study reported by Casey et al.,[63] an umbilical arterial blood pH of 7.0 or less was a poorer predictor of the relative risk for neonatal death during the first 28 days of life than a 5-minute Apgar score of 3 or less.

TABLE 9-2 Studies Reporting Umbilical Cord Arterial Blood Gas Measurements*

Study	Sample Size	pH	P_{CO_2}	Bicarbonate	Base Deficit	P_{O_2}
Huisjes and Aarnoudse (1979)[80]	852	7.20 ± 0.09 (7.02-7.38)				
Sykes et al. (1982)[46]	899	7.20 ± 0.08 (7.04-7.36)			8.3 ± 4.0 (0.3-16.3)	
Eskes et al. (1983)[81]	4667	7.23 ± 0.07 (7.09-7.37)				
Yeomans et al. (1985)[77]	146	7.28 ± 0.05 (7.18-7.38)	49.2 ± 8.4 (32.4-66.0)	22.3 ± 2.5 (17.3-27.3)		
Low (1988)[82]	4500	7.26 ± 0.07 (7.12-7.40)	54.9 ± 9.9 (35.1-74.7)			15.1 ± 4.9 (5.3-24.9)
Ruth and Raivio (1988)[86]	106	7.29 ± 0.07 (7.15-7.43)			4.7 ± 4.0 (–3.3-12.7)	
Thorp et al. (1989)[83]	1694	7.24 ± 0.07 (7.10-7.38)	56.3 ± 8.6 (39.1-73.5)	24.1 ± 2.2 (19.7-28.5)	3.6 ± 2.7 (–1.8-9.0)	17.9 ± 6.9 (4.1-31.7)
Ramin et al. (1989)[78]	1292	7.28 ± 0.07 (7.14-7.42)	49.9 ± 14.2 (21.5-78.3)	23.1 ± 2.8 (17.5-28.7)	3.6 ± 2.8 (–2.0-9.4)	23.7 ± 10.0 (3.7-43.7)
Riley and Johnson (1993)[84]	3522	7.27 ± 0.07 (7.13-7.41)	50.3 ± 11.1 (28.1-72.5)	22.0 ± 3.6 (14.8-29.2)	2.7 ± 2.8 (–2.9-8.3)	18.4 ± 8.2 (2.0-34.8)
Nagel et al. (1995)[85]	1614	7.21 ± 0.09 (7.03-7.39)				

*Data are presented as mean ± 1 SD and (–2 to +2 SD). *Sample size* pertains to cord arterial pH and not necessarily to other parameters.
Modified from Thorp JA, Dildy BA, Yeomans ER, et al. Umbilical cord blood gas analysis at delivery. Am J Obstet Gynecol 1996; 175:517-22.

TABLE 9-3 Criteria Used to Define Types of Acidemia in Neonates with an Umbilical Arterial pH Measurement Less Than 7.20

Classification	P_{CO_2} (mm Hg)	HCO_3^- (mEq/L)	Base Deficit (mEq/L)*
Respiratory	High (> 65)	Normal (≥ 22)	Normal (–6.4 ± 1.9)
Metabolic	Normal (< 65)	Low (≤ 17)	High (–15.9 ± 2.8)
Mixed	High (≥ 65)	Low (≤ 17)	High (–9.6 ± 2.5)

*Means ± SD given in parentheses.
From the American College of Obstetricians and Gynecologists. Assessment of fetal and newborn acid-base status. ACOG Technical Bulletin No. 127. Washington, DC, April 1989.

However, 6264 infants were excluded from their study because umbilical arterial blood gas measurements could not be obtained, and these infants had a higher incidence of neonatal death than those for whom blood gas measurements were available (4.5 per 1000 versus 1.2 per 1000, respectively). In a separate review of 51,519 term deliveries, Yeh et al.[89] found an increased risk for adverse outcomes in infants with a pH less than 7.10, with the lowest risk in infants with a pH between 7.26 and 7.30; however, 75% of infants with neurologic morbidity had a normal pH. Thus, it is important to remember that neonates may suffer multiorgan system damage, including neurologic injury, even in the absence of low pH and Apgar scores.

According to the ACOG Task Force, an umbilical arterial blood pH less than 7.0 and a base deficit greater than or equal to 12 mmol/L at delivery are considered one part of the definition of an acute intrapartum hypoxic event sufficient to cause cerebral palsy.[57] The base deficit and bicarbonate (the metabolic component) values are the most significant factors associated with morbidity in neonates with an umbilical arterial blood pH less than 7.0. Ten percent of infants with an umbilical arterial base deficit of 12 to 16 mmol/L have moderate to severe complications, which increases to 40% when the deficit is greater than 16 mmol/L.[67]

Abnormal FHR patterns and umbilical cord blood gas measurements are not consistently correlated with poor neonatal outcomes.[37] In a longitudinal study that evaluated outcomes at 6.5 years of age, Hafstrom et al.[90] found that infants with an umbilical arterial blood pH less than 7.05 but a normal examination at birth had outcomes that did not differ from those for matched infants with a normal umbilical arterial blood pH.

As Dr. Apgar emphasized in 1962, the most important components of neonatal assessment are a careful physical examination and continued observation for several hours.[45] Additional information can be gained from the antenatal history, Apgar scores, and umbilical cord blood gas and pH measurements, provided that clinicians are aware of the proper methods of interpretation as well as the limitations of these methods of assessment.

Respiration and Circulation

There are some similarities between the initial assessment of the neonate and the initial assessment of an adult who requires resuscitation. In both situations, the physician should give immediate attention to the ABCs of resuscitation (i.e., airway, breathing, circulation).

The normal neonatal respiratory rate is between 30 and 60 breaths per minute. Breathing should begin by 30 seconds and be regular by 90 seconds of age. Failure of the neonate to breathe by 90 seconds of age represents either primary or secondary apnea, based on the neonatal rhesus monkey asphyxia model.[91] In this model, gasping motions were observed for approximately 1 minute immediately after delivery; this was followed by a 1-minute period of apnea (primary apnea), then 5 minutes of gasping motions, and a final period of apnea (secondary or "terminal" apnea). During *primary apnea*, but not secondary apnea, tactile stimulation of the newborn monkey initiated breathing efforts. In addition, although heart rate was low with both periods of apnea, a reduction in blood pressure was observed only during secondary apnea. With the onset of secondary apnea (approximately 8 minutes after birth), the pH was 6.8 and the Pao_2 and $Paco_2$ measurements were less than 2 and 150 mm Hg, respectively.

This experimental model illustrates two important points. First, distinguishing primary from secondary apnea is not possible unless blood pressure and/or blood gases and pH are measured. Second, by the time secondary apnea has begun, blood gas measurements have deteriorated significantly. Therefore, during evaluation of the apneic neonate, aggressive resuscitation must be initiated promptly if tactile stimulation does not result in the initiation of spontaneous breathing.

Assessment of the adequacy of respiratory function requires comprehensive observation for signs of neonatal respiratory distress. These signs include cyanosis, grunting, flaring of the nares, retracting chest motions, and unequal breath sounds. The adequacy of respiratory function can also be assessed by the estimation of Sao_2. The reliability of pulse oximetry for the assessment of neonatal Sao_2 was questioned initially because of concerns about the accuracy of spectrophotometric assessments of fetal hemoglobin and the difficult signal detection caused by the rapidity of the neonate's heart rate.[92,93] The newer generation of pulse oximetry monitors, which employ signal extraction and averaging techniques, are able to provide more reliable measurements, especially in the presence of poor perfusion, patient movement, and ambient light artifacts.[66,94]

Pulse oximetry provides accurate estimates of Sao_2 during periods of stability but may overestimate values during rapid desaturation.[95] In addition, the Sao_2 (Spo_2) measurements may fluctuate in the delivery room as a result of the ongoing transition from the fetal to the neonatal circulation, and it may take more than 10 minutes to achieve a preductal Sao_2 greater than 95% in a healthy term infant. Overall, the newer-generation pulse oximeters reliably provide continuous noninvasive Sao_2 measurements and are useful for neonatal monitoring.[96-98]

The pulse oximeter sensor should be applied to the neonate's right upper extremity, which receives preductal blood flow (see earlier discussion); because CNS blood flow is also preductal, right upper extremity Sao_2 measurements provide a more accurate assessment of CNS oxygenation.[16] Sensor placement can be difficult on skin that is wet and covered with vernix caseosa; therefore, it may be easier to place the sensor over the right radial artery, especially in preterm infants.[94]

Neonatal arterial blood sampling is technically difficult and thus rarely obtained in the delivery room. Cannulation of the umbilical artery is useful in infants who will require frequent blood sampling. This procedure often requires the use of microinstruments (especially in preterm and VLBW infants) and the ability to monitor the infant when obscured from view by surgical drapes; therefore, this procedure is usually performed in the neonatal intensive care unit (NICU).

The normal neonatal heart rate may be greater than 160 beats per minute (bpm) in the very early preterm neonate, but it should be within the range of 120 to 160 bpm by 28 weeks' gestational age. The heart rate can be determined in several ways. The clinician can lightly grasp the base of the umbilical cord and feel the arterial pulsations. (This method cannot be used in situations in which the pulsations become difficult to feel, such as in an infant with a low cardiac output.) Alternatively, the clinician can listen to the apical heartbeat. When either of these two methods is used, the evaluator should tap a hand with each heartbeat so that other members of the resuscitation team are aware of the rate. By contrast, the use of a pulse oximeter provides an audible heart rate, the additional benefit of Sao_2 monitoring, and the ability to eliminate the need for an additional team member.

Measurement of arterial blood pressure is not a priority during the initial assessment and resuscitation of the neonate.[2] However, observation for signs of abnormal circulatory function is considered essential. These signs include cyanosis, pallor, mottled coloring, prolonged capillary refill time, and weakness or absence of pulses in the extremities. One of the causes of abnormal circulatory function is hypovolemia, which should be anticipated in cases of bleeding from the umbilical cord or the fetal side of the placenta or whenever a neonate does not respond appropriately to resuscitation. The hypovolemic neonate may exhibit not only signs of abnormal circulatory function but also tachycardia and tachypnea. (Neonatal hypovolemia usually does not accompany placental abruption, which may cause maternal bleeding or other conditions associated with fetal asphyxia.)

Neurologic Status

The initial neonatal neurologic assessment requires only simple observation. The neonate should demonstrate evidence of vigorous activity, including crying and active flexion of the extremities. Signs of possible neurologic abnormalities include apnea, seizures, hypotonia, and unresponsiveness. Neonates should be assessed for physical signs of hypoxic-ischemic encephalopathy (Table 9-4). The stages of hypoxic-ischemic encephalopathy are associated with different outcomes: stage I, good; stage II,

TABLE 9-4 **Stages of Neonatal Hypoxic-Ischemic Encephalopathy**

Stage I	Stage II	Stage III
Irritable	Lethargic/obtunded	Coma
Normal respirations	Depressed respirations	Apnea
Hypertonic	Hypotonic	Flaccid
Increased reflexes	Decreased reflexes	Absence of reflexes
No seizures	Occasional seizures	Status epilepticus or nearly isoelectric electroencephalogram
Good outcome	Moderate outcome	Poor outcome

Modified from Eicher DJ, Wagner C. Update on neonatal resuscitation. J S C Med Assoc 2002; 98:115.

moderate; and stage III, poor.[99] Although detailed neurologic assessment is performed after the neonate is transferred to the NICU, assessment of tone, baseline heart rate, respirations, and reflex activity is part of both the Apgar scoring system and the assessment for hypoxic-ischemic encephalopathy and is made initially in the delivery room.

Gestational Age

When assessing a very small neonate whose gestational age appears to be lower than that of viability, the evaluator must consider whether it is appropriate to initiate and maintain resuscitation efforts. The neonatal gestational age is often assessed with the use of the scoring systems described initially by Dubowitz et al.[100] and subsequently modified by Ballard et al.[101] The **Dubowitz system** makes use of an external score based on physical characteristics, described previously by Farr et al.,[102,103] and a neurologic score. The **Ballard system** uses simplified scoring criteria to assess gestational age. Ballard et al.[101] eliminated certain physical criteria such as edema and skin color because of the unreliability of these criteria in some clinical conditions. In addition, they abbreviated the neurologic criteria on the basis of observations by Amiel-Tison.[104]

The Dubowitz and Ballard scores are most accurate when used to estimate gestational age at 30 to 42 hours, rather than during the first several minutes, after birth. These scoring systems are also less accurate in very small preterm infants. In one study of 100 preterm infants with birth weights less than 1500 g, agreement among antenatal measures of gestational age (e.g., last menstrual period, ultrasonography determination) and postnatal measures (e.g., Dubowitz and Ballard scores) was poor.[105] Both scoring systems overestimated gestational age in this subset of VLBW infants. Ballard et al.[106] refined their scoring system to provide a more accurate estimate of gestational age in preterm infants (Figure 9-3). The new Ballard score assesses **physical criteria,** such as eyelid fusion, breast tissue, lanugo hair, and genitalia, and **neurologic criteria,** such as wrist "square window." (The square window assessment is performed by flexing the infant's wrist on the forearm and noting the angle between the hypothenar eminence and the ventral aspect of the forearm.) Although the new Ballard score may be more accurate than the older score for the assessment of preterm infants, inconsistencies occur with all of these methods. Of particular interest is the observation that fetuses of different racial origin appear to mature at different rates (i.e., black fetuses mature faster than white fetuses).[107]

Another commonly used criterion for the estimation of gestational age is birth weight. Normal values for birth weight are published and readily available.[108] Although birth weight may help physicians estimate the gestational age of an otherwise healthy preterm infant, physicians cannot rely on birth weight to provide an accurate estimate of gestational age in an infant who suffered from intrauterine growth restriction or who is large for gestational age.

Because of the potential for inaccurate gestational age estimation in the delivery room, it is best not to use these scoring systems to guide decisions regarding the initiation or continuation of neonatal resuscitation immediately after delivery. In most circumstances, the neonate's response to resuscitative efforts is the best indicator as to whether further intervention is warranted.

NEONATAL RESUSCITATION

The equipment and medications needed for neonatal resuscitation are listed in Box 9-3. Equipment, supplies, and medications should be checked regularly to ensure that all components are available and functional.

Although previously published guidelines recommended suctioning of the mouth and nose after delivery of the head, the guidelines published in 2010 do *not* recommend routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born with either clear or meconium-stained amniotic fluid.[2]

Timing of cord clamping may vary by the gestational age and vigor of the infant. Current evidence suggests that a delay in cord clamping for 1 minute after the delivery of vigorous term infants improves iron stores throughout early infancy.[109] In vigorous preterm infants, a brief delay in cord clamping (30 seconds to 3 minutes) is associated with improved blood pressure and a lower incidence of intraventricular hemorrhage[110]; no alterations in Apgar scores or need for delivery room resuscitation have been observed with this practice.[111] In nonvigorous infants, regardless of gestational age, the benefits of delayed cord clamping may be outweighed by the need to promptly initiate resuscitation.

After delivery is complete, the neonate is transferred to the resuscitation area. The availability of sterile blankets allows the individual performing the delivery to

Neuromuscular maturity

	–1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140°-180°	110°-140°	90°-110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Physical maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40 to 50 mm: –1 <40 mm: –2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases anterior two thirds	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1- to 2-mm bud	Raised areola, 3- to 4-mm bud	Full areola, 5- to 10-mm bud	
Eye/ear	Lids fused loosely: –1 Tightly: –2	Lids open, pinna flat, stays folded	Slightly curved pinna, soft, slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals –male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals –female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity rating

Score	Weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

FIGURE 9-3 ■ Modified Ballard scoring system for clinical assessment of maturation in neonates. This scoring system was expanded to include extremely preterm infants, and it was refined to improve the accuracy of assessment of more mature infants. (Modified from Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr 1991; 119:418.)

remain sterile while transferring the infant; this issue is especially important during cesarean deliveries. The timing of delivery should be noted, assessment and appropriate resuscitative measures should be continued, and Apgar scores should be assigned at the appropriate intervals (Figure 9-4).

The physician or nurse should place the infant beneath an overhead radiant warmer and promptly dry the skin of infants delivered at greater than 28 weeks' gestation. The infant who is delivered preterm at less than 28 weeks' gestation should be placed in a polythene bag or wrapping to prevent heat loss.[29,30] Hypothermia can result in increased oxygen consumption and metabolic acidosis[112] and leads to a significantly higher mortality rate among preterm infants.[113]

Selective cerebral hypothermia[114] or whole-body hypothermia[31,32] may protect against brain injury in the asphyxiated infant. The use of intentional hypothermia

BOX 9-3 Equipment and Drugs Needed for Neonatal Resuscitation

Suction Equipment

- Bulb syringe
- Mechanical suction and tubing
- Suction catheters: 5F or 6F, 8F, and 10F or 12F
- 8F feeding tube and 20-mL syringe
- Meconium aspiration device

Bag-and-Mask Equipment

- Neonatal resuscitation bag with a pressure-release valve or pressure manometer and valve to deliver positive end-expiratory pressure (the bag must be capable of delivering 90% to 100% oxygen) or a pressure limiting T-piece resuscitator
- Face masks, term and preterm newborn sizes (masks with cushioned rim preferred)
- Air source with tubing
- Oxygen with flowmeter (flow rate up to 10 L/min) and tubing (including portable oxygen cylinders)
- Blender to mix air and oxygen to adjust oxygen delivery

Intubation Equipment

- Laryngoscope with straight blades: No. 0 (preterm) and No. 1 (term)
- Extra bulbs and batteries for laryngoscope
- Tracheal tubes: 2.5, 3.0, 3.5, and 4.0 mm ID
- Stylet (optional)
- Scissors
- Tape or securing device for tracheal tube
- Alcohol sponges
- CO_2 detector (optional)
- Laryngeal mask airway (optional)

Medications

- Epinephrine 1:10,000 (0.1 mg/mL), 3- or 10-mL ampules
- Isotonic crystalloid (normal saline or lactated Ringer's solution) for volume expansion, 100 or 250 mL
- Sodium bicarbonate 4.2% (5 mEq/10 mL), 10-mL ampules
- Normal saline, 30 mL
- Dextrose 10%, 250 mL
- Normal saline "fish" or "bullet" (optional)
- Feeding tube: 5F (optional)
- Umbilical vessel catheterization supplies:
  - Sterile gloves
  - Scalpel or scissors
  - Povidone-iodine solution
  - Umbilical tape
  - Umbilical catheters: 3.5F, 5F
  - Three-way stopcock
- Syringes: 1, 3, 5, 10, 20, and 50 mL
- Needles: 25, 21, and 18 gauge, or puncture device for needleless system

Miscellaneous

- Gloves and appropriate personal protection
- Radiant warmer or other heat source
- Firm, padded resuscitation surface
- Clock (timer optional)
- Warmed linens
- Stethoscope
- Tape: ½ or ¾ inch
- Cardiac monitor and electrodes and/or pulse oximeter with probe (optional for delivery room)
- Oropharyngeal airways
- Polythene wrap or bags (for infants < 28 weeks' gestation)

ID, internal diameter.

Modified from Textbook of Neonatal Resuscitation. 6th edition. Elk Grove Village, IL, American Academy of Pediatrics and American Heart Association, 2011:216.

therapy requires an NICU with defined protocols and multidisciplinary support. When assessing an infant for hypothermia therapy, the radiant warmer can be turned off to allow passive cooling. With further assessment, if the criteria for hypothermia therapy are not met, the infant can be warmed. Hyperthermia should be avoided in all infants.[2]

The neonate should be positioned in a way that allows the airway to remain open, with the head in the "sniffing" position (the neck flexed on the chest and the head extended on the neck, thereby aligning the oropharynx, pharynx, and hypopharynx). Suctioning of the mouth and nose with a bulb syringe may be necessary if secretions accumulate.

The neonate with a normal respiratory pattern, heart rate, and color requires no further intervention. Often the neonate has a normal respiratory pattern and heart rate but may not be pink. Acrocyanosis often persists for several minutes after delivery and does not require intervention. However, an evaluation for choanal atresia can be performed at this time with the gentle insertion of a small suction catheter through each nostril into the nasopharynx. Vigorous nasal suctioning should be avoided because it can cause trauma to the nasal mucosa and result in progressive edema and airway obstruction. The neonate is an obligate nasal breather; thus, choanal atresia is a potentially lethal anomaly that requires immediate attention. If this anomaly is present (as evidenced by failure of nasal passage of the catheter), the neonate should have an oral airway or endotracheal tube inserted and an evaluation performed for repair of the obstruction. The classic clinical presentation for choanal atresia is an infant with cyanosis and respiratory distress at rest who becomes pink when crying.

Tactile stimulation should be used if the neonate does not breathe immediately; this consists of gently rubbing the back and flicking the soles of the feet. Tactile stimulation does not trigger respiratory efforts during secondary apnea in the neonate. Therefore, if the neonate does not begin to breathe spontaneously after tactile stimulation, the evaluator should begin positive-pressure mask ventilation. If the neonate has an abnormally slow heart rate (i.e., less than 100 bpm), positive-pressure ventilation should be performed until the heart rate rises to the

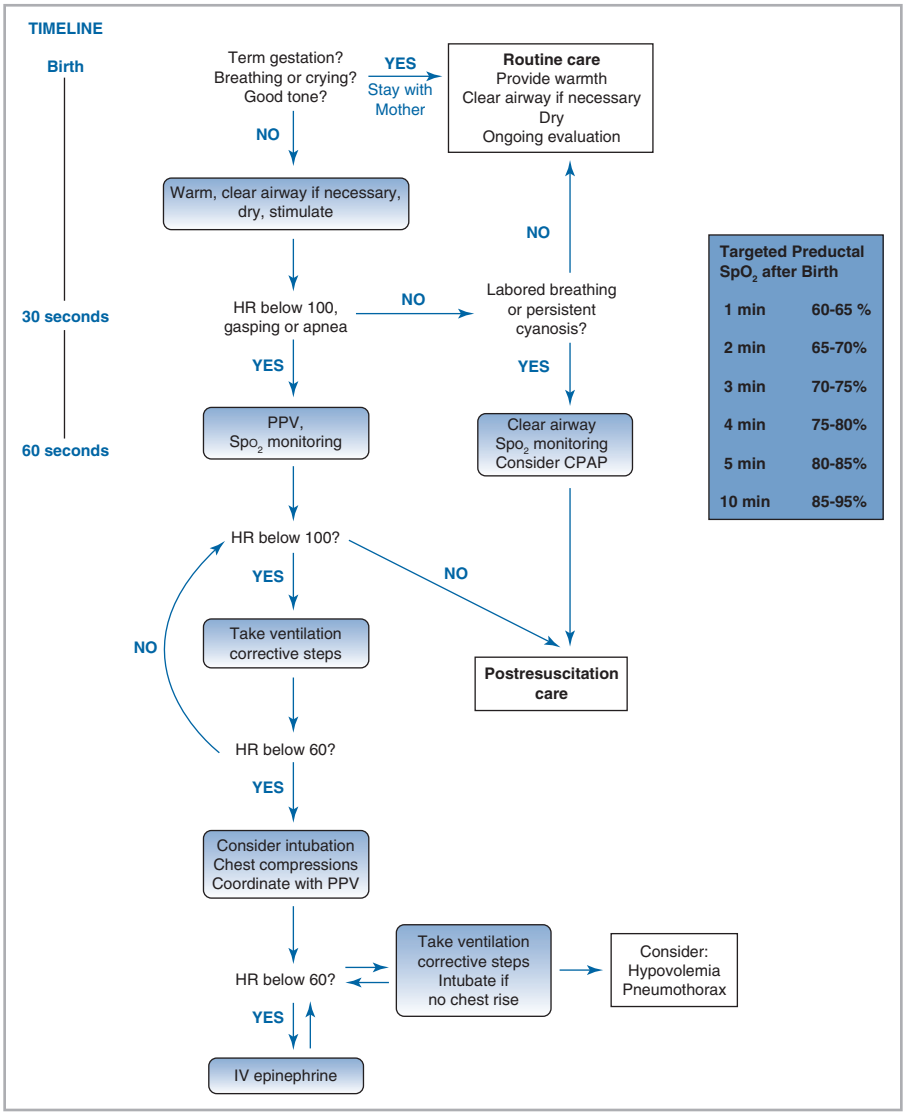

FIGURE 9-4 ■ Algorithm for resuscitation of the newly born infant. *HR,* heart rate; *PPV,* positive-pressure ventilation; *Spo_2,* oxygen saturation. (Modified from Textbook of Neonatal Resuscitation. 6th edition. Elk Grove Village, IL, American Academy of Pediatrics and American Heart Association, 2011:216. Figure by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

normal range. Overzealous tactile stimulation (e.g., slapping the back) is not useful; it provides no advantage over the more moderate methods and can cause traumatic injury. Infants with labored or persistent cyanosis may benefit from continuous positive airway pressure.

High concentrations of oxygen (as opposed to ambient air) can raise production of oxygen free radicals, which have been linked to hypoxia-reoxygenation injury.[115] Additionally, an association between neonatal oxygen supplementation and childhood cancer has been noted with supplemental oxygen exposure for 3 minutes or longer.[116] In two studies, term or near-term infants were randomly assigned to receive neonatal resuscitation with either room air or 100% oxygen; no major outcome differences were observed.[117,118] Subsequently a pooled meta-analysis of five trials, consisting of 1032 term or near-term infants, showed a significantly lower mortality rate with no evidence of harm when resuscitation was performed initially with room air rather than 100% oxygen.[119] The current guidelines for neonatal resuscitation for term infants recommend the use of room air for assisted ventilation. In preterm infants, assisted ventilation should be initiated with an inspired oxygen concentration (Fio_2) of 30% to 90% and should be guided by the response to resuscitation and the use of pulse oximetry to assess oxygenation. The Fio_2 should be lowered as soon as possible to minimize the risk for retinopathy of prematurity and pulmonary toxicity. Sao_2 measurements of 85% to 92% are thought to be adequate and appropriate for neonates of less than 34 weeks' gestation.[117,118,120,121] A meta-analysis detected no significant differences in neurodevelopmental outcomes at 12 to 24 months of age between infants resuscitated with either room air or 100% oxygen.[122]

Positive-pressure ventilation must be performed correctly to ensure that it is effective and does not cause

barotrauma. A ventilation bag with a volume of 250 to 500 mL may be used. The circuit must contain a safety pop-off pressure valve (e.g., at 35 cm H_2O), a visible pressure gauge, or both. An oxygen flow rate of 5 to 10 L/min is adequate. Alternatively, a T-piece, which is a valved mechanical device, may be used; it allows more consistent delivery of target inflation pressures and long inspiratory times. The mask must be of appropriate size and shape to ensure a good seal around the nose and mouth. A variety of masks should be available to accommodate infants of all sizes and gestational ages. For the infant with excessive occipital scalp edema (e.g., caput succedaneum), placing a small roll under the shoulders to alleviate hyperflexion of the neck may be helpful.

During the first assisted breath, positive pressure at 30 cm H_2O in term infants should be maintained for 4 to 5 seconds at the end of inspiration to overcome the surface tension of the lungs and open the alveoli.[123] The neonatal response to a large, rapid inflation of the lungs is a sharp inspiration of its own (Head's paradoxical reflex).[124] Subsequent breaths should be delivered at a rate of 40 to 60 breaths per minute, with intermittent inspiratory pauses to prevent the development of atelectasis. The maximum pressure generated should range between 20 and 30 cm H_2O, with an inspiration-to-expiration ratio of approximately 1 : 1. In preterm infants, whose lungs may be more easily injured, initial inflation pressures of 20 to 25 cm H_2O may be adequate. If mask ventilation is needed for longer than 2 to 3 minutes, the stomach should be emptied with an orogastric catheter. Distention of the stomach with air can compromise respiratory function in the neonate. This maneuver should be performed with care, because pharyngeal stimulation can result in arrhythmias and apnea.[125]

The adequacy of respiratory resuscitation can be monitored from observation of its effect on heart rate; an increase in heart rate is the first consistently reliable sign of effective oxygenation. By contrast, changes in color occur slowly, are difficult to assess, and are a relatively poor index of successful resuscitation.

When the neonate's heart rate is higher than 100 bpm, positive-pressure ventilation can be stopped, and the infant can be reevaluated for spontaneous respiratory effort. If the neonate does not begin to breathe and if an opioid effect is the suspected etiology, administration of **naloxone** is *not* recommended. Naloxone can worsen the neurologic damage caused by asphyxia[126,127] and can precipitate acute neonatal opioid withdrawal, including seizure activity in cases of maternal opioid abuse. Assisted ventilation should be continued until resolution of the opioid effect rather than attempting to reverse it with naloxone.

If positive-pressure mask ventilation does not improve oxygenation (as reflected by an increase in heart rate), prompt tracheal intubation is indicated. Tracheal intubation must be performed gently to avoid damage to the delicate neonatal neck and airway. The size of the neonate's head is large relative to that of its body; therefore, the neonate is in the optimal position when it lies supine. In most cases, it is not necessary to elevate or hyperextend the neonate's head during laryngoscopy. The neonatal larynx is more anterior than that of the adult, and visualization often is easier when cricoid pressure is applied. The practitioner should hold the laryngoscope and apply cricoid pressure with the same hand. The thumb and first two fingers hold the base of the laryngoscope, the third finger rests on the mandible, and the fourth finger applies cricoid pressure. This technique promotes gentleness during airway manipulation. The distance from the gums to the larynx often is surprisingly short. A common mistake is to advance the laryngoscope blade too deeply—past the larynx and into the esophagus. When this error occurs, the larynx falls into view if the laryngoscope blade is withdrawn slowly to allow a second attempt.

The diameter of the endotracheal tube should be large enough to allow adequate ventilation and insertion of a suction catheter (if needed) but small enough to avoid causing trauma and subsequent subglottic stenosis. The ratio of internal diameter to gestational age should be less than 0.1 (e.g., 3.0 mm tube/35 weeks' gestation = 0.09).[128,129]

After tracheal intubation, positive-pressure ventilation should be resumed by means of an appropriate circuit, as described earlier for mask ventilation. Assessment of proper tube placement is accomplished by listening for breath sounds in both axillae. Exhaled CO_2 detection is the recommended method for confirming placement of the tube in the trachea.[2] False-negative results can occur in situations in which the infant is correctly intubated, with the tube in the trachea, but pulmonary blood flow is poor or absent. This may lead to unnecessary extubation in critically ill infants. As noted previously, the F_{IO_2} should be reduced as soon as possible, especially in the preterm neonate. The addition of a pulse oximeter and an oxygen blender allows more targeted delivery of supplemental oxygen to the preterm infant immediately after birth. If the neonate is to remain intubated, a chest radiograph should be obtained to confirm the exact position of the endotracheal tube. The skill and experience required for correct tracheal intubation and effective bag-and-mask ventilation may be lacking in providers who are inexperienced with neonatal resuscitation; as a consequence, the laryngeal mask airway (LMA) has been evaluated as a potential alternative airway device for neonatal resuscitation.[130-132] The LMA is blindly inserted into the pharynx, and a cuff is inflated to provide a low-pressure seal around the larynx. When evaluated in term infants requiring resuscitation at delivery, use of the LMA was found to be highly successful and without complications.[130,131] The revised neonatal resuscitation guidelines state that the LMA is an acceptable alternative means of establishing an airway in infants born at 34 weeks' gestation and greater and weighing over 2000 g; it can be used by appropriately trained providers when bag-and-mask ventilation is ineffective or attempts at tracheal intubation have been unsuccessful.[2]

One cause of unequal breath sounds and eventual circulatory collapse is a tension pneumothorax. Some physicians have recommended that providers of neonatal resuscitation be skilled in needle aspiration of a tension pneumothorax.[1] This maneuver is accomplished by placement of a 22- or 25-gauge needle in the second intercostal space in the midclavicular line (on the side where no

breath or heart sounds are heard). Air will rush out of the needle hub, thereby reducing the tension pneumothorax.

In the vast majority of resuscitations, the neonate responds to ventilatory support. Chest compressions are needed in only 0.03% of deliveries.[133] Chest compressions are indicated when the heart rate is less than 60 bpm despite adequate ventilation with supplemental oxygen for 30 seconds.[2]

The preferred method for providing chest compressions is with the thumbs of both hands and the hands encircling the chest.[2,134] Pressure is applied over the sternum just below an imaginary line drawn between the nipples; pressure applied over the lower part of the sternum or xiphoid can injure the abdomen. The sternum should be compressed to approximately one third the anteroposterior dimension of the chest, and the compression depth must be adequate to produce a palpable pulse.[2,135-137] The compression time should be slightly shorter than the release time, particularly to improve blood flow in the very young infant.[138] Ventilation is compromised if the chest is compressed simultaneously with the administration of positive-pressure ventilation. The recommended ratio of compressions to breaths is 3:1.[139,140] This pattern is given at a rate of 120 events per minute, with 90 chest compressions and 30 breaths administered each minute. Respirations, heart rate, and color should be rechecked every 30 seconds. Compressions should be resumed until the heart rate is 60 bpm or higher. Positive-pressure ventilation with supplemental oxygen titrated to Sao_2 should be continued until the heart rate is higher than 100 bpm.

Medications are rarely required during neonatal resuscitation because most neonates who require resuscitative measures respond well to satisfactory oxygenation and ventilation alone.[141] However, a variety of pharmacologic agents should be available in the delivery room (see Box 9-3). **Epinephrine** (0.01 to 0.03 mg/kg or 0.1 to 0.3 mL/kg of a 1:10,000 solution) should be administered if the heart rate remains lower than 60 bpm after 30 seconds of adequate ventilation and chest compressions.[2] Intravenous administration is the preferred route (via an umbilical venous line). While intravenous access is being established, intratracheal administration through an endotracheal tube may be considered; however, a larger dose of epinephrine (0.05 to 0.1 mg/kg) may be required. Administration of epinephrine is especially important if the heart rate is zero. Epinephrine raises the heart rate (the major determinant of neonatal cardiac output) and restores coronary and cerebral blood flow.[142]

Sodium bicarbonate is used infrequently during resuscitation. Because of its high osmolarity, this agent can cause hepatic injury at any gestational age and cerebral hemorrhage in the preterm infant[143,144]; it may also compromise myocardial and cerebral function.[145,146] It should be given only during prolonged resuscitation and when adequate ventilation and circulation have been established. Arterial blood gas measurements and serum chemistry determinations should guide the use of sodium bicarbonate. The current recommended dose is 1 to 2 mEq/kg of a 0.5 mEq/mL solution given over at least 2 minutes by slow intravenous push.

Atropine is not recommended for use during neonatal resuscitation. Epinephrine is considered the drug of choice for the treatment of bradycardia.

Calcium administration is not recommended for neonatal resuscitation, unless it is given specifically to reverse the effect of magnesium (which may have crossed the placenta from the mother to the fetus). Evidence suggests that calcium administration causes cerebral calcification and decreases survival in stressed neonates.[147]

Volume expanders must be given strictly according to recommended dosage. A continuous infusion is dangerous in the neonate, because it can easily result in the administration of an excessive fluid volume. Fluid overload can cause hepatic capsular rupture, brain swelling in the asphyxiated infant, or intracranial hemorrhage in the preterm infant. Fluids and medications can be administered either intravenously (most commonly through the umbilical vein) or, if necessary, intraosseously.

The cannulation of the umbilical vein involves insertion of a soft catheter into the cut end of the vein (Figure 9-5). The catheter is advanced until blood return is noted, but no more than 2 cm past the abdominal surface. If ongoing vascular access is required during the neonate's hospital course, the soft umbilical catheter can be advanced through the ductus venosus into the inferior vena cava. Care must be taken to avoid leaving the tip in an intermediate location because of possible hepatic damage if a high-osmolarity substance (e.g., improperly diluted sodium bicarbonate) were injected. Other complications of umbilical venous catheterization are hemorrhage and sepsis. The prolonged absence of vascular access in critically ill neonates can lead to hypoglycemia, which in association with hypoxia, can increase the risk for adverse neonatal outcomes.[148]

Intraosseous access is accomplished by insertion of a 20-gauge needle into the proximal tibia approximately 1 cm below the tibial tuberosity.[149] This technique may be easier to perform for practitioners who have little experience with intravenous or umbilical neonatal catheterization. Absorption from the neonatal bone marrow into the general circulation occurs almost immediately.[150,151] This rapid absorption results from the preponderance of red bone marrow over yellow bone marrow; yellow bone marrow is less vascular and is the dominant form of marrow after 5 years of age. Complications related to this technique are rare and include tibial fracture (which occurs more often in older children)[152] and osteomyelitis. The risk for infection is proportional to the duration of intraosseous infusion[153-155]; therefore, the needle should be removed after 1 to 2 hours and, if necessary, a more conventional route of access should be established. Current guidelines state that intraosseous access should be used for medication administration or volume expansion when venous access is difficult to achieve.[2]

Volume expanders should be considered when the infant demonstrates signs of shock, such as pale skin, poor perfusion, and weak pulse, or has not shown adequate response to other resuscitative measures. **Normal saline** and **lactated Ringer's solution** are the preferred volume expanders, given initially at 10 mL/kg over 5 to 10 minutes, with doses repeated as necessary after reassessment for ongoing hypovolemia. Intravascular volume

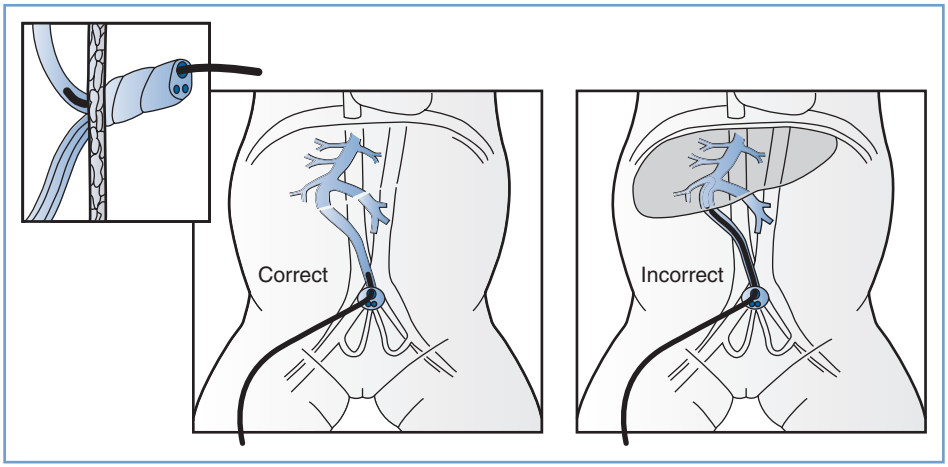

FIGURE 9-5 ■ Cannulation of the umbilical vein. A 3.5F or 5F umbilical catheter with a single end-hole and a radiopaque marker should be used. For emergency use, the catheter should be inserted into the vein of the umbilical stump until the tip of the catheter is just below the skin level but free flow of blood is present. If the catheter is inserted farther, there is a risk for infusing solutions into the liver and possibly causing damage. (Adapted from Textbook of Neonatal Resuscitation. 6th edition. Elk Grove Village, IL, American Academy of Pediatrics and American Heart Association, 2011:216.)

should be assessed through evaluation of heart rate, capillary refill time, and color. If heavy blood loss is suspected, O-negative packed red blood cells may be used according to the same dosage regimen.[2] Red blood cells replete the oxygen-carrying capacity as well as the intravascular volume. O-negative blood should be available at all times for emergency use during neonatal resuscitation. Placental blood has been used for neonatal volume expansion,[156] but this practice is discouraged in most institutions because of the risks of infection or transfusion of clotted blood. Albumin administration is no longer recommended, because it carries a risk for infectious disease and has been associated with higher mortality.[157]

SPECIAL RESUSCITATION CIRCUMSTANCES

Meconium Aspiration

There has been significant interest in the management of the neonate whose airway has been exposed to meconium-containing amniotic fluid. Meconium is present in the intestinal tract of the fetus after approximately 31 weeks' gestation. Meconium-stained amniotic fluid is present in 10% to 15% of all pregnancies; the incidence is higher in post-term pregnancies. Intrapartum passage of meconium may be associated with fetal stress and hypoxia.[158,159]

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate whose airway was exposed to meconium and whose chest radiographic study exhibits characteristic findings, including pulmonary consolidation and atelectasis.[160] Treatment of MAS often involves the use of positive-pressure ventilation and is associated with a 5% to 20% incidence of pneumothorax from pulmonary air leaks.[161] In one study of 176,790 infants born between 1973 and 1987, the annual death rate from MAS was as high as 6 per 10,000 live infants.[162] Extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide have been used for the treatment of pulmonary hypertension associated with MAS and have been observed to reduce mortality rates.[163-165]

Neonatologists have attempted to determine whether peripartum suctioning of the neonate's airway reduces the risk for developing MAS. Gregory et al.[162] published the original study of 80 meconium-exposed neonates who were born either vaginally or by cesarean delivery. All infants underwent tracheal intubation and suctioning after delivery. In 34 infants, no meconium was observed below the vocal cords; none of these infants demonstrated MAS. Meconium was noted below the cords in the remaining 46 infants, and MAS developed in a total of 16 (35%) of these infants. These investigators concluded that "all infants born through thick, particulate, or 'pea soup' meconium should have the trachea aspirated immediately after birth."[162] Subsequent studies documented similar findings for all infants born through meconium-stained fluid,[166] with a suggestion that earlier suctioning could decrease the incidence of MAS.[167] However, additional investigators documented that airway suctioning at birth does not prevent MAS and its associated mortality[168,169]; these studies indicated that MAS was primarily a result of intrauterine events such as asphyxia or sepsis. Hypoxia induces pathologic changes in the pulmonary vasculature, which results in pulmonary hypertension and respiratory distress after birth. The pulmonary damage is independent of meconium aspiration; therefore, it is not prevented by the suctioning of meconium.

Murphy et al.[170] examined the lungs of 11 neonates who had MAS and died within 4 days of birth. Ten of these neonates also had a diagnosis of persistent pulmonary hypertension, and all had evidence of excessive muscularization of the intra-acinar arteries, which is an abnormal finding in the fetus or neonate.[171,172] Meyrick and Reid[173] demonstrated that chronic hypoxia (i.e., at least 4 weeks' duration), but not acute hypoxia, results in pulmonary vascular muscularization in an animal model.

Murphy et al.[170] concluded that the pathologic findings in the 1- to 4-day-old human lung could not be explained by the postdelivery effects of meconium aspiration; a more likely origin was the intrauterine maldevelopment of the pulmonary vasculature. They suggested a potential link between greater intestinal motility, passage of meconium, and precocious muscularization of the intra-acinar arteries.

A prospective study designed to assess the efficacy of routine tracheal suctioning of meconium to prevent MAS indicated little or no benefit to this practice.[174] Among the infants who underwent tracheal suctioning, four experienced MAS and two had laryngeal stridor. By contrast, none of the infants who did not undergo suctioning had complications, suggesting that vigorous neonates who have begun breathing before transfer to the resuscitation table may derive little or no benefit from tracheal suctioning and, in fact, may suffer some harm.

A subsequent review of studies published between 1980 and 1999 found that most cases of severe MAS were not causally related to meconium aspiration but rather resulted from intrauterine stress.[175] The authors concluded that severe MAS is a misnomer because, in most cases, much more than meconium aspiration has contributed to the lung damage. The implication is that when severe MAS occurs, inadequate suctioning at delivery or during resuscitation should not be considered the cause; therefore, other causes of intrauterine lung damage should be investigated.

Amnioinfusion—the instillation of saline into the amniotic cavity—has been used successfully for reduction of cord compression in the presence of oligohydramnios during labor. It has also been proposed as a potential treatment to reduce the incidence of MAS in infants born to women with thick meconium staining of the amniotic fluid. Potential benefits include (1) the reduction of cord compression, thus alleviating fetal compromise and acidemia that contribute to MAS, and (2) the dilution or washing out of the meconium in the amniotic fluid. A large multicenter randomized trial found no difference in rates of MAS or other neonatal disorders with the use of amnioinfusion.[176,177] Thus, the routine practice of amnioinfusion for meconium-stained fluid alone is not recommended.[178]

Current guidelines do not recommend routine intrapartum oropharyngeal and nasopharyngeal suctioning before delivery of the infant's head,[2,179] given that a large multicenter randomized trial showed no benefit to this practice in term-gestation infants.[180] After stabilization of the infant, meconium may be gently cleared from the mouth and nose by means of a bulb syringe or a large suction catheter (e.g., 12F to 14F).

Preterm Infant

The preterm neonate, especially the VLBW infant, is at higher risk for problems with multiple organ systems simply because of immaturity. During resuscitation, the physician should give special attention to the effect of prematurity on the lungs and the brain. Before the addition of surfactant and high-frequency ventilation to the therapeutic armamentarium of the neonatologist, pulmonary hyaline membrane disease (also known as neonatal respiratory distress syndrome) was the overwhelming obstacle to the attempted salvage of the very preterm infant.

Between 1970 and 2005, the proportion of infants weighing less than 1500 g at delivery rose from 1.17% to 1.5%; in 2009, the proportion stabilized at 1.45%.[181] The survival rate of these 500- to 1500-g infants has increased to approximately 85%.[181] Of these, 5% to 10% have what is characterized as cerebral palsy and 25% to 50% exhibit behavioral and cognitive deficits that lead to important school problems (see Chapter 10).[182,183] These VLBW infants constitute a tiny proportion of the birth population, but they are at the highest risk for development of cerebral palsy; infants weighing less than 1500 g at birth account for 25% of cases of this disorder.[58]

Markers for brain injury affecting preterm infants are germinal matrix intraventricular hemorrhage (IVH) and periventricular leukomalacia. The brain injury may occur either as a consequence of the IVH and its sequelae or as an associated finding. The incidence of germinal matrix IVH in preterm infants declined from 35% to 50% in the late 1970s and early 1980s to approximately 15% in the mid 1990s.[184] Despite the decreased incidence of germinal matrix IVH, which is directly related to prematurity,[183] the overall burden of disability has sharply increased in recent years due to the proportion of very preterm infants who are surviving.[184] Periventricular leukomalacia, which is the classic neuropathology associated with hypoxic-ischemic cerebral white matter injury in the preterm infant, commonly accompanies IVH.[185]

The fragility of the immature subependymal germinal matrix predisposes the preterm infant to the development of IVH. The hemorrhage originates from the endothelial cell–lined vessels that course through the germinal matrix in free communication with the venous circulation (i.e., the capillary–venule junction). The mechanism of damage to these endothelial cells and to the integrity of these capillaries has been investigated in animal models[186] and in human neonates by means of Doppler velocimetry.[187]

Volpe,[188,189] who has reviewed the theories of the pathogenesis of germinal matrix IVH, has concluded that the pathogenesis is multifactorial; different combinations of factors are relevant in different patients. The three major categories in the pathogenesis of IVH are intravascular, vascular, and extravascular. **Intravascular factors** include fluctuating cerebral blood flow (CBF), which can result from respiratory disturbances in the ventilated preterm infant with neonatal respiratory distress syndrome[187,190]; increases in CBF[186,191]; increases in cerebral venous pressure[192]; decreases in CBF followed by reperfusion; and platelet and coagulation disturbances.[193] **Vascular factors** include the tenuousness of the capillary integrity of the germinal matrix and the vulnerability of the matrix capillaries to hypoxic-ischemic injury.[194] **Extravascular factors** include deficient vascular support, excessive fibrinolytic activity, and a possible postnatal decrease in extravascular tissue pressure.[195]

Of special interest in the discussion of antepartum and intrapartum care and neonatal resuscitation are the possible interventions that may prevent or lessen the severity

of IVH. The best way to prevent germinal matrix IVH is to prevent preterm birth. Infection and inflammation are the most common identified causes of preterm birth at the lowest relevant gestational age.[196] Antenatal *treatment* of infections has not been proved to prevent preterm labor or premature rupture of membranes[58]; however, *prevention* of infection, if possible, may be an important way to reduce the risk for IVH. Another intervention that lowers the incidence of IVH is the transportation of the preterm mother while the fetus is still *in utero* to a center that specializes in the care of high-risk neonates.[1]

Various antenatal pharmacologic interventions have been evaluated for the prevention of IVH. Clinical trials of antenatal maternal administration of phenobarbital[197,198] and vitamin K[199,200] have yielded conflicting results, and their routine use is not currently recommended.[58]

Corticosteroids are currently the most beneficial antenatal pharmacologic intervention for the prevention of IVH. This effect was first noticed when obstetricians began giving betamethasone and dexamethasone to pregnant women to help accelerate fetal lung maturity. The mechanism behind this protection is thought to be improved neonatal cardiovascular stability, which results in less hypotension and less need for blood pressure treatment in these infants.[201] Antenatal betamethasone administration leads to lower placental vascular resistance and higher placental blood flow.[202] This improvement in placental blood flow may decrease impairment of the preterm infant's cerebral autoregulation. In addition, corticosteroids may stimulate the maturation of the germinal matrix. There is consensus regarding the efficacy of a single course of corticosteroids in patients at risk for preterm delivery, but the risks and benefits of multiple courses of corticosteroids for women who remain undelivered 7 days after the initial dose are still controversial. Obstetricians must balance the possible benefits of these agents against their potentially deleterious effects on neuronal and organ growth (see Chapter 34).

Multiple studies have demonstrated a lower incidence of cerebral palsy in infants of mothers given magnesium sulfate for the treatment of preeclampsia or for tocolysis[203,204]; subsequent studies have observed a similar benefit when magnesium has been given specifically for fetal neuroprotection.[205-207] An ACOG committee opinion[208] now recommends the administration of magnesium sulfate to mothers in preterm labor. Maternal magnesium sulfate administration does not result in a decreased incidence of IVH, although the incidence of high-grade (grade III or IV) lesions may be reduced.[209] Although some investigators have suggested that antenatal exposure to magnesium sulfate results in a higher risk for adverse neonatal outcomes,[210] others have observed no association between umbilical cord blood magnesium concentration and the need for delivery room resuscitation when magnesium was administered for neuroprotection in anticipation of a preterm birth.[211]

Postnatal interventions that may prevent IVH include the avoidance of overly rapid infusion of volume expanders or hypertonic solutions such as sodium bicarbonate.[143,212] The establishment of adequate ventilation is the most beneficial immediate intervention that helps preserve cerebrovascular autoregulation in the preterm infant. The prevention of hypoxemia and hypercarbia is essential, because they are both linked to pressure-passive cerebral circulation, which in turn leads to the development of IVH.[212]

Among infants who exhibit fluctuating CBF velocity, Pearlman et al.[213] found that treatment with pancuronium bromide, which corrects this fluctuation, reduced both the incidence and severity of IVH.[213] Other clinical trials have evaluated the efficacy of other pharmacologic agents for the correction of fluctuating hemodynamic disturbances. Studies of meperidine[214] and fentanyl[215] have shown some benefit, but the side effects and need for prolonged ventilation associated with these agents must be weighed against any potential benefits.

If the use of antepartum and intrapartum pharmacologic prophylaxis against IVH becomes part of preterm delivery management, the practice of obstetric anesthesia for preterm patients will be directly affected. For example, the conventional wisdom is that preterm infants are more sensitive than term infants to the effects of maternally administered agents such as analgesics[216] and that this effect is inherently deleterious. However, if this effect is found to protect the preterm infant brain from factors that may lead to IVH (e.g., hemodynamic instability), perhaps obstetric anesthesia providers will no longer attempt to avoid the placental transfer of pharmacologic agents but will deliberately administer these agents to the mother with the intent that they reach the fetus.

Congenital Anomalies

Occasionally, neonatal resuscitation is complicated by congenital anomalies of the airway or diaphragm. These anomalies may manifest as respiratory distress, which resolves only when appropriate resuscitation techniques are used. For example, neonates are obligatory nose breathers. The diagnosis and management of choanal stenosis and atresia include placement of an oral airway or endotracheal tube until a definitive surgical procedure can be performed.

Other congenital anomalies that cause upper airway obstruction include (1) micrognathia, as in Pierre Robin sequence; (2) macroglossia, as in Beckwith-Wiedemann syndrome or glycogen storage disease type II; (3) laryngeal webs; (4) laryngeal atresia; (5) stenosis or paralysis at the level of the vocal cords; (6) subglottic stenosis; (7) subglottic webs; (8) tracheal agenesis; and (9) tracheal rings. Obstruction also can occur as a result of tumors such as subglottic hemangiomas. The presence of a cleft palate may lead to difficulty with manual ventilation. In an infant with micrognathia or macroglossia, airway patency may be maintained if the neonate is kept in the prone position, which reduces posterior movement of the tongue into the pharynx. If macroglossia is extreme, use of an oral airway or a small nasogastric or orogastric suction catheter may be necessary to prevent complete obstruction of the pharynx by the tongue.

When respiratory distress and difficulty with bag-and-mask ventilation are encountered, laryngoscopy should be performed. The cause of the obstruction may be evident if it is supraglottic in location. Some supraglottic entities

(e.g., laryngeal webs) may be treated successfully by passing an endotracheal tube through the obstruction and into the trachea. Subglottic lesions may require tracheostomy. The help of an otolaryngologist may be invaluable during resuscitation of a neonate with congenital airway obstruction. If there is antepartum evidence of such a condition (e.g., laryngeal stenosis), it is best to have an otolaryngologist present at the time of delivery.[217] If obstruction is discovered after delivery, the resuscitator should not hesitate to call for surgical assistance.

Fetal neck masses such as cervical teratoma and lymphangioma can lead to extrinsic airway compression. The resulting distortion of the airway can result in airway obstruction, and it may be difficult—if not impossible—to secure an airway in a timely fashion at delivery. These masses often are diagnosed before delivery because of the associated occurrence of polyhydramnios resulting from esophageal compression. In these rare cases, a multidisciplinary team should be assembled before delivery to assist in securing the airway. Leichty et al.[218] described a way of providing the time necessary to secure an airway, known as the **ex utero intrapartum treatment (EXIT) procedure** (see Chapter 7). An EXIT procedure delivers the fetal head and shoulders, but keeps the lower torso and umbilical cord intact within the uterus, thereby maintaining placental perfusion and oxygenation. The fetus can be given additional agents intramuscularly (fentanyl, vecuronium, and atropine) to provide fetal analgesia and to prevent movement and breathing. The FHR and Sao_2 are monitored continuously via a pulse oximeter probe attached to the fetal hand. The pediatric surgeon can then perform direct laryngoscopy, rigid bronchoscopy, or tracheostomy if necessary. After establishment of the airway, the delivery of the infant is completed.

The EXIT procedure has been considered an option for fetuses with a number of congenital anomalies.[219,220] A common indication for the EXIT procedure is an intrinsic airway obstruction. Intrinsic airway obstruction of the larynx or upper trachea (e.g., laryngeal web, subglottic cyst, tracheal atresia) can lead to retention of bronchial secretions and subsequent pulmonary distention; this constellation of findings is often classified as **congenital high airway obstruction syndrome (CHAOS).**[219] Use of the EXIT procedure resulted in the first long-term survival of a child with this syndrome.[221]

The EXIT procedure also may be useful in conditions such as severe congenital heart disease, in which the need for emergency ECMO at birth is anticipated. The EXIT procedure allows for the placement of arterial and venous cannulas before umbilical cord clamping, thereby avoiding an unstable period between the termination of placental perfusion and the institution of ECMO. [219] Other possible indications for the EXIT procedure include the resection of congenital cystic adenomatoid malformations and as a first step in separation procedures for conjoined twins with cardiovascular involvement.

Noah et al.[222] compared the short-term maternal outcomes of 34 patients who underwent the EXIT procedure between 1994 and 1999 with those in a control group who underwent nonemergency primary cesarean delivery. The EXIT procedure group had a higher estimated blood loss, but there was no difference in the postoperative hematocrit or duration of hospital stay. The EXIT procedure group also had a higher rate of superficial wound infection (15% versus 2%), but the incidence of endometritis was not different. A review of fetal and maternal outcomes after performance of an EXIT procedure in 12 infants with a giant neck mass found that 11 infants survived and 10 had normal development. All of the six mothers who desired future pregnancies subsequently had uncomplicated deliveries.[223]

Anesthetic considerations for the mother during an EXIT procedure include those relevant to general anesthesia for the mother undergoing cesarean delivery or other surgical procedures during pregnancy (see Chapters 7, 17, and 26). Several volatile halogenated agents have been used for the EXIT procedure, including isoflurane, desflurane, and sevoflurane.[219] The anesthetic management for an EXIT procedure differs from that for a routine cesarean delivery in the following ways: (1) general anesthesia is used much more often than neuraxial anesthesia, (2) a greater depth of anesthesia is achieved and maintained, (3) maximum uterine relaxation is desirable, (4) warm fluid is occasionally instilled into the uterus, and (5) a second anesthesiologist provides care for the fetus.[220]

George et al.[224] described an alternative approach for the EXIT procedure with the use of combined spinal-epidural anesthesia (1.5 mL of bupivacaine 0.75%, fentanyl 15 μg, and morphine 0.15 mg, administered intrathecally, followed by placement of a multiorifice epidural catheter). Supplemental oxygen was provided through a face mask at 6 L/min. Immediately before uterine incision, the patients were given intravenous nitroglycerin 50 to 100 μg, followed by an infusion of nitroglycerin (0.5 to 1.5 μg/kg/min), allowing adequate uterine relaxation for partial delivery of the infant's head. Maternal hypotension occurred in two of the three women and required vasopressor administration. After the infant's airway was secured and the infant's delivery was completed, the nitroglycerin was discontinued at the time of umbilical cord clamping.

Esophageal atresia and **tracheoesophageal fistula** occur in 1 of every 3000 births.[225] There are many variations of these anomalies, the most common being esophageal atresia with a distal tracheoesophageal fistula (80% to 90% of cases). Neonates with a tracheoesophageal fistula are at increased risk for the pulmonary aspiration of gastric contents through the fistula into the lung. When the presence of a tracheoesophageal fistula is not known antepartum, it should be suspected if bubbling secretions are observed during spontaneous or bag-and-mask ventilation. Once a tracheoesophageal fistula is suspected, bag-and-mask ventilation should be discontinued, because its use may contribute to overdistention of the gastrointestinal tract with air, possibly leading to difficulty in ventilation from impingement of the enlarged stomach on the diaphragm. A suction catheter should be placed in the esophageal pouch to facilitate the removal of oral secretions. If mechanical ventilation is necessary, an endotracheal tube should be inserted with the tip distal to the entrance of the fistula. This positioning can be accomplished by performing an intentional right mainstem bronchial intubation followed by slowly

TABLE 9-5 Guidelines for Withholding or Discontinuing Resuscitation

Conditions with high survival, acceptable risk for morbidity	≥ 25 weeks' gestational age Most congenital malformations	Resuscitation nearly always indicated
Conditions with poor prognosis, high risk for morbidity	23 to 25 weeks' gestational age	Parental desires about initiating/continuing resuscitation should be supported
Conditions with almost certain death or unacceptably high morbidity	< 23 weeks' gestational age Birth weight < 400 g Anencephaly Chromosomal abnormalities incompatible with life (e.g., trisomy 13)	Resuscitation not indicated

Modified from Neonatal Resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2010; 126:e1400-1413.

withdrawing the tube until breath sounds are auscultated on the left; a lack of breath sounds over the stomach should then be confirmed. Percutaneous gastrostomy placement may be necessary during resuscitation to facilitate decompression of the gastrointestinal tract.

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 3000 live births.[226] The mortality rate from CDH is 30% to 60%. In 80% to 90% of cases the CDH occurs on the left side and is the result of herniation of the gut through the posterolateral defect of Bochdalek. During formation of the lung, herniation of the gut into the thoracic cavity results in hypoplasia of the lung tissue and pulmonary vasculature. This hypoplasia may be unilateral, but often it is bilateral because of the shift in mediastinal structures to the other side. CDH should be suspected when a neonate has respiratory difficulty and a scaphoid abdomen; this abnormal abdominal shape results from the presence of abdominal contents in the thorax.

During resuscitation of the neonate with CDH, bag-and-mask ventilation is contraindicated because it allows further distention of the gut, which would further impinge on the lung. Tracheal intubation is recommended, followed by the placement of a nasogastric or orogastric tube to ensure decompression of the gastrointestinal tract. Ventilation should consist of low-positive-pressure breaths to decrease the risk for causing a pneumothorax on the side contralateral to the CDH. If a pneumothorax does occur, it must be evacuated promptly. In the neonate, evacuation is accomplished initially by placement of a 22-gauge needle into the second intercostal space in the midclavicular line and aspiration of air with an attached stopcock and syringe. Severe pulmonary hypertension often accompanies CDH. Maintenance of euthermia, normoxia, and adequate systemic blood pressure promotes pulmonary artery blood flow.

Whenever congenital anomalies of the respiratory tract are noted, the presence of other anomalies should be suspected. It is important to evaluate the neonate promptly for cardiac malformations, especially if appropriate resuscitative efforts are not successful. Echocardiography is used to evaluate cardiac structures and function.

ETHICAL CONSIDERATIONS

The current neonatal resuscitation guidelines address the ethical considerations of non-initiation or discontinuation of resuscitation in the delivery room.[2] Extremes of prematurity (< 23 weeks' confirmed gestation) and severe congenital anomalies (e.g., anencephaly, confirmed trisomy 13 or 18) are examples of circumstances when non-initiation of resuscitation is considered appropriate. Because intrapartum confirmation of pertinent information may not be possible, it is recognized that initiation of resuscitation may occur and that its discontinuation may then be appropriate after further information has been obtained and discussion with family has occurred. In some cases, a trial of therapy may be appropriate, which does not always mandate continued support. In situations or conditions in which there is a high rate of survival and acceptable morbidity (i.e., ≥ 25 weeks' gestation and most congenital malformations), resuscitation is generally indicated. For those situations with a poor prognosis, including unlikely survival and potentially high morbidity (i.e., 23 to 25 weeks' gestation), the parents' desires as to initiation of resuscitation should be supported (Table 9-5).[227]

Discontinuation of resuscitation of an infant with cardiopulmonary arrest may be appropriate if spontaneous circulation has not occurred in 15 minutes. After 10 minutes of asystole, survival itself and survival without severe disabilities are very unlikely.[227-232]

NEUROBEHAVIORAL TESTING

It is difficult to detect subtle neurobehavioral differences among neonates during the assignment of Apgar scores or the performance of the initial neurologic examination; therefore, investigators have developed and studied methods of documenting neonatal neurobehavioral status (Table 9-6). In the past, the neonate was considered incapable of exhibiting higher cortical function. However, investigators have noted that the term neonate is able to sense and respond to a variety of stimuli in a well-organized fashion.[233-235]

In 1973, Brazelton[236] described the Neonatal Behavioral Assessment Scale (NBAS) with the following four variables as key determinants of neonatal neurobehavior: (1) various prenatal influences (e.g., infection); (2) the maturity of the infant, especially its CNS; (3) the effects of analgesics and anesthetics administered to the mother before and during delivery; and (4) the effects of difficulties encountered during delivery (e.g., trauma). The NBAS was developed as a tool to detect neurobehavioral

TABLE 9-6 **Neurobehavioral Tests for Neonates**

Neurobehavioral Test	Items Tested	Focus	Uses
Brazelton (Neonatal Behavioral Assessment Scale)	45 individual tests taking 45 minutes	Early cortical function	Evaluates prenatal influences, effects of maturity, maternal medications, effects of difficult delivery
Scanlon (Early Neonatal Behavior Scale)	26 observations taking 6-10 minutes	Early cortical function	Evaluates effects of maternal medications
Amiel-Tison (Neurologic and Adaptive Capacity Score)	20 criteria taking 3-4 minutes	Motor tone	Differentiates drug-induced depression from depression related to asphyxia, trauma, or neurologic disease

abnormalities that resulted from any of these four variables.

This scale consists of 47 individual tests with 27 evaluating behavior and 20 evaluating elicited or provoked responses. The 47 tests can be completed in approximately 45 minutes. The NBAS evaluates the ability of the neonate to perform complex motor behaviors, to alter the state of arousal, and to suppress meaningless stimuli. The goal is to provide an extensive evaluation of neonatal cortical function and to detect subtle differences among groups of infants. Habituation (i.e., the ability to suppress the response to meaningless, repetitive stimuli) is considered an excellent indicator of normal early cortical function.[233]

In 1974, Scanlon et al.[237] described the Early Neonatal Behavioral Scale (ENNS), which consisted of tests that were easy to perform and score quantitatively during the neonatal period. The ENNS was developed primarily for the evaluation of the effects of maternal medications (e.g., analgesic and anesthetic agents) on neonatal neurobehavior. The ENNS consists of (1) 15 observations of muscle tone and power, reflexes (e.g., rooting, sucking, Moro), and response to stimuli (e.g., light, sound, pinprick); (2) 11 observations of the infant's state of wakefulness; (3) an assessment of the ability of the neonate to habituate to repetitive stimuli; and (4) an overall general assessment of neurobehavioral status. This test can be performed in 6 to 10 minutes.

In 1982, Amiel-Tison et al.[238] described the Neurologic and Adaptive Capacity Score (NACS) to differentiate neonatal depression secondary to maternally administered drugs from depression due to asphyxia, birth trauma, or neurologic disease. Whereas the ENNS concentrates on the infant's habituation ability, the NACS emphasizes motor tone as a key indicator of drug-induced abnormal neurobehavior. The basis for this emphasis on neonatal motor tone is explained as follows: unilateral or upper body hypotonus may occur as a result of either birth trauma or anoxia, but global motor depression is more likely a result of anesthetic- or analgesic-induced depression. A total of 20 criteria are tested in the areas of adaptive capacity, passive tone (e.g., scarf sign), active tone (e.g., assessment of the flexor and extensor muscles of the neck), primary reflexes (e.g., Moro), and alertness. The total possible score is 40, and a score of 35 to 40 is considered normal. The NACS can be performed in 3 to 4 minutes.

Amiel-Tison et al.[238] examined inter-observer reliability and assessed the correlation of results between the NACS and ENNS. The inter-observer reliability was 93% for the NACS and 88% for the ENNS. Approximately 92% of infants with high scores on the ENNS scored equally well on the NACS. However, the reliability of NACS has been questioned[239,240]; Halpern et al.[241] examined 200 healthy term infants with the NACS and found poor inter-observer reliability. In contrast, in 2002 Amiel-Tison[242] reported her later experience with the NACS and documented good inter-observer reliability.

Anesthesiologists have used neurobehavioral testing to document the effects of analgesic and anesthetic agents and techniques on neonatal neurobehavior (see Table 9-6); the American Academy of Pediatrics[243] and the U.S. Food and Drug Administration[244,245] have recommended that these investigations be performed. A number of studies have demonstrated transient, serum concentration–dependent depression of neonatal neurobehavior with the maternal administration of systemic agents (e.g., meperidine, diazepam).[246-248] However, in a NBAS examination that controlled for patient and labor and delivery characteristics, only decreased habituation was observed in neonates born to mothers who had received intravenous meperidine.[249] Similarly, maternal administration of intravenous fentanyl appears to minimally affect neonatal NACS examinations.[250]

As is the case with many studies of systemic agents, studies of epidural anesthesia are often confounded by variables that are difficult to control, such as different patient populations, varied durations of labor, and multiple drug administrations. Scanlon et al.[237] introduced the ENNS in a study of the effect of maternal epidural anesthesia on neonatal neurobehavior. The researchers concluded that epidural anesthesia was associated with lower ENNS scores because of decreased muscle strength and tone. In this study, all patients who had received epidural anesthesia were considered part of one group, although 9 patients had received lidocaine and 19 had received mepivacaine. Further investigation showed that epidural lidocaine, even when administered in larger doses for cesarean delivery, does not affect ENNS scores.[251] The difference in ENNS scores between the epidural and nonepidural groups noted in the earlier study[237] was most likely related to the use of mepivacaine rather than lidocaine.[252] As was observed with lidocaine, epidurally administered bupivacaine, 2-chloroprocaine,

and etidocaine—when given for cesarean delivery—do not affect ENNS scores.[251,253] Kuhnert et al.[254] assessed NBAS scores in a group of infants exposed to either epidural lidocaine or 2-chloroprocaine. Although the investigators observed subtle changes in neurobehavior in the group of infants whose mothers had received lidocaine, they concluded that other variables (e.g., mode of delivery) are more likely to affect performance on neurobehavioral testing.

Sepkoski et al.[255] compared NBAS scores between two groups of vaginally delivered infants. In one group, the mothers had received epidural bupivacaine, and in the other group, the mothers had received no anesthesia or analgesia. The infants in the epidural group showed less alertness, less orientation ability, and less motor function maturity than the infants in the control group. However, variables such as duration of labor, incidence of oxytocin administration, and incidence of instrumental delivery were not similar in the two groups. Earlier, Abboud et al.[256] performed ENNS examinations on vaginally delivered infants whose mothers had received epidural bupivacaine. In this study, epidural administration of bupivacaine did not affect the ENNS scores. The maternal doses of epidural bupivacaine and the maternal venous and umbilical cord blood bupivacaine concentrations were similar to those noted by Sepkoski et al.[255] Abboud et al.[256] also noted normal ENNS scores for infants whose mothers had received epidural lidocaine or 2-chloroprocaine.

Critics of the ENNS and NACS claim that the evaluations are unable to demonstrate subtle differences in neurobehavior that would be detected by the more comprehensive NBAS.[257] However, although some differences have been observed in NBAS performance among groups of infants exposed or not exposed to local anesthetics, confounding variables have prevented clear conclusions as to cause and effect.

Hodgkinson et al.[258] observed that the subarachnoid administration of tetracaine for cesarean delivery did not adversely affect ENNS performance. Other studies have indicated that NACS performance is not significantly affected by the maternal epidural administration of opioids[259-264] or epinephrine (in combination with a local anesthetic).[265-268]

The effects of general anesthetic agents on neonatal neurobehavior have been evaluated by the ENNS and NACS. In a prospective, randomized study, Abboud et al.[269] assessed NACS performance at 15 minutes, 2 hours, and 24 hours of age in infants whose mothers received general, epidural, or spinal anesthesia for cesarean delivery. Women who underwent general anesthesia received thiopental 4 mg/kg followed by enflurane 0.5% with nitrous oxide 50% in oxygen. Although the NACS was lower at both 15 minutes and 2 hours of age in the infants in the general anesthesia group than in the infants in the neuraxial anesthesia groups, no difference in NACS results was noted at 24 hours of age.

Hodgkinson et al.[258] used the ENNS to evaluate outcomes among three groups of infants, all of whom were delivered by elective cesarean delivery. One group of women received general anesthesia with thiopental 4 mg/kg followed by 50% nitrous oxide. A second group received general anesthesia with ketamine 1 mg/kg followed by 50% nitrous oxide. A third group received spinal anesthesia with tetracaine 6 to 8 mg. The ENNS evaluations were conducted at 4 to 8 hours of age and again at 24 hours. During the 4- to 8-hour examination, infants in the spinal anesthesia group scored significantly higher on multiple components of the ENNS than did infants in either of the general anesthesia groups. At 24 hours, infants in the spinal anesthesia group scored significantly higher than those in the thiopental group in alertness, total decrement score, and overall assessment. Similarly, infants in the spinal anesthesia group scored higher than those in the ketamine group in alertness and overall assessment. No significant differences existed between the scores of the thiopental group infants and the ketamine group infants.[258] Palahniuk et al.[270] observed similar results in a study that compared groups of infants whose mothers received either epidural anesthesia or general anesthesia for elective cesarean delivery. Infants whose mothers had received thiopental and nitrous oxide scored significantly lower in the alertness component of the ENNS than infants whose mothers had received epidural lidocaine with epinephrine.

Stefani et al.[271] observed that subanesthetic maternal doses of enflurane or nitrous oxide did not affect neonatal neurobehavior (as assessed by ENNS and NACS) at 15 minutes, 2 hours, and 24 hours of age. Abboud et al.[272] obtained similar results from NACS examinations of infants whose mothers had received subanesthetic doses of isoflurane.

The long-term effects of perinatal exposure to either general or neuraxial anesthesia at the time of cesarean delivery compared with vaginal delivery appear limited. In a population-based birth cohort, Sprung et al.[273] found that children exposed to either general or regional anesthesia during cesarean delivery were not more likely to develop learning disabilities than children who were delivered vaginally.

In summary, subtle changes in neonatal neurobehavior may result from factors such as antepartum maternal drug exposure. Parent-infant bonding and the ability of the infant to breast-feed may be adversely affected by these neurobehavioral changes.[233] These transient effects may seem trivial to some observers but important to others. With regard to the long-term neurologic outcome of individual infants, performance during neurobehavioral assessment may aid the observer in the formulation of a prognosis. However, as demonstrated with Apgar scores, the prognostic value of an isolated test score is likely to be lower than the prognostic value of multiple factors considered together during the overall assessment of an individual infant.

KEY POINTS

- The anesthesia provider attending the mother should not be responsible for resuscitation of the neonate. However, all anesthesia providers should be prepared to provide assistance during neonatal resuscitation when it is needed.

- Adverse conditions at birth (e.g., hypoxia, acidosis, profound hypovolemia, hypothermia) may impair the transition from intrauterine to extrauterine life. Impaired transition may manifest as persistent pulmonary hypertension of the newborn.
- The Apgar scoring system gives the practitioner a standard guide for assessing the need for neonatal resuscitation.
- No single factor should be considered prognostic of poor neurologic outcome. A combination of factors, including severe metabolic acidemia and Apgar scores of 3 or less beyond 5 minutes, are included among the criteria that suggest the occurrence of intrapartum hypoxia of sufficient severity to cause long-term neurologic impairment. However, not all infants who fulfill these criteria suffer permanent neurologic injury.
- Severe mixed or metabolic acidemia—but not respiratory acidemia alone—is associated with a higher incidence of neonatal complications and death.
- During evaluation of the apneic neonate, assisted ventilation should be initiated promptly if tactile stimulation does not result in the initiation of spontaneous breathing.
- Air rather than 100% oxygen should be used for initial neonatal resuscitation. If necessary, the administration and titration of supplemental oxygen should be guided by pulse oximetry.
- Meconium-exposed neonates no longer require nasopharyngeal and oropharyngeal suctioning before delivery of the thorax or endotracheal tube suctioning after delivery. Meconium-stained fluid may represent evidence of fetal compromise; thus, the infant may be more likely to require neonatal resuscitation.
- In most circumstances, decisions about the initiation or continuation of resuscitation in the delivery room should be based on the neonate's response to resuscitative efforts rather than an estimation of gestational age. Parental desires should be considered when the prognosis for infant survival is poor.

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CHAPTER 10

Fetal and Neonatal Neurologic Injury

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CHAPTER OUTLINE

The detection and diagnosis of fetal and neonatal brain injury have been advanced by improvements in functional imaging and the identification of potential biochemical markers. Evidence indicates that inflammatory mediators play an important role in the pathophysiology of fetal brain injury. Evidence also suggests that maternal administration of magnesium sulfate before anticipated early preterm birth reduces the risk for cerebral palsy in surviving infants. New data suggest that induced hypothermia is beneficial for the treatment of neonatal hypoxic ischemic encephalopathy. Of specific concern to anesthesia providers is rodent and nonhuman primate data that suggest that fetal exposure to anesthetic agents may have harmful effects on neurogenesis and synapse formation in the developing brain. Overall, however, little progress has been made in reducing the incidence of neonatal brain injury and cerebral palsy.

FETAL BRAIN DEVELOPMENT

Generation of the various cell types that populate the developing brain, and the subsequent layering and organization, is a precisely regulated process encoded by genetic programs and modified by epigenetic influences.[1-4] Contrary to previous dogma, it is now well established that the brain continuously evolves during ontogeny and that these processes are susceptible to subtle changes in the internal and external milieu. Although such neurodevelopmental processes occur throughout the human lifespan, the process is most robust and dynamic during the perinatal period.[5] Much of our understanding of the processes that drive fetal brain development comes from studies in rodents and nonhuman primates.[6] With recent advances in neuroimaging, it is now possible to study brain anatomy and assess neurobehavioral changes in the human fetus.[7]

When pathways leading to orderly brain development are deconstructed, three major events appear critical to the establishment of functional synapses. **Neuronal proliferation, migration,** and **cellular differentiation** occur in a preordained fashion to establish early neural circuitry. These processes often overlap and occur at different rates in different brain regions. **Neurogenesis**, a term that encompasses both neuronal proliferation and subsequent survival, begins with neural stem/progenitor cells in neurogenic niches such as the subventricular zone and the subgranular zone of the dentate gyrus. These neural progenitor cells undergo mitosis to generate immature neurons that migrate in a radial fashion and laminate the cortex in an "inside-out" fashion.[8] Interneurons, which comprise 10% to 15% of the total neuronal cells in the brain, originate from the ganglionic eminences in the developing brain.[9] These newly generated interneurons, which play an indispensable role in circuit inhibition, migrate in a tangential manner to populate

distinct brain areas. Both forms of migration are guided by cell-intrinsic mechanisms as well as by structural scaffolds and humoral mediators such as **gamma-aminobutyric acid (GABA)** and **glutamate**.[10,11]

In humans, neurogenesis starts and peaks at 5 and 25 weeks' gestation, respectively, while neuronal migration is completed between 30 and 36 weeks' gestation.[12] Between 20 and 40 weeks' gestation, these processes are followed by the generation of an array of supporting glial cells, such as astrocytes and oligodendrocytes.[12] Concurrently, synapse formation begins as early as the 10th week of gestation and continues to increase gradually at a rate of approximately 4% per week until the end of the second trimester. After this phase, a robust and exponential increase in synapse formation (almost 40,000 synapses/min) occurs between 28 weeks' and term gestation.[13] These processes, in conjunction with the onset of myelination, result in a fivefold increase in brain volume and the appearance of morphologic features of the mature brain such as sulci and gyri. By 24 weeks' gestation the fetus has all the neural machinery necessary to perceive pain.[14] Many clinicians recommend that appropriate measures should be taken to provide fetal analgesia during fetal surgical procedures from this point onward.[15]

Although the ontogeny of neurotransmitter systems is less well studied, a wealth of animal and human data indicates that these systems appear very early in life, before the phase of active synaptogenesis.[12] The presence of these neuromodulatory substances before synapse formation lends credence to the view that they serve a trophic role during early brain development, a role that is distinct from their predominant role of facilitating synaptic neurotransmission in the mature brain. Among these neurotransmitters, GABA remains the most widely studied (Figure 10-1).[16] Although GABA has an inhibitory action in the mature brain, GABA serves an excitatory role during fetal brain development. The major mechanism for this role reversal is the differential expression of chloride ion transporters NKCC1 and KCC2; these transporters increase the intracellular concentration of chloride in developing neurons.[17] On stimulation of **GABA receptors** that are expressed in neural progenitor cells and immature neurons, chloride ions are actively extruded, causing membrane depolarization rather than the hyperpolarization seen in mature neurons. This depolarizing effect of GABA decreases DNA synthesis and inhibits proliferation of neural progenitor cells,[18] causes concentration- and time-dependent effects on neuronal migration,[11] and plays a major role in activity-dependent synapse formation.[19]

The ***N*-methyl-D-aspartate (NMDA)-subtype glutamate receptors** originate later than the GABA receptors and remain functionally silent because of magnesium ion–induced channel blockade; thus, they play a limited role during early brain development. Dopaminergic, cholinergic, and serotonergic systems develop concomitantly and appear fully functional by the second trimester.[12] Pharmacologic interventions (e.g., ethanol, antiepileptic drugs) that act directly or indirectly on these powerful neuromodulator systems induce long-lasting impairment of fetal brain development, mainly owing to impaired neurogenesis and/or altered neuronal migration.[20-22] Alteration of this excitation-inhibition balance is purported to be responsible for an array of childhood neurodevelopmental disorders.

Experimental studies reveal that the fetal blood-brain barrier is morphologically well developed and functionally competent at term.[23] Convincing evidence confirms that the endothelial tight junctions of the blood-brain barrier are as effective in the term fetus as in the adult, although the exact time that blood-brain barrier competency is established in the human fetus is unknown. In rodents, data suggest that the fetal blood-brain barrier is established between embryonic days 11 and 17 (term gestation is 22 days), a time period that corresponds to approximately the late second and early third trimesters in humans.[24]

CEREBRAL PALSY

History, Definitions, and Significance

In 1861, John Little, an orthopedic surgeon, first described cerebral palsy in a report to the Obstetrical Society of London. Described as a neonatal neurologic disorder associated with difficult labor or birth trauma, the disorder was known as Little's disease until William Osler coined the term *cerebral palsy* in 1888.[25] A precise definition and classification of cerebral palsy has proved elusive. In the forward to the "Report on the Definition and Classification of Cerebral Palsy," published in 2007 in *Developmental Medicine and Child Neurology*, Peter Baxter[25] wrote, "This [supplement] illustrates the difficulties inherent in trying to agree what we mean by the terms we use and that a classification that suits one purpose, such as a diagnostic approach, may not always be ideal for others, such as therapy issues. Defining and classifying cerebral palsy is far from easy. We do need a consensus that can be used in all aspects of day-to-day care and for future research on cerebral palsy."

Today, **cerebral palsy** is defined as a nonprogressive disorder of the central nervous system (CNS) present since birth that includes some impairment of motor function or posture.[25] *Intellectual disability* (formerly known as *mental retardation*) may be present but is not an essential diagnostic criterion. Various forms of cerebral palsy exist, with differences in pathology, pathophysiology, and potential relationships with intrapartum events. The literature on cerebral palsy is difficult to review and understand. Data from individual studies are difficult to compare because of variations in the duration of follow-up, birth weight classifications, inclusion criteria for congenital abnormalities, and exclusion criteria for various causes of death. Terms such as *hypoxic-ischemic encephalopathy of the newborn*, *newborn asphyxia*, *birth asphyxia*, and *asphyxia neonatorum* are difficult to distinguish. Some authorities, including the American College of Obstetricians and Gynecologists (ACOG), have argued that the term *birth asphyxia* should be abandoned.[26]

Intrapartum events continue to receive the blame for some cases of cerebral palsy. It is a widely believed theory that an intrapartum reduction in fetal oxygen delivery may cause cerebral palsy, and early reports in primates

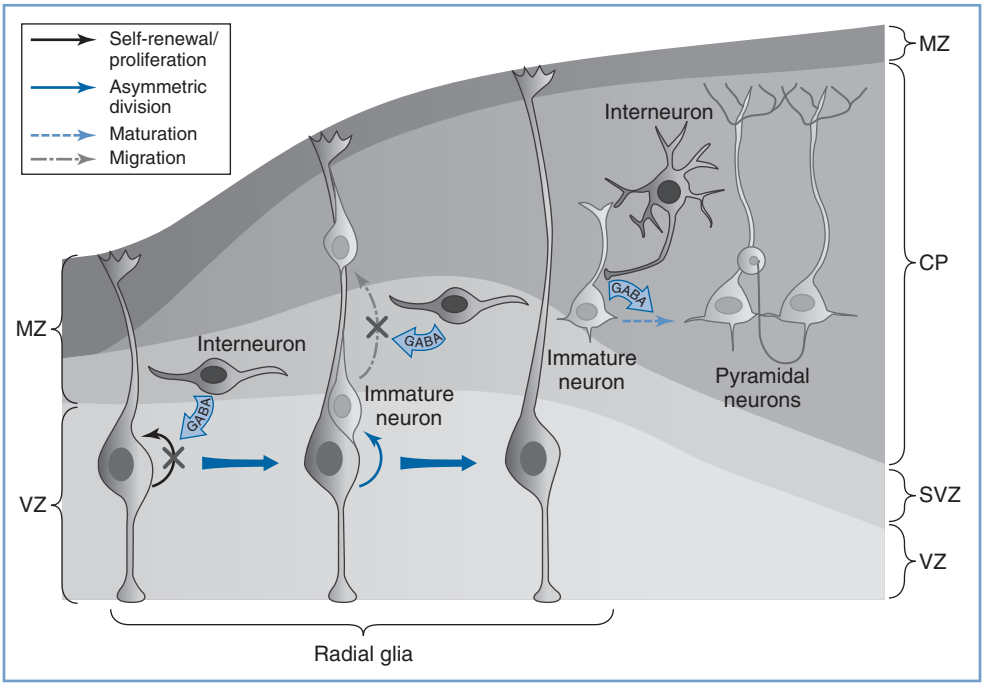

FIGURE 10-1 ■ Gamma–aminobutyric acid's (GABA) role in regulating embryonic cortical development. During corticogenesis, interneurons migrating in the subventricular zone (SVZ) can release GABA and activate GABAergic receptors on the radial glia, depolarizing these progenitors and decreasing their proliferation. Radial glia generate immature pyramidal neurons through asymmetric division, and the migration of these immature neurons along the radial fibers is decreased by GABA signaling. As young neurons assume their position in the cortex and begin to mature, GABA-mediated depolarization by the interneurons is required for the development of dendritic arbors and excitatory synaptic inputs from other pyramidal neurons. *MZ,* marginal zone; *VZ,* ventricular zone; *SVZ,* subventricular zone; *CP,* cortical plate. (From Wang DD, Kriegstein AR. Defining the role of GABA in cortical development. J Physiol 2009; 587:1873-9.)

demonstrated that perinatal asphyxia could cause brain injury.[27] Continuous electronic fetal heart rate (FHR) monitoring, which has largely replaced intermittent FHR auscultation during labor, is believed to prompt the delivery of at-risk fetuses and thus reduce asphyxial events. However, despite a higher incidence of cesarean delivery, no reduction in the incidence of cerebral palsy has been observed since the widespread implementation of continuous electronic FHR monitoring during labor.[28,29] Further, among patients with new-onset late FHR decelerations, an estimated 99% of tracings would be false positive "if used as an indicator for subsequent development of cerebral palsy."[30] This information is probably surprising to the lay public and trial lawyers as well as to obstetricians; a survey of maternal-fetal medicine fellows showed that they, too, have greatly overestimated the diagnostic accuracy of FHR monitoring.[30]

Large randomized trials have not demonstrated better fetal and neonatal outcomes with continuous electronic FHR monitoring than with intermittent FHR auscultation.[31,32] In an editorial citing observations made by Schifrin and Dame,[33] Friedman[34] opined, "The absence of either suggestive or overtly ominous fetal heart rate patterns is reliably reassuring." Unfortunately, there is little objective evidence that reassuring FHR tracings exclude the subsequent occurrence of cerebral palsy. In a 1993 review of published FHR monitoring studies, Rosen and Dickinson[35] could not identify FHR patterns that were consistently associated with neurologic injuries. Moreover, no consistent FHR pattern was observed in a subset of 55 brain-damaged infants. These investigators concluded, "We do not advocate the abandonment of the use of electronic fetal monitoring, but we do believe that it is yet to be proved to be of value in predicting or preventing neurologic morbidity." A more focused application of FHR monitoring may ultimately be found useful. For example, fetal inflammatory changes, which can be associated with neurologic injury, may be associated with characteristic FHR findings.[36] Thus, electronic FHR monitoring provides incomplete data that should be evaluated in the clinical context in which is it used.

Despite significant limitations in the use of intrapartum electronic FHR monitoring, there is no doubt that it will continue to be used for the foreseeable future. In a review of medicolegal issues in FHR monitoring, Schifrin and Cohen[37] noted that despite its limitations, "Monitoring deserves credit for reducing intrapartum death, one of the original rationales for its development."

A 2008 workshop (sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the ACOG, and the Society for Maternal-Fetal Medicine [SMFM]) updated the definitions of various types of FHR tracings to simplify interpretation for providers.[38] As a result, a three-category system was developed. Category I FHR tracings provide the most reassuring evidence of fetal well-being and strongly predict *normal* fetal acid-base status at the time of observation. Category III tracings are the most ominous; these tracings predict *abnormal* fetal acid-base status at the time

of observation and require prompt evaluation. Most FHR tracings are category II (indeterminate). Category II tracings are *not* predictive of *abnormal* fetal acid-base status, but they do not provide sufficient evidence to be classified as either normal or abnormal; these tracings require continued surveillance and reevaluation (see Chapter 8).

Intrapartum events are responsible for some cases of cerebral palsy[39]; however, these cases are few. After exclusion of infants with significant congenital anomalies, intrapartum events—including asphyxial insults—likely account for only 5% to 8% of all cases of cerebral palsy at all gestational ages.[40,41] In 1999, the International Task Force on Cerebral Palsy published a consensus statement summarizing criteria that are necessary and suggestive of an intrapartum etiology for neurologic abnormalities (Box 10-1).[42] In 2010, a proposed evidence-based neonatal workup to confirm or refute allegations of intrapartum asphyxia was published.[43]

BOX 10-1 Criteria to Define an Acute Intrapartum Hypoxic Event as Sufficient to Cause Cerebral Palsy

Essential Criteria (all four must be met)

1. Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7 and base deficit ≥ 12 mmol/L)*
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks' gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type†
4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, and genetic disorders

Criteria That Collectively Suggest an Intrapartum Event—within Close Proximity to Labor and Delivery (e.g., 0 to 48 hours)—but Are Nonspecific to Asphyxial Insults

1. A sentinel (signal) hypoxic event occurring immediately before or during labor
2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal
3. Apgar scores of 0 to 3 beyond 5 minutes
4. Onset of multisystem involvement within 72 hours of birth
5. Early imaging study showing evidence of acute nonfocal cerebral abnormality

*Buffer base is defined as the amount of buffer in blood available to combine with nonvolatile acids. A buffer base of 34 mmol/L is equivalent to a whole blood base deficit of 12 mmol/L.

†Spastic quadriplegia and, less commonly, dyskinetic cerebral palsy are the only types of cerebral palsy associated with acute hypoxic intrapartum events. Spastic quadriplegia is not specific to intrapartum hypoxia. Hemiparetic cerebral palsy, hemiplegic cerebral palsy, spastic diplegia, and ataxia are unlikely to result from acute intrapartum hypoxia.

From Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. Am J Obstet Gynecol 1998; 179:507-13.

Epidemiology and Etiology

The causes of cerebral palsy are not known, but the varying forms suggest a multifactorial etiology. The Collaborative Perinatal Project still represents one of the largest studies of the antecedent factors associated with cerebral palsy. The investigators in this study evaluated the outcomes of 54,000 pregnancies among patients who delivered at 12 university hospitals between 1959 and 1966. They evaluated more than 400 variables in a univariate analysis,[44] which identified potential risk factors that were then subjected to a more rigorous multivariate analysis.[45] Maternal age, parity, socioeconomic status, smoking history, maternal diabetes, duration of labor, or use of anesthesia was not associated with cerebral palsy in the univariate analysis. The factors most strongly associated with cerebral palsy in the multivariate analysis were (1) maternal mental retardation, (2) birth weight of 2000 g or less, and (3) fetal malformations. Other factors associated with cerebral palsy included (1) breech presentation (but not vaginal breech delivery), (2) severe proteinuria (more than 5 g/24 h) during the second half of pregnancy, (3) third-trimester bleeding, and (4) a gestational age of 32 weeks or less. There was a slight association between cerebral palsy and fetal bradycardia, chorioamnionitis, and low placental weight. However, only 37% of the cases of cerebral palsy occurred in patients with one or more of these identified risk factors.

Rosen and Dickinson[46] reviewed studies from Europe, Australia, and the United States that were published between 1985 and 1990 and included data from 1959 to 1982. The incidence of cerebral palsy ranged from 1.8 to 4.9 (composite rate of 2.7) cases per 1000 live births. The incidence of certain conditions in infants with cerebral palsy was as follows: birth weight less than 2500 g, 26%; diplegia, 34%; hemiplegia, 30%; quadriplegia, 20%; and extrapyramidal forms, 16%.

Two more recent studies from Australia reexamined the risk factors for cerebral palsy. A large epidemiologic study from 1998 noted an incidence of neonatal encephalopathy of 3.8 per 1000 term births.[47] The investigators identified preconception and antepartum factors that were associated with neonatal encephalopathy (Box 10-2). In the second study from 2011, the greatest risks for cerebral palsy included (1) preterm birth, (2) fetal growth restriction (also known as intrauterine growth restriction), (3) perinatal infection, and (4) multiple gestation.[48] Upper respiratory tract and gastrointestinal infections during pregnancy and instrumental (forceps or vacuum) vaginal delivery were not associated with cerebral palsy.[48] Evidence suggests that intrapartum factors alone are associated with neonatal encephalopathy in less than 5% of cases.[47,49] These data, along with the recognition that most patients with identified risk factors do not have children with cerebral palsy, have led the majority of investigators to agree that most cases of cerebral palsy cannot be predicted and that the identification of pregnancy-related conditions contributes minimally to the identification of patients at risk for having a child with cerebral palsy.

In 2000, the ACOG and the American Academy of Pediatrics (AAP) convened the Neonatal Encephalopathy

BOX 10-2 Risk Factors for Neonatal Encephalopathy

Preconception Factors*

- Increasing maternal age
- Mother unemployed, unskilled laborer, or stay-at-home
- No private health insurance
- Family history of seizures
- Family history of neurologic disorders
- Infertility treatment

Antepartum Factors*

- Maternal thyroid disease
- Severe preeclampsia
- Bleeding in pregnancy
- Viral illness in pregnancy
- Postdates pregnancy
- Fetal growth restriction
- Placental abnormalities

*Significantly and independently associated with neonatal encephalopathy in multiple logistic regression analysis.

From Penning DH. Fetal and neonatal neurologic injury. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia: Principles and Practice. 4th edition. Philadelphia, Mosby, 2009. Information compiled from Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for neonatal encephalopathy: the Western Australia case-control study. BMJ 1998; 317:1549-53.

and Cerebral Palsy Task Force. The resulting landmark report,[49] which was released in 2003, was reviewed and endorsed by such groups as the U.S. Department of Health, the National Institutes of Health, the SMFM, the Child Neurology Society, the March of Dimes Birth Defects Foundation, the Society of Obstetricians and Gynaecologists of Canada, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. The Task Force extended the earlier international consensus statement regarding the requirements for establishing a causal relationship between intrapartum events and cerebral palsy (see Box 10-1).[42] The consensus statement led to several medicolegal conclusions[42,49]:

1. The only types of cerebral palsy associated with intrapartum hypoxia are spastic quadriplegia and, less commonly, dyskinesia.
2. Intellectual disability, learning disorders, and epilepsy should not be ascribed to birth asphyxia unless accompanied by spastic quadriplegia.
3. No statements about severity should be made before an affected child is 3 to 4 years of age, because mild cases may improve and dyskinesia may not be evident until then.
4. Intrapartum hypoxia sufficient to cause cerebral palsy is always accompanied by neonatal encephalopathy and seizures.

Phelan et al.[50] subsequently confirmed that fetuses that experienced a sudden and sustained deterioration of the FHR, and that subsequently were found to have cerebral palsy, demonstrated characteristics consistent with the ACOG/AAP Task Force criteria[50] for intrapartum asphyxial injury.

Peripartum Asphyxia and Cerebral Palsy

Asphyxia may be defined as insufficient exchange of respiratory gases.[51] Although accurate, this definition does not include an index of severity or have any predictive value. Unfortunately, most studies have not used a uniform definition of *birth asphyxia*.[52-54]

In 1953, Dr. Virginia Apgar, an anesthesiologist, introduced her scoring system to identify newborn infants in need of resuscitation and to assess the adequacy of subsequent resuscitation efforts.[55] Although the Apgar score has also been used to identify infants at risk for cerebral palsy, only a weak association has been found.[56,57] In the Collaborative Perinatal Project, only 1.7% of children with a 1-minute Apgar score of 3 or less developed cerebral palsy.[58] Among infants who weighed more than 2500 g at delivery, the incidence of cerebral palsy was 4.7% if the 5-minute Apgar score was 0 to 3 and 0.2% if the 5-minute Apgar score was at least 7. Among infants who weighed less than 2500 g with the same 5-minute Apgar scores, the incidence of cerebral palsy was 6.7% and 0.8%, respectively. Among all infants, a higher incidence of cerebral palsy was observed if the Apgar score remained 3 or less for longer than 5 minutes. The incidence of early neonatal death increased among those infants with prolonged neonatal depression.

Most infants who subsequently manifest evidence of cerebral palsy have a normal 5-minute Apgar score. In the Collaborative Perinatal Project, only 15% of the infants in whom cerebral palsy later developed had a 5-minute Apgar score of 3 or less, approximately 12% had a score of 4 to 6, and the remaining 73% had a score of at least 7.[58] It must also be noted that preterm delivery is independently associated with a low Apgar score.

Although most cases of cerebral palsy are not attributed to intrapartum insults, intrapartum asphyxia does occur and can have serious consequences. However, the degree of asphyxia necessary to produce irreversible CNS injury is unclear. In some cases, an intrapartum insult that might have otherwise been innocuous might be superimposed on subclinical chronic fetal compromise and result in permanent injury.

Umbilical cord blood gas measurements are often used to diagnose suspected asphyxia. However, the definition of *normal* umbilical cord blood gas and pH measurements remains unclear.[51] In one study of 15,073 *vigorous* neonates (arbitrarily defined as having a 5-minute Apgar score of 7 or more) conducted between 1977 and 1993, the median umbilical arterial blood gas measurements (with the 2.5th percentile in parentheses) were as follows: pH 7.26 (7.10), Po_2 17 (6) mm Hg, Pco_2 52 (74) mm Hg, and base excess –4 (–11) mEq/L.[51] Only small differences in median pH and other measurements were present when infants were grouped according to gestational age. These data suggest that umbilical arterial blood pH in vigorous neonates can be as low as 7.10 and base excess may be as low as –11 mEq/L.

Although intrapartum events are most likely associated with a minority of cerebral palsy cases, clinical studies have attempted to define the associated extent and duration of perinatal asphyxia. Fee et al.[59] defined asphyxia as an umbilical arterial blood pH of less than

7.05 with a base deficit greater than 10 mEq/L; they concluded that this threshold was a poor predictor of adverse neurologic outcomes. Goodwin et al.[60] defined asphyxia as an umbilical arterial blood pH of less than 7.00; with the use of this definition, hypoxic ischemic encephalopathy and abnormal neurologic outcome were associated with acidemia. Goldaber et al.[61] also observed greater neonatal morbidity and mortality among term infants (birth weight > 2500 g) with an umbilical arterial blood pH of less than 7.00.

Low et al.[62,63] also studied complications of intrapartum asphyxia in term and preterm infants. They developed a complication score that expressed the magnitude of neonatal complications. Among term infants, the frequency and severity of newborn complications increased with the severity and duration of metabolic acidosis at birth. Importantly, respiratory acidosis at birth did not predict complications in newborns. Similar results were noted for preterm infants delivered between 32 and 36 weeks' gestation. In contrast, in infants delivered before 32 weeks' gestation, complications were similar in the control and asphyxia (defined as umbilical arterial blood buffer base < 30 mmol/L) groups. When this scoring system was used in term infants, the threshold for moderate or severe newborn complications was an umbilical arterial blood base deficit of 12 mmol/L.[63]

Relatively few studies have followed neurodevelopmental examinations for a sufficient duration to make meaningful conclusions about peripartum predictors of neurologic injury. Nagel et al.[64] performed such examinations in 30 children in whom umbilical arterial blood pH was less than 7.00 at delivery, 28 of whom survived the neonatal period. Evaluation at 1 to 3 years of age detected 3 children who had experienced an episode of hypertonia. The majority of children exhibited no major problems, with only 1 child displaying mild motor developmental delay. Another study examined neonatal complications (neonatal death, grade 3 or 4 intraventricular hemorrhage, gastrointestinal dysfunction, and neonatal seizures) in 35 newborns with an umbilical arterial blood pH of less than 7.00 at delivery, 3 of whom died during the neonatal period.[65] An umbilical arterial blood base deficit greater than or equal to 16 mmol/L and a 5-minute Apgar score less than 7 had a sensitivity and specificity for predicting adverse neonatal outcomes of 79% and 81%, respectively. These investigators did not perform any follow-up neurologic examinations after the neonatal period.[65]

Because metabolic acidosis may be a predictor of complications in newborns, the severity of intrapartum acidosis could be an important variable. Gull et al.[66] studied a small cohort of 27 patients with terminal bradycardia who were delivered vaginally. Not surprisingly, the umbilical arterial blood base deficit was greater in infants with end-stage bradycardia than in controls. The loss of short-term FHR variability for more than 4 minutes during terminal bradycardia correlated with the development of metabolic acidosis.

The relationship between umbilical arterial blood base excess values and the timing of hypoxic injury has been estimated in human and animal studies.[67] In addition, in a 2010 systematic review and meta-analysis, an umbilical cord arterial blood pH less than 7.00 was significantly associated with important, biologically plausible, adverse neonatal outcomes (i.e., neonatal mortality, hypoxic ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy).[68] Unfortunately, this relationship does not consider the role of previous or repetitive hypoxic episodes before the episode in question and therefore cannot accurately pinpoint the time of injury. Fortunately, the human fetus is quite robust, and episodes of intrauterine asphyxia usually yield a normal neonate. A much smaller number of fetuses experiencing such episodes die *in utero*. Blumenthal[69] concluded that there is a fine threshold between normality and death from asphyxia.

The increased presence of nucleated red blood cells in the umbilical circulation at delivery has been proposed as a marker of the occurrence and timing of intrauterine asphyxia.[50,70,71] However, data from these investigations demonstrated considerable variability and were influenced by birth weight and gestational age.[72] Furthermore, the timing of the injury may be difficult to determine with confidence, because multiple episodes of asphyxia may have occurred. In such cases, the nucleated red blood cell count may reflect and implicate only the most recent, but possibly least important, event. Both nucleated red blood cell and lymphocyte counts appear to undergo more sustained elevations in cases of antepartum asphyxia than in cases of intrapartum asphyxia.[49]

Chorioamnionitis, Fever, and Cerebral Palsy

An association between cerebral palsy and chorioamnionitis has been demonstrated in preterm infants and term infants of normal birth weight.[73,74] An elevated maternal temperature is one sign of chorioamnionitis, but alone it is insufficient for the diagnosis. Other signs include, but are not limited to, maternal and fetal tachycardia, foul-smelling amniotic fluid, uterine tenderness, and maternal leukocytosis. The diagnosis remains unproven until confirmed by placental culture or histologic examination.

The mechanism by which chorioamnionitis is associated with cerebral palsy is unclear; however, inflammatory cytokines may play a role (see later discussion).[75-77] A landmark meta-analysis published in 2000 reported that both clinical and histologic chorioamnionitis were strongly associated with an increased risk for cerebral palsy and periventricular leukomalacia in both preterm and term infants.[78] In a 2010 meta-analysis, both histologic (pooled odds ratio [OR], 1.83; 95% confidence interval [CI], 1.17 to 2.89) and clinical chorioamnionitis (OR, 2.42; 95% CI, 1.52 to 3.84) were again found to be significantly associated with cerebral palsy.[79]

Several studies have demonstrated a tendency for maternal temperature to rise after administration of epidural analgesia during labor (see Chapter 37).[80] Although the mechanism of epidural analgesia–associated maternal pyrexia remains unclear, fever due to epidural analgesia alone is not associated with cerebral palsy.[81] Epidural analgesia has been blamed for the common obstetric practice of antibiotic administration to mothers with fever but no other evidence of chorioamnionitis. This

practice may lead to unnecessary neonatal sepsis evaluations and antibiotic exposure.[82] Rather than treat all women with pyrexia for presumed chorioamnionitis, Mayer et al.[83] correctly noted that physicians should make an effort to differentiate true chorioamnionitis from incidental maternal fever. These investigators found that additional signs of chorioamnionitis were present in all cases in which the diagnosis was later confirmed by culture or pathologic examination. Neuraxial anesthesia is not a risk factor for cerebral palsy.[44]

The mode of delivery has been examined as an independent risk factor for **periventricular leukomalacia**, the most common form of ischemic brain injury in surviving preterm infants in whom cerebral palsy later develops. In 99 women with chorioamnionitis who delivered between 25 and 32 weeks' gestation, vaginal delivery had a significant association with periventricular leukomalacia.[84] Because the cesarean delivery group likely included a substantial number of infants with nonreassuring FHR tracings, the better outcomes in these infants is striking. Prospective trials are needed to confirm these retrospective observations.

PATHOPHYSIOLOGY OF FETAL ASPHYXIA

Intrauterine Hypoxemia and the Fetal Brain

The fetus is exclusively dependent on the placenta for oxygen and nutrients; thus, acute and chronic conditions that affect the placenta or the umbilical cord can deprive the fetus of one or more of these vital resources. Recent evidence from experimental animal models and humans suggest that both hypoxemic and inflammatory pathways interact and augment fetal brain damage.

The spectrum of neurologic injury in neonates depends on the duration and gestational age at hypoxemic-ischemic insult. *Acute* hypoxemia during the early- to mid-gestational period in sheep affects the predominant neurodevelopmental events such as neurogenesis and neuronal migration. Such hypoxemia causes the death of cerebellar Purkinje cells and hippocampal pyramidal neurons, as well as impaired neuronal migration.[85] In contrast, acute hypoxemia in late gestation appears to spare the hippocampus and cerebellum but causes neuronal death in the cerebral cortex and striatum.[86] Furthermore, acute perinatal anoxia causes long-term changes in dendritic arborization and synaptic connectivity.[87,88]

Experimental models of *chronic* hypoxemia, based on restriction of placental mass or blood flow, demonstrate an array of completely different effects on the fetal brain. Chronic placental insufficiency relatively spares the fetal brain compared with other organ systems, although it results in reduced fetal brain weight. Overall, neurons appear to survive chronic and mild hypoxemia; even minor behavioral changes appear to resolve fully by adulthood in animal models. It is not known whether these effects are mediated by hypoxemia *per se*, or by other accompanying conditions such as chronic reduction of fetal nutrient supply or altered maternal-fetal endocrine status.

Dysregulation of neuronal calcium transport appears to be the initial pathway by which cerebral hypoxemia causes perinatal neuronal injury.[89] Hypoxia-induced changes in the NMDA receptor increases cellular permeability to calcium; such increases in intracellular calcium trigger a variety of downstream effects, ultimately resulting in generation of free radicals, peroxidation of lipid membranes, and nuclear fragmentation. It has long been recognized that developing oligodendroglia are highly vulnerable to excitotoxic injury in preterm infants.[90] Altered maturation or premature oligodendrocyte death can occur in areas of severe hypoxia-ischemia as a result of up-regulation of inflammatory cytokines by activated microglia, elevated glutamate levels, or depleted levels of the antioxidant glutathione. It is highly likely that a combination of these mechanisms, modified by the nature and duration of insults and gestational age, determine the ultimate neurobehavioral phenotype.

Maternal Inflammation and Fetal Brain Injury

Although the development of the fetal brain is encoded by genetic programming, such programs remain highly susceptible to environmentally induced epigenetic modifications and appear closely intertwined with maternal immune and endocrine systems. Recent experimental and epidemiologic studies reveal that maternal infection and inflammation early in pregnancy can cause an array of neurodevelopmental abnormalities in the offspring such as schizophrenia and autism.[91-94] Among maternal infections, chorioamnionitis is the best characterized and thoroughly investigated model of perinatal neuroinflammation. Although the exact contribution of maternal inflammation to perinatal brain injury is obscured because of the association of chorioamnionitis with preterm delivery and hypoxic-ischemic encephalopathy, inflammatory experimental models have revealed much information on cytokine induction, their transport across the placenta and amniotic fluid, and subsequent activation of the fetal immune system.

The exact mechanism by which maternal inflammation triggers a fetal immune response is likely multifactorial (Figure 10-2). Despite the presence of circulating immune cells as early as 7 weeks' gestation in humans, antigen presentation is suboptimal because of reduced expression of the major histocompatibility complex class II on antigen-presenting cells. Furthermore, the T cells are relatively immature. Therefore, maternally derived humoral mediators seem credible candidates to initiate and perpetuate an inflammatory cascade across the placenta. This idea has gained traction with the identification of maternal interleukin-6 (IL-6) in the fetal circulation as early as the second trimester, suggesting the possibility of transplacental transfer of proinflammatory cytokines.[95] Proinflammatory mediators such as IL-6 cause significant impairment of placental blood flow and fetal hypoxemia in animal models, dysregulate the barrier function of both the placenta and the immature fetal blood-brain barrier, trigger production of acute-phase

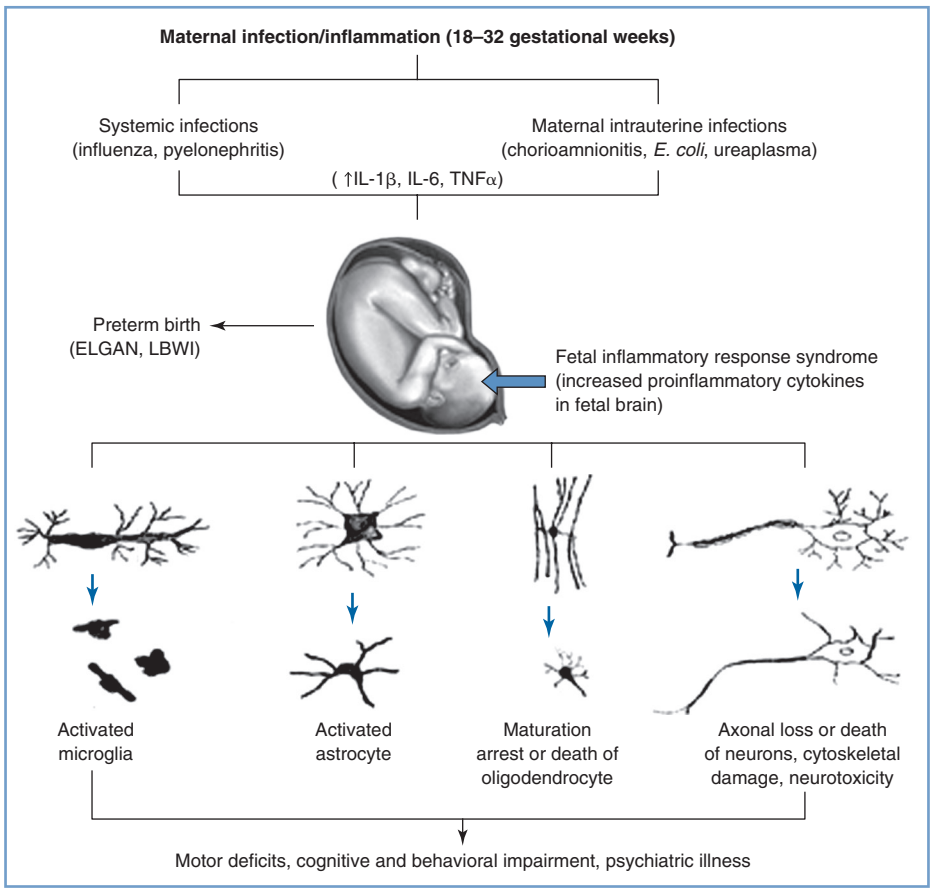

FIGURE 10-2 ■ Probable mechanisms of fetal brain injury with *in utero* exposure to maternal inflammation. *IL,* interleukin; *TNF,* tissue necrosis factor; *LBWI,* low birth weight infant; *ELGAN,* extremely low gestational age neonate. (From Burd I, Balakrishnan B, Kannan S. Models of fetal brain injury, intrauterine inflammation, and preterm birth. Am J Reprod Immunol 2012; 67:287-94.)

proteins from the fetal liver, promote T-cell entry into the immature brain parenchyma, and disrupt the orderly patterning of the fetal cerebral cortex.[91,93,96-99] The role of inflammatory mediators in this phenomenon is reinforced by the direct correlation that exists between plasma levels of IL-6 and the severity of functional deficits in offspring.[100,101] In addition to IL-6, cytokines such as IL-1β, IL-7, and IL-13 are up-regulated in the fetal brain after a prenatal immune insult, a phenomenon that suggests collective activation of the innate fetal immune response.[102]

Both microglia (the major resident macrophages in the developing brain) and the complement system have been implicated as amplifiers of this immune response. During normal fetal development, microglia invade and colonize the fetal brain during the first and second trimesters[103] and are readily activated by proinflammatory mediators such as IL-1β. Activated microglial cells either cause a direct cytotoxic effect on oligodendrocytes and impair myelination or produce long-lasting alterations in neuronal-glial crosstalk, resulting in impaired synaptic function and subsequent neurodevelopmental disorders.[3,91,104]

At the cellular level, numerous mechanisms are involved in propagating the prenatal immune response. Collectively, robust experimental evidence suggests that prenatal inflammation alters fetal brain development at the molecular, cellular, and circuit levels. Epidemiologic studies have shown a strong correlation between maternal infection/inflammation and neurodevelopmental disorders such as schizophrenia and autism.[92,105,106]

Animal Models of Fetal Asphyxia

Much of our knowledge of the fetal response to insufficient exchange of respiratory gases has been gained through the use of animal models. However, the limitations of these models must be acknowledged. Raju[107] reviewed the various animal models of fetal brain injury. At birth, sheep and guinea pig brains are much closer to maturity than the human brain. In this regard, rat pup and human brains are more similar to each other because they both undergo significant extrauterine development (Figure 10-3).[108] Nonetheless, the importance of this distinction has been challenged. Previously, investigators relied mainly on morphologic milestones (e.g., the brain growth spurt) to compare species at different stages of development. A computerized method attempted to more accurately compare observations among 10 species (including humans) by evaluating the mathematical relationships of more than 100 developmental events and factors (e.g., evolutionary, genetic, neurochemical,

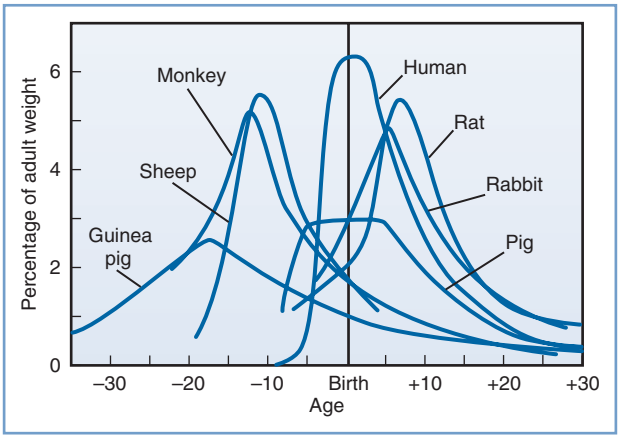

FIGURE 10-3 ■ Brain growth spurts of seven mammalian species expressed as first-order velocity curves of the increase in weight with age. The units of time for each species are as follows: guinea pig (days); rhesus monkey (4 days); sheep (5 days); pig (weeks); human (months); rabbit (2 days); rat (days). Rates are expressed as a percentage of adult weight for each unit of time. (From Penning DH. Fetal and neonatal neurologic injury. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia: Principles and Practice. 4th edition. Philadelphia, Mosby, 2009; modified from Dobbing J, Sands S. Comparative aspects of the brain growth spurt. Early Hum Dev 1979; 3:79-83.)

neuroanatomic).[109] Although all events have not been catalogued for any one species, the iterative process allows information to be added to improve the theoretic model and is freely available online.* This method is not completely understood or accepted but may explain some of the variability observed among various models of developmental brain injury.

One advantage of the chronically instrumented fetal lamb is that it is similar in size to the human fetus, thus facilitating the placement of electrodes and vascular catheters in both the fetus and the mother. Investigators may obtain measurements while the mother (and fetus) remains anesthetized or from awake animals that have recovered from surgery. Studies of animals with continuous instrumentation allow the assessment of fetal breathing movements, gross body movements, brain electrical activity (electroencephalogram), and blood gas and pH measurements. Blood concentrations of glucose, lactate, and various hormones can also be determined. Microdialysis techniques have been used to evaluate neurotransmitter release within the fetal brain *in vivo* in acute, exteriorized, and chronic preparations.[110-112] Other studies have measured fetal cerebral blood flow *in vivo* during episodes of hypoxemia[113] and during maternal infusion of ethanol.[114] Together, these studies have enhanced the understanding of the fetal brain response to pathophysiologic insults *in utero*. Ultimately, these insights may lead to improved diagnoses, treatment, and prevention of fetal brain injury.

Studies have used a variety of methods to produce fetal hypoxemia and acidemia in fetal lambs. Each method attempts to mimic one or more clinically relevant situation(s), including (1) decreased concentration of maternal inspired oxygen for several hours[115] or days[116]; (2) decreased uterine blood flow, which may be accomplished by placement of an adjustable clamp on the common iliac artery[117]; (3) decreased umbilical blood flow, either by total obstruction[118] or by means of a slow, progressive obstruction[119]; (4) selective uteroplacental embolization[120]; (5) maternal hemorrhage[121]; and (6) a combination of two insults, such as hypoxemia plus hypotension.[122]

Care must be exercised in the application of knowledge gained from hypoxia-ischemia studies conducted on nonfetal models (e.g., rat pups) to the problem of insufficient intrauterine gas exchange. The fetus and the fetal brain exist in a relatively hypoxemic environment. Despite preferential streaming of the most highly oxygenated blood to the brain and heart, the average Po_2 measured in the carotid artery of fetal lambs at term is approximately 22 mm Hg.[123] Further, unlike adult conditions in which global anoxia (i.e., cardiac arrest) or focal ischemia (i.e., stroke) is the clinical correlate, fetal asphyxia typically involves diminution, but not absence, of delivery of oxygen, with variable degrees of respiratory or metabolic acidosis. A complete loss of cerebral blood flow rarely occurs, except as a terminal event. Of course, prolonged hypoxemia and decreased oxygen delivery can lead to acidemia and myocardial failure, followed by ischemia and rapid fetal demise. Fetal hypoxemia may result from the compromise of any or all of the steps involved in maternal-fetal oxygen transport (Box 10-3).[124] The impact of repeated hypoxic-ischemic insults should not be underestimated, and numerous clinical scenarios can be envisioned whereby this might occur (e.g., repetitive umbilical cord occlusion, chronic abruption). Moreover, brief insults that may be harmless could cause damage if repeated, as has been demonstrated in adult rats[125] and in fetal lambs.[126]

The neuropathology of intrauterine asphyxia depends, to some extent, on gestational age. In fetal lambs exposed to sustained hypoxemia with developing acidemia, immature fetuses demonstrated a predominantly periventricular injury, whereas mature fetuses had a primarily cortical injury, although there was some overlap (Figure 10-4).[127] This finding is consistent with injury patterns in humans. It is not surprising that the biophysical and biochemical responses to hypoxemia vary between preterm and term fetuses. Matsuda et al.[115] observed that the development of metabolic acidemia, reduced fetal breathing and body movements, and an altered sleep state were much less pronounced in mid-gestational fetal lambs subjected to hypoxemia than in fetal lambs at term.

Neuropathology of Fetal Asphyxia

The mechanism and timing of an asphyxial insult can affect the resulting fetal or neonatal pathology. Acute, complete asphyxia must be distinguished from incomplete, brief, or intermittent asphyxia or chronic hypoxemia. *Complete asphyxia* may occur in the setting of a total placental abruption or umbilical cord occlusion (as may occur with a uterine rupture or umbilical cord prolapse), which if unrecognized and not treated rapidly leads to

*Translating Time across Developing Mammalian Brains: http://www.translatingtime.net/.

BOX 10-3 Factors Decreasing Oxygen Transfer to the Fetus

Environmental Po_2
- High altitude

Maternal Cardiopulmonary Function
- Cyanotic heart disease

O_2 Transport by Maternal Blood
- Anemia
- Cigarette smoking

Placental Blood Flow
- Hypertension
- Diabetes
- Placental abruption
- Uterine contractions

Placental O_2 Transfer
- Placental abruption
- Placental infarcts

Umbilical Blood Flow and Fetal Circulation
- Umbilical cord occlusion
- Maternal heart disease

O_2 Transport by Fetal Blood
- Anemia
- Hemorrhage

From Richardson B. The fetal brain: metabolic and circulatory responses to insufficient exchange of respiratory gases. Clin Invest Med 1993; 16:103-14.

fetal demise. *Incomplete asphyxia* may occur in any setting in which oxygen delivery to the fetus is inadequate to meet all of its needs (e.g., brief and/or repeated episodes of partial umbilical cord occlusion, placental embolization, or incomplete placental abruption). This latter category of asphyxia presumably contributes to the largest proportion of cases of cerebral palsy attributed to antepartum events. In these cases, the insult is not severe enough to lead to immediate fetal death but can profoundly affect fetal brain growth and development. Ongoing studies are attempting to determine whether there is a period of time *in utero* when the fetus is especially vulnerable to neurologic injury.

Using a primate model to perform seminal research on the subject of perinatal brain injury, Myers[27] identified two patterns of injury based on whether the fetus suffered complete or partial asphyxia. True complete asphyxia was demonstrated in fetal monkeys at term subjected to varying durations (0 to 25 minutes) of complete asphyxia. These fetuses were resuscitated when possible, a procedure that often required the use of cardiac massage and epinephrine, and postmortem examinations revealed extensive pathology in brainstem areas. In humans, such a severe intrauterine insult would most likely be incompatible with extrauterine survival. If survival did occur, the infant would show obvious encephalopathy and multiorgan system dysfunction at birth. The second pattern (i.e., partial asphyxia) is more relevant to the discussion of human cerebral palsy. In studies of fetal monkeys subjected to partial asphyxia,[128] some animals demonstrated cortical necrosis, subcortical white matter damage, and

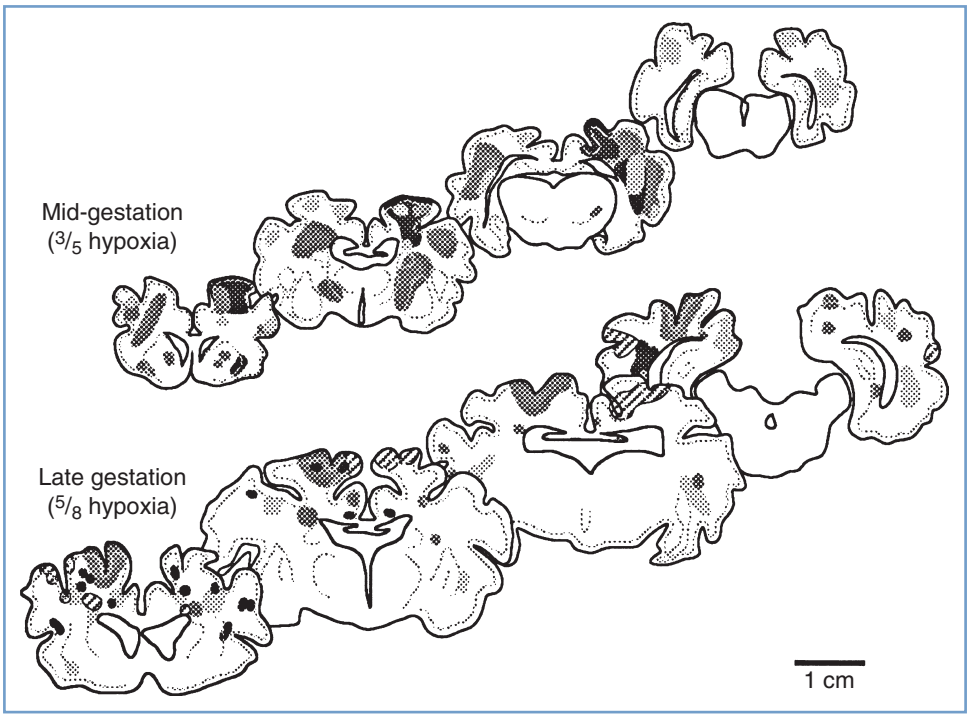

FIGURE 10-4 ■ Composite diagram showing distribution of hypoxic injury in mid-gestational (*top*) and near-term (*bottom*) fetal lambs at 3 days after 8 hours of arterial hypoxemia. Hypoxemia was produced by placing the pregnant ewe in a chamber with reduced ambient oxygen. Each shading pattern represents an individual animal. The severity of injury is not indicated in this diagram. (From Penning DH, Grafe MR, Hammond R, et al. Neuropathology of the near-term and midgestation ovine fetal brain after sustained in utero hypoxemia. Am J Obstet Gynecol 1994; 170:1425-32.)

basal ganglia damage. Although these two studies form the core of our knowledge of perinatal brain injury in primates, there were relatively few animals in each experimental group, and considerable variation in response occurred. Some animals suffered no injury, whereas others could not be resuscitated.

Several investigators have attempted to summarize the neuropathology of fetal and neonatal asphyxia.[128-130] Volpe[131] emphasized that the variation in neuropathology after intrauterine asphyxia depends on the fetal gestational age. Volpe also proposed a framework for these variations. The principal sites of injury in preterm fetuses are the white matter (especially periventricular white matter) and the basal ganglia, whereas older fetuses demonstrate injury primarily in the gray matter of the cortex and cerebellum.

Periventricular leukomalacia is the most common pathologic finding in preterm infants with brain injury.[131] This lesion is characterized by coagulative necrosis of the white matter adjacent to the lateral ventricles and around the foramen of Monro, especially at the external angle of the lateral ventricles and the optic radiation.[132] With long-term survival, the lesion may progress to a widening of the ventricles and hydrocephalus *ex vacuo*. Clinically, periventricular leukomalacia may not be apparent at birth.[129] Developing hydrocephalus may be detected on computed tomography or ultrasonographic examination. In more subtle cases, magnetic resonance imaging (MRI) may show decreased myelination (see later discussion).[133]

The pathophysiology of periventricular leukomalacia is unclear. Conventional wisdom has held that periventricular leukomalacia is an ischemic lesion unique to preterm infants.[134] The insult is thought to occur in an arterial border zone perfused by end-arterial branches of the middle and posterior cerebral arteries. This border zone has been identified by DeReuck,[134] who demonstrated periventricular arborizations between vessels penetrating to the ventricles (i.e., ventriculopedal vessels) and between vessels arising from the ventriculochoroidal arteries (i.e., ventriculofugal vessels). Others have challenged DeReuck's anatomic findings and have questioned whether periventricular leukomalacia is a purely ischemic lesion.[135,136]

White matter in the immature fetal brain may be at increased risk for hypoxic-ischemic injury because of a limited ability of its vessels to vasodilate.[131] If this were true, autoregulation would be precluded in situations of hypotension. However, at least one study has shown that blood flow to white matter actually may increase (relative to gray matter) during fetal asphyxia.[137] Fetal white matter may be more metabolically active than gray matter because of large numbers of actively myelinating cells.[131] In situations of marginal oxygen supply, glia are subsequently at greater risk for injury. One study has suggested that immature astrocytes are more susceptible to ischemic death than mature astrocytes.[138] Studies in fetal lambs have successfully produced pathologic changes similar to those present in infants with periventricular leukomalacia.[127] These models may help clarify the mechanism of this common pathologic correlate of cerebral palsy in the preterm infant.

BOX 10-4 Fetal Cerebral Responses to Asphyxia

Fetal Cerebral Metabolism

- Increased oxygen extraction
- Use of alternative energy sources
- Decreased growth
- Altered behavioral state

Fetal Cerebral O_2 Transport

- Redistribution of cerebral blood flow

From Penning DH. Fetal and neonatal neurologic injury. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia: Principles and Practice. 4th edition. Philadelphia, Mosby, 2009. Modified from Richardson B. The fetal brain: metabolic and circulatory responses to insufficient exchange of respiratory gases. Clin Invest Med 1993; 16:103-14.

Fetal Adaptive Responses

The fetus takes advantage of several adaptive responses for survival and growth in the relatively hypoxemic intrauterine environment; these adaptive changes to intrauterine hypoxemia vary between immature and mature fetuses. Fetal responses to asphyxia may be categorized as an alteration of fetal metabolism or maximization of fetal oxygen transport (Box 10-4).[124] Richardson[139] defined the *oxygen margin of safety* as the extent to which fractional oxygen extraction can increase and fetal arterial Po_2 can decrease before tissue oxygen supplies are inadequate. Regardless of the etiology of decreased oxygen delivery to the fetus, fetal oxygen consumption is maintained by increasing oxygen extraction until oxygen delivery is approximately 50% of normal.[140] Lower levels of tissue oxygen tension result in progressive metabolic acidemia and a terminal decrease in oxygen consumption.[139]

Alterations in substrate use may affect the fetal response to insufficient exchange of respiratory gases. Unlike the adult brain, the fetal brain can use ketone bodies and lactate as alternative energy sources.[141] In gravid ewes, a reduction in uterine blood flow results in reduced fetal glucose consumption.[141] Current opinion holds that hyperglycemia should be avoided in adult humans at risk for ischemia.[142] Hyperglycemia may exacerbate metabolic acidosis by providing substrate for anaerobic metabolism, which increases lactic acid production. However, Vannucci and Mujsce,[143] citing experiments in neonatal rat pups, suggested that the immature brain may respond differently and that glucose administration may actually reduce hypoxic-ischemic brain injury. These investigators did not consider earlier work by Blomstrand et al.,[144] who studied the effects of hypoxia in the anesthetized, exteriorized fetal lamb. In that study, hyperglycemia accelerated the loss of somatosensory evoked potentials, the onset of metabolic acidosis, and the reduction of cerebral oxygen consumption. Until these different observations are reconciled, the maintenance of normoglycemia *in utero* appears prudent.

During chronic hypoxemia, the fetus may also restrict the use of energy derived from oxidative metabolism to maintain essential cellular processes. This may lead to

decreased somatic growth and fetal growth restriction. Using an ovine model of asphyxia, Hooper[145] detected decreased incorporation of tritiated [^{3}H]-thymidine (which reflects decreased DNA turnover and, presumably, decreased cell division) in fetal tissue. The decrease in incorporation of tritiated [^{3}H]-thymidine was not uniform in all tissues. The rates of DNA synthesis were maintained in most fetal tissues (including the fetal brain) but were greatly reduced in the lung, the skeletal muscle, and the thymus gland.

The fetus can conserve additional energy by decreasing breathing and gross body movements. Rurak and Gruber[146] demonstrated a 17% reduction in oxygen consumption in fetal lambs that were paralyzed by a neuromuscular blocking agent. Perceptible fetal movements represent an index of fetal health. Many obstetricians instruct their patients to count episodes of fetal activity for specified periods and to consult them if fetal movements are decreased or absent (see Chapter 6). Fetal hypoxemia results in decreases in both activity and rapid eye movement (REM) sleep in fetal lambs. REM sleep states are associated with an increased cerebral metabolic rate for oxygen ($CMRo_2$).[113] Thus, during periods of fetal stress, reductions in fetal body movements or REM sleep lead to a significant decline in fetal energy expenditure.

Oxygen deprivation typically results in a change in and/or redistribution of fetal cardiac output.[147] The magnitude of these changes depends on the mechanism and severity of oxygen deprivation. Sheldon et al.[148] demonstrated that experimental fetal hypoxemia (produced by the administration of a decreased maternal-inspired concentration of oxygen) resulted in greater blood flow to the brain, myocardium, and adrenal glands. In fetal lambs, a brief (4-minute) complete arrest of uterine and ovarian blood flow resulted in a decrease in blood flow to all organs except the myocardium and adrenal glands.[149]

FETAL AND NEONATAL ASSESSMENT

Fetal Neurobehavioral Assessment

With recent advances in the understanding of prenatal brain development and imaging technology, there is considerable interest in monitoring and codifying fetal neurologic development and behavior to predict postnatal neurodevelopment.[150] The driving principle is that fetal behavioral patterns reflect complex interactions between the maternal environment and primitive neuronal network generators in the developing brain. There is an overwhelming convergence of opinion that most neurodevelopmental disorders have an intrauterine origin and that there is extensive neurobehavioral continuity from the fetal to the neonatal period.[151]

Although the assessment of high-risk pregnancies has included an analysis of certain aspects of fetal behavior, until recently there have been no unified scales for assessment of fetal neurobehavior. Current fetal neurobehavioral scales assess a variety of behaviors that can be categorized into the four main domains described by DiPietro[150]: (1) heart rate, (2) motor activity, (3) existing behavioral state, and (4) responsiveness to external stimuli. The Fetal Neurobehavioral Coding System (FENS) incorporates most elements of fetal behavior and is a direct extension of the NICU Network Neurobehavioral Scale (NNNS) used for neonatal assessment.[152] Using ultrasonography, FENS analysis can identify specific behaviors in fetuses with growth restriction; compared with normally developing fetuses, fetuses with growth restriction demonstrate a delayed appearance of behavioral states, longer behavioral state transitions, and disorganized behavioral patterns. These tests have been validated in other paradigms, including pregnancies that were complicated by maternal diabetes, substance abuse, and cigarette smoking.

A recently developed, more comprehensive scale is the Kurjak Antenatal Neurodevelopmental Test (KANET), which includes an assessment of eight fetal parameters related to fetal behavior, general movements, and other physical signs (e.g., head circumference, presence or absence of overlapping cranial sutures, finger movements).[153] However, these fetal assessment studies are time-consuming and require specific training to codify behaviors. In addition, because the brain structures driving such behaviors have not been clearly identified, it is difficult to understand the significance of differences in behavior, if any.

Fetal Neuroimaging Assessment

In vivo MRI provides details of the architecture of the developing brain beginning in the eighteenth gestational week and can quantify brain growth and structural abnormalities.[154] The use of more sophisticated techniques such as MR tractography and functional fetal MRI is likely to enhance our understanding of normal brain development and thus facilitate identification of abnormal development. Until controlled trials demonstrate adequate sensitivity, specificity, and positive predictive power for these tests, their clinical potential is limited. These potential advantages will need to be balanced against the potential detrimental effects of ultrasonography and MRI on fetal neuronal development and migration.[155]

Neonatal Radiologic Diagnosis of Cerebral Injury

MRI is a useful tool in the diagnosis of neonatal brain injury.[156,157] MRI can assist in the diagnosis of hypoxic ischemic encephalopathy in newborn infants,[158] provide three-dimensional evaluations to determine the volume of gray matter and the extent of white matter myelination (thus providing valuable insights into normal and abnormal brain development),[159] and estimate the timing of the brain injury in patients with cerebral palsy.[160] The presence of cerebral edema confirms recent-onset brain injury; edema develops 6 to 12 hours after injury and resolves within 4 days.[161] Unfortunately, the changes are subtle and the time frame of interest may extend before or after the intrapartum period. Nonetheless, the information can be quite helpful, and early imaging should be performed in cases of suspected brain injury. There is a

strong correlation between anatomic brain lesions detected on MRI and specific types of cerebral palsy.[161] MRI is particularly sensitive in the detection of periventricular leukomalacia, although many children with this MRI abnormality have clinically normal neurologic development.[162]

New imaging techniques, such as diffusion tensor imaging and magnetic resonance spectroscopy, may offer advantages over conventional MRI when performed early (i.e., hours) after a hypoxic-ischemic insult. Diffusion tensor imaging detects the microscopic movement of water particles in brain tissue. Magnetic resonance spectroscopy analyzes the signal of protons attached to molecules such as glutamate, glutamine, and lactate, among others.[163] These methods, developed in rabbit[164] and sheep[165] models of intrauterine hypoxia, detect acute chemical changes in brain tissue and may accurately predict motor outcome in preterm infants.[166] Injury patterns detected with these methods are present for several days and resolve over the next week, at which point the chronic injury becomes visible with conventional MRI. Identification of injuries shortly after birth with these newer techniques can support the hypothesis that an injury occurred within days of delivery.[163] Thus, magnetic resonance spectroscopy and diffusion tensor imaging are powerful new tools for timing the occurrence and understanding the pathophysiology of perinatal brain injury.[163] Cerebral ultrasonography remains a useful technique in the early neurologic neonatal assessment,[167] especially for the critically ill infant who might not be a candidate for transfer to an MRI facility.

ANESTHESIA AND BRAIN INJURY

Anesthetic agents have profound effects on brain metabolism and synaptic transmission. These effects may be direct or indirect and protective or harmful.

Labor Analgesia and the Fetal Brain

Labor analgesia usually entails administration of *lower concentrations* of analgesic/anesthetic agents for a *longer duration* than occurs during administration of anesthesia for surgical procedures. Despite widespread use of analgesic and sedative drugs during labor, little attention has been paid to the neurodevelopmental consequences of antepartum and intrapartum fetal exposure to these drugs. Because neurodevelopmental events at term are quite different from those that occur during the second trimester, there is a need to design experimental studies to investigate the effects of analgesic techniques and drugs administered during the third trimester of pregnancy.

Parenteral Opioids

Among systemic opioids used for labor analgesia, meperidine remains the most widely studied. Although it is well recognized that opioids cross the placenta and enter the fetal circulation,[168] the long-term effects of peripartum opioid exposure on the infant's neurodevelopmental trajectory are unclear. Only a few preclinical studies have addressed this question.[169,170] Endogenous opioid systems are active in the fetal brain, and the presence of their cognate receptors at critical sites during this period suggests that these systems are intricately linked to early neurodevelopment.[171-174] Preclinical evidence suggests that opioid mechanisms play an important role in both early and adult neurogenesis by modulating neuronal progenitor proliferation and differentiation.[175-177] Of concern, fetal rat exposure to morphine during the entire second trimester alters offspring hippocampal development.[178] However, animal studies of opioid abuse in pregnancy should not be extrapolated to peripartum opioid use in humans because of differences in the gestational age as well as differences in drug dose and duration of administration. Only focused studies will reveal the true consequences of intravenous opioid administration for labor analgesia at term gestation.

Neuraxial Techniques

Studies of neuraxial analgesia in labor usually focus on analgesic quality and obstetric and short-term neonatal outcomes. To date, no randomized trials have evaluated the long-term effects of neuraxial analgesia on brain development in offspring. Epidurally administered local anesthetics cross the placenta and enter the fetal circulation. Golub[179] randomized nonlaboring pregnant rhesus monkeys at term to receive epidural bupivacaine (total dose of 1.2 mg/kg) or saline.[179] No differences in specific cognitive deficits were identified between groups; however, exposed offspring demonstrated a prolonged increase in motor disturbance behaviors at 10 to 12 months of age, suggesting that perinatal interventions can alter postnatal behavioral ontogeny. In the only human evidence to date, investigators examined the association between the use of neuraxial labor analgesia and the incidence of childhood learning disabilities in a population-based birth cohort of children from Olmsted County, Minnesota.[180] The incidence of childhood learning disabilities was not associated with the use of neuraxial labor analgesia (adjusted hazard ratio, 1.05).[180]

Inhalational Agents

The use of inhalational anesthetic agents during labor and delivery became popular after the successful use of chloroform by John Snow during Queen Victoria's delivery of Prince Leopold in 1853. Other inhalational agents were subsequently introduced, including nitrous oxide, trichloroethylene, cyclopropane, and methoxyflurane. Although the use of halogenated agents has been supplanted by widespread adoption of neuraxial techniques for labor analgesia, nitrous oxide is still widely used in many countries. Typically it is administered as 50% nitrous oxide in oxygen using a blender device (e.g., Nitronox in the United States) or premixed in a single cylinder (e.g., Entonox in the United Kingdom) (see Chapter 22).

Scientific studies of the fetal and neonatal effects of inhalational analgesics are generally of limited quality.[181,182] Available evidence suggests that inhalational anesthetic

agents, including nitrous oxide, have minimal or no effect on Apgar and neurobehavioral adaptation scores immediately after delivery.[183,184] However, none of these studies has evaluated long-term neurodevelopmental outcomes. This knowledge gap is critical, because robust evidence suggests that early-life neural reprogramming, following pharmacologic and inflammatory insults, affects behavioral development later in life. Of concern is compelling animal evidence that anesthetic agents, when administered during a critical period of brain development, cause widespread neurodegeneration with subsequent learning, memory, and behavioral problems (see later discussion).[185,186] Nitrous oxide, in particular, is now known to be a potent developmental neurotoxin in animal models, yet its effects (if any) on human neurodevelopment are unclear.

Epidemiologic evidence from young children receiving anesthetic agents appears to support the possibility that anesthesia and surgery are associated with learning disabilities and attention deficit disorders later in life.[187] Thus, although the pattern of nitrous oxide administration during labor is unlike its administration for surgical anesthesia, the administration of nitrous oxide for labor analgesia merits closer scientific scrutiny.

Maternal Anesthesia and the Fetal Brain

Despite the popularity of neuraxial techniques in obstetric anesthesia, many pregnant women continue to require general anesthesia for either pregnancy-related or nonobstetric surgical procedures. The commonly used anesthetic agents freely cross the placenta and reach the fetal brain, causing fetal sleep or sedation. Obstetric anesthesia research has focused primarily on the teratogenic effects of anesthetic agents administered during the first trimester (see Chapter 17) and the effects of anesthetic agents on neonatal behavior when administered during cesarean delivery. Historically, the second trimester has been assumed to be a safe period for surgery and anesthesia, primarily because of a lack of targeted studies. However, during the past decade, extensive animal research has shown that anesthetic agents, when administered during the phase of synaptogenesis, can induce a profound neurodegenerative response in the developing brain and cause functional impairment in offspring.[185,188]

Human epidemiologic studies appear to support an association between early childhood exposure to anesthetic agents and subsequent functional impairment. However, it is unclear whether these adverse outcomes result from the underlying disease, surgery, or anesthesia or a combination of these factors.[187,189] A recent study found evidence that repeated anesthesia exposures or a cumulative anesthesia exposure time greater than 2 hours during early childhood was associated with a nearly twofold increase in the incidence of learning disabilities and attention deficit hyperactivity disorder.[189] Because human synaptogenesis appears to begin during the third trimester, there is now serious concern that intrauterine fetal exposure to these anesthetic agents may result in similar functional impairment. Because there is no precise way to monitor human fetal brain development *in utero*, the potential long-term effects of maternal anesthesia on the fetal brain must be investigated in animal models. However, given the considerable differences in neural maturation among species (Figure 10-5; see also Figure 10-3), and the duration of anesthesia exposure in relation to the lifespan of the organism, these results should be interpreted with caution.[190,191]

The exact mechanisms by which anesthetic agents impair early brain development are still under active investigation.[192] Anesthetic agent interactions with GABA and the NMDA-subtype of glutamate receptors decrease activity-dependent synapse formation and cause apoptotic neurodegeneration in multiple areas of the developing brain. These histopathologic changes have been well investigated, especially in the hippocampal formation, which is an area that is crucial for memory. Early exposure to anesthetic agents affects long-term potentiation in the hippocampus and affects spatial working memory in animal models.[185] These changes do not appear to be caused by direct cytotoxicity[193] but rather by a combination of effects on both neuronal and nonneuronal cells in the developing brain (Box 10-5).

Of specific concern are the effects of anesthetic agents on neurogenesis and synapse formation in the fetal brain. Human neural ontogeny suggests that the second trimester is a period of active fetal brain development, with neuroblast proliferation peaking between the 5th and 25th postmenstrual weeks. Because GABA and glutamate play a crucial role in these processes, there is concern that prolonged and nonphysiologic modulation of the fetal GABA and glutamatergic systems, as might occur during second-trimester maternal anesthesia, might affect neurogenesis, neuronal migration, and/or synapse formation.

In one of the first animal studies to simulate a clinically relevant scenario,[194] a single exposure to 1.4% isoflurane (1 MAC [minimum anesthetic concentration]) for 4 hours during the second trimester caused long-lasting impairment of spatial working memory in rodent offspring. Although the exact mechanisms behind these behavioral disturbances are unclear, other studies suggest that midgestational exposure to isoflurane up-regulates the proapoptotic protein caspase-12, decreases overall synapse numbers in the fetal hippocampus, and down-regulates the plasticity-associated protein GAP-43.[195,196] Similar results have been reported in pregnant guinea pigs and macaques, suggesting that the fetal brain remains highly susceptible to maternal mid-trimester anesthesia.[197,198] Furthermore, isoflurane suppresses neurogenesis in rodents both *in vitro* as well as *in vivo*,[199-201] causing a depletion of the neural stem cell pool. At least *in vitro*, this phenomenon appears to be dose dependent.[201] At the present time, the impact of reduced neurogenesis on behavioral deficits and the effect of anesthetic agents on neuronal migration remain unknown.

When these studies are extended to the third trimester, the results are mixed. In one rodent study, maternal administration of 1.3% isoflurane for 6 hours during the third trimester had no effect on offspring neurodevelopment.[202] However, these investigators performed another dose-response study in term rodents and found that maternal administration of 3% isoflurane, but not 1.3%

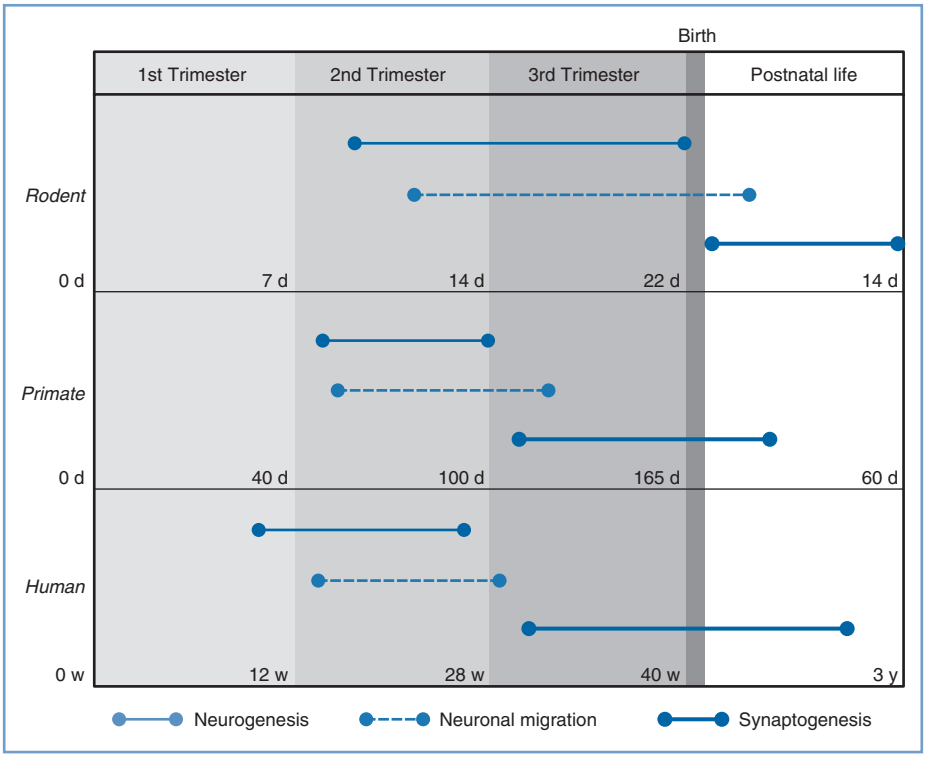

FIGURE 10-5 ■ Time lines of major neurodevelopmental events *in utero* in rodents, nonhuman primates, and humans. Events are as marked in the figure legend (*d,* days; *w,* weeks; *y,* years). Synaptogenesis is predominantly a postnatal event in rodents, unlike that in primates and humans. (From Palanisamy A. Maternal anesthesia and fetal neurodevelopment. Int J Obstet Anesth 2012; 21:152-62.)

BOX 10-5 Salient Features of Developmental Anesthetic Neurotoxicity

- Apoptotic neuronal death during synaptogenesis
- Suppression of neurogenesis
- Morphologically abnormal synapse formation
- Altered dendritic spinogenesis
- Impairment of hippocampal long-term potentiation
- Deformation of neuronal and astroglial cytoskeletal protein
- Aberrant cell cycle reentry during neuronal mitosis
- Neuronal mitochondrial dysfunction
- Abnormal intraneuronal calcium homeostasis

From Palanisamy A. Maternal anesthesia and fetal neurodevelopment. Int J Obstet Anesth 2012; 21:152-62.

isoflurane, for 1 hour caused fetal brain hippocampal neurodegeneration.[203] No neurodegenerative changes were observed after third-trimester exposure in guinea pigs.[197] Thus, collectively, it appears that the fetal brain is less vulnerable to the adverse effects of anesthetic agents during the third trimester. This phenomenon could be due to the stage of neurodevelopment, or more likely, to an increase in the levels of neuroprotective hormones such as estrogen, progesterone, neurosteroids, and oxytocin during the third trimester.

The relative fetal/neonatal safety of third-trimester maternal anesthesia was supported by a robust, population-based birth cohort study (in Olmsted County, Minnesota) that sought to determine the incidence of learning disabilities in children after maternal administration of general or neuraxial anesthesia during cesarean or vaginal delivery.[204] Children exposed to general anesthesia during cesarean delivery were not more likely to develop learning disabilities compared with those born vaginally with no exposure to general anesthesia. Although the study was retrospective and used data from 1976 to 1982, it is reassuring that even the children whose mothers required emergency general anesthesia (presumably secondary to presumed fetal compromise) did not have a higher incidence of learning disability. Further epidemiologic work is required to ascertain the effects of maternal anesthesia during nonobstetric surgery in the second trimester and that of nitrous oxide analgesia during labor.

Meanwhile, the potential for anesthesia-related neurotoxicity will undoubtedly undergo continued scrutiny. In a comprehensive editorial,[205] McGowan and Davis made the following conclusions: Additional animal studies are needed to define molecular mechanisms, risks, and potential treatments for anesthetic-related neurotoxicity in the developing brain; future studies should be relevant to human development and clinical practice; human studies of adequate statistical power are needed to identify any evidence of injury from intrauterine exposure to anesthetic agents; future studies should take advantage of advances in genomics and proteomics and should target the identification of sensitive and specific biomarkers for neurocognitive injury; some forms of developmental brain injury might be prevented or ameliorated by periprocedural therapy (e.g., anti-apoptotic agents such as melatonin).[205,206]

McGowan and Davis[205] affirmed the U.S. Food and Drug Administration's (FDA) conclusion[207] that currently, "there [is] no scientific basis to recommend changes in clinical [anesthesia] practice." They noted that the "real enemy" includes "known and understood causes of brain injury and death," such as hypoxia and cardiovascular collapse. They cautioned, "[W]e must not let our enthusiasm for understanding the possible neurocognitive risks of anesthetics … obscure our awareness of this enemy or prevent us from alleviating pain."[205] The FDA's position was reaffirmed in March 2011.[208]

Fetal Neuroprotection

Throughout gestation, the fetus remains concealed, protected, and nourished by a combination of maternal anatomic and physiologic factors. For example, the amniotic fluid cushions the fetus against trauma, and the placenta serves as a conduit to ensure a continuous supply of maternal nutrients to the developing fetus. Despite these inbuilt protective mechanisms, the fetus remains vulnerable to maternal insults such as infection and fever, drugs, and acute changes in placental physiology. Among all organ systems, the developing central nervous system appears to be most susceptible to such insults. Understanding the developmental aspects of neuroprotective mechanisms will therefore enable generation of targeted neuroprotective therapies.

Role of the Placenta

One of the fundamental neuroprotective mechanisms is the barrier function of the placenta. The placenta serves as a conduit for chemical communication between the mother and the developing fetus; endocrine signals, growth factors, and cytokines freely traverse the placenta, which dynamically adapts to chronic changes in the maternal-fetal environment to preserve fetal growth and viability.[209,210] However, this function also allows transplacental transfer of an array of pharmacologically active molecules either by passive diffusion or active transport.[211] By virtue of its enzymatic machinery, the placenta is capable of detoxification of some of these potentially harmful chemicals, making it the first line of defense against potentially harmful environmental agents.

Although passive diffusion along a concentration gradient is the most widely studied placental transport mechanism, recent studies have elucidated the roles of two important active transport molecules in the syncytiotrophoblast, which actively extrudes xenobiotics: phospho-glycoprotein (P-gp) and breast cancer resistance protein (BRCP).[212] The activity of these transporters varies with gestational age and certain pathophysiologic conditions (e.g., preeclampsia, intrauterine infection) and is influenced by the steroid hormones of pregnancy. Thus, it is possible that placental permeability to certain drugs could depend on a complex interplay of several factors. In addition to this barrier function, the human placenta secretes estrogen and progesterone in very high concentrations; these hormones, as well as others, eventually enter the fetal circulation, where they serve as substrates for *de novo* neurosteroid synthesis in the fetal brain.[213] In particular, allopregnanolone has been shown to exert neuroprotective effects in the fetal brain (see later discussion).[214]

Humoral Mechanisms

Published studies have extensively investigated the intricate and symbiotic relationship between the fetus and maternal hormones throughout pregnancy. Much of our understanding comes from elaborate murine and primate research models in which changes in maternal levels of hormones closely parallel changes in the fetal plasma and/or brain. Throughout pregnancy, there is a gradual rise in the levels of many maternal hormones such as progesterone, estradiol, and oxytocin.[215-217] At term or during labor the levels of these hormones are 40- to 100-fold higher than in the nonpregnant state.

Many of these hormones freely cross the placenta and are transported to the fetal brain, where they profoundly influence neurodevelopment. For example, estradiol and progesterone influence neural stem cell proliferation, modulate apoptosis and synaptogenesis in a region-specific manner, alter subcellular signaling mechanisms, and promote dendritic growth and spinogenesis through specific receptor mechanisms.[215,216] Estradiol, in particular, prevents cell death in both neuronal and non-neuronal cell lines.

Maternal plasma oxytocin levels gradually increase during pregnancy and reach a peak during the second stage of labor. Oxytocin is of particular importance because it has significant effects on GABAergic signaling in fetal neurons. In a series of elegant experiments, investigators showed that oxytocin transiently switched the action of GABA on immature rodent fetal neurons from *depolarizing* to *hyperpolarizing* at term gestation.[218] This finding raises the possibility that oxytocin protects the fetal brain during the stressful process of labor and delivery.[219]

NEUROPROTECTIVE THERAPIES

Magnesium Sulfate and Cerebral Palsy

Until recently there was considerable controversy regarding the role of magnesium sulfate in preventing or possibly exacerbating fetal brain injury. Although some controversy remains, the publication of several large randomized studies of the effect of antenatal maternal magnesium sulfate administration on offspring outcome has dramatically altered practice guidelines and clinical practice.[220-222] Although none of these studies demonstrated significant improvement in the primary outcome, all showed reduced cognitive morbidity and none showed any increase in pediatric morbidity or mortality associated with magnesium sulfate use for neuroprotection.

In a placebo-controlled trial of women who were thought likely to deliver within 24 hours and before 30 weeks' gestation in New Zealand and Australia, Crowther et al.[220] reported a lower incidence of substantial gross motor dysfunction (3.4% versus 6.6%; relative risk [RR], 0.51; 95% CI, 0.29 to 0.91) and combined death or substantial gross motor dysfunction (17% versus 22.7%; RR,

0.75; 95% CI, 0.59 to 0.96) in children whose mothers were randomized to receive antenatal magnesium sulfate treatment. In another large trial from France, which included women in preterm labor before 33 weeks' gestation, a significant reduction in death and/or gross motor dysfunction was again identified in the children whose mothers received magnesium sulfate (25.6% versus 30.8%; OR, 0.62; 95% CI, 0.41 to 0.99).[221] A reduction in death and/or motor or cognitive dysfunction (34.9% versus 40.5%; OR, 0.68; 95% CI, 0.47 to 0.99) was observed in the magnesium-exposed offspring at 2 years of age.[221] Finally, a randomized, controlled multicenter trial in the United States found that fetal exposure to magnesium sulfate within 24 hours of preterm delivery (between 24 and 32 completed weeks' gestational age) did not reduce the combined risk for moderate or severe cerebral palsy or death. However, fetal exposure to magnesium sulfate reduced the risk for moderate or severe cerebral palsy among survivors (1.9% versus 3.5%; RR, 0.55; 95% CI, 0.32 to 0.95) and was associated with a decreased overall rate of cerebral palsy (4.2% versus 7.3%; $P = .004$).[222]

Although the results are optimistic, it is difficult to compare these trials owing to differences in inclusion criteria, study interventions/dosages, and outcomes. Nonetheless, after the publications of these trials, it has been concluded from meta-analyses that fetal exposure to magnesium sulfate may reduce the risk for cerebral palsy without increasing the risk for neonatal death.[223,224]

In 2010, the ACOG and the SMFM released a joint committee opinion that supported antenatal maternal magnesium sulfate administration for fetal neuroprotection, stating that the available evidence suggests that magnesium sulfate administered before anticipated early preterm birth reduces the risk for cerebral palsy in surviving infants.[225] Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring. The ACOG and the SMFM have concluded that it is reasonable to use a protocol based on one of the large randomized trials[220-222]; magnesium sulfate should be offered to women at high risk for anticipated preterm delivery (< 28 to 32 weeks' gestational age) within 24 hours.[220-222] A loading dose of magnesium sulfate 4 to 6 g should be administered, followed by a maintenance infusion of 1 to 2 g/h for 12 to 24 hours, at which point the risk for impending preterm delivery should be reassessed. If there is no longer a concern for impending delivery, the magnesium sulfate should be discontinued and restarted with active labor or when delivery is again thought to be imminent.

Hypothermia

Some investigators have described improved outcomes after the use of hypothermia in neonates at risk for hypoxic ischemic encephalopathy. One group of investigators has described an experimental model of severe intrauterine hypoxia in preterm fetal sheep, in which asphyxia was produced by 25 minutes of complete umbilical cord occlusion.[226] Cerebral hypothermia (fetal extradural temperature reduced from 39° to 29° C) decreased the loss of striatal neurons and oligodendroglia. This finding was associated with improved basal ganglia function after ischemia.

These and other experimental results prompted a randomized clinical trial of whole-body hypothermia for neonates with hypoxic ischemic encephalopathy.[227] Eligible neonates were older than 36 weeks' gestational age, had moderate or severe encephalopathy, and were admitted to the neonatal intensive care unit within 6 hours of birth. Body temperature was lowered to 33.5° C for 72 hours in neonates randomized to hypothermia treatment. Death or moderate to severe disability at 18 to 22 months of age occurred in 44% of 102 infants in the hypothermia group, compared with 62% of 106 infants in the control group (risk ratio, 0.72; 95% CI, 0.54 to 0.95; $P = .01$). Although encouraging, these results are at odds with those from another large multicenter randomized trial.[228] In an editorial attempting to reconcile these opposing results, several possible explanations were suggested.[229] Importantly, in the study that demonstrated no benefit, cooling began later and more time was required to achieve complete cooling, because head (not total body) cooling was employed.[228] Moreover, the study that showed no benefit with hypothermia may have included infants who were so severely affected that no therapy would have been beneficial.[228] This possibility highlights the importance of patient selection in these clinical trials.

In 2012, the whole-body hypothermia investigators published the results of follow-up evaluations of the original study subjects at 6 to 7 years of age. There was no difference in the combined primary outcome of death or an IQ score less than 70 (47% versus 62%, $P = .06$) between the hypothermia group and the control group.[230] The hypothermia group had a lower incidence of death or severe disability (41% versus 60%, $P = .03$), but there was no difference in moderate or severe disability (35% versus 38%, $P = .87$). Attention-executive dysfunction occurred in 4% of the hypothermia group versus 13% of the usual care group ($P = .19$), and visuospatial dysfunction occurred in 4% of the hypothermia group versus 3% of the usual care group ($P = .80$).[230] Thus, although there was no significant difference in the primary outcome, whole-body hypothermia decreased the incidence of death and did not increase the rate of a low IQ score or severe disability among survivors.

A 2013 meta-analysis of 11 randomized controlled trials of hypothermia therapy, which included 1505 term and late preterm infants, concluded that the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects.[231] The authors advised that hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before 6 hours of age. Further trials are necessary to identify appropriate cooling techniques and to refine patient selection.

Experimental Neuroprotection

Perlman[232] has reviewed various strategies for treating hypoxic-ischemic neonatal injuries, including administration of inflammatory mediator modulators, excitatory amino acid receptor agonists and antagonists, free radical

scavengers, and platelet-activating factor antagonists. These emerging therapeutic strategies stem from basic neuroscience research on brain development and the pathophysiology of ischemic injury.

The role of white matter in the attenuation of hypoxic-ischemic brain damage (e.g., through uptake of excitatory amino acids or sequestration of potassium and hydrogen ions) is underappreciated,[233-235] and drugs that inhibit the release of excitatory amino acids or antagonize their receptors may be of benefit.[236] Multiple strategies may be necessary to inhibit the deleterious pathways initiated by brain ischemia and hypoxia.[237] The combination of oxygen free-radical scavengers and calcium entry–blocking agents appears to have some efficacy in limiting postasphyxial injury in neonatal sheep.[238] A "brain cocktail," consisting of free radical scavengers, modifiers of nitric oxide activity, metabolic inhibitors, calcium and iron chelators, and drugs that affect the excitatory amino acid systems, may someday be administered to fetuses and neonates at risk for brain injury. Additional compounds that may inhibit CNS necrosis or apoptosis, either *in utero* or in the neonatal period, include agents that interrupt the inflammatory cascade, progesterone, and other steroids.

Among the pharmacologic candidates for neuroprotection, **erythropoietin** (EPO) appears promising[239]; EPO is known to have wide-ranging actions, including anti-apoptotic and neurotrophic effects. In a preterm fetal sheep model, EPO was shown to reduce axonal damage and decrease the astrocytic and microglial response to maternally administered lipopolysaccharide (which leads to fetal brain damage).[239] In addition, EPO was also shown to confer protection against placental and fetal liver damage, suggesting that EPO could potentially buttress the placental barrier and prevent fetal injury. In the first human clinical study, EPO administration in full-term neonates was associated with an almost 50% reduction in death and disability at 18 months when the hypoxic-ischemic injury was moderate but not severe.[240] Although neonatal EPO therapy does not appear to increase the risk for thrombotic effects, the safety and efficacy of EPO administration to pregnant mothers, and its role in fetal neuroprotection, remains to be investigated.[240]

Another agent with potential for fetal neuroprotection is **melatonin**, a highly effective antioxidant with reliable transplacental transfer and a wide therapeutic index. Administration of melatonin to fetal sheep compromised by experimental umbilical cord occlusion prevents oxidative stress, reduces lipid peroxidation, modulates microglial activation, and decreases the extent of brain damage.[241] The translational potential of other agents such as *N*-acetylcysteine (NAC), allopurinol, neurosteroids such as allopregnanolone, anesthetic agents such as xenon, and creatine appears limited.

The ability to accurately predict which fetuses are at risk for neurologic injury, and when, is still rudimentary, because the most vulnerable periods of fetal development are still unknown, and noninvasive fetal surveillance techniques are not very advanced. The ability to identify these "at risk" infants *in utero* is a necessary step in designing effective therapeutic regimens that interfere minimally with the normal trophic activities of the developing brain.

KEY POINTS

- Cerebral palsy is a nonprogressive disorder of the central nervous system that is present (but rarely obvious) at birth and involves some impairment of motor function or posture. Intellectual disability may or may not be present.
- The term *birth asphyxia* should be used sparingly, if at all, in medical records. More descriptive terms that describe the neonate's tone, color, respiratory effort, and metabolic status should be used when possible.
- The incidence of cerebral palsy is approximately 2 per 1000 live births and has not decreased despite the widespread use of intrapartum fetal heart rate monitoring and a higher cesarean delivery rate.
- The Apgar score is a poor predictor of cerebral palsy.
- Preterm delivery is a risk factor for cerebral palsy
- Spastic quadriplegia and, less commonly, dyskinesia are the only types of cerebral palsy associated with acute intrapartum hypoxic events.
- Intrapartum hypoxia sufficient to cause cerebral palsy is always accompanied by neonatal encephalopathy and seizures.
- Fetal compensatory responses to hypoxemia *in utero* include (1) a redistribution of fetal cardiac output, with increased blood flow to the brain, myocardium, and adrenal glands; (2) decreased fetal energy consumption as a result of decreased fetal breathing and body movements; and (3) maintenance of essential cellular processes at the expense of intrauterine fetal growth.
- Chorioamnionitis is associated with an increased risk for cerebral palsy. Epidural analgesia during labor is associated with an elevated maternal temperature (but not chorioamnionitis). More accurate diagnosis of chorioamnionitis may prevent unnecessary evaluations for sepsis in neonates of mothers with a small rise in temperature during labor.
- No published data suggest that a given anesthetic drug or technique is more likely to protect fetal neurologic function (provided that the anesthetic technique is administered according to the recommended guidelines for good anesthesia practice).
- Better knowledge of the process and regulation of apoptosis (programmed neuronal cell death) may lead to the development of strategies to prevent irreversible fetal neurologic injury.

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PART IV

FOUNDATIONS IN OBSTETRIC ANESTHESIA

Donald Caton, M.D.

As Simpson predicted, physicians used obstetric anesthesia sparingly until patients forced the issue. A major impetus came from early feminists. Suffragettes recognized that they could not participate fully in the economic and political life of the country unless they were healthy. For this reason they made obstetric care, including anesthesia, part of their campaign for political parity.

Early feminists had good reason to be concerned about obstetric care. Despite many improvements in medicine, maternal morbidity and mortality hardly changed between 1830 and 1930. Women were debilitated by the sequelae of poorly managed deliveries and exhausted by frequent pregnancies and management of large families. Accordingly, feminists sought care by obstetricians rather than by midwives, deliveries in hospitals rather than at home, and adequate time for recuperation before returning to their normal responsibilities. Other initiatives were construction of special maternity units, better instruction in obstetrics in medical schools, and training of more obstetricians.

They also campaigned for obstetric anesthesia. Feminists and physicians alike believed that the pain of childbirth, in and of itself, contributed to the disability of women later in life. To improve the quality and availability of anesthesia, feminists founded two organizations: The National Twilight Sleep Association began in the United States just before the beginning of World War I, and the National Birthday Trust Fund started in Great Britain in 1928.

Both organizations influenced the practice of obstetric anesthesia. Physicians explored new ways to manage the pain of childbirth, including the use of rectal ether and intravenous opioids. They also performed many important studies on the use of regional anesthesia.

For obstetricians, regional anesthesia had several advantages. First, it appeared to be safe and easy to administer, a feature that was especially important because qualified anesthesiologists were in short supply. Second, regional anesthesia allowed obstetricians to make more liberal use of operative techniques for vaginal delivery (e.g., episiotomy, use of forceps), which were just coming into vogue. No less important, regional anesthesia appeared to satisfy the desires of women who wanted more comfortable deliveries. These motives prompted the use of various regional blocks, including presacral, paravertebral, spinal, lumbar epidural, and caudal epidural anesthesia. In conjunction with this clinical work, scientists studied the anatomy and physiology of uterine function and childbirth pain, including the neurologic pathways involved in the perception of childbirth pain. Our current practices of obstetric anesthesia, particularly the emphasis on regional anesthesia, are a direct outgrowth of scientific studies and clinical trials that began during this period.[1-4]

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CHAPTER 11

Patient Safety and Team Training

David J. Birnbach, MD, MPH • Eduardo Salas, PhD

CHAPTER OUTLINE

In 2000, the publication of the Institute of Medicine (IOM) report *To Err is Human: Building a Safer Health Care System* was a seminal event for the health care system in the United States.[1] Prior to the publication of this report, many physicians and hospital administrators refused to acknowledge the frequent occurrence of preventable morbidity and the reality that our health care system was not adequately addressing the issue of patient safety. Subsequently, we have learned that tens of thousands of patients die each year as a result of medical errors. In the past decade, numerous changes have been advocated, including mandating minimum nurse-to-patient ratios,[2] reducing working hours of resident physicians,[3] and advancing the science of simulation training and teamwork, particularly in the medical environment.[4,5] Data from high-risk organizations suggest that health care errors do not usually occur because of ill-trained medical personnel but rather are due to systems that "set up" both the patient and the health care provider. As Pratt[6] eloquently stated in a 2012 review of simulation in obstetric anesthesia, "Historically, medicine was simple, largely ineffective, and mostly safe (excluding perhaps trephination and bloodletting). Modern medicine is complex, highly effective, but dangerous." The field of patient safety attempts to reduce that danger, which is very real in the fields of obstetrics and obstetric anesthesiology. Each year in the United States, approximately 600 women die of pregnancy-related causes; 68,000 experience severe obstetric morbidity; and 1.7 million experience delivery-related complications.[7] In this chapter, medical errors are reviewed and several modalities that can be used by labor and delivery unit personnel to reduce both the incidence and sequelae of these errors are highlighted.

PATIENT SAFETY AND MEDICAL ERRORS

Traditional assessments of medical error often blamed individuals and have failed to address the broader systems issues that allowed the error to occur. Newer approaches are based on an understanding that humans will make errors and therefore encourage creation of robust systems to prevent these errors from occurring or to minimize their impact on patients if they occur. This paradigm change has borrowed heavily from other high-risk arenas, such as the aviation and the nuclear industries.

The Swiss Cheese Model

Patients are typically not injured by a single event resulting from a single act of a careless individual. More often an underlying systems problem made the error possible, and numerous individual actions "fall through the cracks" of a system that does not catch them, resulting in error and harm. James Reason described the "Swiss cheese" model of error (Figure 11-1), in which he explained how numerous contributing factors are responsible for the ultimate harm.[8] Reason developed this model to illustrate how analyses of major accidents and catastrophic systems failures tend to reveal multiple, smaller failures that led up to the actual adverse event. In the model, each slice of cheese represents a safety barrier or precaution relevant to a particular hazard. For example, if the hazard were wrong-site surgery, slices of the cheese might include processes for identifying the right or left side on radiology tests, a protocol for signing the correct site when the surgeon and patient first meet, and a second

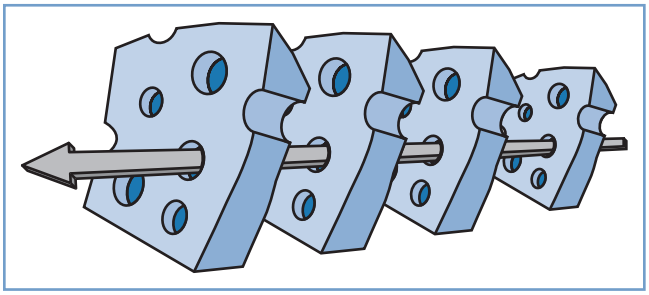

FIGURE 11-1 ■ Swiss cheese model of organizational accidents. (From Reason JT. Human Error. Cambridge, UK, Cambridge University Press, 1990.)

protocol for reviewing the medical record and checking the previously marked site in the operating room. Each barrier has "holes"; hence, the term *Swiss cheese*. For some serious events (e.g., operating on the wrong person) the holes will rarely align; however, even rare cases of harm are unacceptable. Reason's model highlights the need to think of safety as a system—a set of organizational and cultural layers that influence and shape one another. Reason has eloquently summarized the process, stating "rather than being the main instigators of an accident, operators tend to be the inheritors of system defects created by poor design, incorrect installation, faulty maintenance, and bad management decisions. Their part is usually that of adding the final garnish to a lethal brew whose ingredients have already been long in the cooking."[9]

Figure 11-2 illustrates the use of the Swiss cheese model to evaluate a real near-miss case involving the misidentification of an obstetric patient who nearly underwent the wrong procedure (an unwanted tubal ligation). It describes how the combination of numerous system errors came very close to allowing the wrong procedure to be performed. The events unfolded as follows:

1. A nulliparous woman in active labor at term arrived on the labor and delivery unit in severe pain. She spoke a foreign language and was poorly understood by the labor and delivery staff. No translator was called because her husband was helping with the translation.
2. Because the patient was in such severe pain, she rushed to answer all the questions and answered several incorrectly. As per hospital policy (due to HIPAA [Health Insurance Portability and Accountability Act of 1996] regulations), the husband was asked to leave the room while the history was being taken and was therefore not present to assist in the translation.
3. There was another patient on the labor and delivery unit with the same last name and a similar sounding first name. The hospital protocol for this occurrence was not followed. Patient initials, not last names, were listed on the labor and delivery "board," so that other staff were unaware of the identical patient names.
4. The patient developed a nonreassuring fetal heart rate (FHR) tracing and was scheduled for urgent cesarean delivery. The obstetric resident physician informed the anesthesiologist of this decision and, mistaking the two patients with identical names, booked the case for a cesarean delivery *plus* bilateral tubal ligation. Unlike the other patient with the same name, the patient going to the operating room did not want or expect a tubal ligation.
5. The case was delayed because of a shift change, and the obstetricians urged the nurses to hurry. This caused friction between the nurses and obstetricians, and they did not work as a team. There were no "board rounds," and communication between labor and delivery staff and operating room staff was suboptimal.
6. The patient arrived in the operating room and was very anxious and crying. The anesthesiologist administered fentanyl 50 μg to calm the patient and she became very sedated.
7. A "time-out" was performed, but it was not taken seriously. The patient was asleep and did not participate. The attending obstetrician was not present. Conversations continued during the time-out.
8. Following the flawed time-out, it was agreed that this patient was to undergo a primary cesarean delivery and tubal ligation. Her husband was not present during the time-out but was brought to the room immediately after this activity. The surgical procedure began.
9. The attending obstetrician arrived after the start of the procedure and questioned the planned tubal ligation, not because he knew about the second patient but because he was informed that this patient was nulliparous. Immediate investigation revealed that the patient was not supposed to receive a tubal ligation. A major error was narrowly averted.

As in many such situations, a conglomeration of many missteps resulted in the potential for patient harm.

Medical Errors

Today there is widespread interest in changing the health care culture to build safer systems, including ensuring the appropriate physical work environment, developing redundancies in safety procedures, allowing health care workers to report their mistakes (including near misses) without fear of punishment, and providing mechanisms to learn from the experiences. None of these systems will achieve the ultimate goal of patient safety without the support of physicians as well as hospital administrators. In addition, although vital to improving the current condition, these steps do not obviate the need for well-trained and well-rested physicians and nurses. The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Patient Safety in the Surgical Environment summarizes this well when it states: "Common sense dictates that the surgeon and the surgical team should be alert and well rested when initiating major surgical procedures."[10] The opinion also suggests that "adequate backup personnel should be available to relieve individuals who detect diminished performance in themselves or others due to fatigue, so that the risk for error is not increased."[10] Although the Accreditation Council on Graduate Medical Education has enacted restrictions on resident physician work hours to prevent

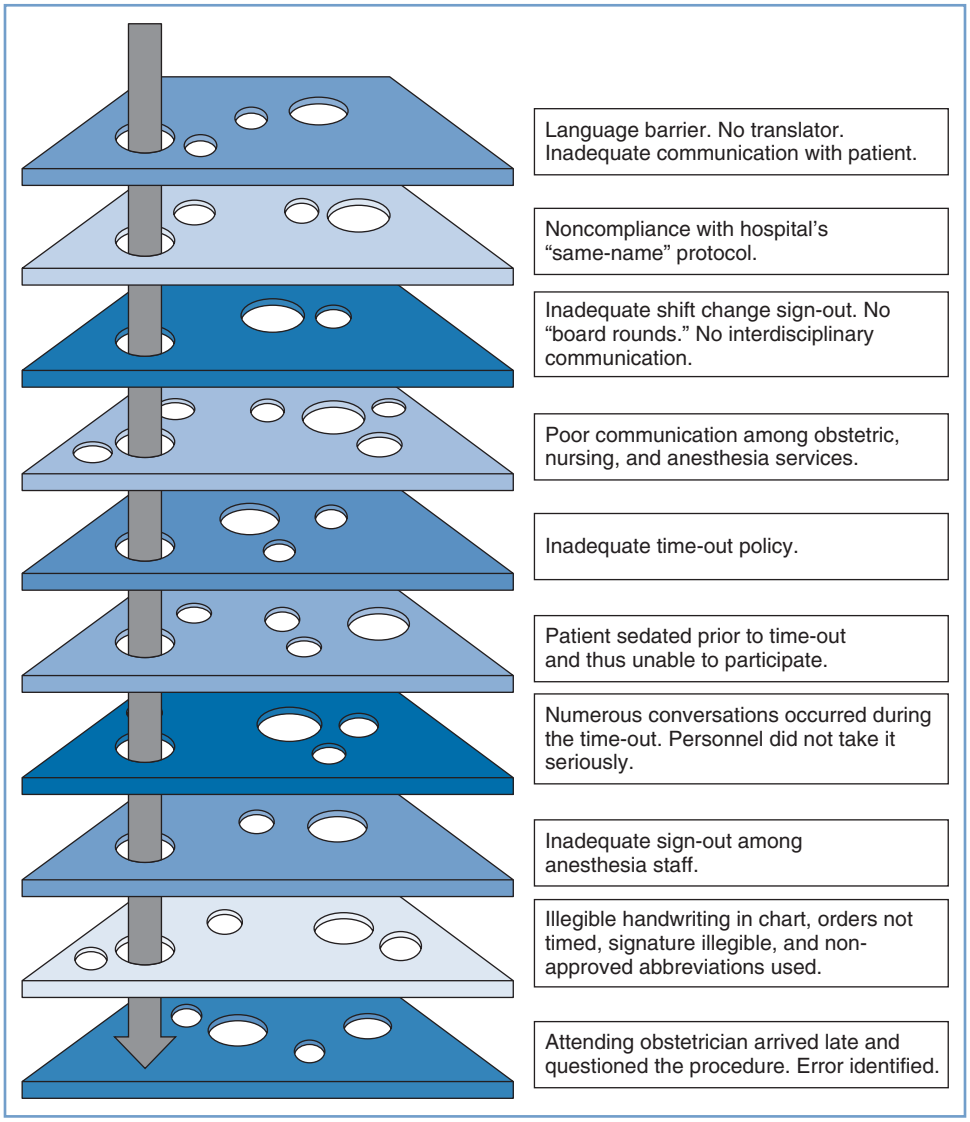

FIGURE 11-2 ■ "Swiss cheese" diagram of near-miss event illustrating how numerous layers/barriers to harm were breached and how these events almost resulted in permanent harm (permanent sterility) to the patient. See text for explanation.

sleep deprivation, there are no such limits on attending physician work hours. Rothschild et al.[11] found that the risk for surgical complications was increased if attending physicians had slept less than 6 hours the night before the procedure.

Another ACOG committee opinion[12] stated that promoting safety requires that all those in the health care environment recognize that the potential for errors exists and that women's health care should be delivered in an environment that encourages disclosure and exchange of information in the event of errors, near misses, and adverse outcomes. The ACOG[12] has recommended the following seven safety objectives:

1. Develop a commitment to encourage a culture of patient safety.
2. Implement recommended safe medication practices.
3. Reduce the likelihood of surgical errors.
4. Improve communication with health care providers.
5. Improve communication with patients.
6. Establish a partnership with patients to improve safety.
7. Make safety a priority in every aspect of practice.

The IOM has defined **medical error** as a "failure of a planned action to be completed as intended, or the use of a wrong plan to achieve an aim." Communication problems are consistently identified as a leading cause of medical errors in obstetrics,[13] and the Joint Commission has found that although the majority of these events have multiple root causes, lack of effective communication along with leadership and human factors are often the primary causes of sentinel events.[14] Several of the 2012 Joint Commission National Patient Safety Goals relate to error reduction on the labor and delivery unit (Box 11-1).[15] Departments of anesthesiology and obstetrics and gynecology should regularly review the national patient safety goals established by the Joint Commission. Hospitals are regularly surveyed to verify their compliance with these goals.

BOX 11-1 Key Joint Commission National Patient Safety Goals: 2012

- Identify patients correctly (NPSG.01.01.01).
  - Use at least two patient identifiers when providing care.
- Improve staff communication. Report critical results of tests and diagnostic procedures on a timely basis (NPSG.02.03.01).
  - Get important test results to the right staff person on time.
- Label all medications, medication containers, and other solutions on and off the sterile field in perioperative and other procedural settings (NPSG.03.04.01).
  - Before a procedure, label all medications.
- Maintain and communicate accurate patient medication information (NPSG.03.06.01).
  - Obtain information on the medications the patient is currently taking when he or she is admitted.
  - Compare the medication information the patient brought to the hospital with the medications ordered for the patient by the hospital to identify and resolve discrepancies.
- Implement evidence-based practices for preventing surgical site infections (NPSG 07.01.01).
  - Use hand cleaning guidelines from the Centers for Disease Control and Prevention or the World Health Organization. Set goals for improving hand cleaning. Use the goals to improve hand cleaning.
- Prevent mistakes in surgery (UP.01.01).
  - Make sure that the correct surgery is done on the correct patient and at the correct place on the patient's body.
  - Pause before the surgery to make sure that a mistake is not being made.

NPSG, National Patient Safety Goal; *UP*, Universal Protocol.
Summarized from the Joint Commission 2012 National Patient Safety Goals. Available at http://www.jointcommission.org/standards_information/npsgs.aspx. Accessed November 2012.

Although those working in health care have made great efforts to reduce preventable patient harm,[16] the progress has not been as dramatic as necessary. Leape and Berwick, two "fathers" of the field of patient safety, suggested that the lack of progress following the release of the initial IOM report is due to the "culture of medicine."[17] They believe that this culture is deeply rooted, both by custom and training, in autonomous individual performance. It remains possible that systematic and appropriate use of medical simulation, along with other important changes to our systems, will facilitate the necessary cultural changes and lead to improved patient safety. Labor and delivery units are no different than other medical care environments, and most still have many opportunities to change culture and practice to optimize patient safety. Nabhan and Ahmed-Tawfik[18] suggested that the concept of patient safety in obstetrics is "not as strong as desirable for the provision of reliable health care." In many units a punitive culture still exists and results in suppression of error reporting, lack of proper communication, and failure of appropriate feedback.[18] Obviously, this culture needs to change before we can significantly improve patient safety. Pronovost and Freishlag[19] eloquently described the operating room environment when they stated that "operating rooms are among the most complex political, social, and cultural structures that exist, full of ritual, drama, hierarchy, and too often conflict." These authors concluded that poor teamwork contributes prominently to most adverse events, including those in the operating room.[19]

TEAMS AND TEAMWORK

Health care should be considered a team activity. Teams take care of patients. Furthermore, health care teams operate in an environment characterized by acute stress, heavy workload, and high stakes for decision and action errors.[20] Individuals have limited capabilities; when their limitations are combined with organizational and environmental complexity, human error is virtually inevitable.[21] The labor and delivery unit is an exceedingly complex environment. In fact, the labor and delivery unit requires intense, error-free vigilance with effective communication and teamwork among various clinical disciplines who, although working together, have probably never trained together. This group includes obstetricians, midwives, nurses, anesthesiologists and nurse anesthetists, and pediatricians. The addition of trainees at all levels and in all disciplines enhances the potential for communication error. Siassakos et al.[22] suggested that one of the most important components of effective training in obstetrics includes multiprofessional training and integration of teamwork training with clinical teaching.

A **team** consists of two or more individuals who have specific roles, perform independent tasks, are adaptable, and share common goals. Salas et al.[23] have defined **teamwork** as a complex yet elegant phenomenon. It can be defined as a "set of interrelated behaviors, actions, cognitions, and attitudes that facilitate the required task work that must be completed."[23] Lack of teamwork has been identified as a leading cause of adverse events in medicine. Team behavior and coordination, particularly communication or team information sharing, are critical for optimizing team performance.[24] Baker et al.[25] stated that to work together effectively, team members must possess specific knowledge, skills, and attitudes (KSAs), including skill in monitoring each other's performance, knowledge of their own and their teammates' task responsibilities, and a positive disposition toward working in a team. These authors have described characteristics of effective teams, which include team leadership, mutual performance monitoring, backup behavior, adaptability, shared mental models, communication, team/collective orientation, and mutual trust. Moreover, effective team performance in complex environments requires that team members hold a shared understanding of the task, their equipment, and their teammates (Table 11-1).[26,27]

Teamwork is essential for safe patient care. The IOM suggested that team training and implementation of team behaviors may improve patient safety.[28] The Joint Commission has recommended a risk-reduction strategy for decreasing perinatal death or injury. This strategy includes the implementation of team training and mock

TABLE 11-1 **Characteristics of Effective Teams**

Knowledge/Skills/ Attitudes	Characteristics of the Team
Leadership	Roles are clear but not overly rigid. Team members believe leaders care about them.
Backup behavior	Members compensate for each other. Members provide feedback to each other.
Mutual performance monitoring	Members understand each other's roles.
Communication adaptability	Members communicate often and anticipate each other.
Mutual trust	Members trust each other's intentions.

Modified from Salas E, Sims DE, Klein C. Cooperation and teamwork at work. In Spielberger CD, editor. Encyclopedia of Applied Physiology. San Diego, CA, Academic Press, 2004:499-505.

emergency drills for shoulder dystocia, emergency cesarean delivery, and maternal hemorrhage.[29]

Team training promotes the acquisition of adaptive behaviors, shared cognitions, and relevant attitudes. It is an instructional strategy that ideally combines practice-based delivery methods with realistic events, guided by medical teamwork competencies (i.e., behaviors, cognitions, and/or attitudes). Murray and Enarson[30] stated that "when a crisis complicates patient care, teamwork among health care professionals is frequently strained, resulting in more frequent as well as more serious failures in managing critical events." This scenario occurs all too often on the labor and delivery unit.

After many years of uncertainty, there is now encouraging evidence that team training improves safety of clinical outcomes, especially in the operating room[31,32] and labor and delivery suite. Neily et al.[32] reported that surgical mortality decreased by 18% at 74 United States Veterans Health Administration hospitals that implemented a team training program, compared with a 7% mortality reduction in 34 control hospitals that did not implement such a program. Nielson et al.[33] reported that team training effectively reduced the decision-to-delivery time for emergency cesarean delivery. Similarly, after mandatory interdisciplinary team training for all labor and delivery staff in a unit in the United Kingdom, the median decision-to-delivery interval for a prolapsed umbilical cord decreased from 25 to 15 minutes. After initiation of team training in a community hospital, Shea-Lewis et al.[34] reported a reduction in the adverse outcome index (AOI: a composite maternal and neonatal adverse outcome index[35]) from 7% to 4%.

Team Leadership

There is a clear difference between the *leadership of individuals* and *team leadership*. One who is leading independent individuals will diagnose a problem, generate possible solutions, and implement the most appropriate solution. In contrast, team leadership does not involve handing down solutions to team members but rather consists of defining team goals, setting expectations, coordinating activities, organizing team resources, and guiding the team toward its goals.[36]

Team leaders can improve team performance in many ways (e.g., by promoting coordination and cooperation). These individuals not only must be technically competent but also must be competent in leadership skills.[20] Anesthesia providers and other physicians do not routinely train to be competent team leaders. Many of the tasks necessary can and must be learned during team training. Simulation may play a key role in this education. Team leadership training has been developed to successfully train specific team leader behaviors, and the implementation of these programs has been shown to improve team performance.[23] Hackman[37] described successful team performance as consisting of three primary elements:

1. Successful accomplishment of the team's goals
2. Satisfaction of team members with the team and commitment to the team's goals
3. The ability of the team to improve different facets of team effectiveness over time

High-Reliability Organizations and Teams

Despite the inevitability of human error, some organizations that operate in complex environments are able to maintain an exceptionally safe workplace. These organizations, including the aviation and nuclear power industries, have been termed *high-reliability organizations* (HROs). These organizations can also be hospitals and other health care organizations. Sundar et al.[38] defined HROs as institutions where individuals, working together in high-acuity situations facing great potential for error and disastrous consequences, consistently deliver care with positive results and minimal errors. Teams that exhibit behaviors that facilitate the characteristics and values held by the HRO may be defined as *high-reliability teams* (HRTs). Wilson et al.[21] have defined five guidelines for HRTs. These teams must:

1. Use closed-loop communication and other forms of information exchange to promote shared situational awareness regarding factors internal and external to the team.
2. Develop shared mental models that allow team members to monitor other members' performance and offer backup assistance when needed.
3. Demonstrate a collective organization that allows members to be assertive, to take advantage of functional expertise, and to seek and value input from other team members.
4. Seek to recognize complexities of their task environment and accordingly develop plans that are adequate and promote flexibility.
5. Use semi-structured feedback mechanisms such as team self-correction to manage, and quickly learn from, errors.

Hunt et al.[39] defined characteristics associated with high-performing teams, including situational awareness,

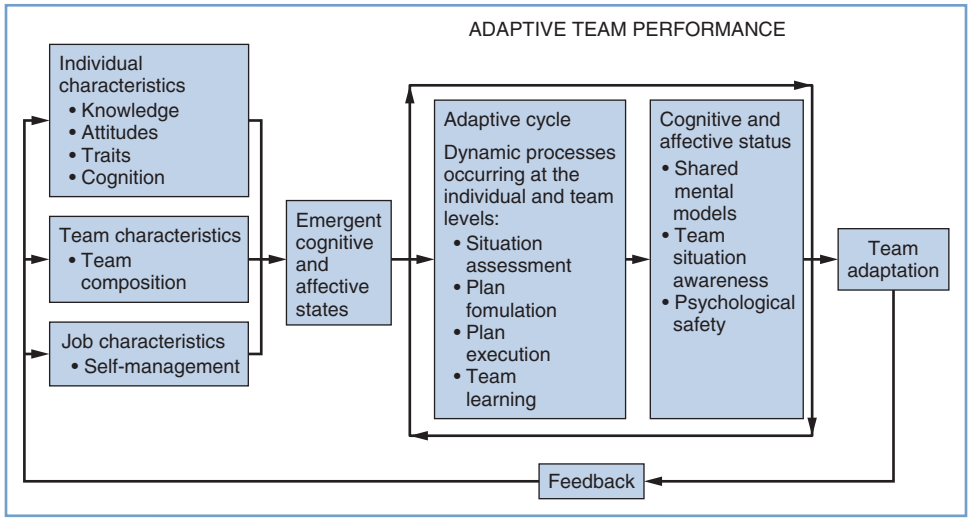

FIGURE 11-3 ■ **Adaptive team performance.** (Modified from Salas E, Rosen MA, Burke CS, et al. The making of a dream team: when expert teams do best. In Ericsson KA, Charness N, Hoffman RR, Feltovich RJ, editors. The Cambridge Handbook of Expertise and Expert Performance. Cambridge, UK, Cambridge University Press 2006:439-456.)

leadership, followership, closed-loop communication, critical language, standardized practice, assertive communication, adaptive behaviors, and workload management. An adaptive team performance framework that illustrates the relationship between variables, emergent states, and the multiple phases of the team adaptation cycle has been described by Salas et al.[40] (Figure 11-3).

Cultural factors may play a large role in team performance. According to Salas et al.,[27] these factors include attitudes (especially as they relate to previous experiences with teams) and motivation. Although it has been suggested that an individual team member's personality may be counterbalanced by others, Janis[41] suggested that openness, conscientiousness, and neuroticism are essential for individuals to succeed in command positions.

Thomas et al.[42] conducted a qualitative assessment of teamwork and suggested that factors that influence the ability to work together could be divided into three categories: provider characteristics (personal attributes, reputation, expertise), workplace factors (staffing, work organization, work environment), and group influences (communication, relationships, and teamwork). These categories can be addressed, at least in part, by working together in teams in a simulated environment and evaluating teamwork and human performance. Lyndon[43] suggested that the application of human performance-based theory has demonstrated that "communication patterns, team function, workload, and coping mechanisms affect both individual and group ability to identify evolving problems and make appropriate management decisions in complex decision-making situations."[43]

Team Training

Patient safety is "predicated on trust, open communication, and effective interdisciplinary teamwork."[44] It is often the *interactions* among health care workers that determine whether a specific plan of care is effective or ineffective.[45] However, in the current environment medical students, residents, attending physicians, nursing students, nurses, and midwives rarely learn or train to work as teams.

The Liaison Committee on Medical Education (LCME), which is jointly composed of members of the American Medical Association and the Association of American Medical Colleges, has affirmed the importance of teaching communications skills and teamwork. For example, LCME standard ED19 states that "there must be specific instruction in communication skills as they relate to professional responsibilities, including communication with patients, families, colleagues, and other health professionals."[46] Teamwork needs to be not only taught but also monitored. Box 11-2 summarizes best practices in team performance measurement for simulation-based training.

Why is teamwork training important for labor and delivery unit personnel? As previously noted, communication problems are consistently identified as a leading cause of medical error, and these problems can be addressed during team training. The 2000-2002 Confidential Enquiries into Maternal Deaths in the United Kingdom emphasized that "emergency drills for maternal resuscitation should be regularly practiced in clinical areas in all maternity units."[47] That report listed six direct maternal deaths plus one late maternal death due to anesthesia. Esophageal intubation was the cause of three maternal deaths. Each of these cases involved a trainee without immediate senior backup; and in two cases, capnography was not used, which was in direct violation of mandatory monitoring requirements. In an accompanying editorial, Ngan Kee[48] stated, "This should give pause for thought to all involved with *training* in obstetric anesthesia" [italics added].[48] These reports remind us not only of the need for appropriate supervision of trainees but also of the need to use simulation-based training for learning and practicing both crisis management and important techniques and procedures that are not frequently encountered in clinical practice. Emergency

BOX 11-2 Summary of Best Practices in Team Performance Measurement

- Ground measures in theory:
  - Use theory to determine what variables to measure.
  - Capture aspects of Input → Process → Output models of team performance.
- Design measures to meet specific learning outcomes.
- Clearly articulate the purpose of measurement.
- Design the measurement system to capture information necessary for making decisions about the learning outcomes.
- Capture competencies.
- Measure multiple levels of performance.
- Link measures to scenario events.
- Focus on observable behaviors.
- Incorporate multiple measures from different sources.
- Capture performance processes in addition to outcomes:
  - Obtain information not only about the end result but also about how the team reached that performance outcome.
- Train observers and structure observation protocols.
- Facilitate post-training debriefing and training remediation.

Modified from Rosen MA, Salas E, Wilson KA, et al. Measuring team performance in simulation-based training: adopting best practices for healthcare. Sim Healthcare 2008; 3:33-41.

administration of general anesthesia for the parturient is such an event.

Simulation-Based Training in Obstetrics

Traditional medical and nursing education has relied on the treatment of real patients in actual clinical settings. Many educators now believe that the current availability of medical simulations and the knowledge gained from the science of team training may improve patient outcomes. Most medical and nursing schools have purchased simulators and are using them in undergraduate and graduate education.

Obstetricians have identified the importance of preparing for clinical emergencies and have reiterated that conducting emergency drills may reduce or prevent the severity of medical emergencies.[49] In addition, simulation may impact patient safety because it offers opportunities to discover latent conditions and performance gaps that could adversely affect patient care.[50,51] During 46 *in situ* simulations of obstetric emergencies, Riley et al.[52] identified 965 breaches of defensive barriers (a system element that serves to prevent system errors from causing injury), of which 47.8% were classified as latent conditions (existing conditions that may interact with ongoing activities to precipitate error). The authors suggested that simulation helps providers recognize and remedy both active failures and latent conditions before they combine to cause bad outcomes.[52]

Research in simulation-based team training has shown that when trainees have an opportunity to practice relevant competencies in a structured scenario and receive diagnostic feedback on their individual and collective performance, simulation performance improves. This clearly indicates the importance of guided practice (by scenario events) and measurement.

Many authors have suggested that drills are useful on the labor and delivery unit.[53-56] Sorenson[54] stated that "mock emergency training is an opportunity for staff to learn to identify risk factors and prepare for interventions in the event of an obstetric emergency." Gardner and Raemer[55] suggested that simulation is a practical and safe approach to the acquisition and maintenance of task-oriented and behavioral skills across the spectrum of medical specialties. In the realm of obstetric anesthesia practice, investigators have demonstrated that simulation may be a useful tool for assessment of performance in a simulated emergency situation (e.g., failed intubation in an obstetric patient) when combined with practice and formal teaching.[56]

Training in perinatal emergencies with high-fidelity simulation improved the speed with which anesthesia providers responded to these emergencies and improved the quality of their care.[57] Lipman et al.[58] demonstrated, in a dramatic fashion, the use of simulation-based assessment to evaluate optimal performance of cardiopulmonary resuscitation during simulated maternal cardiac arrest. The authors demonstrated numerous deficiencies in the performance of key advanced cardiac life support (ACLS) tasks that are critical to resuscitation of a pregnant woman. These tasks included the ability to correctly deliver chest compressions (56% correct), ensure left uterine displacement (44% correct), switching chest compressors every 2 minutes (33% correct), and appropriate defibrillation (6% correct).[58] Box 11-3 outlines the advantages of simulation for research, training, and performance assessment.

When an adverse perinatal outcome associated with an error occurs, it is likely that more than one individual will be involved and blamed.[59] Similarly, when an unexpected injury occurs to a mother or infant, several providers are typically involved, and often there is a problem with the "system" that allowed the error to occur. Obstetricians, anesthesia providers, pediatricians, labor nurses, midwives, and operating room staff all work together as part of this system. Therefore, optimal simulation exercises involve all these key players and evaluate not only their behaviors and communication skills but also problems within the system in which they work. Simulation of reality-based scenarios in the labor and delivery unit or operating room allows anesthesia providers, obstetricians, midwives, nurses, and pediatricians to practice their roles and communication skills. Hunt et al.[39] suggested that medical teams require practiced interaction and communication to be effective and efficient.

Simulation of perinatal events range from high-fidelity human simulators (typically located off site) to low-technology simulations and drills that can be performed on the labor and delivery unit.[31] Simulated scenarios (guided by desired learning outcomes) can be designed to train nurses, obstetric and anesthesia resident physicians, and midwives individually or as teams. However, simulation should not be reserved for individuals in training; attending physicians may also benefit from participation. Simulated events commonly include maternal

BOX 11-3 Advantages of Simulation for Research, Training, and Performance Assessment

- No risk to patients.
- Many scenarios can be presented, including uncommon but critical situations in which a rapid response is needed.
- Participants can see the results of their decisions and actions; errors can be allowed to occur and reach their conclusion (in real life a more capable clinician would be obligated to intervene).
- Identical scenarios can be presented to different clinicians or teams.
- The underlying causes of the situation are known.
- With mannequin-based simulators, clinicians can use actual medical equipment, exposing limitations in the human–machine interface.
- With full re-creations of actual clinical environments, complete interpersonal interactions with other clinical staff can be explored and teamwork, leadership, and communication training can be provided.
- Intensive and intrusive recording of the simulation session is feasible, including audiotaping, videotaping, and even physiologic monitoring of participants. There are no issues of patient confidentiality; the recordings can be preserved for research, performance assessment, or accreditation.

Modified from Gaba DM. Anesthesiology as a model for patient safety in health care. BMJ 2000; 320:785-8.

hemorrhage (antepartum as well as postpartum), failed intubation, failed neuraxial blockade, seizures, cardiac arrest, anaphylaxis, umbilical cord prolapse, and shoulder dystocia. Thomson et al.[60] reported that drills to practice management of eclampsia were successful in the identification of deficiencies in team preparation. They concluded[60]:

> *Repetition of drills in our unit has improved the care of simulated patients with eclampsia. In subsequent drills patient management has followed evidence-based practice, with an enhanced level of efficiency. Staff [are] summoned faster, the resuscitation process is better organized, and drugs are prepared and administered more quickly.*

Similarly, another group reported significant improvement in participants' knowledge after multidisciplinary obstetric training.[61]

Maslovitz et al.[51] used simulation to identify five recurrent obstetric management mistakes:

1. Delay in transporting a bleeding patient to the operating room
2. Unfamiliarity with prostaglandin administration to treat uterine atony
3. Poor cardiopulmonary resuscitation techniques
4. Inadequate documentation of shoulder dystocia (important for the legal defense of these cases)
5. Delayed administration of blood products to reverse disseminated intravascular coagulation

BOX 11-4 Drills Advocated for Use by Labor and Delivery Staff Undergoing Team Training*

- Profound fetal bradycardia
- Magnesium sulfate overdose
- Shoulder dystocia
- Maternal hemorrhage
- Failed tracheal intubation
- Anaphylaxis
- Amniotic fluid embolism
- Severe preeclampsia/eclampsia/HELLP syndrome

**Used at the University of Miami Miller School of Medicine/Jackson Memorial Hospital Center for Patient Safety.*
HELLP, hemolysis, elevated liver enzymes, low platelet count.

The drills advocated for use by labor and delivery staff at the University of Miami Miller School of Medicine/Jackson Memorial Hospital are outlined in Box 11-4.

Simulation-based training must be implemented appropriately if it is to be effective. Salas et al.[5] suggested the following guidelines for appropriate implementation:

1. Understand the training needs and requirements.
2. Embed instructional features (e.g., performance measurement and feedback) within the simulation.
3. Craft the scenarios based on expected/desired learning outcomes.
4. Create opportunities for assessing and diagnosing individual and/or team performance within the simulation.
5. Guide learning.
6. Focus on cognitive/psychological simulation fidelity.
7. Form a mutual partnership between subject matter experts and learning experts.
8. Ensure the effectiveness of the training program.

Simulation exercises may also impact outcome by teaching improved communication to individuals and teams during transfer of patients' care from one set of caregivers to another, (i.e., so-called handovers or hand-offs). A recent survey from the United Kingdom found that handovers were rarely documented in writing and that 4% of units reported critical incidents after inadequate handovers in the preceding 12-month period.[62] This interesting study describes the use of the SBAR technique (situation–background–assessment–recommendation) and the potential to practice sign-offs and handovers during practice drills.

Team Training in Obstetrics

As noted, teamwork is critical for the delivery of quality health care, especially in complex environments such as the labor and delivery unit. Awad et al.[63] reported that medical team training improved communication in the operating room as assessed by team members using a validated scoring system. Why initiate team training on

the obstetric service? The following case report by Sachs[64] illustrates the need:

A healthy 38-year-old woman needed emergency cesarean delivery after a failed instrumental delivery. At surgery, the uterus was found to be ruptured and the fetus was stillborn. After unsuccessful attempts to repair the uterus, the patient underwent a cesarean hysterectomy and required massive transfusion and a 3-week hospital stay.

Was anyone at fault? According to the root cause analysis, lack of teamwork on many levels played a significant role in this patient's hospital course. In particular, Sachs[64] reported that communication was poor and there was a lack of mutual performance cross-monitoring, inadequate conflict resolution, suboptimal situational awareness, and work overload.

Crew Resource Management

Although relatively new to obstetrics, team drills have been successfully used in other areas of medicine, including anesthesia, intensive care, and emergency medicine, often using lessons learned from crew resource management (CRM) training. The human error aspects of many air crashes are thought to include failure of communication, decision making, and leadership.[65] In the airline industry, CRM began as a program to train pilots to reduce error by making better use of human resources in the cockpit.[66] CRM training has led to safety and performance improvements beyond those produced by improvements in equipment and technology.[5,65]

Airlines use many tools to reduce human error; CRM training is just one. Other tools include use of checklists, standardized maintenance, ability to report errors without disciplinary repercussions, and simulator training. Not all of these, however, are easily adaptable to medicine. That said, Helmreich[67] identified several lessons learned from CRM that can be applied to the practice of medicine. He believes that errors in competence require technical training and that errors in decisions or communication require team training. Furthermore, Helmreich[67] suggested that adaptation of CRM to health care similarly requires the development of nonpunitive methods to collect information on errors so that this information can be used to evaluate team performance. It has been suggested that elements of CRM that are useful in medical settings include briefings, conflict resolution procedures, and performance reviews.[23] There is evidence that operator attitudes about teamwork, hierarchy, errors, and stress affect performance among aviators working together in teams.[68] Evidence also suggests that these attitudes are relevant in the health care environment.[69]

Salas et al.[70] suggested that CRM training will not be effective or achieve its desired outcomes in health care without the following 12 prerequisites:

1. The physicians must be "on board."
2. The concept of teamwork becomes part of the "DNA" of the health care professional.
3. CRM is supplemented by other teamwork-focused training strategies.
4. The design, development, and delivery of CRM are scientifically rooted.
5. CRM training is designed systematically.
6. CRM is part of a learning organization's strategy to promote patient safety and quality care.
7. Teamwork is rewarded and reinforced by the health care provider.
8. CRM training is evaluated at multiple levels for specific outcomes.
9. CRM is supported by simulation or practice-based approaches.
10. The health care provider is "ready" to receive training.
11. The patient is part of the team.
12. The team training is recurrent.

Some health care providers will benefit more than others from CRM training and learning. For example, one study noted that physicians with poorer performance at the beginning of CRM training showed greater improvements after training.[71]

Disruptive Behavior

Whereas miscommunication is common on the labor and delivery unit, some events are not caused by difficulties with communication but rather result from disruptive behavior by a team member. It is estimated that 3% to 5% of physicians exhibit disruptive behavior.[72] Disruptive and intimidating behavior occurs frequently on labor and delivery units and is observed in personnel of diverse disciplines, including obstetricians, anesthesia providers, family practitioners, pediatricians, nurses, midwives, and administrators. In one survey, disruptive behavior was reported on more than 60% of labor and delivery units from personnel who responded to a questionnaire.[73]

Disruptive behavior includes angry outbursts, rudeness or verbal attacks, physical threats, intimidation, noncompliance with policies, and sexual harassment. Disruptive behavior contributes to the nursing shortage, near misses, and adverse occurrences. This behavior does not always involve physicians. Termed *horizontal hostility*, it occurs among nurses as well, and includes rudeness, verbal abuse, humiliating statements, unjustly critical statements, withholding information, and gossip.[74] Disruptive behavior is not always effectively managed by the organization[73] and should be considered when using simulation to improve team behaviors.

Options for Simulator Training in Obstetrics

Both high-technology and low-technology approaches to simulation have been used for training labor and delivery staff.[54] Simulation centers often use high-fidelity simulation with interactive computerized mannequins in a realistic working environment (e.g., labor room or operating room) that includes a full complement of working equipment and staff.[75] The mannequin is quite realistic; it has a pulse, heart and breath sounds, ventilatory movements, and electrocardiographic and pulse oximetry tracings. All vital signs can be adjusted via computer control, as can the ability to intubate or ventilate.[75]

Not all simulation exercises and drills for obstetrics need to be performed in high-fidelity simulators. Some authors[76] have argued that classroom training is a better

option, particularly given the high cost[77] and resources necessary for high-fidelity simulation. The inability to arrange for staff of several disciplines to be absent from the labor and delivery unit simultaneously often precludes the use of high-technology simulation and may make on-site exercises more practical.[54]

On the other hand, Gaba[78] has countered that high-fidelity simulation need not be cost-prohibitive and that it provides the required "real-life" experience necessary for training in the management of complex real-life scenarios. Morgan et al.[79] reported an obstetric simulation model that included the participation of real surgeons (rather than actors playing the role of surgeons). This was the first published report of high-fidelity simulation of obstetric team performance with anesthesia providers, nurses, and obstetricians involved in the hands-on management of obstetric crises.

Several options are available for teaching teamwork and crisis intervention in obstetrics. Multidisciplinary obstetric simulated emergency scenarios (MOSES) was developed by the St. Bartholomew Hospital Group in the United Kingdom[80] and involves participation of obstetricians, anesthesia providers, and midwives in team training on a high-fidelity simulator. MedTeams was developed by the U.S. Armed Forces and Dynamics Research Corporation. Originally employed in emergency departments,[65,81,82] it has now been used for labor and delivery teams.[33] The course consists of "train the trainer" sessions that focus on seven dimensions that are essential to teamwork. Behaviorally anchored rating scales (BARS) are used to assess various key behaviors. Additionally, in a 2006 review, Harris et al.[83] discussed the challenges of implementation of team training in an obstetric care environment.

Other evidence-based programs have emerged. TeamSTEPPS was developed by the U.S. Department of Defense and Agency for Healthcare Research and Quality (AHRQ) as a team training and implementation toolkit.[84] The program is adaptable, medically relevant, and based on findings from the science of team performance, and it is applicable to training on labor and delivery units.

What is the evidence that team training and simulation reduce errors and improve outcomes? Morey et al.[65] reported that the MedTeams program reduced errors in the emergency department, and they observed a statistically significant improvement in team behaviors. The clinical error rate in providers who received MedTeams training decreased from 31% to 4%. Grunebaum et al.[85] implemented team training as well as other comprehensive patient safety changes to their obstetric practice and found that their interventions resulted in decreased compensation payments and sentinel events. Clark et al.[86] described implementation of a comprehensive redesign of patient safety processes that was associated with improved patient outcomes and a decline in litigation rates. The authors of the report stressed that "every member of the obstetric team should be not only empowered but also required to intervene and halt any process that is deemed to be dangerous." This behavior can be achieved as part of a team training program.

Accumulating evidence suggests that medical simulation and team training improve teamwork and communication and allow recognition of potential areas of weakness in obstetric care. We, as well as others,[25,38,87] believe that these are viable strategies to mitigate medical errors. We also agree with Pearlman et al.,[88] who stated that "we have the moral imperative as a specialty to fully engage in the identification of our own best practices, to advance safety research in obstetrics and gynecology, and to implement broadly those practices which are best."

In addition to better communication, team training, and simulation-based education, several other changes to our cultures and systems need to occur in order to significantly improve patient safety on the labor and delivery unit. These changes include:

- Learning from our mistakes
- Changing the culture on the labor and delivery floor to one of a "just culture"[89]
- Having buy-in and support from hospital leadership to implement the necessary changes
- Improving the care of the high-risk parturient so that every member of the team is more prepared and working as a team member[90]
- Improving and automating the collection of quality metrics, collecting appropriate data on outcomes, and sharing the data with practitioners on a regular basis[91]
- Developing and implementing systems to reduce drug administration errors[92,93]
- Tearing down the silos so that we learn from each other's mistakes and improvement processes, whether from department to department, hospital to hospital, or country to country[93]

The challenge for the next decade will be to implement these changes and test their effectiveness in improving patient safety.

KEY POINTS

- Medical errors harm tens of thousands of patients each year.
- To err is human; therefore, systems should be developed to prevent or "catch" errors before the patient is harmed.
- Poor communication among health care workers is the primary cause of sentinel events.
- Teamwork is essential to safe patient care, and team training may improve patient safety.
- Simulation-based training is an educational tool that may improve responses to obstetric emergencies.
- Adaptation of some elements of aviation crew resource management training may improve team performance in health care.
- Disruptive behavior interferes with safe patient care and is observed in physicians as well as other members of the health care team.

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CHAPTER 12

Spinal, Epidural, and Caudal Anesthesia: Anatomy, Physiology, and Technique

Naveen Nathan, MD • Cynthia A. Wong, MD

CHAPTER OUTLINE

The art and science of neuraxial anesthesia requires a thorough appreciation of neuroanatomy and the physiologic effects imposed by medications commonly administered via the spinal and/or epidural route. The focus of this chapter is to characterize the anatomic and technical considerations for neuraxial anesthesia. The reader is referred to Chapter 23 for a corresponding discussion of the physiologic and untoward effects of neuraxial analgesia in laboring women and to Chapter 26 for a discussion of neuraxial anesthesia for cesarean delivery. Successful administration and management of neuraxial anesthesia requires well-developed technique moderated by sound clinical judgment.

ANATOMY

Neuraxial Anatomy

The Spinal Cord, Spinal Canal, and Meninges

The cephalad aspect of the spinal cord is continuous with the brainstem through the foramen magnum. The spinal cord most often terminates as the conus medullaris at the level of the lower border of the first lumbar vertebral body. The conus medullaris is attached to the coccyx by means of a neural-fibrous band called the filum terminale, which is surrounded by the nerves of the lower lumbar and sacral roots, known as the cauda equina. Within the bony vertebral column are three membranes: the pia mater, the arachnoid mater, and the dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord. The arachnoid mater is a delicate, nonvascular membrane closely adherent to the third and outermost layer, the dura. The subarachnoid space, located between the pia mater and arachnoid mater, contains (1) cerebrospinal fluid (CSF), (2) spinal nerves, (3) a trabecular network between the two membranes, (4) blood vessels that supply the spinal cord, and (5) lateral extensions of the pia mater—the dentate ligaments. The dura mater is a membrane composed of collagen that encapsulates the spinal cord, the deeper meningeal layers, and the subarachnoid space. This layer forms a connective tissue sheath along the vertical axis of the central nervous system (CNS) that is contiguous with connective tissue covering the lateral extension of spinal nerve roots as they exit the intervertebral foramina. The interface between the dural and arachnoid layers has been described as a potential space capable of expansion

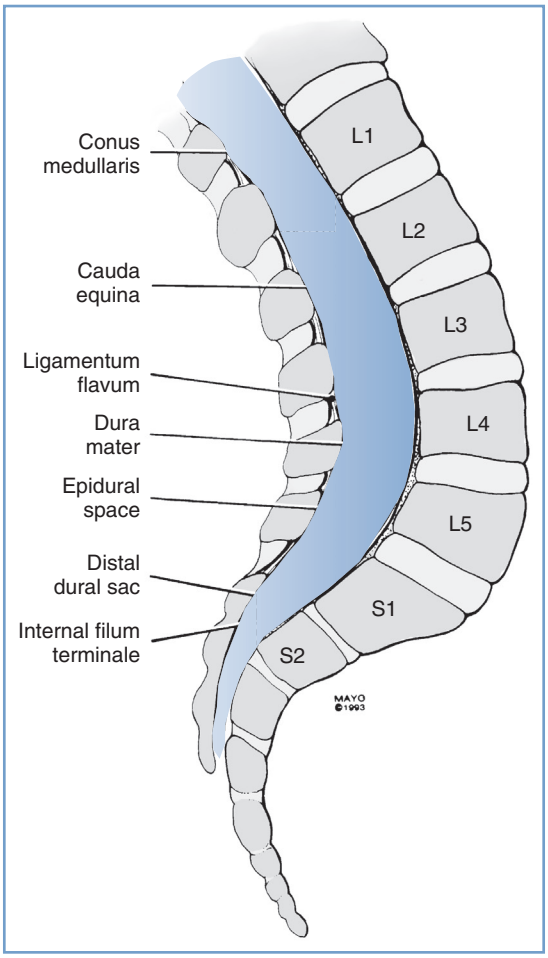

FIGURE 12-1 ■ Distal neuraxial anatomy. In pregnant women, the spinal cord usually ends at the lower border of the first lumbar vertebral body. The subarachnoid space continues to the second sacral vertebral level.

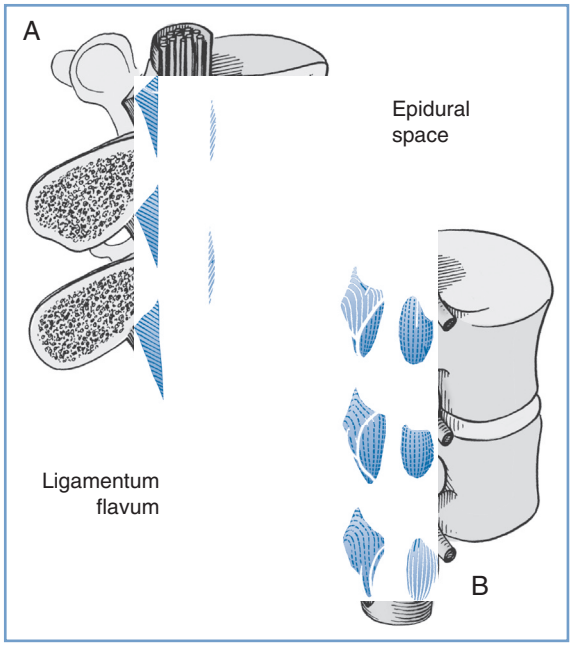

FIGURE 12-2 ■ **A,** Sagittal section of the epidural space demonstrates that the contents of the epidural space depend on the level of the section. **B,** Three-dimensional drawing of the epidural space shows the discontinuity of the epidural contents. However, this potential space can be dilated by the injection of fluid into the epidural space. (Redrawn from Stevens RA. Neuraxial blocks. In Brown DL, editor. Regional Anesthesia and Analgesia. Philadelphia, WB Saunders, 1976:323).

subsequent to mechanical trauma. Unintentional injection of local anesthetic into this *subdural space* may explain some cases of failed spinal anesthesia. It may also explain the rare, slow-to-develop cases of high spinal anesthesia after the inadvertent subdural injection of larger volumes of local anesthetic intended for epidural administration.[1] Although the spinal cord ends at the level of the bodies of L1 and L2 in most patients, the subarachnoid space and cauda equina continue to the S2 level (Figure 12-1).

The Epidural Space

The epidural space is located external to the sac of the dura mater and contains loose connective tissue, adipose tissue, lymphatics, spinal nerve roots, and the internal vertebral venous plexus (Batson's plexus) (Figure 12-2). This space is bound by the posterior longitudinal ligament anteriorly, the ligamentum flavum and the periosteum of the lamina posteriorly, the pedicles of the vertebrae, and the intervertebral foramina with their contents laterally. The epidural space is closed at the foramen magnum where the spinal dura attaches to the dura of the cranium and at the sacral hiatus by the sacrococcygeal ligament. Frequently, anatomic references will illustrate neuraxial anatomy by way of sagittal and/or transverse cross section. This may result in the erroneous impression that the epidural space is a continuous columnar entity that envelops the dural sac at all points about its perimeter. Investigations using cryomicrotome sections and three-dimensional reconstruction of radiologic data verify that the epidural space is in fact discontinuous along the vertical and lateral axes of the spinal canal. It varies in anteroposterior thickness according to dermatomal distribution, being widest at the level of lumbar vertebrae and thinnest in the cervical region.[2,3] Epiduroscopy and epidurography suggest the presence of a dorsal median connective tissue band in some individuals.[4] Anatomic dissection and computed tomographic epidurography have also suggested the presence of epidural space septa. This band (or these septa) may provide an explanation for unilateral or incomplete epidural anesthesia.[5] However, some investigators have suggested that the dorsal median band is an artifact of epidural space distention or an anatomic manifestation of the previously unappreciated epidural space segmentation.[3]

The Vertebral Column and Ligaments

The ligamentum flavum lies posterior to the epidural space (Figure 12-3). The lamina, the spinous processes of the vertebral bodies, and the interspinous ligaments lie posterior to the ligamentum flavum. Posterior to these structures are the supraspinous ligament (which extends

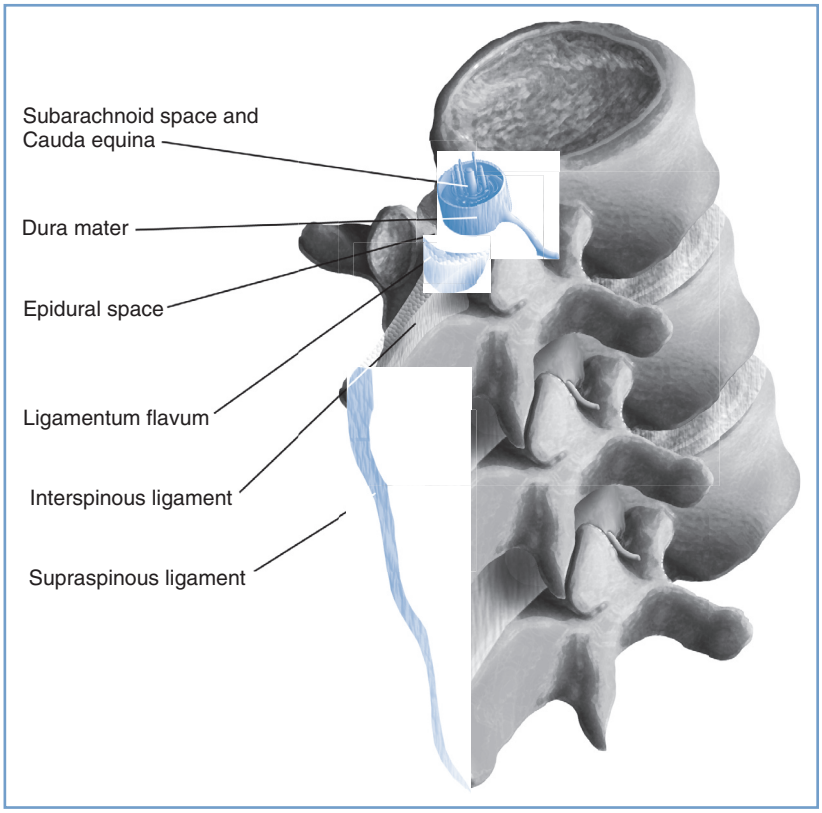

FIGURE 12-3 ■ Central neuraxial anatomy. Note the variable thickness of the ligamentum flavum, which is greatest in the midline and decreases as it fans out laterally. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

from the external occipital protuberance to the coccyx), subcutaneous tissue, and skin. Historically, some have described the ligamentum flavum as a single ligament. In actuality, however, it is composed of two curvilinear ligaments that join in the middle and form an acute angle with a ventral opening.[3,6] Much like the epidural space, the ligamentum flavum is not uniform from skull to sacrum; indeed, it is not uniform even within a single intervertebral space. The thickness of the ligamentum flavum varies with vertebral level, body mass index, and age, as does the distance between the skin and the epidural space (Table 12-1).[7,8]

Anatomic Changes of Pregnancy

The normal anatomic changes of pregnancy affect the use of neuraxial anesthesia techniques. Uterine enlargement and vena caval compression result in engorgement of the epidural veins. Unintentional intravascular epidural catheter cannulation and injection of local anesthetic are more common in pregnant patients than in nonpregnant patients. In addition, the vertebral foraminal veins, which are contiguous with the epidural veins, are enlarged and obstruct one of the pathways for anesthetic egress from the epidural space during administration of epidural anesthesia. The enlarged epidural veins also may displace CSF from the thoracolumbar region of the subarachnoid space, as does the greater intra-abdominal pressure of pregnancy; this displacement partly explains the lowered dose requirement for spinal anesthesia in pregnant women.[9] Subarachnoid dose requirements are also affected by the lower specific gravity of CSF in pregnant patients than in nonpregnant patients.[10]

The hormonal changes of pregnancy affect the perivertebral ligamentous structures, including the ligamentum flavum. The ligamentum flavum may feel less dense and "softer" in pregnant women than in nonpregnant patients; thus, sensing the passage of the epidural needle through the ligamentum flavum may be more difficult. It may also be more difficult for a pregnant woman to achieve flexion of the lumbar spine. Progressive accentuation of lumbar lordosis alters the relationship of surface anatomy to the vertebral column. At least three changes may occur. First, a pregnant woman's pelvis rotates on the long axis of the spinal column; thus, the line joining the iliac crests (Tuffier's line) assumes a more cephalad relationship to the vertebral column (e.g., this imaginary line might cross the vertebral column at the L3 to L4 interspace rather than the L4 to L5 interspace).

TABLE 12-1 **Distance from the Skin to the Epidural Space in 1000 Parturients**

Lumbar Interspace	Distance (cm)		
	MEDIAN	5TH PERCENTILE	95TH PERCENTILE
L1-2	4.23	3.12	6.33
L2-3	4.86	3.29	7.32
L3-4	4.93	3.57	7.44
L4-5	4.78	3.25	6.75

From Harrison GR, Clowes NWB. The depth of the lumbar epidural space from the skin. Anaesthesia 1985; 40:685-7.

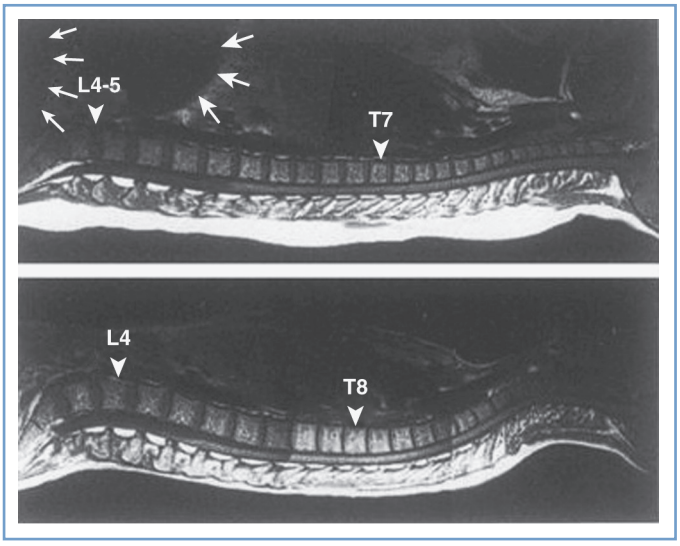

FIGURE 12-4 ■ The curvature of the spinal column in the pregnant female (*top*) and nonpregnant female (*bottom*). The large and small white arrows indicate the uterus and fetal head, respectively. The apex of the lumbar lordosis moves caudad (*triangular arrow*), and the thoracic kyphosis is reduced and moves cephalad *(triangular arrow*) in the pregnant woman. (Reprinted with permission from Hirabayashi Y, Shimizu R, Fukuha H. Anatomical configuration of the spinal column in the supine position. II. Comparison of pregnant and non-pregnant women. Br J Anaesth 1995; 75:6-8.)

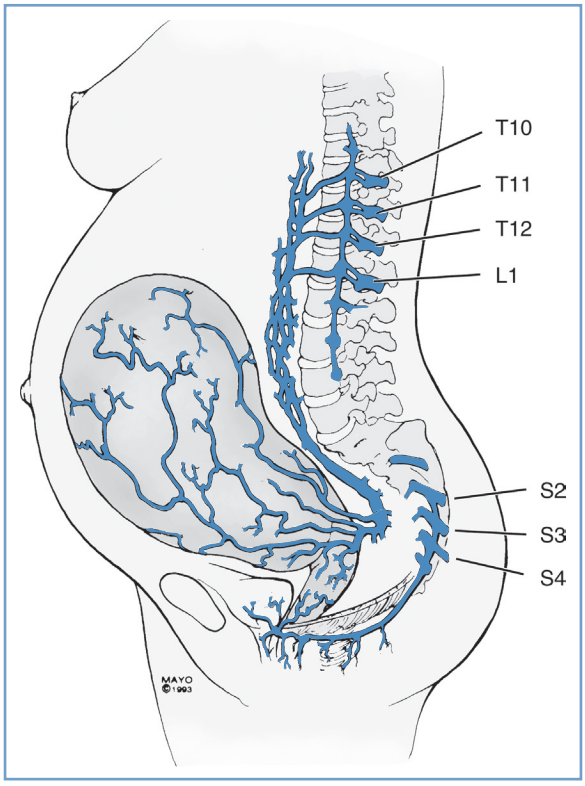

FIGURE 12-5 ■ Pain pathways during labor and delivery. The afferent pain pathways from the cervix and uterus involve nerves that accompany sympathetic fibers and enter the neuraxis at T10 to L1. The pain pathways for the pelvic floor and perineum include the pudendal nerve fibers, which enter the neuraxis at S2 to S4.

Second, there is less space between adjacent lumbar spinous processes during pregnancy. It may be more difficult to use the midline approach to identify the epidural or subarachnoid space in pregnant women. (Thus the often-heard comment, "She has a narrow interspace.") Third, magnetic resonance imaging has shown that the apex of the lumbar lordosis is shifted caudad during pregnancy, and the typical thoracic kyphosis in women is reduced during pregnancy.[11] These changes may influence the spread of subarachnoid anesthetic solutions in supine patients, leading to a higher sensory level in the pregnant patient (Figure 12-4).[12] Finally, labor pain makes it more difficult for some women to assume and maintain an ideal position while the anesthesia provider performs neuraxial anesthesia.

PHYSIOLOGY

Obstetric Pain Pathways

Pain during the first stage of labor results primarily from changes in the lower uterine segment and cervix. Pain is transmitted by visceral afferent nerve fibers that accompany the sympathetic nerves and enter the spinal cord at the T10 to L1 segments. During the late first stage and second stage of labor, pain results from distention of the pelvic floor, vagina, and perineum. Pelvic pain is transmitted by somatic nerve fibers, which enter the spinal cord at the S2 to S4 segments (Figure 12-5).

During cesarean delivery, additional nociceptive pathways are involved in the transmission of pain, and a T4 level of anesthesia is required to provide adequate anesthesia. Most cesarean deliveries are performed with a horizontal (e.g., Pfannenstiel) skin incision, which involves the infraumbilical T11 to T12 dermatomes. During surgery, stretching of the skin may involve dermatomes two to four levels higher. Intraperitoneal manipulation and dissection involve poorly localized visceral pain pathways. Visceral pain may be transmitted by pathways as high as the celiac plexus. Additional somatic pain impulses may occur as a result of diaphragmatic stimulation because the intercostal nerves innervate a portion of the peripheral diaphragm.

Physiology of Neural Blockade

Hormonal changes, anatomic changes, and decreases in CSF specific gravity likely are responsible for the lower local anesthetic dose requirements for spinal anesthesia in pregnant women.[10,13] Local anesthetics produce conduction blockade primarily by blocking sodium channels in nerve membranes, thereby preventing the propagation of neural impulses. Differential blockade is manifested as differences in the extent of cephalad blockade of temperature discrimination and vasomotor tone, sensory loss to pinprick, sensory loss to touch, and motor function. Temperature discrimination and vasomotor tone are blocked to the greatest extent (i.e., most cephalad level)

and motor function to the least extent. During spinal anesthesia, local anesthetics act directly on neural tissue in the subarachnoid space. Regression of anesthesia can be explained by the simple vascular uptake of local anesthetic from the subarachnoid space and spinal cord.[14] Epidural anesthesia has a much smaller zone of differential motor–sensory–sympathetic blockade; this difference suggests that the mechanism of epidural anesthesia must involve more than simple diffusion across the dura. For many years, nerve fiber size was presumed to be the primary determinant of susceptibility to local anesthetic blockade (i.e., smaller fibers are blocked more readily than larger fibers). However, later studies have shown that the length of nerve fiber exposed to local anesthetic is as important as the size of the nerve fiber. Fink[15] hypothesized that the length of nerve fiber exposed to local anesthetic affects the extent of the differential zone of motor and sensory blockade. With spinal anesthesia, the local anesthetic concentration required to block sufficient sodium channels to affect motor, sensory, and sympathetic function is less than that needed for the better-protected nerves found in the epidural space; thus, a wider band of differential blockade occurs during spinal anesthesia than during epidural anesthesia.

The understanding of the mechanisms of spinal and epidural anesthesia likely remains oversimplified. Nonetheless, it seems clear that spinal anesthesia results primarily from the effects of local anesthetic on the spinal cord, whereas epidural anesthesia results from the effects of local anesthetic on nerve tissue within both the epidural and subarachnoid spaces.

BOX 12-1 Suggested Resuscitation Equipment and Drugs That Should Be Available During Administration of Neuraxial Analgesia/Anesthesia

Drugs

- Hypnotic-amnestic agents (propofol, ketamine, midazolam)
- Succinylcholine
- Ephedrine
- Epinephrine
- Phenylephrine
- Atropine
- Calcium chloride
- Sodium bicarbonate
- Naloxone

Equipment

- Oxygen source
- Suction source with tubing and catheters
- Self-inflating bag and mask for positive-pressure ventilation
- Face masks
- Oral airways
- Laryngoscope and assorted blades
- Endotracheal tubes with stylet
- Eschmann stylet (bougie)
- Qualitative carbon dioxide detector

TECHNIQUE

Pre-procedural Considerations

Monitoring

The American Society of Anesthesiologists (ASA) has published guidelines for administration of neuraxial anesthesia in obstetric patients (see Appendix A). Among other things these recommendations address (1) the required presence of qualified anesthesia and obstetric care providers, (2) immediate availability of resuscitation medication and equipment (Box 12-1), (3) mandatory pre-procedural intravenous access, and (4) employment and documentation of maternal vital signs and fetal heart rate (FHR) monitoring.

During the initiation of neuraxial analgesia for labor, all patients are monitored with an automatic blood pressure cuff and a pulse oximeter to facilitate continuous assessment of the maternal heart rate and oxygenation. Maternal blood pressure is measured every 1 to 2 minutes after the administration of the test and therapeutic doses of local anesthetic for approximately 15 to 20 minutes, or until the mother is hemodynamically stable. Subsequently (during maintenance of neuraxial analgesia), maternal blood pressure is measured every 15 to 30 minutes or more frequently if hypotension ensues. Continuous pulse oximetry during maintenance analgesia is used in selected patients (e.g., patients with obstructive sleep apnea or cardiovascular disease). Rarely, invasive hemodynamic monitoring is necessary. The sensory level of analgesia and the intensity of motor block are assessed after the administration of the test and therapeutic doses of local anesthetic. Subsequently, sensory level and motor block are assessed at regular intervals.

Neither the ASA nor the American College of Obstetricians and Gynecologists (ACOG) provides a specific recommendation as to whether continuous FHR monitoring is necessary during performance of neuraxial anesthesia procedures. The ASA Task Force on Obstetric Anesthesia[16] has stated:

> *The fetal heart rate should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor. The Task Force recognizes that continuous electronic recording of the fetal heart rate may not be necessary in every clinical setting and may not be possible during initiation of neuraxial anesthesia.*

The anesthesia provider cannot predict when hypotension will occur during the administration of neuraxial anesthesia. In addition, there is concern that intrathecal administration of an opioid is associated with a higher incidence of nonreassuring FHR patterns than other neuraxial techniques (see Chapter 23).[17] Thus, we believe that continuous electronic FHR monitoring should be performed both during (if possible) and after the administration of neuraxial analgesia in all laboring women. In some cases, the mother's position or maternal obesity precludes the use of an external Doppler device to monitor the FHR. In such cases (especially when there is

concern regarding fetal well-being), it is helpful for the obstetric provider to place a fetal scalp electrode to monitor the FHR.

Informed Consent, Patient-Procedure Verification, and Partner's Presence

Prior to initiation of neuraxial anesthesia, a pre-procedural verification process (i.e., "time-out") is instituted as part of compliance with national patient safety recommendations from hospital accreditation organizations.[18] The participation of the patient, the anesthesia care provider, and a third party such as a member of the nursing staff may lead to the discovery of concerns that should be addressed before the initiation of neuraxial anesthesia. The risk of neuraxial procedures relates to (1) the physical instrumentation of the spinal axis and (2) physiologic changes associated with medication administration via this anatomic route. Contraindications to needle or catheter placement include patient refusal or inability to cooperate, ongoing bleeding diathesis, infection either at the site of intended intervention or untreated systemic blood-borne illness, and increased intracranial pressure predisposing to cerebral herniation. Contraindications to injecting local anesthetics via the epidural or spinal route include severe hypovolemia and allergy to local anesthetics. It would be axiomatic that patient refusal presents an absolute contraindication to an elective procedure. A thorough preoperative assessment of current fetal well-being, maternal volume status, intrapartum systemic opioid use, antibiotic administration for ongoing chorioamnionitis or other infectious process, and a brief reiteration of known maternal disease states, including allergies, will readily identify most of the major concerns that would render neuraxial anesthesia potentially hazardous. The anesthesia provider should weigh the risks and benefits of neuraxial anesthesia for each patient.

Informed consent should include a frank discussion about anesthetic procedures and risks. Surveys of postpartum women have demonstrated that most parturients want to know the possible complications of epidural analgesia, even those that are rare.[19,20] It is best to relay this information before the onset of labor (e.g., during antenatal classes),[21] or early in the intrapartum period, although doing so is not always feasible. Some anesthesia providers fear that distressed, desperate, or sedated parturients may not understand the discussion of anesthetic procedures. However, adequacy of consent can be demonstrated not only by documentation of information provided to the patient but also by the lack of patient objection to a procedure and the cooperation provided by the patient during the procedure.[22] In a survey of North American anesthesiologists, Brull et al.[23] found that a majority of clinicians did not disclose the most severe risks of central neuraxial anesthesia to their patients. Additionally, most anesthesiologists cited inaccurate incidences of these complications. We do not find it difficult to explain the procedure and the risks of neuraxial analgesia to a laboring woman. The preanesthetic evaluation allows the physician to communicate a sense of concern and to demonstrate a commitment to the patient's care. Most laboring women understand the need for informed consent, and they appreciate the opportunity to participate in decisions about their care.

Management of the pregnant patient occurs in a unique clinical care environment in which the presence of the patient's spouse or family member must be addressed. Most often, the dictates of local institutions will establish whether a partner's presence during neuraxial labor analgesia is acceptable. However, hospital policy may be vague enough that the discretion lies in the hands of the anesthesia provider. Intuition may suggest that a partner who remains present during the conduct of neuraxial analgesia may help alleviate the patient's ongoing anxiety regarding the procedure. Conversely, the partner may be so apprehensive or disruptive that the partner's presence becomes counterproductive to the care of the patient. Orbach-Zinger et al.[24] randomized 84 nulliparous women to either presence or absence of their partner during labor epidural catheter placement. Interestingly, patient and partner anxiety, as measured by a validated anxiety questionnaire, were reduced when partners were absent during the procedure.

Patient Positioning

Pregnant women have an exaggerated lumbar lordosis, and it is more difficult for them to flex the lumbar spine. However, most pregnant women are young, and youth usually allows sufficient flexibility to facilitate the insertion of a needle into the epidural or subarachnoid space. Whether the block is initiated in the lateral or sitting position is a matter of provider and patient preference. Notable advantages of the lateral position include (1) orthostatic hypotension is less likely and (2) the position often facilitates continuous FHR monitoring during placement of the epidural catheter. Vincent and Chestnut[25] performed a study in which they observed that neither the sitting nor the lateral position was consistently superior with regard to patient comfort. However, pregnant women who preferred the left lateral decubitus position weighed less and had lower body mass indices than women who preferred the sitting position. The sitting position is likely associated with a higher incidence of orthostatic hypotension and syncope. However, the sitting position is preferred—and may be required—in obese parturients, in whom identification of the midline is usually significantly easier in the sitting position. Further, morbidly obese women may experience hypoxemia when placed in the lateral decubitus position.

One study demonstrated a greater reduction in maternal cardiac output with maximal lumbar flexion in the lateral decubitus position than in the sitting position during identification of the epidural space in laboring women.[26] The researchers speculated that maximal lumbar flexion in the lateral decubitus position results in concealed aortocaval compression. In contrast, they suggested that the uterus falls forward (and thus does not cause aortocaval compression) when the patient assumes the sitting flexed position. They recommended that "the tight fetal curl position be avoided," especially when the patient assumes the lateral decubitus position for identification of the epidural or intrathecal space.

Aortocaval compression must be avoided at all times. The gravid uterus can occlude the inferior vena cava and aorta when the parturient assumes the supine position.[27-29] This position may cause maternal hypotension[30,31] and reduce uteroplacental perfusion,[32] even in the absence of anesthesia. Increased venous tone in the lower extremities helps overcome partial occlusion of the inferior vena cava in unanesthetized pregnant women. If maternal hydration is inadequate and if aortocaval compression is not avoided, the onset of anesthesia-induced sympathetic blockade may result in decreased venous return, cardiac output, and uteroplacental perfusion.[29]

Maternal position during placement of the epidural catheter does not seem to affect the incidence of unintentional dural puncture. However, adoption of the lateral recumbent head-down position for epidural catheter placement may reduce the incidence of epidural venous puncture.[33]

When spinal or epidural anesthesia is performed with the patient in a lateral position, the patient's back should lie at, and parallel to, the edge of the bed, for at least two reasons. First, the edge is the most firm section of the mattress. If the patient lies away from the edge of the bed, the patient's weight will depress the mattress, and the anesthesia provider must work in a "downhill" direction. Second, this position allows anesthesia providers to keep their elbows flexed, facilitating control of fine hand and wrist muscle movements. The plane of the entire back should be perpendicular to the mattress. When asked to flex the lower back, patients typically roll the top shoulder forward, an action that rotates the spine (which is undesirable) but does not flex the lower back.

Similarly, patients positioned sitting should have their feet supported by a stool with the backs of their knees against the edge of the bed, a maneuver that helps position the patient's back closer to the anesthesia provider. The shoulders should be relaxed symmetrically over the hips and buttocks. Beds in obstetric units often break at the foot, and the split in the mattress encourages the patient's seat to slope downhill if she is straddling the mattress split; this position will cause spine rotation and may make the procedure more difficult.

When spinal anesthesia is performed, the patient's posture relative to the baricity of the anesthetic solution should be considered, because it influences the extent of blockade, the latency of blockade, and the incidence of hypotension. The incidence, timing, and extent of hypotension in the period immediately after initiation of the block depend on the type of block (e.g., spinal, epidural, or combined spinal-epidural [CSE]), drug characteristics (e.g., baricity, concentration), patient position during the procedure, and patient position in the period following the procedure. For example, when spinal anesthesia is initiated with a hyperbaric solution for instrumental vaginal delivery, it often makes sense for the patient to be sitting to ensure the rapid onset of sacral anesthesia. Conversely, spinal anesthesia for cervical cerclage can be initiated with the patient in the steep lateral Trendelenburg position with a hypobaric anesthetic solution.

Posture has less influence on the spread of epidural anesthesia.[34-36] During epidural anesthesia, a unilateral block more likely results from the malposition of the catheter (or perhaps an anatomic barrier within the epidural space) than from patient position, particularly after a bolus injection. Norris and Dewan[34] observed that gravity did not augment the spread of anesthesia in patients receiving epidural anesthesia for cesarean delivery, and they concluded that posture does not need to be manipulated to ensure adequate bilateral epidural anesthesia. In at least two studies it was noted that the use of the sitting position is not necessary for the development of good sacral anesthesia when large volumes of epidural local anesthetic are given for cesarean delivery.[34,36] However, Reid and Thorburn[36] observed that use of the sitting position appeared to delay the spread of anesthesia to the midthoracic dermatomes. In comparison with the bolus administration of epidural local anesthetic, the extent of blockade may be more gravity dependent when the anesthetic is administered as a continuous infusion over a prolonged period.

Some anesthesiologists contend that maternal position after epidural catheter placement affects the efficacy of epidural analgesia, although this is a matter of some dispute. Beilin et al.[37] observed that the placement of the laboring woman in the supine position with a 30-degree leftward tilt was associated with better epidural analgesia than maintenance of the left lateral decubitus position. In contrast, Preston et al.[38] observed no difference in analgesia and a significantly higher incidence of fetal bradycardia with the supine wedged position than with the full lateral position.

Caudal anesthesia is used infrequently in modern obstetric anesthesia practice. However, there remain some circumstances in which a caudal technique is useful and/or advantageous. It is a good choice for the second stage of labor in selected patients in whom the lumbar epidural approach is hazardous or contraindicated (e.g., fusion or instrumentation of the lumbar spine). In most cases, caudal anesthesia can be successfully performed with the patient in a lateral decubitus position.

Aseptic Technique

There appears to be a great degree of practice variation among anesthesia providers with respect to aseptic technique during administration of neuraxial anesthesia.[39-41] This lack of consensus may result from an underappreciation of the gravity of infectious complications related to neuraxial anesthesia.[42-44] Indeed the incidence of epidural abscess and spinal meningitis is generally so low that many of the available recommendations are based on evidence from other domains of infection control (e.g., surgical wound site and central venous catheter–related infection).[45-47] Nonetheless, neurologic compromise resulting from neuraxial infection can be a devastating complication.

Infection of the epidural space tends to result in the formation of an abscess, most commonly formed by *Staphylococcus aureus* found in the epidermis of either the patient or the anesthesia provider. In contrast, meningitis associated with neuraxial procedures is most commonly caused by *Streptococcus viridans.* Viridans species of streptococcus may reside in the oronasopharyngeal tract of providers or patients or in the vagina. Potential routes

of infection include the (1) epidural catheter track, (2) bloodstream, (3) equipment, and (4) injectate. A more in-depth discussion of neuraxial infection is found in Chapter 32.

Guidelines describing aseptic technique for regional and neuraxial anesthetic procedures have been published by professional anesthesiology organizations, including the ASA, the Association of Anaesthetists of Great Britain and Ireland, and the American Society of Regional Anesthesia and Pain Medicine.[47-49] The following recommendations deserve emphasis:

1. Given that the oropharyngeal and skin flora of the anesthesia provider are implicated in many cases of neuraxial infection, the provider should don a surgical facemask and hat before initiation of spinal/epidural anesthesia. Microbial sampling in laminar-flow operating theaters has shown a 22-fold increase in bacterial counts when a facemask and hat are not worn.[50]
2. Washing hands with an alcohol-based antiseptic solution is recommended because this has been shown to be superior to antimicrobial soap.[51] Jewelry (e.g., rings, watches) should be removed before and sterile gloves worn after hand cleansing.
3. The patient's skin should be decontaminated, preferably with a chlorhexidine-in-alcohol solution.[47] An abundance of evidence affirms the superior bacteriocidal and bacteriostatic efficacy of chlorhexidine compared with povidone-iodine.[46,52] If chlorhexidine is not available, then povidone-iodine with alcohol, rather than povidone-iodine alone, is preferred.[47,53] Of importance, the anesthesia provider is encouraged to exercise patience in allowing the antiseptic to dry, because a major mechanism of antisepsis is the desiccating action of alcohol.

Equipment and Placement of Needle/Catheter

Spinal Anesthesia

The first equipment decision involves determining whether to perform a single-shot or continuous technique. Continuous spinal anesthesia is not a new technique; indeed, some physicians performed continuous spinal anesthesia more than 50 years ago. Currently, a large-bore epidural needle and catheter must be used for continuous spinal anesthesia, because the U.S. Food and Drug Administration rescinded approval for the use of small-bore microcatheters in 1992.[54] Therefore, the risk for post–dural puncture headache is significant. This technique is useful after *unintentional* dural puncture with an epidural needle. In the morbidly obese patient, it may be easier to manipulate and advance a rigid epidural needle than a more flexible spinal needle; thus the technique is useful for establishing continuous analgesia or anesthesia in this patient population, particularly when the need for anesthesia is urgent. However, for most obstetric patients, a single-shot technique is preferred for spinal anesthesia.

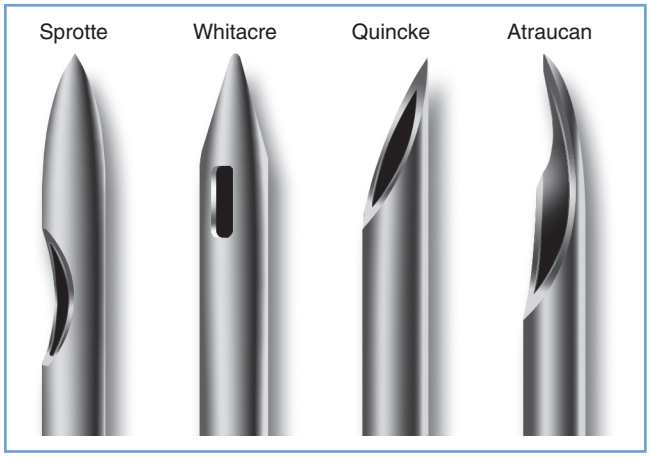

FIGURE 12-6 ■ Spinal needle assortment often used in parturients. Each needle is shown in an open-bevel view and an oblique orientation. The Whitacre and Sprotte needles have cone-shaped bevels, whereas the Quincke has a cutting bevel. (Other sizes are available in some of these needle designs.)

The primary equipment choice for spinal anesthesia concerns the type and size of the spinal needle. Cutting-bevel needles (e.g., Quincke) are rarely used in contemporary obstetric anesthesia practice because of the unacceptably high incidence of post–dural puncture headache associated with their use.[55] Instead, non-cutting needles (e.g., Whitacre, Sprotte, Gertie Marx) are used almost exclusively (Figure 12-6). Some anesthesia providers refer to the non-cutting needles as "pencil-point needles." It is now believed that the pencil-point needles cause more trauma to the dura, which then results in a more intense inflammatory response than occurs with cutting-bevel needles. Presumably, the inflammation results in more rapid closure of the dural defect.[56]

Needle size must also be determined. Larger needles offer a greater fidelity of tactile feedback as the anesthesia provider traverses tissue planes of variable impedance when performing spinal anesthesia. Furthermore, larger needles are more likely to withstand the high resistance encountered when contacting bone without bending or shearing. In general, the "ease-of-use" advantages associated with larger needles must be balanced against a lower incidence of post–dural puncture headache with smaller needles. Most anesthesia providers use 25- or 27-gauge non-cutting needles for routine spinal anesthesia in obstetric patients. However, anesthesia providers should make individual decisions based on their own skills, practice setting, and the patient. The urgency of the procedure may also influence the choice of needle size. For example, a 27-gauge needle might be chosen for spinal anesthesia for an elective procedure, and a larger (e.g., 22-gauge) needle might be chosen when the subarachnoid space must be entered quickly because of severe fetal compromise.

With a small-gauge needle (i.e., 24-gauge or smaller), use of an introducer needle is preferable. The introducer needle engages the interspinous ligament and more accurately guides the trajectory of the smaller spinal needle than is possible with use of a small-gauge spinal needle

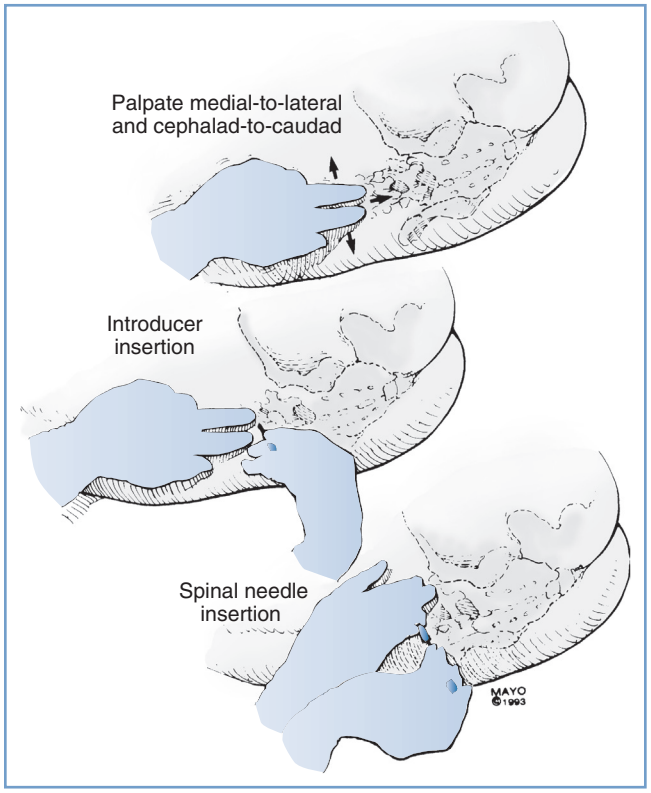

FIGURE 12-7 ■ The midline approach for spinal needle insertion requires accurate identification of a lumbar interspinous space. The palpating fingers are rolled in a medial-to-lateral and cephalad-to-caudad direction; an introducer is then inserted through the interspinous space almost perpendicular to the lumbar spinous process. Once the introducer is seated in the interspinous ligament, the spinal needle is inserted; the needle is stabilized in a tripod fashion during insertion (much like a dart being thrown).

alone. The introducer needle also aids with skin puncture; it is often difficult to puncture the skin with noncutting needles.

Either the midline or the paramedian approach can be used to enter the subarachnoid space. The midline approach requires the patient to reduce her lumbar lordosis to allow access to the subarachnoid space between adjacent spinous processes (usually L3 to L4, sometimes L4 to L5 or L2 to L3). The interspinous space may be identified with one (usually the thumb or index finger) or two fingers (usually the index and middle fingers) of the anesthesia provider's nondominant hand. The single finger "slides" along the skin in the midline from cephalad to caudad until it "settles" into an interspinous space. The two fingers identify the interspinous space by palpating the caudad border of the more cephalad spine. The fingers identify the midline by rolling in a medial-to-lateral direction (Figure 12-7).

Next, the anesthesia provider injects local anesthetic intradermally and subcutaneously. The introducer needle is inserted into the substance of the interspinous ligament. It is helpful if the introducer needle is embedded in the interspinous ligament; therefore, obese patients may require a longer introducer needle. The introducer needle should lie in the sagittal midline plane. It is then grasped and steadied with the fingers of the nondominant hand while the dominant hand holds the spinal needle like a dart. The fifth finger may be used as a tripod against the patient's back to prevent patient movement from causing unintentional needle insertion to a level deeper than intended, and to "brake" the needle. As the needle passes through the ligamentum flavum and the dura, characteristic changes in resistance are noted. A "pop" is often perceived as the needle tip traverses the ligamentum flavum. A subsequent and more pronounced pop is perceived as the needle tip exits the dura-arachnoid. The stylet is removed, and CSF should appear in the needle hub. If CSF does not appear, the stylet is replaced, and the needle is advanced a few millimeters and again checked for CSF flow. This process continues until either bone is encountered or CSF returns through the needle. If neither occurs, the needle and introducer are withdrawn and the process is repeated.

Although with time and practice the tactile feedback produced by advancing a needle through tissues of variable resistance will become utterly familiar to the anesthesia provider, the novice may be unsure of the anatomic position of the needle tip, especially if unexpected resistance (i.e., contact with bone) or an unexpected and premature "pop sensation" is encountered during needle advancement. A stepwise problem-solving approach is reasonable. First, the anesthesia provider should reconfirm that (1) the patient has normal anatomy (i.e., not scoliotic), (2) she is acceptably positioned at an appropriate height for the anesthesia provider, and (3) the chosen point of needle insertion is the true midline plane. If these assertions are true, and the needle tip encounters bone, it is highly likely that the osseous structure is either the inferior or superior spinous process. One of two maneuvers may overcome this barrier. After slight withdrawal of the needle, simple angulation in a cephalad or caudad direction may redirect the needle trajectory sufficiently to achieve access to the central neuraxial canal. One must appreciate the "toughness" of the interspinous ligament. Even a 17-gauge epidural needle can be bent if the angle is changed without some prior retraction of the needle. Furthermore, if a spinal needle/introducer complex is used, care must be exercised that angulation of the spinal needle does not occur without first withdrawing it into the lumen of the introducer. Thereafter, the entire spinal needle/introducer complex is angulated before the spinal needle is re-advanced. Angulation of the spinal needle without first withdrawing it into the introducer creates a fulcrum at the junction of the introducer tip where the spinal needle emerges and can potentially damage or even shear the delicate spinal needle (Figure 12-8).[57]

Alternatively, the needle may be withdrawn fully into subcutaneous tissue and either raised or lowered (cephalad or caudad) while still maintaining an angulation that is parallel to the original trajectory. Which approach is more effective may depend on the reason for the initial bone contact. If the patient has very narrow interspaces, then careful raising or lowering of the needle while maintaining a trajectory parallel to the floor may be appropriate. However, if the patient is overly flexed forward, it is possible that her lumbar spinous processes are projecting

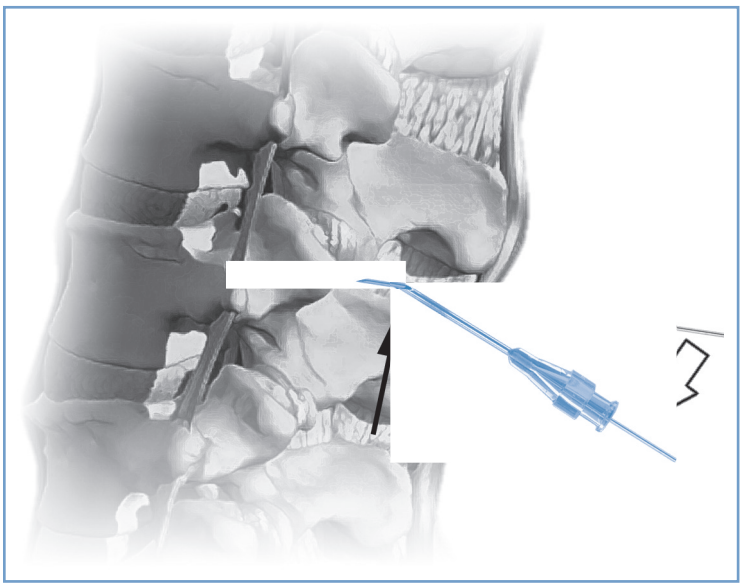

FIGURE 12-8 ■ Change of needle trajectory during spinal anesthesia. Note that if both the spinal needle and its introducer needle are manipulated without prior retraction of the spinal needle into the lumen of the introducer (*open arrow*), a fulcrum is created (*dark arrow*) where the risk for bending or shearing the delicate spinal needle may occur. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

in a slightly upward angulation (relative to the perpendicular transverse plane). This may require that the needle be re-angulated accordingly. If bone is still encountered despite all these considerations, it is likely that the needle tip is in fact *not* in the midline plane and is contacting the vertebral lamina. This may occur if the initial skin puncture is not in the midline, the needle tip deviates from the midline as it is advanced, or the patient's spine is rotated (either from poor positioning or scoliosis). Clues that the needle tip is not midline include (1) the patient complaining of lateralizing pain, (2) lack of CSF flow despite appropriate needle depth, and (3) the perception of "soft" or "mushy" tissue during needle advancement (paraspinous tissue) rather than the more "rigid" ligamentous tissue, or even a false "pop" as the needle tip exits the interspinous ligament laterally into paraspinous tissue. Much like the progressive modifications described earlier for correct alignment in the superoinferior plane, so too can these approaches be employed for redirecting in the lateral plane (Figure 12-9). The novice is advised to make systematic changes in a stepwise fashion, rather than indiscriminately changing needle direction without first considering the anatomic problem.

Once CSF is freely dripping from the needle hub, the dorsum of the provider's nondominant hand steadies the spinal needle against the patient's back while the syringe with local anesthetic is attached to the needle. After aspirating to ensure the free flow of CSF, the anesthesia provider injects the local anesthetic at a rate of approximately 0.2 mL per second. After completion of the injection, some anesthesia providers again aspirate approximately 0.2 mL of CSF and reinject it into the subarachnoid space. This last step reconfirms the needle location and clears the needle of the remaining local anesthetic. The patient is then repositioned as appropriate.

For most patients, the midline approach is faster and less painful than the paramedian approach. The midline approach is also easier to teach than the paramedian approach, because it requires mental projection of the anatomy in only two planes, whereas the paramedian approach requires appreciation of a third plane and estimation of the depth of the subarachnoid space from the skin (Figure 12-10).

Nevertheless, the paramedian approach is a useful technique that allows for the successful identification of the subarachnoid or epidural space in difficult cases. The paramedian approach does not require that the patient fully reduce her lumbar lordosis. This approach exploits the larger target that is available when the needle is inserted slightly off the midline.

A common error that is made with the paramedian approach is the insertion of the needle too far off the midline; the vertebral lamina then becomes a barrier to needle insertion. With the paramedian approach, the palpating fingers should again identify the caudad edge of the more cephalad spinous process. A skin wheal is raised 1 cm lateral and 1 cm caudad to this point; a longer needle is then used to infiltrate the deeper tissues in a cephalomedial plane. This step contrasts to the midline approach, in which the local anesthetic is not injected beyond the subcutaneous tissue. The spinal introducer is then inserted 10 to 15 degrees off the sagittal plane in a cephalomedial direction, and the spinal needle is advanced through the introducer needle toward the subarachnoid space. Another common error is to use an excessive cephalad angle with initial needle insertion. When the needle is inserted correctly and contacts bone, it is redirected slightly cephalad. If bone is again encountered, but at a deeper level, the slight stepwise increase in cephalad angulation is continued, and the needle is "walked" up and off the lamina. As with the midline approach, the characteristic feel of the ligamentum flavum and dura can be appreciated. The aim of the paramedian approach is to puncture the dura in the midline, even though the needle is inserted off the midline. Use of the paramedian approach requires insertion of a greater length of needle.

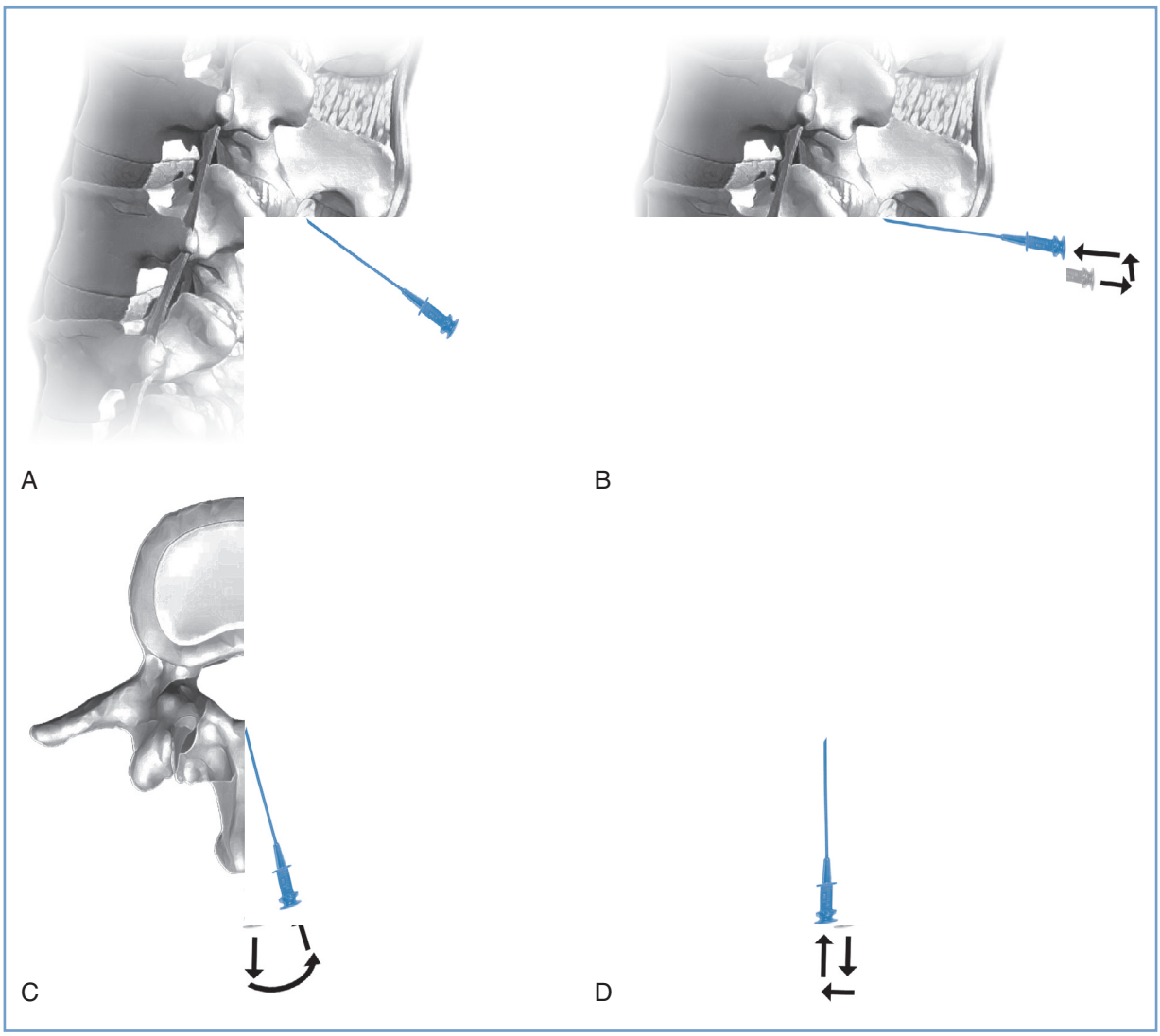

FIGURE 12-9 ■ Troubleshooting contact with bony structures during needle placement. The gray needle represents the initial needle trajectory; the blue needle represents the adjusted needle trajectory. **A,** Assuming correct midline needle placement, the needle can be retracted slightly and angulated to overcome a spinous process. **B,** Alternatively, the needle may be "lifted" after slight retraction while keeping the original trajectory constant. **C,** Assuming the needle is deviating from the midline plane and contacting lamina, an action similar to that in *A* may be executed. **D,** Alternatively a stepwise lateral shift similar in concept to that shown in *B* may correctly achieve midline alignment. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

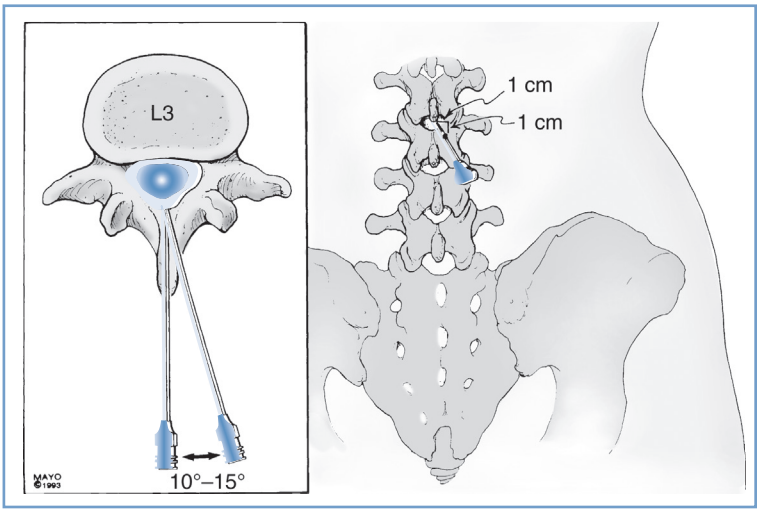

FIGURE 12-10 ■ Vertebral anatomy of midline and paramedian approaches for spinal and epidural anesthesia. The midline approach requires anatomic projection in only two planes: sagittal and horizontal. The paramedian approach also requires consideration of the oblique plane. However, the paramedian approach requires less patient cooperation in reducing lumbar lordosis to allow for successful needle insertion. The paramedian needle insertion site is made 1 cm lateral and 1 cm caudad to the caudad edge of the more cephalad spinous process. The paramedian needle is inserted 10 to 15 degrees off the sagittal plane (*inset*).

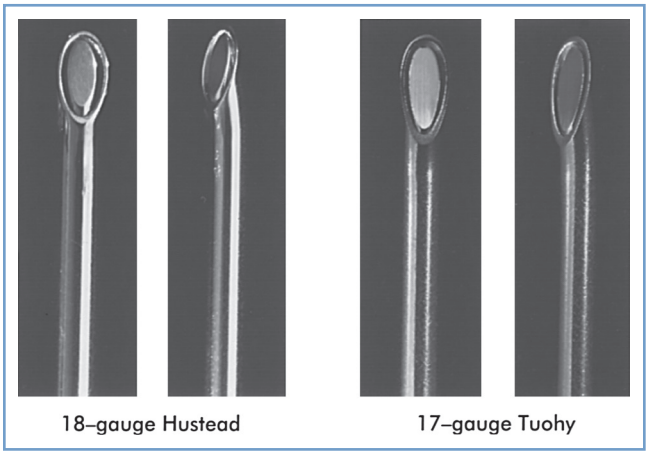

FIGURE 12-11 ■ Epidural needles often used in parturients. Each needle is shown in an open-bevel view and an oblique orientation. The 18-gauge Hustead and 17-gauge Tuohy needles have lateral-facing openings, which direct epidural catheters to enter the epidural space more easily than if a single-shot Crawford needle design is used. (Other sizes and needle designs are available for obstetric epidural anesthesia.)

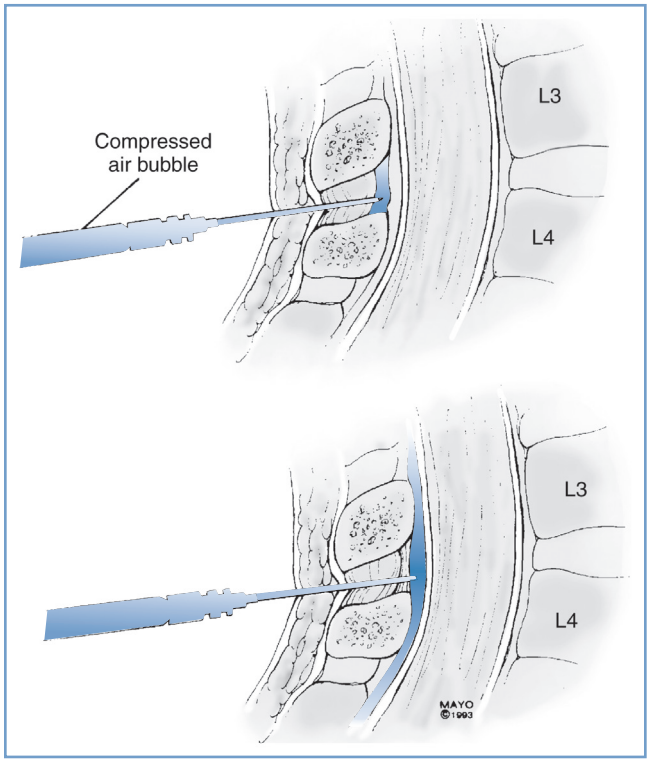

FIGURE 12-12 ■ Loss-of-resistance technique for identifying the epidural space. The needle is first inserted into the interspinous ligament or ligamentum flavum, and a syringe containing an air bubble in saline is attached to the hub. After compression of the air bubble by pressure on the syringe-plunger, the needle is carefully advanced until a loss of resistance to syringe-plunger pressure is noted as the needle enters the epidural space.

Once CSF is obtained, the block is performed as it is with the midline approach.

During the performance of any nerve block technique, needle advancement should stop if the patient complains of pain. If pain is the result of inadequate soft tissue anesthesia, additional local anesthetic should be injected. Pain or paresthesias may also result from needle contact with central nerves or the spinal cord. Patient perception of paresthesias during the initiation of spinal anesthesia may indicate that the needle tip is in the subarachnoid space. The anesthesia provider should remove the stylet and check for CSF. If the paresthesia has resolved, the local anesthetic may be injected. If the paresthesia persists, however, the needle should be withdrawn and repositioned. In any case, the anesthesia provider should never inject the local anesthetic if the patient is complaining of paresthesias or lancinating pain, either of which may signal injection into a nerve or the spinal cord.

Epidural Anesthesia

Special equipment for epidural analgesia or anesthesia includes an epidural needle, an epidural catheter (for a continuous technique), and a loss-of-resistance syringe (for the loss-of-resistance technique to identify the epidural space). Single-shot epidural anesthesia is rarely used in obstetric practice, because the major advantage of epidural over spinal anesthesia is the ability to provide continuous anesthesia or analgesia without puncturing the dura with a large needle. An epidural needle with a lateral opening (e.g., Hustead, Tuohy) is most commonly used because it allows a catheter to be threaded through its orifice (Figure 12-11).

Two methods are used to identify the epidural space during needle advancement: (1) hanging drop method and (2) loss-of-resistance method. The majority of anesthesia providers use the loss-of-resistance method (Figure 12-12).

The traditional loss-of-resistance syringe is a finely ground glass syringe with a Luer-Lok connector. Plastic syringes are now available, and the choice is generally a matter of the anesthesia provider's preference. The syringe is filled with 2 to 4 mL of saline, air, or saline with a small (0.25 to 0.5 mL) air bubble. There is some controversy regarding the use of air versus saline for detecting the point of loss of resistance.[58] Saline causes some syringe plungers to stick and may be confused with CSF during initiation of CSE anesthesia. Conversely, injection of air into the epidural space may contribute to patchy anesthesia,[59] and unintentional pneumocephalus may increase the risk for post–dural puncture headache.[60]

Prior investigations have suggested superiority of loss-of-resistance with saline over air with respect to block success. This conclusion is further supported by the results of a meta-analysis that pooled six controlled trials (n = 1037) in which laboring women were randomized to receive loss-of-resistance to air versus liquid (saline or local anesthetic solution).[61] This analysis suggested an increased risk for unblocked segments when loss-of-resistance to air was used, presumably owing to air bubbles leaking through the intervertebral foramina and residing adjacent to nerve roots.[62] No differences were found with respect to the occurrence of paresthesias or unintentional dural puncture or the need for additional

analgesic medication or epidural catheter replacement. The authors recommended a cautious interpretation of their analysis because many of the endpoints studied (e.g., "block success") do not have widely accepted definitions. In contrast, Schier et al.[63] report a meta-analysis that included both obstetric and nonobstetric patients (n = 4422), which suggested no significant difference between loss-of-resistance to air versus saline in the occurrence of difficult catheter insertion, paresthesias, intravascular catheter insertion, unintentional dural puncture, post–dural puncture headache, and partial block. Lastly, in a retrospective study of loss-of-resistance to air versus saline by Segal and Arendt,[64] no significant differences in block success were found in 929 patients. The authors intentionally chose a retrospective approach to the question; they stated that because "it is impossible to mask the anesthesiologist to the medium used for loss-of-resistance, [they] hypothesized that randomized controlled trials might *overestimate* the difference between air and saline by forcing the operator to use a less-preferred technique in half of the subjects."

Regardless of the technique used, success depends on correct placement of the needle tip within the ligamentum flavum. The needle should be advanced sufficiently into the interspinous ligament before the syringe is attached or before the hanging drop of solution is placed into the needle hub. This approach has at least three advantages. First, it encourages the anesthesia provider to use proprioception while directing and advancing the needle. Second, it shortens the time required for successful identification of the epidural space. Third, it lowers the likelihood of a false-positive loss of resistance. Undoubtedly, this false-positive identification of the epidural space is responsible for many cases of unsuccessful epidural anesthesia; it is even possible to insert a catheter between the interspinous ligament and the ligamentum flavum.

During advancement of the needle-syringe assembly, the needle should be moved toward the epidural space by the provider's nondominant hand while the thumb of the dominant hand applies constant pressure on the syringe plunger, thereby compressing the small air bubble. Alternatively, the intermittent, oscillating technique is typically employed when using the loss-of-resistance to air technique. When the needle enters the epidural space, the pressure applied to the syringe plunger causes the solution or air to flow easily into the epidural space (see Figure 12-12).

In most obstetric cases, the anesthesia provider inserts a catheter and uses an intermittent bolus or continuous infusion technique to maintain analgesia. Most practitioners insert the catheter before injecting local anesthetic to allow for the slow, incremental injection of local anesthetic/opioid solution and the more controlled development of epidural anesthesia. If the principal reason for using an epidural technique is the provision of continuous analgesia, it seems most practical to insert the catheter before injecting the therapeutic dose of local anesthetic so that correct catheter placement can be verified promptly.

Several types of single-use, disposable epidural catheters are available. Catheters are made from plastic materials and differ as to the degree of "stiffness." Wire-embedded catheters are more flexible and are associated with a lower incidence of paresthesias and intravascular placement during catheter insertion.[33,65,66] The single-orifice catheter has one opening at its tip, whereas the multi-orifice catheter has a closed "bullet" tip with three lateral orifices between 0.5 and 1.5 cm from the tip (Figure 12-13).

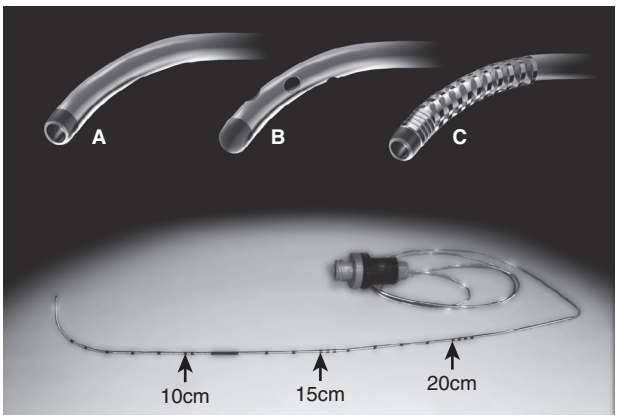

FIGURE 12-13 ■ Epidural catheters. **A,** Single-orifice catheter; **B,** multi-orifice catheter with bullet tip; **C,** coiled wire reinforced catheter. *Bottom,* Epidural catheter with centimeter markings along distal end and Luer-Lok connector at proximal end. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

The proposed advantage of single-orifice, open-end catheters is that the injection of drugs is restricted to a single anatomic site. In theory, this arrangement should facilitate the detection of intravenous or subarachnoid placement of the catheter. Likewise, a theoretical disadvantage of multi-orifice, closed-end catheters is that local anesthetic may be injected into more than one anatomic site (e.g., both the epidural and subarachnoid spaces). A catheter initially placed in the epidural space can migrate into a vein or the subdural or subarachnoid space. Fortunately, this does not seem to be a common clinical problem. Regardless of the choice of catheter, aspiration should be performed before each dose of local anesthetic is injected.

An advantage of the multi-orifice catheter over the single-orifice catheter is the consistent ability to aspirate fluid (either blood or CSF) when the catheter is in a vessel or the subarachnoid space.[67] Multi-orifice catheters may lead to more even distribution of local anesthetic and a lower incidence of "patchy" or unilateral anesthesia when the anesthetic is injected as a bolus.[68] However, during an infusion into the epidural space, the solution exits only the most proximal hole,[69] and multi-orifice catheters thus behave like single-orifice catheters.

If the catheter is placed before the test and therapeutic doses of local anesthetic, it may be helpful to inject 5 to 10 mL of saline before threading the catheter, because this may reduce the incidence of epidural vein cannulation,[33] particularly when using stiffer epidural catheters. Rolbin et al.[70] noted that there was no advantage to the injection of 3 mL of fluid into the epidural space before insertion of the epidural catheter.

Six to eight centimeters of catheter are threaded into the epidural space before the epidural needle is removed. The catheter may then be pulled back until it is at the desired distance at the skin. Occasionally, the anesthesia provider will have difficulty advancing the catheter past the tip of the epidural needle. This difficulty may indicate that the epidural needle tip is not in the epidural space. However, if the provider is convinced that the needle is correctly placed, several maneuvers may facilitate catheter advancement. Often, having the patient take a deep breath allows catheter advancement. Saline may be injected through the epidural needle if this has not been done. Although some providers rotate the epidural needle in an attempt to successfully advance the catheter, we do not recommend this maneuver, because it may increase the risk for dural puncture. Instead, the epidural needle should be withdrawn 0.5 to 1 cm and again advanced into the epidural space.

Many techniques are available for securing the epidural catheter at the skin entry site. If a catheter will be used for prolonged intrapartum or postoperative analgesia, care providers should be able to assess the skin surrounding the catheter. A transparent, sterile adhesive dressing applied over the catheter after application of skin adhesive generally works well, and the periphery of the dressing can be reinforced with tape. The position of the epidural catheter may change significantly with patient movement from the sitting-flexed to the sitting-upright or lateral decubitus position.[71] D'Angelo et al.[72] found that the risk for catheter dislodgement was higher when catheters were inserted 2 cm into the epidural space, but the risk for unilateral blockade was greater when catheters were inserted 6 to 8 cm. Therefore, if the catheter is to be used for a short period (e.g., during cesarean delivery), it should be left 2 to 4 cm into the epidural space. In contrast, if the catheter will be used for many hours (e.g., during labor), it should be left 4 to 6 cm into the space. To minimize catheter movement at the skin, the patient should be positioned sitting upright or in the lateral position before the catheter is secured, especially if the patient is obese.[71]

The potential for the contamination of local anesthetic solutions has prompted the use of micropore filters during the administration of continuous epidural analgesia for labor. There is no evidence that filters decrease the rate of infection or of injection of undesirable foreign substances.[73] Additionally, filters may reduce the reliability of aspiration[74] and absorb local anesthetic solution, unless they are primed.[75] We believe that micropore filters have little use in clinical obstetric anesthesia practice.

Combined Spinal-Epidural Anesthesia

Combined spinal-epidural anesthesia combines the advantages and mitigates the disadvantages of single-shot spinal anesthesia and continuous epidural anesthesia (Box 12-2). Anesthesia is initiated with a subarachnoid injection of local anesthetic and maintained via an epidural catheter. It is useful for both cesarean delivery anesthesia and labor analgesia. For cesarean delivery, the injection of the smaller dose of local anesthetic required for spinal (compared with epidural) anesthesia is inherently safer with regard to the possibility of unintentional intravascular injection. Additionally, the anesthesia provider can inject a local anesthetic dose that is lower than the ED_{95} (effective dose in 95% of cases) without fear of inadequate anesthesia. These lower doses result in less maternal hypotension.[76] If surgical anesthesia is inadequate, the block can be "rescued" with epidural administration of local anesthetic. For example, a randomized trial comparing 7, 8, and 9 mg of intrathecal bupivacaine administered as part of a CSE technique for cesarean delivery produced equivalent latencies to T4 sensory block with lower rates of maternal hypotension in the lowest dose group.[77] The shorter duration of action seen in the low-dose (7 mg) group was easily addressed through the administration of local anesthetic via the indwelling epidural catheter. Compared with conventional epidural anesthesia for cesarean delivery, CSE anesthesia is associated with a more rapid onset of surgical anesthesia, less intraoperative pain and discomfort (e.g., a more dense block), better muscle relaxation, and less shivering and vomiting.[78]

During labor, CSE analgesia is associated with a faster onset of analgesia and is generally achieved with an opioid alone or an opioid combined with a small dose of local anesthetic. Studies differ as to whether CSE analgesia is associated with higher maternal satisfaction and fewer requests for supplemental analgesia. Goodman et al.[79] randomized 100 parous women in early labor to receive either CSE or conventional epidural analgesia. There were no differences in requests for supplemental analgesia, although pain scores were lower in the CSE group within the first 30 minutes. This study harbors

BOX 12-2 Advantages of Combined Spinal-Epidural Anesthetic Technique

Compared with Epidural Anesthesia

- Lower maternal, fetal, and neonatal plasma concentrations of anesthetic agents
- More rapid onset of analgesia and anesthesia
- More dense sensory blockade
- Complete early labor analgesia with opioid alone (no local anesthetic necessary)
- Lower failure rate

Compared with Spinal Anesthesia

- Technically easier in obese individuals: The epidural needle acts as an introducer for the spinal needle (it is easier to advance a rigid epidural needle)
- Ability to titrate anesthetic dose: Start with low subarachnoid dose, and titrate to effect using epidural injection
- Results in less hypotension
- Ability to extend the extent of neuroblockade: Spinal anesthesia for forceps delivery may be extended to epidural anesthesia for cesarean after failed forceps delivery
- Continuous technique: ability to extend duration of anesthesia

limitations echoed by many of its predecessors, including (1) question of equipotency between the techniques, (2) inadequate sample size for assessment of secondary outcomes, and (3) inability to truly blind the study (the difference in analgesia latency readily identifies group allocation). A 2007 systematic review comparing CSE and epidural labor analgesia concluded that onset was faster with the CSE technique, but that there was no evidence for differences in maternal satisfaction, mode of delivery, ability to ambulate, or incidence of hypotension between the two techniques.[80] Several studies have found a lower incidence of failed epidural analgesia after the initiation of analgesia with a CSE technique.[81,82] Presumably, verification of the correct placement of the spinal needle by visualization of CSF increases the likelihood that the tip of the epidural needle is correctly placed in the epidural space.

A disadvantage of the CSE technique is that the correct placement of the epidural catheter in the epidural space cannot be verified until spinal anesthesia wanes. Therefore, if a functioning epidural catheter is important to the safe care of the mother and fetus (e.g., in the setting of a suspected difficult airway or nonreassuring fetal status), a CSE technique may not be the technique of choice.

There are several techniques for initiation of CSE anesthesia/analgesia.[83] The most popular is the needle-through-needle technique, in which the epidural needle is sited in the epidural space and serves as an introducer for the spinal needle. The spinal needle passes through the epidural needle to puncture the dura. After injection of the subarachnoid dose, the spinal needle is removed, and the epidural catheter is threaded through the epidural needle. An alternative technique uses two skin punctures and two different interspaces: the spinal needle and epidural needle and catheter are introduced sequentially in two different interspaces.

The needle-through-needle technique requires a long spinal needle. Typically, a small (25-gauge or smaller) non-cutting needle is used to minimize the risk for post–dural puncture headache. The tip of the spinal needle must protrude 12 to 17 mm beyond the tip of the epidural needle when the two needles are fully engaged (Figure 12-14). Failure to puncture the dura and visualize CSF occurred in 25% of patients when the spinal needle protruded 9 mm, compared with no patients when the needle protruded 17 mm.[84] A 127-mm spinal needle is commonly used with a standard 9-cm epidural needle. However, because of differences in hub configurations among needles, the two hubs may not "mesh," and spinal needle protrusion may vary with specific needle combinations. Alternatively, manufacturers now sell CSE needle "kits," in which the spinal needle is designed for a specific epidural needle. An additional small non–Luer-Lok syringe (1 to 3 mL) is required for the spinal dose.

CSE anesthesia is initiated much like epidural anesthesia. The epidural needle is sited in the epidural space (Figure 12-15). Prior to inserting the epidural catheter, the spinal needle is introduced through the epidural needle with the anesthesia provider's dominant hand, while the nondominant hand is anchored against the patient's back to serve as a brake for further advancement of the spinal needle. The provider usually perceives the tip of the spinal needle passing the tip of the epidural needle as a slight increase in resistance. Spinal needle advancement should stop immediately after the anesthesia provider perceives the dural puncture "pop." Dural puncture is verified by visualization of CSF after removal of the spinal needle stylet. The provider's nondominant hand is anchored on the patient's back, and the spinal and epidural needle hubs are grasped together between the thumb and index finger of this hand. The dominant hand attaches the spinal syringe and injects the drug. We do not attempt to aspirate CSF, because it may not be possible to do so through long, small-bore needles and because attempted aspiration may result in movement of the spinal needle. After removal of the spinal syringe and needle as a unit, the epidural catheter is threaded in the usual fashion.

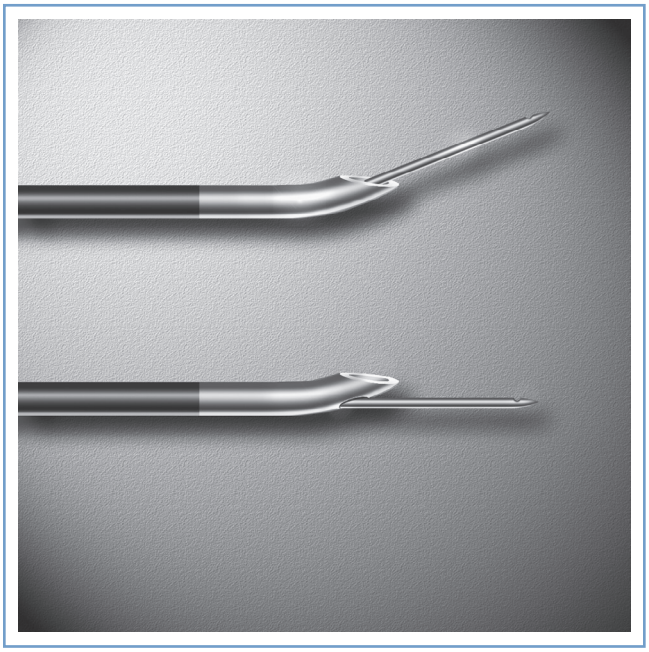

FIGURE 12-14 ■ Combined spinal-epidural needle configuration. *Top,* Spinal needle exits the epidural needle through the normal epidural needle bevel. Because the epidural needle bevel opening faces sideways, the spinal needle exits the epidural needle at a slight angle to the long axis of the epidural needle. *Bottom,* Spinal needle exits the epidural needle through a special orifice. The axes of the spinal and epidural needles are aligned. The spinal needle must protrude from the tip of the epidural 12 to 17 mm when the hubs are engaged, or the ability to puncture the dura with the spinal needle is compromised. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Failure to puncture the dura with the spinal needle may occur in several circumstances (Figure 12-16). The epidural needle tip may not be located in the epidural space, or the needle tip may be correctly placed, but the spinal needle may fail to puncture the dura or may not reach the dura because of the depth of the posterior epidural space. Alternatively, the epidural needle may be angled away from the midline or in a sagittal plane off the midline and the spinal needle may traverse the lateral epidural space without puncturing the dura. In this latter circumstance, the anesthesia provider may elect to

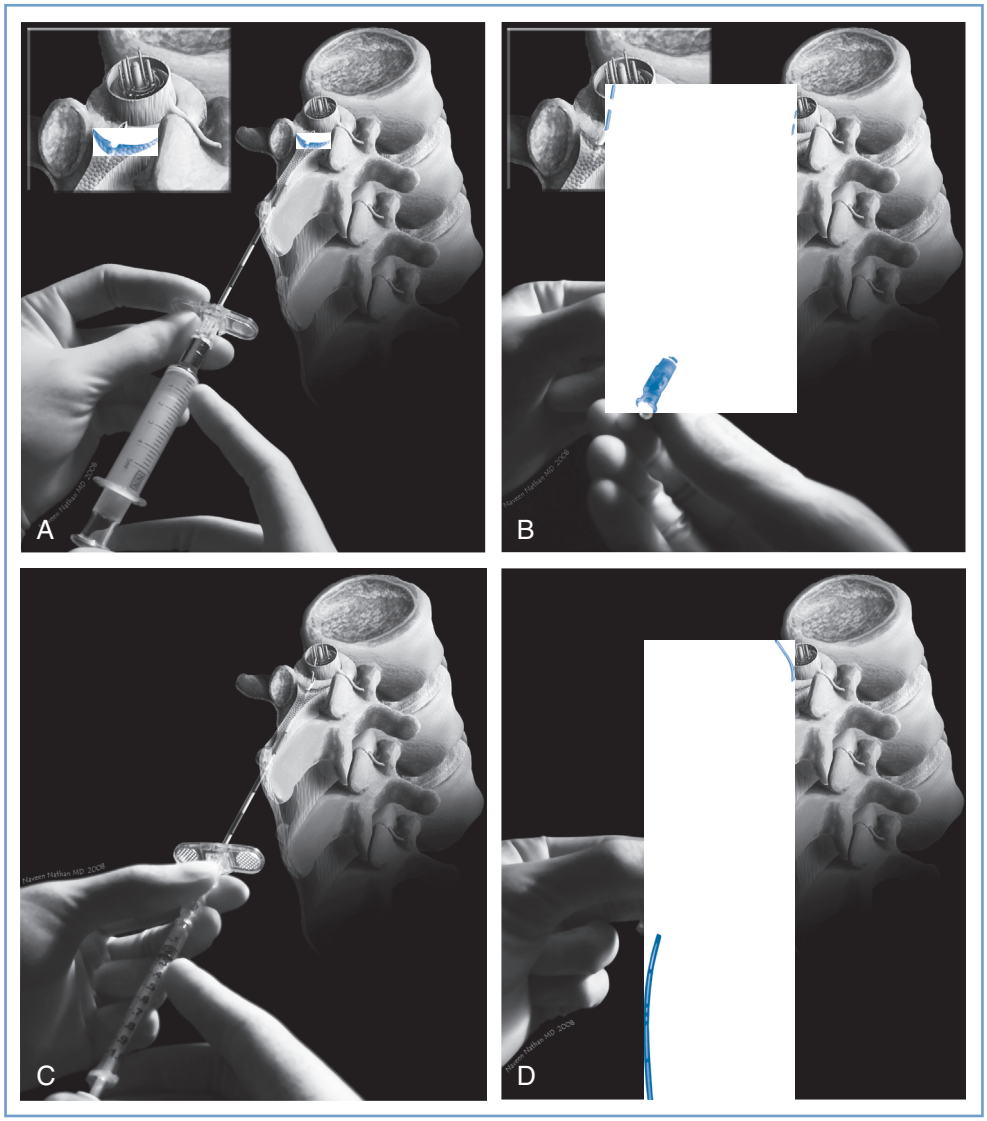

FIGURE 12-15 ■ Needle-through-needle combined spinal-epidural technique. **A,** The epidural needle is sited in the epidural space. **B,** The long spinal needle is passed through the epidural needle and punctures the dura mater. The operator's nondominant hand stabilizes the spinal and epidural needles, and the spinal needle stylet is withdrawn. Cerebrospinal fluid is seen spontaneously dripping from the spinal needle. **C,** The syringe is attached to the spinal needle, and the intrathecal dose is injected. **D,** The spinal needle is withdrawn, and the epidural catheter is threaded through the epidural needle into the epidural space. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

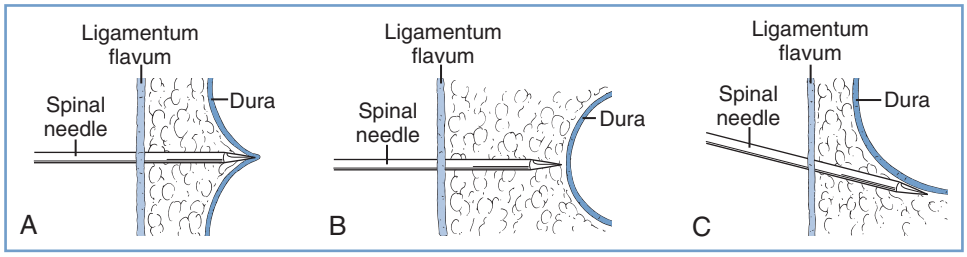

FIGURE 12-16 ■ Reasons for failure of the combined spinal-epidural technique. **A,** The spinal needle tents the dura but does not puncture it. **B,** The spinal needle does not reach the dura. **C,** The spinal needle passes to the side of the dural sac. (Redrawn with permission from Riley ET, Hamilton CL, Ratner EF, Cohen SE. A comparison of the 24-gauge Sprotte and Gertie Marx spinal needles for combined spinal-epidural analgesia during labor. Anesthesiology 2002; 97:574.)

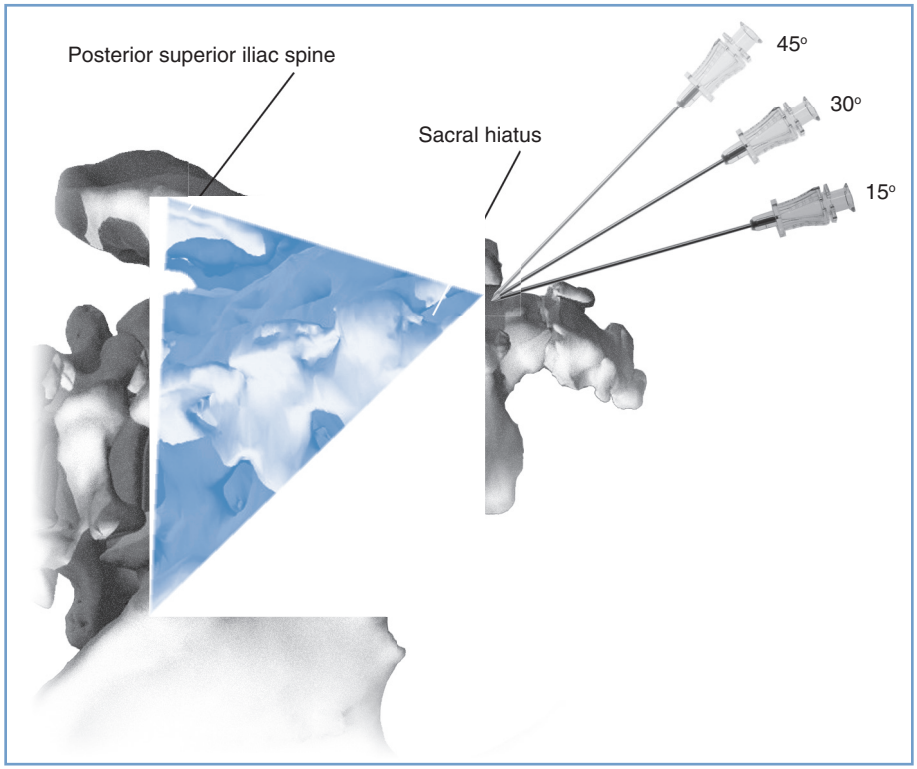

FIGURE 12-17 ■ The location of the sacral hiatus for caudal anesthesia is facilitated by the identification of the posterior superior iliac spines. The posterior superior spines are marked, and a line drawn between them forms one edge of an equilateral triangle. If the triangle is completed as illustrated, the sacral hiatus should underlie the caudad tip of the equilateral triangle. Once the sacral hiatus is identified, the needle is inserted by insertion and withdrawal in a stepwise fashion from an initial 45-degree angle off the coronal plane. In pregnant women, the needle eventually enters the caudal canal at an angle approximately 15 degrees off the coronal plane. If the needle is placed properly, no subcutaneous "lump" develops after the injection of the local anesthetic solution. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

abandon the CSE technique and continue with epidural anesthesia (if convinced that the epidural needle tip is in the epidural space) or to reposition the epidural needle and reattempt the CSE technique.

Caudal Anesthesia

Equipment for caudal anesthesia is similar to that used for lumbar epidural techniques, except that a needle with a lateral-faced opening is not needed. A blunt-tipped needle is satisfactory even when a catheter is used, because the angle of needle insertion allows insertion of the catheter. Successful administration of caudal anesthesia requires the accurate identification of the sacral hiatus. The sacrococcygeal ligament (an extension of the ligamentum flavum) overlies the sacral hiatus between the sacral cornua. Identification of the posterior superior iliac spines facilitates the identification of the sacral cornua; the location of the sacral hiatus is approximated by using the line between them as one side of an equilateral triangle (Figure 12-17). Once the sacral hiatus is identified, the palpating fingers are placed on the cornua, the skin is anesthetized, and the caudal needle is inserted with the hub at an angle approximately 45 degrees from the skin. A decrease in resistance is noted when the needle enters the caudal canal. The needle is advanced until it contacts bone (i.e., the dorsal aspect of the ventral plate of the sacrum). Next, the needle is withdrawn slightly and redirected so that the angle of insertion relative to the skin surface is decreased. In pregnant women, the final angle is approximately 15 degrees from a plane parallel to the sacrum.

Accurate placement of the caudal needle is verified primarily from the "feel" of the needle passing through the sacrococcygeal ligament. An additional maneuver may help providers with less experience to verify correct needle placement: Once the needle is believed to be within the caudal canal, 5 mL of saline is rapidly injected through the needle while the anesthesia provider's other hand is placed over the dorsum of the sacrum. If the needle is placed correctly, no mass or pressure wave is detected over the midline of the sacrum. Conversely, if the needle is malpositioned (often posterior to the caudal canal), a fluid mass or pressure wave is felt by the palpating hand.

The needle should be advanced only 1 to 2 cm into the caudal canal. Dural puncture or unintentional intravascular cannulation is more likely to occur with deeper insertion. A test dose similar to that used during administration of lumbar epidural anesthesia should be administered.

Ultrasonographic Guidance

Traditionally, surface anatomy visualization and palpation have been used to assess landmarks before initiation of

the neuraxial procedure. This landmark-guided technique is effective for the vast majority of patients and, as a consequence, the use of ultrasonography has not played as prominent a role in neuraxial anesthesia as it has in peripheral nerve blockade. There exist, however, unique clinical circumstances in which immediate pre-procedural imaging of epidural anatomy can be highly beneficial. Such may be the case in patients with morbid obesity, derangements of spinal anatomy such as scoliosis or spinal stenosis, or a history of spinal instrumentation, and in patients in whom identification of specific vertebral levels might be warranted (e.g., known preexisting disc herniation or nerve root compression at a specific interspace). Unlike the use of ultrasonography for vascular access and peripheral nerve block techniques, ultrasonography for neuraxial techniques is not used in real time. Indeed, the real-time use of ultrasonography during administration of neuraxial anesthesia can be prohibitively cumbersome, is fraught with a tangible risk for violating aseptic technique, and raises unanswered questions about what untoward effects may result should ultrasound coupling medium (gel) breach neuraxial structures. Most often ultrasonography is a pre-procedural tool to aid the operator in the assessment of needle insertion site, needle angle, and estimated depth of the epidural space.

It remains to be seen whether neuraxial ultrasonography can significantly impact the clinical success of neuraxial procedures, whether that is measured in terms of time to completion of the spinal or epidural anesthesia procedure, or block success and patient satisfaction. Additionally, reductions in the incidence of complications of neuraxial anesthesia, such as unintentional dural puncture, have yet to be realized.

In the obstetric population, four randomized controlled trials have explored outcomes related to block success using the traditional landmark-based technique versus the ultrasound-aided technique.[85-88] Only one, however, divorced the unblinded ultrasonographer from those supervising the block and rendering assessments of success.[88] In this investigation,[88] 370 parturients receiving epidural labor analgesia were randomized to receive pre-procedural ultrasonographic imaging for determination of depth to epidural space or no imaging (control group). The estimated depth to the epidural space was conveyed to 15 first-year residents with little or no previous neuraxial anesthesia experience, who performed the blocks under the supervision of a staff anesthesiologist who was blinded to the group assignment. Obese patients were not excluded from this study, and there were no significant differences between groups in demographic factors. The authors found a significant reduction in the number of attempts needed to place the epidural catheter and in the need for catheter replacement in the ultrasonography group. There was no difference in the rate of unintentional dural puncture, although the study was underpowered for assessment of this outcome. The calculated number of epidural catheter placements with ultrasonography needed to avoid replacing one failed catheter (number needed to treat) was 26. Of note, the residents were not themselves randomized, nor were they tracked according to the number of cumulative procedures with and without ultrasonography. From the perspective of introducing trainees to the technique of neuraxial anesthesia procedures, ultrasonographic imaging may yet play a more substantial educational role.

How does pre-procedural ultrasonographic imaging affect neuraxial anesthesia success for patients anticipated to endure difficult needle placement? Chin et al.[89] identified 120 patients presenting for elective lower extremity orthopedic surgery who were predicted to endure difficult administration of spinal anesthesia. Their basis for qualifying these patients as "difficult" included a body mass index greater than 35 kg/m^2 with nonpalpable spinous processes, the presence of moderate to severe scoliosis, or a history of spinal surgery involving excision of two or more lumbar spinous processes. These subjects were randomized to receive pre-procedural ultrasonographic imaging of epidural anatomy or a conventional landmark-based technique. The total number of attempts required before successful dural puncture was twofold higher in the landmark control group than in the ultrasonography group. Although the average time spent completing the spinal anesthesia procedure was longer in the control group than in the ultrasonography group (mean = 7.3 minutes versus 5.0 minutes, respectively), if one accounted for the pre-procedural ultrasonographic examination, the *total* procedure time was shorter in the control group (7.9 minutes versus 12.2 minutes).

How accurately do pre-procedural ultrasonoanatomic measurements correlate to the actual distance from the skin to the epidural space? In general, although the correlation is high, ultrasonographic measurements of neuraxial anatomy may underestimate the true distance from skin to epidural space in the context of neuraxial procedures.[88,90-92] The factors that influence the small disparity between the two include (1) differences between the angulation of the imaging beam versus the angulation of the needle; (2) differences between the degree of exerted pressure and skin compression of the ultrasound probe versus the needle; (3) current lack of fidelity in the ability of ultrasonography to discriminate between ligamentum flavum, epidural space, and dura mater; and (4) operator dependency of typical onscreen measurement tools such as digital calipers. In a general obstetric population, the mean difference between the needle depth and ultrasonographic depth to the epidural space was 0.01 cm (95% confidence interval, –0.67 to 0.69 cm),[92] whereas in a second study by the same investigators in which subjects were limited to obese parturients, the mean difference was 0.3 cm (95% confidence interval, –0.7 cm to 1.3 cm).[90]

A low-frequency (2- to 5-Hz) curvilinear probe allows visualization of neuraxial structures beneath the skin. Low-frequency waves are preferable owing to the requisite depth of penetration. The curvilinear array allows enough ultrasonic scope to capture lateral structures such as the transverse processes. The ultrasound beam can be used to identify first the spinous processes if these are not palpable, then the interspinous spaces, and, finally, ligamentous structures. The ligamentum flavum and dura mater are dense tissues and will appear hyperechoic (white), like bone, whereas the less dense epidural and subarachnoid spaces will appear hypoechoic (black). A

variety of imaging planes are now well described. Transverse and median sagittal as well as paramedian sagittal approaches have been documented. The transverse-interlaminar view is likely to be of most use when attempting neuraxial procedures using the midline approach. On the other hand, the paramedian sagittal view may be of use if a paramedian approach is anticipated (Figure 12-18). With the median sagittal approach, the spinous process will produce a shadow when the beam is placed directly over it, thus reducing the ability to appreciate any ligaments beyond it.

EPIDURAL TEST DOSE

Epidural catheter placement may be complicated by blood vessel or dural puncture with the needle or catheter. To prevent possible local anesthetic toxicity and high or total spinal anesthesia, the anesthesia provider must recognize the unintentional intravenous or subarachnoid placement of the needle or catheter. The purpose of the test dose is to allow early recognition of a malpositioned catheter. The ideal test dose must be readily available, safe, and effective. Its use should have a high sensitivity (i.e., low false-negative rate) and a high specificity (i.e., low false-positive rate). The intravascular and intrathecal test doses may be combined (a single injection to test for both intravascular and subarachnoid placement) or administered separately. A negative response to an epidural test dose does not guarantee the correct placement of the epidural catheter in the epidural space, nor does it guarantee that the catheter is not malpositioned in a blood vessel or the subarachnoid space. Rather, it decreases the likelihood that

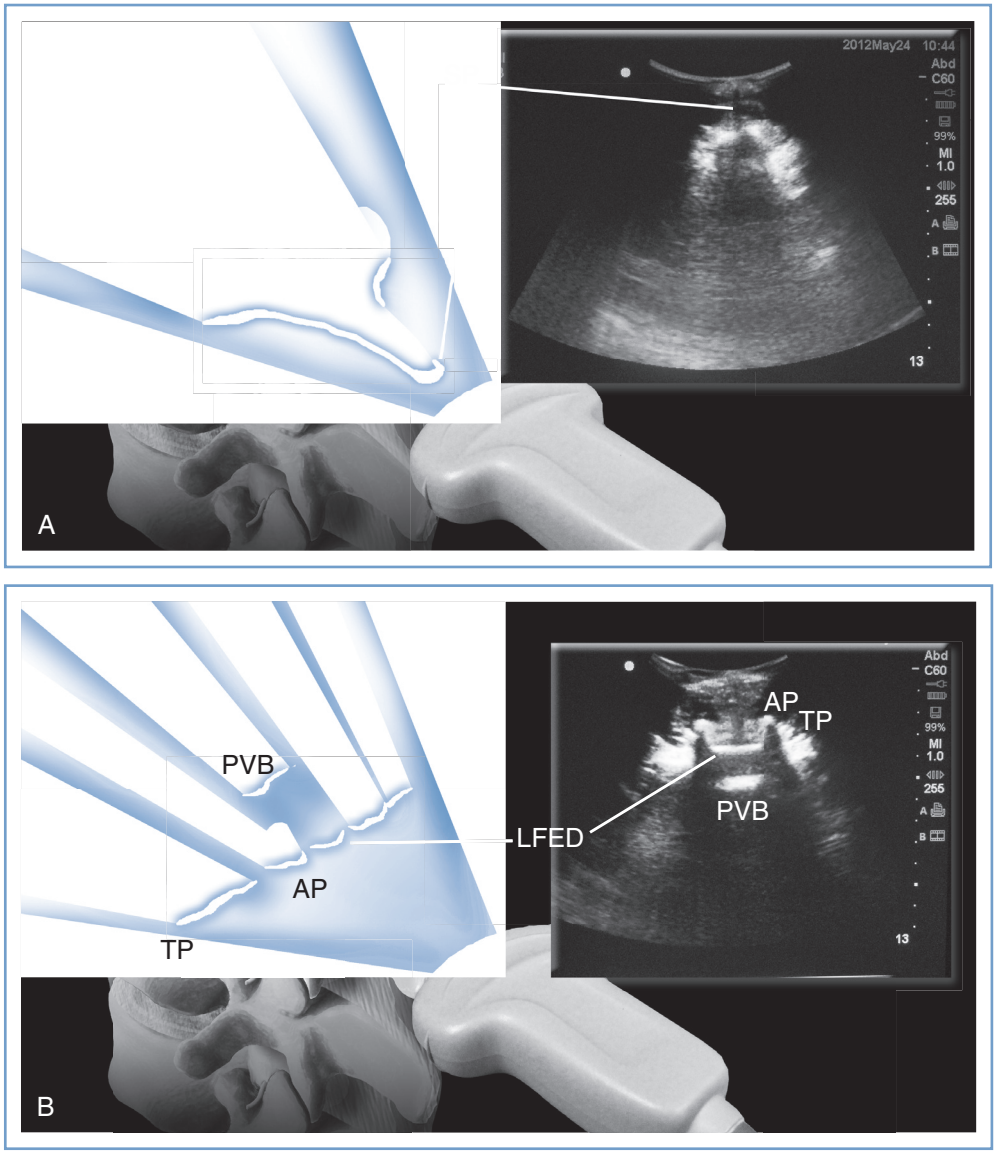

FIGURE 12-18 ■ Use of ultrasonography. **A,** Transverse spinous process view: A long, dark shadow is cast with little to no discernible anatomy beyond the osseous tip of the spinous process (*SP*). **B,** Transverse interlaminar view: ultrasound waves propagate through the interspinous ligament leading to signals partially reflected by the ligamentum flavum–epidural space–dura mater complex (*LFED*). The rays that continue to transmit through this complex encounter the posterior wall of the vertebral body (*PVB*). Articular (*AP*) and transverse processes (*TP*) can be seen as well.

Continued

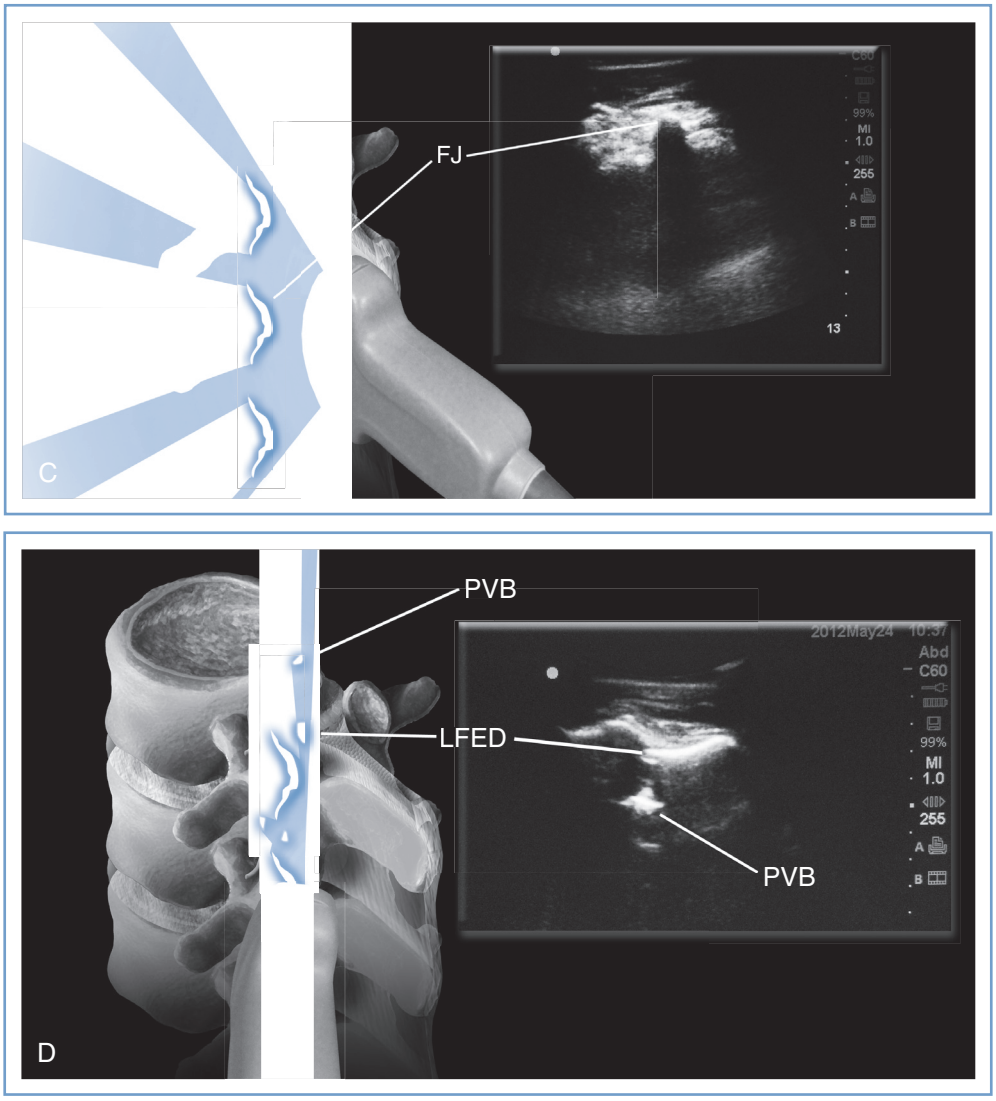

FIGURE 12-18, cont'd ■ C, Paramedian view: a so-called sawtooth pattern may be seen as the lamina and facet joints (*FJ*) are captured by this view, typically achieved 1 cm lateral to the midline sagittal plane. **D,** Paramedian view: by angulating the ultrasound probe, the ultrasound waves may escape through the interlaminar and transforaminal "windows" and capture the ligamentum flavum-epidural space-dura mater complex (LFED) as well as the posterior surface of the vertebral body (PVB). (Drawings by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

the catheter tip is in a blood vessel or the subarachnoid space.

Intravascular Test Dose

The ideal method for excluding intravenous placement of the catheter is controversial. Intravascular placement of the epidural catheter may occur in as many as 7% to 8.5% of obstetric patients.[93] Failure to recognize intravenous placement of the epidural catheter and subsequent intravenous injection of a large dose of local anesthetic may lead to systemic local anesthetic toxicity, with CNS symptoms, seizures, cardiovascular collapse, and death.[94]

The most common intravascular test dose contains epinephrine 15 µg. In normal volunteers, intravenous injection of epinephrine 15 µg (3 mL of a 1:200,000 solution) reliably causes tachycardia.[95,96] An increase in heart rate of 20 beats per minute (bpm) within 45 seconds was 100% sensitive and specific for intravascular injection in unpremedicated patients.[95] An increase in systolic blood pressure of between 15 and 25 mm Hg was also observed. Some anesthesiologists have expressed concerns about the use of an epinephrine-containing test dose in laboring women. Intravenous epinephrine may cause a transient decline in uterine blood flow as a result of alpha-adrenergic receptor–mediated constriction of the uterine arteries (Figure 12-19).[97-99]

However, this decrease in uterine blood flow is transient and comparable to the decrease that occurs during a uterine contraction. Youngstrom et al.[100] noted that this intravenous dose of epinephrine did not worsen fetal condition in acidotic fetal lambs. In healthy parturients, any transient effect of epinephrine on uterine blood flow likely represents a less severe insult than systemic local

anesthetic toxicity. An epinephrine-containing test dose, however, may not be appropriate in parturients with severe hypertension or uteroplacental insufficiency.

Some anesthesiologists argue that the epinephrine-containing test dose lacks *specificity* in laboring women. The maternal tachycardic response to intravenous injection of epinephrine cannot always be distinguished from other causes of tachycardia (e.g., pain during a uterine contraction) (Figure 12-20).[101,102]

Cartwright et al.[101] noted that 12% of laboring women had an increase in heart rate of at least 30 bpm after epidural injection of 3 mL of 0.5% bupivacaine without epinephrine. A study in laboring women compared the intravenous injection of epinephrine (10 to 15 µg) with that of saline; the sensitivity was 100%, the area under the receiver operator curve was 0.91 to 0.93, and the negative predictive value was 100%.[103] However, the positive predictive value was 55% to 73%. The results suggested that if a positive heart rate response to an epinephrine-containing test dose occurs in 20% of patients, 5% to 9% of epidural catheters would be identified incorrectly as intravascular and removed unnecessarily. Colonna-Romano and Nagaraj[104] concluded that the intravenous injection of an epinephrine-containing test dose results in "a sudden and fast acceleration in maternal heart rate within one minute." Thus, careful assessment of the rate of increase in maternal heart rate may help distinguish a contraction-induced increase in heart rate from the effect of intravenously injected epinephrine, thereby improving the *specificity* of the epinephrine test. It is unclear whether such an assessment is clinically practical or will actually reduce the incidence of false-positive results.[105]

Additionally, some anesthesiologists argue that the epinephrine-containing test dose lacks *sensitivity* (the ability to elicit a predictable increase in heart rate when the catheter is intravascular). An increase in maternal heart rate of 25 bpm occurring within 2 minutes of drug injection and lasting at least 15 seconds was observed in only 5 of 10 laboring women who received intravenous epinephrine 15 µg.[106] Detection of intravenous epinephrine injection was improved when the authors retrospectively defined a positive maternal tachycardic response as a 10-bpm increase above the maximum maternal heart rate observed in the 2-minute period preceding the epinephrine injection. Others have confirmed that these

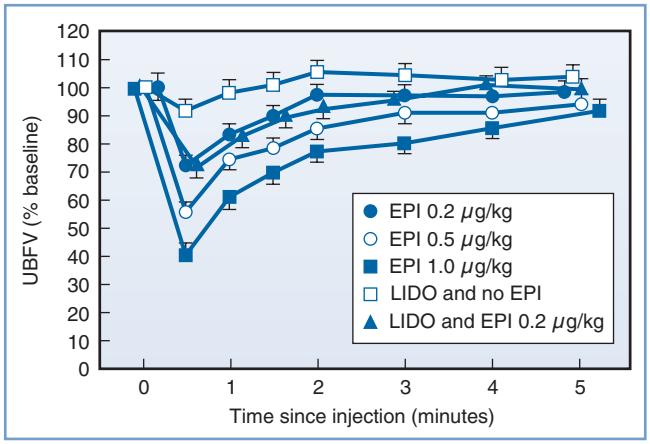

FIGURE 12-19 ■ The effect of intravenous epinephrine (*EPI*), lidocaine (*LIDO*), and lidocaine with epinephrine on uterine artery blood flow velocity (*UBFV*) in the pregnant guinea pig. The dose of lidocaine was 0.4 mg/kg. Values are presented as mean ± standard error of mean (SEM) percentage of baseline. (From Chestnut DH, Weiner CP, Martin JG, et al. Effect of intravenous epinephrine on uterine artery blood flow velocity in the pregnant guinea pig. Anesthesiology 1986; 65:633-6.)

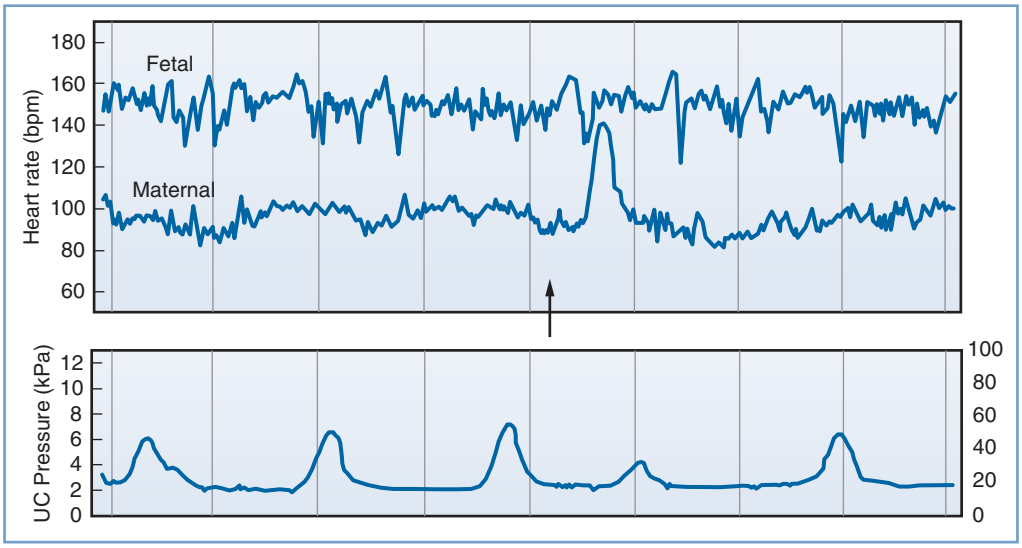

FIGURE 12-20 ■ Heart rate of a laboring patient (maternal heart rate [MHR]), fetal heart rate, and uterine contractions (*UC*) are shown. This tracing was obtained with the use of an FHR monitor with dual heart rate capacity. Note the variability of the MHR with uterine contractions. An intravenous injection of bupivacaine 12.5 mg and epinephrine 12.5 µg was given (*arrow*). Note the marked increase in MHR in response to intravenous injection of the test dose. The maternal tachycardia had a duration of approximately 40 seconds. (From Van Zundert AA, Vaes LE, De Wolf AM. ECG monitoring of mother and fetus during epidural anesthesia. Anesthesiology 1987; 66:584-5.)

TABLE 12-2 **Epidural Test Dose Regimens***

Test Dose Components	Positive Intravascular Test Dose	Positive Intrathecal Test Dose
Combined Intrathecal and Intravenous Test Dose:		
Lidocaine 1.5% with epinephrine 5 μg/mL (1:200,000): 3 mL Bupivacaine 0.25% with epinephrine 5 μg/mL (1:200,000): 3 mL	Increase in heart rate of 20 bpm within 1 minute	Motor blockade at 3-5 minutes†
Intravenous Test Dose:		
Lidocaine 100 mg Bupivacaine 25 mg 2-Chloroprocaine 100 mg	Tinnitus, circumoral numbness, "dizziness"	
Fentanyl 100 μg	Dizziness, drowsiness	
Air 1 mL	Change in Doppler heart sounds over right side of heart	
Intrathecal Test Dose:		
Lidocaine 40-60 mg Bupivacaine 7.5 mg		Motor blockade at 3-5 minutes†

*Test doses may be less sensitive in premedicated patients, patients treated with a beta-adrenergic receptor antagonist, pregnant patients, and anesthetized patients.
†Weakness in hip flexion.
Modified from Yilmaz M, Wong CA. Technique of neuraxial anesthesia. In Wong CA, editor. Spinal and Epidural Anesthesia. New York, McGraw-Hill, 2007:27-73.

revised criteria improve the sensitivity of the epinephrine-containing test dose in laboring women.[103] These findings stress the importance of tracking the chronotropic variability that occurs in laboring patients during neuraxial anesthesia procedures to reduce the risk for misinterpretation of the test dose.

The usefulness of an epinephrine-containing test dose also improves if additional information is obtained. For example, investigators administered intravenous bupivacaine 12.5 mg with epinephrine 12.5 μg or saline to laboring women.[107] They correctly identified the test solution in 39 of 40 women when they assessed maternal heart rate, blood pressure, uterine contractions, the timing of the injection, the presence of analgesia, and subjective signs and symptoms of intravascular injection (e.g., palpitations, lightheadedness, dizziness). The tachycardic response to intravenous epinephrine is not a reliable indicator of intravascular injection in patients who have received a beta-adrenergic receptor antagonist.[95]

Other means of identifying intravascular placement of an epidural catheter have been proposed and may be clinically useful in specific patients (Table 12-2). Intravenous administration of isoproterenol 5 μg consistently results in tachycardia in pregnant women.[108,109] Data from animals[99,110] and noninvasive measurements in parturients[109] suggest that isoproterenol is devoid of the adverse effects of epinephrine on uterine blood flow, and limited neurotoxicity evaluations have not revealed adverse effects.[110,111] However, isoproterenol has not been approved for epidural or intrathecal administration. Given the lack of adequate information regarding potential neurotoxicity, we do not recommend the use of isoproterenol as an epidural test dose.

Leighton et al.[112] have advocated the use of air as an objective marker of intravascular injection. Intravenous injection of 1 or 2 mL of air through a single-orifice catheter consistently produces changes in heart sounds as detected by the use of precordial Doppler ultrasonography.[112] (The external FHR monitor can be used for this purpose.) False-negative results may occur when small volumes of air are injected through a multi-orifice epidural catheter; thus, the air test is not a reliable test for intravascular injection when multi-orifice epidural catheters are used.[113]

Local anesthetic–induced symptoms of subclinical CNS toxicity have also been evaluated as a means of recognizing the unintentional intravenous injection of epidural medications. Colonna-Romano et al.[114] administered intravenous saline, lidocaine 100 mg, or 2-chloroprocaine 100 mg to laboring women. Observers blinded as to which substance was administered recorded the presence of CNS symptoms (i.e., dizziness, tinnitus, funny taste) after intravenous injection of local anesthetic. Lidocaine 100 mg was a reliable marker of intravenous injection when the symptoms of tinnitus and funny taste were considered (sensitivity 100%; specificity 81%). 2-Chloroprocaine was less reliable (sensitivity 81% to 94%; specificity 69% to 81%). In a volunteer study, a dose of 1.5 mg/kg of 2-chloroprocaine was necessary to produce a probability of 90% that the subject would report symptoms of intravenous injection.[115]

Administration of fentanyl 100 μg has been described as a test for intravenous injection.[116] Morris et al.[117] evaluated the accuracy and reliability of the fentanyl test dose in a double-blind study in which either intravenous or epidural fentanyl 100 μg was administered to parturients, and the investigators sought evidence of the occurrence of sedation, dizziness, euphoria, and/or analgesia. Dizziness was the most reliable symptom of intravenous fentanyl injection, with a sensitivity of 92% and a specificity of 92%.

Some situations reduce the reliability of subjective symptoms as a signal of intravenous injection of a drug. Tests that rely on the self-reporting of subjective

symptoms require clear communication with the patient and thus are less useful when the anesthesia provider and patient speak different languages. Patient exhaustion and/or prior opioid administration also may affect the reliability of the test.

Lastly, the epidural catheter design and speed of injection may affect the reliability of the epidural test dose. An epinephrine-containing test dose should be injected rapidly; otherwise rapid redistribution and metabolism of the drug decrease the actual dose administered to chronoreceptors. Multi-orifice epidural catheters have three potential sites of exit for injected fluid or air, and the orifices may lie within two different body compartments. If injected too slowly, air or fluid preferentially exits the proximal orifice. The speed of injection used in clinical practice typically exceeds that required to ensure that fluid will exit all three orifices. In contrast, air must be injected at a much greater speed to ensure that it exits all three orifices; this speed is not practical for clinical use. The distal orifice is both the most difficult to test and the one most likely to be positioned outside the epidural space.[118]

Intrathecal Test Dose

The intrathecal test dose should allow easy identification of subarachnoid (intrathecal) placement of the catheter without causing high or total spinal anesthesia and hemodynamic compromise. Bupivacaine (7.5 mg) and lidocaine (45 to 60 mg) are the local anesthetics most often used for an intrathecal test dose (see Table 12-2; Figure 12-21).[119,120]

In a study of older, nonpregnant patients receiving continuous spinal anesthesia for surgery, Colonna-Romano et al.[120] used plain lidocaine 45 mg plus epinephrine 15 μg and assessed patient perception of lower extremity warmth and heaviness, sensory loss to pinprick, and ability to perform a straight-leg raise. Patients usually perceived warmth in their legs within 1 minute of the intrathecal injection; however, impaired straight-leg raise 4 minutes after an intrathecal test dose injection was the only test that had a sensitivity of 100% for intrathecal injection. The application of these data to pregnant patients is unclear.

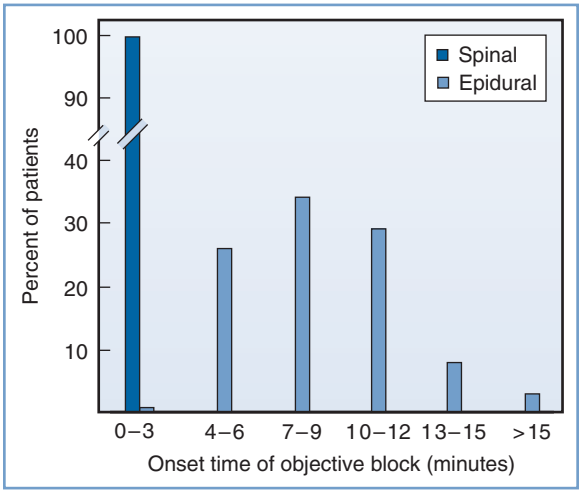

FIGURE 12-21 ■ Percentage of pregnant patients who demonstrated objective evidence of anesthesia (defined as the loss of sensation to pinprick) after epidural injection of 2 to 3 mL of hyperbaric 1.5% lidocaine with 1:200,000 epinephrine (*light teal bars*) (n = 250) or after intrathecal injection of 2 mL of hyperbaric 1.5% lidocaine with 1:200,000 epinephrine (*dark teal bar*) (n = 15). (From Abraham RA, Harris AP, Maxwell LG, et al. The efficacy of 1.5% lidocaine with 7.5% dextrose and epinephrine as an epidural test dose for obstetrics. Anesthesiology 1986; 64:116-9.)

Richardson et al.[121] described the rapid onset (1 to 3 minutes) of high levels of spinal anesthesia with motor block and hypotension in five parturients who had received a test dose of plain lidocaine 45 mg plus epinephrine 15 μg. This solution is slightly hypobaric relative to CSF at body temperature; thus, the upright posture of these parturients during the injection may have contributed to the high levels of spinal anesthesia. The anesthesia provider must recognize the possible range of responses to the dose of local anesthetic used to assess the position of an epidural catheter and should perform a careful assessment of sensory, motor, and sympathetic function 3 to 5 minutes after administration of the test dose before concluding that the intrathecal test dose result is negative. Ropivacaine 15 mg is *not* a useful intrathecal test dose because the slow onset of motor blockade precludes timely diagnosis of intrathecal injection.[122] 2-Chloroprocaine is the only local anesthetic that can be used as a single, combined intravascular and intrathecal test dose; in most patients, 100 mg results in dense, but not total, spinal anesthesia after intrathecal injection and produces systemic signs of subclinical toxicity (tinnitus, funny taste) after intravascular injection.

The epidural injection of local anesthetic for the purpose of ruling out intrathecal or intravascular catheter placement augments *epidural* analgesia and should be considered in the calculation of the initial therapeutic dose of local anesthetic. Several groups of investigators demonstrated that the test dose enhanced the density of epidural blockade and adversely affected the ability to ambulate. A test dose containing lidocaine 45 mg/epinephrine 15 μg adversely affected the ability to ambulate when injected immediately before initiation of epidural analgesia with 0.125% bupivacaine (18.75 mg) with sufentanil (10 μg).[123] Similarly, the same test dose interfered with ambulation when administered immediately after the intrathecal injection of bupivacaine 2.5 mg and fentanyl 25 μg.[124] Finally, a lidocaine 60 mg/epinephrine 15 μg test dose adversely affected the ability to ambulate in women who received neostigmine 500 μg with sufentanil 10 μg for initiation of analgesia.[125]

Techniques to Minimize Local Anesthetic Toxicity

No perfect test dose exists. Some anesthesia providers elect not to administer a test dose because it contributes to motor blockade.[123,124] In addition, aspiration of a *multi-orifice* epidural catheter for blood has 98% sensitivity for detection of an intravascular location.[67] Inadvertent intravascular injection of a solution containing a low

concentration of local anesthetic is unlikely to result in serious morbidity. However, this conclusion depends heavily on the use of small doses of local anesthetic.[126] Laboring women may need large doses of local anesthetic for operative delivery. In some cases, large doses are administered quickly (without incremental injection) for emergency cesarean delivery. The anesthesia provider wants to determine as soon as possible that the epidural catheter is correctly positioned within the epidural space. Even if no morbidity results, it is inconvenient for both the patient and the anesthesia provider to have to repeat the procedure and replace the catheter once the drape has been removed and the patient has been repositioned. The epinephrine-containing test dose provides an objective marker of intravascular injection that has stood the test of time. Thus, we typically give a test dose that contains either bupivacaine 7.5 mg or lidocaine 45 to 60 mg with 15 μg of epinephrine. No matter whether a test dose is injected, drugs should be injected incrementally into the epidural space, because no test is 100% sensitive and catheters may migrate during use. Each incremental dose should be treated as a "test dose" (i.e., the dose should be small enough that it will not cause systemic toxicity if unintentionally injected intravascularly or total spinal anesthesia if injected intrathecally). Pregnant women are very difficult to resuscitate from local anesthetic cardiovascular toxicity.[94]

Steps to minimize the possibility of local anesthetic toxicity are summarized in Box 12-3. They include observation for passive return of CSF or blood (by lowering the proximal end of the epidural catheter below the insertion site), administration of the test dose between contractions, aspiration before each dose, incremental dose administration, maintaining verbal contact with the patient, and assessment for an appropriate level and density of sensory and motor blockade (which indicates correct placement of the catheter in the epidural space).

BOX 12-3 Steps to Decrease Risk for Unintentional Intravenous or Subarachnoid Injection of Local Anesthetic

- Lower the proximal end of the catheter below the site of insertion. Observe for the passive return of blood or cerebrospinal fluid.
- Aspirate before injecting each dose of local anesthetic.
- Give the test dose between uterine contractions.
- Use dilute solutions of local anesthetic during labor.
- Do not inject more than 5 mL of local anesthetic as a single bolus.
- Maintain verbal contact with the patient.
- If little or no block is produced after the injection of an appropriate dose of local anesthetic, assume that the local anesthetic was injected intravenously and remove the catheter.

CHOICE OF DRUG*

The dose requirement of both epidural and spinal local anesthetics is decreased approximately 25% in pregnancy owing to anatomic and physiologic changes (see Chapter 2). These alterations begin to revert to the prepregnancy state within hours of delivery.

Spinal Anesthesia

Anesthesia providers may give spinal anesthesia for cerclage, nonobstetric surgery during pregnancy, instrumental vaginal delivery, cesarean delivery, removal of a retained placenta, or postpartum tubal ligation. Spinal analgesia may be used for labor analgesia. Cesarean delivery represents the most common indication for spinal anesthesia in pregnant women. Most anesthesia providers administer a hyperbaric solution of local anesthetic for spinal anesthesia in obstetric patients. Use of a hyperbaric solution as compared with an isobaric solution results in a faster onset of block and a higher maximum sensory level with a shorter duration of blockade.[127] The urgency and anticipated duration of surgery dictate the choice of local anesthetic agent. The most common choice in the United States is bupivacaine. Other agents include lidocaine and tetracaine. Ropivacaine and levobupivacaine may be used but are not approved for spinal administration in the United States, and levobupivacaine is not available in the United States. Lidocaine provides a short to intermediate duration of action. Bupivacaine, tetracaine, levobupivacaine, and ropivacaine provide intermediate to long durations of action.

Anesthesia providers often add an opioid to the local anesthetic to improve the quality of anesthesia, particularly with regard to visceral stimulation, and to provide postoperative analgesia.[128,129] The addition of an opioid to the local anesthetic decreases the incidence of intraoperative nausea and vomiting. The short-acting, lipid-soluble opioids (i.e., fentanyl, sufentanil) contribute to intraoperative anesthesia, and morphine is often administered for postoperative analgesia. Epinephrine may be added to prolong block duration and perhaps improve block density. It was hoped that other adjuncts (e.g., clonidine, neostigmine) might allow for the administration of a lower dose of local anesthetic and thereby minimize sympatholytic side effects and hasten recovery. Side effects from these other adjuncts, however, have precluded their wide use in obstetric anesthesia practice (see Chapters 23, 26, and 28).

Epidural Anesthesia

Local anesthetic agents available for epidural administration in obstetric patients include 2-chloroprocaine, lidocaine, mepivacaine, bupivacaine, ropivacaine, and etidocaine. Mepivacaine and etidocaine are used infrequently in obstetric anesthesia practice.

Bupivacaine remains the most popular local anesthetic for analgesia during labor and vaginal delivery

*Chapter 13 contains a detailed discussion of anesthetic agents used for neuraxial anesthetic techniques.

because of its differential sensory blockade, long duration of action, low frequency of tachyphylaxis, and low cost. Anesthesia providers infrequently administer bupivacaine for cesarean delivery because of the risk for cardiac toxicity and maternal mortality after unintentional intravascular injection of the drug.

Ropivacaine has gained popularity as an agent for epidural analgesia and anesthesia because it may result in less cardiac toxicity and greater differential sensory blockade than bupivacaine.[130]

Levobupivacaine also has a more favorable safety profile than bupivacaine. Clinical trials have shown that ropivacaine and levobupivacaine have potency[131] and analgesic qualities similar to those of bupivacaine,[132,133] with the probable exception of less motor nerve block.[134]

Bupivacaine, ropivacaine, and levobupivacaine all have longer durations of action than lidocaine, and they may be preferred over shorter-acting agents when a longer duration of anesthesia or analgesia is desirable. They are more commonly used for maintenance of epidural labor analgesia, whereas the shorter-acting agents are used for epidural surgical anesthesia. Despite some variation among reports, published clinical studies suggest no more than slight differences in onset and potency, and no differences in quality or duration of neural blockade, among the three drugs. However, bupivacaine is more cardiotoxic than the other agents *in vitro* and probably after unintentional intravascular administration.[135] It would seem prudent to use ropivacaine or levobupivacaine rather than bupivacaine when a bolus dose of a concentrated solution is being given. When administered as a low concentration infusion, improved safety has not been demonstrated with ropivacaine and levobupivacaine compared with bupivacaine.

The most popular choice of local anesthetic for epidural anesthesia for cesarean delivery is **2% lidocaine with epinephrine.** The addition of epinephrine (5 μg/mL) causes a modest prolongation of the block. The major advantage of epinephrine is that it improves the quality of epidural lidocaine anesthesia. Lam et al.[136] have shown that epidural labor analgesia can be extended to surgical anesthesia for cesarean delivery in 5.2 ± 1.5 minutes (mean ± SD) with the addition of bicarbonate and fentanyl to 2% lidocaine with epinephrine.

Many anesthesia providers reserve **2-chloroprocaine** for cases in which rapid extension of epidural anesthesia for vaginal delivery or urgent cesarean delivery is necessary. The onset of surgical anesthesia was several minutes faster with 2-chloroprocaine compared with lidocaine with freshly mixed epinephrine and sodium bicarbonate in the setting of urgent caesarean delivery after epidural labor analgesia.[137] Therefore, when time is of the essence, 2-chloroprocaine is the drug of choice. Typically, in an emergency, a large volume of concentrated local anesthetic solution is injected quickly. An additional advantage of 2-chloroprocaine in this situation is that it is rapidly metabolized by plasma esterases. Therefore, the unintentional intravascular injection of a large volume of 2-chloroprocaine may be less likely to have serious adverse consequences. A potential disadvantage of 2-chloroprocaine is that it may interfere with the subsequent actions of opioids[138] and bupivacaine,[139] although this possibility is controversial.[140]

As in spinal anesthesia, epidural opioids work synergistically with local anesthetics. Fentanyl 50 to 100 μg or sufentanil 5 to 10 μg is frequently added to an amide local anesthetic for both labor analgesia (allowing a lower dose of local anesthetic and less motor block) and cesarean delivery (resulting in a denser block with better blockade of visceral stimulation). **Sodium bicarbonate** may be added to lidocaine[141] and 2-chloroprocaine[142] (1 mEq/10 mL local anesthetic) to decrease latency.

Caudal Anesthesia

The drugs used for caudal epidural anesthesia are identical to those used for lumbar epidural block. However, a much larger volume (e.g., 25 to 35 mL) of local anesthetic solution must be administered to extend a caudal block for cesarean delivery or labor analgesia. Such large volumes entail a greater risk for systemic local anesthetic toxicity. Additionally, the caudal epidural space is highly vascular, which further predisposes to intravasation of drugs administered via this route.

COMPLICATIONS OF NEURAXIAL TECHNIQUES

Unintentional Dural Puncture

Unintentional dural puncture with an epidural needle occurs at a rate of approximately 1.5% in the obstetric population.[143] Approximately 52% of women will experience a post–dural puncture headache after puncture with an epidural needle (see Chapter 31). Techniques to minimize the incidence of unintentional dural puncture include (1) identification of the ligamentum flavum during epidural needle advancement; (2) understanding the likely depth of the epidural space in an individual patient; (3) advancement of the needle between contractions, when unexpected patient movement is less likely; (4) adequate control of the needle-syringe assembly during advancement of the needle; and (5) clearing the needle of clotted blood or bone plugs. Norris et al.[144] observed that post–dural puncture headache after unintentional dural puncture was less likely to result in headache if the epidural needle bevel faced lateral rather than cephalad. In contrast, Richardson and Wissler[145] found no difference between the two orientations. An *in vitro* study using cadaver dura found that the fluid leakage rate through dural tears was not dependent on the orientation of the dura relative to the needle bevel.[146] We prefer to insert the epidural needle with the bevel oriented in a cephalad direction so that there is no need to rotate the needle bevel within the epidural space. Cephalad bevel orientation also increases the likelihood of successful epidural anesthesia.[147]

The management of unintentional dural puncture depends on the clinical setting. If advancement of an epidural needle results in dural trespass and the free flow of CSF is perceived in the barrel of the epidural syringe, the anesthesia provider should halt advancement of the

epidural needle and either remove the epidural needle if the plan is to resite the epidural catheter or replace the stylet back into the lumen of the epidural needle to prevent further egress of CSF if the plan is to administer intrathecal medication or perform a continuous spinal technique. Reinjection of CSF contained in the syringe should not be entertained because there is a high likelihood that air will concomitantly be introduced into the subarachnoid space and cause pneumocephalus. The risks and benefits of administering an intrathecal dose of anesthetic should be considered. Although intrathecal administration of local anesthetic through the epidural needle will result in rapid analgesia for an uncomfortable patient, the rapid efflux of CSF may render the injectate ineffective. Additionally, spinal analgesia may mask paresthesias during subsequent attempts at neuraxial anesthesia. Furthermore, spinal anesthesia may cause profound hypotension. If the patient is sitting, and likely to remain so for the next few minutes, the anesthesia provider may struggle to manage two problems instead of one (i.e., a challenging neuraxial procedure and maternal hypotension). However, rapid provision of analgesia may enable the patient to better assume an optimal position without moving. One option is to administer intrathecal opioid, thus providing analgesia without the risk for hypotension.

The anesthesia provider has two options after unintentional dural puncture: site the epidural catheter within the subarachnoid space and use a continuous spinal anesthetic technique or site the epidural catheter in a different interspace (i.e., starting afresh). Evidence is conflicting as to whether the insertion of an epidural catheter through the dural puncture site decreases the incidence of post–dural puncture headache.[148] Continuous spinal anesthesia is an attractive option if identification of the epidural space has been difficult or if the anticipated duration of epidural anesthesia or analgesia is relatively short (e.g., cesarean delivery, or vaginal delivery in parous women). The major disadvantage of an intrathecal catheter is the risk that it may be mistaken for an epidural catheter. Given that the local anesthetic dose required for epidural anesthesia is many times greater than that required for spinal anesthesia, unintentional administration of an epidural dose into the subarachnoid space will lead to total spinal anesthesia. Therefore, on a busy labor and delivery unit where multiple providers are giving anesthesia care, it may be safer to use an epidural catheter rather than an intrathecal catheter in women in whom prolonged analgesia is anticipated.

Thus, the anesthesia provider may elect to initiate epidural anesthesia in another lumbar epidural interspace. However, even if the attempt results in a correctly placed catheter, the provider must be wary of an unexpectedly high level of anesthesia after the epidural administration of usual doses of local anesthetic.[149,150] Leach and Smith[150] reported a patient who had an extensive block after unintentional dural puncture and subsequent epidural injection of bupivacaine. They presented radiologic evidence of the spread of local anesthetic from the epidural space to the subarachnoid space. The extent to which a dural tear affects the movement of substances from the epidural space to the subarachnoid space depends on the size of the hole, the lipophilicity of the drug (highly lipophilic drugs cross quickly regardless of the presence of a hole, whereas water-soluble drugs cross more quickly in the presence of a hole),[151] and whether the drug is administered into the epidural space as a bolus or an infusion. Rapid bolus administration of medications through an epidural catheter in a patient with a known dural puncture with a large-bore needle significantly increases the likelihood of high spinal anesthesia.

Unfortunately, there is no reliable method to decrease the risk for post–dural puncture headache once dural puncture occurs. Obese patients appear to be at lower risk than lean patients for the development of headache.[152] A prophylactic blood patch (injection of autologous blood before removal of the epidural catheter and before onset of a headache) does not reduce the risk for post–dural puncture headache.[148,153]

Occasionally, unintentional dural puncture is not recognized until the epidural catheter is threaded and CSF spontaneously appears at the proximal end of the catheter, or the catheter aspiration or intrathecal test dose is positive. Finally, an epidural catheter that has been correctly sited in the epidural space may migrate into the subarachnoid space. The most significant clinical threat in this scenario is the continued use of a large volume infusion of local anesthetic drug intended for epidural administration. Thus, during prolonged epidural labor analgesia, the patient should be monitored for evidence of high or dense neuraxial anesthesia.

Unintentional Intravascular or Subarachnoid Injection

The unintentional injection of large doses of local anesthetics into the subarachnoid space can lead to catastrophe. The rapid onset of high or total spinal anesthesia results in profound hypotension, loss of consciousness, and apnea secondary to hypoperfusion of the brain stem. Prompt treatment necessitates assisted ventilation, volume resuscitation, and pharmacologic support of blood pressure. Administration of chronotropic agents such as epinephrine may also be necessary if blockade of cardiac sympathetic drive results in bradycardia. The patient is at high risk for awareness in this setting, and the judicious use of an amnestic agent such as midazolam should be considered once cardiorespiratory stability has been restored.

The incidence of intravascular catheter placement varies according to catheter type,[33,65] patient population,[154] and proper placement of the epidural needle tip in the midline. Pregnant women are at higher risk for unintentional intravenous cannulation due to the engorgement of epidural veins. Intravascular injection of a local anesthetic may initially result in altered sensorium, tinnitus, and perioral numbness. Higher blood concentrations may result in seizures, and even higher concentrations may cause dysrhythmias and cardiovascular collapse (see Chapter 13). Management of intravascular toxicity includes prompt institution of advanced cardiac life support (ACLS), gamma-aminobutyric acid (GABA)–potentiating agents such as benzodiazepines to mitigate seizure activity, and the use of intralipid emulsion to

detoxify the patient. Several modifications have been made to the conventional ACLS protocol for the specific treatment of local anesthetic-induced cardiac arrest.[155] These include using small, judicious doses of intravenous epinephrine for circulatory support (10 to 100 μg boluses in adults), avoidance of vasopressin, and the use of amiodarone in place of local anesthetics for treatment of ventricular arrhythmias.

Inadequate Anesthesia

Pain during anesthesia represents a higher proportion of obstetric malpractice claims than of nonobstetric claims.[156] During labor, inadequate epidural analgesia may result from the inadequate extent of sensory blockade, nonuniform blockade, or inadequate density of blockade. When called to evaluate breakthrough pain, the anesthesia provider should first evaluate the extent of bilateral sensory blockade in *both the cephalad and caudad directions.* Particularly if labor is progressing quickly, the extent of sacral blockade may not be adequate. In this case, epidural injection of a large volume of local anesthetic may improve sacral blockade. In contrast, if the extent of sensory blockade is adequate but the patient is still experiencing pain, the density of blockade may be insufficient. In this case, the provider should reestablish and maintain analgesia using a more concentrated solution of local anesthetic.

Why do some obstetric epidural anesthetics fail over time? Collier[157] administered epidural radiocontrast dye in 25 parturients reporting unsatisfactory analgesia. The two major causes of inadequate block in this small study were transforaminal migration of the catheter tip and an obstructive barrier in the epidural space. Total block failure usually results from failure to identify the epidural space correctly or from malposition of the catheter tip outside the epidural space (e.g., in a neuroforamen). A unilateral block may occur despite the use of good technique. Unilateral blocks can often be prevented by limiting the length of catheter within the epidural space to 3 cm or less. The problem with limited insertion of the catheter is that, in some patients, the catheter tends to migrate outward over time. (Patients undergoing surgery remain still; by contrast, laboring women change position frequently.) Obese women seem to be at higher risk for outward migration of the catheter tip. Prospective studies suggest that 4 to 6 cm is the optimal depth of epidural catheter insertion in laboring women.[71,72,158]

Whether catheter withdrawal in the setting of breakthrough pain is beneficial is not clear. Beilin et al.[159] compared catheter withdrawal followed by injection of local anesthetic with injection of local anesthetic without catheter withdrawal for the treatment of breakthrough pain. The ability to rescue analgesia was not different between the groups. Gielen et al.[160] performed a radiologic study in which they observed no consistent relationship between catheter position and the asymmetric onset of sympathetic blockade. Unilateral or patchy sensory blockade likely results from the nonuniform distribution of local anesthetic solution in the epidural space.[161] Injection of a large volume of dilute local anesthetic solution into the epidural space usually corrects this problem, regardless of the location of the tip of the epidural catheter (provided it is actually in the epidural space). If analgesia cannot be rescued with a second injection, the catheter should be removed and replaced at another interspace.

The management of inadequate anesthesia is more problematic during cesarean delivery. Failure of spinal anesthesia may result from the maldistribution of local anesthetic within the subarachnoid space.[162,163] If inadequate spinal anesthesia is noted before incision, the anesthesia provider may augment the block with additional local anesthetic by either performing a second spinal anesthetic procedure or placing an epidural catheter. However, care must be taken if performing a second spinal anesthetic procedure. In the ASA Closed-Claims Project database, Drasner and Rigler[162] identified three cases of cauda equina syndrome complicating spinal anesthesia. In two cases, "failed spinal" anesthesia had occurred, followed by a repeat injection of local anesthetic. The researchers recommended that anesthesia providers determine the presence of anesthesia in the sacral dermatomes before giving additional local anesthetic into the subarachnoid space. Additionally, they stated that if CSF was aspirated during the original procedure, it should be assumed that local anesthetic was delivered into the subarachnoid space, and the total dose of local anesthetic be limited to the maximum dose a clinician would consider reasonable to administer in a single injection.[162] If partial blockade is present (even if it is limited to the sacral dermatomes), the second dose should be reduced accordingly. It may also be advisable to perform the second procedure at a different interspace or make other changes to the original procedure (e.g., alter the patient's position, use a local anesthetic with different baricity, or straighten the lumbosacral curvature).

If the patient complains of pain after incision, the anesthesia provider must decide between the administration of inhalation or intravenous analgesia and the administration of general anesthesia. Supplemental analgesia may be provided by giving 60% nitrous oxide in oxygen, small incremental boluses of ketamine (0.1 to 0.25 mg/kg), or small boluses of intravenous opioid. Supplemental infiltration of the wound with local anesthetic is sometimes helpful, especially when spinal anesthesia regresses near the end of an unexpectedly long operation. The anesthesia provider must ensure that the patient remains sufficiently alert to protect her airway. In most cases, severe pain unrelieved by modest doses of analgesic drug requires rapid-sequence induction of general anesthesia followed by endotracheal intubation and general anesthesia.

In some cases, inadequate epidural anesthesia results from failure to give a sufficient dose of local anesthetic or failure to wait a sufficient time after its administration. For example, after the epidural administration of 0.5% bupivacaine, approximately 20 minutes must pass to achieve an adequate level of anesthesia, and additional local anesthetic may be needed to achieve an adequate density of blockade. In urgent cases or in cases with a "missed" segment, local infiltration with a local anesthetic often results in satisfactory anesthesia. Sometimes it is difficult to separate the beneficial effect of the local

infiltration from the beneficial effect of waiting for the obstetrician to obtain, prepare, and inject the local anesthetic solution. Finally, the anesthesia provider should exercise caution when initiating spinal anesthesia after failure of epidural anesthesia because of a greater incidence of high spinal anesthesia in this setting.[164] Presumably, the large volume of local anesthetic within, or near, the epidural space results in decreased lumbar CSF volume, which predisposes to high spinal anesthesia. It may be advisable to reduce the dose of intrathecal local anesthetic, particularly in the presence of partial epidural blockade.

Equipment Problems

The frequency of major equipment malfunction is very low during the administration of neuraxial anesthesia. Most anesthesia providers in the United States use disposable needles, and the plastic needle hubs are attached to the needles' shafts with epoxy. Rarely, a needle breaks at the hub-shaft junction.[165] If a needle should break, the portion of the needle that remains in the patient should be removed, because it may migrate and cause injury.

An epidural or spinal catheter may shear and break off if the catheter is withdrawn through a needle; thus an epidural or spinal catheter should never be withdrawn in this manner. Rather, if the catheter must be withdrawn, the needle and catheter should be withdrawn as a unit. It is also possible to break a catheter during attempts at removing it, although this is rare. If resistance to catheter removal is encountered, the patient should assume a position that reduces lumbar lordosis, thereby lessening the kinking of the catheter between perivertebral structures. If position change is not successful, the catheter should be taped under tension to the patient's back and left undisturbed for several hours. The catheter usually works its way out and is then easy to remove. Once the catheter has been removed successfully, it should be examined to ensure that it has been removed completely. Complete removal of the catheter should be documented in the medical record.

Rarely, catheters do break on removal. We favor aggressive attempts to remove broken *spinal* catheters. However, it may be unnecessary to remove broken *epidural* catheters; rather, in these circumstances, the patient can be informed of the complication and observed over time. The incidence of catheter migration or other delayed sequelae appears to be low. Computed tomography may help identify the precise location of a broken catheter.[166]

During use, an epidural catheter occasionally becomes disconnected from the catheter connector. Options include replacing the epidural catheter or reconnecting the connector to the catheter. Langevin et al.[167] used an *in vitro* model to investigate whether microbial contamination precludes reconnection. They found that an area of the interior of the catheter distal to the disconnection may remain sterile for up to 8 hours if the fluid column within the catheter remains static (i.e., if "fluid does not move within the catheter when it is raised above the level of the patient").[167] Therefore, they concluded that it *may* be safe to decontaminate the exterior of the catheter, cut the catheter with a sterile instrument, and reconnect it to a new sterile connector. However, given the potential catastrophic consequences of neuraxial infection, we recommend replacing the catheter. Also, wire-embedded catheters cannot be cut.

KEY POINTS

- Physiologic changes of pregnancy alter neuraxial anatomy; alterations include accentuation of lumbar lordosis, a "softer" ligamentum flavum, and decreased space in the spinal canal due to vascular engorgement of epidural veins.
- Physiologic changes of pregnancy cause a more pronounced response to neuraxial anesthesia–induced sympathetic blockade than is seen in nonpregnant patients. These include higher baseline sympathetic tone and aortocaval compression.
- Pregnant women, particularly those with neuraxial blockade, should not be cared for in the supine position but rather in lateral tilt or in the full lateral position.
- Correct patient positioning, equipment, and technique are important to the success and safety of neuraxial techniques.
- The midline approach is faster and less painful than the paramedian approach to the epidural or subarachnoid space. However, the paramedian approach may allow for the successful identification of the subarachnoid or epidural space in difficult cases.
- Use of a non-cutting ("pencil-point") needle for spinal anesthesia reduces the incidence of post–dural puncture headache.
- Combined spinal-epidural anesthesia has the advantages of both spinal anesthesia and epidural anesthesia.
- Approximately 20% to 30% less local anesthetic is required for epidural and spinal anesthesia in pregnant patients than in nonpregnant patients.
- Multiple techniques (e.g., test dose, aspiration, incremental dose injection) should be used to reduce the incidence and risk for unintentional subarachnoid or intravascular injection, because no one technique will completely exclude all cases of malpositioned needles or catheters.

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CHAPTER 13

Local Anesthetics and Opioids

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CHAPTER OUTLINE

Local anesthetics and opioids are often used for pain relief in obstetric practice. Local anesthetics may be used for infiltration anesthesia, peripheral (pudendal) nerve block, or neuraxial block, whereas opioids are administered both systemically and neuraxially. The physiologic changes that occur during pregnancy may affect the pharmacology of both local anesthetics and opioids. In turn, these analgesic drugs may have effects on the mother and the fetus.

LOCAL ANESTHETICS

Molecular Structure

All local anesthetic molecules except cocaine contain a desaturated carbon ring (aromatic portion) and a tertiary amine connected by an alkyl chain (Figure 13-1). The intermediate alkyl chain, by virtue of its ester or amide linkage, is the basis for the classification of local anesthetics as **amino-esters** (which are hydrolyzed by pseudocholinesterase) and **amino-amides** (which undergo hepatic microsomal metabolism) (Table 13-1). The aromatic ring of the esters, which renders the molecule lipid soluble, is a derivative of benzoic acid. The amide aromatic ring is a homologue of aniline. The tertiary-amine portion acts as a proton acceptor; thus, local anesthetics behave as weak bases. In its quaternary (i.e., "protonated") form, the terminal amine is the water-soluble portion. The Henderson-Hasselbalch equation predicts the relative proportions of local anesthetic that exist in the ionized and un-ionized form. The higher the pK_B (base dissociation constant) relative to physiologic pH, the smaller the proportion of drug that exists in the un-ionized form. All amide local anesthetics (with the exception of lidocaine) exist as stereoisomers because of the presence of an asymmetric carbon adjacent to the terminal amine.

Clinical formulations of local anesthetics are prepared as hydrochloride salts to increase their solubility in water. These solutions are usually acidic (i.e., pH of 4 to 6) to enhance formation of the water-soluble quaternary amine and to prevent oxidation of the epinephrine present in epinephrine-containing solutions.

Chirality

With the exception of lidocaine, amide local anesthetics are known as **chiral compounds** because they have a single asymmetric carbon adjacent to the amino group and thus exist in isomeric forms that are mirror images of each other. The direction in which the isomers rotate polarized light distinguishes them as either dextrorotary (D) or levorotary (L) isomers. This distinction is

important, because individual isomers of the same drug may have different biologic effects. As a rule, the levorotary isomer of a drug has greater vasoconstrictor activity and a longer duration of action but less potential for systemic toxicity than the dextrorotary form.[1]

In the past, single-isomer formulations were costly to produce; and for that reason, local anesthetics used clinically (e.g., **bupivacaine**) have contained a racemic mixture of both the dextrorotary and levorotary forms of the drug. However, with improved techniques of selective extraction, two commercially available single-isomer formulations of local anesthetic are now available, ropivacaine and levobupivacaine. **Levobupivacaine** is the levorotary isomer of bupivacaine; it is currently not marketed in the United States. **Ropivacaine** is a homologue of mepivacaine and bupivacaine, but, unlike these other local anesthetics, it is formulated as a single levorotary isomer rather than as a racemic mixture. A propyl group on the pipechol ring distinguishes ropivacaine from bupivacaine (which has a butyl group) and mepivacaine (which has a methyl group).[2] Thus, it is not surprising that the physicochemical characteristics of ropivacaine are intermediate between those of mepivacaine and bupivacaine.

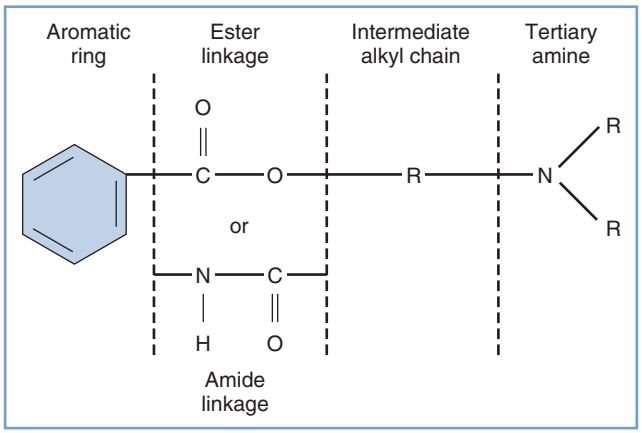

FIGURE 13-1 ■ Structure of the molecule of a local anesthetic. *R,* alkyl group. (Modified from Santos AC, Pedersen H. Local anesthetics in obstetrics. In Petrie RH, editor. Perinatal Pharmacology. Cambridge, MA, Blackwell Scientific, 1989:373.)

The reduction in systemic toxicity observed with administration of the levorotary isomers may be both drug and concentration dependent. For example, one study in isolated guinea pig hearts noted that bupivacaine isomers lengthened atrioventricular conduction time more than ropivacaine isomers did. In contrast to other measured variables, "atrioventricular conduction time showed evident stereoselectivity" for bupivacaine at the lowest concentration studied (0.5 μM) but only at much higher concentrations for ropivacaine (> 30 μM).[3]

Mechanism of Action

At rest, the interior of a nerve cell is negatively charged in relation to its exterior. This resting potential of 60 to 90 mV exists because the concentration of sodium in the extracellular space greatly exceeds that in the intracellular space. The converse is true for potassium. Excitation results in the opening of membrane channels, which allows sodium ions to flow freely down their concentration gradient into the cell interior. Thus, the electrical potential within the nerve cell becomes less negative until, at the critical threshold, rapid depolarization occurs. This depolarization is needed to initiate the same sequence of events in adjacent membrane segments and for propagation of the action potential. Thereafter, sodium channels close and the membrane once again becomes impermeable to the influx of sodium. The negative resting membrane potential is reestablished as sodium is removed from the cell by active transport. At the same time, potassium passively accumulates within the resting cell.

Interference with sodium-ion conductance appears to be the mechanism by which local anesthetics reversibly inhibit the propagation of the action potential. Four major theories attempt to explain this effect. The most prominent hypothesis is that the local anesthetic interacts with receptors in the nerve cell membrane that control channels involved in sodium conductance.[4] There may be more than one site at which local anesthetics bind to sodium-channel receptors (Figure 13-2).

The Meyer-Overton theory offers a second explanation for local anesthetic action. This hypothesis suggests that the lipid-soluble portion of the local anesthetic

TABLE 13-1 **Physicochemical Characteristics and Fetal-to-Maternal (F/M) Blood Concentration Ratios at Delivery for Commonly Used Local Anesthetic Agents**

	Molecular Weight (Base) (Da)	pK_B	Lipid Solubility*	% Protein Bound	F/M Ratio
Esters:					
2-Chloroprocaine	271	8.9	0.14	—	—
Tetracaine	264	8.6	4.1	—	—
Amides:					
Lidocaine	234	7.9	2.9	64	0.5-0.7
Bupivacaine (and levobupivacaine)	288	8.2	28	96	0.2-0.4
Ropivacaine	274	8.0	3	90-95	0.2

*N-heptane/pH = 7.4 buffer.

Modified from Santos AC, Pedersen H. Local anesthetics in obstetrics. In Petrie RH, editor. Perinatal Pharmacology. Cambridge, MA, Blackwell Scientific, 1989:375.

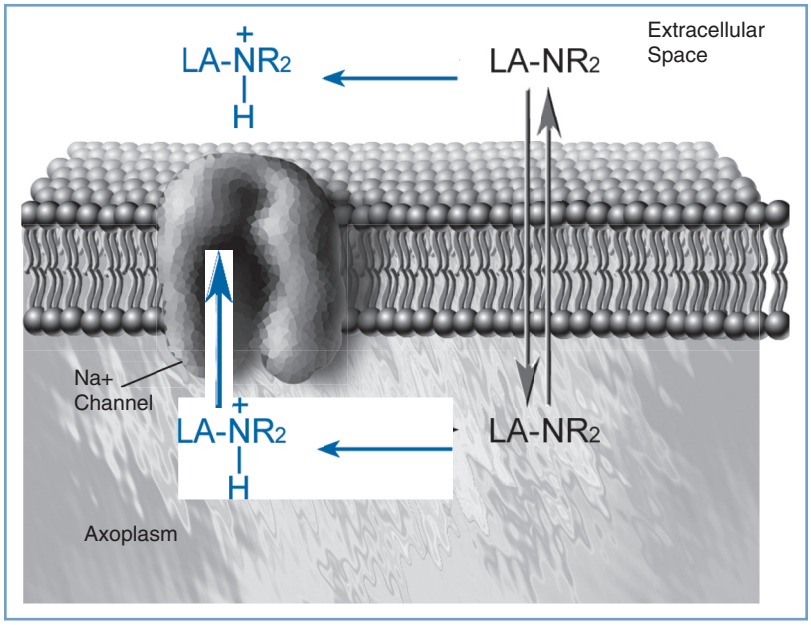

FIGURE 13-2 ■ Local anesthetic access to the sodium channel. The uncharged molecule (LA-NR_2) diffuses most easily across the lipid membrane and interacts with the sodium channel at an intramembranous site. The charged molecule (LA-NR_2H^+) gains access to a specific receptor on the sodium channel in the intracellular space. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

molecule expands the cell membrane and interferes with rapid sodium conductance. A third possibility is that local anesthetics may alter the membrane surface charge, a change that would inhibit propagation of the action potential. Fourth, local anesthetics may displace calcium from sites that control sodium conductance.

Both the un-ionized and ionized forms of a local anesthetic are involved in pharmacologic activity. The un-ionized base, which is lipid soluble, diffuses through the cell membrane, whereas the charged form is much more active in blocking the sodium channel.

Pharmacodynamics

Pregnant women typically require smaller doses of local anesthetic compared with nonpregnant women for neuraxial blockade. This effect may be evident as early as the second trimester.[5,6] This difference has been attributed to enhanced spread of local anesthetic due to epidural venous engorgement. However, mechanical effects alone do not account for the observation that the spread of spinal and epidural analgesia in early pregnancy is similar to that in pregnant women at term.[5-7] In fact, pregnancy may also enhance neuronal sensitivity to local anesthetics. For example, pregnancy increases median nerve susceptibility to lidocaine.[8] *In vitro* studies demonstrated that the onset of neural blockade was faster, and lower concentrations of bupivacaine were required to block vagal fibers, in pregnant rabbits than in nonpregnant rabbits.[9]

Hormonal and biochemical changes may be responsible for the greater susceptibility to neural blockade during pregnancy. For example, one study demonstrated an enhanced effect of bupivacaine in isolated vagus fibers from nonpregnant, ovariectomized rabbits who had received long-term (4 days) but not short-term exposure to progesterone.[10] A higher pH and lower bicarbonate and total carbon dioxide content have been demonstrated in cerebrospinal fluid (CSF) from women undergoing cesarean delivery than in CSF from age-matched nonpregnant controls. A higher pH increases the proportion of local anesthetic that exists as the base form and facilitates diffusion of the drug across nerve membranes.[7]

Pharmacokinetics

Pregnancy is associated with progressive physiologic adaptations that may influence drug disposition (see Chapter 2). However, it is difficult to predict with certainty the effects of pregnancy on the pharmacokinetics of an individual drug.

2-Chloroprocaine

2-Chloroprocaine is hydrolyzed rapidly by plasma pseudocholinesterase to chloroaminobenzoic acid and H_2O. The *in vitro* half-life of 2-chloroprocaine in sera from men is less than 15 seconds.[11] Although pregnancy is associated with a 30% to 40% decrease in pseudocholinesterase activity, the half-life of 2-chloroprocaine in maternal plasma *in vitro* is 11 to 21 seconds. After epidural injection, the half-life of 2-chloroprocaine in the mother ranges from 1.5 to 6.4 minutes.[12] The longer half-life after epidural administration results from continued absorption of the drug from the injection site. Administration of 2-chloroprocaine to patients with low pseudocholinesterase activity may result in prolonged local anesthetic effect and a greater potential for systemic toxicity.[13]

Lidocaine

The volume of the central compartment and the volume of distribution are greater in pregnant ewes than in nonpregnant ewes.[14,15] Bloedow et al.[15] observed that the total body clearance of lidocaine was similar in the two

groups of animals. They concluded that the elimination half-life of lidocaine, which depends on the balance between volume of distribution and clearance, was longer in pregnant ewes.[15] In contrast, Santos et al.[14] concluded that the elimination half-life of lidocaine was similar in the two groups of sheep because the total body clearance of the drug was greater in pregnant animals than in nonpregnant animals. This discrepancy could result from differences in the complexity of the surgical preparation and the allowed recovery period. In pregnant women, the elimination half-life of lidocaine after epidural injection is approximately 114 minutes.[16]

Lidocaine is metabolized to two active compounds, monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Monoethylglycinexylidide can be detected in maternal plasma within 10 to 20 minutes after neuraxial injection of lidocaine, whereas glycinexylidide can be detected within 1 hour of epidural injection but rarely after subarachnoid injection.[17,18] Urinary excretion of unchanged lidocaine is negligible in sheep (i.e., < 2% of the administered dose) and is not affected by pregnancy.[14]

The physiologic changes that occur during pregnancy are progressive. However, little information is available about the pharmacokinetics of local anesthetics before term. In one study, total clearance of lidocaine was similar at 119 and 138 days' gestation in gravid ewes (term is 148 days).[19]

Lidocaine is predominantly bound to alpha$_1$-acid glycoprotein (AAG) in plasma.[20] Pregnancy leads to a decreased concentration of AAG; thus, the free plasma fraction of lidocaine is higher in term pregnant women than in nonpregnant controls.[20] The increase in the free fraction of lidocaine occurs early in gestation and is progressive.[21]

Bupivacaine

At least two studies compared the pharmacokinetics of bupivacaine after epidural administration in pregnant and nonpregnant women.[22,23] The absorption rate, the area under the concentration-time curve, and the elimination half-life (12 to 13 hours) were similar in the two groups. The elimination half-life of bupivacaine after epidural administration is much longer than that reported after intravenous injection, largely because the drug is continuously absorbed over time from the epidural space.

After intravenous injection, the volume of distribution of bupivacaine is lower in pregnant sheep than in nonpregnant sheep.[24] In contrast, ovine pregnancy is associated with a greater volume of distribution of lidocaine.[14,15] The differences in gestational effects on the volume of distribution of the two local anesthetics may result from the greater binding of bupivacaine to plasma proteins during gestation (whereas the converse occurs with lidocaine).[24] In one study, urinary excretion of unchanged bupivacaine was not affected by pregnancy and was less than 1% of the administered dose.[22] Nonetheless, low concentrations of bupivacaine may be detected in the urine of pregnant women for as long as 3 days after delivery.[25]

Bupivacaine undergoes dealkylation in the liver to 2,6-pipecolyxylidide (PPX). After epidural injection of bupivacaine for cesarean delivery, PPX was detected in maternal plasma within 5 minutes and remained detectable for as long as 24 hours.[25] With the lower doses required for labor analgesia, PPX was found only if the block was maintained with multiple reinjections during a period that exceeded 4 hours.[26] Pregnancy may affect metabolism of bupivacaine.[22] For example, pregnant women have higher serum PPX concentrations, but the unconjugated 4-hydroxy metabolite is not produced in significant amounts. The reason for this finding is unclear but may be related to the effects of hormonal changes on hepatic enzyme systems. Both progesterone and estradiol are competitive inhibitors of microsomal oxidases, whereas reductive enzymes are induced by progesterone.[24] Bupivacaine is bound extensively to AAG and albumin.[27] This protein binding is reduced during late pregnancy in humans.[28]

Long-acting pipechol amide local anesthetics, such as bupivacaine, are beneficial for neuraxial labor analgesia because they produce a relative motor-sparing block as compared with other local anesthetics. The effective dose in 50% of cases (ED_{50}) for motor block after intrathecally administered bupivacaine was lower in pregnant than in nonpregnant women (3.96 mg and 4.14 mg, respectively).[29]

Ropivacaine

Pregnant sheep have a smaller volume of distribution and a slower clearance of ropivacaine than nonpregnant animals.[24] However, the relationship between volume of distribution and clearance is such that the elimination half-life is similar in pregnant and nonpregnant animals.

After intravenous injection in laboratory animals, the elimination half-life of ropivacaine is shorter than that of bupivacaine.[24,30] Similar findings have been described after intravenous injection in nonpregnant human volunteers.[31] The shorter elimination half-life of ropivacaine has been attributed to a faster clearance and a shorter mean residence time than for bupivacaine.[24]

Peak plasma concentration (C_{max}) after epidural administration of 0.5% ropivacaine and 0.5% bupivacaine for cesarean delivery are similar (1.3 μg/mL and 1.1 μg/mL, respectively).[32] The elimination half-life of ropivacaine is 5.2 ± 0.6 hours, which is shorter than that for bupivacaine, at 10.9 ± 1.1 hours. No difference in clearance between the two drugs has been noted.

Like bupivacaine, ropivacaine is metabolized by hepatic microsomal cytochrome P450. The major metabolite is PPX, and minor metabolites are 3′- and 4′-hydroxy-ropivacaine.[33]

Ropivacaine is highly bound (approximately 92%) to plasma proteins but less so than bupivacaine (96%).[34] Indeed, at plasma concentrations occurring during epidural anesthesia for cesarean delivery, the free fraction of ropivacaine is almost twice that of bupivacaine.[32] In sheep, pregnancy is associated with a greater binding of ropivacaine (and bupivacaine) to plasma proteins.[24] In pregnant women undergoing epidural analgesia, the free fraction of ropivacaine decreases as the concentration of AAG increases, up to the point at which the receptors are saturated.[35] However, there is little correlation between

the free fraction and umbilical cord blood levels of ropivacaine at delivery.[35]

Effect of Histamine (H_2)-Receptor Antagonists

Histamine (H_2)-receptor antagonists (e.g., cimetidine, ranitidine, famotidine) are administered to increase gastric pH and reduce the parturient's risk for aspiration pneumonitis. Drug disposition may be affected by binding to hepatic cytochrome P450, thereby reducing hepatic blood flow and renal clearance, especially with cimetidine. However, short-term administration of H_2-receptor antagonists does not alter the pharmacokinetics of amide local anesthetics in pregnant women.[36,37]

Effects of Preeclampsia

Pathophysiologic changes associated with preeclampsia (e.g., reduced hepatic blood flow, abnormal liver function, decreased intravascular volume) may also affect maternal blood concentrations of local anesthetics (see Chapter 36). For example, Ramanathan et al.[38] found that total body clearance of lidocaine after epidural injection was significantly lower in preeclamptic women than in normotensive women; however, the elimination half-life of lidocaine was similar in the two groups. Nonetheless, decreased clearance may result in greater drug accumulation with repeated injections of lidocaine in women with preeclampsia. In contrast, long-acting amides have a relatively low hepatic extraction, and changes in liver blood flow with preeclampsia may have less effect on the metabolic clearance.

Effect of Diurnal Variation

Pain may exhibit temporal variation in intensity due to diurnal neuroendocrine or external factors. Further, the pharmacokinetics and pharmacodynamics of local anesthetics may exhibit temporal patterns (i.e., chronobiology). In one study, the duration of action of epidural bupivacaine was approximately 25% longer when it was administered between 7:00 AM and 7:00 PM than between 7:00 PM and 7:00 AM.[39] In contrast, another study found no diurnal variation with intrathecal bupivacaine administered for labor analgesia.[40] The authors suggested that observed temporal differences in duration of analgesia may be explained by external influences such as shift changes for nurses and anesthesiologists.[40]

Toxicity

Systemic absorption or intravascular injection of a local anesthetic may result in local anesthetic systemic toxicity (LAST). Toxicity most often involves the central nervous system (CNS), but cardiovascular toxicity also may occur. Less common are tissue toxicity and hypersensitivity reactions.

Central Nervous System Toxicity

The severity of CNS effects is proportional to the blood concentration of local anesthetic. This relationship is well described for lidocaine (Figure 13-3). Initially, the patient may complain of numbness of the tongue, tinnitus, or lightheadedness. At high plasma concentrations, convulsions occur because of a selective blockade of central inhibitory neurons that leads to increased CNS excitation.[41] At still higher concentrations, generalized CNS depression or coma may result from reversible blockade of both inhibitory and excitatory neuronal pathways. Finally, depression of the brainstem and cardiorespiratory centers may occur.

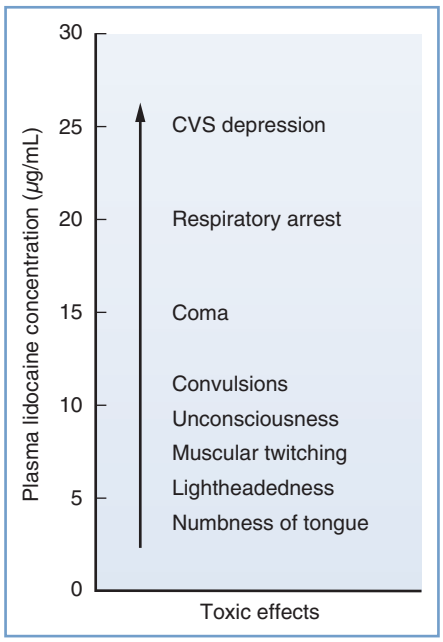

FIGURE 13-3 ■ Signs and symptoms of systemic toxicity with increasing lidocaine concentrations. *CVS,* cardiovascular system. (Modified from Carpenter RL, Mackey DC. Local anesthetics. In Barash PG, Cullen BF, Stoelting RK, editors. Clinical Anesthesia. Philadelphia, Lippincott, 1992:527.)

The relative toxicity of a local anesthetic correlates with its potency. For lidocaine, etidocaine, and bupivacaine, the ratio of the mean cumulative doses that cause convulsions in dogs is approximately 4:2:1, which is similar to their relative anesthetic potencies.[42] The same relative toxicity was demonstrated in human volunteers.[43] Local anesthetics may be ranked in order of decreasing CNS toxicity as follows: bupivacaine, ropivacaine, levobupivacaine, lidocaine, and 2-chloroprocaine.[44] Tetracaine, etidocaine, and mepivacaine are used rarely in obstetric anesthesia practice.

Other factors (e.g., the speed of injection) may affect CNS toxicity. In humans, the mean dose of etidocaine that elicited signs of CNS toxicity was lower during a 20-mg/min infusion than during a 10-mg/min infusion.[43] The seizure threshold also may be affected by metabolic factors. For example, in cats, an increase in $Paco_2$ or a decrease in pH results in a reduction in the seizure-dose threshold for local anesthetics. Respiratory acidosis may result in delivery of more drug to the brain; alternatively, respiratory acidosis may result in "ion trapping" of the local anesthetic and/or an increase in the unbound fraction of drug available for pharmacologic effect.[45-47]

Cardiovascular Toxicity

The cardiovascular system is much more resistant than the CNS to the toxic effects of local anesthetics. Severe, direct cardiovascular depression is rare, especially in association with the use of lidocaine. Prompt administration of oxygen and, if necessary, initiation of ventilatory and circulatory support usually prevent cardiac arrest after unintentional intravenous injection of lidocaine.[48] Progressive depression of myocardial function and profound vasodilation occur only at extremely high plasma concentrations.[48] In contrast, the more potent amide local anesthetics (i.e., bupivacaine) have a more narrow margin of safety, expressed as the ratio between the dose (or plasma concentration) required to produce cardiovascular collapse and the dose (or plasma concentration) required to produce convulsions.[48] A partial explanation is the fact that supraconvulsant doses of bupivacaine (but not of lidocaine) precipitate lethal ventricular arrhythmias.[49-51] These arrhythmias may be caused by exaggerated electrophysiologic effects (e.g., depression of ventricular conduction) out of proportion to bupivacaine's anesthetic potency.[52]

Two theories have been proposed to explain why malignant ventricular arrhythmias occur with bupivacaine but not with lidocaine. Both bupivacaine and lidocaine rapidly block cardiac sodium channels during systole, but bupivacaine dissociates from these channels during diastole at a much slower rate than lidocaine.[52] Thus, at physiologic heart rates, the diastolic period is of sufficient duration for lidocaine to dissociate from sodium channels, whereas a bupivacaine block becomes intensified. This difference makes bupivacaine much more potent than lidocaine in depressing conduction and inducing reentrant-type ventricular arrhythmias. Alternatively, other investigators have suggested that high concentrations of local anesthetic in the brainstem may lead to systemic hypotension, bradycardia, and ventricular arrhythmias.[53] These effects occur more commonly with bupivacaine because of its high lipid solubility, which facilitates transfer across the blood-brain barrier. An echocardiographic study in anesthetized dogs suggested that bolus injection of bupivacaine results in systolic dysfunction, especially involving the right ventricle, which precedes the occurrence of arrhythmias.[54]

Systemic Toxicity of Ropivacaine and Levobupivacaine

In perfused preparations of myocardium, ropivacaine is intermediate between bupivacaine and lidocaine in its depressant effect on cardiac excitation and conduction as well as in its potential to induce reentrant-type ventricular arrhythmias.[34] In dogs, the margin of safety between convulsive or lethal doses and plasma concentrations of drug is greater for ropivacaine than for bupivacaine but less than that for lidocaine.[55] The arrhythmogenicity of ropivacaine in pigs also is intermediate between that of lidocaine and bupivacaine.[56] In sheep, the ratio of fatal doses of bupivacaine, ropivacaine, and lidocaine is 1:2:9.[57] Ropivacaine was found to cause fewer CNS symptoms and was 25% less toxic than bupivacaine (as defined by the doses and plasma concentrations that were tolerated) when administered to healthy male volunteers.[58]

Most studies comparing the systemic toxicity of ropivacaine and bupivacaine have used equal doses of each, and, therefore, cannot resolve the controversy as to whether ropivacaine truly is less cardiotoxic or merely less potent than bupivacaine. This issue would be of concern only if larger doses of ropivacaine than bupivacaine were required to produce comparable regional blocks. Indeed, several studies in laboring women suggest that ropivacaine is 25% to 40% less potent than bupivacaine.[59-61] Thus, the need for a larger dose of ropivacaine may negate the expected benefits of its apparently wider margin of safety. However, results from one laboratory study showed that ropivacaine produces less cardiotoxicity than bupivacaine, even when given at equipotent doses.[62]

Long-acting amide local anesthetics—even the newer drugs—are very potent and may cause cardiac arrest with a misplaced injection or relative overdose. Indeed, several cardiac arrests have been reported with the use of ropivacaine,[63,64] including one in a woman undergoing a cesarean delivery with epidural anesthesia.[65] In contrast to that induced by bupivacaine,[66] resuscitation from a cardiac arrest induced by ropivacaine may be successful more often than not.[63-65]

Evidence suggests that levobupivacaine causes fewer arrhythmias than the racemic drug. Valenzuela et al.[67] demonstrated that levobupivacaine caused less inhibition of inactivated sodium channels than either the dextrorotary or racemic drug. In comparison with dextrorotary and racemic bupivacaine, levobupivacaine resulted in less QRS widening and a lower frequency of malignant ventricular arrhythmias in isolated, perfused rabbit hearts.[68] Similarly, levobupivacaine produced less second-degree heart block and atrioventricular conduction delay than the other two forms of the drug in isolated perfused guinea pig hearts.[3]

In laboratory animals, the systemic toxicity of levobupivacaine is intermediate between that of bupivacaine and ropivacaine.[69] Potency ratio data for epidural bupivacaine, ropivacaine, and levobupivacaine in laboring women are inconsistent, but studies suggest that levobupivacaine is equipotent or less potent than bupivacaine (see Chapter 23).[70,71] Altogether, published data and clinical experience suggest that any benefits from the reduction in risk for systemic toxicity with levobupivacaine are not obtained at the expense of efficacy. Like ropivacaine, levobupivacaine may cause cardiac arrest but is associated with a better response to resuscitation than racemic bupivacaine.[72]

Effects of Pregnancy on Systemic Toxicity

Central Nervous System Toxicity. It is unclear whether pregnancy lowers the seizure threshold for amide local anesthetic agents. In one study, seizures occurred at lower doses of bupivacaine, levobupivacaine, and ropivacaine in pregnant ewes than in nonpregnant ewes.[69] However, the difference was small (10% to 15%) and probably of negligible clinical significance. In studies in sheep and rats,

pregnancy did not reduce the doses required to cause convulsions after intravenous administration of mepivacaine, bupivacaine, or lidocaine.[51,73] Magnesium sulfate, which is frequently used in obstetric practice, does not affect the seizure-dose threshold of lidocaine.[74]

Cardiovascular Toxicity. In 1979, Albright[66] alerted anesthesiologists to several cases of sudden cardiovascular collapse after unintentional intravascular injection of bupivacaine and etidocaine in pregnant women. The fact that cardiac arrest occurred concurrently with or shortly after the onset of convulsions was especially disconcerting. Most of these cases were fatal, and subsequent controversy centered on whether resuscitation was instituted promptly and effectively. Nonetheless, the U.S. Food and Drug Administration (FDA) restricted the use of the highest concentration (0.75%) of bupivacaine in pregnant women.

Several physiologic changes that occur during pregnancy place the parturient at higher risk for refractory cardiac arrest than the nonpregnant patient. First, reduced functional residual capacity and a higher metabolic rate increase the risk for and hasten the onset of hypoxemia during periods of hypoventilation or apnea. Second, aortocaval compression decreases the efficacy of closed-chest cardiac massage in the supine position.[75] Third, a large bolus of drug injected into an epidural vein might reach the heart rapidly through a dilated azygous system. However, none of these factors adequately explains why cardiac arrest and difficult resuscitation are very rare in parturients intoxicated with lidocaine or mepivacaine.[66,76]

Results of laboratory studies of the effects of pregnancy on bupivacaine cardiotoxicity have been contradictory. Pregnancy-related hormones enhance the cardiotoxicity and arrhythmogenicity of bupivacaine *in vitro*.[77,78] For example, the magnitude and severity of bupivacaine-induced electrophysiologic changes are greater in myocardium obtained from nonpregnant rabbits treated with progesterone or beta-estradiol than in myocardium from untreated controls.[77,78] The electrophysiologic effects of lidocaine are less pronounced than those of bupivacaine, even in hormonally treated animals. Studies conducted *in vivo* have been less conclusive. In earlier investigations, significantly lower doses and plasma concentrations of bupivacaine, but not of mepivacaine or lidocaine, were required to produce circulatory collapse in pregnant sheep than in nonpregnant sheep.[49-51] However, a study involving a larger number of sheep and more rigorous methods (e.g., randomization, blinding) failed to confirm that pregnancy enhances the cardiotoxicity of bupivacaine.[69]

Progesterone does not increase myocardial sensitivity to ropivacaine.[79] Likewise, pregnancy does not enhance the systemic toxicity of ropivacaine or levobupivacaine in sheep.[69]

Extrapolation of results of animal studies to obstetric anesthesia practice is difficult, for several reasons. First, in the aforementioned sheep studies, the drug was administered by constant-rate intravenous infusion. In contrast, in pregnant women intoxicated with bupivacaine, cardiac arrest occurred after unintended intravascular injection of a large bolus of drug. Second, a potential for bias existed in the animal studies because randomization and blinding were not used in all studies and some relied on historical controls.[49-51] Third, it is unclear whether resuscitation in the reported clinical cases was accompanied by prompt and effective relief of aortocaval compression.[75]

Nonetheless, bupivacaine remains a popular local anesthetic for obstetric anesthesia. In current practice, heightened vigilance, use of an appropriate test dose, and fractionation of the therapeutic dose have made epidural anesthesia a safe technique for use in obstetric patients (see Chapter 12). In a study of anesthesia-related maternal mortality, Hawkins et al.[80] noted that the number of maternal deaths resulting from local anesthetic toxicity decreased after 1984, the year that the FDA withdrew approval for the epidural administration of 0.75% bupivacaine in obstetric patients. However, LAST has been recognized for decades as an important potential cause of maternal mortality.[81] In our judgment, adherence to the aforementioned clinical precautions—rather than the proscription against the epidural administration of 0.75% bupivacaine—has been responsible for the lower number of maternal deaths due to LAST. Anesthesia providers should be aware that intravenous injection of 0.25% and 0.5% bupivacaine can also cause LAST.

The availability of single levorotary isomers of a local anesthetic may be advantageous because these drugs have a greater margin of safety than bupivacaine, with similar blocking properties, although at a higher cost. From the standpoint of systemic toxicity, the use of these isoforms may be more beneficial in parturients undergoing cesarean delivery, who require higher doses than administered for analgesia during labor. Nonetheless, a greater margin of safety with these new drugs should not be a substitute for proper technique.

Treatment of Systemic Toxicity

Meticulous attention to good technique and adherence to guidelines for maximum recommended dose are mandatory. (The use of a test dose to identify misplaced injections is discussed in Chapter 12.) Incremental injection of the therapeutic dose, careful observation of the patient, and monitoring of vital signs usually provide early warning of an impending reaction. In mild cases, discontinuation of the administration of drug, administration of supplemental oxygen, and maintenance of normal ventilation often limit the severity of the reaction. In 2012, the American Society of Regional Anesthesia and Pain Medicine developed a checklist for managing LAST (Box 13-1). In patients who show signs of CNS excitation, a small dose of an intravenous sedative-hypnotic drug with strong anticonvulsant properties such as a benzodiazepine (diazepam up to 5 mg or midazolam 1 to 2 mg) or propofol (10 to 20 mg) may prevent progression to convulsions.[82] In one study, prophylactic administration of a benzodiazepine reduced the incidence of both convulsions and mortality in mice intoxicated with amide local anesthetics.[83] However, propofol should be avoided in patients with cardiovascular instability because of its cardiovascular depressant properties.[82]

BOX 13-1 Management of Local Anesthetic Systemic Toxicity

- Call for help.
  - Alert obstetrician of possible need for emergency delivery.
- Position patient with left uterine displacement.
- Initial management:
  - Airway management: ventilate with 100% oxygen.
  - Seizure suppression: Benzodiazepines are preferred. (**Avoid** propofol if cardiovascular instability is present.)
  - Alert the nearest facility with cardiopulmonary bypass capability.
- Management of cardiac arrhythmias:
  - Basic and advanced cardiac life support*
  - **Reduce** individual epinephrine doses to < 1 µg/kg.
  - **Avoid** vasopressin, calcium entry-blocking agents, beta-adrenergic blockers, and local anesthetics.
- If clinically unstable or symptoms progress, infuse 20% lipid emulsion.
  - Bolus 1.5 mL/kg (lean body mass) intravenously over 1 min (approximately 100 mL)
  - Continuous intravenous infusion 0.25 mL/kg/min (approximately 18 mL/min)
  - Repeat bolus once or twice for persistent cardiovascular collapse.
  - Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low.
  - Continue infusion for at least 10 min after cardiovascular stability is achieved.
  - Maximum dose: approximately 10 mL/kg over the first 30 min

*Advanced cardiac life support should be modified for pregnancy (see Chapter 55).

Modified from Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med 2012; 37:16-18.

If convulsions should occur, oxygenation and ventilation must be maintained to prevent hypoxemia, hypercarbia, and acidosis.[45,46,82,84] Patency of the airway must be restored. It may be necessary to suction the airway first in some patients. Management should consist of administration of 100% oxygen and tracheal intubation, if required. Convulsions may be terminated quickly with a small dose of a benzodiazepine. Maternal circulation should be supported by maintenance of left uterine displacement and administration of a vasopressor as needed. Because a high plasma concentration of local anesthetic may cause myocardial depression and vasodilation, a mixed alpha- and beta-adrenergic agonist (e.g., ephedrine) may be preferable to a pure alpha-adrenergic agonist. Vasopressin, calcium entry-blocking agents, beta-adrenergic blocking agents, and local anesthetics should be avoided.[82] Fortunately, convulsions induced by intravenous injection of a relatively small dose of local anesthetic are usually self-limited because of rapid redistribution of the drug.

Persistent hypotension and bradycardia may require administration of epinephrine. However, individual epinephrine doses should not exceed 1 µg/kg.[82] In a dog study of bupivacaine toxicity,[85] amrinone was superior to epinephrine in improving cardiac contractility depressed by bupivacaine. Bupivacaine-induced ventricular arrhythmias should not be treated with lidocaine, because local anesthetic toxicity is additive.

Cardiac arrest should be treated according to the American Heart Association's Advanced Cardiac Life Support (ACLS) guidelines, modified for pregnancy (see Chapter 55).[86] The pelvis should be tilted leftward to prevent or relieve aortocaval compression, which renders cardiac massage ineffective. Prompt cesarean delivery of the infant may be necessary to relieve aortocaval compression (venous return) and restore maternal circulation. Prolonged resuscitation may be needed until myocardial washout of bupivacaine has occurred.[52]

Lipid emulsion therapy has been incorporated into guidelines for the treatment of LAST.[82,86] The salutary effect of lipid emulsion therapy may be related to the greater affinity of bupivacaine for the lipid and the dissociation of bupivacaine from the cardiac sodium channels or to the binding of plasma bupivacaine by the lipid fraction in the blood. Alternatively, others have proposed that bupivacaine poisons the normal energy transport mechanisms in the mitochondria and that lipid emulsion bypasses those mechanisms to provide energy substrate.[87] In a suspected case of bupivacaine intoxication in a parturient, manifested by facial and limb twitching and unconsciousness, prophylactic administration of 100 mL of lipid emulsion prevented progression to full cardiovascular collapse.[88] At least one case report has described the successful use of lipid emulsion to treat refractory cardiac arrest due to LAST.[89]

The timing of lipid emulsion administration is controversial.[82] Early treatment may prevent cardiovascular collapse, but only a few patients progress to cardiovascular collapse. The decision to administer lipid emulsion should be based on "clinical severity and rate of progression of LAST."[82] Propofol should *not* be used to treat LAST; its lipid content is inadequate, and the cardiodepressant effects of the drug are detrimental during resuscitation from LAST. A protocol for treatment of LAST, including the administration of lipid emulsion, is presented in Box 13-1.

After maternal recovery, fetal condition should be assessed promptly. In theory, a delay in delivery may allow back-diffusion of local anesthetic from the fetus to the mother, which may be of benefit to the neonate by decreasing neonatal plasma bupivacaine levels. Laboratory studies have demonstrated this phenomenon after the administration of bupivacaine[90] but not lidocaine.[91]

Tissue Toxicity

Neurologic complications of neuraxial anesthesia are rare and result mostly from direct neural trauma, infection, injection of toxic doses of local anesthetic, or the injection of the wrong drug.

In 1980, several cases of prolonged or permanent sensory and motor deficits after subarachnoid injection of a large dose of 2-chloroprocaine intended for epidural block were described.[92] Studies comparing the neurotoxicity of 2-chloroprocaine with that of other local anesthetics have yielded conflicting results, most likely related

to the use of different methodologies and different species.[93,94] It has been suggested that neurotoxicity was caused by sodium metabisulfite, an antioxidant present in the commercial formulation used in the reported cases.[93] The pH of this formulation was between 2.7 and 4.0. In CSF rendered more acidic by 2-chloroprocaine, metabisulfite generates sulfur dioxide, which is lipid soluble and can diffuse into the nerve cells.[95] Intracellular hydration of sulfur dioxide generates sulfurous acid, which may cause profound intracellular acidosis and irreversible damage.

Subsequently, the manufacturer released another preparation of 2-chloroprocaine, which was free of bisulfite but contained ethylenediaminetetraacetic acid (EDTA). This was followed by several reports of severe, incapacitating paralumbar pain and spasm associated with epidural injection of large volumes of drug.[96] The etiology is unclear, although chelation of calcium by disodium EDTA may result in a reduced tissue calcium concentration and local tetany of the affected muscles.

In a 2004 study, Taniguchi et al.[97] suggested that sodium bisulfite was the "scapegoat" for 2-chloroprocaine neurotoxicity. They concluded that neurologic deficits associated with unintentional intrathecal injection of 2-chloroprocaine likely resulted from a direct effect of the 2-chloroprocaine, not the sodium bisulfite.

The current preparation of 2-chloroprocaine that is marketed for *epidural* administration does not contain EDTA or other preservatives. It is packaged in colored vials to reduce the oxidation of the 2-chloroprocaine. Low-dose, preservative-free 2-chloroprocaine (30 to 60 mg) is now being studied as a possible alternative to lidocaine for spinal anesthesia.[98]

Lidocaine has been used for spinal anesthesia for more than 50 years, in thousands upon thousands of patients, with apparent safety. However, **cauda equina syndrome,** sacral nerve root deficits, or transient neurologic toxicity can occur after subarachnoid injection of lidocaine.[99,100] Neurotoxicity of local anesthetics is concentration dependent[101] and is not unique to lidocaine.[102,103] Some investigators have speculated that slow injection of local anesthetic through a spinal microcatheter results in maldistribution and pooling of high concentrations of hyperbaric lidocaine in the cauda equina area, resulting in neurotoxicity and cauda equina syndrome.[99,100]

Milder manifestations of neurotoxicity also may occur. As early as 1954, mild, transient neurologic symptoms were reported after spinal anesthesia with lidocaine.[104] **Transient neurologic symptoms** (TNS) (dysesthesia or low back pain radiating to the buttocks, thighs, and calves) have been observed in surgical patients even after conventional (i.e., single-shot) spinal anesthesia with hyperbaric 5% lidocaine (see Chapter 32).[100] In response to concerns that intrathecal injection of hyperbaric 5% lidocaine might be associated with TNS, in 1994 the FDA Advisory Committee on Anesthetic Drugs recommended that the injected drug concentration be reduced by dilution with an equal volume of either preservative-free saline or CSF. However, Pollock et al.[105] reported that there was no difference in the incidence of TNS when spinal lidocaine 50 mg was diluted to 2%, 1%, or 0.5% solutions before administration and that the overall incidence of TNS did not differ from that of historic controls given 5% lidocaine.

Interestingly, the exposure of frog sciatic nerve to lidocaine results in a progressive, irreversible loss of impulse activity beginning at a concentration of 1%.[101] The investigators in this study noted that "the range of lidocaine that produces such changes in mammalian nerve awaits determination."[101] Meanwhile, it seems prudent to take the following precautions[99,106]:

1. Dilute the commercial 5% lidocaine for intrathecal injection as recommended by the FDA.
2. Administer the lowest possible dose.
3. Avoid the use of hyperbaric lidocaine in clinical conditions (e.g., obesity) or situations (e.g., the lithotomy position) that may be associated with a higher incidence of TNS.

Generally, if pencil-point, side-hole spinal needles are used, it is recommended that the injection port should be directed cephalad. However, an epidemiologic survey did not implicate dose and needle bevel direction as factors that affect the risk for TNS.[106] A meta-analysis of randomized controlled trials comparing spinal lidocaine with other local anesthetics (bupivacaine, prilocaine, procaine, and mepivacaine) found that the relative risk (RR) for development of TNS was higher with lidocaine than with the other local anesthetic agents (RR, 4.35; 95% confidence interval [CI], 1.98 to 9.54).[107] It has not been conclusively proven that TNS are manifestations of neurotoxicity.

Pregnancy may be associated with a reduced risk for TNS. Studies suggest that the incidence of TNS after spinal anesthesia with lidocaine or bupivacaine is equally low (< 3%) in women having cesarean delivery and those undergoing postpartum tubal ligation.[108,109]

Allergic Reactions

True allergy to a local anesthetic is rare.[110] Further, anaphylactic and anaphylactoid reactions may be the result of additives such as methylparaben and metabisulfite.[110,111] Clinical criteria are important in the diagnosis because there is often a delay in obtaining confirmatory laboratory data. The alleged allergy to a local anesthetic can be substantiated in only 15% of patients by a history of urticaria, bronchospasm, facial edema, and/or cardiovascular instability.[112] Adverse reactions (e.g., CNS and cardiovascular symptoms) may mimic hypersensitivity but may not actually be a result of hypersensitivity. These symptoms may be caused by hyperventilation or vasovagal syncope during injection of the drug, sympathetic stimulation (e.g., palpitations, tachycardia) from epinephrine, or edema related to the injection itself (Box 13-2).

Some pregnant women claim to be allergic to "Novocaine" or "the caine" drugs. Obstetricians should refer such patients to an allergist and an anesthesiologist for appropriate evaluation well before the expected date of delivery. In many cases, a carefully obtained history excludes true hypersensitivity. If IgE-mediated hypersensitivity is suspected, patients should be referred to an allergist for further evaluation. Phillips et al.[111] recommended testing with skin prick or intradermal testing

BOX 13-2 Non–IgE-Mediated Reactions to Local Anesthetics

- Psychomotor responses
  - Vasovagal episode
  - Hyperventilation or panic attack
  - Endogenous sympathetic stimulation
- Responses to procedural trauma
- Delayed hypersensitivity reaction
- Non–IgE-mediated reaction to another agent
  - Epinephrine
  - Metabisulfite and other additives
- IgE-mediated reaction to another agent
  - Additives and preservatives
  - Latex
  - Antibiotic

Modified from Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. Br J Anaesth 2012; 108:903-911.

TABLE 13-2 A Protocol for Provocative Dose Testing with Local Anesthetics

Step	Route	Volume (mL)	Dilution*
1	Skin prick		Undiluted
2	Subcutaneous	0.1	Undiluted
3	Subcutaneous	0.5	Undiluted
4	Subcutaneous	1.0	Undiluted
5	Subcutaneous	2.0	Undiluted

*See text for initial dilution suggestions for patients with a history of severe allergy.

From Chandler MJ, Grammer LC, Patterson R. Provocative challenge with local anesthetics in patients with a prior history of reaction. J Allergy Clin Immunol 1987; 79:885.

using appropriate positive (diluted histamine) and negative (normal saline) controls. Intradermal testing is more sensitive but is associated with a false-positive rate of 8% to 15%.[110] If the skin testing is negative, subcutaneous provocative dose testing is a useful method to confirm that the drug is safe to use clinically.[111] Alternatively, if skin testing is positive, the testing sequence (skin testing followed by provocative subcutaneous testing) should be repeated with an alternative agent.

The subcutaneous provocative test can be performed by any physician qualified to manage hypersensitivity reactions. Appropriate emergency equipment and drugs (e.g., epinephrine, H_1- and H_2-receptor antagonists) should be immediately available for resuscitation. Although not mentioned in many protocols, establishing intravenous access before testing seems prudent. The back and the ventral aspects of the forearm are the preferred sites for testing. Areas with abnormal skin coloration or dermographia should be avoided. A history of recent treatment with antihistamines, salicylates, or corticosteroids may alter the test results.[113]

The following protocol has been proposed by Chandler et al.[114] (Table 13-2) and has been used successfully in at least one published case.[115] After a negative needle-prick test, increasing volumes of undiluted local anesthetic (typically 1% concentration) are injected subcutaneously at 15-minute intervals. In patients with an especially strong history of a severe reaction, the series may be preceded by injection of diluted solutions (e.g., a 1:100 solution, followed by a 1:10 solution). A fresh syringe and a 30-gauge needle should be used for each subsequent injection. Additional refinements may consist of the use of both a negative control and a positive control injection. A local anesthetic that is not in the same class as the drug in question should be tested; if an ester is suspected as the offending agent, testing should be performed with an amide agent, and vice versa. If possible, the drug tested should be suitable for local infiltration and for epidural and subarachnoid block.

The test is considered positive if there is a change in the patient's clinical status or if a skin wheal more than 10 mm in diameter, with or without a flare, arises within 10 minutes of injection and persists for at least 30 minutes.[113] If provocative dose testing is completed without a reaction, the local anesthetic used and the final dose given should be recorded; the patient (and the referring physician) should be informed that her risk for an adverse reaction to subsequent administration of that drug and dose is no greater than that for the general population.[114,115]

Management of an Allergic Reaction. Pharmacologic therapy of a severe allergic reaction involves (1) inhibition of mediator synthesis and release, (2) reversal of the effects of these mediators on target organs, and (3) prevention of the recruitment of other inflammatory processes. In general, catecholamines, phosphodiesterase inhibitors, antihistamines, and corticosteroids have been used for this purpose (Box 13-3).[116] Higher doses of catecholamines may be required in a patient who has received sympathetic blockade. In addition, pregnancy itself decreases responsiveness to catecholamines.[117] Despite its potential adverse effect on uterine blood flow, epinephrine remains the cornerstone of therapy for allergic reactions. In one reported case, a mother was treated successfully with epinephrine 100 µg without any apparent adverse effects on the newborn.[118]

Effects on the Uterus and Placenta

Uterine Blood Flow

The association of paracervical block anesthesia with fetal bradycardia has been attributed to the high concentration of local anesthetic deposited in the vicinity of the uterine arteries (see Chapter 24). Human uterine artery segments obtained at the time of cesarean hysterectomy constrict when exposed to high concentrations of lidocaine,[119] mepivacaine,[119] or bupivacaine.[120]

These findings also have been confirmed in laboratory animals. Fishburne et al.[121] observed a dose-related decrease in uterine blood flow during uterine arterial infusion of 2-chloroprocaine, lidocaine, or bupivacaine in gravid ewes. A 25% reduction in uterine blood flow occurred at the following calculated plasma

BOX 13-3 Management of Anaphylaxis

Initial Therapy

- Stop administration of antigen.
- Maintain airway with 100% oxygen.
- Discontinue all anesthetic agents.
- Start intravascular volume expansion: 2-4 L of crystalloid/colloid (25-50 mL/kg) to treat hypotension.
- Give epinephrine:
  - 5-10 μg intravenously for treatment of hypotension; titrate as needed
  - 0.5-1.0 mg intravenously for treatment of cardiovascular collapse

Secondary Treatments

- Catecholamine infusions (starting doses):
  - Epinephrine: 4-8 μg/min (0.05-0.1 μg/kg/min)
  - Norepinephrine: 4-8 μg/min (0.05-0.1 μg/kg/min)
  - Isoproterenol: 0.05-0.1 μg/min
- Antihistamines: 0.5-1.0 mg/kg of diphenhydramine
- Corticosteroids: 0.25-1.0 g of hydrocortisone; alternatively, 1-2 g (25 mg/kg) of methylprednisolone
- Bicarbonate: 0.5-1.0 mEq/kg in patients with persistent hypotension or acidosis
- Airway evaluation (before extubation)

From Levy JH. Anaphylactic Reactions in Anesthesia and Intensive Care. Stoneham, MA, Butterworth-Heinemann, 1992:162.

concentrations of local anesthetic: bupivacaine, 7 μg/mL; 2-chloroprocaine, 11.5 μg/mL; and lidocaine, 19.5 μg/mL. However, when plasma local anesthetic concentrations mimic those that occur in ordinary clinical practice, local anesthetics have no adverse effect on uterine blood flow.[122-124] In pregnant ewes, uterine blood flow remained unchanged during an intravenous infusion of lidocaine or bupivacaine that resulted in plasma concentrations of 0.81 to 4.60 and 1.5 to 2.0 μg/mL, respectively.[122,124] Similarly, intravenous injection of 2-chloroprocaine, 0.67 and 1.34 mg/kg, did not reduce uterine blood flow velocity in pregnant guinea pigs.[123]

Pregnancy may enhance uterine vascular reactivity to local anesthetic agents. Isolated human uterine artery segments obtained from term parturients constrict at a lower lidocaine concentration than uterine artery segments from nonpregnant patients.[119,125] Uterine artery sensitivity to local anesthetics increases as early as the second trimester of pregnancy and may be related to an increase in estrogen levels.[119,121] However, these studies were performed before the recognition of the importance of intact vascular endothelium in the *in vitro* assessment of vascular tone.

The exact mechanism by which high concentrations of local anesthetics cause uterine artery vasoconstriction (while causing dilation in other vascular beds) is unclear. This vasoconstriction may result from modulation of calcium-channel regulation because verapamil and nifedipine ablate the response.[125] Alternatively, local anesthetics may affect cyclic nucleotides and alter the ionic content and contractility of uterine vascular smooth muscle.[126] Clinical experience with the use of local anesthetics supports the view that clinical concentrations of these drugs do not adversely affect the uterine vasculature (see Chapter 3).[127,128]

All local anesthetics can reduce uterine blood flow at plasma concentrations that greatly exceed those occurring during the routine practice of obstetric anesthesia.[121] There has been an added concern that the levorotary isomers of local anesthetics, which produce vasoconstriction at clinical doses,[129] may reduce uteroplacental perfusion and adversely affect fetal well-being. It is reassuring to note that ropivacaine, even at plasma concentrations that are almost two times greater than would be expected to occur during clinical use, does not reduce uterine blood flow or affect fetal heart rate (FHR), blood pressure, or acid-base measurements in pregnant sheep.[122] In humans, Doppler velocimetry studies have shown that ropivacaine has little effect on the uteroplacental or fetal circulation when it is administered to provide epidural anesthesia for cesarean delivery.[127] Similarly, clinically relevant plasma concentrations of levobupivacaine had no adverse effect on uterine blood flow.[122]

Umbilical Blood Flow

Fetal well-being also depends on the adequacy of fetal perfusion of the placenta. The regulatory mechanisms that control flow through the umbilical vessels are poorly understood. Lidocaine does not affect spiral strips obtained from human umbilical artery segments at concentrations up to 5 μg/mL, but it produces relaxation in concentrations from 30 to 900 μg/mL.[130] Bupivacaine also does not constrict umbilical artery segments at clinically relevant concentrations of 0.3 and 1 μg/mL.[130] At higher concentrations, the effect of bupivacaine appears to be biphasic. Constriction occurs at concentrations of 5 to 25 μg/mL, and relaxation occurs at concentrations greater than 125 μg/mL.[130,131] Hypercarbia but not hypoxemia lessens the contractile response of umbilical vessels to bupivacaine *in vitro*.[132]

Decreases in umbilical blood flow of as much as 43% accompany intravenous administration of lidocaine 4 mg/kg in pregnant sheep.[133] However, plasma concentrations of the drug were higher than would be expected with clinical use, and all ewes exhibited signs of CNS toxicity, which may reduce umbilical blood flow.

Advances in noninvasive Doppler imaging have facilitated clinical assessment of umbilical cord blood flow velocity. The ratio of the systolic (S) peak to the diastolic (D) trough of the umbilical artery waveform is used as a measure of vascular resistance. The S/D ratio in the umbilical artery decreases during normal pregnancy, and high ratios usually are associated with fetal compromise (see Chapter 6). Local anesthetics administered for epidural anesthesia do not adversely affect the umbilical artery S/D ratio.[134,135] In fact, labor epidural analgesia with 1.5% lidocaine or 2% 2-chloroprocaine resulted in a decrease in the S/D ratio.[134,135] This favorable change may have resulted from pain relief. Other investigators have noted no appreciable change or a slight decrease in the S/D ratio after the epidural administration of amide local anesthetics for elective cesarean delivery.[127,128,136]

Uterine Tone and Contractility

Changes in uterine tone and contractility may affect uteroplacental perfusion. Local anesthetics exert direct effects on uterine smooth muscle. One study reported that exposure to high concentrations of local anesthetic *in vitro* led to contraction of human myometrial segments obtained at the time of cesarean delivery.[137] These findings have been corroborated in laboratory animals.[138] Further, Belitzky et al.[139] observed that direct intramyometrial injection of 1% procaine resulted in uterine hyperstimulation and fetal compromise in pregnant women. In all of these reports, the myometrium was exposed to higher than normal concentrations of the drug. In other studies, however, intravenous infusion of lidocaine or bupivacaine that resulted in clinically relevant plasma concentrations did not affect uterine tone or uterine activity in pregnant ewes.[122,124] In a recent study using electrohysterogram monitoring, levobupivacaine caused less uterine muscle relaxation after intramyometrial injection in rats than did bupivacaine.[140]

Drug Interactions with 2-Chloroprocaine and Lidocaine

Epidural 2-chloroprocaine may affect the efficacy of other drugs administered in the neuraxis. Previous administration of 2-chloroprocaine (even a test dose) may reduce the quality and duration of analgesia produced by subsequent epidural injection of morphine or fentanyl.[141,142] Several hypotheses have been proposed for this antagonism. The low pH of the 2-chloroprocaine solution may result in acidification of the epidural space and thus may favor formation of the poorly diffusible, charged form of the opioid. Second, it has been suggested that 2-chloroprocaine (or its metabolite, chloroaminobenzoic acid) may act as a specific μ-opioid receptor antagonist because a κ-opioid receptor agonist (e.g., butorphanol) is not antagonized by 2-chloroprocaine.[141] However, using an *in vitro* hippocampal slice model, Coda et al.[143] concluded that 2-chloroprocaine opioid antagonism did not appear to act through a μ-opioid receptor. Third, a "window" may be caused by the rapid regression of 2-chloroprocaine before the onset of analgesia with epidural morphine.[144] This mechanism is supported by the results of a study[145] in which women who received spinal bupivacaine anesthesia for cesarean delivery were randomly assigned to receive either epidural morphine with 2-chloroprocaine or epidural morphine with saline-placebo. There was no difference in post–cesarean delivery epidural morphine analgesia between the two groups; presumably the spinal bupivacaine provided adequate analgesia until the onset of epidural morphine analgesia.[145]

2-Chloroprocaine also reduces the subsequent efficacy of bupivacaine.[146] Corke et al.[147] suggested that chloroaminobenzoic acid is responsible for this effect. Administration of buffered 2-chloroprocaine does not prevent the antagonism of epidural bupivacaine.[148]

The use of neuraxial opioids alone or in combination with local anesthetics has become ubiquitous in obstetric anesthesia for enhancing analgesia during labor or for providing effective pain relief after cesarean delivery. Lidocaine is a frequently used drug for epidural anesthesia during cesarean delivery. In a recent study,[149] epidural administration of 20 to 35 mL of epidural 2% lidocaine with fentanyl 1 hour before administration of extended-release epidural morphine increased the peak plasma concentration(C_{max}) of morphine when compared with similar women who received a combined spinal-epidural (CSE) technique (intrathecal bupivacaine and fentanyl) with no epidural medication for cesarean delivery (see Chapter 28).

Potency of Bupivacaine, Ropivacaine, and Levobupivacaine

The levorotary compounds ropivacaine and levobupivacaine were developed because of the concerns about the safety of high doses of bupivacaine. Many studies have addressed the question of relative potency among the three drugs. Ropivacaine is approximately 10 times less lipid soluble (*N*-heptane/buffer) than bupivacaine, a difference that is important for two reasons.[2] First, ropivacaine may penetrate more slowly into the large, heavily myelinated motor neurons, resulting in less motor block than occurs with bupivacaine. Second, the issue raises questions as to whether ropivacaine is equipotent to bupivacaine. Indeed, a higher dose of ropivacaine is required to produce a sensory and motor block comparable with that produced by bupivacaine after spinal injection.[150,151] Similarly, the EC_{50} (the local anesthetic concentration at which 50% of women have pain relief, also known as the minimum local anesthetic concentration [MLAC]) of epidural ropivacaine is almost twice as great as that of epidural bupivacaine in laboring women.[59] Critics of the use of EC_{50} data to compare potency argue that it provides no information on the shape and slope of the dose-effect relationship, which can vary with drug concentration, and further, that it provides no information on the effective clinical dose (ED_{95} [effective dose in 95% of cases]).[152]

Studies of the EC_{50} of epidural levobupivacaine are conflicting; one study found that levobupivacaine was essentially equipotent to bupivacaine,[70] whereas others suggest that ropivacaine and levobupivacaine have similar potency.[153,154] Levobupivacaine may have a greater motor-sparing effect than bupivacaine when given for the initial intrathecal injection. For example, in one study, none of 37 women who received intrathecal levobupivacaine 2.5 mg (with sufentanil and epinephrine) had evidence of motor block.[155] In contrast, 13 of 38 (34%) women given intrathecal bupivacaine 2.5 mg demonstrated a Bromage grade 1 motor block.

In obstetric anesthesia practice, the clinical effects of epidural levobupivacaine and ropivacaine are indistinguishable from those of epidural bupivacaine for labor analgesia.[156] The choice of bupivacaine, levobupivacaine, or ropivacaine does not affect the method of delivery or neonatal condition.[156] For cesarean delivery, epidural levobupivacaine 0.5% is virtually identical to epidural bupivacaine 0.5%.[157] The levorotary isomers (ropivacaine and levobupivacaine) may provide a greater margin of

safety when large volumes of a concentrated solution of local anesthetic are required (e.g., epidural anesthesia for cesarean delivery). However, there may be little advantage to using levobupivacaine or ropivacaine when dilute solutions are used for epidural labor analgesia or when a small dose is used for spinal anesthesia.

Placental Transfer

Most drugs, including local anesthetics, cross the placenta. The factors that influence the placental transfer of a drug include (1) the physicochemical characteristics of the drug, (2) the concentration of free drug in the maternal blood, (3) the permeability of the placenta, and (4) the hemodynamic events occurring within the fetal-maternal unit.

Local anesthetics cross placental membranes by a process of simple (i.e., passive) diffusion. The rate of transfer (not necessarily the amount) of a particular drug is described by the Fick equation, as follows:

$$\frac{Q}{t} = \frac{K \times A(C_m - C_f)}{D}$$

where Q/t is the rate of diffusion; K is the diffusion constant for the drug; A is the surface area available for transfer; C_m is free drug concentration in the maternal blood; C_f is the free drug concentration in the fetal blood; and D is the thickness of the trophoblastic epithelium. In general, K is affected by molecular size, lipid solubility, and the degree of ionization.

Molecular Size

Compounds with a molecular weight of less than 500 Da cross the placenta easily, whereas drugs like digoxin, which have a molecular weight higher than 500 Da, have a slower rate of diffusion.[158] Molecular weights of local anesthetics range from 234 to 288 Da (see Table 13-1). These small differences in molecular weight should not affect the rate of placental transfer because the diffusion constant (K) is inversely proportional to the square root of the molecular weight.[159]

Ionization and Lipid Solubility

Local anesthetics are weak bases; they have a relatively low degree of ionization and considerable lipid solubility at physiologic pH. The basic un-ionized local anesthetic molecule is more lipid soluble than the ionized moiety and determines placental transfer in a protein-free perfusate.[160]

The relationship between pH and pK_B may affect drug accumulation in the fetus. For the amide local anesthetics, pK_B values are close enough to physiologic pH that changes in fetal pH may alter the balance between ionized and un-ionized drug. In the acidotic fetus, a greater proportion of drug in the ionized form results in a larger total amount of local anesthetic in fetal plasma, because of "ion trapping" (Figure 13-4).[161-163] Elimination of lidocaine from fetal blood is slower in the asphyxiated fetus than in the nonasphyxiated fetus.[133] Accumulation of lidocaine may be greater in fetal tissues, where the pH is even lower than that in fetal blood.[163]

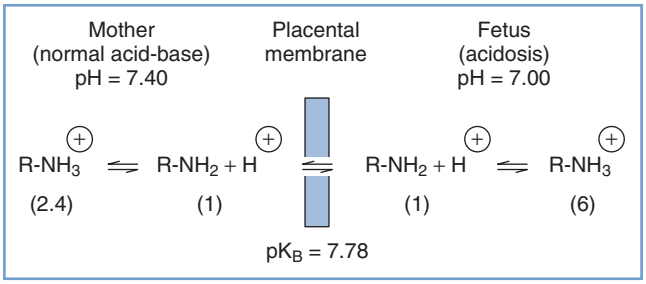

FIGURE 13-4 ■ "Ion trapping" of a local anesthetic. The numbers in parentheses represent relative numbers of molecules. (From the American College of Obstetricians and Gynecologists. Obstet Gynecol 1976; 48:29.)

Protein Binding

Perhaps most confusing and least understood are the effects of protein binding on placental transfer. Amide local anesthetics are bound predominantly to AAG and to a much lesser extent to albumin.[20] The extent of protein binding varies among the local anesthetic agents (see Table 13-1). For a given local anesthetic, the proportion of free drug increases as blood concentration increases because of the saturation of binding sites. Binding of local anesthetics in the fetal plasma is approximately half that in the mother.[90,91]

The fetal-to-maternal (F/M) blood concentration ratios of amide local anesthetic agents are listed in Table 13-1. The lower F/M blood concentration ratios of highly protein-bound drugs (e.g., bupivacaine) have been attributed to their more restricted placental transfer compared with less protein-bound drugs (e.g., lidocaine). Indeed, the rate of bupivacaine transfer across rabbit placenta perfused *in situ* is lower than that of lidocaine transfer.[164,165] Some investigators have suggested that protein binding in the maternal plasma should not affect the diffusion of drugs across the placenta because the dissociation from plasma proteins is essentially instantaneous.[159,166] In more recent studies, the relatively low umbilical vein–to–maternal vein blood concentration ratio for bupivacaine has been attributed to differences in protein binding between maternal plasma and fetal plasma (Figure 13-5).[90,91,167,168] Let us assume that the total concentration of lidocaine or bupivacaine in the maternal plasma is 2 mg/L. Lidocaine and bupivacaine are approximately 50% and 90% bound to maternal plasma proteins, respectively. Thus, the free concentrations of drug available for placental transfer are 1.0 and 0.2 mg/L, respectively. At equilibrium, the concentration of free drug is equal on the two sides of the placenta. In the fetus, however, lidocaine and bupivacaine are approximately 25% and 50% bound to fetal plasma proteins, respectively. Thus, the total lidocaine concentration in fetal plasma is 1.33 mg/L, resulting in an F/M ratio of 0.67; for bupivacaine, the corresponding values are 0.4 mg/L and 0.2.

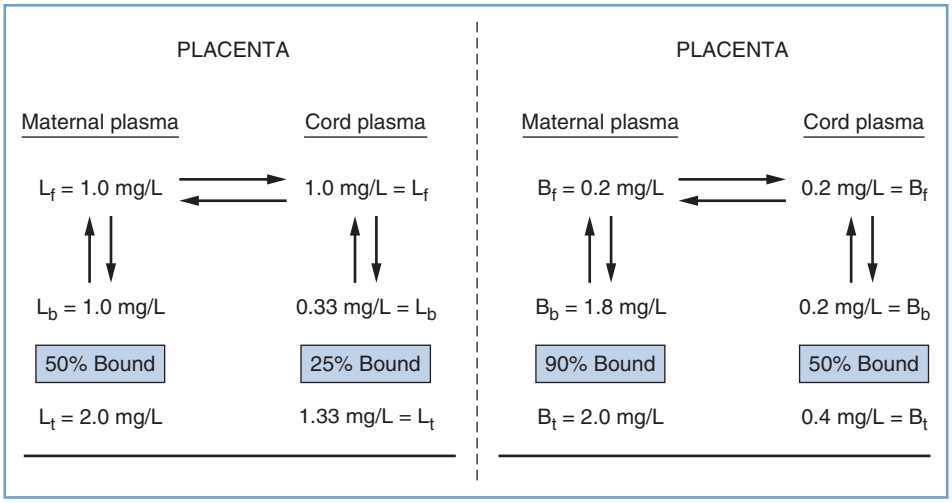

FIGURE 13-5 ■ Demonstration of how distribution of local anesthetics across the placenta may be predicted from differences in drug protein binding in maternal and fetal plasma. *Left,* lidocaine (*L*); *f, b, t,* free, bound, and total drug concentrations, respectively. *Right,* bupivacaine (*B*). Lidocaine umbilical cord–to–maternal plasma ratio (F/M) = 0.67; bupivacaine F/M = 0.20. (From Tucker GT, Mather LE. Properties, absorption, and disposition of local anesthetic agents. In Cousins MJ, Bridenbaugh PO, editors. Neural Blockade in Clinical Anesthesia and Management of Pain. 2nd edition. Philadelphia, Lippincott, 1988:95.)

Substantial accumulation of bupivacaine occurred in human fetuses whose mothers received the drug for epidural anesthesia.[25] After delivery, measurable plasma and urine concentrations persisted for as long as 3 days.[25] *In vitro* studies using a perfused human placental model have found that the placental transfer of ropivacaine is similar to that of bupivacaine.[169] Intravenous infusion of ropivacaine or bupivacaine to pregnant sheep results in steady-state maternal plasma concentrations of 1.5 to 1.6 μg/mL and fetal concentrations of approximately 0.28 μg/mL.[122] Tissue concentrations of ropivacaine in fetal heart, brain, liver, lung, kidneys, and adrenal glands were similar to those of bupivacaine.[122] Datta et al.[32] noted that the free fraction of ropivacaine at delivery was approximately twice that of bupivacaine in neonates whose mothers received the drug for epidural anesthesia during labor or cesarean delivery.

Maternal Blood Concentration of Drug

The maternal blood concentration of local anesthetic is determined by (1) the dose, (2) the site of administration, (3) metabolism and excretion, and (4) the effects of adjuvants such as epinephrine (see later discussion). For a given local anesthetic, the maternal blood concentration determines fetal drug exposure and is the only variable of the Fick equation that may be influenced by the clinician.

Dose. In general, higher doses result in higher maternal and fetal blood concentrations. For example, Kuhnert et al.[18] found that doubling the mean (± SD) dose of epidural lidocaine from 300 ± 195 mg to 595 ± 127 mg almost doubled the concentration in umbilical cord blood. The elimination half-life of amide local anesthetics is relatively long; thus, repeated epidural injection or continuous infusion of the drug may lead to accumulation in the maternal plasma. This statement does not apply to 2-chloroprocaine, however, which is rapidly hydrolyzed by pseudocholinesterase.[12]

Site of Administration. The rates of absorption and peak plasma concentrations depend on the vascularity at the site of administration. The peak plasma concentration of lidocaine is achieved within 9 to 10 minutes after paracervical block. In contrast, absorption from the lumbar epidural space, which is less vascular, occurs at a slower rate; the peak plasma concentration is not achieved until 25 to 40 minutes after administration.[18,170] Injection of local anesthetic into the caudal rather than the lumbar epidural space may result in higher blood levels because of the need for a higher drug volume to provide comparable anesthesia to that provided by lumbar epidural injection.[171]

In the past, it was thought that subarachnoid administration of a local anesthetic resulted in less systemic absorption than epidural administration. However, peak blood concentrations of lidocaine have been reported to be similar after subarachnoid and epidural administration.[172] In another study, subarachnoid administration of lidocaine 75 mg for cesarean delivery resulted in low but measurable fetal plasma concentrations of the drug.[17]

Placenta

Maturation of the placenta may affect the rate of drug transfer. In pregnant mice, diazepam and its metabolites cross the placenta more rapidly in late pregnancy.[173] Uptake and metabolism of drugs by the placenta would be expected to reduce transfer to the fetus. However, placental drug uptake of local anesthetics is limited, and it is unlikely that this organ metabolizes the amide local anesthetic agents.[174] This may not be true for the ester local anesthetics. For example, cocaine is biotransformed when it is incubated with human

placental microsomal fraction, presumably because of cholinesterase activity within the placenta.[175] Placental metabolism of para-aminobenzoic acid also has been demonstrated.[176]

Teratogenicity

The teratogenicity of anesthetics is not an issue during parturition, but local anesthetics often are used for procedures during the first trimester of pregnancy. *In vitro* studies have suggested that local anesthetics may have some adverse developmental effects. Even at low concentrations, these agents have caused reversible reduction of cell division in tissue culture.[177-182] However, structural anomalies have not been observed in intact animals.[183-185] Mid-pregnancy administration of lidocaine or mepivacaine in rats has been associated with behavioral changes in the offspring.[186,187]

Extrapolation of laboratory findings to humans is tenuous for several reasons. First, a drug may be teratogenic in one species but not in others. Second, a 1-hour drug exposure in a pregnant rat (with a gestation of 21 days) is excessive and not analogous to several hours of clinical anesthesia during human pregnancy. Third, the doses of local anesthetics used in animal studies greatly exceed those administered for clinical anesthesia. Indeed, a large, multicenter study demonstrated that the risk for congenital anomalies in humans was not increased by the administration of benzocaine, procaine, tetracaine, or lidocaine during early pregnancy.[188] However, a twofold increase in the incidence of congenital anomalies was noted in infants whose mothers had received mepivacaine. The small number of patients who received mepivacaine in this study (n = 82) and the fact that no adverse effects occurred with the use of other amide agents have raised doubts about the validity of this observation.[189]

Fetal and Neonatal Effects

Pharmacokinetics

Local anesthetics, once transferred across the placenta, are distributed in the fetus. Factors that influence tissue uptake of the drug include (1) fetal plasma protein binding, (2) lipid solubility, (3) the degree of ionization of the drug, and (4) hemodynamic changes that affect the distribution of fetal cardiac output. The fetal plasma protein-binding capacity of local anesthetics is approximately 50% that of maternal plasma.[90,91,190] Thus, at any given total plasma concentration of local anesthetic, there is greater availability of free drug in the fetus than in the mother.[90,91,190-192] Studies have examined the distribution of lidocaine in fetal tissues after an intravenous injection of the drug to animals.[19,193] The higher concentration of lidocaine in the liver, myocardium, and brain (compared with other fetal tissues) reflects rapid distribution of the drug to highly perfused tissues. The only organ in which lidocaine concentrations in the fetus have been found to exceed those in the mother is the liver. This finding is not surprising, given the high lipid content of the fetal liver and the fact that it receives most of the blood returning from the placenta by means of the umbilical vein.[193] Fetal acidosis and hypoxemia result in circulatory adaptations that increase blood flow to vital organs (e.g., brain, heart, adrenal glands).[194] The concentration of lidocaine in these organs is higher in asphyxiated fetuses than in healthy fetuses.[163,194]

Any drug that reaches the fetus undergoes metabolism and excretion. The term newborn has the hepatic enzymes necessary to metabolize local anesthetics.[17,18,195-197] Nonetheless, the elimination half-life of these drugs is longer in the neonate than in the adult.[196,197] The use of mepivacaine in obstetric epidural analgesia fell into disfavor after a report indicating that the elimination half-life of the drug in the neonate was approximately 9 hours, or three times as long as the neonatal half-life for lidocaine.[198] It is ironic that it was later discovered that the neonatal elimination half-life for bupivacaine may be as long as 14 hours.[199]

Morishima et al.[197] compared the pharmacokinetics of lidocaine among adult ewes and fetal and neonatal lambs. The metabolic (hepatic) clearance in the lambs was similar to that in adults, and renal clearance was greater than that in adults. Nonetheless, the elimination half-life was more prolonged in the lambs. This latter finding has been attributed to a greater volume of distribution in the lamb. Thus, at any given time, a smaller fraction of lidocaine accumulated in the body is available for clearance by hepatic metabolism. The greater renal clearance noted in neonates is a result of decreased protein binding, which increases the proportion of drug available to the kidneys for excretion.

The elimination half-life of local anesthetics in the fetus is similar to that in the adult because, unlike the newborn, the fetus can excrete drug across the placenta back to the mother.[90,197] With bupivacaine, this transfer may occur even though the total plasma drug concentration in the mother may exceed that in the fetus.[90]

Systemic Toxicity

In general, the neonate is more sensitive than the adult to the depressant effects of drugs. However, the seizure threshold for local anesthetics in the neonate appears to be similar to that in the adult.[200]

Morishima et al.[201] compared the relative CNS toxicity and cardiovascular toxicity of lidocaine in adult ewes and fetal and neonatal lambs. Greater doses (when calculated on a milligram-per-kilogram basis) were required to elicit toxic manifestations in the fetus and neonatal lamb than in the adult. However, the plasma concentrations of the drug associated with toxic manifestations were similar in the three groups of animals. The greater dose tolerated by fetuses than by neonates and adults was attributed to placental clearance of drug back to the mother and better maintenance of blood gas tensions during convulsions. In the neonate, a large volume of distribution is most likely responsible for the high doses of local anesthetic required to have toxic effects.

Studies of bupivacaine cardiotoxicity are inconsistent. *In vitro*, the sinoatrial node of neonatal guinea pigs was found to be more sensitive than that of adults to the cardiodepressant effect of bupivacaine.[202] In contrast, 2-day-old piglets demonstrated greater resistance than

older animals to the arrhythmogenic and CNS effects of bupivacaine.[203]

Fetal Heart Rate

Changes in FHR after administration of local anesthetics are most often related to indirect effects such as maternal hypotension and uterine tachysystole (see Chapter 23). Local anesthetics probably have little direct effect on FHR, except perhaps after paracervical block. Rather, labor itself may be the single most important factor that alters FHR patterns.[204] Transient changes in FHR variability and an increase in the incidence of periodic decelerations have been observed during administration of neuraxial analgesia in laboring women.[205,206] In contrast, in the absence of labor, FHR patterns are not affected even by the larger doses of local anesthetics required during administration of epidural anesthesia for cesarean delivery.[204] The FHR changes noted in laboring women were transient and did not affect the condition of their newborns.[205,206] In a recent study, investigators found no significant difference in the number or type of fetal electrocardiographic ST-segment changes (ST-waveform analysis [STAN] events) in women with a high-risk singleton gestation who received epidural analgesia for labor when compared with a control group of women who did not receive epidural analgesia.[207]

Neurobehavioral Tests

Neurobehavioral tests have been developed to detect subtle changes in organized behavior in the newborn. These tests include the Brazelton Neonatal Behavioral Assessment Scale (NBAS), the Early Neonatal Neurobehavioral Scale (ENNS), and the Neurologic and Adaptive Capacity Score (NACS). All the tests are subjective and complex and lack specificity.

Other perinatal factors appear to have a more important effect on neonatal test performance than the choice of local anesthetic.[208] Indeed, neurobehavioral tests have been shown not to be a reliable measure of drug effect in the newborn.[209]

Preterm Fetus and Newborn

It has become axiomatic that the preterm infant is more vulnerable than the term infant to the effects of analgesic and anesthetic drugs. Causes of enhanced drug sensitivity in the preterm newborn that have been postulated are as follows: (1) less protein is available for drug binding, (2) higher levels of bilirubin are present and may compete with the drug for protein binding, (3) greater access of the drug to the CNS occurs because of a poorly developed blood-brain barrier, (4) the preterm infant has greater total body water and less fat content, and (5) the preterm infant has a diminished ability to metabolize and excrete drugs. Unfortunately, few systematic studies have determined the maternal and fetal pharmacokinetics and pharmacodynamics of drugs throughout gestation; nevertheless, these deficiencies of the preterm infant may not be as serious as we have been led to believe. Although the plasma albumin and AAG concentrations are lower in the preterm fetus, these factors primarily affect drugs that are highly bound to these proteins. Most local anesthetics, however, exhibit only low to moderate degrees of binding in fetal plasma.[90,91]

The placenta efficiently eliminates fetal bilirubin. Thus, the hyperbilirubinemia of prematurity normally occurs in the postpartum period. Bupivacaine has been implicated as a possible cause of neonatal jaundice.[210,211] High affinity of the drug for fetal erythrocyte membranes may lead to a decrease in filterability and deformability, which may render red blood cells more prone to hemolysis.[211] However, increased bilirubin production has not been demonstrated in newborns whose mothers received bupivacaine for epidural anesthesia during labor and cesarean delivery.[212,213]

Greater total body water in the preterm fetus results in a larger volume of distribution for drugs. Thus, to achieve equal blood concentrations, the immature fetus must receive a greater amount of drug transplacentally than the mature fetus.

The diminished ability to metabolize or excrete drugs associated with prematurity is certainly not a universal phenomenon. One study of the pharmacokinetics of lidocaine in preterm newborns noted that plasma clearance was similar to that in adults.[196]

During anesthesia for preterm labor, concerns about drug effects on the newborn are far less important than the prevention of asphyxia and trauma to the fetus. Indeed, healthy preterm fetal lambs tolerated clinically relevant plasma concentrations of lidocaine (e.g., approximately 1.5 μg/mL) as well as mature ones.[19,214]

Asphyxia

Circulatory adaptations important for fetal survival during asphyxia result in increased blood flow and oxygen delivery to vital organs (e.g., heart, brain, adrenal glands).[194] Little information exists about the effects of local anesthetics on these fetal responses. Adaptation to asphyxia was unaffected in mature fetal lambs exposed to lidocaine.[194] In contrast, lidocaine adversely affected asphyxiated preterm fetal lambs, which experienced a further deterioration of acid-base status and a reduction in cardiac output and blood flow to the brain and heart (Figure 13-6).[215] Also in asphyxiated preterm fetal lambs, exposure to bupivacaine reduced blood flow to vital organs; however, FHR, blood pressure, and acid-base measurements did not change.[216]

After performing an *in vitro* study using perfused human placentas, Johnson et al.[217] suggested that bupivacaine might be preferable to lidocaine in the presence of fetal acidosis because the greater maternal protein binding of bupivacaine may limit its placental transfer. However, this methodology does not consider the potential for greater fetal tissue uptake of bupivacaine (than of lidocaine) because bupivacaine is more lipid soluble and more protein bound than lidocaine.

In 1997, Santos et al.[216] reported that the effects of bupivacaine appeared less severe than those of lidocaine in asphyxiated preterm fetal lambs. However, the lidocaine data were generated in a separate experiment reported in 1989.[215] There are inherent limitations in a

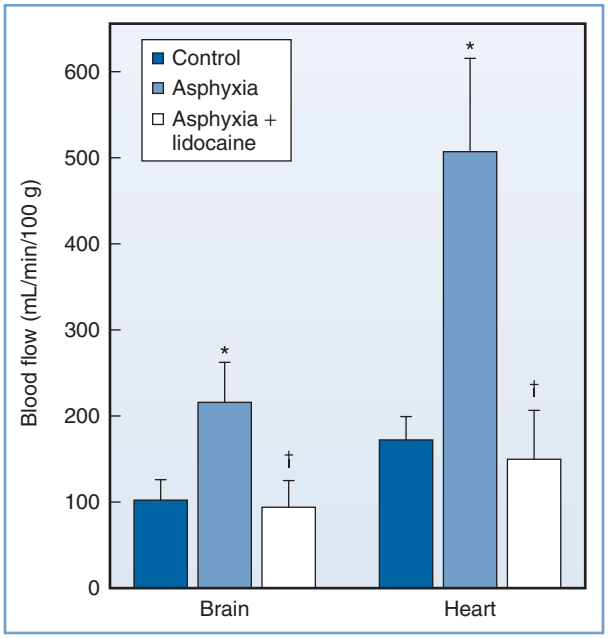

FIGURE 13-6 ■ Blood flow to the brain and heart in the preterm fetal lamb before and during asphyxia and during exposure to lidocaine while asphyxiated (mean ± SEM). *Significantly different from control. †Significantly different from asphyxia. (Modified from Morishima HO, Pedersen H, Santos AC, et al. Adverse effects of maternally administered lidocaine on the asphyxiated preterm fetal lamb. Anesthesiology 1989; 71:110-5.)

historical comparison of two studies performed 8 years apart. Further, it is unclear whether these findings are applicable to humans because both lidocaine and bupivacaine have enjoyed a long history of safe use in obstetric anesthesia practice; prospective clinical studies are required before one drug can be recommended over the other in the setting of fetal asphyxia.

OPIOIDS

Neuraxial opioid administration is unique in that it produces analgesia without loss of sensation or proprioception. Opioids are often co-administered with local anesthetic agents during intrapartum administration of neuraxial analgesia and anesthesia.

The term *opioid* refers to a series of compounds that are related to opium. These compounds may be classified as follows: (1) naturally occurring (e.g., morphine), (2) semisynthetic compounds (e.g., dihydromorphone), and (3) synthetic compounds (e.g., fentanyl) (Box 13-4). The only three naturally occurring opioids of clinical significance are morphine, codeine, and papaverine. These substances can be obtained from the poppy plant known botanically as *Papaver somniferum.* Development of synthetic drugs with morphine-like properties has led to development of the broad term *opioid.* These substances bind to several subpopulations of opioid receptors with resulting morphine-like effects. More than 30 years ago, identification of a dense concentration of opioid receptors in the dorsal horn of the spinal cord led to the use

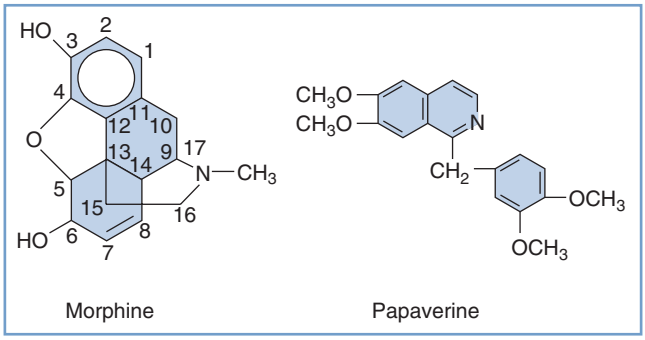

FIGURE 13-7 ■ Naturally occurring opioids: phenanthrenes (e.g., morphine) and benzylisoquinolines (e.g., papaverine).

BOX 13-4 Classification of Opioid Compounds

Naturally Occurring Compounds
- Morphine
- Codeine
- Papaverine
- Thebaine

Semisynthetic Compounds
- Heroin (diamorphine)
- Dihydromorphone
- Thebaine derivatives (e.g., etorphine, buprenorphine)

Synthetic Compounds
- Morphinan series (e.g., levorphanol, butorphanol)
- Diphenylpropylamine series (e.g., methadone)
- Benzomorphan series (e.g., pentazocine)
- Phenylpiperidine series (e.g., meperidine, fentanyl, sufentanil, alfentanil, remifentanil)

of neuraxial opioids as important adjuncts in obstetric anesthesia.

Molecular Structure

Naturally occurring opioids of significance can be divided into two distinct chemical classes, phenanthrenes (e.g., morphine) and benzylisoquinolines (e.g., papaverine) (Figure 13-7). The phenanthrenes are five-ring structures, and the benzylisoquinolines are three-ring structures. The semisynthetic opioids are morphine derivatives that have undergone relatively simple modification of the morphine molecule. For example, substitution of an ester for the hydroxyl group on carbon 6 of morphine results in hydromorphone (Figure 13-8). Synthetic opioids can be classified into the following four groups: (1) morphinan derivatives (e.g., levorphanol), (2) diphenyl or methadone derivatives (e.g., methadone, D-propoxyphene), (3) benzomorphan derivatives (phenazocine, pentazocine), and (4) phenylpiperidines (e.g., meperidine, fentanyl, sufentanil).

Structurally, opioids are complex three-dimensional compounds that often exist as two optical isomers (e.g., morphine).[218] Usually the levorotary isomer is the only

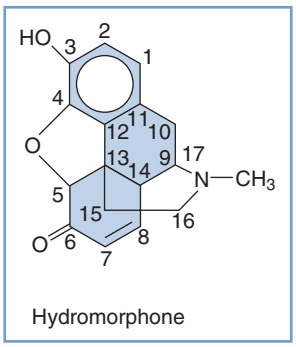

FIGURE 13-8 ■ Semisynthetic opioids are morphine derivatives. For example, substitution of an ester for the hydroxyl group on carbon 6 of morphine results in hydromorphone.

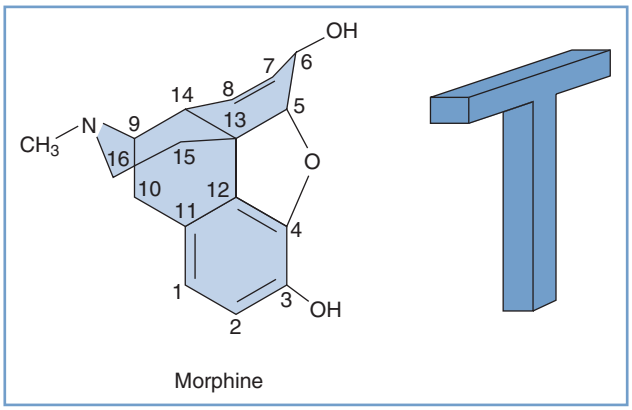

FIGURE 13-9 ■ The T-shaped molecule of morphine.

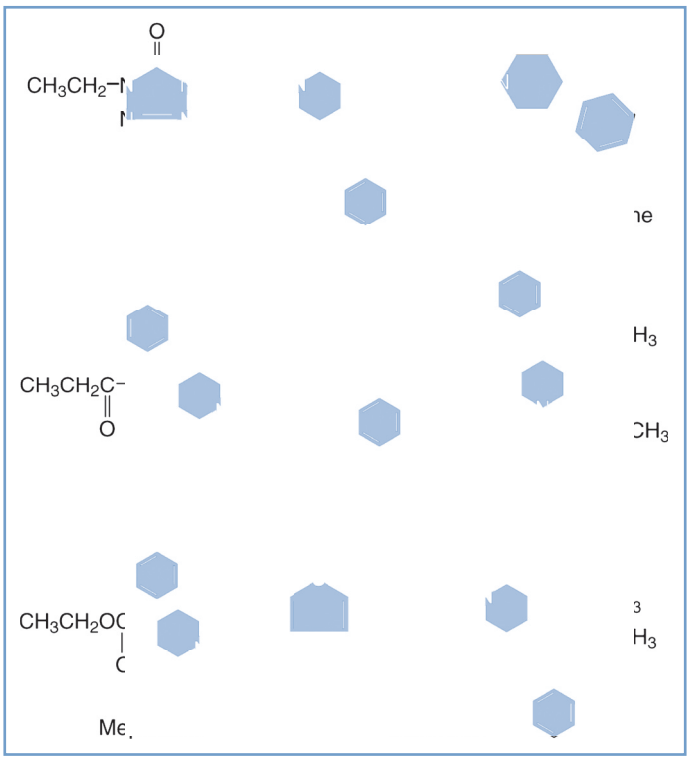

FIGURE 13-10 ■ Chemical structures of phenylpiperidine, meperidine, and the 4-anilinopiperidine derivatives fentanyl, sufentanil, alfentanil, and remifentanil.

isomer capable of producing analgesia. Analgesic activity of the opioid compound depends on its stereochemical structure.[219] Even relatively minor molecular alterations (e.g., extent of ionization) can produce significant alterations in the pharmacologic activity of the opioid.

Morphine is the prototypical opioid. It is a five-ring structure that conforms to a T shape.[220] Three of the rings lie in one plane, and the other two rings are perpendicular to the plane. This forms the basis for the T (Figure 13-9). Morphine demonstrates several other characteristics that are common to other opioids: (1) a tertiary, positively charged basic nitrogen; (2) a quaternary carbon that is separated from the basic nitrogen by an ethane chain and attached to a phenyl group; (3) a phenolic hydroxyl group (morphine derivatives) or a ketone group (meperidine); and (4) the presence of an aromatic ring.[220]

A phenylpiperidine structure (i.e., an aromatic ring attached to a six-member ring containing five carbons and one nitrogen) is also part of the morphine molecule and is present in some other opioids (e.g., fentanyl) (Figure 13-10).[220] Phenylalanine and tyrosine moieties are structural elements that are important to all opioids, including endogenous neurotransmitters and modulators.[221,222] The poppy plant synthesizes morphine from two tyrosine molecules; many opioids contain a structure that is similar to alanine.[220]

Mechanism of Action

Since first described in 1979,[223] neuraxial opioid administration has become a mainstay in obstetric anesthesia practice. Clinical and laboratory research has focused on the mechanisms of synaptic transmission as well as the study of opioids and neurotransmitters that modulate this transmission.

Pain perception involves a complex series of nociceptive transmissions that begin with stimulation of sensory nerves in the periphery, resulting in generation of action potentials within the spinal cord and synaptic transmission to other supraspinal sites. Intraspinal administration of an opioid exploits the pharmacology of pain-modulating and pain-relieving systems that exist within the spinal cord (see Figure 20-9). In early studies, Yaksh[224] demonstrated that morphine could produce selective suppression of nociceptive processing without affecting motor function, sympathetic tone, or proprioception when it was administered to the superficial layers of the dorsal horn of the spinal cord. However, when small amounts of opioid were administered to the cortex, the effects on nociceptive processing were negligible. Collectively, this work demonstrated that small doses of opioid can be selectively administered to a receptor site (i.e., spinal cord) and produce profound analgesia. In contrast, systemic administration of a much larger dose of opioid results in activation of multiple central and peripheral receptors to produce analgesia, but with unwanted side effects.

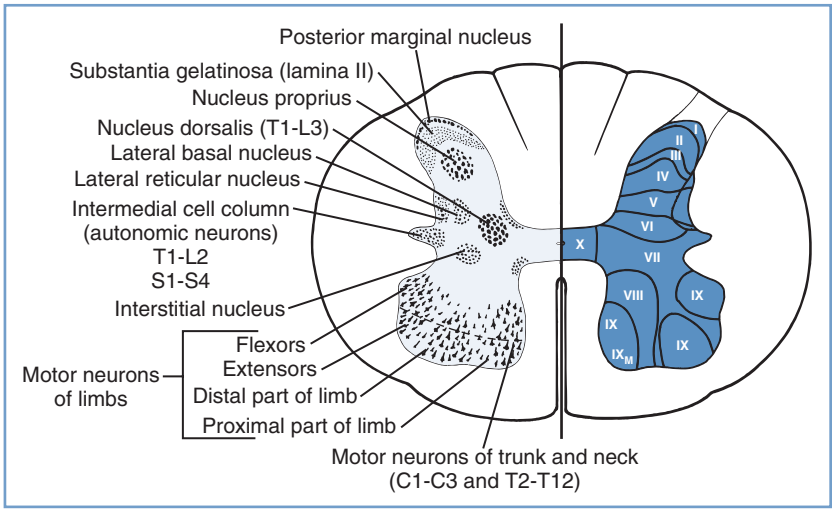

FIGURE 13-11 ■ Architecture of the spinal cord, showing the gray matter nuclei (*left*) and Rexed laminae (*right*). (From Ross BK, Hughes SC. Epidural and spinal narcotic analgesia. Clin Obstet Gynecol 1987; 30:552-65.)

All opioids produce analgesia by binding to G protein–coupled opioid receptors. Activation of opioid receptors subsequently inhibits both adenylate cyclase– and voltage-gated calcium channels. Inhibition of these calcium channels inhibits the release of excitatory afferent neurotransmitters, including glutamate, substance P, and other tachykinins.[225,226] The result is inhibition of ascending nociceptive stimuli from the dorsal horn of the spinal cord.

Opioid receptors are nonuniformly distributed throughout the CNS. Although parenterally administered opioids most likely have both direct spinal and supraspinal effects, neuraxially administered opioids block the transmission of pain-related information by binding at presynaptic and postsynaptic receptor sites in the dorsal horn of the spinal cord (i.e., Rexed laminae I, II, V) (Figure 13-11). However, the rate and extent of neuraxial analgesia depends largely on the specific drug's physicochemical properties and ability to reach the opioid receptors in the spinal cord.

The following three broad classes of opioid receptors have been identified: (1) mu (μ) receptor for morphine type, (2) kappa (κ) receptor for ketocyclazocine type, and (3) delta (δ) receptor.[225] A fourth receptor, the opioid receptor–like-1 (ORL-1) receptor, has structural homology to the classic opioid receptors, but its endogenous ligand, orphanin (OFQ) (also called nociceptin [N]), binds poorly to the classic opioid receptors.[227] Its role in pain modulation is not well characterized but appears distinctive from that of the classic opioid system.[225] Each opioid receptor is encoded by a different gene and mediates different physiologic effects (Table 13-3). Although all of these receptors may be involved with pain processing, the μ or κ receptors have the most important clinical pharmacologic effects.

The distinct receptor subtypes have significance in neuraxial opioid administration and drug development. Common pharmacologic effects (e.g., analgesia, respiratory depression) of morphine are mediated by μ-opioid receptors. Functional subclasses of μ-opioid receptors have been characterized; however, only one gene has been identified for the μ-opioid receptor. Some specific functions have been ascribed to μ-opioid receptor subtypes, including mediation of respiratory depression and spinal opioid analgesia by μ_2 receptors and production of supraspinal analgesia by μ_1 receptors.[228] Although subtype-specific μ agonists may have greater efficacy and less toxicity, no receptor-specific agents have been developed for clinical use.

Morphine also has effects at κ- and δ-opioid receptors when higher doses are administered. Responsible for analgesic, sedative, dysphoric, and diuretic effects,[225] κ receptors are located both within the CNS and peripherally.[229] Peripheral κ-opioid receptor agonists have been shown to modulate visceral pain, particularly in conditions that involve inflammation.[229]

The δ receptor is responsible for mediating some of the analgesic effects of the endogenous opioids (e.g., enkephalins, prodynorphan, pro-opiomelanocortin, pro-orphanin, endomorphins) in the spinal cord.[230] Few of the opioids have effects at the δ receptor in clinically relevant

TABLE 13-3 Subtypes of Opioid Receptors

Receptor Type	Physiologic Response	Receptor Agonist
Mu (μ)	Analgesia Miosis Bradycardia Sedation Respiratory depression Decreased gastrointestinal transit	Morphine Fentanyl Sufentanil Meperidine
Kappa (κ)	Analgesia Sedation Respiratory depression Diuresis Psychotomimesis	Buprenorphine Pentazocine
Delta (δ)	Analgesia	Prodynorphin Endomorphins Enkephalins

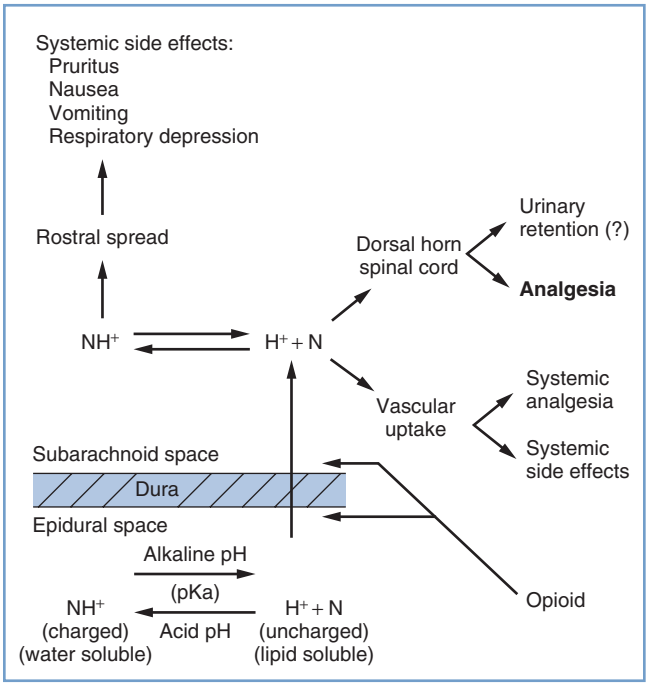

FIGURE 13-12 ■ Epidural opioids traverse the dura and arachnoid membranes, diffuse through cerebrospinal fluid, and cross the pia membrane before reaching the spinal cord. Several factors, including physicochemical properties (e.g., pKa), affect the distribution of opioids within the neuraxis. (From Ross BK, Hughes SC. Epidural and spinal narcotic analgesia. Clin Obstet Gynecol 1987; 30:552-65.)

doses, but if a μ agonist is administered in a high enough dose to treat an opioid-tolerant patient, the drug may be less selective and produce δ effects.

Pharmacokinetics and Pharmacodynamics

Many of the pharmacologic differences observed among neuraxially administered opioids depend on an opioid's ability to reach opioid receptors. An opioid's physicochemical properties, especially lipophilicity or hydrophilicity, largely determine the bioavailability of neuraxially administered opioids as well as the drug's ability to produce spinally mediated analgesia.

Before G protein–receptor activation can occur, the opioid must undergo a series of complex processes. Although several mechanisms have been proposed to explain the movement of opioids from the epidural space to the spinal cord, studies demonstrate that the only relevant mechanism is diffusion through the spinal meninges.[231-233] The opioid must traverse the dura and arachnoid membranes, diffuse through the CSF, and cross the pia membrane to reach the spinal cord (Figure 13-12). Once the drug reaches the surface of the spinal cord, it must diffuse through the white matter and then the gray matter to reach the site of action, the dorsal horn.[234] The rate and extent of opioid transfer to receptors largely depend on a drug's physicochemical properties, particularly lipid solubility, because competing processes (e.g., uptake into the epidural fat or systemic circulation) limit the agent's diffusion to opioid receptors. Greater lipid solubility of a drug results in more rapid onset of analgesia. For example, fentanyl is a highly lipid-soluble opioid (i.e., 600 times more lipid soluble than morphine); therefore, it has a more rapid onset of action than morphine (Table 13-4).

TABLE 13-4 **Physicochemical Properties of Opioids Used for Neuraxial Analgesia**

Opioid	Lipid Solubility*	pKa	Protein Binding (%)
Morphine	1.4	7.9	35
Meperidine	39	8.5	70
Diamorphine	280	7.8	40
Fentanyl	816	8.4	84
Sufentanil	1727	8.0	93

*Octanol-water partition coefficient.
Data from Camu F, Vanlersberghe C. Pharmacology of systemic analgesics. Best Pract Res Clin Anaesthesiol 2002; 16:475-88; and McLeod GA, Munishankar B, Columb MO. Is the clinical efficacy of epidural diamorphine concentration-dependent when used as analgesia for labour? Br J Anaesth 2005; 94:229-33.

Latency, potency, and duration are also affected by other physicochemical properties, including molecular weight, pKa, and protein binding. For example, the lower the pKa, the greater the percentage of opioid existing in uncharged form (i.e., the anionic base) at a pH of 7.4. In the uncharged form, opioids penetrate the dura mater and dorsal horn more easily, resulting in a more rapid onset of analgesia.

The boundaries of the epidural space are the vertebral bodies, ligaments, and spinal meninges. Fat and the epidural venous plexus account for a large volume of the epidural space. The spinal meninges consist of the dura, arachnoid, and pia mater. Of these membranes, the arachnoid is the primary barrier for drug transfer from the epidural space to the spinal cord.[235] The arachnoid mater has multiple layers of overlapping cells that represent both a hydrophilic domain (consisting of extracellular and intracellular fluid) and a hydrophobic domain (the cell membranes).[232] For an opioid to navigate the arachnoid, it must diffuse through both domains before entering the CSF. Therefore, drugs of intermediate hydrophobicity move most readily across the arachnoid. Other physical characteristics of drugs (e.g., molecular weight) do not appear to play an important role in determining redistribution from the epidural space to the subarachnoid space.[232]

The efficacy of a drug also depends on its physicochemical properties, particularly lipid solubility. For example, the amount of drug that is sequestered in the epidural fat is entirely dependent on the drug's octanol-to-buffer distribution coefficient.[236] Consequently, lipophilic drugs (e.g., fentanyl) with a high octanol-to-buffer coefficient may never reach the arachnoid membrane and may partition in epidural fat. This lack of drug transfer across the meninges results in poor CSF bioavailability. To evaluate movement of opioids from the epidural to the subarachnoid space, Bernards et al.[236] used a porcine

model to continuously sample opioid concentrations in the epidural and intrathecal spaces. Using microdialysis techniques, the investigators measured the redistribution of morphine, alfentanil, fentanyl, and sufentanil out of the epidural space. (These opioids were administered by epidural bolus injection.) Opioid concentrations were measured over time in the epidural space, subarachnoid space, systemic venous plasma, and epidural venous plasma. Results suggested that there was a strong linear relationship between lipid solubility and mean residence time, indicating that more lipid-soluble opioids spent a longer time in the epidural space. Consequently, these drugs partition themselves into the epidural fat with ongoing slow release back into the epidural space. Because of their long residence time in the epidural space, more lipid-soluble drugs are found in lower concentrations in the CSF (i.e., decreased bioavailability to opioid receptors in the dorsal horn).

Several human studies have evaluated whether epidurally administered fentanyl produces analgesia by a selective spinal mechanism or by systemic absorption and redistribution. Results of studies of lipophilic opioids (administered by epidural infusion) have suggested that low concentrations of lipophilic opioids are subject to rapid vascular uptake from the epidural space or sequestration in epidural fat, thereby limiting access to the spinal cord.[237-239] However, other studies have suggested the occurrence of a spinal effect when lipophilic opioids are administered by epidural bolus injection[240] or by epidural infusion of short duration.[241] Ginosar et al.[242] compared the analgesic effects of epidural bolus injection and epidural infusion of fentanyl in human volunteers. Study results suggested that epidural fentanyl infusion produced analgesia by uptake into the systemic circulation with redistribution to brain and peripheral opioid receptors. However, epidural bolus administration of fentanyl produced analgesia by selective spinal mechanisms. These results were consistent with previous reports that an epidural fentanyl bolus results in a larger amount of fentanyl in the epidural space than occurs at any time during an epidural infusion, leading to the greater availability of drug to activate opioid receptors in the dorsal horn of the spinal cord.

Although hydrophilic drugs (e.g., morphine) are subject to less systemic and epidural fat uptake than lipophilic drugs, the transfer of the former into the CSF is an inefficient process because they have difficulty in crossing the lipid bilayer of the arachnoid. However, despite these inefficiencies, morphine content in the spinal cord is significantly greater than lipophilic drug (e.g., fentanyl) content,[243] and morphine has much greater bioavailability in the spinal cord than do fentanyl and sufentanil.[236,243] In summary, although morphine clearly produces analgesia via a spinal mechanism, the extent of spinal analgesia produced by the neuraxial administration of fentanyl is less clear.

After a drug reaches the subarachnoid space, either by diffusion across the meninges or by direct injection into the CSF, its effects depend on its lipid solubility. All opioids produce at least some analgesia by spinal-specific mechanisms. Movement of these drugs within the CSF depends on their physicochemical properties. Drugs can diffuse within the CSF in either a cephalad or a caudad direction. Both morphine and fentanyl have been shown to move rapidly within the CSF.[244] Lipophilic drugs can also return to the epidural space by traversing previously mentioned structures.

Ummenhofer et al.[243] used a porcine model to investigate intrathecal administration of opioids. These investigators found that lipophilic opioids have a very large volume of distribution compared with hydrophilic drugs; the volume of distribution of sufentanil was 40 times greater than that of morphine. The reason is sufentanil's extreme lipid solubility, with the drug rapidly leaving the CSF and entering the epidural fat, from which it is absorbed systemically.[245]

The ultimate goal of neuraxial opioid administration is for the drug to penetrate the dorsal horn of the spinal cord and activate μ-opioid receptors. A drug's ability to move from the CSF to the dorsal horn depends on its physicochemical properties. Of the clinically relevant opioids, morphine has the most favorable physicochemical properties to allow penetration of the dorsal horn of the spinal cord (i.e., gray matter). Because of its extreme lipid solubility, sufentanil redistributes itself or partitions itself on the superficial layer (i.e., white matter) of the spinal cord.[243] Data suggest that the spinal bioavailability of the hydrophilic drugs (e.g., morphine, hydromorphone) is greater than that of hydrophobic opioids (e.g., fentanyl, sufentanil).

An extended-release formulation of morphine has been developed to prolong the duration of a single epidural injection of morphine or obviate the need for a continuous catheter. Multivesicular liposomal preparations gradually release morphine so that a larger epidural dose can be administered, providing analgesia for up to 48 hours (see Chapter 28). Studies that have compared extended-release epidural morphine (EREM) 10 to 15 mg with conventional epidural morphine for provision of analgesia after cesarean delivery have determined that EREM provided superior and prolonged analgesia.[246,247] The most recent American Society of Anesthesiologists Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration state that "the literature reports no significant difference in the frequency of respiratory depression when [EREM] is compared with conventional (i.e., immediate release) epidural morphine."[248] However, in a study of patients undergoing cesarean delivery, Atkinson Ralls et al.[149] observed that epidural administration of 20 to 35 mL of epidural lidocaine 2% with fentanyl 1 hour before administration of EREM (8 mg) increased the mean (± SD) peak plasma concentration (C_{max}) in the EREM group (11.1 ± 4.9 ng/mL) compared with a group that received a CSE anesthetic technique without epidural medication (8.3 ± 7.1 ng/mL) ($P = .038$). Further, the EREM group had an increased incidence of vomiting, hypotension, and use of supplemental oxygen. Patients who receive EREM should be monitored at least once every hour during the first 12 hours after administration and at least once every 2 hours for the next 12 hours (i.e., from 12 to 24 hours).[248] After 24 hours, monitoring should be performed at least once every 4 hours for a minimum of 48 hours. Increased

intensity and duration of monitoring should be considered in patients at increased risk for respiratory depression (e.g., obesity) or in the setting of concomitant administration of opioid analgesics or sedative-hypnotics by other routes. Extra precautions should be taken when patients receive EREM within 1 hour of large doses of local anesthetic[149] or when unintentional spinal administration occurs.[249]

In summary, the onset and duration of analgesia as well as side effects produced by neuraxial opioid administration depend on the specific type of opioid receptor that is activated as well as the dose, lipid solubility, and rate of movement and clearance of the opioid in the CSF.

Pharmacogenetics

Pain associated with labor and delivery is influenced by a multitude of physiologic, psychosocial, and environmental factors. However, genetic variations have also been suggested to alter a patient's sensation, experience, and perception of pain. Recent advances in genomic research have led to identification of more than 100 variants (polymorphisms) in the μ-opioid receptor gene (*OPRM1*).[250] Although inconsistent, results of some studies suggest that a single-nucleotide polymorphism (SNP) in *OPRM1* at position 118 (initially known as 118A>G, now annotated 304A>G; rs1799971) may influence responses to opioid analgesics.[251] The allelic frequency of the 304A>G polymorphism is population dependent; it is more common in Asians and less frequent in whites and blacks.

The role of the 304A>G polymorphism has been investigated in obstetric anesthesia. Using both up-down sequential allocation and random allocation methods, Landau et al.[252] estimated the ED_{50} of intrathecal fentanyl, administered as part of a CSE technique for labor analgesia in nulliparous women with and without the 304A>G variant. The ED_{50} of intrathecal fentanyl in women with the variant allele was *lower* than in women without the allele (1.5- to 2-fold difference). However, when Wong et al.[253] investigated the effect of the 304A>G allele on the duration of intrathecal fentanyl labor analgesia (25 μg), they found no significant difference in the duration of analgesia or in the treatment of breakthrough pain in women with the variant allele. Camorcia et al.[254] examined the effect of the 304A>G variant on the ED_{50} of epidural sufentanil in nulliparous women. Similar to the findings of the Landau et al. study,[252] the estimated ED_{50} was significantly lower in women with the variant allele (20.2 μg; 95% CI, 14.2 to 23.6) compared with women without the variant (25.2 μg; 95% CI, 23.2 to 26.4) ($P = .03$).

The potential role of the 304A>G polymorphism in influencing opioid analgesic requirements after cesarean delivery has been investigated in several studies. Wong et al.,[253] in a mixed race/ethnicity population, found no difference in duration of intrathecal morphine analgesia or need for supplemental analgesia in women carrying the variant allele. In contrast, Sia et al.[255] reported that Asian women with the variant allele had *increased* breakthrough pain (as assessed by patient-controlled intravenous morphine requirements) after intrathecal administration of morphine compared with women without the variant allele. In a second study, the variant allele was found to independently predict increased postoperative morphine use in women undergoing cesarean delivery.[256]

The results of these studies are difficult to reconcile.[257] Although genetic components may influence patients' responses to nociceptive stimuli, current evidence suggests that genetic polymorphism in *OPRM1* plays a minor role, if any, in opioid pain management.[251,257] A recent meta-analysis examining the 304A>G variant of *OPRM1* failed to identify a strong association between this variant allele and the response to opioids in different clinical settings.[251]

Toxicity

Any agent that is injected into the epidural or subarachnoid space should be administered with caution owing to the potential for neurotoxicity and permanent neurologic damage. Although there is concern about injecting any type of medication into the neuraxis, the epidural space is more forgiving than the subarachnoid space (see Chapter 32). In many cases, clinicians have injected medications that were not well tested in animal models. Yaksh and Collins[258] have urged careful administration of neuraxial drugs, stating that "studies in animals should precede human use of spinally administered drugs."

The most commonly administered neuraxial opioids in obstetric patients are preservative-free morphine, fentanyl, and sufentanil. Preservative-free morphine is commercially available for both epidural and intrathecal administration. To evaluate preservative-free morphine for potential neurotoxicity, Abouleish et al.[259] examined the short- and long-term effects of intrathecal morphine injection in monkeys. The meninges, nerve roots, and dorsal root ganglia were examined macroscopically and microscopically in both the study and the control groups. The researchers found no evidence of demyelination, arachnoiditis, or necrosis in either group.

Fentanyl is also available in a preservative-free formulation. Despite its widespread clinical use, few studies have assessed the histologic, physiologic, or clinical evidence of neurotoxicity with spinally administered fentanyl. One *in vitro* study evaluated the effects of fentanyl administration on nerve conduction.[260] Histopathologic studies of isolated rabbit vagus nerve axons did not show localized nerve damage after nerves were bathed in an isotonic solution of fentanyl. When axons were bathed in a hypotonic solution of fentanyl, permanent conduction deficits were noted. However, *in vivo*, relatively large doses of fentanyl would be required to create a hypotonic intrathecal environment.

Although no formal neurotoxicology studies have evaluated sufentanil administration in humans, there are no clinical reports of neurotoxicity despite its widespread use. In one study, sufentanil was administered to cats through an indwelling intrathecal catheter over 5 days.[261] Sabbe et al.[262] administered clinically relevant doses of intrathecal sufentanil to dogs over several weeks and reported no histopathologic changes. In a sheep model, Rawal et al.[263] demonstrated dose-dependent spinal cord

TABLE 13-5 Incidence of Adverse Side Effects after Intrathecal Injection of 0.5 or 1.0 mg of Morphine

	Incidence (%)		
Side Effect	MORPHINE 0.5 mg (n = 12)	MORPHINE 1 mg (n = 18)	OVERALL (n = 30)
Pruritus	58	94	80
Nausea/vomiting	50	56	53
Urinary retention	42	44	43
Drowsiness	33	50	43
Respiratory depression	0	6	3

Modified from Abboud TK, Shnider SM, Dailey PA, et al. Intrathecal administration of hyperbaric morphine for the relief of pain in labour. Br J Anaesth 1984; 56:1351-60.

histopathologic changes after intrathecal administration of sufentanil (50 to 100 μg) every 6 hours for 72 hours. These doses are much larger than those used in clinical practice. It is possible that these findings reflect an artifact of experimental design (e.g., the frequent administration of a large-volume, hypotonic preparation).

Despite the paucity of data about possible neurotoxicity, both fentanyl and sufentanil are widely used in clinical practice. These drugs are not approved by the FDA for neuraxial use. However, there are no published reports of neurologic deficits after epidural or intrathecal administration of either agent in humans, and these drugs appear to be safe for neuraxial administration. In general, anesthesia providers should exercise extreme caution before injecting any untested agent into the spinal or epidural space, in order to prevent irritation or damage to neural structures.

Side Effects

Neuraxial opioid administration is associated with beneficial effects as well as potential complications and side effects. Intrathecal administration of relatively large doses of morphine is associated with a high incidence of side effects, including somnolence, nausea and vomiting, pruritus, and respiratory depression (Table 13-5). However, epidural and intrathecal injection of more lipid-soluble opioids have fewer side effects.

Sensory Changes

An early study evaluating intrathecal sufentanil in laboring women reported sensory changes and hypotension, although no local anesthetics were administered.[264] Other investigators have reported high cervical sensory blockade associated with mental status changes, dysphagia, dyspnea, and automatisms after intrathecal sufentanil injection.[265-268] These symptoms are likely to be related to a dose-dependent opioid effect rather than neuraxial blockade–induced sympathectomy.[269] Further, these changes do not predict the quality or duration of analgesia or degree of hemodynamic change.[269] These sensory changes can be clinically significant, especially when they extend to the cervical dermatomes. Patients may feel that they cannot breathe or swallow, an effect that can be distressing. Fortunately, neither intrathecal sufentanil nor fentanyl affects the efferent limb of the nervous system, and motor function is not impaired. Patients should be reassured that their respiratory efforts are not impaired and that these symptoms will subside in 30 to 60 minutes. One report described the use of naloxone to treat the sensory changes associated with intrathecal sufentanil.[265]

Nausea and Vomiting

Nausea and vomiting are common during labor and delivery. Intrapartum nausea and vomiting can occur from a variety of causes, including pregnancy, physiology of labor itself, pain associated with labor, and parenteral administration of an opioid that may have preceded the neuraxial opioid administration. Therefore, it is difficult to determine the incidence of nausea and vomiting as direct side effects of neuraxial analgesia. Although the mechanism of neuraxial opioid–mediated nausea is unclear, there are suggestions that it may be caused by modulation of afferent input to the area postrema (i.e., the chemoreceptor trigger zone) or at the nucleus of the tractus solitarius, a key relay station in the visceral sensory network.[270] Interestingly, nausea is more common after intrathecal administration of opioids to patients who have undergone cesarean delivery than in patients who received the same intrathecal regimen during labor and delivery. Norris et al.[271] reported that women receiving epidural or intrathecal opioid analgesia during labor had an incidence of nausea and vomiting of only 1.0% and 2.4%, respectively.

A number of treatments are available with minimal side effects. A meta-analysis suggested that **metoclopramide** administration (10 mg) before initiation of spinal anesthesia or after delivery resulted in a significant reduction in intraoperative nausea and vomiting as well as early postoperative nausea and vomiting.[272] One explanation for metoclopramide's efficacy is that it promotes gastric emptying. **Ondansetron** is also used in many centers for prophylaxis and treatment of opioid-induced nausea. In a study comparing transdermal scopolamine 1.5 mg, intravenous ondansetron 4 mg, and placebo, **scopolamine** was an effective prophylactic medication against nausea in parturients who received intrathecal morphine for analgesia after cesarean delivery.[273] However, the use of scopolamine may be limited by bothersome side effects, including dry mouth, drowsiness, and blurred vision. George et al.[274] performed a systematic review of randomized, controlled trials comparing prophylaxis or treatment of nausea and vomiting using one of the 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists or placebo in women receiving spinal anesthesia with intrathecal morphine for cesarean delivery. The authors determined that 5-HT_3 receptor antagonists reduced the incidence of postoperative nausea and vomiting as well as the need for postoperative rescue antiemetic therapy when compared with placebo.

Although **droperidol** is effective for the treatment of nausea, the FDA has issued a "black box" warning against

its use because of concern for QT-interval prolongation in association with droperidol administration. Intravenous **cyclizine** 50 mg was shown to be superior to **dexamethasone** 8 mg in reducing nausea after intrathecal morphine administration for cesarean delivery.[275] Another systematic review of randomized controlled trials compared dexamethasone with placebo for the prevention of postoperative nausea and vomiting in patients receiving neuraxial morphine as part of a neuraxial technique.[276] Results suggested that dexamethasone is an effective antiemetic agent, and doses used for antiemetic prophylaxis enhanced postoperative analgesia compared with placebo.

Pruritus

Pruritus is the most common side effect of neuraxial opioid administration.[264,277] Presentation is highly variable, but the incidence and severity seem to be dose dependent, especially with epidural opioid administration.[278] Onset of the pruritus occurs shortly after analgesia develops, and even small doses of intrathecal sufentanil may produce significant pruritus.[279] Some observers have noted a segmental pruritus, especially with lipophilic opioids. For example, patients often complain of perineal and truncal pruritus after intrathecal sufentanil injection.[264] Pruritus occurs more commonly with intrathecal opioid administration than with epidural administration (in one study,[271] 41.4% versus 1.3%, respectively). The incidence and severity of pruritus may be reduced by administration of a lower dose of opioid[279,280] or co-administration of the opioid with a local anesthetic.[281] Many patients do not complain about the pruritus and appear asymptomatic; however, when questioned, they acknowledge the symptom.

Although the cause of opioid-induced pruritus is unknown, it appears to be unrelated to histamine release.[282] Some investigators have suggested that pruritus results from a perturbation of sensory input resulting from rostral spread of the opioid within the CSF to the trigeminal nucleus or subnucleus caudalis.[282] Itch-specific neuronal pathways may interact with pain pathways so that continuing activity of the pain-processing system suppresses activity in the spinal itch-processing neurons. Consequently, if pain is inhibited, pruritus can be unmasked (e.g., intrathecal morphine–induced pruritus). Pruritus can also be inhibited by pain (e.g., antipruritic effect of scratching).[283]

The serotoninergic system may contribute to modulation of pain by providing a balance between nociception and anti-nociception in the network of pain-processing neurons.[284,285] The dorsal horn of the spinal cord and the spinal tract of the trigeminal nerve are abundant in 5-HT_3 receptors. Because morphine is known to activate 5-HT_3 receptors by a mechanism independent of opioid receptors,[286] it is postulated that morphine may directly stimulate 5-HT_3 receptors and may cause intrathecal morphine–induced pruritus. Consequently, occupation of 5-HT_3 receptors by a 5-HT_3–receptor antagonist potentially prevents the pruritus.

Iatrou et al.[287] performed a randomized, double-blind, placebo-controlled study to evaluate the prophylactic effects of **ondansetron** and **dolasetron** in the treatment of intrathecal morphine–induced pruritus. Study results demonstrated that patients who received preemptive 5-HT_3–receptor antagonists reported significantly less pruritus and pruritus of less severity during the first 8 postoperative hours than patients who received placebo. The frequency of pruritus was reduced by 48% and 70% for ondansetron and dolasetron, respectively, compared with placebo. A quantitative systematic review evaluated the efficacy of prophylactic 5-HT_3 receptor antagonists for the prophylaxis and treatment of neuraxial opioid-induced pruritus. The investigators determined that prophylactic 5-HT_3 receptor antagonists did not alter the incidence of pruritus compared with placebo but did reduce the incidence of *severe* pruritus and the need for therapy.[274] Additionally, 5-HT_3 receptor antagonists were efficacious for the treatment of established pruritus.

Other treatments of intrathecal opioid–induced pruritus include administration of intravenous **naloxone** (40 to 80 μg) or **diphenhydramine** (25 mg). Despite the probability that the pruritus is unrelated to histamine release, there may be some benefit from the modest sedation that follows diphenhydramine administration. Administration of **nalbuphine** (2.5 to 5 mg intravenously[288,289] or 10 mg subcutaneously[288,290]) may also be helpful in reducing symptoms. The advantage of nalbuphine compared with naloxone is that it is less likely to reverse neuraxial opioid analgesia.[289] Although propofol 10 to 20 mg was found effective for the treatment of pruritus in several studies in nonobstetric patients, its efficacy was no better than placebo in an obstetric study.[291] Regardless of the chosen treatment, pruritus can contribute significantly to patient dissatisfaction and should be treated promptly upon request.

Hypotension

Decreased blood pressure was reported in early studies that evaluated intrathecal opioid administration.[264,269] Although hypotension occurs in 5% to 10% of parturients who receive intrathecal opioids,[264,269] the incidence is higher when a local anesthetic or clonidine is added to the opioid. Early reports suggested that hypotension was due to a sympathectomy, but later work suggests that hypotension results from pain relief[292] and decreased maternal levels of catecholamines, especially epinephrine.[293] Wang et al.[294] demonstrated that intrathecal opioids block the afferent information from A-delta and C-fibers to the spinal cord but that efferent nerve impulses (e.g., sympathetic efferents) are not directly blocked.

Respiratory Depression

All opioids can cause respiratory depression regardless of their route of administration. When opioids are administered either epidurally or intrathecally, the following factors affect the risk for respiratory depression: (1) choice of drug and its pharmacokinetics, (2) drug dose, and (3) concomitantly administered CNS depressants. The most important factor affecting the onset time of respiratory depression induced by intrathecal opioids

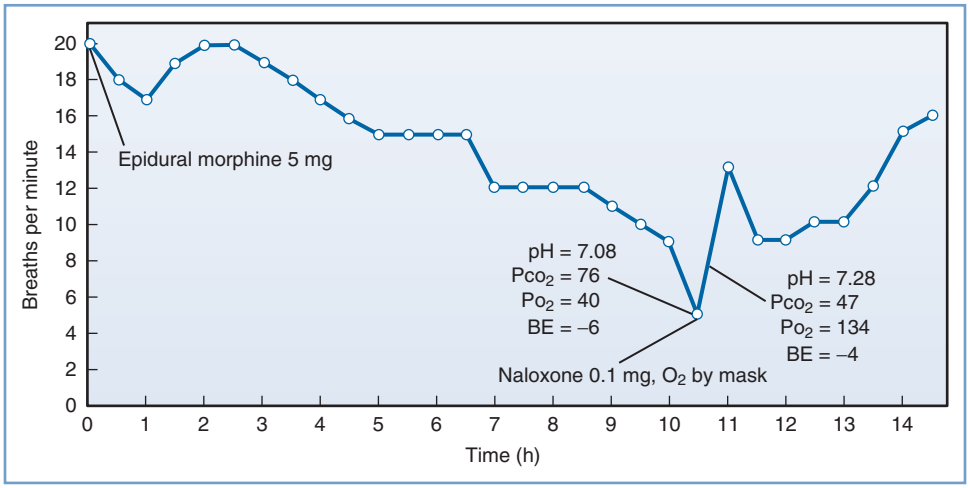

FIGURE 13-13 ■ Respiratory rate of an obstetric patient who received 5 mg of morphine after cesarean delivery and who experienced delayed respiratory depression. (From Leicht CH, Hughes SC, Dailey PA, et al. Epidural morphine sulfate for analgesia after cesarean section: a prospective report of 1000 patients [abstract]. Anesthesiology 1986; 65:A366.)

is lipid solubility.[270] Respiratory depression may occur within minutes after the administration of a lipophilic opioid (e.g., fentanyl, sufentanil) because of rapid absorption of the opioid from the CSF to lipophilic tissues.[234] Its subsequent clearance and elimination are similar to those of the drug when injected intravenously; thus the "time frame" for respiratory depression is short. In contrast, hydrophilic drugs (e.g., morphine, hydromorphone) are associated with a delayed onset of respiratory depression. This potentially serious side effect occurs because these hydrophilic opioids remain in the CSF for several hours. Although this characteristic improves the bioavailability of these opioids, rostral migration and absorption of the drug into the respiratory centers in the brainstem can produce respiratory depression 6 to 12 hours after injection (Figure 13-13).

The dose of opioid has also been shown to be an important factor in the occurrence of respiratory depression. The usual dose of intrathecal morphine for analgesia after cesarean delivery is 0.1 to 0.2 mg. Not surprisingly, an early report of respiratory depression occurred after administration of intrathecal morphine 1 mg.[295] In a dose-response study, Palmer et al.[296] concluded that there was little justification for giving more than 0.1 mg of intrathecal morphine for analgesia after cesarean delivery. In a dose-response study of epidural morphine administration after cesarean delivery, investigators concluded that the quality of analgesia increases as the dose of epidural morphine increases to 3.75 mg but that increasing the dose to 5 mg does not improve analgesia.[297]

Studies in nonobstetric surgical patients suggest that the risk for respiratory depression after the epidural administration of EREM is also dose related.[298,299] Carvalho et al.[247] compared EREM (10 mg) administration with standard epidural morphine (4 mg) administration in healthy women undergoing cesarean delivery and found that EREM reduced opioid consumption for 48 hours without significant risk for respiratory depression. However, the authors cautioned that the study's small sample size may not accurately reflect the true incidence of respiratory depression in obstetric patients who have received the extended-release preparation.

Although most cases of respiratory depression associated with sufentanil administration occur with larger doses, respiratory depression has also been reported with as little as 10 μg of intrathecal sufentanil administered for labor analgesia.[300,301] Larger doses (e.g., 15 μg) have not been found to produce better or more prolonged analgesia but do result in increased plasma opioid concentrations and a higher risk for respiratory depression. In a female volunteer study, Lu et al.[245] reported that doses of intrathecal sufentanil larger than 12.5 μg did not produce a proportionate increase in intensity or duration of analgesia. Similarly, there is little benefit to increasing the dose of intrathecal fentanyl beyond 25 μg when it is used as the sole agent for labor analgesia. These higher doses (i.e., more than 10 μg of sufentanil or more than 25 μg of fentanyl) should not be used in routine clinical practice. Respiratory depression has been reported with as little as 100 μg of epidural fentanyl.[302]

Several case reports have implicated previous parenteral administration of opioid as a contributing factor in respiratory arrest associated with intrathecal sufentanil administration in laboring women.[303,304] For example, Jaffee et al.[305] reported a case of apnea and unresponsiveness in a parturient who had received several doses of intravenous fentanyl in the 4 hours before intrathecal sufentanil administration. Although the pregnancy-induced increase in respiratory drive continues throughout labor and into the postpartum period and may provide some protection against respiratory depression, respiratory depression is the most serious side effect of neuraxial opioid administration.

Practice guidelines from the American Society of Anesthesiologists recommend that all patients who receive neuraxial opioids should be monitored for adequacy of **ventilation** (e.g., respiratory rate, depth of respiration), **oxygenation** (e.g., pulse oximetry when appropriate), and **level of consciousness**.[248] In patients who receive a single neuraxial injection of a lipophilic opioid (e.g., fentanyl), monitoring should be continual

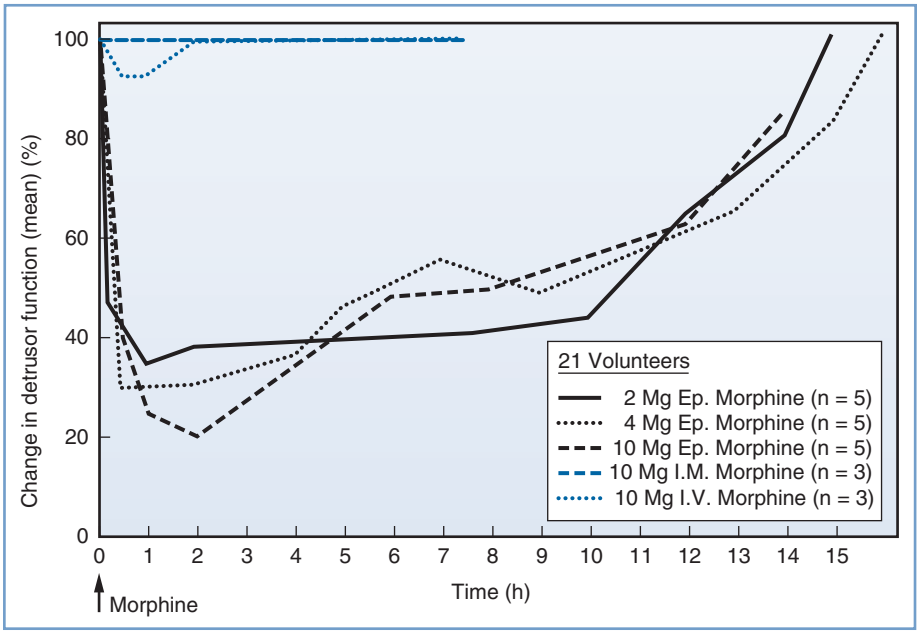

FIGURE 13-14 ■ Urodynamic effects of epidural (Ep.), intramuscular (I.M.), and intravenous (I.V.) morphine administration in male volunteers. Depression of detrusor muscle function persisted for many hours after epidural morphine administration. This did not occur with parenteral opioids and may represent a local spinal cause (i.e., opioid receptors). (From Rawal N, Mollefors K, Axelsson K, et al. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg 1983; 62:641-7.)

for the first 20 minutes after administration, followed by monitoring at least once per hour until 2 hours have passed. In patients who receive a single neuraxial injection of a hydrophilic opioid (e.g., morphine), monitoring should be performed at least hourly for the first 12 hours and then at least every 2 hours for the next 12 hours after opioid administration (and then every 4 hours for *another* 24 hours in patients who receive epidural EREM). For patients who receive a continuous infusion of a neuraxial opioid, monitoring should be performed hourly during the first 12 hours, every 2 hours for the next 12 hours, and then every 4 hours for the duration of the opioid infusion. In addition, the guidelines state that greater duration and intensity of monitoring and/or additional methods of monitoring may be indicated in patients at increased risk for respiratory depression (e.g., obesity, obstructive sleep apnea, concomitant administration of opioid analgesics by other routes).

Urinary Retention

Urinary retention is a bothersome side effect of intraspinal opioid administration. The incidence varies widely. It is more common with neuraxial opioid administration than with intramuscular or intravenous administration of equivalent doses. Urinary retention is unrelated to systemic absorption and is dose independent. The onset of urinary retention appears to parallel the onset of analgesia. Evidence suggests that the rapid onset of this side effect is produced by relaxation of the detrusor muscle (Figure 13-14),[306] which most likely results from the sacral spinal action of opioids. Urinary retention can be treated with naloxone; however, because many parturients require catheterization for other reasons, urinary retention is often treated with bladder catheterization.

Delayed Gastric Emptying

Labor may delay gastric emptying, and opioids may further exacerbate this delay (see Chapter 29). Parenterally administered opioids are known to delay gastric emptying in laboring women.[307] However, clinically useful doses of epidural fentanyl have minimal effects on gastric emptying. Intrathecal administration of fentanyl produces greater delays in gastric emptying than epidural administration.[308] Delays in gastric emptying may increase the risk for nausea and vomiting and also increase the risk for aspiration if general anesthesia is necessary for emergency cesarean delivery.

Recrudescence of Herpes Simplex Virus Infections

Genital herpes infection (herpes simplex virus [HSV]) is the most common type of herpes-virus infection during pregnancy[309]; however, oral HSV infections (common cold sore or fever blister) resulting from reactivation of latent HSV infection also occur during pregnancy. Reports have suggested a relationship between neuraxial opioid administration and reactivation of oral herpes infection.[310] Crone et al.[311] reported a 10% incidence of reactivation after cesarean delivery in patients who had received epidural morphine, compared with a 1% incidence in similar patients who did not receive epidural morphine. These observations have been confirmed in two prospective studies.[312,313] Davies et al.[314] reported an increased incidence of postpartum herpes infection in patients with a history of HSV-1 who had received intrathecal morphine. Two case reports have reported an association between intraspinal administration of fentanyl and meperidine and reactivation of oral herpes infection.[315,316]

The mechanism of herpes reaction is unknown.[310] Viral reactivation is known to occur with exposure to ultraviolet light, immunosuppression, trauma, and fever. Proposed causes include (1) a skin trigger mechanism, whereby pruritus and scratching trigger reactivation; (2) an altered immunologic response[317]; and (3) a ganglion trigger mechanism, whereby the intraspinal opioid spreads rostrally and binds to the trigeminal nerve.[318] The ganglion trigger mechanism involves an alteration of sensory modulation that results in reactivation. We are unaware of any serious maternal or neonatal complications that have resulted from neuraxial administration of an opioid and reactivation of oral herpes infection.

Placental Transfer and Fetal and Neonatal Effects

Neuraxial opioid administration may have a direct effect on the infant (i.e., respiratory depression at delivery) that results from systemic absorption of the opioid followed by transplacental transfer. The fetus may also be affected indirectly by opioid-related maternal side effects (i.e., hypoxemia, respiratory depression).

Neonatal Depression

Systemic opioid absorption can result in neonatal respiratory depression, which is sometimes observed after systemic opioid administration during labor.[319,320] Neuraxial opioid analgesia techniques may result in better Apgar scores and umbilical cord blood gas and pH measurements at delivery. Despite the rapid systemic uptake of intrathecally administered opioids, the neuraxial analgesia requires the administration of smaller doses of opioid.

Several studies have evaluated neonatal outcome after continuous maternal epidural infusion of opioids and local anesthetics.[321-323] Collectively, these studies have demonstrated that maternal epidural opioid administration by continuous infusion rarely results in drug accumulation and subsequent neonatal depression. Reynolds et al.[324] performed a systematic review of randomized and nonrandomized studies comparing epidural with systemic opioid analgesia. They reviewed 12 trials with a total study population of 2102 parturients. Epidural analgesia was associated with better umbilical cord blood acid-base measurements than systemic opioids, suggesting that placental perfusion and gas exchange was well preserved despite maternal sympathetic blockade and effective analgesia. Although not all of the studies used neuraxial opioid infusions, the researchers suggested that replacement of systemic opioids with modest doses of neuraxial opioids not only produces superior analgesia but also may have a favorable effect on neonatal outcome.[324]

Fetal Heart Rate Abnormalities

Although epidural or intrathecal opioid administration has little direct effect on FHR,[325] worrisome abnormalities such as late decelerations and fetal bradycardia have been observed after intrathecal lipophilic opioid administration. Several reports have described the abrupt onset of fetal bradycardia after intrathecal administration of fentanyl or sufentanil.[326-328] Clarke et al.[327] suggested that the bradycardia is an indirect effect of decreased circulating maternal epinephrine associated with the rapid onset of analgesia. Epinephrine has a tocolytic effect and causes uterine relaxation by stimulating β_2-adrenergic receptors. Consequently, reduced epinephrine levels may lead to increased uterine tone. Because uteroplacental perfusion occurs during periods of uterine diastole (i.e., uterine relaxation), uterine tachysystole may result in diminished uteroplacental perfusion and fetal hypoxia. Norepinephrine is known to have a uterine-stimulating effect[329]; thus the decrease in epinephrine concentration alongside an unchanged norepinephrine concentration may produce uterine hyperactivity and fetal compromise.

Other mechanisms may also be relevant. Van de Velde et al.[330] questioned the catecholamine imbalance theory, because intrathecal bupivacaine combined with low-dose sufentanil (1.5 μg) produced analgesia similar to that provided by intrathecal sufentanil (7.5 μg), but the incidence of fetal bradycardia was higher with sufentanil 7.5 μg. Russell et al.[331] demonstrated that intravenous opioids have central effects, altering the release of oxytocin and vasopressin and inducing uterine hyperactivity. Lipid-soluble opioids undergo rapid systemic redistribution after neuraxial injection; therefore, even neuraxial opioids may have central effects.

Initial reports indicated that the incidence of FHR abnormalities with intrathecal opioid analgesia was 15% to 20%.[264,332] One published report suggests that uterine tachysystole and fetal bradycardia may follow administration of either intrathecal or epidural analgesia during labor.[333] FHR tracings were assessed after administration of either intrathecal sufentanil or epidural bupivacaine. There were no observed differences in the incidence of FHR abnormalities (i.e., recurrent late decelerations and/or bradycardia) between groups (22% in the intrathecal sufentanil group versus 23% in the epidural bupivacaine group).[333] In contrast, Mardirosoff et al.[334] performed a systematic review of all randomized trials comparing intrathecal with non-intrathecal administration of opioids in laboring women. Twenty-four trials met criteria; the study population included 3513 women. The relative risk for FHR abnormalities in patients receiving spinal opioids was 1.81 (95% CI, 1.04 to 3.14). The risks of cesarean delivery for FHR abnormalities were similar in the two groups (6.0% for intrathecal administration versus 7.8% for other methods).

In a prospective study, Van de Velde et al.[330] investigated whether intrathecal sufentanil 7.5 μg produced more FHR abnormalities than either conventional epidural analgesia or intrathecal bupivacaine combined with sufentanil 1.5 μg. The high-dose sufentanil group had more FHR abnormalities (i.e., late decelerations, fetal bradycardia) but less hypotension than the low-dose sufentanil/bupivacaine group. The incidence of FHR abnormalities was similar in the low-dose sufentanil/bupivacaine and conventional epidural analgesia groups. The rates of cesarean delivery for FHR abnormalities were similar in the three groups. Although FHR

abnormalities are worrisome, most published trials have not reported a higher risk for emergency cesarean delivery with intrathecal opioid analgesia.[330,334,335] However, Gambling et al.[336] reported more operative deliveries for nonreassuring fetal status after administration of intrathecal sufentanil 10 μg than with parenteral meperidine analgesia. The study's conclusions, however, were limited in that the two study groups differed in frequency of FHR assessment.

In a randomized trial, Abrao et al.[337] evaluated the effects of CSE versus traditional epidural analgesia on basal uterine tone and the occurrence of FHR abnormalities. Use of the CSE technique was the only independent predictor of an increase in basal intrauterine pressure of 10 mm Hg or more (OR, 3.53; 95% CI, 1.21 to 10.36; $P = .022$). The authors also demonstrated that the only predictor of FHR abnormalities was an increase in intrauterine pressure after initiation of analgesia (OR, 18.62; 95% CI, 4.46 to 77.72). A decrease in visual analog scale pain scores immediately after administration of analgesia was also correlated with an increased probability of increased intrauterine pressure and FHR abnormalities. Although there were no emergency cesarean deliveries that resulted from either neuraxial technique, the authors concluded that more studies are needed to better understand the effects of the CSE technique on labor progress and fetal physiology.[337] However, in a letter-to-the-editor, Landau et al.[338] suggested that the analgesic techniques were not equipotent. Additionally, monitoring for FHR abnormalities was only performed for 15 minutes. Given that the onset of analgesia is slower with epidural compared with CSE techniques, FHR abnormalities may occur earlier after intrathecal analgesia.

Given the potential risk for fetal bradycardia after neuraxial analgesia in laboring women, the FHR should be monitored before and after the initiation of epidural and intrathecal analgesia. FHR changes are usually transient and may be managed successfully with conservative measures, including (1) supplemental oxygen administration, (2) position changes to relieve aortocaval compression, (3) vasopressor therapy to treat hypotension, (4) discontinuation of oxytocin infusion, (5) intravenous fluid bolus administration, and (6) administration of a tocolytic agent for persistent uterine tachysystole.

Historically, intravenous or subcutaneous **terbutaline** was used to treat persistent uterine tachysystole. More recently, **nitroglycerin** has been used with some success. Nitroglycerin has several advantages compared with terbutaline. First, nitroglycerin has a short duration of action and labor resumes shortly after the period of tachysystole. In addition, nitroglycerin rarely produces significant hypotension, and if hypotension occurs, it is easily treated. Several studies have evaluated nitroglycerin for the treatment of uterine hypertonus. Mercier et al.[339] described consistent success in treating FHR abnormalities resulting from uterine tachysystole after the administration of one or two doses of nitroglycerin (60 to 90 μg), and Bell[340] described the successful use of sublingual nitroglycerin (400 μg) in the treatment of uterine tachysystole. In a randomized trial comparing intravenous terbutaline 250 μg to nitroglycerin 400 μg for the treatment of intrapartum tachysystole and nonreassuring FHR tracings, acute intrauterine resuscitation success rates were similar between the two groups (72% versus 64% for terbutaline and nitroglycerin, respectively; $P = .38$), but the incidence of tachysystole 10 minutes after drug administration was lower in the terbutaline group.[341] Therefore, if there is no response within 2 to 3 minutes of nitroglycerin administration, terbutaline 0.25 mg (250 μg) should be administered and preparations should be made for emergency cesarean delivery if the fetal bradycardia does not resolve.

ADJUVANTS

Epinephrine

Epinephrine is often added to epidural and spinal local anesthetic solutions to increase the duration of anesthesia, reduce peak plasma drug concentrations, improve block reliability, and intensify analgesia/anesthesia.[342-344] Uptake of epinephrine varies with the choice and concentration of local anesthetic as well as the concentration of epinephrine. The effect of epinephrine is greater when it is combined with lidocaine than when it is combined with bupivacaine.[159,198] Even concentrations of epinephrine as low as 3.3 μg/mL (1:300,000) have been shown to be effective in reducing the plasma concentrations of lidocaine.[344]

The efficacy of epinephrine depends on the specific local anesthetic as well as the site of injection. Epinephrine prolongs the duration of epidural lidocaine anesthesia by reducing uptake of local anesthetic into the systemic circulation through constriction of the epidural venous plexus. This effect helps maintain the concentration of local anesthetic at the site of injection. During epidural administration, epinephrine provides optimal results when added to lidocaine in a concentration of 5 μg/mL (1:200,000); this concentration of epinephrine nearly doubles the duration of epidural lidocaine anesthesia.[345] In contrast to lidocaine, the addition of epinephrine 3.3 μg/mL to epidural bupivacaine 0.5% had no effect on maternal venous plasma concentrations of drug in laboring women.[346] Similarly, Reynolds et al.[347] observed no effect when epinephrine 5 μg/mL was added to bupivacaine during administration of epidural anesthesia for cesarean delivery. Epinephrine did not prolong the epidural anesthesia produced by ropivacaine,[348] nor did it alter absorption of lidocaine after subarachnoid injection.[349] In contrast, one group reported that the addition of epinephrine to bupivacaine resulted in a 50% decrease in maternal plasma concentrations of bupivacaine after *paracervical* block.[350]

Greater reliability and intensity of the block are sometimes observed when epinephrine is added to epidurally administered local anesthetics. Epinephrine has intrinsic analgesic effects that are produced by stimulation of α_2-adrenergic receptors. These presynaptic adrenergic receptors are found at the terminals of primary afferent neurons. They can also be found centrally on neurons in superficial laminae of the spinal cord and in several brainstem nuclei.

In addition to the intrinsic analgesic effects of epinephrine, the inherent lipid solubility of each local anesthetic affects the degree of sensory blockade. Each local anesthetic has a lipid-to-water partition coefficient that determines the drug uptake between the aqueous and lipid phases within the spinal canal. The outcome of competition between these lipid and aqueous phases depends on the lipid solubility of the local anesthetic. If a local anesthetic is more lipid soluble, the advantage of adding epinephrine to the local anesthetic is less significant. For example, the lipid-to-water partition coefficient of lidocaine is 2.7. When epinephrine is added to lidocaine, there is marked improvement in the intensity of the block. However, because bupivacaine has a lipid-to-water partition coefficient 10 times greater than that of lidocaine, the effect of epinephrine on a bupivacaine block is less pronounced. Because ropivacaine has a lipid-to-water partition coefficient similar to that of lidocaine, epinephrine will intensify a ropivacaine block. However, the duration of the block remains unchanged.

Despite the advantages of epinephrine, concern remains about the effects of epinephrine on uterine blood flow and the maternal cardiovascular system. In healthy fetuses, epidural administration of epinephrine does not affect umbilical cord blood flow. However, in fetuses with increased vascular resistance, epidural epinephrine administration can increase the umbilical artery S/D ratio.[351] Studies of the effects of epinephrine on the placental transfer of local anesthetics have yielded contradictory results. In rabbits, epinephrine did not affect the F/M ratio of bupivacaine.[352] As a result of the addition of epinephrine, the F/M ratio for bupivacaine has been found to be increased[353] or unchanged.[346,350,354] For lidocaine, the F/M ratio has variously been reported to be increased,[198,355] decreased,[344] or unchanged.[356]

Bicarbonate

The addition of sodium bicarbonate to a local anesthetic solution increases the pH closer to the pKa of the local anesthetic. This change increases the proportion of drug in un-ionized form that is available to penetrate the nerve sheath and membrane, thereby accelerating the onset of the block and decreasing the minimum concentration required for conduction blockade.[357] Most studies have demonstrated that the addition of sodium bicarbonate to lidocaine, bupivacaine, or 2-chloroprocaine hastens the onset of epidural blockade by as much as 10 minutes.[148,358-360] The speed of onset of a ropivacaine block does not seem to be affected by alkalinization, but as with the other local anesthetics, evidence suggests that alkalinization intensifies epidural ropivacaine anesthesia and improves spread to sacral dermatomes.[361] The effects of alkalinization are most pronounced in epinephrine-containing solutions, particularly commercially prepared epinephrine-containing formulations. These solutions are prepared at a lower pH, ranging from 3.2 to 4.2.[362] The lower pH of these solutions helps preserve the epinephrine but increases the latency of onset.

Sodium bicarbonate 1 mEq/mL (8.4%) may be freshly added to local anesthetic solutions shortly before use (Table 13-6). Alkalinization of bupivacaine must be performed carefully because the margin between satisfactory alkalinization and complete precipitation is very narrow. All local anesthetics have a tendency to precipitate, so solutions containing bicarbonate should be inspected for precipitation before being administered.

TABLE 13-6 Alkalinization of Local Anesthetic Solutions

Local Anesthetic	Sodium Bicarbonate (mL)*
Lidocaine	1.0
Bupivacaine	0.1
2-Chloroprocaine	0.3

*Sodium bicarbonate 8.4% (1 mEq/mL) added to 10 mL local anesthetic solution. Suggested doses are from Warren DT, Neal JM, Bernards CM. Neuraxial anesthesia. In Longnecker DE, Newman MF, Brown DL, Zapol WM, editors. Anesthesiology. 2nd edition. New York, McGraw-Hill, 2012. Available at http://www.accessanesthesiology.com/content/56638559. Accessed August 2013..

Hypotension occurs more frequently with epidural administration of an alkalinized local anesthetic than with administration of an unbuffered solution.[363] This likely results from an accelerated onset of sympathetic blockade. Carbonated salts of local anesthetics can also be administered for a rapid onset of epidural blockade. However, these drugs have limited availability. Like alkalinized local anesthetics, these preparations are more likely to produce hypotension.

Clonidine

α_2-Adrenergic agonists (e.g., **clonidine**) have been investigated as adjuvants to local anesthetics and opioids to improve analgesic efficacy without increasing side effects. The advantage of clonidine is its ability to provide analgesia without affecting sensation or producing motor blockade.[364] However, epidural and intrathecal administration of α_2-adrenergic agonists are known to produce hypotension, probably by acting on α_2-adrenergic receptors on preganglionic cholinergic neurons.[365] In addition, α_2-adrenergic agonists produce dose-dependent sedation, which results from α_2-adrenergic stimulation in the locus ceruleus.[366]

Neuraxial clonidine has been administered for labor as well as analgesia after cesarean delivery. It exerts its effects by binding to α_2-adrenergic receptors located on primary afferent terminals of the spinal cord, substantia gelatinosa, and brainstem nuclei[367] as well as via a cholinergic mechanism.[368] Conduction blockade is produced by increases in potassium conductance and in acetylcholine and norepinephrine in the CSF, leading to decreased release of substance P and subsequent analgesia.[369]

Approximately 70% of alpha-adrenergic receptors on human myometrium are α_2-adrenergic receptors[370]; therefore, the potential effects of clonidine on labor and delivery have been evaluated. In an *in vitro* study, clonidine directly enhanced the frequency and amplitude of human myometrial contraction.[371] α_2-Adrenergic receptor stimulation in the uterus could theoretically enhance uterine contractions and decrease uterine blood

flow.[365] Indeed, in animal studies, large doses of clonidine produced a decrease in FHR.[372] This effect probably resulted from direct fetal transfer of drug and from direct and indirect effects on baroreflexes. However, this effect is unlikely to occur with clinical doses of neuraxial clonidine.

Multiple studies have evaluated neuraxial clonidine administration in humans as an analgesic adjunct during labor and delivery (see Chapter 23). When combined with local anesthetics and opioids, lower doses may be used, resulting in less hypotension and sedation. The FDA has issued a "black box" warning against its use in obstetric patients because of concerns about hemodynamic instability after its use. Therefore, clonidine is rarely used for labor analgesia in North America; however, it is more widely used in some European countries. Clonidine may be particularly useful in women in whom other epidural analgesics are contraindicated or in those who have breakthrough pain with standard local anesthetic/opioid solutions despite a functioning epidural catheter. In this setting, the bolus administration of clonidine 75 μg without a local anesthetic is not usually associated with hypotension. It appears safe to add small doses of intrathecal clonidine (15 to 30 μg) to opioids or local anesthetics, but side effects must be treated promptly to avoid fetal compromise.

Epidural clonidine has been administered for analgesia after cesarean delivery. One study suggested that epidural clonidine (400 to 800 μg) provided postoperative analgesia, but a continuous infusion was required after 6 hours.[373] Others have demonstrated that epidural clonidine (75 to 150 μg) lengthens the duration of postoperative analgesia without increasing the incidence of side effects.[374,375]

Neostigmine

Both nicotinic and muscarinic cholinergic receptors are present in the dorsal horn of the spinal cord. Neostigmine prevents breakdown of acetylcholine in the spinal cord. The acetylcholine then binds to muscarinic and nicotinic receptors of the spinal cord.[376-378] Stimulation of muscarinic receptors facilitates release of gamma-aminobutyric acid (GABA) in the dorsal horn of the spinal cord, resulting in analgesia.[368,379] Neostigmine and clonidine use a common pathway to produce analgesia mediated through acetylcholine release.

Several studies have evaluated the addition of neostigmine to intrathecal labor analgesics. Although results of these studies were inconsistent in terms of prolonging the duration of labor analgesia, all studies found that intrathecal administration of neostigmine produced severe nausea unresponsive to standard antiemetics.[380,381] These important gastrointestinal side effects limit its clinical use despite its ability to potentiate the analgesic effects of intrathecal opioids and clonidine.

Epidural neostigmine alone has limited efficacy. Neostigmine appears to be more effective at alleviating somatic pain than visceral pain.[382,383] Visceral afferents are located deep within the spinal cord. Because neostigmine has low lipid solubility, it has a limited ability to traverse biologic membranes. When it is administered without other agents, it is unable to reach these visceral afferents responsible for much of labor pain.[384] This accounts for the limited efficacy of neostigmine epidurally administered as the sole agent. However, when combined with epidural sufentanil or clonidine for initiation of analgesia, neostigmine produces selective analgesia without side effects.[385,386] Large doses of neostigmine can potentially reduce uteroplacental blood flow by CNS activation and direct stimulation of uterine contractions.[387] When administered for analgesia after cesarean delivery, epidural neostigmine (75 to 300 μg) produced modest analgesia without nausea or vomiting, but the incidence of sedation was increased.[388] Neostigmine is not routinely used in clinical practice, and its neuraxial administration is not approved by the FDA.

KEY POINTS

- Pregnancy enhances the effect of local anesthetic agents.
- Appropriate administration of epidural anesthesia does not adversely affect uterine tone or uterine or umbilical blood flow.
- Bupivacaine has greater cardiotoxicity than lidocaine because of its greater electrophysiologic effects, which predispose to ventricular arrhythmias.
- Single (levorotary) isomer formulations of amide local anesthetics, such as ropivacaine and levobupivacaine, have a lower potential for cardiotoxicity than racemic bupivacaine.
- The decision to initiate lipid therapy for treatment of local anesthetic systemic toxicity should be based on clinical severity and rate of progression of symptoms.
- Fetal acidosis results in a greater accumulation of amide local anesthetic in the fetus.
- Local anesthetics, as used clinically, are not teratogenic.
- The elimination half-life of amide local anesthetics is longer in the newborn than in the adult because the former has a greater volume of distribution.
- The fetus and newborn seem to be no more vulnerable to the toxic effects of local anesthetics than the adult.
- Neonatal neurobehavior depends on many factors other than the choice of local anesthetic.
- Alkalinization of a local anesthetic solution shortens the latency of neural blockade but increases the risk for hypotension during administration of epidural anesthesia.
- Neuraxial opioid administration produces analgesia without loss of sensation or proprioception.
- The combination of a neuraxial local anesthetic and an opioid increases block density and allows

for administration of a lower total dose of local anesthetic and a lower incidence of side effects.

- Spinal bioavailability of the hydrophilic drugs (e.g., morphine, hydromorphone) is greater than that of hydrophobic (lipophilic) opioids (e.g., fentanyl, sufentanil).
- The most common side effects of neuraxial opioid administration are pruritus and nausea and vomiting. Fetal bradycardia and maternal respiratory depression are the most serious complications.

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PART V

ANESTHESIA BEFORE AND DURING PREGNANCY

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During the early years of obstetric anesthesia, physicians were primarily concerned with its effect on neonatal respiration. Almost 25 years passed before some investigators began to suspect that anesthesia might cause other problems. In fact, it was the suspicion that chloroform caused icterus neonatorum that originally stimulated Paul Zweifel to study placental transmission.

Icterus neonatorum was not Zweifel's original interest. Under the guidance of Adolf Gusserow, one of the preeminent obstetricians in Europe, Zweifel had been studying glucose metabolism during pregnancy. In the course of his work, Zweifel unexpectedly found a reducing compound in the urine of infants whose mothers had received chloroform during labor. At first he suspected that the compound might be glucose, thinking that the metabolism of this compound had somehow been altered by chloroform. After further testing, however, he learned that the reducing substance was not glucose but chloroform itself.

Zweifel thought that chloroform, transmitted to the fetus during labor, might explain some cases of neonatal jaundice. By 1876, physicians already knew that chloroform affected the liver. To cause icterus neonatorum, sufficient quantities of the drug would have to traverse the placenta during the course of a normal labor; the rapidity of transfer was a point of contention among clinicians. To establish the possibility, Zweifel performed experiments that identified chloroform in fetal blood and urine.[1,2]

Zweifel later discounted chloroform as a cause of icterus neonatorum, and the issue was dropped. Another 75 years passed before physicians began to appreciate that drug exposure during pregnancy might have deleterious effects. Events that called attention to the problem included (1) sequelae from radiation exposure after the first use of the atomic bomb; (2) the skeletal deformities associated with the use of thalidomide, a drug once used to treat the nausea of early pregnancy; and (3) the high incidence of genital tumors among daughters of women who had been given diethylstilbestrol during pregnancy. By then the public had also been alerted through the publication of Rachel Carson's *Silent Spring*, which contained graphic descriptions of the environmental effects of the indiscriminant use of insecticides. Physicians also knew more about embryology and toxicology, better techniques for testing drugs were available, procedures for collecting information were standardized, and information about complications was disseminated. Undoubtedly, greater public awareness of these developments contributed to the resurgence of natural childbirth after 1950.

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CHAPTER 14

Pharmacology and Nonanesthetic Drugs during Pregnancy and Lactation

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CHAPTER OUTLINE

Drug therapy during pregnancy can be complex because the physiologic changes of pregnancy may alter drug disposition and effect. Maternal medications may have direct effects on the fetus after placental transfer or indirect effects through changes in placental and uterine function. Even after delivery, drug transfer to breast milk may be a concern. Nevertheless, pregnant women still require medications to treat many acute and chronic conditions. The challenge is finding the balance between the benefits and risks of therapy.

It would seem prudent to use only drugs considered safe in pregnancy. Unfortunately, the potential adverse effects of many drugs remain unclear. Pregnant women are not usually included in early clinical trials, and because of the low incidence of some complications, the first suggestion of adverse effects may be revealed only from post-marketing surveillance and registries of complications. This uncertainty about safety, and the difficulties in determining what public information is reliable, may convince mothers to refuse appropriate drug treatment. New improved drugs are available in many areas of therapeutics, but many prescribers prefer to use older drugs that have a longer empirical history of safety.

Maternal variations in drug effect are not usually difficult to manage, and a change in dosing regimen or the choice of drug may be all that is required. The greatest fears and concerns are for potential fetal effects that may manifest as teratogenicity with fetal loss or congenital malformations, fetal growth restriction (also known as intrauterine growth restriction), preterm labor, and other complications. Impaired development and behavioral problems may manifest after delivery.

The anesthesia provider should understand the implications of pregnancy on drug disposition and effect. Although not usually responsible for primary maternal drug therapy, he or she will encounter women taking many different medications and may sometimes need to

administer a variety of nonanesthetic drugs during the peripartum period, either for maintenance of chronic therapy or for acute indications, especially when managing critically ill patients.

In this chapter, how maternal physiology affects pharmacology is summarized, teratology and fetal effects of the main classes of drugs the anesthesia provider is likely to encounter are addressed, and drug transfer to breast milk is reviewed. The more common perioperative drugs are used as examples. Specific drugs used in the management of individual obstetric conditions are discussed in other chapters.

CHANGES IN DRUG DISPOSITION AND EFFECT

Pharmacogenetics

Genetic differences are responsible for some of the variation in drug response among individuals. Pregnancy does not obviously modify these pharmacogenetic differences, although some obstetric conditions such as preeclampsia are related to complex genetic factors. There are, however, some examples in which underlying genetic differences do affect obstetric management.[1]

The metabolism of codeine to morphine is greatly affected by polymorphisms of the cytochrome P450 (CYP) isoenzyme CYP2D6. It has been recognized only recently that mothers who are ultrarapid metabolizers may produce and transfer sufficient morphine through breast milk to cause neonatal central nervous system (CNS) depression and even death.[2]

Two of the possible changes at the β_2-adrenergic receptor are an arginine-to-glycine substitution at codon 16 (Arg16Gly) and a glutamine-to-glutamate substitution at codon 27 (Glu27Gln). When β_2-receptor agonists were used for tocolysis, Arg16 homozygotes had longer gestation and better neonatal outcome.[3] In the management of hypotension during spinal anesthesia for cesarean delivery, Gly16 homozygotes and Glu27 homozygotes required less ephedrine.[4]

The μ-opioid receptor gene may have an adenine-to-guanine substitution at nucleotide position 118 (A118G). There have been many studies of the effects of this polymorphism on opioid dose requirements and response, although the studies in obstetric patients have had conflicting results. For example, laboring women who were AA homozygous had an increased intrathecal fentanyl requirement for analgesia.[5] In contrast, AA homozygous women receiving intrathecal morphine for postcesarean analgesia reported less pain and required less patient-controlled morphine but had a higher incidence of nausea and vomiting.[6] Wong[7] summarized the conflicting evidence and noted that the true effect of this polymorphism is probably small. Many other genetic factors influence opioid disposition and response, and even more factors influence pain perception. Indeed, a meta-analysis found that A118G polymorphism only explained 7% of the variability in opioid requirements.[8] Thus, at present there are no indications for pharmacogenetic testing in routine obstetric practice.[9]

Pharmacokinetic Changes

The major physiologic changes during pregnancy would be expected to alter drug disposition.[10,11] However, the magnitude and time course of these changes vary throughout pregnancy and among individuals. The results of many older studies are unreliable because the studies were often of low quality. Thus, making generalizations about the effects of pregnancy on drug disposition can be difficult, and individualized dosing is important.

Maternal Pharmacokinetics

Absorption and Uptake. Oral absorption and bioavailability are not usually affected by pregnancy, although nausea and vomiting may limit oral intake. Intestinal motility is decreased during pregnancy, but gastric emptying is only delayed during labor or after opioid administration. Cardiac output is increased by 30% to 50% during pregnancy, and the increased blood flow to skin and mucous membranes will enhance absorption from these sites. Reduced functional residual capacity and increased minute ventilation lead to increased pulmonary uptake of inhalational anesthetic agents.

Distribution. The increased cardiac output during pregnancy increases distribution of drug to all tissues. Drugs acting peripherally (e.g., neuromuscular blockers) will be delivered to their site of action more quickly. However, the onset of intravenous and inhalational anesthetics is dependent on the time course of their cerebral drug concentrations. A delay in the increase in arterial and brain anesthetic concentrations will result from increased peripheral perfusion. Increased peripheral perfusion will, however, increase the return of drug during the elimination phase. Total body water increases on average by 8 L, and intravascular plasma volume is increased by 40%, whereas extravascular volume increases by a variable amount, depending on weight gain and edema. Thus, hydrophilic drugs, such as neuromuscular blockers, will have a small increase in the volume of distribution. Body fat is increased on average by 4 kg, but this is unimportant given the large volume of distribution of lipophilic drugs.

Changes in protein binding are more important clinically. Plasma albumin concentration is reduced to about 70% of normal, whereas α_1-acid glycoprotein concentration is largely unchanged. Protein binding of drugs may be reduced by increased concentrations of free fatty acids and other endogenous displacing substances. This leads to increased concentrations of free drug, but with chronic drug administration this is offset by increased clearance of that free drug. The total (free + bound) concentration of drug will decrease, and it may be necessary to reset the therapeutic target range lower to compensate. Thus, it is important to know whether monitored concentrations are for free or total drug. Only a few drugs (e.g., theophylline, phenytoin) require monitoring and modification of dose because of changes in protein binding.

Metabolism. Most drugs are metabolized in the liver, and the rate of metabolism may depend on hepatic blood flow or intrinsic enzyme activity. Although cardiac output

is increased in pregnancy, it is not clear whether blood flow to the liver is significantly increased. Two studies using clearance of markers concluded that hepatic blood flow was unchanged,[12,13] whereas another using Doppler ultrasonography reported unchanged hepatic arterial flow during pregnancy but increased portal venous flow after 28 weeks' gestation.[14] More importantly, some cytochrome P450 isoenzymes (CYP3A4, CYP2D6, and CYP2C9) and uridine diphosphate glucuronosyltransferase (UGT) isoenzymes (UGT1A4 and UGT2B7) have increased activity during pregnancy,[10,15] which increases the metabolism of drugs such as phenytoin (CYP2C9), midazolam (CYP3A4), and morphine (UGT2B7). Other isoenzymes (CYP1A2 and CYP2C19) have decreased activity, which reduces the metabolism of drugs such as caffeine and theophylline (CYP1A2).

Elimination. Renal blood flow is increased by 60% to 80% and glomerular filtration rate is increased by 50% in pregnancy; thus, the renal excretion of unchanged drugs such as cephalosporin antibiotics is increased. There is also increased activity of transporter proteins such as renal P-glycoprotein, which may contribute to the increased clearance of digoxin in pregnancy.[16] Increased minute ventilation enhances elimination of inhalational anesthetic agents.

The physiologic changes of pregnancy will affect individual drugs depending on their physicochemical characteristics and metabolic pathways. Bioavailability is not usually changed significantly. Changes in volume of distribution as a result of changes in protein binding may affect drugs such as phenytoin, but monitoring and modification of therapy is usually straightforward. Drugs metabolized by the liver may require increases or decreases in dose, depending on the metabolic pathway involved. Drugs excreted unchanged by the kidneys often require an increased dose.

Placental Transfer and Metabolism

Our understanding of placental transfer and metabolism is rapidly improving (see Chapter 4). Early research was often limited to measuring drug concentrations in the umbilical vessels and maternal vein at delivery. Results were variable and difficult to interpret, especially for drugs such as anesthetic agents that are administered shortly before delivery. Umbilical blood samples are obtained at variable times after drug exposure, well before steady-state conditions are achieved. The theory of a placental barrier was proposed because maternal and fetal concentrations were often different. However, differences in concentrations of binding proteins are mainly responsible for the fetal-maternal distribution of drugs at steady state.[17] The fetal concentration of albumin is slightly greater than in the mother, but α_1-acid glycoprotein concentration is only a third of the maternal value at term. Umbilical-to-maternal blood ratios of total drug may be misleading because it is the free drug that equilibrates across the placenta. Maternal-to-fetal ratios of drugs do not provide information on the rate of drug transfer or the amount of drug that has already been transferred to the fetus.

Drug transfer across the placenta was previously thought to occur mainly by diffusion. This would favor the movement of lipophilic drugs, and placental perfusion would be an important factor affecting transfer. Fetal pH is lower than maternal pH, so that weak bases become more ionized in the fetus, thus limiting their transfer back across the placenta. Normally, the difference in pH is only 0.1 and this "ion trapping" is irrelevant, but fetal acidosis can significantly increase the fetal concentration of drugs such as local anesthetics.

It is now known that the placenta contains many drug transporters that can modify fetal drug exposure, and these are particularly relevant when trying to use transplacental pharmacotherapy to deliver drugs to the fetus.[18,19] For example, in the treatment of sustained fetal tachyarrhythmia, placental P-glycoprotein, an adenosine triphosphate–dependent drug efflux pump, will reduce net transfer of substrates such as digoxin and verapamil from the mother. With maternal human immunodeficiency virus (HIV) infection, treatment of the fetus is also required, but drug transporters limit the transfer of some antiviral drugs, such as protease inhibitors.

The placenta also contains many enzymes, especially those such as UGT that catalyze phase II conjugation reactions.[19,20] Clearance of substrates by UGT in full-term placentas may be sufficient to contribute to overall maternal metabolism.

Fetal and Neonatal Elimination. The fetus and neonate metabolize drugs, but at a reduced rate compared with adults.[21,22] The fetal circulation guides drug transferred across the placenta to undergo first-pass hepatic metabolism, but some drug will bypass the liver. Renal blood flow is minimal until near term, and any excreted products would just pass into the amniotic fluid to be swallowed. Elimination of drugs by the fetus is thus mainly reliant on placental transfer. It would seem prudent to minimize the amount of drug transferred to the neonate and choose drugs that are eliminated rapidly. Relatively large minute ventilation promotes neonatal elimination of inhalational anesthetic agents, and this may be further increased by assisted ventilation.

Pharmacodynamic Changes

Changes in the concentrations of various hormones may alter the response to other substances. In particular, progesterone and endorphins may enhance sedation and antinociception, respectively. A pharmacodynamic difference specifically refers to a change in response to a given effect-site concentration, but it is difficult during pregnancy to carry out the high-fidelity studies necessary for accurate pharmacokinetic-pharmacodynamic modeling. Thus, the demonstrations of pharmacodynamic changes in pregnancy have been limited to specific experimental designs where there are large differences in effect.

General Anesthesia

Early animal studies showed that maternal anesthetic requirements were reduced during pregnancy. Minimum alveolar concentration (MAC) values for inhalational

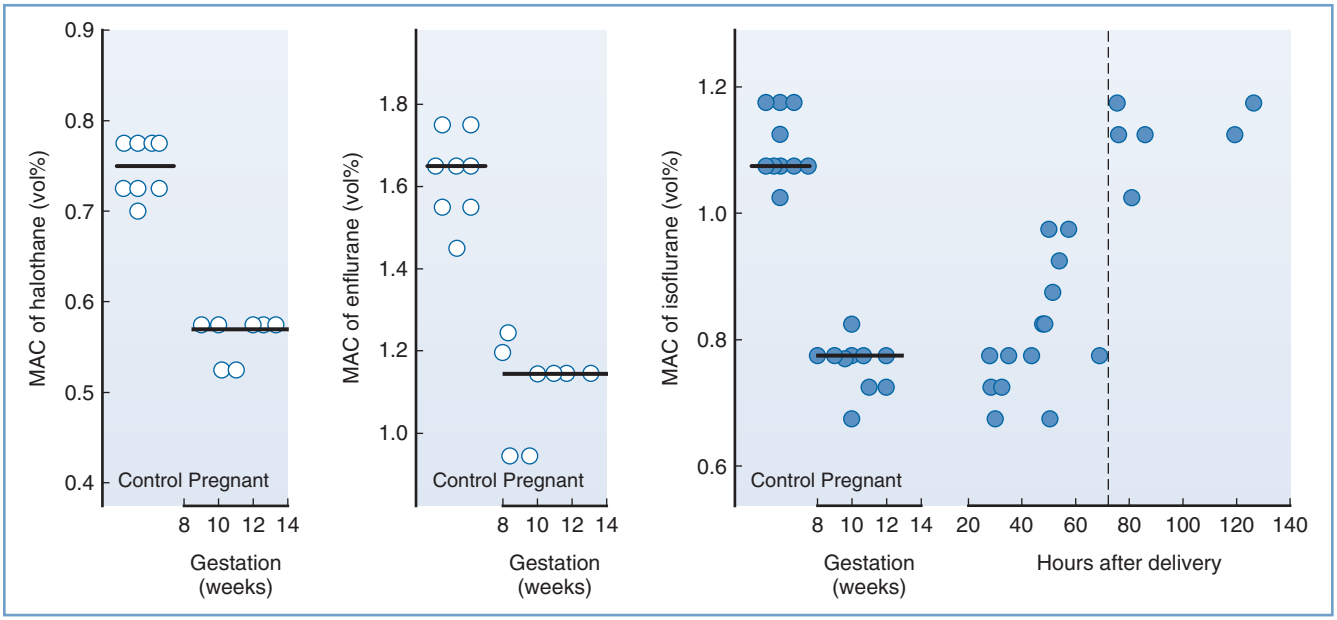

FIGURE 14-1 ■ Changes in minimum alveolar concentration (MAC), determined by response to transcutaneous electrical stimulation, for halothane, enflurane, and isoflurane in early pregnancy and for isoflurane in the early postpartum period. (Reproduced with permission from Gin T. Obstetric pharmacology. In Evers AS, Maze M, Kharasch ED, editors. Anesthetic Pharmacology: Basic Principles and Clinical Practice, 2nd edition. Cambridge, Cambridge University Press, 2011:948-62. Original data from references 25, 26, and 27.)

agents were reduced by 25% to 40% in pregnant ewes[23] and by 16% to 19% in pregnant rats.[24] Ethical and practical difficulties with research in pregnant women delayed confirmation of this finding in humans. Isoflurane MAC (determined using transcutaneous electrical stimulation instead of the classic skin incision) was decreased by 28% in women undergoing termination of pregnancy at 8 to 12 weeks' gestation.[25] Similar reductions in MAC were found for enflurane (30%) and halothane (27%).[26] MAC was reduced by 30% in the immediate postpartum period, with a return to nonpregnant values by 12 to 72 hours after delivery (Figure 14-1).[27,28]

Progesterone is probably the cause of the reduced anesthetic requirements during pregnancy; chronic progesterone administration reduced MAC in rabbits, dogs, and sheep.[29-31] Although human studies have not found a good correlation between progesterone concentrations and the reduction in anesthetic requirement, a poor correlation may be expected if the effect of progesterone is not dose-dependent; it is possible that progesterone concentrations only need to exceed a low threshold to decrease anesthetic requirements. Lower concentrations of sevoflurane were required to maintain anesthesia in nonpregnant women during the luteal phase of the menstrual cycle, when progesterone concentrations are elevated, compared with during the follicular phase.[32] The progesterone concentrations during pregnancy are much greater than those seen during the luteal phase of the menstrual cycle. The reduced MAC during pregnancy may also be a result of the increased endogenous endorphins that mediate the increase in nociceptive threshold during pregnancy; it is well known that opioids reduce MAC.

Pregnancy also alters other measures of anesthetic effect. In early pregnancy, the isoflurane concentration required for hypnosis was reduced by 31% and the bispectral index (BIS) was decreased at isoflurane concentrations over the range 0.1% to 2.0%.[33] During the second trimester, the sevoflurane concentration required to achieve a targeted BIS of 50 was reduced by 31%.[34] Both in early and term pregnancy, the median concentration of nitrous oxide required for loss of consciousness (MAC_{awake}) was reduced by 25% to 27%.[35] One study did not show any difference in electroencephalographic (EEG) measures between women having cesarean delivery or gynecologic surgery, but there were many confounding factors such as the study being conducted partly during and partly after surgery, the concurrent use of significant doses of fentanyl, large variations in EEG measures, and small sample size.[36]

The data for intravenous anesthetic agents are more variable, partly because of methodologic challenges. It is difficult to produce a stable effect-site concentration of intravenous drugs to allow accurate measurement of drug effect. Increased cardiac output usually results in an increase in intravenous anesthetic dose requirements to produce central effects, and this change would counter any decrease in requirements with pregnancy. The bolus dose of thiopental for hypnosis (failure to open eyes to command) was 17% lower, and that for anesthesia (no purposeful movement to a transcutaneous electrical stimulus) was 18% lower in early pregnancy compared with nonpregnant women (Figure 14-2).[37] A similar reduction was found in the early postpartum period, less than 60 hours after delivery.[38]

Studies using target-controlled infusions may not be reliable because the pharmacokinetic models may not be accurate in pregnancy, and they are known to predict concentrations poorly at induction of anesthesia. These methodologic problems may be the reason one study

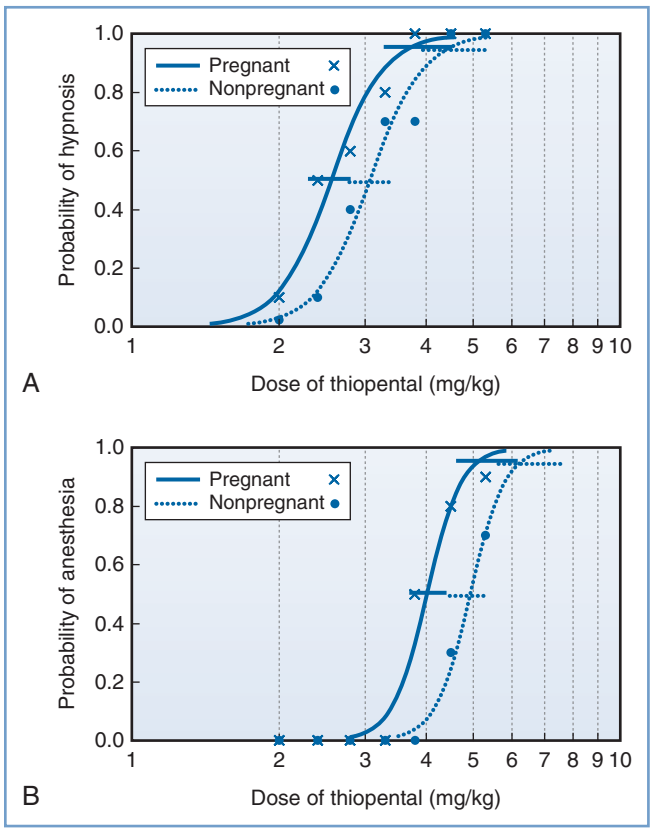

FIGURE 14-2 ■ Calculated dose-response curves (log[dose] scale) for thiopental for hypnosis (**A**) and anesthesia (**B**) in pregnant and nonpregnant women. The 95% confidence intervals for the values of ED_{50} and ED_{95} are also displayed, slightly offset for clarity. Raw data are shown for pregnant women (x) and nonpregnant women (●). (Modified with permission from Gin T, Mainland P, Chan MTV, Short TG. Decreased thiopental requirements in early pregnancy. Anesthesiology 1997; 86:73-8.)

found no differences in the concentration of propofol required for loss of consciousness in early pregnancy.[39] Another study used a slow infusion of propofol for induction of anesthesia and found that the dose and calculated effect-site concentrations at loss of consciousness were 8% lower than in nonpregnant women.[40] The reduction in anesthetic requirement for intravenous agents appears to be less (8% to 18%) than that for inhalational agents (approximately 30%). It is not known whether this reflects real differences between the drugs or the methodologic problems just outlined.

Local Anesthesia

The spread of neuraxial block is increased in pregnant women (see Chapter 2). This has been shown as early as the first trimester for epidural anesthesia[41] and the second trimester for spinal anesthesia.[42] One small study suggested that although the spread of epidural block was increased, the latency and density of sensory and motor block were not.[43] However, two more recent studies showed that the median effective dose of intrathecal bupivacaine for motor block was decreased by 13% to 35% in pregnant women at term.[44,45] Magnetic resonance imaging has confirmed that pregnant women have increased epidural blood volume, decreasing the capacity of the epidural space and decreasing the volume of lumbar cerebrospinal fluid.[46,47] These mechanical factors would explain the increased spread of local anesthetic. However, several studies have also shown that there is increased sensitivity to local anesthetics during pregnancy. The onset of conduction block in the vagus nerve with bupivacaine was faster in pregnant versus nonpregnant rabbits.[48,49] Sciatic nerve block was of longer duration and the lidocaine content in the nerves was lower at the time of return of deep pain in pregnant versus nonpregnant rats.[50] Sensory nerve action potentials were inhibited to a greater extent during median nerve block at the wrist with lidocaine in pregnant versus nonpregnant women.[51] The increased sensitivity may be caused by progesterone because exogenously administered progesterone increased the susceptibility of rabbit vagus nerves to bupivacaine.[52] One study found no changes in conduction block in pregnant rats and suggested that enhanced block may be due to pregnancy-induced changes that facilitate diffusion of local anesthetic or an interaction with endogenous analgesic systems.[53]

Analgesia

Pregnancy is associated with increases in nociceptive response thresholds that are mediated by endogenous opioid systems.[54,55] The changes in threshold can be reproduced using exogenous progesterone and estrogen and appear to involve spinal cord kappa (κ) and delta (δ) opioid receptors and descending spinal α_2-noradrenergic pathways.[56] Early human studies produced mixed results, probably because of methodologic problems. Recent controlled studies showed that heat pain threshold was increased in term pregnant women, and this persisted during the first 24 to 48 hours after delivery.[57,58] Given the many different factors that influence pain behavior, especially those unique to pregnancy and delivery, it is difficult to determine how this change in pain threshold influences perioperative analgesic requirements.

DRUG USE DURING PREGNANCY

General Teratology

Teratology is the study of abnormal development or birth defects. Teratogens are substances that act to irreversibly alter growth, structure, or function of the developing embryo.[59] Ideally, preclinical studies would identify teratogens, but drug teratogenicity unfortunately can be markedly species-specific. For example, **thalidomide** produces phocomelia in primates but not in rodents.

In the United States, major malformations affect 2% to 3% of neonates.[60] A *major malformation* is defined as one that is incompatible with survival (e.g., anencephaly), one that requires major surgery for correction (e.g., cleft palate, congenital heart disease), or one that causes mental retardation. If all minor malformations (e.g., ear tags, extra digits) are included, the incidence of congenital anomalies may be as high as 7% to 10%. Exogenous causes of birth defects (e.g., radiation, infections,

maternal metabolic disorders, drugs, environmental chemicals) account for almost 10% of all major birth defects and therefore affect only 0.2% to 0.3% of all births. Drug exposure explains only 2% to 3% of birth defects, and the majority of birth defects are of unknown etiology.

To avoid unnecessary and potentially teratogenic exposures, nonpharmacologic techniques should be used when possible and drugs should be used only when necessary. The risk-to-benefit ratio should justify the use of a drug given to a pregnant woman, and the minimum effective dose should be employed. Long-term effects of fetal drug exposure may not become apparent for many years. Therefore, physicians and patients should exercise caution in the use of any drug during pregnancy. On the other hand, the physician should ask the following question: what would be the appropriate treatment in the nonpregnant patient with the same condition? In most cases, the answer is the same as that for women who are pregnant.[61]

Sensitive serum pregnancy tests can diagnose pregnancy as early as 1 week after conception. Before drug therapy is started, a sensitive test should be used if there is any question about drug safety during a potential pregnancy.

It is also important to remember that the male partner may be taking teratogenic drugs and the drug may be present in semen at low concentrations. Although the magnitude of fetal risk is unclear, men are advised to avoid drugs such as **thalidomide**, **ribavirin**, and **isotretinoin** if their partners could become pregnant.

The maternal and fetal genotype and phenotype can affect individual susceptibility to an agent. For example, fetuses with low levels of the enzyme epoxide hydrolase are more likely to manifest fetal hydantoin syndrome than those with normal levels of this enzyme.[62]

Drug teratogenicity is affected by the timing of exposure. Teratogen exposure in the first 2 weeks after conception is generally thought to be an all-or-nothing phenomenon (i.e., having either no effect or resulting in spontaneous fetal loss). Among women with a 28-day menstrual cycle, the classic period of susceptibility to teratogenic agents is during the period of organogenesis, which occurs primarily at 2½ to 8 weeks after conception (31 to 71 days, or 4 to 10 weeks, after the first day of the last menstrual period) (Figure 14-3). During organogenesis, each organ system has different critical periods of sensitivity and there may be striking differences in effect. When administered between 35 and 37 days' gestation, thalidomide produces ear malformations; when administered between 41 and 44 days' gestation, it produces amelia or phocomelia. After this period, embryonic development is characterized primarily by increasing organ size; thus, the principal effect of exposure consists of growth restriction and/or effects on the nervous system and gonadal tissue. For example, diethylstilbestrol exposure during the second trimester results in uterine anomalies that do not become apparent until after puberty. Fetal alcohol syndrome may occur with chronic exposure to alcohol during pregnancy.

The drug dosing regimen can influence teratogenicity. In most cases, administration of a low dose has no effect whereas malformations may occur at intermediate doses and death may occur at higher doses. Fetal death may allow organ-specific teratogenic activity to go unnoticed. Small doses administered over several days may have an effect different from that observed with the same total dose administered at one time. Sequential drug administration may induce the production of an enzyme that metabolizes the drug and thus results in less exposure. Constant exposure may destroy cells that would have catabolized the drug if it had been administered in periodic doses. Combinations of agents may produce different degrees of malformation and growth restriction from those that occur with drugs administered individually. For example, fetuses whose mothers receive combination anticonvulsant therapy are at the highest risk for malformations, including neural tube defects and facial dysmorphic features.

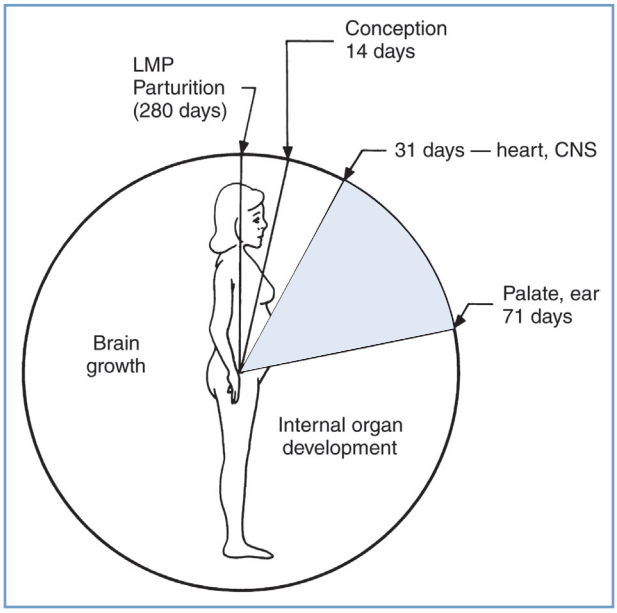

FIGURE 14-3 ■ Gestational clock showing the classic teratogenic period. *CNS,* central nervous system; *LMP,* day of last menstrual period. (From Niebyl JR. Drug Use in Pregnancy. 2nd edition. Philadelphia, Lea & Febiger, 1988:2.)

U.S. Food and Drug Administration Categories

In 1979, the U.S. Food and Drug Administration (FDA) introduced a drug classification system to discourage nonessential use of medications during pregnancy (Box 14-1).

Unfortunately, maternal anxiety related to medication use can lead to unnecessary pregnancy terminations. Several characteristics of the FDA drug classification system contribute to public perception—and *misperception*—of the dangers of using medication during pregnancy. Although only 20 to 30 commonly used drugs are known teratogens, 7% of all the medications that are listed in the *Physicians' Desk Reference* are classified as Category X.[63,64] All new medications are classified as Category C, leading to an exaggerated impression of

BOX 14-1 U.S. Food and Drug Administration Drug Classification System

Category A

Controlled studies have shown no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B

No evidence of human fetal risk exists. Either animal reproduction studies have not demonstrated fetal risk but no controlled studies in pregnant women have been reported or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).

Category C

Risk cannot be ruled out. Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) but no controlled studies in women have been reported, or studies in women and animals are not available. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D

Positive evidence of human fetal risk exists. However, the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed for a life-threatening condition or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X

Contraindicated in pregnancy. Studies in animals or human beings have demonstrated fetal abnormalities, or evidence exists of fetal risk based on human experience, or both, and the risk in pregnant women clearly outweighs any possible benefit. These drugs are contraindicated in women who are or may become pregnant.

Modified from Friedman JM. Report of the Teratology Society Public Affairs Committee symposium on FDA classification of drugs. Teratology 1993; 48:5-6.

the danger of many medications. In addition, the manufacturer's prescribing information for many drugs may state that the drug is not approved for use in pregnancy despite a long history of uncomplicated unlicensed or "off-label" use.[65]

The FDA categories imply a progressive fetal risk from Category A to X; however, the drugs in different categories may pose similar risks but may be listed in different categories on the basis of risk-to-benefit considerations. In addition, the categories create the impression that drugs within a category present similar risks whereas the category definition permits inclusion (in the same category) of drugs that vary in type, degree, and extent of risk.

Use of potentially teratogenic drugs in pregnancy is surprisingly commonplace. Over 63% of pregnant patients in Canada filled a prescription for at least one drug, with almost 8% filling a prescription for a Category D or X medication.[66]

When counseling patients or responding to queries from physicians, we prefer to avoid referring to the *Physicians' Desk Reference*. Rather, we use specific descriptions in teratogen databases to provide the best information available. Many resources are freely available online, in addition to the commercially available databases (Table 14-1).

The Teratology Society has suggested abandonment of the FDA classification scheme.[63] In 1997, the FDA held a public meeting to discuss labeling of drugs. There was consensus that the current classification scheme is probably oversimplified and confusing, does not address the range of clinical situations or the range of possible effects, and should be replaced with narrative labeling. Subsequently, a concept paper was presented that outlined a new model for labeling and included sections such as "clinical management statement," "summary risk assessment," and "discussion of data" for both pregnant and breast-feeding women.[67] This proposal has not yet been implemented. The FDA Office of Women's Health has created a pregnancy registry website, which lists a variety of registries that women who have used specific medications during pregnancy can consult (see Table 14-1). In 2008, the FDA stated they will eliminate the A, B, C, D, X classification system.[68] As of 2013, the new system has yet to be implemented despite completion of the 90-day comment period some time earlier.[69]

Analgesics

There is no known teratogenic risk associated with the use of **acetaminophen** (**paracetamol**),[70] which is the preferred mild analgesic or antipyretic during pregnancy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have not been associated with an increased risk for birth defects overall, but the occasional review has suggested an association with specific defects.[71] For example, **aspirin** is not associated with an overall increase in rates of congenital malformations, but one review suggested a higher risk for gastroschisis.[72] Aspirin is not usually the first choice of NSAID, but low-dose aspirin may still have a role in some situations, such as preventing fetal loss associated with antiphospholipid antibody syndrome.[73] Studies of the use of NSAIDs and aspirin in the first trimester have reported increased risk for pregnancy loss (adjusted odds ratio [OR], 1.8 to 8.1).[71] In the second trimester, their use has been associated with fetal cryptorchidism. In the third trimester, NSAIDs and aspirin are usually avoided because of significant fetal risks, such as renal injury, oligohydramnios, and intrauterine constriction of the ductus arteriosus, an effect that increases with advancing gestational age.[74] Renal injury, necrotizing enterocolitis, and intracranial hemorrhage are other potential complications.

Opioids such as **propoxyphene** and **codeine** have no known teratogenic risk,[75] but they have well-known potential for addiction. Excessive antepartum use can also lead to neonatal opioid-withdrawal symptoms.[76] Surprisingly, a recent case-control study found that maternal

TABLE 14-1 **Internet Resources for Additional Drug and Teratogen Information**

American Academy of Pediatrics: The Transfer of Drugs and Other Chemicals into Human Milk	http://pediatrics.aappublications.org/content/108/3/776.full.html
The American Botanical Council	http://www.herbalgram.org
The American College of Obstetricians and Gynecologists	http://www.acog.org/About_ACOG/ACOG_Departments/Resource_Center/WEBTREATS_Teratology_Toxicology
Motherisk	http://www.motherisk.org
Organization of Teratology Information Specialists: Fact sheets on exposure during pregnancy to a variety of diseases, medications, and herbal remedies	http://otispregnancy.org/otis_fact_sheets.asp
The National Library of Medicine PubMed	http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
The National Institutes of Health National Center for Complementary and Alternative Medicine	http://nccam.nih.gov
The National Institutes of Health Office of Dietary Supplements	http://dietary-supplements.info.nih.gov
Perinatology.com: Drugs in Pregnancy and Breastfeeding	http://www.perinatology.com/exposures/druglist.htm
The Reproductive Toxicology Center*	http://www.reprotox.org
RxList: The Internet Drug Index	http://www.rxlist.com
SafeFetus.com	http://www.safefetus.com
University of Washington Clinical Teratology Web*	http://depts.washington.edu/~terisweb
U.S. Food and Drug Administration Office of Women's Health	http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofWomensHealth/
Drugs and Lactation Database (LactMed)	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

*Databases, including Reprotox, Reprotext, Teris, and Shepard's Catalog of Teratogenic Agents, can be purchased from these websites.

opioid treatment (mostly codeine and **hydrocodone**) between 1 month before pregnancy and the first trimester was associated with an increased OR of 1.8 to 2.7 for various cardiac birth defects, spina bifida, and gastroschisis.[77]

Tramadol has analgesic effects from weak opioid activity and inhibition of serotonin and norepinephrine uptake. Despite availability in some countries for more than 30 years, few data are available regarding potential adverse effects in pregnancy. Tramadol exposure in early pregnancy was associated with a higher number of spontaneous abortions, and it should be avoided in the first trimester.[78] Chronic tramadol use in later pregnancy may result in neonatal withdrawal syndrome.

Sedatives

Human epidemiologic studies of the possible teratogenic effects of various tranquilizers are inconsistent. One report of nearly 400 patients found a 12% incidence of birth defects in the offspring of **meprobamate** users.[79] Another study of similar size did not identify any higher risk for malformations.[80] These latter two articles found similar results for **chlordiazepoxide**.[79,80] A recent study evaluating meprobamate used in high doses to attempt suicide did not show any teratogenic or fetotoxic effects.[81] A sample of 35 pregnant women who self-poisoned with chlordiazepoxide showed no association with congenital abnormalities but did show dose-related fetal growth restriction.[82]

Some studies have suggested that first-trimester exposure to **diazepam** increases the risk for cleft lip with or without cleft palate, neural tube defects, intestinal atresia, and limb defects.[83] Other reports have *not* suggested an increase in rate of congenital abnormalities after fetal exposure to benzodiazepines. In a case-control study of 611 infants with cleft lip or cleft palate and 2498 controls with other birth defects, after adjustment of the data for potential confounders, no association between diazepam and cleft palate was found (OR, 0.8 for cleft lip with or without cleft palate, with 95% confidence interval [CI] of 0.4 to 1.7, and OR, 0.8 for cleft palate alone, with 95% CI of 0.2 to 2.5).[84] Reanalysis of the Hungarian Case-Control Surveillance of Congenital Abnormality data also showed a weak relationship between exposure to diazepam in early pregnancy and neural tube defects, limb deficiency defects, and possibly intestinal atresia or stenosis.[83] One study found no difference in the incidence of congenital anomalies between 460 women exposed to benzodiazepines during pregnancy and 424 control women without such exposure (i.e., 3.1% versus 2.6%, respectively).[84] Perinatal use of diazepam has been associated with hypotonia, hypothermia, and respiratory depression.[85] Overall, it appears that the teratogenic risk of benzodiazepines is small at most,[86,87] but there may be a small risk for preterm birth and low birth weight.[88] Benzodiazepines should only be used in the first trimester if the perceived benefit offsets the possible teratogenic risks and later neonatal effects of continued use. Some benzodiazepines such as **temazepam** are classified as FDA Category X.

Anticonvulsants

Epilepsy is the most common serious neurologic problem during pregnancy.[89] It has been estimated that 3 to 5 births per thousand will be to women with epilepsy.[90] All anticonvulsants cross the placenta. The fetal congenital anomaly rate in pregnant women with epilepsy who ingest anticonvulsant drugs is 4% to 8%, compared with a background incidence in the general population of 2% to 3%.[91,92] A twofold higher risk for minor

malformations also exists in this population.[92] Cleft lip, with or without cleft palate, and congenital heart disease are especially common. Administration of valproic acid or carbamazepine entails a 1% risk for neural tube defects and other malformations; thus, alpha-fetoprotein screening and targeted ultrasonography are appropriate for patients taking these agents. In addition, the offspring of epileptic women have a 2% to 3% incidence of epilepsy, which is five times that of the general population.

Holmes et al.[93] attempted to refute the unproven theory that women with epilepsy have a genetic propensity to have children with a higher risk for birth defects that is separate from the greater risk associated with the use of anticonvulsants. These investigators studied children of women who had a history of seizures but took no medications during the pregnancy. There was no difference in physical features or cognitive function between these children and a group of matched controls. In a second study, Holmes et al.[94] screened 128,049 pregnant women at delivery to identify the following three groups of infants: (1) those exposed to anticonvulsant drugs, (2) those unexposed to anticonvulsant drugs but with a maternal history of seizures, and (3) those unexposed to anticonvulsant drugs with no maternal history of seizures (control group). The frequency of anticonvulsant embryopathy was higher in the 223 infants exposed to one anticonvulsant drug than in the 508 control infants (20.6% versus 8.5%, respectively; OR, 2.8; 95% CI, 1.1 to 9.7). The frequency was also higher in 93 infants exposed to two or more anticonvulsant drugs than in the controls (28.0% versus 8.5%; OR, 4.2; 95% CI, 1.1 to 5.1). The 98 infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during pregnancy did not have a higher frequency of abnormalities than the control infants. The investigators concluded that "a distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself." A more recent meta-analysis also did not support the view that epilepsy *per se* represents a teratogenic risk.[95]

Possible causes of these congenital malformations include genetic differences in drug metabolism, the specific drugs themselves, and deficiency states (e.g., decreased folate levels) induced by the drugs. No congenital malformations appear to be unique to any one anticonvulsant. The characteristics of these syndromes are so similar that the broad term **fetal anticonvulsant syndrome**, consisting primarily of orofacial, cardiovascular, and digital malformations, has been applied to almost every anticonvulsant drug.[96]

Among women taking **phenytoin**, there is a 2% to 5% risk for major congenital anomalies, primarily midline heart defects, orofacial clefts, and urogenital defects.[91] **Fetal hydantoin syndrome** is a constellation of minor anomalies, such as craniofacial abnormalities (short nose, flat nasal bridge, wide lips, hypertelorism, ptosis, epicanthal folds, low-set ears, and low hairline) and limb anomalies (distal digital hypoplasia, absent nails, and altered palmar crease). In addition, neonatal growth and performance delays have been documented. The risk for fetal hydantoin syndrome for the child of a woman taking phenytoin is approximately 10%.[94] Phenytoin may act as a competitive inhibitor of the placental transport of vitamin K. This results in a decrease in fetal coagulation factors II, VII, IX, and X. In addition, phenytoin may induce fetal hepatic metabolism of the coagulation factors. The resulting reduction in fetal coagulation factors is associated with a higher risk for hemorrhagic disease of the newborn.[97] To help prevent this coagulopathy, some physicians advocate oral vitamin K supplementation (10 mg daily) for pregnant epileptic patients during the last month of pregnancy in addition to the parenteral administration of vitamin K to the neonate at birth.[98] Several anticonvulsant medications have metabolites that typically are eliminated by the enzyme epoxide hydrolase. In one study, 19 women taking phenytoin underwent amniocentesis. All 4 of the women with low enzyme activity in amniocytes had affected fetuses. The 15 fetuses with normal amniocyte epoxide hydrolase activity did not have the characteristics of fetal hydantoin syndrome.[62]

Carbamazepine is used to treat all types of seizure disorders, with the exception of petit mal epilepsy. It is most commonly used in the treatment of psychomotor (temporal lobe) epilepsy and grand mal epilepsy. In a prospective study involving 72 women with epilepsy who were taking carbamazepine, the incidence of congenital anomalies was higher in the 35 fetuses exposed only to this drug. There was an 11% incidence of craniofacial defects, a 26% incidence of fingernail hypoplasia, and a 20% incidence of developmental delay.[99] This constellation of fetal effects, named **fetal carbamazepine syndrome**, closely resembles the malformations seen in cases of fetal hydantoin syndrome. In addition, maternal carbamazepine exposure has been specifically associated with spina bifida. An analysis of all available data involving cohorts of pregnant women ingesting carbamazepine supports the conclusion that fetal exposure to this drug carries a 0.5% to 1% risk for spina bifida.[100] Although it is generally agreed that the use of carbamazepine in pregnancy is associated with a risk for neural tube defects and other anomalies, the exact magnitude of the risk from use of carbamazepine alone is unclear.[101-104]

Phenobarbital is used in the treatment of partial and generalized tonic-clonic seizures and status epilepticus.[105] Fetal exposure to phenobarbital has been associated with major malformations, such as congenital heart defects and orofacial clefting. **Fetal phenobarbital syndrome** is characterized by minor dysmorphic features similar to those seen with fetal hydantoin syndrome.[91] Fetal exposure to phenobarbital has also been associated with decreased intellectual and cognitive development in neonates and children. Maternal phenobarbital use during pregnancy can result in hemorrhagic disease of the newborn and neonatal withdrawal symptoms after delivery. The withdrawal symptoms consist mostly of irritability, begin at about 7 days of life, and usually last for 2 to 6 weeks.[105]

Valproic acid is used to treat absence and generalized tonic-clonic seizures. Infants exposed to valproic acid have a 1% to 2% risk for spina bifida. The neural tube defect tends to be lumbosacral. Fetal valproic acid exposure has also been associated with cardiac defects,

orofacial clefting, and genitourinary anomalies. **Fetal valproate syndrome** has been described; it is characterized by dysmorphic features, including epicanthal folds, shallow orbits, hypertelorism, low-set ears, flat nasal bridge, upturned nasal tip, microcephaly, thin vermillion borders, downturned mouth, thin overlapping fingers and toes, and hyperconvex fingernails.[91] Jentink et al.[106] found a markedly increased risk for spina bifida (OR, 12.7) craniosynostosis, cleft palate, atrial septal defect, and hypospadias. They concluded that valproic acid monotherapy should be avoided during pregnancy. A report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society concluded that valproic acid and polytherapy should be avoided if possible during the first trimester to decrease the risk for major congenital malformations.[107] They also concluded that, if possible, avoidance of valproic acid and polytherapy throughout pregnancy should be considered, and avoidance of phenytoin and phenobarbital throughout pregnancy may be considered, to prevent poor cognitive outcomes.[107] Other reviews have also confirmed that valproic acid and carbamazepine are associated with neural tube defects and that valproic acid is associated with hypospadias, thus lending further support to limiting its use in women of reproductive age.

There are insufficient data to establish risks for birth defects with the newer anticonvulsants.[108,109] **Felbamate** was approved by the FDA for monotherapy, but later its use was severely restricted because of its association with aplastic anemia and hepatic failure. **Gabapentin** was initially released in the United States as an adjunctive treatment for partial seizures and secondarily generated tonic-clonic seizures. This agent inhibits dopamine release in the CNS. **Lamotrigine** appears to have efficacy comparable to that of carbamazepine in the monotherapy for partial epilepsy. An inhibitor of dihydrofolate reductase, lamotrigine decreases embryonic folate levels in experimental animals. This finding raises the concern that human use of lamotrigine may result in developmental toxicity. The manufacturer has established a registry to evaluate this possibility. A preliminary report from this registry has described a 6% rate of congenital malformations in fetuses exposed to this drug; this rate does not represent a clear increase in the baseline rate of malformations. However, there have not been sufficient numbers of fetal exposures to support any definitive conclusions.[110-112]

Many patients who present to prenatal clinics are already taking these newer anticonvulsants. Patients should be counseled that even though little information is available, no clear evidence of their teratogenicity exists. Some investigators have suggested avoiding the newer anticonvulsants until evidence of their safety is accumulated.[105] Even in the two decades since newer agents such as lamotrigine were introduced, definitive evaluation of their teratogenic potential has not been published.

Some women may be taking anticonvulsant drugs without having been reevaluated recently for their need to continue drug therapy. If a patient with idiopathic epilepsy has been seizure-free for 2 years and has normal EEG findings, the neurologist may try to withdraw the drug before pregnancy.[113]

If a patient first presents for care during pregnancy, most authorities agree that the benefits of anticonvulsant therapy during pregnancy outweigh the risks of discontinuing the drug. The blood level of the drug should be monitored to minimize the dose needed to ensure a therapeutic level of drug.

Antidepressants

A summation of 14 studies assessing the effect of fetal exposure to **tricyclic antidepressants** evaluated 414 cases of first-trimester exposure[114]; when the study data were pooled or viewed individually, no significant association between fetal exposure to tricyclic antidepressants and congenital malformations was found.[114] In a surveillance study of Michigan Medicaid recipients,[115] 467 neonates had been exposed to amitriptyline and 75 neonates had been exposed to imipramine during the first trimester; there was no association between tricyclic antidepressant use and congenital anomalies. However, a large review of data from the Swedish Medical Birth Register reported that use of tricyclic antidepressants was associated with a greater risk for congenital malformations compared with other antidepressants.[116] Results of the latter study are making their way into reviews that state a concern about tricyclic antidepressants.[117] Overall, tricyclic antidepressants have been replaced by **selective serotonin reuptake inhibitors** (SSRIs) as first-line therapy for depression (see Chapter 51).[118]

The SSRIs include **sertraline**, **paroxetine**, **fluoxetine**, and **citalopram**. No higher risk for major malformations or developmental (language and behavior) abnormalities was identified with their use in earlier studies.[119-121] In a multicenter evaluation of birth defects, use of SSRIs was not associated with a higher risk for cardiac defects.[122] However, in analyses of the individual medications, sertraline was associated with an increased risk for septal defects (OR, 2.0; 95% CI, 1.2 to 4.0), and paroxetine was associated with a higher risk for right ventricular outflow tract obstruction (OR, 3.3; 95% CI, 1.3 to 8.8). Sertraline was also associated with an increased risk for omphalocele, but this association was based on only three subjects. Another study found significantly higher risks for craniosynostosis, omphalocele, and anencephaly in association with exposure to SSRIs as a group; this study also found an association between paroxetine and right ventricular outflow tract lesions.[123] The association of septal heart defects with sertraline[124,125] and citalopram has been seen in other studies.[124]

A cohort study compared postnatal outcome for infants exposed to fluoxetine in late gestation (up to the time of delivery) with that for infants whose exposure was limited to the first trimester.[126] Infants exposed in the third trimester had a greater incidence of perinatal complications, including preterm delivery, admission to the special care nursery, poor neonatal adaptation, lower mean birth weight, and shorter body length.[126] A subsequent study suggested an association between the maternal use of SSRIs in late pregnancy and a higher risk for persistent pulmonary hypertension of the newborn (PPNH).[127] The association between SSRIs and PPHN has been confirmed in other studies, which showed an increase from

the background rate of 1.2/1000 neonates to about 3/1000, and appears to be a class effect.[128]

The American College of Obstetricians and Gynecologists (ACOG) has recommended that use of paroxetine in pregnant women (and in women planning pregnancy) be avoided, if possible.[129] In addition, it was suggested that fetal echocardiography should be considered in women who have used paroxetine during early pregnancy. Further, the ACOG has stated that treatment with all SSRIs should be individualized.[129] A report from the American Psychiatric Association and the ACOG concluded that although antidepressant use in pregnancy is well studied, available research has not yet adequately controlled for other factors such as maternal illness and behaviors that can adversely affect pregnancy.[130]

Lithium

In the International Registry of Lithium Babies, 25 of 217 (11.5%) infants exposed to lithium during the first trimester of pregnancy were malformed.[131] Eighteen infants had cardiovascular anomalies, and six had the rare Ebstein anomaly, which occurs only once in 20,000 nonexposed pregnancies. Subsequent studies have suggested that ascertainment bias may have flawed the findings; the reported risk for anomalies after lithium exposure is much less than that reported by the registry.

In a cohort study linking the Swedish Birth Registry with the records of women with bipolar disorder, 59 infants were identified whose mothers had been treated with lithium early in pregnancy.[132] Four (6.8%) of the 59 infants exposed to lithium had congenital heart disease, compared with 2 (0.9%) of 228 infants not exposed to lithium (relative risk [RR], 7.7; 95% CI, 1.5 to 41.2). None of the infants had Ebstein anomaly. In a prospective cohort study of 148 women treated with lithium during the first trimester and 148 controls not exposed to any known teratogen, there was no significant difference between groups in the incidence of major congenital anomalies or cardiac malformations,[132] although one lithium-exposed infant did have Ebstein anomaly. The investigators concluded that lithium is not a major human teratogen, but they recommended that women exposed to lithium be offered ultrasonography and fetal echocardiography.[133] If the data are pooled, these two cohort studies do not suggest a statistically significant increase in risk for congenital malformations or cardiac malformations in women exposed to lithium during pregnancy. Although the risk for congenital malformations associated with intrauterine lithium exposure is likely to be lower than previously reported, an absence of risk cannot be assumed from the available data. Recent reviews of available data have come to the same conclusion that the risk for anomalies is small, but it is prudent to perform fetal echocardiography after first-trimester exposure.[134]

Two published cases associated polyhydramnios with maternal lithium treatment.[135,136] Nephrogenic diabetes insipidus has been reported in adults taking lithium; thus, the presumed mechanism of polyhydramnios is fetal diabetes insipidus. Polyhydramnios may signal fetal lithium toxicity.

Pregnancy accelerates the excretion of lithium, so serum lithium levels should be monitored in pregnant women.[137] Perinatal effects of lithium include hypotonia, lethargy, and poor feeding in the infant. In addition, complications (e.g., goiter, hypothyroidism) similar to those seen in adults taking lithium have been noted in neonates.

Some authorities recommend discontinuation of lithium and substitution with another medication during pregnancy. However, the discontinuation of lithium is associated with a 70% chance of relapse of the affective disorder in 1 year, as opposed to a 20% risk for relapse with continuation of lithium therapy.[131]

Cardiovascular Drugs

There are no reports of teratogenicity related to the use of inotropic agents such as **dopamine**, **dobutamine**, or **digoxin**. Physicians should monitor the maternal digoxin level to ensure a therapeutic level of drug during pregnancy.

Methyldopa and **labetalol** are often used to treat mild chronic hypertension during pregnancy. There is no evidence of teratogenicity or other adverse fetal effects with either of these drugs. In one randomized double-blind trial of 152 women with hypertension, there were no malformations in either the labetalol group or the placebo group, although the exposure to labetalol occurred in the second and third trimesters.[138]

In a large analysis of published trials involving beta-adrenergic receptor antagonist therapy, there was little or no information on teratogenicity for the multiple agents studied, including **atenolol**, **labetalol**, **metoprolol**, **oxprenolol**, **pindolol**, and **propranolol**.[139] Maternal administration of propranolol may result in modest fetal growth restriction.[140] It seems prudent to use ultrasonography to assess intrauterine fetal growth in women receiving propranolol. Maternal administration of propranolol within 2 hours of delivery may result in neonatal bradycardia.[75] Atenolol was associated with lower birth weight and a trend toward more frequent preterm delivery than with other antihypertensive drugs and with no therapy. These effects were more pronounced when the drug was administered earlier in pregnancy and for a long duration.[141] In one study, treatment of hypertension (mostly with atenolol) reduced the risk for severe hypertension and preterm labor.[141] In a randomized clinical trial, the same group observed that atenolol prevented preeclampsia but resulted in the birth of infants who weighed 440 g less than infants in the placebo group.[142]

The **angiotensin-converting enzyme (ACE) inhibitors** initially did not appear to be teratogenic when administered during the first trimester.[143] However, a 2007 study suggested an increase in the incidence of congenital anomalies, particularly cardiac and CNS defects, after first-trimester exposure to ACE inhibitors.[144] Some authorities contend that this study had major limitations.[145] A very large epidemiologic database study of 465,754 mother-infant pairs showed no difference in abnormality rate between women who used ACE inhibitors during the first trimester, those who used other antihypertensive agents, and those who had hypertension but

used no medications.[146] The authors postulated that any increased risk for birth defects may be due to the hypertension. A different set of investigators made the same conclusion.[147] Later in pregnancy, ACE inhibitors can cause fetal renal failure and oligohydramnios, which may result in fetal limb contractures, craniofacial deformities, and pulmonary hypoplasia[148]; therefore, use of ACE inhibitors should be avoided if possible during this period.

Amiodarone is structurally similar to thyroxine and contains 37% iodine by weight. In a review of 64 reported pregnancies in which amiodarone was administered to the mothers, there was no clear increase in the incidence of malformations. However, 11 (17%) infants had evidence of hypothyroidism, and two (3%) neonates had goiter.[149,150] The use of amiodarone in pregnancy was associated with mild abnormalities of neurodevelopment in some of the hypothyroid infants, although this was also observed in some euthyroid infants.[150] This agent is most often used during pregnancy to treat fetal arrhythmias, and first-trimester exposure is rare.

Respiratory Drugs

Maternal asthma is relatively common in pregnancy, affecting 4% to 8% of pregnant women. It is important to maintain appropriate treatment because asthma can increase the risk for adverse fetal and maternal outcomes.[151]

Inhaled **β_2-adrenergic receptor agonists**, **cromolyn sodium**, and **corticosteroids** have not been associated with congenital malformations. Currently, **albuterol** is the preferred short-acting β_2-receptor agonist, and **salmeterol** is the preferred long-acting β_2-receptor agonist. **Budesonide** is the recommended inhaled corticosteroid because it has a long history of safe usage, but there is no evidence against the other options, which include **beclomethasone**, **ciclesonide**, **fluticasone**, **flunisolide**, **mometasone**, and **triamcinolone**.

Severe persistent asthma may require systemic oral corticosteroid therapy, and this has been associated with low birth weight and a three- to five-fold increase in the relative risk for cleft lip and palate.[152,153] However, other studies have found no adverse effects and, given the risks from severe asthma, oral corticosteroids should be used if required.

The **5-lipoxygenase inhibitors** and **leukotriene receptor antagonists** are newer agents with no evidence of teratogenicity.[154] Women using **montelukast** enrolled in several teratogen information services around the world showed no increased risk for birth defects in 160 live births.[155]

Methylxanthines such as **theophylline** and **aminophylline** have no adverse fetal effects, but the protein binding and metabolism of theophylline are both reduced during pregnancy, making it necessary to monitor drug concentrations and adjust maintenance doses.

Anticoagulants

Warfarin use in early pregnancy can result in an embryopathy similar to the X-linked chondrodysplasia punctata. The embryopathy can occur with fetal exposure between 6 and 12 weeks' gestation. Because deficiency of arylsulfatase E is responsible for the chondrodysplasia, the embryopathy may result from inhibition of arylsulfatase E by warfarin. The period between 6 and 9 weeks' gestation is especially critical. Fetal warfarin syndrome consists of nasal hypoplasia, depressed nasal bridge (often with a deep groove between the alae and nasal tip), stippled epiphyses, nail hypoplasia, mental retardation, and growth restriction. Second- and third-trimester exposures can result in other adverse fetal effects, including microcephaly, blindness, deafness, and growth restriction. Three prospective studies of women exposed only in the second and third trimesters found that the incidence of malformations must be exceedingly low because there was no evidence of fetal or neonatal CNS or eye abnormalities.[156] Some evidence suggests that a lower dose (< 5 mg/day) has less teratogenic potential.[157]

Heparin is a large, water-soluble molecule that does not cross the placenta. Maternal administration does not have an adverse effect on the fetus, and heparin is the drug of choice for most pregnant women who require anticoagulation daily. Daily administration of 20,000 units of **standard unfractionated heparin** for more than 20 weeks may be associated with maternal bone demineralization.[158] Unfractionated heparin should be used for prolonged periods only when it is clearly necessary.

Low-molecular-weight heparin (LMWH) has some advantages over standard unfractionated heparin.[159] LMWH does not cross the placenta and has a longer half-life than standard unfractionated heparin, which typically allows once-daily dosing in nonpregnant patients. In addition, LMWH has a more predictable dose-response relationship in nonpregnant patients, which obviates monitoring. However, pregnancy is associated with a higher volume of distribution and accelerated clearance of LMWH. Use of LMWH thromboprophylaxis during pregnancy requires adjustments in the dose of LMWH to accommodate for the changes in the pharmacokinetics of this drug that occur during pregnancy. For example, pregnant women may require twice-daily doses.[160]

Full anticoagulation is necessary in pregnant women with cardiac valve prostheses. In a systematic review of anticoagulation in pregnant women with mechanical heart valves, Chan et al.[161] evaluated outcomes with the following three anticoagulation regimens: (1) oral anticoagulants (most commonly warfarin) given throughout pregnancy, (2) heparin administered during the first trimester and then warfarin for the duration of pregnancy, and (3) heparin administered throughout pregnancy. The data demonstrated progressively higher rates of maternal death with regimens 1, 2, and 3 (1.8%, 4.2%, and 15.0%, respectively). The use of warfarin throughout pregnancy was associated with warfarin embryopathy in 6.4% of live-born infants. The substitution of heparin at or before 6 weeks' gestation eliminated that risk.[161]

For women with prosthetic heart valves, the American College of Chest Physicians (ACCP) has recommended use of one of the following three regimens: (1) adjusted-dose LMWH twice-daily throughout pregnancy, with doses adjusted to achieve the manufacturer's peak anti–factor Xa LMWH levels 4 hours after subcutaneous

injection; (2) adjusted-dose unfractionated heparin administered subcutaneously every 12 hours throughout pregnancy, with doses adjusted to keep the mid-interval activated partial thromboplastin time at least twice control or to attain an anti–factor Xa heparin level of 0.35 to 0.70 units/mL; or (3) unfractionated heparin or LMWH as just described until the 13th week of pregnancy, with substitution by vitamin K antagonists until close to delivery, when unfractionated heparin or LMWH is resumed.[160] In women at very high risk for thromboembolism in whom there is concern about the efficacy and safety of unfractionated heparin or LMWH, it is suggested to administer vitamin K antagonists throughout pregnancy with replacement by unfractionated heparin or LMWH close to delivery.[160] In high-risk women with prosthetic heart valves, it is suggested to add low-dose aspirin 75 to 100 mg/day.[160]

Antiemetics

Most women in early pregnancy have nausea, with or without vomiting (see Chapter 2 and Chapter 16).[162] Complementary therapies such as acupressure and ginger may be effective, but approximately 10% of women will require drug therapy. Although many different drugs can be effective, **vitamin B_6** should be the drug of choice.[163] A combination of vitamin B_6 with the antihistamine **doxylamine** was previously available as Bendectin, but this was withdrawn by the manufacturer in 1983 because of allegations of teratogenicity that were later found to be false. Other formulations are now available, and there is no evidence of teratogenicity with them or other antihistamines. **Trimethobenzamide** is structurally related to antihistamines such as **diphenhydramine**, but it has only weak antihistamine activity. The mechanism of action is unclear, but it probably acts at the chemoreceptor trigger zone. It has few side effects but also variable efficacy. Nausea and vomiting can also be treated with phenothiazines, but they may cause sedation.

The prokinetic agent and dopamine antagonist **metoclopramide** is not sedating, but it has a "black box" warning because chronic usage has been associated with rare cases of tardive dyskinesia. There are no specific safety concerns during pregnancy. A multicenter study did not observe an increased incidence of anomalies,[164] and a large trial of 3458 women exposed to metoclopramide in the first trimester found no association with increased risk for birth defects, low birth weight, preterm delivery, or perinatal death.[165]

The 5-hydroxytryptamine receptor antagonists are widely used and very effective antiemetics with few side effects, so they are also increasingly being used in pregnancy. Ondansetron was similar in efficacy to promethazine for the treatment of hyperemesis gravidarum but less sedating.[166] There is no evidence that it has a teratogenic effect.[167]

Corticosteroids such as **dexamethasone** are now commonly used for postoperative and chemotherapy-induced nausea and vomiting. **Methylprednisolone** has been used for refractory nausea and vomiting during pregnancy. However, a meta-analysis concluded that the use of glucocorticoids before 10 weeks' gestation was associated with a threefold to fivefold increased risk for cleft lip with or without cleft palate[152]; and thus, they should not be used during this period.

Antihistamines

Some pregnant patients may be treated with antihistamines for allergies or upper respiratory tract infections. These drugs provide symptomatic therapy with no influence on the course of the disease. If considered necessary, combinations of drugs should be avoided if possible. Topical nasal sprays result in less fetal exposure than systemic medication. One study suggested an association between pseudoephedrine and defects attributable to vascular disruption, including gastroschisis, small intestinal atresia, and hemifacial microsomia.[168] Physicians should discourage the use of nonprescription drugs for trivial indications because the long-term fetal effects of the chronic maternal use of these drugs are unknown.

Sedating or first-generation antihistamines are available in over-the-counter medications and have not been reported to increase fetal risk.[169] Examples include **chlorpheniramine**, **diphenhydramine**, **methapyrilene**, **thonzylamine**, **pyrilamine**, **tripelennamine**, **phenyltoloxamine**, and **buclizine**. Despite conflicting reports, a meta-analysis found no evidence to implicate **brompheniramine** as a teratogen.[170] In the Boston Collaborative Program,[171] none of the sedating antihistamines was associated with malformations. Two combination products—**triprolidine with pseudoephedrine** (Actifed) and **phenylpropanolamine with chlorpheniramine** (Ornade)—were not associated with malformations. In a cohort of 1502 women, antihistamines were not associated with congenital malformations.[172] **Azatadine** was not found to be teratogenic among 127 Michigan Medicaid recipients.[115]

Limited safety information is available for the nonsedating antihistamines. In a cohort study, 114 women exposed to **astemizole** were matched with 114 women exposed to known nonteratogens.[173] There were two major malformations in the astemizole group and two in the control group. In a study of 39 women exposed to **cetirizine**, the rate of malformations was no higher than in a control group.[174] This finding was replicated in a study performed through a teratogen information service.[175] There are no controlled human studies for **loratadine** or **fexofenadine**. Desloratadine is the major metabolite of loratadine; most data do not point to a risk for congenital abnormalities.[169]

Several antihistamines have primary indications not directly related to upper respiratory complaints. **Hydroxyzine** is used for treatment of pruritus, **meclizine** for dizziness, **diphenhydramine** for sleep and pruritus, and **doxylamine** (a component of the former Bendectin) for treatment of nausea and vomiting of pregnancy. A meta-analysis of antihistamines used mostly for morning sickness in early pregnancy found a protective effect against malformations (OR, 0.76; 95% CI, 0.60 to 0.94).[176] This apparent benefit may have resulted from an association between maternal nausea and good fetal outcomes rather than from a direct effect of antihistamines.

Anti-infective Drugs

Sepsis is a leading cause of maternal mortality. When administering perioperative antibiotics, anesthesia providers should be aware of the considerations regarding their use during pregnancy.[177] Although **penicillins** and **cephalosporins** are considered first-line treatment because of their long safety record, therapy is ultimately guided by local microbiology policies and bacterial sensitivity.

Tetracyclines should not be administered after the fifth week of pregnancy. They bind to developing enamel and cause discoloration of the teeth. They affect deciduous teeth when administered between approximately 26 weeks' gestation and 6 months of age in the infant, and they affect permanent teeth only if administered to children between approximately 6 months and 5 years of age. In addition, tetracyclines deposit in developing osseous sites and inhibit bone growth beginning in the second trimester.[177]

Quinolones (e.g., **ciprofloxacin**, **norfloxacin**) should not be used in pregnancy or in children. They have a high affinity for bone tissue and cartilage and may cause arthropathies in children. However, no malformations or musculoskeletal problems were noted in 38 infants exposed during the first trimester.[177]

Malaria is a significant cause of maternal and fetal death. Pregnant women should avoid traveling to malaria-endemic areas, but **chloroquine** or **mefloquine** can be used for malaria chemoprophylaxis. They are not associated with an increase in spontaneous abortions or congenital malformations. **Doxycycline**, **primaquine**, and **atovaquone-proguanil** are not to be used in pregnancy.

Treatment of herpes simplex and herpes zoster infections in the first trimester with **acyclovir** or **valacyclovir** has not been associated with an increased risk for birth defects.[178]

Zidovudine has been studied because of its role in the treatment of acquired immunodeficiency syndrome (AIDS). In a prospective cohort study, children exposed to it during the perinatal period in the Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076) were studied to a median age of 4.2 years; no adverse effects were observed.[179] Combination antiretroviral therapy has not been associated with major infant toxicity, even when the therapy was initiated in the first trimester of pregnancy.[180]

The Antiretroviral Pregnancy Registry was established in 1989 to detect any major teratogenic effect of the **antiretroviral drugs**. Each year it enrolls approximately 15% of all HIV-positive women who give birth to live infants in the United States plus a small number from other countries. It depends on voluntary reporting of prenatal exposure; therefore, drug-associated adverse events may not necessarily reflect true rates. Results of retrospective and clinical studies are also reviewed. Through January 2013, no apparent increase in the frequency of birth defects after first-trimester exposure to antiretroviral drugs compared with population-based comparators was reported.[181] A modest but statistically significant elevation of defect rates with **didanosine** and **nelfinavir** was reported, the clinical relevance of which is unclear.

It is generally appropriate to administer **vaccinations** during pregnancy because the risks of the disease may outweigh the risk of the vaccine. No evidence exists of risk to the fetus from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids. However, live vaccines pose a theoretical risk to the fetus, so vaccination with live attenuated virus (e.g., **varicella**, **measles-mumps-rubella** [MMR]) or tuberculosis (e.g., **bacillus Calmette Guérin** [BCG]) is considered contraindicated.[182] Influenza vaccination is recommended with the inactivated virus preparation.[183] Prevention and treatment of influenza with either **zanamivir** or **oseltamivir** is possible during pregnancy[184]; no adverse fetal effects have been reported.[185]

Caffeine

No evidence suggests that caffeine has teratogenic effects in humans. Early uncontrolled studies suggested that heavy ingestion of caffeine was associated with an increased incidence of spontaneous abortion, low birth weight, preterm delivery, and stillbirth. However, these studies did not control for the use of tobacco and alcohol. A contemporary meta-analysis showed no association with caffeine consumption and preterm birth.[186] In 2010, the ACOG published a committee opinion based on studies of caffeine use in pregnancy.[187] They concluded that (1) daily intake of less than 200 mg of caffeine was not associated with an increased risk for miscarriage, but contradictory data did not allow for a recommendation regarding daily intake above this level; (2) moderate caffeine intake does not appear to contribute to preterm birth; and (3) the association between caffeine intake and fetal growth restriction was equivocal. A subsequent review concluded with more certainty that moderate or even high amounts of caffeine-containing foods and beverages did not increase the risk for congenital malformations, miscarriage, or growth restriction.[188]

Smoking Cessation Therapies

Smoking during pregnancy is clearly linked to multiple adverse fetal, neonatal, and childhood effects. Drug interventions to stop smoking include nicotine replacement therapy, antidepressants, **bupropion** (dopamine and norepinephrine reuptake inhibitor and nicotine antagonist), **bromocriptine** (dopamine agonist), **varenicline** (nicotine partial agonist), and **cytisine** (plant alkaloid). Bupropion and bromocriptine therapy were not associated with congenital malformations or other adverse outcomes.[189] Animal data show no increase in malformations with varenicline, but there are no human data.

Specific Highly Teratogenic Drugs

Some drugs are so highly teratogenic that two simultaneous forms of reliable contraception are recommended or required during treatment of either partner, sometimes to be continued for months or years after stopping the

drug. Some examples are (1) **thalidomide**, which is still used for erythema nodosum leprosum and multiple myeloma; (2) the antiviral **ribavirin**, which is used for hepatitis C and viral hemorrhagic fevers; (3) **isotretinoin**, which is used for cystic acne; and (4) **acitretin**, which is used for severe psoriasis.

DRUG USE DURING LACTATION

General Principles

Nursing mothers are understandably concerned about the transfer of drugs and chemicals to breast milk. Correct advice is important to prevent them from unnecessarily stopping breast-feeding or discontinuing appropriate drug treatment. Unfortunately, it can be difficult to decide which of the many, sometimes conflicting, sources of public information to trust. Pharmaceutical information leaflets from the manufacturers often discourage the use of drugs during breast-feeding simply as a general precaution. The most comprehensive up-to-date information is found in the Drugs and Lactation database (LactMed) of the National Library of Medicine's Toxicology Data Network (TOXNET).[190] The American Academy of Pediatrics (AAP) has published policy statements on the benefits of breast-feeding[191] and the use of drugs during lactation.[192] The Centers for Disease Control and Prevention (CDC) provides online information regarding breast-feeding and various toxins and infectious diseases.[193]

Only a few types of drugs such as cytotoxic and immunosuppressive drugs (e.g., **cyclophosphamide**, **methotrexate**) and radioactive compounds are strongly contraindicated during breast-feeding.[59] Mothers breast-feeding infants with glucose-6-phosphate-dehydrogenase (G6PD) deficiency should avoid drugs such as **sulfonamides**, including the combination of **sulfamethoxazole and trimethoprim**, **nitrofurantoin**, and **primaquine**.

Maternal drugs may also affect lactation, and some are used therapeutically for this purpose. Drugs that increase the secretion of prolactin can stimulate milk production; these include dopamine antagonists such as **phenothiazines**, **haloperidol**, **metoclopramide**, and **domperidone**, as well as **sulpiride**, **risperidone**, and **methyldopa**. Drugs that decrease the production of milk include diuretics, estrogen, and dopamine agonists such as **bromocriptine**, **cabergoline**, **lisuride**, and **quinagolide**. Bromocriptine is no longer approved for postpartum lactation suppression because of its association with puerperal seizures, stroke, and myocardial infarction. Women who smoke also have lower milk production.

Drug transfer to breast milk occurs by passive diffusion, but transporter systems are also present.[194] The rate of passive transfer into breast milk depends on the lipid solubility, molecular weight, degree of ionization, and protein binding of the drug. Nonionized molecules of small molecular weight (e.g., **ethanol**) are readily transferred into breast milk. Drugs that have more than 85% maternal protein binding are often not detectable in the infant.[195]

The amount of a drug in breast milk is a variable fraction of the maternal blood concentration, which is proportional to the maternal dose. Quoted maternal milk-to-plasma ratios can vary because drug transfer is a time-dependent process. Even when calculated under steady-state conditions, there can be large individual variation. Absolute infant dose (μg/kg/day) can be calculated as the product of the average concentration in milk and the estimated daily volume of milk intake, and relative infant dose can be estimated by dividing absolute infant dose by the maternal dose.[196] It has been suggested that a relative infant dose less than 10% is generally safe,[196] but this will also depend on the oral bioavailability of the drug in the infant and the relative toxicity of individual agents. However, physicians and patients should be aware of the following disclaimers. First, in the case of toxic drugs, any exposure may be inappropriate. Second, the infant may be allergic to a drug consumed by the mother. Third, there may be unknown, long-term effects of even small doses of drugs. Fourth, individual variability in drug disposition may lead to unexpectedly high maternal blood and breast milk concentrations. Finally, infants have immature enzyme systems and metabolic pathways and some drugs are eliminated more slowly. The benefits of breast-feeding are well known, and the risk of drug exposure must be weighed against these benefits.

Lactation is not fully established during the first several days postpartum. The neonate receives only a small volume of colostrum, and little drug is excreted through milk at this time. Thus, only very small amounts of drugs administered after vaginal or cesarean delivery would reach the neonate and significant effects should be unlikely. However, neonatal metabolism and elimination are also poorly developed, and several days of maternal opioid analgesia with drugs such as **meperidine (pethidine)** and **codeine** may result in neonatal accumulation and side effects.

When a mother requires a daily dose of a drug during lactation, the minimum effective dose should be used. Some mothers requiring long-term therapy would already have been taking drugs during pregnancy, and the fetus would have been exposed to concentrations much greater than those achieved in the infant through breast-feeding. Thus, if a drug has been acceptable during pregnancy, it is often reasonable to continue it during breast-feeding unless there are drug-specific factors to the contrary.[197] For example, poor neonatal elimination of **lamotrigine** may eventually lead to drug accumulation in the infant and adverse effects. In general, medications should be taken after breast-feeding, and long-acting preparations should be avoided. If the infant nurses less frequently overnight, ingestion of a drug dose at night after nursing will decrease the infant's exposure.

Anesthetic Drugs

There are generally no concerns regarding anesthetic drugs and perioperative medicines in the breast milk of women who require an anesthetic.[198,199] However, the prolonged use of postoperative medications such as analgesics will obviously increase the infant dose, the potential effects of which are discussed next.

Analgesics

No harmful effects of **acetaminophen** or **NSAIDs** have been noted except for **aspirin**.[71] Some NSAIDs specifically recommended as compatible with breast-feeding are ibuprofen, flurbiprofen, naproxen, and celecoxib. Other NSAIDs may be discouraged simply because of limited information, although there are some concerns about diflunisal and carisoprodol based on animal data.[192] Surprisingly, the FDA has singled out **ketorolac** with a "black box" warning that it is "contraindicated in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates"; the basis for this decision is unclear. Theoretically, NSAIDs with antiplatelet effects should be avoided by mothers who are breast-feeding neonates with platelet dysfunction. With aspirin, there is limited transfer of salicylic acid into breast milk because it exists mostly in the ionized form. After single oral doses, peak milk levels occur at approximately 3 hours with milk-to-plasma concentration ratios between 0.03 and 0.05.[200] However, maternal ingestion of *high doses* (e.g., more than 16 tablets per day) may result in maternal and breast milk concentrations sufficiently high to affect platelet aggregation in the infant. Reduced neonatal clearance of salicylic acid may lead to drug accumulation and toxic effects, even when repeated exposures are small.[201] Because of these concerns, the World Health Organization (WHO) Working Group on Human Lactation has classified salicylates as unsafe for use by nursing women.[202] Low doses of aspirin prescribed as anti-platelet therapy may be acceptable.[192]

It was thought previously that opioids used by nursing mothers were highly unlikely to have adverse effects on breast-fed infants. Normal maternal doses of **codeine**, **morphine**, **tramadol**, and **meperidine** do not have obvious adverse effects on most nursing infants.[78,192] The dose detectable in breast milk is 1% to 2% of the mother's dose and is unlikely to have significant pharmacologic activity. However, in one patient who took **propoxyphene** in a suicide attempt, the breast milk concentration of propoxyphene was half that of the maternal serum level.[203] Theoretically, a breast-feeding infant could receive up to 1 mg of propoxyphene per day if the mother were to consume the maximum dose.

Neonates are particularly vulnerable because their drug metabolism and elimination are poorly developed. Neonates of mothers receiving meperidine by intravenous patient-controlled analgesia after cesarean delivery had significant neurobehavioral depression by the third day.[204] The cumulative maternal meperidine dose at 48 hours postpartum was 14 mg/kg. No neonatal depression was seen in a morphine group in whom the cumulative maternal dose at 48 hours was 2.1 mg/kg. Both opioids and their major metabolites accumulated in colostrum. In a subsequent study,[205] the cumulative opioid doses at 48 hours were lower (meperidine 4.7 mg/kg and morphine 0.54 mg/kg), but infants in the morphine group were still more alert and oriented. With lower maternal morphine doses, concentrations in colostrum may even be undetectable.[206]

Recently, it has been recognized that infants of breast-feeding mothers taking **codeine** may have CNS depression. In 2006, the full-term 13-day-old infant of a mother taking a modest dose of codeine for episiotomy pain died of an apparent morphine overdose. It was discovered that the mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2×2 gene duplication, making her an ultrarapid metabolizer of codeine. This condition resulted in a breast milk morphine concentration of 87 ng/mL, compared with the expected typical range of 1.9 to 20.5 ng/mL.[207] This case prompted the FDA to release a Public Health Advisory advising caution in the use of codeine-containing medications by breast-feeding women.[208] The FDA recommended that the lowest effective dose for the shortest necessary duration should be used and that women should be taught how to recognize signs of high morphine levels in their infants. The number of ultrarapid metabolizers is estimated to vary between 1 and 28 per 100 people.[208] In addition, genetic variability in UGT2B7 may increase the formation of active morphine-6-glucuronide. It is estimated that 1.4% of Western European women would have both the CYP2D6 and UGT2B7 variants promoting neonatal depression.[209]

Ultra-rapid metabolism has been reported as a problem for breast-feeding only with codeine, although the FDA suggested that "it has the potential to affect other opioids."[208] Maternal oxycodone for postpartum analgesia has been associated with neonatal depression.[210] However, polymorphisms have less effect on the metabolism and analgesic effects of oxycodone, hydrocodone, and tramadol than codeine.[211]

Sedatives

Long-acting drugs such as **diazepam** are metabolized slowly in the infant, and accumulation can lead to sedation and poor feeding. Perinatal use of diazepam has been associated with hypotonia, hypothermia, and respiratory depression.[85] If a sedative must be used in a lactating woman, a relatively short-acting agent with inactive metabolites, such as **oxazepam**, **lorazepam**, **alprazolam**, or **midazolam**, is recommended.[212] The infant should be monitored for sedation during maternal drug use and for withdrawal symptoms after the medication is stopped or after discontinuation of breast-feeding.[213]

Anticonvulsants

Carbamazepine and **valproic acid** have low excretion into breast milk and are considered the safest choices.[214] Studies have detected only small amounts of **phenytoin**, **phenobarbital**, and **diazepam** in breast milk.[215,216] However, infants eliminate phenobarbital and diazepam slowly, so these agents may accumulate. Women taking a barbiturate or a benzodiazepine should observe their infants for evidence of sedation and withdrawal.[92,192] There are conflicting recommendations for the newer anticonvulsants. **Lamotrigine** concentrations in breast-fed infants can be very high, and some recommend that the drug should be avoided.[214] However, other authors note that the mother has usually been taking this drug throughout pregnancy already and that there is no evidence to recommend stopping the drug.[217]

Cruikshank et al.[218] measured breast milk magnesium concentrations in 10 preeclamptic women who were

receiving magnesium sulfate 1 g/h intravenously for 24 hours after delivery. The mean breast milk magnesium concentration was 6.4 ± 0.4 mg/dL, compared with 4.8 ± 0.5 mg/dL in controls. Breast milk calcium concentrations were not affected by magnesium sulfate therapy.

Antidepressants and Lithium

Psychotropic agents may be of concern because many of these medications have long half-lives and the effect of even small doses on the developing nervous system is not known. Nevertheless, the many medications available to treat depression or postpartum depression appear to have little if any immediate effect on the infant.[219] Many antidepressants have low milk-to-plasma ratios. There are few reports of neonatal problems with the use of SSRIs and related drugs.[220] **Fluoxetine** and its metabolite have relatively long elimination half-lives, so other drugs such as **sertraline** and **paroxetine** are preferred.[221]

Breast milk concentrations of **lithium** are one third to one half of maternal serum concentrations,[222,223] and infant serum concentrations during breast-feeding are much lower than fetal serum concentrations that occur when mothers take lithium during pregnancy. Neonatal clearance of lithium is reduced, and it may be useful to monitor neonatal lithium concentrations.

Cardiovascular Drugs

Amiodarone concentrations in the infant are unpredictable but may be sufficiently high to cause cardiac effects. Iodine released during its metabolism may cause thyroid dysfunction. Amiodarone has a very long half-life and is still excreted in breast milk weeks after stopping the drug.

Beta-adrenergic receptor antagonists with low protein binding have relatively higher transfer to breast milk, and those excreted renally are more likely to accumulate in neonates. Thus, **atenolol** with 10% protein binding and 85% renal excretion would not be the best choice. Breast milk concentrations of atenolol are approximately three times maternal plasma concentrations.[224] Even though the total infant dose is only 1% of the maternal therapeutic dose, and the infant plasma concentration would not normally cause side effects in the infant, atenolol has been associated with neonatal cyanosis and bradycardia.

Other common drugs such as ACE inhibitors and antihypertensives are considered safe. However, diuretics may reduce milk production. Maternal protein binding of **digoxin** limits infant drug exposure; after a maternal dose of 0.25 mg, a peak breast milk concentration of 0.6 to 1.0 ng/mL occurs and the milk-to-plasma concentration ratio at the 4-hour peak is between 0.8 and 0.9 ng/mL. In 24 hours an infant might receive approximately 1% of the maternal digoxin dose,[225] and no adverse effects have been reported in nursing infants of mothers taking this drug. Breast milk **clonidine** concentrations are almost twice maternal serum concentrations. However, this exposure does not seem to have any adverse effects on the infant.[226]

There are no safety data for **statins**, but they are not recommended during breast-feeding because of concerns that they may disrupt infant lipid metabolism.

Respiratory Drugs and Corticosteroids

Salbutamol, **terbutaline**, and **salmeterol** inhalers are considered compatible with breast-feeding. Maximum milk concentrations of **theophylline** are achieved between 1 and 3 hours after an oral dose. It has been calculated that the nursing infant receives less than 1% of the maternal dose. Such exposure appears to have no adverse effects.

Inhaled and oral corticosteroids are also considered safe. Katz and Duncan[227] obtained breast milk 2 hours after an oral dose of 10 mg of **prednisone** in one nursing mother. They detected breast milk concentrations of prednisone and prednisolone that would be unlikely to result in any deleterious effect on the infant. McKenzie et al.[228] administered 5 mg of radioactive prednisolone to seven patients and found that 0.14% (a negligible quantity) of the radioactive label was secreted in the milk in the subsequent 60 hours. Thus, breast-feeding is not contraindicated in mothers taking corticosteroids. Even at a maternal dosage of 80 mg/day, the nursing infant would ingest a dose equivalent to less than 10% of its endogenous cortisol production.[229]

Anticoagulants

Most mothers who require anticoagulation may continue to nurse their infants with no problems. **Warfarin** is 98% protein bound. Orme et al.[230] reported no warfarin in breast milk or infant plasma in seven women taking warfarin 5 to 12 mg/day. Similarly, de Swiet and Lewis[231] found that warfarin appears in breast milk in insignificant quantities. **Heparin** does not cross significantly into breast milk and is not active when administered orally.

Antihistamines

No harmful effects have been noted with maternal use of antihistamines.[232] These drugs do not appear to affect the milk supply. Little antihistamine is excreted into breast milk, further confirming safety of use during lactation.[169]

In theory, histamine type 2 (H_2)-receptor antagonists might suppress gastric acidity or cause CNS stimulation in the infant, but these effects have not been confirmed in published studies. **Famotidine**, **nizatidine**, and **roxatidine** are less concentrated in breast milk and may be preferable to cimetidine.[233]

Anti-infective Drugs

Penicillin and its derivatives are safe in nursing mothers. With the usual therapeutic doses of **ampicillin**, the milk-to-plasma concentration ratio is 0.2 or less and no adverse effects are noted in nursing infants.[234] Theoretically, infant diarrhea or candidiasis might occur with prolonged therapy. **Cephalosporins** appear in trace amounts in breast milk and are also safe.

Sulfonamides displace bilirubin from binding sites on albumin, so these drugs are best avoided during the first 5 days of life or in mothers of preterm infants with hyperbilirubinemia. Sulfonamides appear in breast milk in

small amounts. **Sulfasalazine** has been associated with diarrhea and bloody diarrhea in an infant.[192] Sulfonamides should be avoided in infants with G6PD deficiency.

Tetracyclines are normally avoided during breast-feeding because of the potential for tooth staining and delayed bone growth. The breast milk concentration of tetracycline is about half the maternal plasma concentration, but tetracycline has a high affinity for both calcium and protein, and the amount of free tetracycline available for systemic absorption is very small. Thus, some references consider a short course of tetracyclines to be compatible with breast-feeding. Similarly, **quinolones** are usually avoided in pregnancy, but there is disagreement over their safety during breast-feeding.

Maternal administration of **acyclovir** does not contraindicate breast-feeding. If a mother takes 1 g/day, the infant probably receives less than 1 mg/day, a very low dose.[235]

Most vaccines, except for yellow-fever and smallpox, can be administered during breast-feeding.[192]

Caffeine

Moderate maternal intake of caffeine does not adversely affect the breast-fed infant. One study noted that breast milk contains only 1% of the total maternal dose of caffeine.[236] If a mother drinks excessive amounts of coffee, caffeine might accumulate in the infant and the infant might show signs of caffeine stimulation (e.g., irritability, poor sleeping pattern). Nursing mothers should limit their intake to a moderate level of caffeinated beverages (e.g., 2 to 3 cups per day).[192]

KEY POINTS

- Physiologic changes of pregnancy can alter drug disposition and drug effect.
- Maternal drug therapy is relatively easy to manage by changing the dose or switching the drug.
- General and local anesthetic requirements are reduced during pregnancy.
- Appropriate maternal treatment is essential to maintain fetal health.
- Mothers are concerned about many adverse fetal outcomes, including teratogenic effects, fetal loss, fetal growth restriction, preterm labor, and other complications of pregnancy.
- The basis of safety for many drugs during pregnancy is a long history of uneventful use.
- The critical period of organ development extends from approximately day 31 to day 71 after the first day of the last menstrual period.
- Administration of anticonvulsants is associated with an increased risk for congenital anomalies. Monotherapy is associated with less risk than therapy with two or more drugs.
- Many psychotropic drugs are not recommended for use during pregnancy.
- Heparin does not cross the placenta. Low-molecular-weight heparin is generally the anticoagulant of choice during pregnancy.
- Most antibiotics are safe during pregnancy. Tetracyclines should be avoided during pregnancy because they cause tooth discoloration and inhibit bone growth in the fetus. Quinolones are contraindicated during pregnancy.
- Vaccination is recommended in pregnant women except for live vaccines.
- Prevention and treatment of influenza with zanamivir and oseltamivir is possible.
- Most drugs are safe for use during lactation. Typically only 1% to 2% of the maternal dose appears in breast milk.
- Codeine can be rapidly converted to morphine by some mothers, leading to large amounts in breast milk and significant neonatal opioid depression.

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CHAPTER 15

In Vitro Fertilization and Other Assisted Reproductive Technology

Lawrence C. Tsen, MD

CHAPTER OUTLINE

In 1978, Steptoe and Edwards[1] reported the first live birth of an infant produced from *in vitro* fertilization (IVF) techniques. Their case highlighted the laparoscopic recovery of a single oocyte just before ovulation in a natural menstrual cycle; after *in vitro* insemination, the resulting embryo was grown in culture media for 2.5 days to the eight-cell stage and was transferred to the uterine cavity (i.e., embryo transfer [ET]).

IVF techniques were initially developed as a treatment for infertility secondary to chronic fallopian tube disease. Current indications for this emerging spectrum of new techniques, which as a group are referred to as assisted reproductive technology (ART), include (1) inadequate oocyte quality or number (donor oocyte therapy), irreparability or absence of the uterus (surrogate uterus programs), and significant co-morbidities (embryo and ovarian tissue cryopreservation) in women; (2) sperm deficiencies in men; and (3) certain genetic aberrations in couples.[2]

In 1981, Edwards[3] estimated that 15 to 20 infants would be born worldwide through the use of IVF and ET techniques. Advances in the science and international acceptance of ART procedures have resulted in a dramatic increase in the number of infants born globally (Figure 15-1).[4] A similar increase in the use of these technologies has been witnessed in the United States (Figure 15-2); in 2011, the initiation of 163,038 ART cycles resulted in the birth of 61,610 infants.[5]

Despite the application of ART procedures to more diverse and challenging causes of infertility, the probability of a live birth after a cycle of hormonal stimulation has increased from 6% in 1985 to 30% in 2011.[5] Attention to subtle differences in culture media as well as improvements in laboratory methods, retrieval routes, and transfer techniques are primarily responsible for these improved results.[6] Given the importance of small alterations to the overall success of ART, coupled with the associated costs (i.e., approximately $10,000 for each cycle that progresses to transfer and limited insurance coverage for these procedures),[7] it is prudent for anesthesia providers to be aware of the potential effects that anesthetic agents may have on gametes or embryos.

ASSISTED REPRODUCTIVE TECHNOLOGY PROCEDURES

Hormonal Stimulation

Although the success of IVF was initially limited by the *single* preovulatory oocyte generated with each natural menstrual cycle,[1] the introduction of follicular hormonal stimulation has significantly increased the probability of a live birth through the retrieval of *multiple* oocytes per cycle. Hormonal regimens typically initiate a cycle with gonadotropin-releasing hormone agonist to induce pituitary and ovarian suppression, followed by follicle-stimulating hormone and human menopausal gonadotropin to stimulate the development and growth of multiple ovarian follicles. Human chorionic gonadotropin (hCG) is later added to induce maturation and demargination of the oocyte from the follicular wall before retrieval. Although the goal of these regimens is the generation of 10 to 15 oocytes, superovulation can occur, resulting in the production of as many as 70 oocytes. All visible ovarian follicles are aspirated (see later discussion), with each follicle usually containing a single oocyte.

After oocyte retrieval, pituitary function is usually insufficient to provide adequate hormonal support to the growing corpus luteum. For this reason, parenteral progesterone is often provided daily until either the results of the pregnancy test are known or the first trimester of pregnancy is completed.

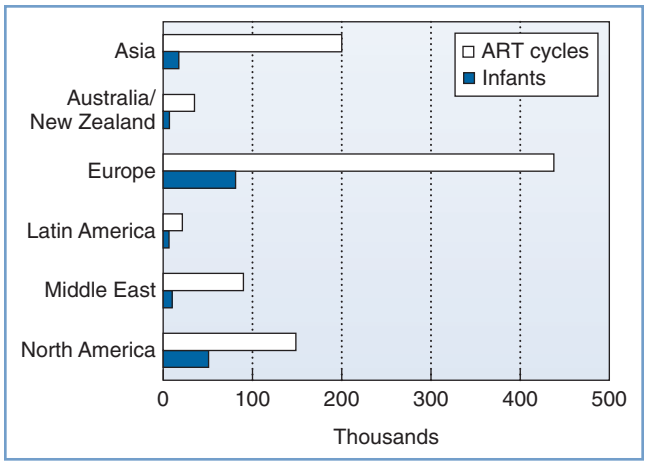

FIGURE 15-1 ■ Numbers of initiated assisted reproductive technology (*ART*) cycles and infants born worldwide by region in 2011 (from data accumulated in 2003 from 54 countries) as reported by the International Committee for Monitoring Assisted Reproductive Technology (ICMART). (Data from Nygren KG, Sullivan E, Zegers-Hochschild F, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) world report. Assisted Reproductive Technology 2003. Fertil Steril 2011; 95:2209-22, 22.e1-17.)

Oocyte Retrieval

Originally conducted with direct visualization of the ovarian follicles through pelvic laparoscopy,[1] the majority of oocyte retrievals are currently performed through a transvaginal approach with ultrasonographic guidance (Figure 15-3).[8] Laparoscopic oocyte retrieval is typically reserved for situations in which tubal transfer is planned (i.e., gamete intrafallopian transfer [GIFT] or zygote intrafallopian transfer [ZIFT]; see later discussions).

Oocyte retrieval is performed 34 to 36 hours after hCG administration. Retrieval must be performed promptly to prevent spontaneous ovulation from reducing the number of mature oocytes. With the use of a transvaginal ultrasound probe to visualize the ovary, mature follicles are punctured and aspirated with a needle introduced through the vaginal fornix. Oocytes are immediately washed in culture media and examined microscopically to determine their stage of meiosis. Oocytes are classified as postmature metaphase II, mature metaphase II, metaphase I, or prophase I on the basis of their nuclear, cytoplasmic, and extracellular composition.

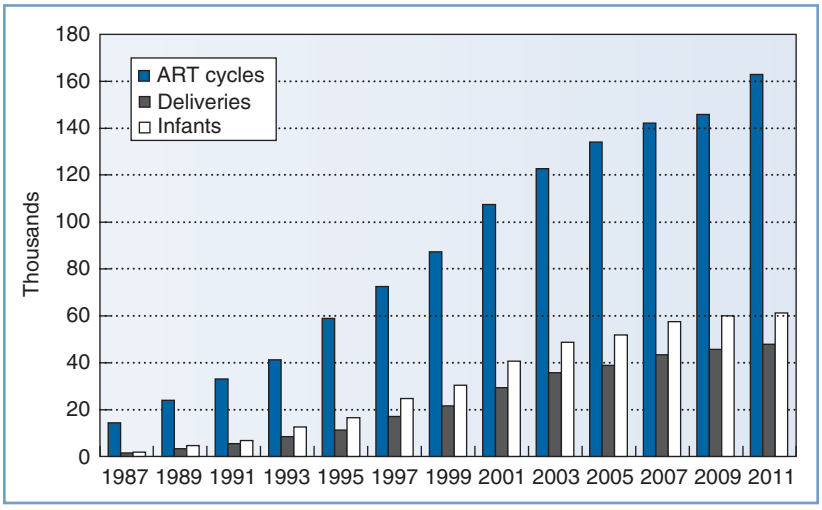

FIGURE 15-2 ■ Numbers of assisted reproductive technology (*ART*) cycles performed, live-birth deliveries, and infants born in the United States using ART from 1987 through 2011, as reported to the Centers for Disease Control and Prevention, Division of Reproductive Health, and the Society for Assisted Reproductive Technology Registry. (Data from U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Reproductive Health. 2011 Assisted Reproductive Technology [ART] Report. Atlanta, CDC/DRH, 2013.)

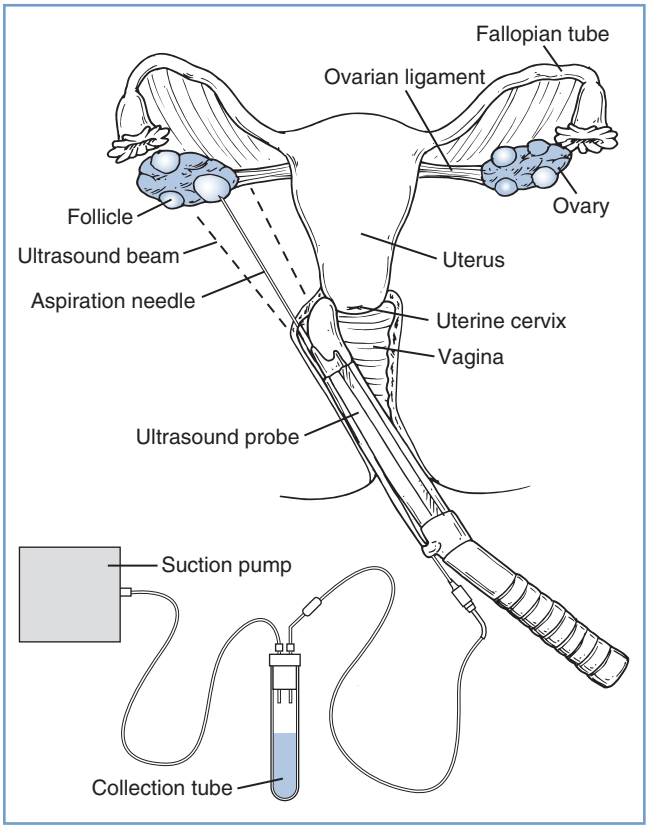

FIGURE 15-3 ■ Transvaginal ultrasound-guided oocyte retrieval. The ultrasound probe is placed in the vagina and advanced into the posterior fornix. The needle, previously inserted through the needle guide, is advanced through the vaginal wall and ovarian capsule. (Redrawn from Steinbrook R. Egg donation and human embryonic stem-cell research. N Engl J Med 2006; 354:324-6. Copyright © 2006 Massachusetts Medical Society. All rights reserved.)

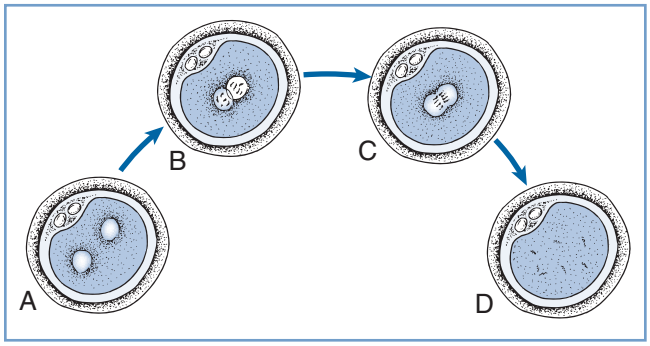

FIGURE 15-4 ■ Pronuclear stage prezygote. **A,** At 8 to 10 hours after insemination, pronuclei are barely visible and may be spaced slightly apart. **B,** After 12 hours, pronuclei have migrated to the center of the cell and are clearly seen. **C,** At 20 to 22 hours, nuclear envelopes break down and pronuclei begin to fade from view. **D,** The one-cell zygote before the first cleavage. (Redrawn from Veeck LL. Atlas of the Human Oocyte and Early Conceptus. Baltimore, Williams & Wilkins, 1991:43.)

In Vitro Fertilization

Although the term *in vitro fertilization* is often used synonymously with any aspect of ART, technically it applies only to the process of oocyte fertilization with spermatozoa in culture media. After a microscopic examination, oocytes are incubated for 4 to 6 hours in culture media that resembles human fallopian tube fluid and are then inseminated. The insemination process is sometimes delayed with immature oocytes (e.g., metaphase I) in an attempt to increase the probability of normal (i.e., monospermic) fertilization.

At 16 to 20 hours after insemination the oocytes are examined for evidence of fertilization (i.e., the presence of two pronuclei and two polar bodies in the perivitelline space) (Figure 15-4).[9] The advantages of IVF include the ability to document the process of fertilization and to use techniques to improve sperm motility or penetration (e.g., intracytoplasmic sperm injection). IVF followed by ET represents approximately 99% of the ART procedures used in the United States[5]; less than 1% occurs via GIFT or ZIFT procedures (see later discussions). Male factor infertility is present in approximately 35% of the couples seeking ART procedures, and intracytoplasmic sperm injection is currently used in more than 65% of the cases treated annually in the United States.[5]

Embryo Transfer

Embryos resulting from IVF may be transferred into the fallopian tubes (i.e., ZIFT) or the uterine cavity (IVF-ET). Most ET procedures are performed transcervically 3 days after retrieval, with the embryos transferred via a catheter. The advantages of transcervical ET are (1) simplicity—it does not require laparoscopy or anesthesia; (2) low cost, especially compared with laparoscopic intrafallopian transfer procedures; and (3) the ability to proceed without patent fallopian tube(s). The primary disadvantage of transcervical ET is that the probability of successful pregnancy is slightly less than that with an ET performed directly into the fallopian tubes (i.e., ZIFT). Embryos in excess of those required for transfer may be frozen in 1,2-propanediol or glycerol and stored for possible later transfer.

Gamete Intrafallopian Transfer

GIFT procedures consist of the transabdominal or transvaginal collection of oocytes followed by a microscopic inspection of the oocytes' quality and maturation in a laboratory adjacent to the operating room. Mature oocytes are aspirated into a transfer catheter with washed partner or donor sperm, and the contents (gametes) are injected into the distal 3 to 6 cm of one or both fallopian tubes. The catheter is subsequently inspected microscopically to verify that oocytes have not been retained. The GIFT procedure does not involve IVF, because fertilization occurs *in vivo* in the natural milieu of the fallopian tube.

Specific advantages of the GIFT procedure include (1) the convenience of oocyte retrieval and ET occurring within a single operative event, (2) the elimination of IVF, and (3) the fact that the embryos reach the uterine cavity at a potentially more appropriate (i.e., later) stage of

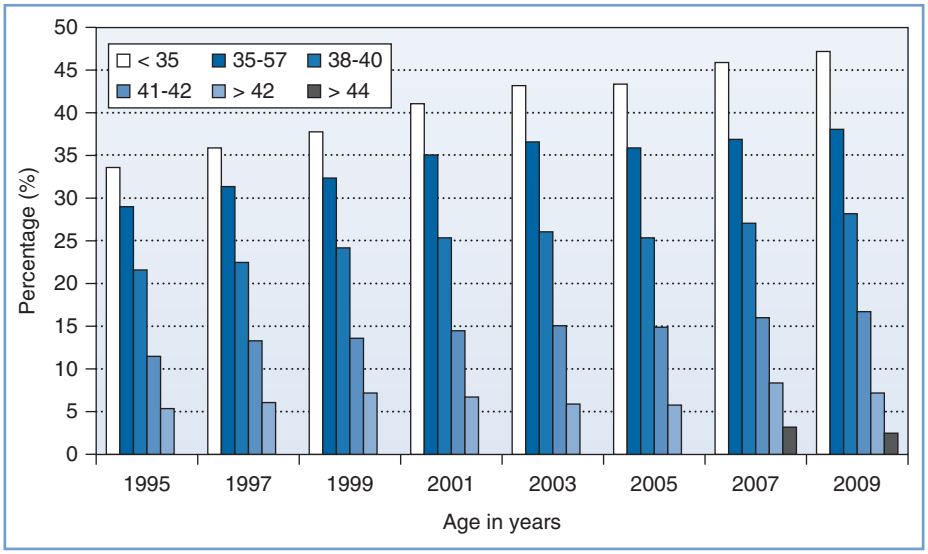

FIGURE 15-5 ■ Percentage of transfers that resulted in live births with assisted reproductive technology (ART) cycles using fresh nondonor eggs or embryos, according to the women's age in the years from 1995 to 2009, as reported to the Centers for Disease Control and Prevention, Division of Reproductive Health, and the Society for Assisted Reproductive Technology Registry. The first year in which data for women older than 42 were subdivided into ages 43 to 44 and older than 44 was in 2007. (Data from U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Reproductive Health. 2009 Assisted Reproductive Technology (ART) Report. Atlanta, CDC/DRH, 2011.)

development than with IVF-ET.[10] The primary disadvantage is that fertilization cannot be documented; an issue that may be critical when this capacity is in question (e.g., couples with male or immunologic factors). Normally, 50% to 70% of inseminated oocytes become fertilized[11]; however, lower fertilization rates are often observed in couples with severe male factor infertility or in women with antisperm antibodies. Other limitations are the required presence of at least one patent fallopian tube and the requirement for laparoscopic surgery.

Zygote Intrafallopian Transfer

ZIFT (also known as pronuclear stage transfer [PROST]) consists of oocyte retrieval followed by IVF. At 16 to 20 hours after insemination the oocytes are examined for the presence of two distinct pronuclei (i.e., the pronuclear stage; see Figure 15-4), which indicates that fertilization has occurred. The patient is anesthetized for laparoscopy, and pronuclear stage embryos (usually no more than four) are transferred through a catheter into the distal portion of a fallopian tube (as described for GIFT). Advantages of ZIFT include (1) the documentation of fertilization, (2) the avoidance of laparoscopy if fertilization is not successful (approximately 13% of inseminations),[5] (3) a shorter exposure to the laboratory environment than with IVF-ET, and (4) the potential for embryos to reach the uterine cavity at a more appropriate stage of development than with IVF-ET (i.e., approximately the fifth day after insemination). Its disadvantages and limitations include (1) the added inconvenience and cost of a two-stage procedure, (2) the requirement for laparoscopic surgery, and (3) the presence of at least one patent fallopian tube.

SUCCESS OF ASSISTED REPRODUCTIVE TECHNOLOGY

The Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) collaborate with the Centers for Disease Control and Prevention (CDC) to maintain a data registry and analyze the results of all ART cycles initiated during each calendar year in the United States.[5]

Maternal age is the dominant factor in determining the likelihood of a successful pregnancy after an ART procedure (Figure 15-5). For example, in 2010, 41.5% of IVF cycles in women younger than 35 years led to the delivery of one or more infants.[5] By contrast, in a similar group of women older than 42 years who met optimal fertility criteria, only 6% of these procedures resulted in a live birth.[5] In 2010, the average age of a woman having an ART procedure in the United States was 36 years.

Although pregnancy and delivery rates have historically been greater for tubal transfers (i.e., GIFT, ZIFT) than for transcervical uterine transfers (IVF-ET), greater parity in these rates has developed in recent years.[5,11] The early postovulatory uterine environment has been postulated to be unfavorable to early embryo growth.[11] Tubal transfer procedures allow embryos 3 to 5 days to reach the uterine cavity, when the environment for implantation may be more receptive. Lower implantation rates after transcervical ET may also be explained by (1) adverse uterine effects produced by the transfer procedure, (2) uterine contractions expelling transfer fluid and embryos,[12] and (3) the absence of yet undiscovered tubal factors that promote early embryo growth and implantation.[11,13]

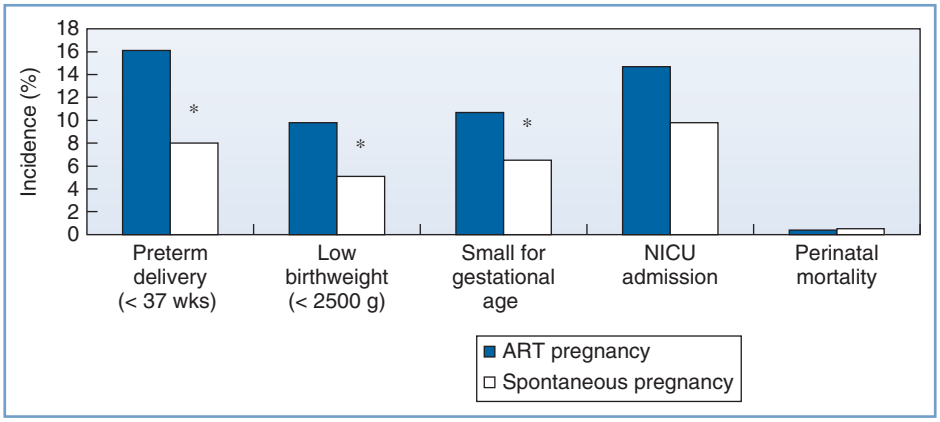

FIGURE 15-6 ■ Outcomes associated with singleton births from assisted reproductive technology (*ART*) and spontaneous pregnancies in the general population. *$P < .05$. *NICU,* Neonatal intensive care unit. (Data from D'Angelo DV, Whitehead N, Helms K, et al. Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment. Fertil Steril 2011; 96:314-20.)

OBSTETRIC COMPLICATIONS

ART hormonal stimulation regimens are associated with increased coagulation and decreased fibrinolysis when evaluated by individual hemostatic markers and global assessment tools (i.e., thromboelastography).[14,15] These alterations are especially significant in the setting of the most common ovarian stimulation complication, a phenomenon termed *ovarian hyperstimulation syndrome* (OHSS). Mild cases of OHSS may manifest as abdominal discomfort, bilateral ovarian enlargement, and ascites, whereas severe cases may result in follicular rupture and hemorrhage, pleural effusion, hemoconcentration, oliguria, and thromboembolic events.[16-18] The anesthetic implications of OHSS include increased free drug concentrations (see later discussion) and greater perioperative pain from larger follicle numbers. The fullest expression of the syndrome usually occurs after oocyte retrieval, particularly if the decision is made to proceed with an ET, which maintains exposure to endogenous and exogenous hormones. Rarely, an emergency laparoscopy or laparotomy is required for excision of a ruptured ovarian cyst or the release of an ovarian pedicle torsion.[18] Abdominal paracentesis and thoracentesis may be necessary before the induction of general anesthesia in patients with respiratory compromise due to massive ascites or pleural effusions.

Multiple-gestation pregnancies represented 31% of the deliveries that followed ART procedures in the United States in 2010, of which 91% were twins.[5] The transfer of a greater number of embryos or oocytes increases both the probability of a live birth and the likelihood of a multifetal pregnancy. Although many infertile couples would prefer a twin or triplet pregnancy, maternal and perinatal morbidity and mortality for multiple versus singleton gestation pregnancies is at least doubled.[19] In addition, overall medical costs escalate with each additional fetus, particularly if the birth occurs preterm. Within the United States in 2006, 62% of ART twins and 97% of ART triplets were delivered preterm, resulting in an estimated financial burden of $1 billion.[20] In an effort to reduce the incidence and sequelae of multifetal pregnancies, many ART programs and societies, and even some countries, have mandated a limit on the number of embryos or oocytes that are transferred.[21] In the presence of triplet or higher-order gestation pregnancies, selective reductions can be performed; however, these procedures are subject to a number of medical and ethical considerations.

Ectopic pregnancies occur up to five times more frequently in ART pregnancies than with natural pregnancies (2%), primarily owing to the greater prevalence of fallopian tube disease among infertility patients.[22] The transfer site (uterine versus fallopian tube) *per se* does not appear to be a predisposing factor in the development of ectopic pregnancies; however, a greater number occur after uterine transfer, because women with bilateral tubal disease are not candidates for GIFT or ZIFT procedures. In approximately 10% of ectopic pregnancy cases, the ectopic embryo develops in conjunction with an ongoing intrauterine pregnancy and requires a termination or surgical removal within the first trimester.[22]

Preterm delivery, low birth-weight, and small-for-gestational-age infants are more common with ART singleton pregnancies than with natural pregnancies, although the prevalence of admission into the neonatal intensive care unit, duration of infant hospital stay after birth, and the incidence of infant death appear similar (Figure 15-6).[23] The difference appears to be a result of infertility per se rather than the ART procedures, because previously infertile women who conceive independent of ART also are at greater risk for preterm delivery.[23]

EFFECTS OF ANESTHESIA ON REPRODUCTION

General Considerations

In 1987, Boyers et al.[24] reported that oocytes recovered by laparoscopic techniques in patients who had received

general anesthesia (i.e., isoflurane or enflurane with a 50% nitrous-oxygen mixture) were less likely to be fertilized if the duration of the procedure was prolonged. Specifically, fertilization rates for the first- and last-recovered oocytes were 69% and 54%, respectively, when the difference in exposure time exceeded 5 minutes. The investigators advanced the following two plausible explanations for this difference: (1) the acidification of follicular fluid by intraperitoneal carbon dioxide and (2) the effects of anesthesia. This study prompted an assessment of anesthetic agents and techniques used during ART procedures.

Ideally, anesthetic techniques and agents used for ART procedures should not interfere with oocyte fertilization or early embryo development and implantation. Although anesthetic agents have been reported to interfere with some aspects of reproductive physiology in some species under certain conditions, the literature must be interpreted with caution. For example, one study concluded that oocyte cleavage rates were significantly lower with general anesthesia than with epidural anesthesia.[25] However, a laparoscopic (instead of transvaginal) retrieval method was used in the general anesthesia group, and carbon dioxide pneumoperitoneum may significantly decrease both follicular fluid pH and oocyte fertilization rates. Another report commented on the effects of different anesthetic techniques, but it did not disclose the actual anesthetic agents that were administered in the study.[26] In addition, conclusions based on animal data may not reflect the human experience owing to interspecies and assay method differences.[27]

Assessment of specific anesthetic drugs must also be interpreted in context; relevant factors include (1) the method of administration, (2) dose of anesthetic agents, (3) combination with other drugs, (4) timing of administration, and (5) duration of exposure. For example, local anesthetic agents yield dissimilar pharmacokinetic profiles when administered via paracervical, epidural, and intrathecal techniques. Anesthetic agents may also affect unfertilized oocytes and fertilized embryos differently; thus, studies of anesthetic agents used for a GIFT (prefertilization) procedure should not be directly compared with studies of agents used for a ZIFT (postfertilization) procedure. Finally, significantly greater free concentrations of certain agents (e.g., bupivacaine) exist during ART stimulation because of a decrease in plasma protein binding capacity.[28] Thus, when selecting anesthetic techniques or agents for an ART procedure, the clinician should weigh their known benefits (e.g., greater hemodynamic stability, less nausea, less psychomotor impairment) and hypothetical risks (e.g., lower delivery rates).

Local Anesthetic Agents

In animal models, the effect of local anesthetic agents on reproductive physiology appears to be related to the agent, timing, and dose of exposure. Using mouse oocytes incubated for 30 minutes in culture media with known concentrations of lidocaine, bupivacaine, or 2-chloroprocaine, Schnell et al.[29] demonstrated that lidocaine and 2-chloroprocaine adversely affected both fertilization and embryo development at concentrations of

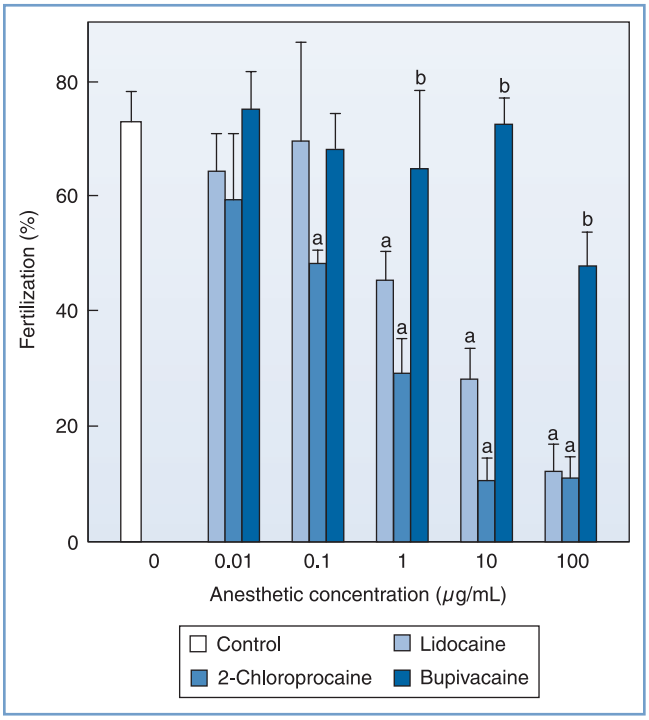

FIGURE 15-7 ■ Fertilization of mouse oocytes at 48 hours (mean ± SD) for each anesthetic exposure group. *a, P* < .05 (anesthetics compared with control); *b, P* < .05 (lidocaine and 2-chloroprocaine compared with bupivacaine). (Modified from Schnell VL, Sacco AG, Savoy-Moore RT, et al. Effects of oocyte exposure to local anesthetics on in vitro fertilization and embryo development in the mouse. Reprod Toxicol 1992; 6:323-7, with permission from Elsevier Science, Kidlington, UK.)

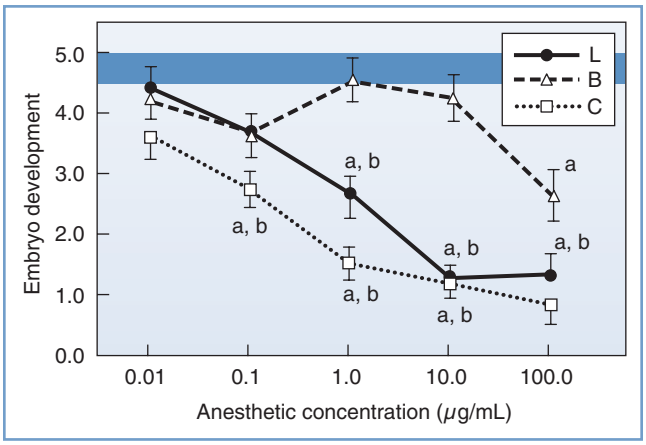

FIGURE 15-8 ■ Embryo development scores (mean ± SD) at 72 hours as a function of anesthetic concentration. Shaded area represents embryo development score (4.75 ± 0.28) for the control mouse embryos. *a, P* < .01 (lidocaine [*L*], bupivacaine [*B*], and 2-chloroprocaine [*C*] compared with control); *b, P* < .01 (bupivacaine compared with lidocaine and 2-chloroprocaine). (Modified from Schnell VL, Sacco AG, Savoy-Moore RT, et al. Effects of oocyte exposure to local anesthetics on in vitro fertilization and embryo development in the mouse. Reprod Toxicol 1992; 6:323-7.)

1.0 and 0.1 μg/mL, respectively (Figures 15-7 and 15-8). In contrast, bupivacaine produced adverse effects only at the greatest concentration studied (100 μg/mL). Similarly, Del Valle et al.[30] demonstrated that after 48 hours of culture, 24% of mouse embryos exposed to lidocaine

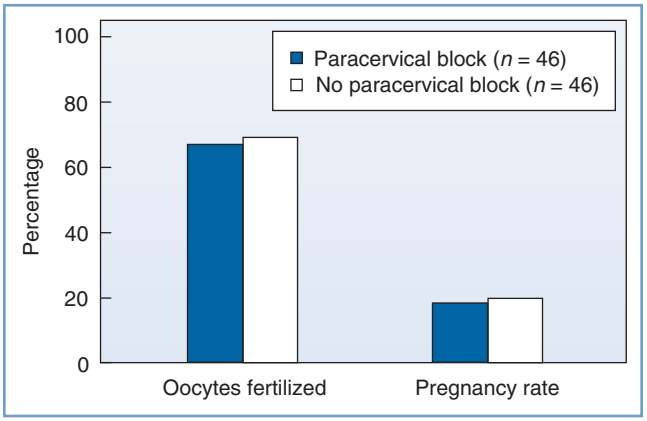

FIGURE 15-9 ■ Fertilization and pregnancy rates after transvaginal oocyte retrieval with and without lidocaine paracervical block. Fertilization and cleavage rates did not differ in the two groups. (Modified from Wikland M, Evers H, Jakobsson AH, et al. The concentration of lidocaine in follicular fluid when used for paracervical block in a human IVF-ET programme. Hum Reprod 1990; 5:920-3.)

10 µg/mL, in comparison with none in the control group, showed evidence of degeneration. Finally, Ahuja et al.[31] noted that hamster oocytes exposed to procaine or tetracaine demonstrated impaired zona reactions, potentially allowing additional sperm to enter the oocyte and create abnormal chromosomal numbers (polyploidy).

These *in vitro* findings may have limited clinical relevance, however, given the lower anesthetic concentrations that occur in clinical practice and the washing and screening procedures that oocytes undergo before fertilization and transfer. Human trial data corroborate the minimal effect that local anesthetic agents have on oocytes or embryos during oocyte retrieval, GIFT, or ZIFT procedures. Wikland et al.[32] reported that the incidence of oocyte fertilization and clinical pregnancy was not reduced among women who received a modified paracervical block with lidocaine for transvaginal oocyte retrieval (Figure 15-9). Favorable pregnancy rates have also been reported after GIFT procedures performed during epidural lidocaine anesthesia.[25]

Opioids and Benzodiazepines

Fentanyl, alfentanil, remifentanil, and meperidine do not appear to interfere with either fertilization or preimplantation embryo development in animal and human trials.[33,34] When given during oocyte retrieval, fentanyl and alfentanil were detected in extremely low (or undetectable) follicular fluid concentrations.[35] With alfentanil, a 10:1 ratio between serum and follicular fluid was observed 15 minutes after the initial bolus dose.[36] Morphine appears unique in terms of adverse effects; when sea urchin eggs were incubated in morphine (equivalent to a human dose of 50 mg), more than one sperm entered approximately 30% of the oocytes.[37]

Midazolam administered systemically in preovulatory mice did not impair fertilization or embryo development *in vivo* or *in vitro*, even when given in doses up to 500 times those used clinically.[38] When used in small bolus or infusion doses for anxiolysis and sedation for ART in humans, midazolam has not been detected in follicular fluid and does not appear to be teratogenic.[39,40]

Propofol, Thiopental, and Ketamine

Most animal and human trials suggest minimal to no detrimental effects of propofol on fertilization and early embryo development,[41-45] despite accumulating in a dose- and duration-dependent manner within the follicular fluid.[46-48] General anesthesia provided with propofol and a 50% oxygen-air mixture was associated with fertilization, embryo cleavage, and implantation rates similar to those produced by a paracervical block with mepivacaine.[44] Hamster oocytes exposed to very high concentrations of propofol (20 µg/mL) demonstrated no DNA damage—even through two metaphases—when evaluated by sister chromatid exchange assays, a sensitive index of genotoxic effects.[49] These concentrations were 40 times greater than those detected clinically in the follicular fluid of patients undergoing oocyte retrieval.[46,47] The induction and maintenance of general anesthesia with propofol for GIFT procedures demonstrated negligible differences in reproductive outcomes from women receiving other forms of anesthesia.[42] By contrast, a smaller incidence of ongoing pregnancies was observed among women given propofol–nitrous oxide anesthesia for ZIFT procedures when compared with thiopental–nitrous oxide–isoflurane anesthesia.[50] Further investigation is necessary to further elucidate the full effects of propofol on various reproductive outcomes.

Both thiopental and thiamylal (5 mg/kg) can be detected in follicular fluid as early as 11 minutes after their administration for induction of general anesthesia in patients undergoing GIFT procedures.[51] No adverse reproductive effects have been observed with these agents, and when they were specifically compared with propofol (2.7 mg/kg) for GIFT procedures, no differences in clinical pregnancy rates were noted.[43]

Ketamine (0.75 mg/kg), administered with midazolam (0.06 mg/kg), has been reported to be an acceptable alternative to general anesthesia with isoflurane for oocyte retrieval.[52] No differences in reproductive outcomes were observed; however, the study was inadequately powered to adequately assess this result.

Nitrous Oxide

Nitrous oxide reduces methionine synthetase activity, nonmethylated folate derivatives, and DNA synthesis in animals and humans.[53,54] Nitrous oxide also impairs the function of mitotic spindles in cell cultures.[55] Although Warren et al.[56] reported that two-cell mouse embryos exposed to nitrous oxide within 4 hours of the expected onset of cleavage were less likely to develop to the blastocyst stage (Figure 15-10), this difference had resolved by later stages of embryo development.[34]

Clinical studies of anesthesia for laparoscopic ART procedures support the administration of nitrous oxide during GIFT and ZIFT procedures.[42,50,57] In a multicenter study, Beilin et al.[42] observed a delivery rate of 35% among women given nitrous oxide for GIFT

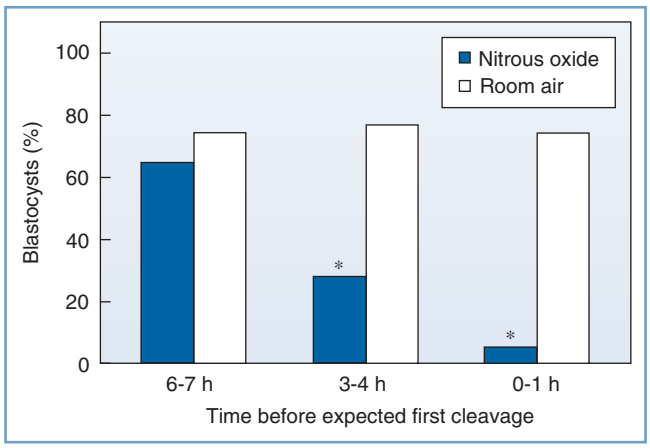

FIGURE 15-10 ■ Developmental outcome of two-cell mouse embryos exposed to 60% nitrous oxide/40% oxygen for 30 minutes in vitro. Administration of nitrous oxide within 4 hours of anticipated cleavage decreased the percentage of embryos reaching the blastocyst stage. **P* < .05 compared with the room air (i.e., control) group. (Modified from Warren JR, Shaw B, Steinkampf MP. Effects of nitrous oxide on preimplantation mouse embryo cleavage and development. Biol Reprod 1990; 43:158-61.)

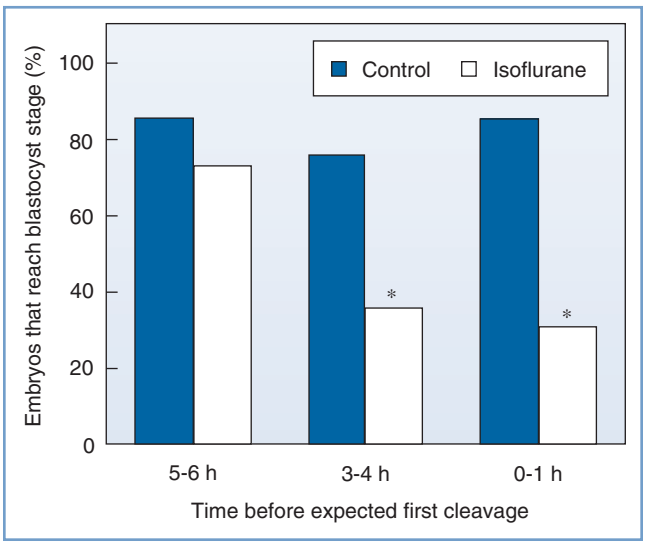

FIGURE 15-11 ■ Developmental outcome of two-cell mouse embryos exposed in vitro to 3% isoflurane for 30 minutes at various times in relation to expected onset of the first cleavage in vitro. **P* < .01. (Modified from Warren JR, Shaw B, Steinkampf MP. Inhibition of preimplantation mouse embryo development by isoflurane. Am J Obstet Gynecol 1992; 166:693-8.)

procedures, compared with 30% among women who did not receive nitrous oxide. In women undergoing oocyte retrieval, Handa-Tsutsui and Kodaka[58] reported lower target-controlled propofol doses with a 50% oxygen–nitrous oxide mixture than with an oxygen-air mixture. The authors reported that there were no alterations in pregnancy rates, but the study was not adequately powered to determine this difference.

Volatile Halogenated Agents

Volatile halogenated agents have been observed to depress DNA synthesis and mitosis in cell cultures.[59,60] Sturrock and Nunn[59] noted that volatile halogenated agents prevent cytoplasmic cleavage during mitosis, leading to a greater number of abnormal mitotic figures (e.g., tripolar and tetrapolar nuclear phases). Isoflurane adversely affects embryo development *in vitro*.[34,61] Warren et al.[61] reported that two-cell mouse embryos exposed to 3% (but not 1.5%) isoflurane for 1 hour were less likely to develop to the blastocyst stage (Figure 15-11), but only when isoflurane was given within 4 hours of the predicted onset of cleavage. It is questionable whether studies of two-cell mouse embryos are applicable to human oocytes and spermatozoa exposed during GIFT procedures or to one-cell embryos exposed during ZIFT procedures.

Volatile halogenated agents may also affect ART outcomes through an increase in prolactin levels. High prolactin levels have been associated with diminished oocyte development and uterine receptivity (see later discussion); whether volatile halogenated agents can affect mature oocytes in the process of being retrieved, however, is questionable. Critchlow et al.[62] observed dramatic rises in plasma prolactin levels with an enflurane in nitrous oxide–oxygen technique for GIFT procedures, although these changes did not occur until 4 to 10 minutes after induction and did not affect follicular fluid prolactin levels or fertilization rates.

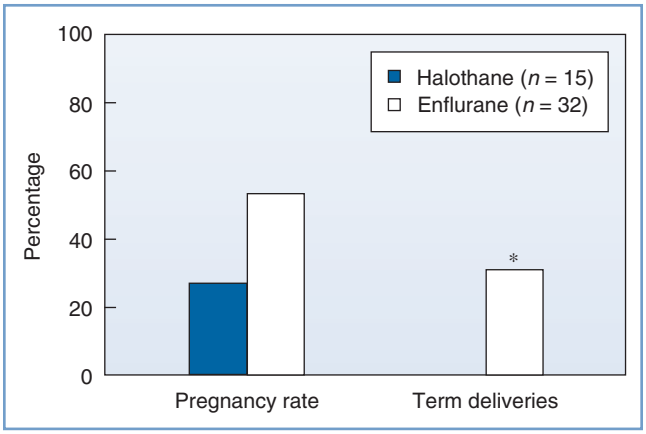

FIGURE 15-12 ■ Pregnancy and term delivery rates after halothane and enflurane anesthesia for gamete intrafallopian transfer (GIFT). The percentage of term pregnancies after GIFT was greater after enflurane–nitrous oxide anesthesia than after halothane–nitrous oxide anesthesia. **P* < .05 compared with the halothane group. (Modified from Critchlow BM, Ibrahim Z, Pollard BJ. General anaesthesia for gamete intra-fallopian transfer. Eur J Anaesthesiol 1991; 8:381-4.)

Volatile anesthetic agents have been compared in clinical studies. Fishel et al.[63] reported that pregnancy rates were significantly lower among women given halothane anesthesia for ET than in a similar group of women given enflurane; of interest, the anesthesia was administered in an attempt to decrease uterine activity during ET. Similarly, Critchlow et al.[62] reported lower pregnancy and delivery rates among women who received halothane for GIFT procedures than in women who received enflurane (Figure 15-12). General anesthesia with volatile halogenated agents has also been compared with monitored

anesthesia care (MAC). In a retrospective sequential study design, Wilhelm et al.[33] noted lower pregnancy rates in patients undergoing oocyte retrieval with general anesthesia (i.e., isoflurane or propofol in combination with 60% nitrous oxide in oxygen) than in subsequent patients who received a remifentanil-based MAC technique. The investigators acknowledged that the success rates of ART programs have improved over time and that it is possible that physician-related factors may have played a role in the improved success during the second MAC phase of the study.[33]

These data suggest that volatile halogenated anesthetic agents can affect ART outcomes, with known and potential differences associated with the selected agent. For example, the metabolic byproduct of sevoflurane, compound A, has been associated with genotoxic ovarian cell effects, although reproductive outcomes have not been assessed.[64] As a consequence, although volatile agents continue to be used for ART procedures, caution is advised in the selection of newer agents, such as sevoflurane, desflurane, and isodesox (a combination of 1% desflurane, 0.25% isoflurane, and 60% oxygen in nitrogen),[65] until further work has been done.

Antiemetic Agents

At least one study noted that droperidol and metoclopramide rapidly induce hyperprolactinemia with subsequent impairment of ovarian follicle maturation and corpus luteum function.[66] When these agents are given as a single dose immediately prior to oocyte retrieval, it is unlikely that the mature oocyte will be affected; however, if they are given on a routine basis after retrieval, the uterine receptivity to the embryo could be affected. Forman et al.[67] demonstrated that low plasma prolactin concentrations during ART procedures were associated with a higher incidence of pregnancy.

ANESTHETIC MANAGEMENT

Because most patients undergoing ART procedures are young and otherwise healthy, many institutions do not require preoperative laboratory studies, electrocardiograms, or chest radiographs before the procedure. However, the application of ART procedures to patients with a growing spectrum of pathologic processes, such as morbid obesity, cancer (with oocyte retrieval performed prior to chemotherapy or radiation therapy), and severe cardiac, pulmonary, or renal morbidities (with oocyte retrieval performed for ET in surrogate gestational carriers), has created special concerns that should be addressed individually.[68]

All patients should follow the fasting guidelines typically used for patients undergoing ambulatory surgery. In patients with risk factors for pulmonary aspiration of gastric contents, a nonparticulate antacid should be given before the procedure. On occasion, a patient may not adhere to strict fasting guidelines; and although delay or cancellation of the procedure is an option, the decision should be made after careful analysis of the potential risks and benefits. If the window for maximal oocyte retrieval (34 to 36 hours after hCG administration) is missed, spontaneous ovulation with loss of oocytes can occur, invalidating the considerable effort and expense that have been incurred to that point. Moreover, if oocyte retrieval is not performed, the patient would be at increased risk for OHSS, with its potential for significant morbidity. In contrast, the risk for pulmonary aspiration of gastric contents is low, particularly when spinal anesthesia is administered (see later discussion).

As with other ambulatory surgery cases, the ideal anesthetic technique provides effective pain relief with minimal postoperative nausea, sedation, pain, and psychomotor impairment.

Ultrasonographic-Guided Transvaginal Oocyte Retrieval

Although transvaginal oocyte retrievals can be performed under paracervical, spinal, epidural, and general anesthetic techniques, MAC is the most commonly used technique.[69,70] It is usually adequate for surgical analgesia, but MAC may need to progress to loss of consciousness (i.e., general anesthesia) to prevent patient movement at critical times; this problem has been observed in highly anxious patients.[71] The need for additional pain relief should be anticipated when the needle penetrates the cul-de-sac and, later, each ovary. Of interest, one report noted a greater rate of hospital admission after oocyte retrieval, mostly secondary to intra-abdominal bleeding, when MAC was used than when general anesthesia was used.[72] Self-administered inhalational analgesia with isodesox (see earlier discussion) by face mask was associated with less effective analgesia and less patient satisfaction than physician-administered intravenous analgesia.[65]

Because paracervical anesthesia incompletely blocks sensation from the vaginal and ovarian pain fibers, additional analgesia is required, even when greater doses of local anesthetic are used.[73] Epidural and spinal techniques provide excellent pain relief with minimal oocyte exposure to anesthetic agents. Compared with sedation with propofol and mask-assisted ventilation with nitrous oxide, epidural bupivacaine anesthesia resulted in fewer complications, especially nausea and emesis.[74] Spinal anesthesia may be preferable to epidural anesthesia owing to the reduced anesthetic failure rate, reduced systemic and follicular concentrations of anesthetic agent, and faster recovery profile.[75] Spinal administration of 1.5% hyperbaric lidocaine (60 mg) is associated with significantly shorter recovery times than spinal administration of 5% hyperbaric lidocaine (60 mg) in patients undergoing ART procedures.[76] The addition of intrathecal fentanyl 10 μg to lidocaine 45 mg improves postoperative analgesia for the first 24 hours, with no increase in time to urination, ambulation, and discharge, in comparison with intrathecal lidocaine alone.[77] Low-dose spinal bupivacaine has been evaluated for use in these patients, given the frequent association of spinal lidocaine with postoperative transient neurologic symptoms. However, the prolonged time to urination and discharge may prevent this agent from becoming a commonly used alternative.[78]

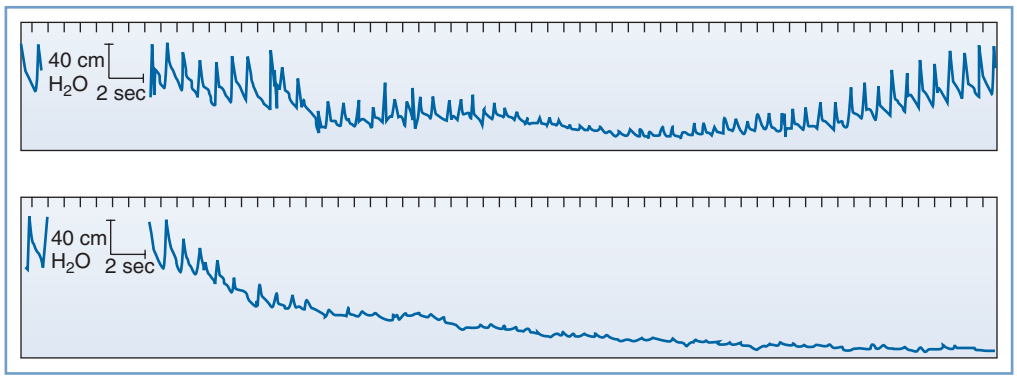

FIGURE 15-13 ■ Arterial tracings after rapid intravenous injection of 7.5 mL/kg of carbon dioxide (*top*) and helium (*bottom*). Recovery occurs within 1 minute after the carbon dioxide injection, but complete cardiovascular collapse occurs after the helium injection. (Modified from Wolf JS, Carrier S, Stoller ML. Gas embolism: helium is more lethal than carbon dioxide. J Laparoendosc Surg 1994; 4:173-7.)

General anesthesia can be provided by total intravenous anesthesia (TIVA) using propofol (titrated) and fentanyl (50 to 100 µg). Midazolam (1 to 2 mg) can be used as an optional premedication. With TIVA, most patients can be managed with spontaneous ventilation via high-flow oxygen mask and the use of carbon dioxide analysis.[40] (Individuals with significant risk factors for aspiration should undergo tracheal intubation with a cuffed endotracheal tube.) This anesthetic technique can produce mean bispectral index scores that range from 47 to 53 and modified Ramsay sedation scores that are consistent with general anesthesia[79] and results in greater patient satisfaction than MAC, owing to better pain relief and less awareness during the surgical procedure.[40] Alternatively, tracheal intubation and maintenance of anesthesia with a volatile halogenated agent has been used successfully; however, greater rates of nausea and emesis and more unplanned admissions have been observed with this technique than with a propofol, alfentanil, and air-oxygen mixture.[80]

Novel analgesic measures have been investigated during oocyte retrieval. One study evaluated electroacupuncture as an alternative to intravenous alfentanil, although both groups also received a paracervical block, and the acupuncture group experienced greater degrees of preoperative stress and longer periods of discomfort during oocyte aspiration.[81]

Embryo Transfer

Described as relatively painless, transcervical ET procedures are most commonly performed without analgesia or anesthesia; however, on rare occasion, intravenous sedation or regional or general anesthesia may be requested. In contrast, transabdominal gamete or embryo transfer procedures (i.e., GIFT, ZIFT) are usually performed via laparoscopy under local, neuraxial, or general anesthesia. The anesthetic management for these procedures and the associated concerns with regard to the laparoscopic technique and the Trendelenburg position are described here. Major intraoperative complications associated with laparoscopy are rare but include gastric or intestinal perforation, hemorrhage, pneumothorax, pneumopericardium, mediastinal emphysema, gas embolism, and cardiac arrest.[82]

Pneumoperitoneum and the Trendelenburg Position

Carbon dioxide is the gas most commonly used to establish pneumoperitoneum. The high blood solubility of carbon dioxide facilitates absorption from the peritoneal cavity after laparoscopic surgery and may represent a life-saving property of the gas in the rare but potentially catastrophic event of gas embolization. For example, rapid intravenous injection of 5 to 10 mL/kg of carbon dioxide produces only transient (<1 minute) hypotension in anesthetized dogs (Figure 15-13),[83] whereas intravascular administration of a similar volume of a less soluble gas (e.g., helium, oxygen, nitrogen) is usually fatal.

Signs of embolization of large quantities of carbon dioxide (or any other gas) in anesthetized patients may include hypocapnia, hypotension, hypoxemia, ST-segment and T-wave changes, arrhythmias, and audible changes in the heart sounds.[84] Initial treatment of carbon dioxide embolism should include release of the pneumoperitoneum and pharmacologic support of the circulation. If initial resuscitation efforts are unsuccessful, aspiration of gas from the right atrium (using a multi-orifice central venous catheter) should be considered. Although the use of the left lateral recumbent position (Durant's maneuver), with or without head-down positioning, has been suggested to facilitate removal of the postulated air lock from the right side of the heart,[85] laboratory evidence suggests that this maneuver may have a detrimental effect on cardiac function after venous gas embolism.[86]

Nearly as soluble in blood as carbon dioxide, nitrous oxide is associated with less peritoneal and diaphragmatic irritation[87] and has been suggested for the establishment of pneumoperitoneum in awake patients undergoing laparoscopy. A major disadvantage of nitrous oxide is its ability to support combustion, which could increase the possibility of an explosion if the surgeon uses electrocautery.

GIFT and ZIFT procedures are often performed with the patient in the Trendelenburg position to facilitate

visualization of the fallopian tubes and other pelvic structures. Although their use is controversial, shoulder braces placed to prevent the patient from moving cephalad on the operating table should be positioned with padding against the acromioclavicular joints to prevent brachial plexus damage. The adduction of the patient's arms against her trunk has been suggested to reduce the risk for a brachial plexus injury, but the efficacy of this precaution is unproven.

Both pneumoperitoneum and the Trendelenburg position produce physiologic changes. Hemodynamic effects of moderate pneumoperitoneum (< 20 mm Hg) in a patient in the Trendelenburg position include increased mean arterial and central venous pressures, increased systemic vascular resistance, and decreased stroke volume and cardiac output.[88] Heart rate usually does not change, but in some patients pneumoperitoneum may elicit sinus bradycardia, heart block, or even cardiac arrest. Finally, pneumoperitoneum aggravates the respiratory effects of the Trendelenburg position (e.g., reduced chest wall compliance, increased venous admixture). Overall, most healthy patients easily tolerate the cardiovascular and pulmonary effects of intra-abdominal pressures lower than 20 mm Hg.

Laparoscopic-Assisted Reproductive Technology

The anesthetic plan for GIFT procedures is typically dictated by the method (i.e., transabdominal or transvaginal) of oocyte retrieval. Many ART programs harvest oocytes transabdominally during pelvic laparoscopy, the principal advantage being that the patient is positioned and anesthetized once for both the retrieval and transfer portions of the procedure. The major disadvantage of this technique is that oocytes are exposed to both carbon dioxide pneumoperitoneum and anesthetic agents. The induction of general anesthesia for GIFT procedures can be delayed until just before the skin incision in an effort to minimize unnecessary exposure to these agents. Induction is usually performed with intravenous propofol, lidocaine, fentanyl, and either succinylcholine or rocuronium. After tracheal intubation, the anesthesia provider may decompress the patient's stomach with a suction catheter or Salem sump tube to reduce the risk for gastric perforation during instrumentation. Subsequently, a volatile halogenated agent in oxygen and air, with or without a short-acting muscle relaxant, is given to maintain anesthesia. The use of a propofol–nitrous oxide technique has been associated with less postoperative sedation, lower pain scores, and less emesis than an isoflurane–nitrous oxide technique.[50]

Alternatively, oocytes can be retrieved transvaginally and transferred—as oocytes or embryos—laparoscopically. Of interest, this is the technique most commonly used with ZIFT procedures, whereby oocyte retrieval and IVF occur on the day before the ZIFT procedure. Advantages to the combined transvaginal/transabdominal approach include (1) the avoidance of laparoscopy in the 1% to 2% of cases in which oocyte quality or number is inadequate to justify proceeding with a tubal transfer[3] and (2) the elimination of oocyte exposure to the carbon dioxide pneumoperitoneum. Disadvantages of this method include (1) the need to reposition the patient before laparoscopy and (2) a prolonged total operative time if performed on the same day (GIFT) or the need for a second procedure if performed on consecutive days (ZIFT).

A few patients prefer spinal or epidural anesthesia for GIFT procedures.[89,90] Healthy, nonobese patients have been reported to successfully undergo laparoscopic surgery in the Trendelenburg position with high thoracic (i.e., T2 to T4) spinal or epidural anesthesia.[89-92] Limiting intraperitoneal pressure to less than 10 mm Hg may facilitate the use of neuraxial anesthesia for these procedures. Obese women are not ideal candidates for neuraxial anesthesia in laparoscopic surgery.

Adequate analgesia for laparoscopic ART procedures has also been reported with the use of local anesthesia supplemented with intravenous sedation.[93-96] Padilla et al.[93] observed that the quality of intraoperative analgesia can be improved by limiting maximal intra-abdominal pressure to 8 to 10 mm Hg, reducing the rate of carbon dioxide insufflation to 1 L/min, and minimizing ovarian manipulation. The difficulty and pain frequently associated with cannulation of the fallopian tubes, however, may make local anesthesia an unwise choice for laparoscopic ART procedures. Waterstone et al.[94] noted that all 21 patients undergoing local anesthesia for laparoscopy experienced some discomfort when their fallopian tubes were mobilized. The use of local anesthesia should not be interpreted as being devoid of risk for serious complications (e.g., bradycardia, cardiac arrest). These life-threatening complications are rare, but the management and outcome are greatly assisted by individuals skilled in airway management and cardiopulmonary resuscitation.[97]

Postoperative Management

The incidence of anesthetic or surgical complications requiring hospital admission after ART procedures is low. Oskowitz et al.[72] reported admission rates after oocyte retrieval and GIFT procedures of 0.16% and 0.18%, respectively. The most common indications for hospitalization were hemoperitoneum and syncope after oocyte retrieval, and nausea, vomiting, and bowel injury after laparoscopic GIFT procedures. Abdominal pain and uterine cramping occur commonly after oocyte retrieval. Incisional pain and referred shoulder pain as a result of diaphragmatic irritation can also occur after laparoscopic ART procedures. Postprocedural discomfort is related primarily to the number of follicles retrieved (rather than the hormonal alterations induced by the stimulation cycle); and when it follows an anesthetic regimen that includes an opioid, it is graded as minimal to moderate. Abdominal discomfort can be managed with the use of a heating pad and small doses of intravenous fentanyl (25 to 50 μg) or oral analgesic agents (acetaminophen 500 mg to 1 g).[98] The use of nonsteroidal anti-inflammatory drugs should be avoided because changes in the prostaglandin milieu can affect embryo implantation.[99]

Nausea and emesis can also occur; however, exposure to droperidol and metoclopramide should be limited (see earlier discussion); treatment with nondopaminergic

agents can be considered. Prior to discharge, patients should be able to drink and retain liquids, ambulate, and void. Patients undergoing anesthesia for an ART procedure should be called 24 hours after the procedure to allow assessment of recovery and potential complications.

FUTURE CONSIDERATIONS

The use of ART procedures has been extended to include patients within a broader range of ages and co-morbidities. Check et al.[100] reported the successful delivery of infants through the use of donor oocytes, IVF, and ET in two postmenopausal women who were 51 years old; women in the seventh decade have also successfully delivered infants. In addition, more programs are participating in the preservation of ovarian tissue, as a means of extending reproductive capability. Future studies should assess the short- and long-term maternal and perinatal consequences of ART procedures as well as the obstetric and anesthetic implications.[101]

Technical improvements in ultrasonography as well as fiberoptic methods of oocyte retrieval and fallopian tube cannulation could potentially make laparoscopic interventions less invasive or unnecessary. For example, small-diameter laparoscopes with optical views comparable to conventional instruments have allowed "mini-laparoscopic" procedures to be performed for GIFT procedures.[96] These alterations may allow for changes in anesthetic options.

The identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success is an important process to which anesthesia providers can and should contribute.

KEY POINTS

- Assisted reproductive technology (ART) includes techniques that are being applied to an increasingly diverse population of patients with a wide range of co-morbidities.
- ART procedures usually involve a regimen of hormonal stimulation and oocyte retrieval followed by either *in vitro* fertilization with embryo transfer (IVF-ET) or gamete intrafallopian transfer (GIFT) procedures.
- Hormonal stimulation creates a number of oocytes for retrieval. On occasion, ovarian hyperstimulation syndrome can occur, with severe cases being associated with ascites, pleural effusion, hemoconcentration, oliguria, and thromboembolic events.
- Oocyte retrieval must be performed promptly, or ovulation will reduce the number of mature oocytes available for harvesting. Embryo transfer usually occurs transcervically; however, laparoscopic techniques (zygote intrafallopian transfer [ZIFT]) can be used.
- Monitored anesthesia care (MAC), neuraxial anesthesia, and general anesthesia have all been used successfully to anesthetize women for ART procedures. MAC may have to progress to loss of consciousness (i.e., general anesthesia) to prevent patient movement at critical times during the procedure.
- Laboratory studies have suggested that local anesthetic agents, nitrous oxide, and the volatile halogenated agents interfere with some aspects of reproductive physiology *in vitro*. However, few clinical data show that brief administration of any contemporary anesthetic agent (except halothane) for an ART procedure adversely affects live-birth rates.
- The identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success is an important process to which anesthesia providers can and should contribute.

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CHAPTER 16

Problems of Early Pregnancy

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CHAPTER OUTLINE

Obstetric disease of early pregnancy may result in significant maternal morbidity and even mortality. Safe care of patients with obstetric disease involves a thorough understanding of the physiologic changes of early pregnancy as well as the specific issues associated with each pathologic condition.

PHYSIOLOGIC CHANGES OF EARLY PREGNANCY

Respiratory System

The respiratory system undergoes profound physiologic changes during early pregnancy. Increased progesterone concentration stimulates respiratory efforts by increasing the sensitivity of the respiratory center to carbon dioxide. Minute ventilation increases by at least 15% by 12 weeks' gestation and by 25% by 20 weeks' gestation. This results from an increase in tidal volume (respiratory rate is unchanged) and exceeds the increase in oxygen consumption. The result is a respiratory alkalosis with maternal arterial partial pressure of carbon dioxide decreasing to 30 to 33 mm Hg by 10 to 12 weeks' gestation. Moreover, maternal arterial partial pressure of oxygen increases to 106 to 108 mm Hg in the first trimester. Decreased bicarbonate concentration partially compensates for the modest respiratory alkalosis that results from the physiologic hyperventilation, leading to a maternal pH that is slightly above normal (i.e., approximately 7.44). There is little or no change in lung capacities during the first half of pregnancy. Women in early pregnancy who undergo mechanical ventilation require increased minute ventilation.

Cardiovascular System

The cardiovascular system also undergoes profound changes early in pregnancy. Cardiac output increases 20% to 25% by 8 weeks' gestation and 35% to 40% by 20 weeks' gestation. Systemic vascular resistance decreases 30% by 8 weeks' gestation. Maternal mean arterial pressure decreases approximately 6 mm Hg at 16 to 24 weeks' gestation and returns to normal near term.

Aortocaval compression typically occurs after 18 to 20 weeks' gestation, when the uterine fundus reaches the umbilicus and is large enough to compress the aorta and vena cava when the patient is supine. Left uterine displacement is rarely needed in early pregnancy, but when the uterine size is equivalent to an 18- to 20-week gestation, left uterine displacement should be attained by elevating the right hip 15 degrees off midline with a wedge or blankets. The need for left uterine displacement occurs earlier in gestation in the presence of multiple gestation, polyhydramnios, or gestational trophoblastic disease.

Blood volume increases throughout pregnancy; the average prepregnancy blood volume of 4350 mL (76 mL/kg) increases to 4700 mL (81 mL/kg) at 12 weeks' gestation, to 5500 mL (89 mL/kg) at 20 weeks' gestation, and

to approximately 6600 mL (97 mL/kg) at term. The increase in blood volume is primarily the result of greater plasma volume because red blood cell volume increases to a smaller degree (27 mL/kg). Because pregnant women have an expanded blood volume, they typically tolerate a blood loss of 500 to 1500 mL during the first half of pregnancy. A blood loss of 500 to 1500 mL rarely requires blood transfusion, provided that the blood loss is replaced with an adequate volume of crystalloid or colloid.

Gastrointestinal System

An increased progesterone level causes relaxation of lower esophageal sphincter tone as early as the first trimester. Fasting gastric volume is approximately 30 mL in both nonpregnant women and women in early pregnancy. Metoclopramide 10 mg, administered intravenously 15 to 30 minutes before anesthesia, can reduce this volume by 50%.[1] In a study of 100 pregnant women undergoing general anesthesia by mask at 6 to 22 weeks' gestation, a pH electrode showed reflux of gastric contents into the esophagus in 17% of patients.[2] Most episodes of reflux occurred in patients who experienced hiccups. Only 2% had regurgitation of gastric contents into the pharynx, and no patient demonstrated clinical evidence of pulmonary aspiration.

General anesthesia may be safely administered by means of a mask or a laryngeal mask airway by experienced anesthesia providers in selected obstetric patients during early pregnancy. Many anesthesia providers are comfortable managing an airway without tracheal intubation until 18 to 20 weeks' gestation, when the uterus moves out of the pelvis. The latter movement leads to anatomic and intragastric pressure changes that predispose to gastroesophageal reflux. Some anesthesia providers prefer to intubate the trachea of pregnant women who require general anesthesia as early as 12 to 14 weeks' gestation, given that hormonal changes leading to sphincter relaxation are present early in pregnancy. Patients who receive general anesthesia during the first half of pregnancy should be intubated if they are at increased risk for gastric content aspiration (e.g., history of gastroesophageal reflux, morbid obesity, food ingestion within 6 to 8 hours). Pharmacologic prophylaxis (e.g., sodium citrate, a histamine-2 (H_2) receptor antagonist, and/or metoclopramide) is likely to further reduce the risk for aspiration pneumonia (see Chapter 29). Neuraxial anesthesia is associated with a lower risk for aspiration than general anesthesia.

Nervous System

During early pregnancy, the nervous system is more sensitive to general and local anesthetic agents. The minimum alveolar concentration (MAC) for volatile anesthetic agents is decreased by approximately 30%, although the underlying mechanism for this change is unclear. A recent study that compared patients undergoing cesarean delivery with nonpregnant patients undergoing elective gynecologic surgery found no difference between groups in electroencephalographic measures during general anesthesia with similar end-tidal concentrations of sevoflurane.[3] Because it is well-proven that MAC decreases in pregnancy, this study implies that MAC in pregnant women may not correlate well with depth of anesthesia. Further research is needed in this area.

ECTOPIC PREGNANCY

Ectopic pregnancy occurs when the fertilized ovum implants outside the endometrial lining of the uterus. Death, infertility, and recurrent ectopic pregnancy are possible sequelae. The frequency of ectopic pregnancy in the United States increased fourfold to fivefold between 1970 and 1992 but appears to have stabilized at a rate of approximately 16 per 1000 pregnancies.[4,5] A higher prevalence of associated risk factors, especially pelvic inflammatory disease, as well as earlier diagnosis of previously unrecognized ectopic pregnancies may account for the reported increase.

Ruptured ectopic pregnancy is a leading cause of pregnancy-related maternal death during the first trimester and accounts for 6% of all pregnancy-related maternal deaths in the United States.[6,7] Most deaths result from hemorrhage (93%); infection (2.5%), embolism (2.1%), and anesthetic complications (1.3%) are less common causes.[8] More than 30% of women who have had an ectopic pregnancy subsequently suffer from infertility, and 5% to 23% have a second ectopic pregnancy.[9]

The number of deaths from ectopic pregnancy decreased in the United States from 1970 through 2007. The case-fatality rate decreased from 35.5 deaths per 10,000 ectopic pregnancies in 1970 to 3.8 per 10,000 in 1989,[10] and the ectopic pregnancy mortality ratio decreased from 1.15 deaths per 100,000 live births in 1980 through 1984 to 0.5 death per 100,000 live births in 2003 through 2007.[11] The U.S. Centers for Disease Control and Prevention attributes this decline to "improvements in the sensitivity, accuracy, and use of pregnancy testing, ultrasound for diagnosis, and improvements in therapeutic modalities, including laparoscopic surgery and medical management of ectopic pregnancy."[12] However, a recent cluster of 11 maternal deaths from ectopic pregnancy in Florida between 2009 and 2010 increased Florida's ectopic pregnancy mortality ratio from 0.6 death per 100,000 live births in 1999 through 2008 to 2.5 deaths per 100,000 live births in 2009 through 2010.[12] Because these women collapsed (likely from acute rupture and hemorrhage) without ever seeking health care, it was believed that limited access to early care may have contributed to the adverse outcomes. Further, of the 11 women who died, 6 tested positive for illicit drugs at autopsy. Ectopic pregnancy deaths historically have been more common in teenagers[10] and are 3 to 18 times higher in African-American women than in white women.[6,8,10]

Factors that alter the normal fallopian tube transport system for the fertilized ovum increase the risk for ectopic pregnancy. These factors include (1) previous ectopic pregnancy; (2) previous tubal surgery; (3) pelvic inflammation, especially infection with *Chlamydia trachomatis;* (4) congenital anatomic distortion such as that caused by

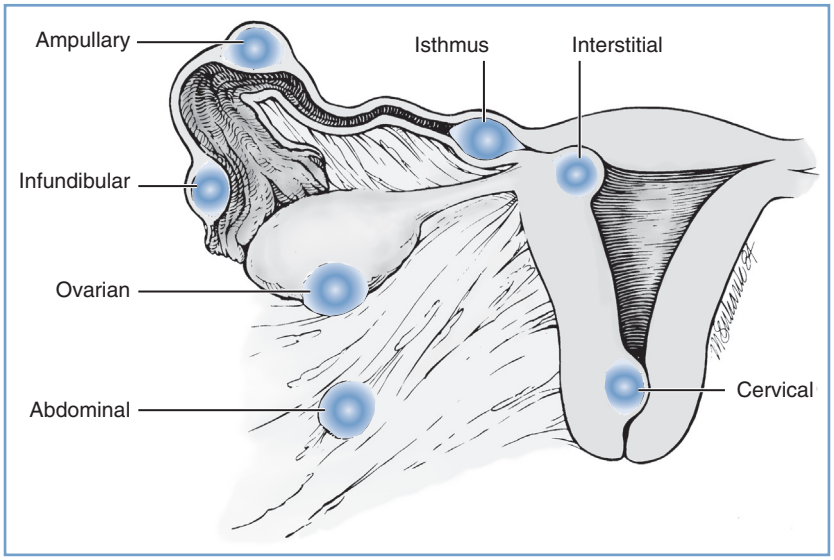

FIGURE 16-1 ■ **Potential locations of ectopic pregnancies. The majority occur in the ampullary portion of the fallopian tube.** (Reprinted from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009. Modified from DeCherney AH, Seifer DB. Ectopic pregnancy. In Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: Normal and Problem Pregnancies. 2nd edition. New York, Churchill Livingstone, 1991:811.)

exposure to diethylstilbestrol *in utero;* (5) previous pelvic or abdominal surgery; (6) use of a contraceptive intrauterine device, which may be associated with interstitial ectopic pregnancy; (7) delayed ovulation; (8) hormonal changes associated with ovulation induction or progestin-only oral contraceptives; (9) lifestyle factors (e.g., smoking, vaginal douching); (10) history of infertility; and (11) assisted reproductive technology (ART) procedures (e.g., zygote transfer into the fallopian tube or uterine cavity).[13] However, one third of patients with ectopic pregnancies have no identifiable risk factors.

The fertilized ovum can implant anywhere along the path of migration or in the abdominal cavity (Figure 16-1). Most ectopic pregnancies (98%) are **tubal** (infundibular or fimbrial, 6%; ampullary, 78%; isthmic, 12%; interstitial or cornual, 2%). The remaining 2% implant on the **cervix, vagina,** or **ovary** or elsewhere in the **abdomen.**[14] An increasing number of **cesarean scar** ectopic pregnancies, which may be on a continuum with **early placenta accreta,** are being reported.

In patients who undergo ART procedures, ectopic pregnancies have been reported in approximately 2% of pregnancies.[13] Most of these pregnancies are tubal; however, approximately 6% are ovarian, abdominal, or cervical, and 12% to 15% are **heterotopic** (see later discussion).[14]

Clinical Presentation

The clinical presentation of the patient with an ectopic pregnancy depends on the gestational age, site of implantation, and extent of hemorrhage. Prior to rupture, the signs and symptoms are often subtle. Classic clinical signs of impending rupture or a ruptured tubal pregnancy include abdominal or pelvic pain (95%), delayed menses (75% to 95%), and vaginal bleeding (60% to 80%). Vaginal bleeding results from the breakdown and shedding of the decidual lining of the uterine wall, which is probably associated with decreased hormone production by the corpus luteum and inadequate human chorionic gonadotropin (hCG) production by the ectopic trophoblast. Pain often precedes vaginal bleeding. Patients with hemorrhage (with or without tubal rupture) may experience dizziness or syncope, may have the urge to defecate because of the effect of blood in the cul-de-sac, and may have shoulder pain from diaphragmatic irritation by intra-abdominal blood.

Physical findings include abdominal tenderness with or without rebound (80% to 95%), a uterus that is smaller than expected for dates (30%), and a tender adnexal mass (30% to 50%). A bulging cul-de-sac suggests hemoperitoneum. With significant hemorrhage there may be signs of shock, but some patients may appear hemodynamically stable despite a hemoperitoneum volume of 1000 to 1500 mL; presumably, these patients have an ectopic pregnancy with slow bleeding and are able to compensate for the gradual blood loss.

Diagnosis

Ectopic pregnancy should be excluded in any patient who has pelvic pain and a positive pregnancy test. In a woman of reproductive age, the symptoms of ectopic pregnancy must be differentiated from (1) a threatened, inevitable, or incomplete abortion; (2) infection after attempted abortion; (3) pelvic inflammatory disease; (4) a degenerating fibroid; (5) appendicitis and other gastrointestinal diseases; (6) ovarian torsion; (7) a ruptured or bleeding ovarian cyst; (8) a trapped retroverted uterus in pregnancy; and (9) nephrolithiasis.

Current tests allow early diagnosis of ectopic pregnancy and prompt treatment that decreases morbidity and mortality.[9] Diagnostic algorithms include the following guidelines:

1. Ultrasonography can reliably confirm only the presence of an intrauterine pregnancy. The ectopic pregnancy itself may be difficult to visualize.[15] **Transvaginal ultrasonography** is the current modality of choice because it can detect an intrauterine gestational sac as soon as 21 days after conception (when the beta-hCG concentration is greater than 1400 mIU/mL with use of the International Reference Preparation [IRP] standard). **Transabdominal ultrasonography** can visualize an intrauterine pregnancy when the serum beta-hCG concentration is higher than 6000 to 6500 mIU/mL IRP.[16]
2. A serial beta-hCG concentration that decreases, plateaus, or shows a subnormal increase (< 53% over 48 hours) usually indicates a nonviable pregnancy—either an ectopic pregnancy or an impending abortion.[17] With a spontaneous abortion, a decline in beta-hCG concentration of at least 21% to 35% should be seen over 2 days. A slower decline is suggestive of an ectopic pregnancy. A beta-hCG concentration greater than 100,000 mIU/mL is usually associated with a viable intrauterine pregnancy.[18]
3. A serum progesterone concentration greater than 25 ng/mL is usually associated with a viable pregnancy. A concentration less than or equal to 5 ng/mL usually indicates a nonviable pregnancy but cannot distinguish a spontaneous abortion from an ectopic pregnancy.[19] Most ectopic pregnancies are associated with progesterone levels between 5 and 25 ng/mL, a fact that limits the usefulness of this test.
4. Uterine curettage can be performed when nonviability is established. Identification of trophoblastic villi confirms miscarriage of an intrauterine pregnancy. Absence of villi signals either a complete spontaneous abortion (confirmed by rapidly decreasing beta-hCG concentration) or an ectopic pregnancy.

In the past, culdocentesis was used to aid in the diagnosis of hemoperitoneum and ectopic pregnancy. Although a positive result is highly predictive of hemoperitoneum, the advent of pelvic ultrasonography and rapid quantitative beta-hCG tests limits its value in the diagnosis of ectopic pregnancy.

Obstetric Management

Management options for ectopic pregnancy are expectant, medical, and surgical. Management choice depends on the symptoms and diagnostic findings.

Expectant management may be used for selected asymptomatic patients with early tubal ectopic pregnancies and stable or decreasing beta-hCG levels. Successful resolution has been reported in approximately 50% of these selected patients.[4] If expectant management is unsuccessful, a medical or surgical approach is required.

The American College of Obstetricians and Gynecologists (ACOG) as well as the American Society of Reproductive Medicine have published guidelines for the **medical management** of ectopic pregnancy.[20,21] Systemic, intramuscular, oral, and intragestational forms of chemotherapy have been used successfully in the medical management of ectopic pregnancy. **Methotrexate,** a folate antagonist that interrupts DNA synthesis and thus cell replication, inhibits growth of trophoblastic cells of the placenta and is commonly used to treat ectopic pregnancy. Because methotrexate is toxic to all rapidly-dividing tissues of the body, there are many contraindications to medical treatment of ectopic pregnancy, including immunodeficiency and pulmonary, liver, renal, or hematologic disease. Further, the ACOG has recommended that only early tubal pregnancies (i.e., no cardiac activity, a gestational sac with a diameter < 3.5 to 4.0 cm, and no evidence of tubal rupture or hemoperitoneum) be treated with methotrexate.

Methotrexate treatment protocols include a single-dose regimen, a two-dose regimen, and a fixed multidose regimen; the multidose regimen is reserved for patients with high beta-hCG levels (i.e., > 5000 mIU/mL). From day 4 to day 7 after methotrexate treatment, a decrease in beta-hCG level of 15% must be present to consider the treatment successful. Otherwise, repeat methotrexate treatment or surgical intervention is required. Follow up and close monitoring until beta-hCG level reaches nonpregnant values is imperative because of the risk for rupture and hemorrhage. Side effects of methotrexate can be severe and include abdominal pain, vomiting, stomatitis, severe neutropenia, and pneumonitis. Compared with surgical management, medical management of ectopic pregnancy provides no difference in overall tubal preservation, tubal patency, risk for repeat ectopic pregnancy, or success of future pregnancies.

Surgical management depends on the location of the pregnancy, the hemodynamic stability of the patient, the available equipment, and the surgeon's expertise. Most often, diagnostic laparoscopy is performed to confirm the diagnosis and locate the ectopic pregnancy. For tubal ectopic pregnancies, a salpingostomy, salpingotomy, or salpingectomy (usually partial) is performed by means of laparoscopy or laparotomy. To aid hemostasis during laparoscopic removal of the ectopic pregnancy, some obstetricians inject dilute vasopressin into the surface of the fallopian tube. This agent causes marked blanching of the tube and results in a relatively bloodless surgical field. If the vasopressin is accidentally injected intravenously, a marked increase in maternal blood pressure may occur.

A laparotomy is indicated if the surgeon is not trained in operative laparoscopy, laparoscopic removal is anticipated to be difficult (e.g., tube diameter > 6 cm or an interstitial location of the ectopic pregnancy), or there is uncontrollable bleeding. Laparotomy should be performed immediately if there is hemodynamic instability; these cases often require a partial or total salpingectomy. If a partial salpingectomy is performed, tubal repair may be performed primarily or during a second operation. Although some experts have noted that outcomes from randomized trials comparing salpingostomy and salpingectomy are lacking,[22] the risk for persistent ectopic pregnancy may be higher after salpingostomy than after salpingectomy.[23]

Interstitial, cervical, cesarean scar, and abdominal ectopic pregnancies as well as early placenta accreta may

present significant diagnostic and therapeutic challenges, resulting in delay of diagnosis and treatment. There is potential for massive hemorrhage because of disruption of organs and adjacent tissues. The desire to preserve fertility may result in greater blood loss as tissue and organ preservation are attempted.

Interstitial pregnancy often goes unrecognized and may manifest as uterine wall rupture, massive hemorrhage, and shock. Conservative surgery (e.g., cornual resection) may be attempted, but hysterectomy may be required if uterine damage is severe.

Cervical pregnancy often results in massive hemorrhage because of the inability of the cervix to contract. In the past, most cervical pregnancies necessitated hysterectomy to control hemorrhage. More current management options that have greater likelihood of maintaining fertility include (1) methotrexate therapy, (2) local excision, (3) cerclage and tamponade, (4) ligation of the hypogastric arteries or the cervical branches of the uterine arteries, and (5) angiographic embolization of the uterine arteries followed by a dilation and evacuation (D and E) procedure (see later discussion).[24]

Cesarean scar pregnancy occurs when a gestational sac implants in the uterine scar defect (niche) at the site of a previous cesarean delivery. Cesarean scar pregnancy has a high complication rate. Although relatively rare, its incidence is rising with increasing cesarean delivery rates and currently may be as high as 1 in 1800 pregnancies.[25,26] Jurkovic et al.[26] described two types of cesarean scar pregnancies: (1) implantation on the scar with enlargement into the uterine cavity, and (2) implantation into a scar defect with growth into the myometrium. Depending on its progression, the former type may grow normally or may be treated medically. Scar implantation results in an increased risk for hemorrhage at delivery. Growth into the myometrium may lead to eventual rupture and bleeding in the first trimester; prompt surgical intervention is preferred over medical management in this situation.

In a review of 112 cases of cesarean scar pregnancies, Rotas et al.[25] found that approximately half occurred in women with only one previous cesarean delivery. Many patients have vaginal bleeding, abdominal cramps, and/or lower abdominal pain. Up to one third of cases may be asymptomatic and are diagnosed during routine ultrasonography. A review of 751 published cases of cesarean scar pregnancy found that the diagnosis was missed in 107 of 751 cases (13.6%).[27] Transvaginal ultrasonography was the best diagnostic tool. There were a total of 31 different primary treatment approaches, which included hysterectomy, dilation and curettage (D and C), hysteroscopic excision, uterine artery embolization, and intragestational aspiration or injection of methotrexate or potassium. Complications occurred in 331 of the 751 cases (44.1%), of which the most common was hemorrhage. The authors noted that local methotrexate and hysteroscopic-directed procedures had the lowest complication rates and that curettage, systemic methotrexate therapy, or embolization as single treatments should be avoided.

The incidence of **early placenta accreta** is also rising as a result of increasing cesarean delivery rates. It is defined as penetration of the placenta into the myometrium, which is discovered in the first or early second trimester. Because of similarities in pathogenesis, it is thought—although not confirmed—that early placenta accreta may develop from cesarean scar pregnancy. A recent review found that 15 of 47 (32%) patients with early placenta accreta had spontaneous uterine rupture, in most cases followed by bleeding and shock, which resulted in laparotomy, hysterectomy, or uterine artery embolization.[27] Although the gestational age is early, it is imperative that the anesthesia team is aware of the risk for hemorrhage during surgical intervention for cesarean scar pregnancy and early placenta accreta.

Abdominal pregnancy is defined as implantation in the peritoneal cavity, not including the fallopian tubes, ovaries, or ligaments, and is associated with a high incidence of maternal morbidity and fetal demise.[28] In a recently published series of advanced extrauterine pregnancies, Worley et al.[29] identified ten women who presented with extrauterine pregnancies beyond 18 weeks' gestation, of whom three met the diagnostic criteria for abdominal pregnancy. All patients had difficult surgery, nine patients required blood transfusion, and only five fetuses survived after complicated courses.

Diagnosis of abdominal pregnancy can be difficult, historically being missed in as many as one of nine cases.[28] The diagnosis was missed prior to delivery in four of the ten cases in the series of Worley et al.[29] Abdominal pain, vaginal bleeding, symptoms consistent with partial bowel obstruction, shock, or death may be the first indication of this unusual type of pregnancy. Ultrasonography is useful but may miss the diagnosis in more than 50% of cases. Magnetic resonance imaging may prove to be a more sensitive diagnostic tool.

If an extrauterine pregnancy is suspected in early gestation, laparoscopy can be used to diagnose and remove gestational products. If the extrauterine pregnancy is not identified until late gestation, it is associated with decreased placental perfusion (which typically results in fetal growth restriction) and oligohydramnios (which often results in pulmonary hypoplasia and anatomic deformities). In 1993, Stevens[30] reviewed published cases of abdominal pregnancy since 1809 and found that 63% of infants survived when born after 30 weeks' gestation.

Management of an advanced extrauterine pregnancy consists of laparotomy and delivery of the fetus. Once the fetus is delivered, management of the placenta is controversial and fraught with hazard. Removal of the placenta is associated with massive hemorrhage, prolonged and complicated surgery (e.g., bowel resection), and an increased risk for maternal mortality. A decision to leave the placenta *in situ* results in a higher risk for infectious morbidity as well as a potential greater need for additional surgery.[30,31] In the series of Worley et al.,[29] the placenta was left *in situ* in two patients, both of whom developed serious complications. The site of placental implantation and the ability to adequately ligate the blood supply often dictates the obstetrician's decision about management of the placenta.

Heterotopic pregnancy describes the simultaneous occurrence of an ectopic and an intrauterine pregnancy.

Historically, it was thought to occur in 1 in 30,000 spontaneous pregnancies.[32] However, in patients undergoing ART, 0.2% to 3% of pregnancies may be heterotopic.[14,33] Difficulty visualizing the entire fallopian tube on ultrasonography, combined with normal or slightly elevated beta-hCG measurements (i.e., low serum levels from the ectopic pregnancy combined with normal levels from the intrauterine pregnancy), make the early diagnosis of heterotopic pregnancy difficult.[34] This diagnosis should be suspected in cases in which clinical signs of an ectopic pregnancy and a confirmed intrauterine pregnancy coexist. In most cases, the ectopic pregnancy is removed surgically, which can be difficult when trying to maintain the intrauterine pregnancy. Alternatively, transvaginal ultrasonography–guided injection of potassium chloride into the ectopic pregnancy has been performed successfully; however, as many as 55% of patients may require subsequent surgery.[35] The patient often sustains the normal intrauterine pregnancy to term.

Patients with ectopic pregnancies who are Rh-negative should receive Rh_0(D) immune globulin.[36]

Anesthetic Management

Patients with an unruptured tubal pregnancy usually have normal intravascular volume, minimal bleeding before and during surgery, and low anesthetic and surgical risk. Anesthetic considerations for laparoscopy or laparotomy are summarized in Box 16-1. Although most patients may prefer general anesthesia, neuraxial anesthesia with an upper sensory level to at least T4 may be an alternative in selected patients. Shoulder pain from diaphragmatic irritation may occur and can be treated with intravenous analgesics (e.g., fentanyl 1 to 2 μg/kg).

A ruptured ectopic pregnancy may be associated with significant preoperative blood loss, but estimation of the extent of this is difficult because young women may have normal blood pressure despite a markedly reduced circulating blood volume. General anesthesia, with preparation for hemorrhage, is preferred if significant bleeding has occurred (e.g., ruptured tubal pregnancy) or is likely to occur (e.g., cervical, interstitial, cornual, cesarean scar, or abdominal ectopic pregnancy, or early placenta accreta). Intraoperative autologous blood transfusion can be used, and it may be useful especially in developing countries, where blood bank supplies are limited and women typically present late with significant hemoperitoneum and/or hypovolemic shock.[37] The desire to preserve fertility often results in greater blood loss as tissue and organ preservation are attempted.

BOX 16-1 Suggested Anesthetic Techniques for Laparoscopy or Laparotomy for Patients with Ectopic Pregnancy

General Considerations

- Blood typing and antibody screening
- Aspiration prophylaxis if patient has a full stomach
- Routine noninvasive monitors
- Large-bore peripheral intravenous catheter
- Urinary catheter
- If major bleeding has occurred or is expected to occur (e.g., ruptured tubal, interstitial, cervical, uterine scar, or abdominal ectopic pregnancy):
  - Two or more intravenous catheters
  - Typing and crossmatching of blood
  - Consideration of invasive hemodynamic monitoring (e.g., arterial catheter, central venous pressure catheter)
  - Consideration of intraoperative cell salvage
- Although general anesthesia is usually preferred, neuraxial (spinal or epidural) anesthesia may be considered for hemodynamically stable patients with a low likelihood of significant hemorrhage (i.e., unruptured tubal pregnancy):
  - Intravenous fluids, vasopressors, supplemental oxygen, and minimal sedation given as clinically indicated.

General Anesthesia

- Rapid-sequence induction with cricoid pressure if the patient has a full stomach
- Induction: propofol or thiopental (ketamine or etomidate should be considered if patient is hemodynamically unstable)
- Muscle relaxant
- Tracheal intubation
- Maintenance: volatile or intravenous anesthetic agents
- Placement of an oral gastric tube, performance of suctioning, and removal of the tube
- Reversal of neuromuscular blockade and extubation when the patient is awake and responds to verbal commands

Spinal Anesthesia

- Single injection with a small-gauge spinal needle: hyperbaric bupivacaine 12 mg with fentanyl 10 to 25 μg to achieve T4 sensory blockade

Epidural Anesthesia

- Placement of midlumbar epidural needle and catheter
- Lidocaine 2% with epinephrine 5 μg/mL (1:200,000), approximately 20 mL, and fentanyl 100 μg, injected incrementally, to achieve T4 sensory blockade

Modified from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

ABORTION AND INTRAUTERINE FETAL DEMISE

Abortion refers to a pregnancy loss or termination, either before 20 weeks' gestation or when the fetus weighs less than 500 g. It can occur spontaneously or may be performed electively for personal or medical reasons. A total of 825,564 elective abortions were reported in the United States in 2008, a rate of 16 abortions per 1000 women and a ratio of approximately 234 abortions per 1000 live births.[38] The total number of abortions and rate of abortions (number of abortions per 1000 women) in the United States steadily declined from 1999 through 2007 and then remained static from 2007 to 2008.[38] Between

1999 and 2008, the number, rate, and ratio (number per 1000 live births) of elective abortions in the United States declined by 3%, 4%, and 10%, respectively.[38]

In 2008, 62.8% of elective abortions were performed before 8 weeks' gestation, 91.4% were performed before 13 weeks' gestation, and 1.3% were performed after 21 weeks' gestation.[38] Most (75.9%) were performed by D and C at less than 13 weeks' gestation, although some (14.6%) were induced medically, most commonly using methotrexate and misoprostol, or mifepristone and misoprostol before 8 weeks' gestation.[38]

Of the 4693 reported pregnancy-related maternal deaths from 1998 to 2005 in the United States, 3% were the result of induced or spontaneous abortion.[39] Deaths are usually the result of sepsis, hemorrhage, or embolism.[40] Of the 20 abortion-related maternal deaths in the United States in 2003, 10 were related to spontaneous abortion and 10 women died after legal elective abortion (6 after surgical procedures and 4 after medical or nonsurgical procedures).

From a global perspective, abortion is a significant cause of maternal death. A review of causes of maternal death from 1997 to 2002 by the World Health Organization (WHO) reported that in some areas of Latin America and the Caribbean as many as 30% of maternal deaths are caused by abortion.[41] In 2006, the WHO estimated that 12, 23, and 37 maternal deaths per 100,000 live births occur as a result of induced abortion in South Asia, Latin America/Caribbean, and sub-Saharan Africa, respectively.[41] It is likely that many of these abortions are performed by unskilled individuals in a nonsterile environment that does not meet minimal medical standards. The exact number of maternal deaths that result from induced abortion is unknown and likely underreported.[41,42]

Spontaneous abortion occurs in 10% to 15% of clinically recognized pregnancies; when subclinical pregnancies are also considered, the incidence of spontaneous pregnancy loss may be as high as 60%.[43] Although most spontaneous abortions manifest clinically at 8 to 14 weeks' gestation, ultrasonography suggests that fetal demise usually occurs before 8 weeks' gestation. If the fetus is viable at 8 weeks' gestation, the incidence of subsequent fetal loss is only 3%.

The etiology of spontaneous abortion varies among patients. Chromosomal abnormalities are responsible for at least 50% to 80% of all spontaneous abortions.[44] Other causes include (1) immunologic mechanisms, (2) maternal infections, (3) endocrine abnormalities (e.g., poorly-controlled diabetes mellitus), (4) uterine anomalies, (5) incompetent cervix, (6) debilitating maternal disease, (7) maternal clotting disorders, (8) trauma, and possibly (9) environmental exposures (e.g., irradiation, smoking, certain drugs).

Although some studies (conducted before scavenging of anesthetic gases was routine) suggested a higher incidence of spontaneous abortion among women who were exposed to trace concentrations of anesthetic agents in operating rooms,[45] reevaluation of these data demonstrated significant flaws in study design, casting doubt on the original conclusions.[46] Later studies have shown no increased incidence of spontaneous abortion in women working in operating rooms.[47]

Clinical Presentation and Obstetric Management

The clinical presentation and management of spontaneous abortion vary. A **threatened abortion** is defined as uterine bleeding without cervical dilation before 20 weeks' gestation. Bleeding may be accompanied by cramping or backache. Once the diagnosis is confirmed, the patient's activities are restricted until symptoms resolve. Approximately 25% of pregnancies are complicated by a threatened abortion; approximately half of affected women progress to a spontaneous abortion.[48]

An **inevitable abortion** is defined as cervical dilation or rupture of membranes without expulsion of the fetus or placenta. Spontaneous expulsion of the uterine contents usually occurs, but infection can be a complication.

A **complete abortion** is defined as a total, spontaneous expulsion of the fetus and placenta. Partial expulsion of the uterine contents (i.e., an **incomplete abortion**) is more common after 8 weeks' gestation. Persistent bleeding and cramping after expulsion of tissue are signs of an incomplete abortion. An incomplete abortion usually requires a D and E or a D and C procedure to remove any remaining fetal or placental tissue. A D and C procedure refers to dilation of the cervix followed by curettage, which is typically by suction. A D and E procedure involves greater cervical dilation followed by evacuation of the uterus with surgical instruments. Typically, the latter is required after ossification of the fetal bones, which usually occurs around 13 to 15 weeks' gestation. A D and E procedure is associated with more complications. Oxytocin and/or an ergot alkaloid (e.g., methylergonovine) increases uterine tone and may be administered intraoperatively and/or postoperatively to decrease the amount of uterine bleeding.

Fetal death may go unrecognized for several weeks in a patient with a **missed abortion.** Occasionally, coagulation defects such as disseminated intravascular coagulation (DIC) may complicate intrauterine fetal death; this possibility is more likely when fetal demise occurs at an advanced gestational age. If spontaneous expulsion of the uterine contents does not occur after a brief period of observation, evacuation of the uterus is indicated. Management options include placement of intracervical laminaria or intravaginal or intracervical placement of a prostaglandin E_2 (PGE_2) preparation. This can be followed by induction of labor or a D and C or D and E procedure. Side effects of prostaglandins include nausea, vomiting, diarrhea, and fever. Intra-amniotic instillation of hypertonic saline is not recommended in cases of intrauterine fetal death because coagulation defects may be induced or enhanced.

Recurrent or **habitual abortion** refers to the occurrence of three or more consecutive spontaneous abortions in the same patient.

Obstetric Complications

Complications of D and C and D and E procedures include cervical laceration, uterine perforation, hemorrhage, retained products of conception, and infection. The risk for these complications is increased in

pregnancies that have progressed beyond the first trimester and is greater for D and E procedures than for D and C procedures. Vasovagal events, postabortal syndrome (i.e., intrauterine blood clots with uterine atony, associated with lower abdominal pain, tachycardia, and diaphoresis), DIC, and unrecognized ectopic pregnancy can also occur. Management of uterine perforation may involve simple observation or immediate laparotomy with repair. Management depends on the suspected severity of injury to the uterus and adjacent structures.

Serious infection (e.g., **septic abortion**) complicates approximately 1 in 200,000 spontaneous abortions. It is more common after induced abortion, particularly illegal abortion.[49] Septic abortion causes significant morbidity and is life threatening. Blood cultures should be taken, and broad-spectrum intravenous antibiotics should be administered promptly. Patients with hemodynamic instability may require invasive hemodynamic monitoring to guide fluid, blood, and vasoactive drug therapy. Lower genital tract or bowel injury should be excluded, and the uterus should promptly be re-evacuated. Occasionally, hysterectomy is necessary and may be lifesaving.

Rh_0(D) immune globulin should be administered to prevent Rh sensitization in Rh-negative woman who abort. It should also be given to Rh-negative women with a threatened abortion because a positive Kleihauer-Betke test result (indicating transplacental hemorrhage of fetal blood into the maternal circulation) has been demonstrated in 11% of these patients.[50]

Women who suffer spontaneous abortion are at increased risk for depressive disorders during the 6 months after miscarriage[51] (see Chapter 51).

Anesthetic Management

Several anesthetic techniques are appropriate for D and C and D and E procedures (Box 16-2). The choice depends on several factors (e.g., whether the cervix is dilated; the gestational age and ossification of the fetus; the presence of significant blood loss, sepsis, or a full stomach; and the emotional state and preference of the patient). Dilation of the cervix is relatively painful, whereas suction and curettage are less painful. If the cervix is dilated and the products of conception can be curettaged and suctioned, sedation with or without a paracervical block may suffice. If the cervix is not dilated, paracervical block and sedation, spinal or epidural anesthesia (with sensory blockade from T10 to S4), or general anesthesia should be used. General anesthesia may be most appropriate if the patient is emotionally upset or if the gestational age is 13 to 15 weeks or greater (which requires a greater degree of cervical dilation for a D and E procedure). Selected patients may

BOX 16-2 Suggested Anesthetic Techniques for Dilation and Uterine Suction Curettage (D and C) or Evacuation (D and E) for Spontaneous or Induced Abortion

General Considerations

- Blood typing and antibody screening or typing and crossmatching in patients with a large blood loss or those with advanced gestation
- Aspiration prophylaxis if patient has a full stomach
- Routine noninvasive monitors
- One peripheral intravenous catheter
- Administration of a short-acting benzodiazepine (e.g., midazolam) may be indicated for patients who prefer sedation and/or amnesia
- Neuraxial (spinal or epidural) anesthesia for hemodynamically stable patients without sepsis is an option:
  - Intravenous fluids, vasopressors, supplemental oxygen, and minimal sedation given as clinically indicated
- Oxytocin and/or an ergot alkaloid available
- General anesthesia may be most appropriate for patients with anticipated blood loss or for patients requiring a D and E (e.g., gestation > 15 weeks' with large fetal size and fetal ossification)
- In patients with significant blood loss: observation of the patient on the operating table for evidence of hypotension for at least 5 minutes after the legs have been lowered from the lithotomy to the supine position

Monitored Anesthesia Care (well tolerated when the cervix is dilated and gestational age is first trimester)

- Intravenous analgesia with fentanyl, alfentanil, or remifentanil and sedation with midazolam or propofol
- Paracervical block if needed

Spinal Anesthesia

- Single injection with a small-gauge spinal needle: lidocaine 40 mg or hyperbaric bupivacaine 7.5 mg, with fentanyl 10 to 20 µg, to achieve sensory blockade from T10 to S4

Epidural Anesthesia

- Placement of midlumbar epidural needle and catheter
- Lidocaine 2% with epinephrine 5 µg/mL (12 to 15 mL) and fentanyl 100 µg, injected incrementally, to achieve sensory blockade from T10 to S4

General Anesthesia

- Rapid-sequence induction with cricoid pressure if the patient has a full stomach
- Induction: propofol or thiopental (ketamine or etomidate in cases of severe hemorrhage)
- Mask anesthesia or laryngeal mask airway during early pregnancy if stomach is empty and the patient is hemodynamically stable; otherwise tracheal intubation with a muscle relaxant
- Maintenance: volatile or intravenous anesthetic agents
  - High concentration (> 0.5 MAC) of a volatile anesthetic agent should be avoided if there is significant bleeding or evidence of uterine atony
- Insertion and removal of an oral gastric tube (if trachea is intubated) to evacuate the stomach
- Tracheal extubation when the patient is awake and responds to verbal commands

Modified from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

benefit from premedication with a short-acting benzodiazepine (e.g., midazolam).

Typically, the cervix is already dilated in patients who have had significant preoperative bleeding; rarely does a patient with a closed cervix have significant bleeding. In the presence of significant bleeding, intravascular volume should be restored first. A paracervical block and sedation may then be adequate. Substantial hemorrhage represents a relative contraindication to the use of spinal or epidural anesthesia, which probably should also be avoided in patients with evidence of sepsis.

General anesthesia may be induced with propofol or thiopental, although ketamine or etomidate may be preferred in patients with significant bleeding. Large doses (1.5 to 2.0 mg/kg) of ketamine increase uterine tone,[52] which may be advantageous in patients who require evacuation of the uterus.

Drugs administered for general anesthesia may influence blood loss during the procedure. Volatile anesthetic agents cause dose-dependent relaxation of uterine smooth muscle[53] and have been associated with increased uterine bleeding.[54,55] In two studies that compared blood loss during general anesthesia for elective first-trimester abortion, blood loss was greater when anesthesia was maintained with isoflurane compared with propofol.[54,55] However, the differences were small considering the blood volume expansion that occurs during pregnancy. Some obstetricians contend that relaxation of the uterus (caused by administration of a volatile anesthetic agent) increases the risk for uterine perforation, and they prefer that administration of a volatile anesthetic agent during a D and C or D and E procedure be avoided.

General anesthesia is commonly maintained with oxygen, nitrous oxide, and an opioid. A propofol infusion or a low concentration (< 0.5 MAC) of a volatile agent may be added. The volatile agent should be avoided or discontinued if there is any evidence of uterine atony. In most cases, oxytocin diluted in crystalloid is administered intravenously to increase uterine tone and decrease blood loss.

The D and C or D and E procedure is performed with the patient in the lithotomy position. After the procedure is completed and the patient's legs are lowered, hypotension may develop in patients who have lost a substantial amount of blood, especially if neuraxial anesthesia has been used.

CERVICAL INSUFFICIENCY OR INCOMPETENCE

An inherent or traumatic deficiency in the structure or function of the uterine cervix results in **cervical insufficiency or incompetence,** which is defined as the inability to sustain a pregnancy to full term. Cervical insufficiency is characterized by recurrent second-trimester pregnancy losses with (1) painless cervical dilation; (2) herniation followed by rupture of the fetal membranes; and (3) a short labor with delivery of a live, immature infant.

The true incidence of cervical insufficiency is difficult to determine owing to a lack of objective clinical findings and definitive diagnostic tests. The reported incidence varies from 1 in 100 to 1 in 2000. The U.S. *National Vital Statistics Report* for 2004 cited a rate of 4.4 cervical cerclages performed per 1000 live births.[56] Lidegaard[57] reported an incidence of cervical incompetence of 4.6 women per 1000 births in Denmark between 1980 and 1990.

Potential causes of cervical insufficiency include cervical trauma, congenital abnormalities, intrauterine infection, endocervical inflammation, deficiencies in cervical collagen and elastin, and hormonal abnormalities.[58] A common cause of cervical insufficiency is trauma, occurring at the time of a previous vaginal delivery or a surgical procedure (e.g., D and C, conization of the cervix, partial amputation or resection of the cervix, cervical cauterization). Congenital abnormalities of the reproductive tract (e.g., unicornuate or bicornuate uterus) may be present in as many as 2% of patients with cervical insufficiency. Some anomalies may result from maternal exposure to diethylstilbestrol *in utero.*

Warren et al.[59] found that more than 25% of women with a diagnosis of cervical insufficiency have a positive family history of cervical insufficiency as well as a greater frequency of two genes associated with abnormalities of connective tissue, collagen, and extracellular matrix. Other recent studies have found high rates of intra-amniotic inflammation (measured by elevated amniotic fluid matrix metalloproteinase-8 concentration) mostly without signs of infection in patients with acute cervical insufficiency or an asymptomatic shortened cervix.[60,61] The presence of this inflammation was a risk factor for impending preterm delivery.[60,61] Further research in this area could determine if there is potential for this observation to translate into therapy to prevent preterm labor.

Diagnosis

Cervical insufficiency remains a clinical diagnosis. A definitive diagnosis is made when herniating fetal membranes are visualized or palpated through a partially dilated cervix during the second trimester. A characteristic history from a previous pregnancy allows the presumptive diagnosis of cervical insufficiency, once other causes of recurrent pregnancy loss have been excluded. History suggestive of the diagnosis of cervical insufficiency consists of two or more second-trimester pregnancy losses, loss of each successive pregnancy at an earlier gestational age, painless cervical dilation to 4 to 6 cm, and cervical trauma or anomaly.[62] Uterine contractions, vaginal bleeding, or chorioamnionitis during a previous pregnancy suggests that other mechanisms are responsible for pregnancy loss.

Symptoms of cervical insufficiency include increased vaginal discharge, lower abdominal or back pressure or discomfort, vaginal fullness, and urinary frequency.

A higher risk for preterm birth has been associated with shortened cervical length at early gestational age.[63,64] Recent trials have indicated that vaginal progesterone treatment in women with a shortened cervix is effective in prevention of preterm birth and neonatal morbidity.[65,66] Physical examination may reveal cervical shortening and/or cervical abnormalities. Historically, it has been

debated whether serial ultrasonographic evaluations of cervical length and dilation should be considered in the early second trimester for pregnant women at high risk for cervical insufficiency.[62,67,68] However, a recent decision and economic analysis concluded that, of four alternatives examined, universal transvaginal ultrasonographic assessment of cervical length at the time of routine anatomic ultrasonography and subsequent treatment with daily vaginal progesterone for women with a short cervix was the most cost-effective strategy and was associated with the greatest reduction in preterm birth less than 34 weeks' gestation.[69]

Obstetric Management

Management of cervical insufficiency remains controversial.[58,70,71] A meta-analysis by Berghella et al.[72] concluded that cerclage does not prevent preterm birth in all women and can actually be detrimental in multifetal pregnancies. Current evidence, however, shows significant benefit in reducing preterm birth in women with singleton gestation who have had a previous preterm birth, have a shortened cervical length, and are less than 24 weeks' gestation.[73] It was estimated that in these patients, 20 cerclages are needed to prevent one perinatal death and more than 6500 infants per year could be saved in the United States by this management.[74]

The most common cerclage procedures are the modified **Shirodkar cerclage** and the **McDonald cerclage,** both of which are performed transvaginally. A ligature (e.g., polyester fiber [Mersilene] tape) is placed around the cervix at or near the level of the internal cervical os. In the more invasive modified Shirodkar procedure, the cervical mucosa is incised anteriorly and posteriorly, the bladder may be advanced, the ligature is placed submucosally and then tied, and the mucosal incisions are closed. The cervical mucosa is left intact with the McDonald cerclage; a purse-string ligature is placed around the cervix and then tied (Figure 16-2). These two procedures result in comparable rates of fetal survival in patients with no history of a previous cerclage.[75] In one study, better outcome (i.e., more advanced gestational age) was obtained when a Shirodkar cerclage was performed in patients who had a previous cerclage.[76]

Transvaginal cerclage can be performed in most patients with an incompetent cervix. However, if no substantial cervical tissue is present (e.g., severe cervical laceration, congenital or traumatic cervical shortening) or if a previous transvaginal cerclage has failed, a **transabdominal cerclage** may be performed, either before or during pregnancy.[77] Although a posterior colpotomy and division of the transabdominal cerclage occasionally are performed in an attempt to allow vaginal delivery, most patients with transabdominal cerclage undergo cesarean delivery. The transabdominal cerclage can remain *in situ* if further pregnancies are desired, or it can be removed at the time of cesarean delivery.

Although the efficacy of perioperative antibiotics and/or tocolytic drugs has not been confirmed, some obstetricians may choose to use them.[62]

Contraindications to cerclage procedures include preterm labor, vaginal bleeding, fetal anomalies, fetal death, rupture of membranes, placental abruption, and chorioamnionitis. Some obstetricians obtain specimens for culture of the amniotic fluid and/or cervix before placement of a cerclage.

Cerclage can be performed (1) prophylactically, before or during pregnancy (interval or primary cerclage); (2) therapeutically, when cervical changes are noted in the current pregnancy (secondary cerclage); or (3) emergently, in patients with marked cervical changes, including membrane exposure to the vaginal milieu (tertiary cerclage).

Interval cerclage may increase the risk for infertility and may prevent easy evacuation of the uterus in the case of a first-trimester spontaneous abortion. Because prophylactic cerclage is more effective than emergency cerclage (historical data show fetal survival is 78% to 87%

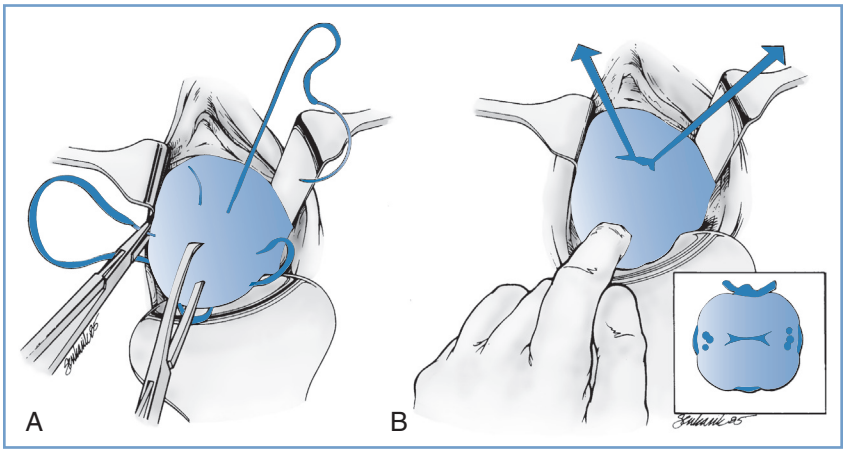

FIGURE 16-2 ■ Placement of sutures for McDonald cervical cerclage. **A,** A double-headed polyester fiber (Mersilene) band with four "bites" is placed in the cervix, avoiding the vessels. **B,** The suture is placed high up on the cervix, close to the cervical-vaginal junction, approximately at the level of the internal os. (Reprinted from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009. Modified from Iams JD. Preterm birth. In Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: Normal and Problem Pregnancies. 4th edition. New York, Churchill Livingstone, 2002:803.)

versus 42% to 68%, respectively[78,79]), most obstetricians perform prophylactic cerclage in the at-risk patient at 12 to 18 weeks' gestation, once fetal viability is established. A cervical dilation of 2 cm or more is associated with a greater risk of premature rupture of membranes and/or preterm delivery.[76]

The greatest risk during the performance of emergency cerclage is rupture of the membranes. Several techniques have been described to facilitate replacement of the bulging fetal membranes into the uterus. Uterine relaxation is essential, which can be facilitated by administration of a volatile anesthetic agent. Alternatively, a tocolytic drug (e.g., terbutaline) may be administered. The steep Trendelenburg position allows for gravity assistance.

To assist in reduction of herniated membranes, some obstetricians fill the urinary bladder with sterile saline. Insertion of a 16-mm Foley catheter (with the tip removed) into the cervical canal with subsequent inflation of the balloon with 30 to 60 mL of saline has also been described.[80] The balloon is deflated and the catheter is removed at the end of the procedure.

Cervical cerclage is associated with a 0.6% risk for perioperative complications.[81] Immediate complications include rupture of the fetal membranes, hemorrhage, and preterm labor. Delayed complications include infection, suture displacement, cervical stenosis secondary to scarring, and cervical lacerations and uterine rupture if labor proceeds with the cerclage in place. Rarely, sepsis may result in death. Overall, patients who have had a cerclage have a higher rate of cesarean delivery. The Shirodkar procedure is associated with a rate of cesarean delivery almost double that associated with a McDonald cerclage (31% versus 17%, respectively).[76]

Anesthetic Management

Transvaginal cervical cerclage is usually performed under spinal, epidural, or general anesthesia (Box 16-3). The degree of cervical dilation may influence the choice of anesthesia. If the cervix is not dilated, spinal, epidural, or general anesthesia may be administered. Although McCulloch et al.[82] described the use of pudendal nerve block for McDonald cerclage, this may not provide adequate anesthesia for many patients. Spinal anesthesia provides a rapid, predictable onset of sacral anesthesia, which is desirable for these procedures. Sensory blockade from sacral dermatomes to T10 is necessary, because both the cervix (L1 to T10) and vagina and perineum (S2 to S4) require anesthesia.

If the cervix is dilated—and especially if the fetal membranes are bulging—the choice of anesthesia is less straightforward. The advantages and disadvantages of each anesthetic technique must be weighed carefully. It is important to produce adequate analgesia for the mother and to prevent an increase in intra-abdominal and intrauterine pressure that may lead to further bulging and possible rupture of the fetal membranes.

General anesthesia may be preferred in the patient with a dilated cervix and bulging fetal membranes. Administration of a volatile anesthetic agent relaxes uterine smooth muscle and results in a decrease in intrauterine pressure. A decrease in intrauterine pressure facilitates replacement of the bulging membranes and placement of the cerclage. On occasion, an amniocentesis may be performed before or during a cerclage procedure in an attempt to decrease intrauterine pressure and facilitate reduction of the fetal membranes. During induction and maintenance of general anesthesia, it is important to avoid endotracheal tube–induced coughing, which might raise intrauterine pressure. In addition, vomiting significantly raises intrauterine pressure.

Administration of neuraxial anesthesia obviates the need for tracheal intubation and the possibility of coughing on the endotracheal tube. Although some physicians worry that the acute dorsiflexion needed during initiation

BOX 16-3 Suggested Anesthetic Techniques for Transvaginal Cervical Cerclage

General Considerations

- Aspiration prophylaxis if patient has a full stomach
- Routine noninvasive monitors
- One peripheral intravenous catheter
- Neuraxial anesthesia (spinal or epidural):
  - Intravenous fluids, vasopressors, supplemental oxygen, and minimal sedation given as clinically indicated
- Left uterine displacement if the pregnancy is greater than 18 to 20 weeks' gestation
- Consideration of fetal heart rate (FHR) monitoring:
  - Less than 24 weeks' gestation: FHR checked before and after procedure
  - Greater than 24 weeks' gestation: continuous FHR monitoring during and after the procedure

Spinal Anesthesia

- Single injection with a small-gauge spinal needle: lidocaine 40 mg or bupivacaine 7.5 mg, with fentanyl 10 to 20 μg, to achieve sensory blockade from T10 to S4
- If patient is in the Trendelenburg position for emergency cerclage, avoid hyperbaric local anesthetic

Epidural Anesthesia

- Placement of midlumbar epidural needle and catheter
- Lidocaine 2% with epinephrine 5 μg/mL (12 to 15 mL) and fentanyl 100 μg, injected incrementally, to achieve sensory blockade from T10 to S4

General Anesthesia (if cervix is dilated and uterine relaxation is needed)

- Induction: propofol or thiopental
- Tracheal intubation is preferable in patients with a full stomach or at greater than 18 to 20 weeks' gestation; otherwise, mask anesthesia or laryngeal mask airway acceptable
- Maintenance: volatile or intravenous (a volatile anesthetic agent may be useful to provide uterine relaxation)
- Avoidance of large increases in intra-abdominal and intrauterine pressures (e.g., patient coughing on endotracheal tube, vomiting)

Modified from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

of the neuraxial blockade may raise intrauterine pressure, many prefer the avoidance of general anesthesia during pregnancy whenever possible.

Few clinical studies have compared obstetric outcomes after administration of neuraxial anesthesia and general anesthesia for cerclage. One retrospective study observed no difference in fetal outcome after administration of either general anesthesia (375 cases) or epidural anesthesia (114 cases).[83] Another study found no significant difference in plasma oxytocin levels or postoperative uterine activity between women who received either spinal or general anesthesia for a Shirodkar cerclage.[84]

Fetal heart rate monitoring should be considered during the procedure if the pregnancy is sufficiently advanced to allow monitoring to be performed easily. In theory, it is possible that replacement of bulging membranes and closure of the cervix may raise intrauterine pressure with a subsequent reduction in placental blood flow. In this case, it would be reasonable to give a tocolytic agent to help reduce intrauterine pressure.

The transvaginal cerclage is removed at 37 to 38 weeks' gestation, or earlier if rupture of membranes or onset of labor occurs. Removal of a McDonald cerclage often requires no anesthesia. Anesthesia (e.g., paracervical block, spinal anesthesia, epidural anesthesia) is usually necessary for removal of a Shirodkar cerclage. If the Shirodkar cerclage is epithelialized, some obstetricians elect to leave it intact and perform an elective cesarean delivery.

Labor often begins within a few hours or days after suture removal. If an epidural catheter was placed for cerclage removal, the epidural anesthetic can be allowed to regress while the patient is observed for evidence of cervical dilation and the onset of labor. When labor begins, epidural labor analgesia can be initiated by injection of drugs through the *in situ* catheter.

GESTATIONAL TROPHOBLASTIC DISEASE

In normal pregnancy, trophoblastic tissue forms the placenta. Abnormal trophoblastic proliferation results in **gestational trophoblastic disease** (GTD). When GTD persists after the pregnancy is concluded (diagnosed by persistent elevation of beta-hCG), it is called persistent gestational trophoblastic disease (PGTD).

Prior to 1970, most cases of PGTD were fatal. Early diagnosis and effective chemotherapy have reduced the mortality rate to 0.1% in Great Britain and the Netherlands and to 1% in the United States.[85,86] This improvement may be related to the fact that trophoblastic cells produce beta-hCG, which provides an easily assayed biochemical marker to aid in detection and to monitor treatment. Further, it is thought that cytotoxic chemotherapeutic drugs are particularly effective against PGTD because the latter arises from a genotype that is not entirely that of the patient, thus facilitating rejection of the trophoblastic cells and leaving them vulnerable to this therapy.[87]

However, some women still die of GTD, often as a result of late presentation and drug resistance or concomitant human immunodeficiency virus infection.[88] GTD caused 0.3% of all pregnancy-related maternal deaths in the United States between 1991 and 1999.[8] Risk factors for GTD include advanced or very young maternal age, previous molar pregnancy, and, possibly, nutritional factors.

Categorization and Etiology

The classification and terminology applied to GTD are varied and can be confusing because GTD encompasses a heterogeneous group of diseases. GTD is also called **gestational trophoblastic tumor** or **gestational trophoblastic neoplasia,** although in this context neoplasia simply means "new grown" and does not necessarily differentiate benign from malignant forms of GTD.

In 2003, the WHO classified GTD into eight categories (Box 16-4). The pathologic and clinical features of GTD are summarized in Table 16-1.[89] Discussion of placental site trophoblastic tumor, exaggerated placental site, placental site nodules and plaques, as well as miscellaneous and unclassified trophoblastic lesions, is beyond the scope of this chapter. Here the focus is mainly on molar pregnancies. Overall, it is helpful to simply remember that GTD always involves trophoblastic cells that have abnormally proliferated and/or invaded and/or metastasized to distant sites in the body.

GTD can be categorized according to **pathologic features** of the trophoblastic cells, **malignant potential** of the trophoblastic cells, or the **genetic makeup** of the trophoblastic cells.

Pathologically, although all GTD arises from trophoblast, hydatidiform moles and gestational choriocarcinoma arise from **villous trophoblast,** whereas exaggerated placental site, placental site nodule, placental site trophoblastic tumor, and epithelioid trophoblastic tumor arise from **intermediate trophoblast.** Further differentiation of the pathologic features of GTD is outlined in Table 16-1. **Gestational choriocarcinoma** typically results from a single trophoblastic cell line that has become malignant and metastasized to distant sites in the body. It can occur after a molar pregnancy, a normal pregnancy, or even a pregnancy loss.

The spectrum from the most benign to the most malignant form of GTD is as follows: (1) **partial hydatidiform mole,** (2) **complete hydatidiform mole,** (3) **invasive mole,** and (4) **gestational choriocarcinoma.** Benign

BOX 16-4 World Health Organization Classification of Gestational Trophoblastic Disease

- Hydatidiform mole:
  - Complete mole
  - Partial mole
- Invasive hydatidiform mole
- Choriocarcinoma
- Placental site trophoblastic tumor
- Trophoblastic lesions, miscellaneous
- Exaggerated placental site
- Placental site nodules and plaques
- Unclassified trophoblastic lesion

TABLE 16-1 **Pathologic and Clinical Features of Gestational Trophoblastic Disease**

Gestational Trophoblastic Disease	Pathologic Features	Clinical Features
Hydatidiform mole, complete	46,XX (mainly); 46,XY Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia	15%-20% trophoblastic sequelae Beta-hCG often > 100,000 mIU/mL Medical complications
Hydatidiform mole, partial	Triploid (69,XXY; 69,XYY; 69,XXX) Abnormal fetus/embryo Focal swelling of villi Focal trophoblastic hyperplasia	< 5% trophoblastic sequelae Beta-hCG usually < 100,000 mIU/mL Rare medical complications
Invasive mole	Myometrial invasion Swollen villi Hyperplastic trophoblast	15% metastatic, to lung/vagina Most often diagnosed clinically, rather than pathologically
Choriocarcinoma	Abnormal trophoblastic hyperplasia and anaplasia Absent villi Hemorrhage, necrosis	Vascular spread to distant sites: lung/brain/liver Malignant disease
Placental site trophoblastic tumor	Tumor cells infiltrate myometrium with vascular/lymphatic invasion Intermediate cells/absent villi Less hemorrhage and necrosis Tumor cells stain positive for hPL	Extremely rare Beta-hCG levels less reliable indicator Relatively chemoresistant Mainly surgical treatment

hCG, human chorionic gonadotropin; *hPL,* human placental lactogen.
(From Lurain JR. Gestational trophoblastic disease. I. Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 2010; 203:531-9.)

forms of GTD include complete or partial molar pregnancies that have not demonstrated myometrial invasion. Malignant forms of GTD include invasive mole (complete or partial molar pregnancies that have demonstrated myometrial invasion), gestational choriocarcinoma, and placental site trophoblastic tumor. The latter diseases metastasize, most often to the lungs and brain, and are fatal if not treated. Complete molar pregnancies have a higher rate of associated complications and a higher rate of subsequent PGTD than partial molar pregnancies. Approximately 20% of patients with complete molar pregnancy have postmolar nonmetastatic PGTD (70% to 90%) or malignant PGTD (10% to 30%) and require chemotherapy; in contrast, only 5% of patients with partial molar pregnancy require chemotherapy.[90]

GTD can also be classified according to the genetic makeup of the trophoblastic cells. The various means by which the unusual genetic events occur in GTD are outlined here; further details are available elsewhere.[87] Typically, the genetic makeup of trophoblastic cells in complete hydatidiform molar pregnancy is **androgenic,** meaning nearly all of the genome of the trophoblastic cell arises from the sperm. It can be either **diploid** (two sets of 23 chromosomes [e.g., 46,XY]) or **triploid** (three sets of 23 chromosomes [e.g., 69,XXY]). An ovum lacking chromosomes is fertilized most commonly by one sperm cell with reduplication (46,XX androgenic) or by two sperm cells (dispermy, 46,XX or 46,XY androgenic). No fetus develops. Approximately 90% of hydatidiform moles are complete.[91]

Typically, the genetic makeup of a partial hydatidiform molar pregnancy is **diandric,** meaning the chromosomes arise from both the egg and the sperm but is complicated by triploid conception (69,XXX or 69,XXY). One set of haploid chromosomes is maternal, and there is either reduplication of the paternal donation after fertilization by a single sperm or the egg is fertilized by two separate sperm. Because both maternal and paternal chromosomes are present, it is possible for a fetus to form with a partial mole. As a result, patients with partial mole may have a preoperative diagnosis of incomplete or missed abortion.

Invasive mole is also called *chorioadenoma destruens.* Because this describes any mole (complete or partial) that has invaded into the myometrium, it can have the genetic makeup of either a complete or partial mole. However, most invasive moles result from complete moles.

Complete and Partial Hydatidiform Mole

The reported incidence of hydatidiform mole varies. In the United States, it is detected in 1 in 600 elective abortions and 1 in 1500 pregnancies. Rates of 1 in 400 pregnancies are reported in Korea and Indonesia and among Native Americans.[85,92,93] Coexistence of an intact fetus with molar components is extremely rare, occurring in 1 in 22,000 to 1 in 100,000 pregnancies.[92]

Patients may have a complete molar pregnancy diagnosed during first trimester ultrasonography, or they may have vaginal bleeding after delayed menses, suggestive of a threatened, missed, or incomplete abortion. They may spontaneously pass hydropic vesicles. The absence of fetal cardiac activity, a uterus large for gestational age, and a marked elevation of beta-hCG strongly suggest the diagnosis of hydatidiform mole. Diagnosis may be made after a D and C for an incomplete abortion[92]; baseline chest radiography and quantitative beta-hCG levels should be obtained promptly after surgery in such cases.

Molar pregnancies produce hCG in amounts proportional to the neoplastic volume. Excessive uterine size is associated with a marked elevation of serum beta-hCG concentration (> 100,000 mIU/mL) secondary to a large tumor volume. Large ovarian cysts, hyperemesis

gravidarum, and early onset of gestational hypertension are also strongly suggestive of GTD. Ultrasonography may show characteristic multi-echogenic regions that represent hydropic villi or hemorrhagic foci.

Persistent and Malignant Gestational Trophoblastic Disease

Persistent or malignant GTD can develop after any gestational event, including normal pregnancy, spontaneous or elective abortion, ectopic pregnancy, and molar pregnancy. Histologic forms of postmolar PGTD include noninvasive trophoblastic proliferation, invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumor. Diagnosis of postmolar PGTD is made when beta-hCG levels plateau or rise.[92,93]

Signs and symptoms of malignant GTD after a nonmolar gestational event are very subtle and diagnosis may be delayed. A quantitative beta-hCG measurement should be performed in any patient with continued or abnormal vaginal bleeding 6 weeks after the end of gestation. In any woman of reproductive age with metastatic disease from an unknown primary tumor, the diagnosis of gestational choriocarcinoma should be considered, given the fact that metastases of gestational choriocarcinoma can occur anywhere. The vagina, liver, lung, and brain are the most frequently involved sites. Signs and symptoms are related to the affected site. Biopsy of metastases is rarely needed and can result in profuse bleeding. The diagnosis of metastatic GTD is suggested with a positive beta-hCG result and no pregnancy.[85,92,93]

Details on staging and risk-factor scoring of GTD and their implications for therapy and prognosis are available elsewhere.[90,94,95]

Medical Complications

Routine use of ultrasonography has led to earlier diagnosis of molar pregnancy, which has reduced the incidence of medical complications. However, excessive uterine size occurs in up to half of patients with complete molar pregnancy and is associated with a higher incidence of medical complications. Medical complications occur in about 25% of patients with uterine size of more than 14 to 16 weeks' gestation; they include ovarian theca-lutein cysts, hyperemesis gravidarum, gestational hypertension, anemia, hyperthyroidism, DIC, and sepsis (Table 16-2).[90,92-94,96-99]

Ovarian theca-lutein cysts occur primarily in patients with extremely high serum beta-hCG concentration (>100,000 mIU/mL).[97] They typically regress over 2 to 3 months; rarely, torsion, rupture, or infarction may necessitate oophorectomy. Patients with theca-lutein cysts and a uterus more than 4 weeks larger than expected (for dates) have a 50% likelihood of development of postmolar GTN.[85]

Hyperemesis gravidarum can lead to significant electrolyte disturbances and volume depletion, all of which should be corrected before surgery.

Gestational hypertension occurs in up to 27% of women with molar pregnancy, typically in patients with an excessively large uterus.[98] **Preeclampsia** may be diagnosed if proteinuria accompanies hypertension, although early presentation does not fit usual definitions (see Chapter 36). Although it is thought that convulsions rarely occur in these patients,[97] prophylactic use of magnesium sulfate should be considered. An antihypertensive agent (e.g., hydralazine, labetalol) should be given as required to reduce blood pressure. GTD should be strongly suspected in any patient who develops hypertension during early pregnancy.

Anemia frequently complicates a complete molar pregnancy. The visible vaginal bleeding may underrepresent the total amount of hemorrhage. Occult bleeding into and around the tumor results in multiple hemorrhagic foci. Because blood loss may occur gradually, the patient may have a normal intravascular volume despite the presence of severe anemia. In the 1970s and 1980s, blood transfusion was required in as many as 32% to 45% of patients.[96,99] With earlier diagnosis using ultrasonography, the incidence of transfusion may be less than in the past. Nonetheless, blood typing and antibody screening should be performed preoperatively.

Although it occurs infrequently, **hyperthyroidism** may result from a marked elevation of hCG,[100] which can have a thyrotropin-like effect. Alternatively, hyperthyroidism may result from some other thyrotropic substance produced by the neoplasm.[100] Anesthesia or surgery can precipitate thyroid storm (i.e., sinus tachycardia, atrial fibrillation, hyperthermia, cardiovascular collapse), which is treated using a beta-adrenergic antagonist.

Historically, **acute cardiopulmonary distress** was observed after evacuation of molar pregnancy in as many as 27% of patients.[97,101-103] A higher risk for cardiopulmonary complications occurs in patients with a uterine size of 16 weeks or greater.[101,104] Signs and symptoms include chest pain, cough, tachycardia, tachypnea, hypoxemia, diffuse rales, and chest radiographic evidence of bilateral pulmonary infiltrates. It is thought that **trophoblastic embolization** may be the etiology of cardiopulmonary distress in more than half of cases.[103,104] Other causes include (1) high-output cardiac failure from thyrotoxicosis, (2) pulmonary congestion from severe

TABLE 16-2 Complications of Complete Molar Pregnancies

Complication	Incidence (%)
Excessive uterine size	30-53
Ovarian theca-lutein cysts (> 6 cm)	4-50
Hyperemesis gravidarum	14-29
Gestational hypertension	11-27
Anemia (hemoglobin < 10 g/dL)	10-54
Hyperthyroidism	1-7
Trophoblastic emboli	2-7
Acute cardiopulmonary distress	6-27
Malignant sequelae (metastasis)	4-36
Other (renal, disseminated intravascular coagulation, infection)	Rare

Data from references 88, 90, 94, 96-98, and 100-102. Reprinted from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

anemia, (3) gestational hypertension or preeclampsia, (4) aspiration pneumonitis, and (5) iatrogenic fluid overload.[103,104] Symptoms usually develop within 12 hours of uterine evacuation.[103] Some patients require tracheal intubation, mechanical ventilation, and invasive hemodynamic monitoring. Symptoms usually subside within 72 hours; however, massive embolization or adult respiratory distress syndrome may result in death. If the patient survives trophoblastic embolization, malignant sequelae often develop.[94,103,105]

Obstetric Management

The following preoperative tests are recommended for patients with suspected hydatidiform mole: (1) complete blood count including platelet count, (2) coagulation studies, (3) renal and liver function studies, (3) blood typing and antibody screening, (4) quantitative beta-hCG level, and (5) chest radiography.[92,93] Prompt molar evacuation should be instituted, because a delay in uterine evacuation may raise the risk for complications. Once the patient is stabilized, suction curettage is performed to evacuate the uterus in patients who want to preserve fertility. Real-time ultrasonography may help the obstetrician perform a complete evacuation of the uterus in patients with excessive uterine size.[106] Hysterectomy is performed in patients who have completed childbearing. Hysterotomy and medical induction of labor are not recommended because they are associated with increased blood loss and a higher incidence of postmolar PGTD.[93] Rh_0(D) immune globulin should be administered to Rh-negative patients.

After uterine evacuation, the beta-hCG level should be measured weekly until it is undetectable for 3 weeks, then monthly for 6 months and every 2 months for another 6 months. Frequent pelvic examinations are performed while beta-hCG levels remain high. Thorough evaluation of the patient with GTD includes screening for evidence of metastasis (e.g., vagina, liver, lung, brain) and other potential complications. Prevention of pregnancy for 12 months is recommended.[85]

Malignant GTD should be managed by an experienced team in a trophoblastic center to minimize mortality.[85,92-94] Chemotherapy is indicated in patients with (1) histologic evidence of invasive mole or choriocarcinoma, (2) an increase in beta-hCG levels of 10% or greater in three or more samples taken over at least 2 weeks, (3) a plateau of beta-hCG levels in four or more samples taken over 3 consecutive weeks, (4) persistence of measurable beta-hCG levels 6 months after molar evacuation, or (5) evidence of metastasis.[95] Some patients may require delayed hysterectomy, thoracotomy for resection of pulmonary metastasis, and/or liver or brain irradiation.

Anesthetic Management

Preoperative assessment of the patient with a molar pregnancy consists of evaluation for specific complications of molar pregnancy, including hyperemesis gravidarum, gestational hypertension and preeclampsia, anemia, and thyrotoxicosis. The main anesthetic considerations are the potential for rapid and significant blood loss and the risk for cardiopulmonary distress with uterine evacuation. The anesthesia provider should establish adequate intravenous access, and blood products should be immediately available. Invasive arterial pressure and/or central venous pressure monitoring may be indicated in the patient with hypoxemia, severe anemia, hemorrhage, severe gestational hypertension or preeclampsia, hyperthyroidism, or a uterus of more than 16 weeks' size.[107]

Although neuraxial anesthesia has been described, general anesthesia is often preferred because of the potential for rapid, substantial blood loss and cardiopulmonary distress during evacuation of the uterus (Box 16-5). For patients with acute hemorrhage and hypovolemia, induction with thiopental or propofol may cause marked hypotension. In hyperthyroid patients, ketamine may result in marked tachycardia.[108] Etomidate is an excellent choice for patients with preoperative bleeding and preoperative evidence of hyperthyroidism. Anesthesia can be maintained using either an inhalational or intravenous technique, although it may be necessary to avoid volatile anesthetic agents in some patients to optimize uterine contractility,[109] and care should be exercised with the use of a propofol infusion in hemodynamically unstable patients.

An intravenous oxytocin infusion (20 IU/L of crystalloid) is begun either before[97,101] or during[94] uterine evacuation. Oxytocin helps the uterus contract, facilitating safe curettage and reducing blood loss. Some obstetricians have speculated that oxytocin may decrease trophoblastic embolization by constricting the uterine veins.[101] Postoperatively, the patient should be monitored closely for any evidence of uterine hemorrhage or cardiopulmonary distress.

BOX 16-5 Suggested Anesthetic Technique for Patients with Gestational Trophoblastic Neoplasm

Preoperative Evaluation

- Evaluation for complications of molar pregnancy
- Measurement of baseline arterial blood gas levels

General Anesthesia

- Routine noninvasive monitors
- Consideration of invasive hemodynamic monitoring in patients with hypoxemia, gestational hypertension or preeclampsia, severe anemia, hyperthyroidism, or a uterine size greater than 16 weeks' gestation
- Two large-gauge peripheral intravenous catheters
- Immediate availability of blood
- Induction: etomidate if evidence of hemorrhage or hemodynamically unstable
- Tracheal intubation with a muscle relaxant
- Maintenance: inhalation or intravenous technique Avoid volatile agents if optimization of uterine contractility is required, and exercise caution with the use of a propofol infusion in hemodynamically unstable patients
- Oxytocin infusion (20 IU/L) after cervical dilation or after partial uterine evacuation

Modified from Chantigian RC, Chantigian PDM. Problems in early pregnancy. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

HYPEREMESIS GRAVIDARUM

As many as 50% to 80% of women experience nausea and vomiting during pregnancy; this is the most common indication for admission to the hospital during the first trimester of pregnancy. Symptoms are often worse during the morning hours, thus the term *morning sickness*. Symptoms typically improve or resolve by the end of the first trimester.

On rare occasions, pregnant women experience a persistent and severe form of nausea and vomiting called **hyperemesis gravidarum.** This is believed to be an extreme form of normal nausea and vomiting of pregnancy, although there is no single accepted definition. These women may develop dehydration, ketonuria, nutritional compromise, weight loss, electrolyte abnormalities, and/or transient hepatic and renal dysfunction. Intravenous rehydration, correction of electrolyte abnormalities, antiemetics, and, rarely, hyperalimentation are indicated.

Hyperemesis gravidarum may be associated with multiple gestation, thyrotoxicosis, and/or GTD. Diagnosis is by exclusion, and many other underlying diseases should be ruled out, including gastrointestinal diseases (e.g., hepatitis, cholecystitis, pancreatitis, partial bowel obstruction), genitourinary diseases (e.g., pyelonephritis, uremia, ovarian torsion, kidney stones), metabolic disorders, neurologic or psychiatric disorders, acute fatty liver of pregnancy, drug toxicity, and preeclampsia.

CORPUS LUTEUM CYSTS

Symptomatic corpus luteum cysts occasionally occur during early pregnancy. Typically, they resolve over several weeks. In some cases, hemorrhage or ovarian torsion necessitates ovarian cystectomy or oophorectomy. After the cyst is removed, the fetus usually is not affected, provided that supplemental progesterone is administered until 10 to 12 weeks' gestation.

KEY POINTS

- Aortocaval compression does not develop until the uterine fundus reaches the umbilicus (i.e., 18 to 20 weeks' gestation in a normal singleton pregnancy, or earlier in conditions with an enlarged uterus). Left uterine tilt should be initiated when the potential for aortocaval compression exists.
- General anesthesia may be administered by mask or laryngeal mask airway (LMA) for selected extra-abdominal procedures during the first 18 to 20 weeks of pregnancy, provided that the patient fulfills the criteria for an empty stomach and there is no difficulty with mask ventilation. Some anesthesia providers prefer to limit the use of mask anesthesia or the LMA to the first 12 to 14 weeks of pregnancy.
- During pregnancy, the nervous system is more sensitive to local anesthetics and perhaps general anesthetic agents. Lower doses of these drugs should be considered, although it is important to be aware of the greater risk for intraoperative awareness during cesarean delivery.
- Most ectopic pregnancies are located in one of the fallopian tubes. Ruptured tubal pregnancies, as well as interstitial, cervical, cesarean scar, and abdominal ectopic pregnancies as well as pregnancies with early placenta accreta, may result in substantial hemorrhage.
- The most painful part of a dilation and uterine evacuation procedure is the dilation of the cervix. If the cervix is already dilated and the fetal size is first trimester, sedation (with or without paracervical block) often suffices. If the cervix is closed, either a paracervical block with sedation or neuraxial or general anesthesia may be necessary. If the fetal size is advanced (>13 to 15 weeks' gestation), many anesthesia providers prefer general anesthesia because of the greater surgical stimulation and risk for bleeding complications.
- Neuraxial anesthesia is an excellent choice for prophylactic cervical cerclage. In a patient who requires emergency cervical cerclage, it is important to prevent a marked increase in intra-abdominal and intrauterine pressures, which might cause rupture of bulging fetal membranes.
- The patient with a molar pregnancy may have hyperemesis gravidarum, gestational hypertension, severe anemia, and/or hyperthyroidism. These complications are more common in patients with excessive uterine size.
- Rapid and profound blood loss is possible with uterine evacuation of a molar pregnancy, and acute cardiopulmonary distress can develop after uterine evacuation.

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CHAPTER 17

Nonobstetric Surgery during Pregnancy

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CHAPTER OUTLINE

Estimates of the frequency of nonobstetric surgery performed during pregnancy range from 0.3% to 2.2%.[1,2] Thus, as many as 93,000 and 110,000 pregnant women in the United States and the European Union, respectively, may require a surgical or anesthetic intervention each year. These numbers are likely to be an underestimation, because pregnancy may be unrecognized at the time of operation. The reported incidence of positive pregnancy tests in women of childbearing age ranged from 0.002% in women presenting for orthopedic surgery[3] to 0.3% in women presenting to an ambulatory surgery center[4] to 2.6% in women scheduled to undergo elective sterilization procedures.[5]

The practice of routine pregnancy testing for all women of childbearing age presenting for elective surgery and anesthesia is controversial. The American Society of Anesthesiologists Task Force on Preanesthesia Evaluation states "…the literature is inadequate to inform patients or physicians on whether anesthesia causes harmful effect in early pregnancy. Pregnancy testing may be offered to female patients of childbearing age and for whom the result would change the patient's management."[6] In 2000, the U.K. National Institute for Health and Clinical Excellence (NICE) issued preoperative screening guidelines recommending routine pregnancy testing for "female patients who say that it is possible they may be pregnant."[7] There was uncertainty among the Guideline Development Group as to whether women should undergo pregnancy testing if the last menstrual period was documented or if women stated that it was not possible that they were pregnant.[7] This guideline was poorly followed, resulting in 42 serious incidents, 3 pregnancy losses, and several cases of litigation between 2003 and 2009.[8] In 2010, the U.K. National Patient Safety Agency stated that women should be offered a pregnancy test "if there is any possibility that a woman could be pregnant."[8] In certain populations, medical history alone may be an unreliable means of excluding the possibility of pregnancy.[6,7] Thus, some institutions routinely perform pregnancy tests on all women of childbearing age who present for elective surgery.[3]

Surgery may be necessary during any stage of pregnancy. Among 5405 Swedish women who had operations during pregnancy, 42% occurred during the first trimester, 35% during the second trimester, and 23% during the third trimester.[1] Laparoscopy for gynecologic indications was the most common first-trimester procedure (34%), whereas appendectomy was the most common procedure during the remainder of pregnancy. Indications for pregnancy-related surgery include cervical incompetence, the presence of ovarian cysts, and conditions amenable to fetal surgery (see Chapter 7). Indications for non–pregnancy-related surgery include the presence of acute abdominal disease (most commonly appendicitis and cholecystitis), malignancies, and trauma.

When caring for pregnant women undergoing nonobstetric surgery, anesthesia providers must consider both the mother and the fetus. Standard anesthetic procedures

may have to be modified to accommodate pregnancy-induced maternal physiologic changes and the presence of the fetus. The Confidential Enquiries into Maternal and Child Health in the United Kingdom demonstrate that, even in early pregnancy, mothers die of hemorrhage, sepsis, thromboembolism, and anesthesia; substandard care is often present.[9] Erekson et al.[10] analyzed 2005 to 2009 data from the American College of Surgeons National Surgical Quality Improvement Program database. The rate of major complications (e.g., infections, reoperation, wound problems, respiratory complications, venous thromboembolism, blood transfusion, maternal death) for antenatal nonobstetric surgery was approximately 6%.[10]

Possible risks to the fetus of antenatal surgery include (1) the effects of the disease process itself, or related therapy; (2) the teratogenicity of anesthetic agents or other drugs administered during the perioperative period; (3) intraoperative perturbations of uteroplacental perfusion and/or fetal oxygenation; and (4) the risk for abortion or preterm delivery.

MATERNAL SAFETY: ALTERED MATERNAL PHYSIOLOGY

During pregnancy, profound changes in maternal physiology result from increased concentrations of various hormones, mechanical effects of the gravid uterus, greater metabolic demand, and the hemodynamic consequences of the low-pressure placental circulation. Hormonal changes are likely responsible for most of the changes that occur during the first trimester. Mechanical effects become apparent when the uterus emerges from the pelvis during the second half of gestation (see Chapter 2).

Respiratory System and Acid-Base Balance Changes

Alveolar ventilation increases by 30% or more by mid pregnancy. This increase results in chronic respiratory alkalosis with a $Paco_2$ of 28 to 32 mm Hg, a slightly alkaline pH (approximately 7.44), and decreased levels of bicarbonate and buffer base. Although oxygen consumption is increased, Pao_2 usually increases only slightly or remains within the normal range. Functional residual capacity (FRC) diminishes by approximately 20% as the uterus expands, resulting in decreased oxygen reserve and the potential for airway closure. When FRC is decreased further (e.g., from morbid obesity; perioperative intra-abdominal distention; placement of the patient in the supine, Trendelenburg, or lithotomy position; or induction of anesthesia), airway closure may be sufficient to cause hypoxemia.

Weight gain during pregnancy and capillary engorgement of the respiratory tract mucosa lead to more frequent problems with mask ventilation and tracheal intubation (see Chapter 30). Failed intubation (a leading cause of anesthesia-related maternal death) is as much a risk during early pregnancy with nonobstetric surgery as it is during cesarean delivery.[9]

Decreased FRC, increased oxygen consumption, and diminished buffering capacity result in the rapid development of hypoxemia and acidosis during periods of hypoventilation or apnea. Moreover, induction of inhalation anesthesia occurs more rapidly during pregnancy because alveolar hyperventilation and decreased FRC allow faster equilibration of inhaled agents. In addition, induction of anesthesia is accelerated owing to the 30% to 40% decrease in the minimum alveolar concentration (MAC) for volatile anesthetic agents that occurs even during early gestation.[11] The anesthesia provider must be especially vigilant when administering subanesthetic concentrations of analgesic and anesthetic agents to the pregnant patient, in whom unconsciousness can occur quickly and unexpectedly.

Cardiovascular System Changes

Cardiac output increases by up to 50% during pregnancy because of increases in heart rate and stroke volume; both systemic and pulmonary vascular resistances decrease, but myocardial contractility is unaffected. Early in pregnancy (i.e., by 6 weeks' gestation), significant cardiovascular alterations are present.[12] By 8 weeks' gestation, 57% of the increase in cardiac output, 78% of the increase in stroke volume, and 90% of the decrease in systemic vascular resistance that are typically achieved by 24 weeks' gestation have occurred.[13]

During the second half of gestation, the uterus compresses the inferior vena cava when the mother lies supine; the compression reduces venous return and cardiac output by approximately 30%. Although upper extremity blood pressure may be maintained by compensatory vasoconstriction and tachycardia, uteroplacental perfusion is jeopardized whenever the mother lies supine. In some women, frank hypotension may occur in the supine position, especially when neuraxial or general anesthesia attenuates or abolishes normal compensatory mechanisms. For these reasons, it is essential to displace the uterus laterally during any operation performed after 18 to 20 weeks' gestation. Vena caval compression also results in distention of the epidural venous plexus, which increases the likelihood of intravascular injection of local anesthetic during the administration of epidural anesthesia. The reduced capacity of the epidural space most likely contributes to the enhanced spread of epidural local anesthetic solution that is observed during pregnancy.

Changes in Blood Volume and Blood Constituents

Blood volume expands in the first trimester and increases 30% to 45% by term. Dilutional anemia occurs as a result of the smaller increase in red blood cell volume than in plasma volume. Although moderate blood loss is well tolerated during pregnancy, preexisting anemia decreases the patient's reserve when significant hemorrhage occurs. Pregnancy is associated with benign leukocytosis; consequently, the white blood cell count is an unreliable indicator of infection. In general, pregnancy induces a hypercoagulable state, with increases in fibrinogen; factors VII, VIII, X, and XII; and fibrin degradation

products. Pregnancy is associated with enhancement of platelet turnover, clotting, and fibrinolysis; there is a wide range in the normal platelet count. Thus, pregnancy represents a state of accelerated but compensated intravascular coagulation. Although thrombocytopenia may be present in some pregnant women, these patients may still be hypercoagulable. During the postoperative period, pregnant surgical patients are at high risk for thromboembolic complications; thus, thromboembolism prophylaxis is recommended.[14]

Gastrointestinal System Changes

Incompetence of the lower esophageal sphincter and distortion of gastric and pyloric anatomy during pregnancy increase the risk for gastroesophageal reflux, despite similar gastric emptying rates in pregnant and nonpregnant patients[15]; thus the pregnant woman is at risk for regurgitation of gastric contents and aspiration pneumonitis. It is unclear at what stage during pregnancy this risk becomes significant. Although lower esophageal sphincter tone is impaired early in pregnancy (especially in patients with heartburn),[16] the mechanically induced factors do not become relevant until later in pregnancy. It seems prudent to consider any pregnant patient as having a higher risk for aspiration after mid gestation; some anesthesia providers contend that pregnant women are at increased risk for aspiration from the beginning of the second trimester onward.[16]

Altered Responses to Anesthesia

In addition to the decrease in MAC for inhaled anesthetic agents, thiopental requirements begin to decrease early in pregnancy.[17] The effects of pregnancy on propofol requirements are conflicting.[18,19] Higuchi et al.[18] found that the median effective dose for loss of consciousness (ED_{50}) was unchanged in pregnancy, whereas Mongardon et al.[19] reported that lower propofol doses were required to achieve loss of consciousness in early pregnancy compared with the nonpregnant state. This effect appeared unrelated to increased progesterone levels. More extensive neural blockade is attained with epidural and spinal anesthesia in pregnant patients than in nonpregnant patients (see Chapter 12). Pregnancy also enhances the response to peripheral neural blockade.

Plasma cholinesterase levels decrease by approximately 25% from early in pregnancy until the seventh postpartum day. Fortunately, prolonged neuromuscular blockade with succinylcholine is uncommon, because the larger volume available for drug distribution offsets the impact of decreased drug hydrolysis.[20] Nonetheless, the dose of succinylcholine should be controlled carefully in the pregnant patient, and the anesthesia provider should monitor neuromuscular blockade with a nerve stimulator to ensure adequate reversal before extubation.

Decreased protein binding associated with lower albumin and alpha-glycoprotein concentrations during pregnancy may result in a larger fraction of unbound drug, with the potential for greater drug toxicity during pregnancy.[21] Pregnant surgical patients may require drugs that are infrequently used during pregnancy; limited information may exist on the effects of pregnancy on the response to these drugs. Cautious administration of such agents is advisable, because their pharmacokinetic and pharmacodynamic profiles may differ from those in nonpregnant patients. Pregnancy-associated changes in volume of distribution (due to changes in body composition and/or plasma protein binding capacity), metabolic activity, and hepatic or renal elimination (due to changes in glomerular filtration rate and tubular transport processes) may contribute to changes in drug effects and metabolism.[22] For example, in pregnant women, cefazolin clearance is approximately twice as high between 20 and 40 weeks' gestation and acetaminophen clearance is increased, compared with nonpregnant women.[23,24]

FETAL CONSIDERATIONS

Risk for Teratogenicity

Although maternal catastrophes that cause severe maternal hypoxia or hypotension pose the greatest risk to the fetus, considerable attention has focused on the role of anesthetic agents as abortifacients and teratogens. *Teratogenicity* has been defined as any significant postnatal change in function or form in an offspring after prenatal treatment. Concern about the potential harmful effects of anesthetic agents stems from their known effects on mammalian cells, which include reversible decreases in cell motility, prolongation of DNA synthesis, and inhibition of cell division. Despite these concerns, no data specifically link any of these cellular events with teratogenic changes. Unfortunately, prospective clinical studies of the teratogenic effects of anesthetic agents are impractical; such studies would require huge numbers of patients exposed to the drug under investigation. Therefore, investigations of anesthetic agents have taken one of the following directions: (1) studies of the reproductive effects of anesthetic agents in small animals, (2) epidemiologic surveys of operating room personnel constantly exposed to subanesthetic concentrations of inhalation agents, and (3) studies of pregnancy outcome in women who have undergone surgery while pregnant.

Principles of Teratogenicity

A number of important factors influence the teratogenic potential of a substance, including species susceptibility, dose of the substance, duration and timing of exposure, and genetic predisposition. Like other toxicologic phenomena, the effects of teratogens are dose dependent (Figure 17-1).[25] Most teratologists accept the principle that any agent can be teratogenic in an animal provided that enough is given at the right time. Thus, the finding of teratogenesis of an agent after the single administration of a high dose, or the long-term administration of a low dose, does not imply that a single, short exposure (e.g., during a typical anesthetic) would incur similar risk. The interaction between dose and timing is also critical. A small dose of a teratogen may cause malformations or death in the susceptible early embryo, whereas much larger doses may prove harmless to the fetus,[25] as was

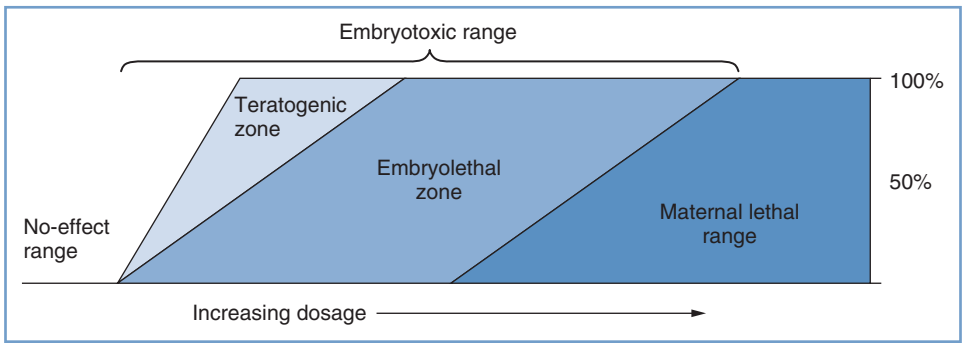

FIGURE 17-1 ■ Toxic manifestations with increasing dosage of a teratogen. A no-effect range of dosage occurs below the threshold, at which embryotoxic effects abruptly appear. Teratogenesis and embryolethality often have similar thresholds and may increase at roughly parallel rates as dosage increases to a point at which all conceptuses are affected. Increasing dosage causes increased embryolethality, but teratogenicity appears to decrease, because many defective embryos die before term. A further increase in dosage reaches the maternal lethal range. (Modified from Wilson JG. Environment and Birth Defects. New York, Academic Press, 1973:31.)

shown with thalidomide. Most studies have used small animals (e.g., chick embryos, mice, rats), and their results cannot necessarily be extrapolated to other species, especially humans. Of the more than 2200 agents listed in *Shepard's Catalog of Teratogenic Agents*,[26] approximately 1200 are teratogenic in animals, but only about 30 of these are known to cause defects in humans.

Manifestations of teratogenicity include death, structural abnormality, growth restriction, and functional deficiency.[25] Depending on when it occurs, death is referred to as abortion, fetal death, or stillbirth in humans and as fetal resorption in animals. Structural abnormalities can lead to death if they are severe, although death may occur in the absence of congenital anomalies. Growth restriction is considered a manifestation of teratogenesis and may relate to multiple factors, including placental insufficiency and genetic and environmental factors. Functional deficiencies include a number of behavioral and learning abnormalities, the study of which is called *behavioral teratology*. The stage of gestation at which exposure occurs determines the target organs or tissues, the types of defects, and the severity of damage. Most structural abnormalities result from exposure during the period of organogenesis, which extends from approximately day 31 to day 71 after the first day of the last menstrual period. Figure 17-2 shows the critical stages of development and the related susceptibility of different organs to teratogens. Functional deficiencies are usually associated with exposure during late pregnancy or even after birth, because the central nervous system (CNS) continues to mature during this period.

Consideration of the possible teratogenicity of anesthetic agents must be viewed against the naturally high occurrence of adverse pregnancy outcomes. Roberts and Lowe[27] estimated that as many as 80% of human conceptions are ultimately lost; many are lost even before pregnancy is recognized. The incidence of congenital anomalies among humans is approximately 3%, most of which are unexplained. Indeed, exposure to drugs and environmental toxins accounts for only 2% to 3% of such defects (Table 17-1).[25] Shepard[26] has listed several criteria for determining that an agent is a human teratogen, including the following: (1) proven exposure to the agent at the critical time of development; (2) consistent findings in two or more high-quality epidemiologic studies; (3) careful delineation of the clinical cases, ideally with the identification of a specific defect or syndrome; and (4) an association that "makes biological sense." Documentation of teratogenicity in experimental animals is important but not essential. The list of agents or factors that are proven human teratogens does not include anesthetic agents (which are listed as "unlikely teratogens") or any drug routinely used during the course of anesthesia (Box 17-1).

Nondrug Factors Encountered in the Perioperative Period

Derangements of Normal Physiology. Anesthesia and surgery can cause derangements of maternal physiology that may result in hypoxia, hypercapnia, stress, and abnormalities of temperature and carbohydrate metabolism. These states may be teratogenic themselves, or they may enhance the teratogenicity of other agents.[26] Severe hypoglycemia and prolonged hypoxia and hypercarbia have caused congenital anomalies in laboratory animals,[26,28] but there is no evidence to support teratogenicity after brief episodes in humans. The chronic hypoxemia experienced by mothers at high altitudes results in the delivery of infants with lower birth weights but with no increase in the rate of congenital defects.[26] Maternal stress and anxiety are teratogenic in animals,[29] but their significance as human teratogens remains questionable; supporting epidemiologic studies are lacking. Hypothermia is not teratogenic, whereas hyperthermia is teratogenic in both animals and humans.[26] Congenital anomalies, especially involving the CNS, have repeatedly been associated with maternal fever during the first half of pregnancy. It must be remembered that fetal temperature is on average 0.5°C to 1°C higher than maternal temperature. Embryonic oxidative stress from reactive oxygen species has been implicated as one of the mechanisms involved in teratogenicity of many agents.[30]

Diagnostic Procedures. Ionizing radiation is a human teratogen that can result in an increased, dose-related risk

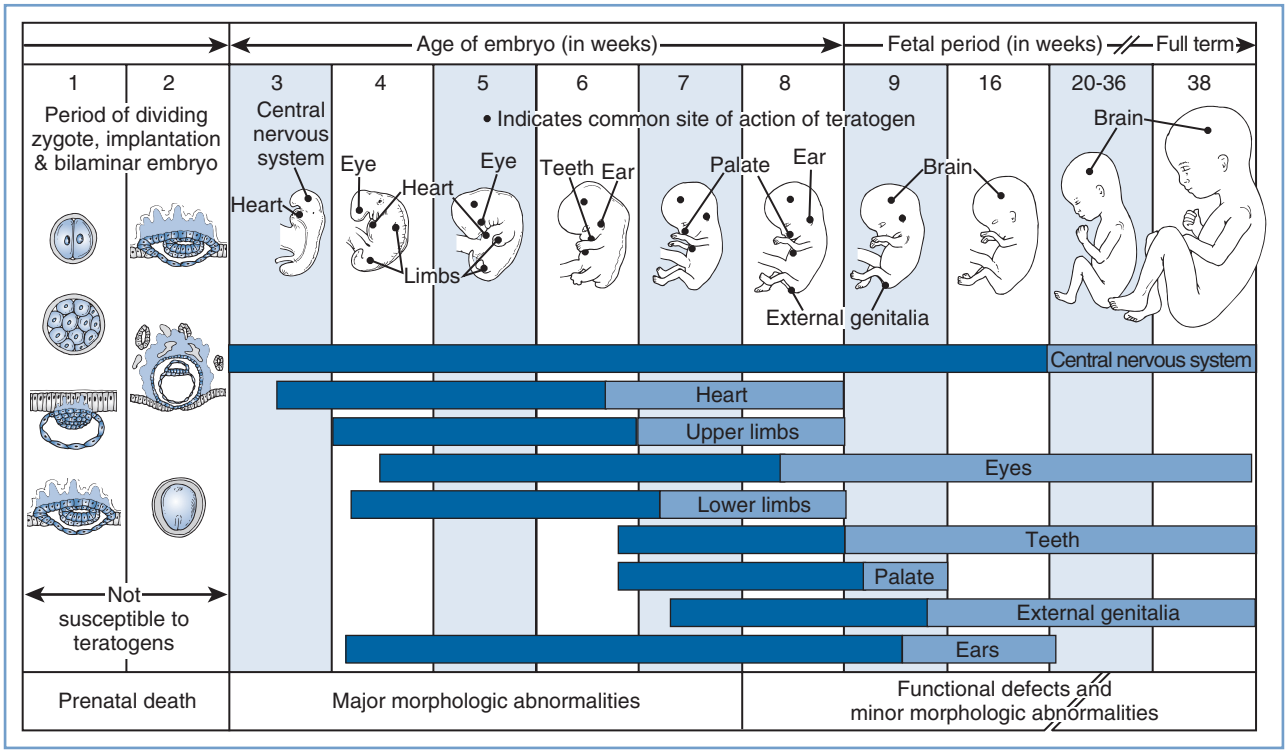

FIGURE 17-2 ■ Critical periods in human development. During the first 2 weeks of development, the embryo typically is not susceptible to teratogens. During these predifferentiation stages, a substance either damages all or most cells of the embryo, resulting in its death, or damages only a few cells, allowing the embryo to recover without development of defects. The dark bars denote highly sensitive periods, whereas the light bars indicate periods of lesser sensitivity. The ages shown refer to the actual ages of the embryo and fetus. Clinical estimates of gestational age represent intervals beginning with the first day of the last menstrual period. Because fertilization typically occurs 2 weeks after the first day of the last menstrual period, the reader should add 14 days to the ages shown here to convert to the estimated gestational ages that are used clinically. (Redrawn from Moore KL. The Developing Human. 4th edition. Philadelphia, WB Saunders, 1993:156.)

TABLE 17-1 Etiology of Human Developmental Abnormalities

Causes of Developmental Defects in Humans	Percentage
Genetic transmission	20
Chromosomal aberration	3-5
Environmental causes:	
Radiation	< 1
Infection	2-3
Maternal metabolic imbalance	1-2
Drugs and environmental chemicals	2-3
Unknown	65-70
TOTAL	100

Modified from Wilson JG. Environmental and Birth Defects. New York, Academic Press, 1973:49.

BOX 17-1 Teratogenic Agents in Humans

RADIATION

Atomic weapons, radioiodine, therapeutic uses

INFECTIONS

Cytomegalovirus, *Herpesvirus hominis*, parvovirus B19, rubella virus, syphilis, toxoplasmosis, Venezuelan equine encephalitis virus

MATERNAL METABOLIC IMBALANCE

Alcoholism, cretinism, diabetes, folic acid deficiency, hyperthermia, phenylketonuria, rheumatic disease and congenital heart block, virilizing tumors

DRUGS AND CHEMICALS

Aminopterin and methylaminopterin, androgenic hormones, busulfan, captopril, chlorobiphenyls, cocaine, warfarin anticoagulants, cyclophosphamide, diethylstilbestrol, phenytoin, enalapril, etretinate, iodides (goiter), lithium, mercury (organic), methimazole (scalp defects), penicillamine, 13-*cis*-retinoic acid (Accutane), tetracyclines, thalidomide, trimethadione, valproic acid

Modified from Shepard TH, Lemire RJ. Catalog of Teratogenic Agents. 13th edition. Baltimore, Johns Hopkins University Press, 2010.

TABLE 17-2 Fetal Radiation Exposure for Common Diagnostic Procedures

Procedure	Mean Exposure (mGy)	Maximum Exposure (mGy)
Conventional Radiographic Examination		
Abdomen	1.4	4.2
Chest	< 0.01	< 0.01
Intravenous urogram	1.7	10
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	< 0.01	< 0.01
Thoracic spine	< 0.01	< 0.01
Fluoroscopic Examination		
Barium meal (upper GI)	1.1	5.8
Barium enema	6.8	24
Computed Tomography		
Abdomen	8.0	49
Head	0.06	0.96
Chest	< 0.005	< 0.005
Lumbar spine	2.4	8.6
Pelvis	25	79

GI, gastrointestinal.
From Valentin J. Pregnancy and medical radiation. ICRP Publication 84. Ann ICRP 2000; 30:1-43.

TABLE 17-3 Estimated Fetal Radiation Exposure for Common Interventional Radiologic Procedures

Procedure	Estimate (mGy)	Range (mGy)
Cardiac catheter ablation	0.15-0.6*	
ERCP	3.1	0.01-55.9
TIPS creation	5.5	
Pulmonary angiography	0.02-0.46	
Uterine fibroid embolization	42	
Cerebral angiography	0.06	

ERCP, endoscopic retrograde cholangiopancreatography; TIPS, transjugular intrahepatic portosystemic shunt.
*Depending on procedure duration.
Modified from Dauer LT, Thornton RH, Miller DL, et al. Radiation management for interventions using fluoroscopic or computed tomographic guidance during pregnancy. J Vasc Interv Radiol 2012; 23:19-32.

for malignant disease, genetic disease, congenital anomalies, and/or fetal death.[26,31] The effects of radiation are often classified as being *deterministic* or *stochastic.* Deterministic effects are dose related and are observed above a certain threshold dose (e.g., pregnancy loss, growth restriction, mental retardation, organ malformation). In contrast, stochastic effects are possible at any level of exposure with no minimum threshold but with the likelihood of worsening effects at higher doses. An increased risk for childhood cancer is a stochastic effect when fetuses are exposed to ionizing radiation *in utero.* The type and severity of effects vary with the radiation exposure to the uterus and fetus and with the gestational age of the fetus.

Radiation is expressed as grays (Gy) or milligrays (mGy) (1 Gy = 100 rad) and is evaluated as cumulative dose (i.e., background radiation and medical diagnostic radiation) throughout the entire pregnancy. Background radiation during gestation is 1.3 to 5.8 mGy.[31] There is no evidence that radiation exposure less than 50 mGy is associated with a teratogenic effect in either humans or animals.[31] The absorbed *fetal dose* for all conventional radiographic imaging procedures outside the abdomen and pelvis is negligible and is well below 50 mGy (Table 17-2). However, direct radiographic examination of the abdomen and pelvis (e.g., abdominal computed tomography) and abdominal imaging studies that include fluoroscopy (e.g., barium enema) may result in more significant fetal radiation exposure, with a dose that may approach 100 mGy.[31,32] Helical computed tomography for suspected pulmonary embolism results in a lower fetal radiation dose than ventilation perfusion scanning. Interventional radiologic procedures (e.g., cerebral angiography, cerebral embolization, endoscopic retrograde cholangiopancreatography) are frequently complex and prolonged, particularly when surgery is not an option. These procedures, especially the abdominal interventions, expose the fetus to a significant radiation dose; thus, a number of societies have developed guidance for the use of these technologies during pregnancy (Table 17-3).[33]

In contrast to the negligible risk for teratogenicity, observational studies suggest that there is a slightly higher risk for childhood cancer at radiation doses greater than or equal to 10 mGy.[32] The relative risk for childhood malignancy after maternal abdominal radiation exposure has been estimated to be 2.28 (95% confidence interval, 1.31 to 3.97).[31] Nonetheless, if the mother's condition necessitates diagnostic testing and radiation exposure, and no other acceptable imaging modality is available, testing should not be withheld if the benefits to the mother (and, by extension, the fetus) are judged to outweigh the risks. Delayed diagnosis of a critical condition may result in significant harm to the mother and, by extension, to the fetus. The radiographer should adhere to the ALARA principle (*a*s *l*ow *a*s *r*easonably *a*chievable) and take measures to minimize the absorbed dose of radiation, including abdominal shielding, reduced scan length, and milliampere modulation.

Intravenous **iodinated contrast media** crosses the placenta to the fetus when administered in the usual clinical doses and can potentially cause neonatal hypothyroidism; however, the use of radiopaque (iodide containing) contrast media during pregnancy is acceptable.[34]

Diagnostic **ultrasonography** during pregnancy has long been considered to be devoid of embryotoxic effects. In animals, ultrasound intensities up to 20 W/cm^2 have been found to be safe.[35,36] However, when higher intensities (> 30 W/cm^2) have been used, or when repeated exposure has occurred during early pregnancy, postnatal neurobehavioral effects have been described.[36,37] Ultrasound waves also increase the fetal temperature, and hyperthermia is a known teratogen. Modern diagnostic ultrasound equipment is capable of inducing significant

increases in temperature, especially when imaging is prolonged. Miller et al.[38] concluded that these temperature increments were within the range of temperatures that could be teratogenic. Epidemiologic human data are reassuring; no biologic effects have been documented from diagnostic ultrasonographic examinations in the pregnant patient, despite widespread use over several decades. Nonetheless, it must be stressed that these epidemiologic studies were conducted in an era when ultrasound equipment was less potent and ultrasound-related increases in temperature were lower. Doppler interrogation emits significantly more acoustic intensity than pulse-echo imaging equipment; thus, more heat is generated. Therefore, Doppler technology should be used judiciously, keeping the exposure time and acoustic output to the lowest level possible.

No adverse effects on pregnancy and neonatal outcome were noted in a small series of pregnant patients (n = 26) exposed to **gadolinium** (paramagnetic contrast medium).[39] However, gadolinium-based MRI contrast agents readily cross the placenta, enter the fetal circulation, and are excreted by the fetal kidneys into the amniotic fluid, where they may be swallowed by the fetus or resorbed by the mother. Although no toxic effects have been described after gadolinium administration, the long-term consequences remain unknown. The American College of Radiology recommends that intravenous gadolinium be avoided during pregnancy and used only if absolutely essential.[40]

Systemic Agents

Animal Studies. Early studies documented teratogenicity in rodents after a variety of neurotropic agents (e.g., opioids, tricyclic antidepressants).[41,42] The fetuses exhibited a characteristic group of CNS malformations as well as skeletal abnormalities and growth restriction. Whether these investigations truly reflect the teratogenic potential of opioids is questionable, however, because the respiratory depression and impaired feeding that accompany large bolus injections of opioids also may be teratogenic. In a study designed to avoid such problems, Fujinaga and Mazze[43] maintained clinically relevant concentrations of morphine throughout most of pregnancy in rats by means of continuously implanted osmotic mini-pumps. Structural anomalies were not observed at any morphine dose, although fetal growth restriction was present, and mortality was increased among the offspring. Using the same methodology, Fujinaga et al.[44,45] found fentanyl, sufentanil, and alfentanil completely devoid of teratogenic effects. Additional animal studies have confirmed the absence of teratogenicity with other opioids.[46]

Many tranquilizers and anxiolytics taken by pregnant women have been investigated less systematically than opioids. Animal studies have demonstrated structural or behavioral teratogenesis after exposure to some of the barbiturate, phenothiazine, and tricyclic antidepressant agents.[47,48] The reader is referred to standard teratology reference sources for animal data related to specific drugs.[26,49] The package insert provided by a drug's manufacturer typically describes unpublished in-house studies related to the drug's reproductive effects.

Studies in rodents and nonhuman primates indicate that exposure of the immature brain to anesthetic agents such as propofol, thiopental, and ketamine (i.e., agents classified as *N*-methyl-D-aspartate [NMDA] antagonists and gamma-aminobutyric acid [GABA] agonists)] are associated with brain cell apoptosis and functional learning deficits.[50,51] Whether this effect occurs in humans or other species remains to be determined (see Chapter 10). These observed changes may represent indirect effects, such as hypoxia or hypoglycemia, as well as direct effects of the anesthetic agent on the developing brain.

Human Studies. Teratogenesis has not been associated with the use of any of the commonly used induction agents—including the barbiturates, ketamine, and the benzodiazepines—when they were administered in clinical doses during anesthesia.[26] Similarly, no evidence supports the teratogenicity of opioids in humans; there is no increase in the incidence of congenital anomalies among offspring of mothers who use morphine or methadone during pregnancy.[26,49]

Although human data relating to long-term tranquilizer therapy have raised questions about the possible teratogenicity of some agents, most studies are retrospective and suffer from a variety of methodologic flaws. Benzodiazepine therapy became controversial after an association between maternal diazepam ingestion during the first trimester and infants with cleft palate, with or without cleft lip, was reported.[52] Subsequently, prospective work in 854 women who ingested diazepam during the first trimester did not demonstrate a higher risk associated with benzodiazepine therapy.[53] Although the present consensus among teratologists is that diazepam is not a proven human teratogen,[26] it is appropriate to consider the risk-to-benefit ratio before initiating long-term benzodiazepine therapy during the first trimester. No evidence suggests that a single dose of a benzodiazepine (e.g., midazolam) during the course of anesthesia is harmful to the fetus.

Local Anesthetics

Procaine, lidocaine, and bupivacaine cause reversible cytotoxic effects in cultures of hamster fibroblasts.[54] However, no evidence supports morphologic or behavioral teratogenicity associated with lidocaine administration in rats,[55] and no evidence supports teratogenicity associated with any local anesthetic used clinically in humans.[26] Maternal cocaine abuse is associated with adverse reproductive outcomes, including abnormal neonatal behavior and, in some reports, a higher incidence of congenital defects of the genitourinary and gastrointestinal tracts.[26] The greatest risk to the fetus most likely results from the high incidence of placental abruption associated with maternal cocaine use (see Chapter 54).

Muscle Relaxants

Testing muscle relaxants for teratogenicity using standard *in vivo* animal studies either is complicated by maternal respiratory depression and the need for mechanical ventilation (a complex undertaking in rats or mice) or

requires the administration of very low doses of the drug. Fujinaga et al.[56] used the whole-embryo rat culture system to investigate the reproductive toxicity of high doses of D-tubocurarine, pancuronium, atracurium, and vecuronium. Although dose-dependent toxicity was manifested, these effects occurred only at concentrations 30-fold greater than those encountered in clinical practice. These findings are consistent with earlier studies demonstrating no toxicity with small doses of muscle relaxants.[57] Given that fetal blood concentrations of muscle relaxants are only 10% to 20% of maternal concentrations, these drugs appear to have a wide margin of safety when administered to the mother during organogenesis.

Whether their administration later in gestation has adverse effects is unclear. Prolonged disturbance of normal muscular activity by muscle relaxants has caused axial and limb deformities in the chick but has seldom been seen in other experimental animals. Although one case report described arthrogryposis (i.e., persistent joint flexure) in the infant of a woman with tetanus who received D-tubocurarine for 19 days beginning at 55 days' gestation, the patient also was hypoxic and received multiple other drugs.[58] Many women have received muscle relaxants for several days during late gestation without adverse effect on the neonate.

Inhalation Anesthetics

Animal Studies.

Volatile Agents. Many studies have shown that, under certain conditions, the volatile halogenated anesthetic agents can produce teratogenic changes in chicks or small rodents. Basford and Fink[59] observed skeletal abnormalities but no increase in fetal loss when rats were exposed *in utero* to 0.8% halothane for 12 hours on days 8 and 9 of pregnancy (i.e., the "critical period" in the 21-day rat gestation). Long-term exposure to subanesthetic concentrations of halothane caused fetal growth restriction in rats but no increase in the incidence of congenital anomalies,[60] whereas isoflurane had no adverse effects.[61]

More significant reproductive effects have occurred with greater exposures to anesthetic agents. Fetal skeletal abnormalities or death followed repeated or prolonged maternal exposure of mice to anesthetic concentrations of volatile anesthetic agents.[62] However, teratogenicity in these studies most likely was caused by the physiologic changes (e.g., profound hypothermia, hypoventilation) associated with anesthesia rather than by the anesthetic agent itself. Moreover, some strains of mice are especially likely to demonstrate anomalies such as cleft palate. Mazze et al.[63] exposed rats to 0.75 MAC of halothane, isoflurane, or enflurane, or 0.55 MAC of nitrous oxide for 6 hours daily on 3 consecutive days at various stages of pregnancy. The animals remained conscious throughout the study, and normal feeding and sleep patterns were preserved. Under these conditions, no teratogenic effects were associated with any of the volatile agents. The only positive finding was a threefold increase in the rate of fetal resorption with nitrous oxide. No evidence has suggested reproductive toxicity with either sevoflurane or desflurane in clinical concentrations.

Nitrous Oxide. In contrast to the volatile halogenated agents, nitrous oxide is a weak teratogen in rodents under certain conditions, even when normal homeostasis is maintained. Rats continually exposed to 50% to 70% nitrous oxide for 2 to 6 days (starting on day 8 of gestation) had an increased incidence of congenital abnormalities.[63,64] To exclude the possibility that adverse effects were a consequence of the anesthetic state, Lane et al.[65] exposed rats to 70% nitrous oxide or to a similar concentration of xenon (a slightly more potent anesthetic devoid of biochemical effects) for 24 hours on day 9 of gestation; abnormalities occurred only in the nitrous oxide group. With the exception of one study in which extremely prolonged exposure to a low concentration of nitrous oxide had some minor effects,[66] at least 50% nitrous oxide has been required to consistently produce anomalies.[64] The threshold exposure time has not been rigorously determined, although exposure for at least 24 hours typically was necessary.

In vivo and embryo culture studies in rats have confirmed that nitrous oxide has several adverse reproductive effects, each of which results from exposure at a specific period of susceptibility.[67,68] Fetal resorptions occurred after exposure on days 8 and 11 of gestation, skeletal anomalies after exposure on day 8 or 9, and visceral anomalies (including *situs inversus*) only when exposure occurred on day 8.[69]

Initially, teratogenicity associated with nitrous oxide was thought to result from its oxidation of vitamin B_{12}, which interferes with its function as a coenzyme for methionine synthase.[70] Transmethylation from methyltetrahydrofolate to homocysteine to produce tetrahydrofolate (THF) and methionine is catalyzed by methionine synthase (Figure 17-3). Thus, methionine synthase inhibition could cause a decrease in THF (with a resultant decrease in DNA synthesis) and lower methionine levels (with resultant impairment of methylation reactions). Nitrous oxide rapidly inactivates methionine synthase in both animals[71] and humans.[72] Prolonged human exposure to nitrous oxide leads to neurologic and hematologic symptoms, the latter probably resulting from diminished DNA synthesis.[70] The hematologic—but not the neurologic—changes are prevented by the co-administration of folinic acid (5-formyl THF) with nitrous oxide, with the goal of restoring DNA synthesis.

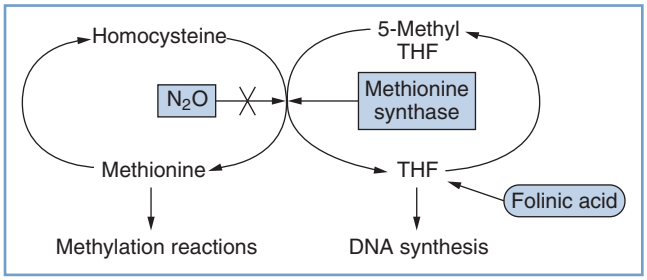

FIGURE 17-3 ■ Pathway showing the inhibition of methionine synthase by nitrous oxide (N_2O) and its potential metabolic consequences (e.g., decreased DNA synthesis and impaired methylation reactions). *THF,* tetrahydrofolate. (Courtesy M. Fujinaga, Palo Alto, CA.)

Considerable evidence indicates that methionine synthase inhibition and a consequent lack of THF are not solely responsible for the teratogenic effects of nitrous oxide. First, maximal inhibition of methionine synthase activity occurs at concentrations of nitrous oxide that are much lower than those required to produce teratogenic effects.[73] Second, folinic acid, which bypasses the effect of methionine synthase inhibition on THF formation, partially prevents only one of the structural abnormalities (i.e., minor skeletal defects) produced by nitrous oxide.[74] Third, the administration of isoflurane or halothane with nitrous oxide prevents almost all of the teratogenic effects but does not prevent the decrease in methionine synthase activity.[75,76] Fourth, studies using an *in vitro* whole-embryo rat culture system have shown that supplementation of nitrous oxide with methionine (but not with folinic acid) almost completely prevents growth restriction and all malformations with the exception of *situs inversus*.[77] Additional studies have implicated α_1-adrenergic receptor stimulation in the production of *situs inversus* by nitrous oxide.[68,78,79] Postulated mechanisms by which sympathetic stimulation might have adverse reproductive effects include a decrease in uterine blood flow and overstimulation of G protein–dependent membrane signal transduction pathways.[80] There is also evidence that nitrous oxide may cause neuronal apoptosis in rats.[81]

In summary, evidence suggests that the etiology of nitrous oxide teratogenicity in rats is complex and multifactorial. Determination of the relative roles of methionine deficiency and sympathetic stimulation or other mechanisms awaits performance of further studies. Although nitrous oxide is considered a weak teratogen in rats and mice, reproductive effects occur only after prolonged exposure to high concentrations that are unlikely to be encountered in humans during clinical anesthesia. Whether nitrous oxide administration is associated with neuronal apoptosis and learning impairments in humans remains to be determined.

Human Studies.

Occupational Exposure to Waste Anesthetic Agents. Epidemiologic surveys dating from the 1960s and 1970s suggested that reproductive hazards (e.g., spontaneous abortion, congenital anomalies) were associated with operating room and dental surgery work.[82-86] These hazards were attributed to exposure to trace concentrations of anesthetic agents, principally nitrous oxide. Critical reviews of these studies questioned their conclusions. The reviewers noted that response bias, inappropriate control groups, lack of verification of medical data, and exposure to multiple environmental factors made definitive conclusions impossible.[87-89]

The most consistent risk associated with occupational exposure was spontaneous abortion, which carried a relative risk ratio of 1.3. The ratio for congenital anomalies (1.2) had borderline statistical significance.[87,89] These relative risks are well within the range that might be explained by bias or uncontrolled variables.[89] For example, the relative risk of second-trimester abortion among women who drink one or two alcoholic drinks per day is 1.98; this risk increases to 3.53 with more than three drinks daily.[90] Similarly, cigarette smoking carries a relative risk of 1.8 for spontaneous abortion.[91]

Shirangi et al.[92] conducted a questionnaire-based survey of 2028 female veterinarians; information on 744 pregnancies regarding the risk for preterm birth (< 37 weeks) was collected. The prevalence of preterm birth in women exposed to unscavenged anesthetic gases was 7.3%, compared with 5.7% in the general population. The identification of the specific gas used was not requested; however, halothane, nitrous oxide, enflurane, and methoxyflurane were the most commonly used anesthetic gases during the study period. A hazards model predicted a 2.5-fold increase in preterm delivery risk in women exposed to unscavenged gas 1 or more hours per week compared with an unexposed group. Of note, a 3.7-fold increased risk was observed in veterinarians working greater than 45 hours a week compared with fewer than 45 hours.

Other studies have not confirmed an association between operating room work and higher reproductive risk.[93,94] Pregnancy outcomes were comparable in exposed and nonexposed operating room nurses when questionnaire information was matched with objective data obtained from medical records and registries of abortions, births, and congenital anomalies.[93] Similarly, in a 10-year prospective survey of all female physicians in the United Kingdom, Spence[94] found no differences in reproductive outcome when anesthesiologists were compared with other working female physicians. Although these studies may have missed a higher incidence of very early abortion, their data do not support a statistically demonstrable reproductive hazard resulting from operating room exposure to anesthetic agents.

It is possible that the higher waste levels of nitrous oxide encountered in dentists' offices pose a reproductive risk.[85,95] In 1980, Cohen et al.[85] reported a doubling of the spontaneous abortion rate among exposed female chair-side assistants and the wives of exposed male dentists. The incidence of birth defects among the children of exposed dental assistants was slightly higher than that for nonexposed assistants. However, the validity of this finding is doubtful; the incidence of anomalies among the offspring of nonexposed dentists was similar to that of the exposed assistants. Moreover, the expected dose-response relationship did not exist. In another study,[95] reduced fertility was reported among female dental assistants working with nitrous oxide in an unscavenged environment for more than 5 hours per week. However, because the affected group consisted of only 19 individuals, it is difficult to draw firm conclusions from these data. Overall, the epidemiologic data do not support an increased risk for congenital anomalies with long-term exposure to nitrous oxide.

Studies of Operations Performed during Pregnancy. In 1963, Smith[96] reviewed the obstetric records of 18,493 pregnant women. Sixty-seven (0.36%) had had an operation during pregnancy; only 10 procedures occurred during the first trimester. Fetal mortality was 11.2%, with the poorest survival occurring after operations for appendiceal abscess and cervical incompetence. In 1965, Shnider and Webster[97] examined the records of 9073 obstetric patients; 147 (1.6%) of this group had had

operations during pregnancy. Preterm delivery followed operation in 8.8% of patients, and the incidences of perinatal mortality and low-birth-weight (LBW) infants were increased in patients who had surgery during pregnancy. Brodsky et al.[2] surveyed 12,929 pregnant dental assistants and wives of male dentists, 2% of whom had operations during gestation. Spontaneous abortions were more common in the surgical group than in the control group (8% versus 5.1% during the first trimester and 6.9% versus 1.4% during the second trimester, respectively). None of these three studies reported a higher incidence of congenital anomalies among infants of women who underwent surgery during pregnancy. Two additional studies[98,99] that focused on the risks associated with nitrous oxide anesthesia during early pregnancy found no increase in the incidence of congenital abnormalities or spontaneous abortions.

Duncan et al.[100] used health insurance data to study the entire Manitoba, Canada, population between 1971 and 1978, matching 2565 women who had operations during pregnancy with similar controls who did not undergo surgery. Type of anesthesia was classified as nil (18%), general (57%), spinal/nerve block (2%), or local (24%). Although the incidence of congenital anomalies was similar in the surgical and control groups, spontaneous abortion was more common among women who had general anesthesia for surgery during the first or second trimester. This was true for both gynecologic procedures (relative risk [RR], 2.00) and nongynecologic procedures (RR, 1.58). Unfortunately, no conclusions regarding the relationship between anesthetic technique and fetal loss could be drawn, because most of the gynecologic and other major procedures were performed with general anesthesia. As in most studies, it is difficult to separate the effects of the anesthetic technique from those of the surgical procedure.

In the largest study to date, Mazze and Källén[1] linked data from three Swedish health care registries—the Medical Birth Registry, the Registry of Congenital Malformations, and the Hospital Discharge Registry—for the years 1973 to 1981. Among the population of 720,000 pregnant women, 5405 (0.75%) had nonobstetric surgery, including 2252 who had procedures during the first trimester. (Cervical cerclage was excluded from analysis.) Of the women who had surgery, 54% received general anesthesia, which included nitrous oxide in 97% of cases. The researchers examined the following adverse outcomes: (1) congenital anomalies, (2) stillbirths, (3) neonatal death within 7 days, and (4) LBW or very low-birth-weight (VLBW) infants. There was no difference between surgical and control patients with regard to the incidence of stillbirth or the overall incidence of congenital anomalies (Figure 17-4). Although the overall rate of anomalies among infants of women who had first-trimester operations was not higher, this group did have a higher-than-expected incidence of neural tube defects (6.0 observed versus 2.5 expected).[101] Five of the 6 women whose infants had these defects were among the 572 women who had had surgery during gestational weeks 4 to 5, which is the period of neural tube formation; the researchers cautioned that this finding could have been a chance association.[101] However, if a true causal relationship exists between neural tube defects and anesthesia at this stage of gestation, it could represent an eightfold to ninefold increase in the risk for this anomaly (i.e., an absolute risk of almost 1%). Other positive findings were a higher incidence of LBW and VLBW infants in the surgical group, which resulted from both preterm delivery and fetal growth restriction (also known as intrauterine growth restriction).[1] A predictable consequence of preterm delivery was a higher number of deaths of live-born infants within the first 7 days of life. Finally, no anesthetic technique or operation was associated with a significantly higher number of adverse outcomes.

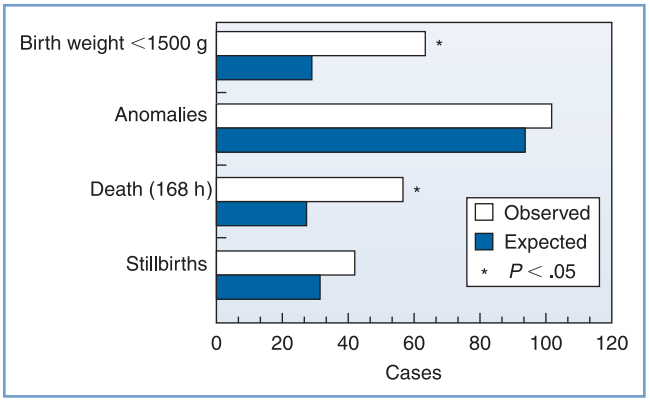

FIGURE 17-4 ■ **Total number of observed and expected adverse outcomes among women having nonobstetric operations during pregnancy. Incidences of infants with a birth weight of less than 1500 g and of infants born alive who died within 168 hours of birth were significantly increased.** (Modified from Mazze RI, Källén B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol 1989; 161:1178.)

A case-control study of infants born in Atlanta between 1968 and 1980 gathered information regarding first-trimester exposure to general anesthesia from the mothers of 694 infants with major CNS defects and 2984 control mothers.[102] A striking association was found between general anesthesia exposure and hydrocephalus in conjunction with another major defect (the strongest association was with hydrocephalus and eye defects). Limitations of this study include its retrospective nature and a lack of information about the types of surgery, the anesthetic agents used, and the presence or absence of complications. The investigators cautioned that further studies are necessary to confirm their observations.

In summary, although anesthesia and surgery are associated with a higher incidence of abortion, fetal growth restriction, and perinatal mortality, these adverse outcomes can often be attributed to the procedure, the site of surgery (e.g., proximity to the uterus), and/or the underlying maternal condition. Evidence does not suggest that anesthesia during pregnancy results in an overall increase in congenital abnormalities, and there is no evidence of a relationship between outcome and type of anesthesia.

Behavioral Teratology

It is well known that some teratogens produce enduring behavioral abnormalities without any observable

morphologic changes. The CNS may be especially sensitive to such influences during the period of major myelination, which in humans extends from the fourth intrauterine month to the second postnatal month (see Chapter 10). Several studies have shown that brief intrauterine exposure to halothane adversely affects postnatal learning behavior and causes CNS degeneration and decreased brain weight in rats.[103-105] The fetal nervous system in the rat is most susceptible to the effects of halothane during the second trimester.[103] Maternal administration of systemic drugs—including barbiturates, meperidine, and promethazine—has also resulted in behavioral changes in offspring,[106-108] whereas no effect has been noted with the administration of lidocaine.[55] In humans, investigations of the effects of maternally administered analgesics at delivery have revealed transient, dose-related depression of neonatal behavior.

Currently used general anesthetic agents act by one of two principal mechanisms, (1) the potentiation of $GABA_A$ receptors (benzodiazepines, volatile halogenated agents, and barbiturates) or (2) the antagonism of NMDA receptors (nitrous oxide and ketamine). Drugs that act by either of these mechanisms appear to induce widespread neuronal apoptosis in the developing rat brain when administered during the period of synaptogenesis (i.e., the brain growth-spurt period).[81,109-111] Jevtovic-Todorovic et al.[81] observed that the administration of a general anesthetic "cocktail" (midazolam, isoflurane, and nitrous oxide), in doses sufficient to maintain general anesthesia for 6 hours in 7-day-old infant rats, resulted in widespread apoptotic neurodegeneration in the developing brain, deficits in hippocampal synaptic function, and persistent memory/learning impairments. They concluded that these deficits are "subtle enough to be easily overlooked" but may persist into adolescence and adulthood.[81] Ikonomidou et al.[110] described neurodegeneration in rat pups after NMDA receptor antagonism. These data suggest that prolonged exposure to anesthetic agents at a critical period in brain development may accelerate the normal developmental process of apoptotic neurodegeneration, potentially resulting in prolonged behavioral deficits.[112] Thus, the safety of providing anesthesia during early life has been questioned.[113]

The implications, if any, for the human fetus during the maternal administration of general anesthesia are unknown because there are methodologic issues with these animal studies. Surgery may result not only in exposure to anesthetic agents but also in derangements in maternal physiology (e.g., hypoxia, stress, hypoglycemia) that can lead to apoptosis during the critical period of neuronal development.[114] Also, it should be noted that in experimental studies the rats typically were exposed to large doses of anesthetic agents for prolonged periods. Hayashi et al.[115] demonstrated that a single dose of ketamine did not lead to apoptosis but that its repeated administration for several hours caused neuronal degeneration. It is also important to remember that painful stimuli per se can cause long-term behavioral changes.[116] Finally, the species model may be important. For example, McClain et al.[117] did not observe any histologic or functional effects of exposure to general anesthesia in fetal lambs. Anand and Soriano[113] concluded:

> *Clearer understanding of the mechanisms by which exposures to pain/stress or prolonged anesthesia in the perinatal period can alter the survival or development of immature neurons and glia may prevent some long-term neurobehavioral abnormalities in humans. In the meantime, clinicians should administer anesthetic agents to newborn infants or pregnant mothers but avoid prolonged periods of anesthetic exposure.... Alleviation of pain and stress during the perinatal period should remain an essential clinical goal until further research defines the clinical importance of [experimental] results [observed in animals].*

After a review of the data and a public hearing in March 2007, the Anesthetic and Life Support Drugs Advisory Committee of the U.S. Food and Drug Administration stated that currently "there are not adequate data to extrapolate the animal findings to humans."[118]

Fetal Effects of Anesthesia

Maintenance of Fetal Well-Being

The most serious fetal risk associated with maternal surgery during pregnancy is that of intrauterine asphyxia. Because fetal oxygenation depends on maternal oxygenation, maintenance of normal maternal arterial oxygen tension, oxygen-carrying capacity, oxygen affinity, and uteroplacental perfusion are critical to fetal well-being.

Maternal and Fetal Oxygenation. Transient mild to moderate decreases in maternal Pao_2 are well tolerated by the fetus, because fetal hemoglobin has a high affinity for oxygen. Severe maternal **hypoxemia** results in fetal hypoxia and, if persistent, may cause fetal death. Any complication that causes profound maternal hypoxemia (e.g., difficult intubation, esophageal intubation, pulmonary aspiration, total spinal anesthesia, systemic local anesthetic toxicity) is a potential threat to the fetus.

Studies of isolated human placental vessels have suggested that **hyperoxia** might cause uteroplacental vasoconstriction, with potential impairment of fetal oxygen delivery.[119] This fear has proved to be unfounded, because studies in pregnant women have demonstrated better fetal oxygenation with increasing maternal Pao_2.[120] Fetal Pao_2 never exceeds 60 mm Hg, even when maternal Pao_2 increases to 600 mm Hg, because of a large maternal-fetal oxygen tension gradient (see Chapter 4). Thus, intrauterine retrolental fibroplasia and premature closure of the ductus arteriosus cannot result from high levels of maternal Pao_2. McClain et al.[117] observed that the maternal administration of general anesthesia for 4 hours in gravid ewes produced an initial—but not sustained—increase in fetal systemic oxygenation, which was accompanied by a sustained increase in fetal cerebral oxygenation. The investigators hypothesized that the increase in fetal cerebral oxygenation resulted from greater cerebral perfusion, lower cerebral metabolic rate, or both. Histologic examination found no evidence of neurotoxicity.

Maternal Carbon Dioxide and Acid-Base Status. Maternal **hypercapnia** can cause fetal acidosis, because fetal $Paco_2$ correlates directly with maternal $Paco_2$. Although mild fetal respiratory acidosis is of little consequence, severe acidosis can cause fetal myocardial depression and hypotension. Maternal **hyperventilation** with low maternal $Paco_2$ and high pH can adversely affect fetal oxygenation by means of several mechanisms.[121-123] **Respiratory** or **metabolic alkalosis** can compromise maternal-fetal oxygen transfer by causing umbilical artery constriction[121] and by shifting the maternal oxyhemoglobin dissociation curve to the left.[122] In addition, hyperventilation, independent of changes in $Paco_2$, may reduce uterine blood flow and cause fetal acidosis.[123] This decrease most likely is a consequence of mechanical ventilation, whereby increased intrathoracic pressure reduces venous return and cardiac output, which in turn decreases uteroplacental perfusion. Thus, hyperventilation should be avoided in the pregnant surgical patient. Rather, the $Paco_2$ should be kept in the normal range for pregnancy.

Uteroplacental Perfusion. Maternal **hypotension** from any cause can jeopardize uteroplacental perfusion and cause fetal asphyxia. The most common causes of hypotension in the pregnant patient undergoing surgery include (1) deep levels of general anesthesia, (2) sympathectomy with high levels of spinal or epidural blockade, (3) aortocaval compression, (4) hemorrhage, and (5) hypovolemia. In monkeys, prolonged hypotension (i.e., systolic blood pressure < 75 mm Hg) caused by deep halothane anesthesia resulted in fetal hypoxia, acidosis, and hypotension.[124] After experiencing as much as 5 hours of severe partial asphyxia *in utero* (pH < 7.00 for at least 1 hour), neonatal monkeys were depressed and experienced seizures. Postnatal survival was poor, and pathologic brain changes included swelling, necrosis, and hemorrhage. The clinical course and neuropathologic findings in these animals resembled those in infants known to have suffered severe intrauterine asphyxia and who died within a few days of birth. Despite these alarming data, case reports have described good outcome after deliberate induction of moderate degrees of hypotension during pregnancy, usually to facilitate performance of a neurosurgical procedure.[125] Fetal and neonatal outcomes were unaffected when maternal systolic blood pressure was kept between 70 to 80 mm Hg, even when pressures as low as 50 mm Hg were briefly permitted. In such circumstances, the risk to the fetus must be balanced against the risk for uncontrolled maternal bleeding or stroke.

The multiple factors that influence uteroplacental blood flow are discussed in detail in Chapter 3. Of particular relevance to the pregnant surgical patient are drugs that cause uterine vasoconstriction. Preoperative anxiety and light anesthesia increase circulating catecholamines, possibly impairing uterine blood flow.[126] Drugs that cause uterine hypertonus (e.g., ketamine in early pregnancy in doses higher than 2 mg/kg,[127] toxic doses of local anesthetics[128]) may increase uterine vascular resistance, decreasing uteroplacental perfusion.

New evidence has challenged the historic view that the mixed-adrenergic agonist ephedrine is preferred to the alpha-adrenergic agonist phenylephrine for the treatment of hypotension during the administration of neuraxial anesthesia in obstetric patients (see Chapter 26).[129,130] A meta-analysis of randomized controlled trials comparing ephedrine with phenylephrine for the treatment of hypotension during spinal anesthesia for cesarean delivery resulted in the following conclusions: (1) there was no difference between phenylephrine and ephedrine for the prevention and treatment of maternal hypotension, (2) maternal bradycardia was more likely to occur with phenylephrine than with ephedrine, (3) women given phenylephrine had neonates with higher umbilical arterial blood pH measurements than those given ephedrine, and (4) there was no difference between the two vasopressors in the incidence of true fetal acidosis (i.e., umbilical arterial blood pH < 7.20).[129] Cooper et al.[130] randomly assigned 147 patients to receive phenylephrine, ephedrine, or both for the maintenance of maternal arterial pressure during spinal anesthesia for elective cesarean delivery. Fetal acidosis was more common in the women who received ephedrine. The investigators speculated that "increased fetal metabolic rate, secondary to ephedrine-induced beta-adrenergic stimulation, was the most likely mechanism for the increased incidence of fetal acidosis in the ephedrine group."[130] Ngan Kee et al.[131] demonstrated that placental transfer was greater for ephedrine than phenylephrine and fetal metabolism was greater for phenylephrine than ephedrine. They also observed increased fetal concentrations of lactate, glucose, and catecholamines with ephedrine compared with phenylephrine, thus supporting the hypothesis that the lower fetal pH observed with ephedrine is related to metabolic effects secondary to stimulation of fetal beta-adrenergic receptors. Therefore, the use of phenylephrine to treat maternal hypotension is acceptable and may be preferable to ephedrine. However, the potential for phenylephrine to decrease maternal cardiac output and alter uteroplacental perfusion, despite treating hypotension, should be further studied.[132]

Fetal Effects of Inhalation Agents

The volatile halogenated anesthetic agents can affect the fetus directly (by depressing the fetal cardiovascular system or CNS) or indirectly (by causing maternal hypoxia or hypotension). Studies in gravid ewes have shown minimal fetal effects with maternal administration of moderate concentrations of a volatile agent.[133] Uterine perfusion was maintained during the inhalation of 1.0 and 1.5 MAC halothane or isoflurane, because uterine vasodilation compensated for small decreases in maternal blood pressure. Higher concentrations (e.g., 2.0 MAC) given for prolonged periods induced marked maternal hypotension. Consequently, reduced uteroplacental blood flow resulted in fetal hypoxia, diminished fetal cardiac output, and fetal acidosis.[134]

The effects of anesthesia on the stressed fetal lamb remain unclear. In one study, the administration of 1% halothane to the mothers of asphyxiated fetal lambs caused severe fetal hypotension, worsening of fetal acidosis, and decreases in cerebral blood flow and oxygen

delivery.[134] In other studies, acidosis that was less severe or of a shorter duration was associated with the maintenance of fetal cardiac output and a preservation of the balance between oxygen supply and demand.[135-137] The protective compensatory mechanisms that exist during asphyxia may be abolished by high but not low concentrations of volatile agents.

The relevance of these data to the human mother undergoing surgery during pregnancy is not clear. Clinical experience does not support avoidance of volatile agents, provided that maternal hypotension is prevented. Indeed, the depressant effect of these agents on myometrial contractility may be beneficial. If intraoperative fetal heart rate (FHR) monitoring reveals signs of fetal compromise, it may be advisable to discontinue the volatile agent until the fetal condition improves.

Fetal Effects of Systemic Drugs

Opioids and induction agents decrease FHR variability, possibly to a greater extent than the inhalation agents.[138,139] This finding most likely signals the presence of an anesthetized fetus and is not a cause for concern in the absence of maternal hypotension or other abnormalities. Fetal respiratory depression is relevant only if cesarean delivery is to be performed at the same time as the surgical procedure. Even then, high-dose opioid anesthesia need not be avoided when it is indicated for maternal reasons (e.g., anesthesia for patients with cardiac disease). The pediatrician should be informed of maternal drug administration so that preparations can be made to support neonatal respiration. Some data indicate that remifentanil may result in less neonatal depression than longer-acting opioids.[140,141]

Maternal administration of muscle relaxants and reversal agents typically has not proved to be problematic for the fetus. It has been suggested that rapid intravenous injection of an anticholinesterase agent might stimulate acetylcholine release, which might cause increased uterine tone and thus precipitate preterm labor.[142] Although this concern is unproven, slow administration of an anticholinesterase (after prior injection of an anticholinergic agent) is recommended. Atropine rapidly crosses the placenta and, when given in large doses, causes fetal tachycardia and loss of FHR variability.[143] Although neither atropine nor glycopyrrolate significantly affects FHR when standard clinical doses are administered,[144] glycopyrrolate is often recommended because it crosses the placenta less readily and may be a more effective antisialagogue. Although limited transplacental passage of neostigmine is expected, significant transfer occasionally may occur. One case report described mild fetal bradycardia when neostigmine was administered with glycopyrrolate during emergence from general anesthesia at 31 weeks' gestation.[145] This problem did not occur during the administration of a second general anesthetic to the same patient 4 days later, when atropine was administered with neostigmine, presumably because atropine undergoes greater placental transfer than glycopyrrolate. Because the effects of reversal agents are unpredictable, the monitoring of FHR during maternal drug administration is suggested.

Sodium nitroprusside and esmolol have been used during pregnancy to induce hypotension during surgical procedures. Standard doses of nitroprusside have proved to be safe for the fetus[146]; the risk for fetal cyanide toxicity appears to be low, provided that tachyphylaxis does not occur and the total dose is limited. The use of esmolol during pregnancy remains controversial. Ostman et al.[147] observed minimal fetal effects after the administration of esmolol in gravid ewes, whereas Eisenach and Castro[148] reported significant decreases in FHR and blood pressure as well as a modest reduction in fetal Pao_2. Fetal effects dissipated rapidly in the first study but persisted for 30 minutes or more in the second. Two case reports have described small decreases in FHR but no morbidity when esmolol was administered with nitroprusside during neurosurgical procedures.[149,150] In contrast, severe fetal compromise followed the administration of esmolol at 38 weeks' gestation to correct maternal supraventricular tachycardia.[151] Because fetal tachycardia preceded the onset of severe bradycardia in this case, the authors speculated that fetal compromise resulted from reduced maternal cardiac output rather than fetal beta-adrenergic receptor blockade.

Prevention of Preterm Labor

Most epidemiologic studies of nonobstetric surgery during pregnancy have reported a higher incidence of abortion and preterm delivery.[1,97,98,152] It is unclear whether the surgery, manipulation of the uterus, or the underlying condition is responsible. In a study of 778 women who underwent appendectomy during pregnancy, Mazze and Källén[152] found that 22% of women who underwent surgery between 24 and 36 weeks' gestation delivered in the week after surgery. In the women in whom pregnancy continued beyond a week after surgery there was no further increase in the rate of preterm birth. Although this study's database was unsuitable for determining the incidence of preterm delivery in women who had surgery before 24 weeks' gestation, a similar increase appeared likely. Second-trimester procedures and operations that do not involve uterine manipulation carry the lowest risk for preterm labor.

Although the volatile agents depress myometrial irritability and thus are theoretically advantageous for abdominal procedures, evidence does not show that any one anesthetic agent or technique positively or negatively influences the risk for preterm labor. Published evidence does not support the routine use of prophylactic tocolytic agents.[153] Monitoring for uterine contractions may be performed intraoperatively with an external tocodynamometer (when technically feasible) and for several days postoperatively, allowing tocolytic therapy to be instituted, if appropriate. Additional surveillance is necessary in patients who receive potent postoperative analgesics, who may be unaware of mild uterine contractions.

A relatively new class of tocolytic agents—oxytocin receptor antagonists (e.g., atosiban)—has been investigated.[154] Atosiban selectively blunts the calcium influx in the myometrium and thus inhibits myometrial contractility. However, atosiban, in laboratory conditions, blocks the protective effects of oxytocin in fetal/neonatal neurons

after hypoxic-ischemic insults.[155] Whether greater surveillance and early tocolytic therapy will reduce the risk for preterm delivery after surgery during pregnancy is not known.

Magnesium sulfate is among the most common drugs used in pregnancy as a tocolytic, anticonvulsant, or fetal neuroprotective agent. Antenatal magnesium sulfate has been shown to reduce the incidence and severity of cerebral palsy after very preterm birth (see Chapter 10).[156] However, magnesium has concurrent effects that are relevant to the delivery of anesthesia, including an increase in the rate of onset of neuromuscular blockade,[157] the reestablishment of neuromuscular blockade in patients recovering from a nondepolarizing muscle relaxant,[158] a reduction in general anesthetic requirements,[159] and possible impairment in coagulation (as a calcium antagonist).[160]

PRACTICAL CONSIDERATIONS

Timing of Surgery

Elective surgery should not be performed during pregnancy. When possible, surgery should be avoided during the first trimester, especially during the period of organogenesis. The second trimester is the optimal time to perform surgery, because the risk for preterm labor is lowest at that time. Urgent operation is often indicated for abdominal emergencies, some malignancies, and neurosurgical and cardiac conditions. The management and timing of most acute surgical procedures should mimic that for nonpregnant patients.[161,162] The risk for perinatal loss is increased when maternal appendicitis is advanced.[162] Appendiceal perforation may be more common in pregnant patients than in nonpregnant patients because diagnostic difficulties may delay performance of surgery. Generalized peritonitis may also be more likely because increased steroid levels during pregnancy may suppress the normal inflammatory response and prevent the "walling off" of the appendix by the omentum.[162]

In the event of a serious maternal illness, the remote fetal risks associated with anesthesia and surgery are of secondary importance. The primary goal is to preserve the life of the mother. Hypothermia,[163] induced hypotension,[125] cardiopulmonary bypass,[164] and liver transplantation[165] have been associated with successful neonatal outcomes. The decision to perform simultaneous cesarean delivery depends on a number of factors, including the gestational age, the risk to the mother of a trial of labor at a later date, and the presence of intra-abdominal sepsis. Cesarean delivery may be performed immediately before the surgical procedure to avoid fetal risks associated with special patient positioning (e.g., the sitting or prone position),[166] prolonged anesthesia, major intraoperative blood loss, maternal hyperventilation, deliberate hypotension, or cardiopulmonary bypass.[164]

Abdominal Emergencies

Acute abdominal disease occurs in 1 in 500 to 1 in 635 pregnancies.[167,168] Accurate diagnosis, especially of an acute abdominal crisis (e.g., appendicitis, cholecystitis), can be very difficult during pregnancy.[162] Box 17-2 lists some of the conditions that must be considered in the differential diagnosis of abdominal pain during pregnancy. Nausea, vomiting, constipation, and abdominal distention are common symptoms of both normal pregnancy and abdominal pathology. Abdominal tenderness may be indistinguishable from ligamentous or uterine contraction pain. The expanding uterus makes a physical examination of the abdomen difficult. For example, the appendix rotates counterclockwise; thus, as term approaches, the tip typically lies over the right kidney (Figure 17-5).[169] Because the white blood cell count in normal pregnancy may reach 15,000/mm^3, it must be markedly elevated to be diagnostically helpful. Additional delay results from the reluctance to perform necessary imaging studies involving radiation. In 1991, Mazze and Källén[152] reported the misdiagnosis of appendicitis during

BOX 17-2 Nonobstetric Abdominal Crises in Pregnancy

Medical Conditions

- Abdominal crises due to systemic disease
  - Sickle cell disease
  - Diabetic ketoacidosis
  - Porphyria
- Renal disease
  - Glomerulonephritis
  - Pyelonephritis
- Pulmonary disease
  - Basal pneumonia with pleurisy
- Cholecystitis and pancreatitis (early, uncomplicated)
- Myocardial infarction, pericarditis
- Drug addiction (withdrawal symptoms)

Surgical Conditions

Gynecologic Problems

- Ovarian cyst/tumor
  - Rupture
  - Torsion
  - Hemorrhage
  - Infection
- Torsion of a fallopian tube
- Tubo-ovarian abscess
- Uterine myoma
  - Degeneration
  - Infection
  - Torsion

Nongynecologic Problems

- Acute appendicitis
- Acute cholecystitis and its complications
- Acute pancreatitis and its complications
- Intestinal obstruction
- Trauma with visceral injury or hemorrhage
- Vascular accidents (e.g., ruptured abdominal aneurysm)
- Peptic ulcer

Modified from Fainstat T, Bhat N. Surgical resolution of nonobstetric abdominal crises complicating pregnancy. In Baden JM, Brodsky JB, editors. The Pregnant Surgical Patient. Mount Kisco, NY, Futura Publishing, 1985:154.

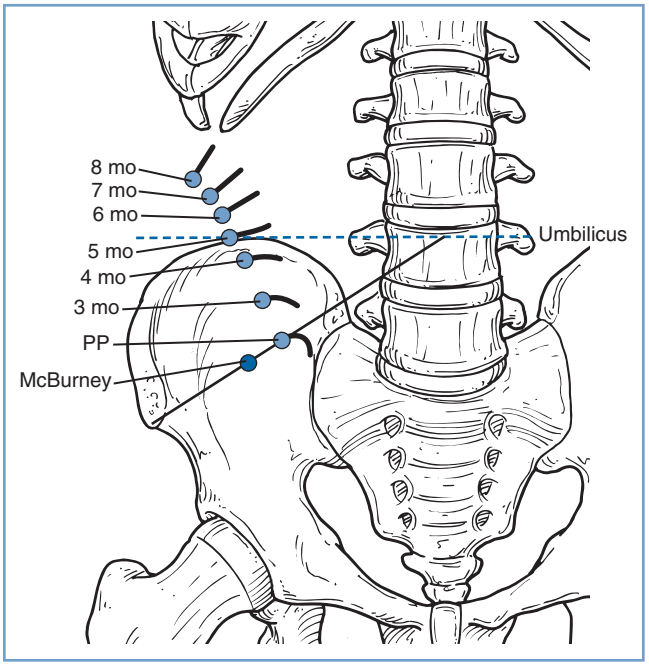

FIGURE 17-5 ■ Changes in position and direction of the appendix during pregnancy. *PP,* pulse pressure. (Redrawn from Baer JL, Reis RA, Arens RA. Appendicitis in pregnancy with changes in position and axis of normal appendix in pregnancy. JAMA 1932; 98:1359.)

pregnancy in 36% of cases, with a lower rate (23%) during the first trimester than during the last two trimesters (43%). More reassuringly, using 2005 to 2009 data from the American College of Surgeons (ACS) National Surgical Quality Improvement Program, Silvestri et al.[170] compared surgical outcomes in a large cohort of pregnant and nonpregnant women (857 pregnant and 20,029 nonpregnant cases of appendectomy, and 436 pregnant and 32,915 nonpregnant cases of cholecystectomy); no difference was noted in postoperative 30-day morbidity and mortality.

Sometimes, the correct diagnosis is determined only at operation. The selection of the procedure and choice of incision are influenced by the stage of gestation, the nature of the surgical problem, the certainty of the probable diagnosis, and the experience of the surgeon. Laparoscopy is performed during pregnancy for both diagnostic and therapeutic indications with increasing frequency. Laparotomy continues to be performed for many abdominal conditions that occur during the later stages of pregnancy.

Laparoscopy

Concerns exist about the effects of laparoscopy on fetal well-being, especially the risks for (1) uterine or fetal trauma, (2) fetal acidosis from absorbed carbon dioxide, and (3) decreased maternal cardiac output and uteroplacental perfusion resulting from an iatrogenic increase in intra-abdominal pressure. In some animal studies, maternal and fetal acidosis and tachycardia have occurred during intra-abdominal insufflation, perhaps because maternal ventilation was guided by measurements of end-tidal rather than arterial carbon dioxide levels.[171] In a study in gravid ewes, a marked increase in $Paco_2$ to end-tidal CO_2 gradient developed during CO_2 insufflation, suggesting that $Paco_2$ should be used to guide ventilation if maternal and fetal acidosis are to be avoided.[171] Uteroplacental perfusion decreased by 61% in one study in which gravid ewes were subjected to a CO_2 pneumoperitoneum at a pressure of 20 mm Hg (although there were no adverse fetal consequences).[172] It is unclear whether the severity of acidosis and decrement in uteroplacental perfusion are related to insufflation pressure.[171]

Many practitioners believe, however, that the potential benefits of laparoscopic surgery compared with open abdominal surgery outweigh the risks. Potential benefits include (1) shorter hospitalization, (2) less postoperative pain, (3) decreased risk for thromboembolic and wound complications, and (4) faster return to normal activities, including earlier return of normal gastrointestinal function, less uterine irritability, and less fetal depression.[173] Laparoscopy is being performed with growing frequency in pregnant women.[173-176] In a 1994 survey of laparoendoscopic surgeons, Reedy et al.[174] obtained data from 413 laparoscopic procedures performed during pregnancy and reviewed an additional 55 previously published cases. Among the procedures surveyed, 48% were cholecystectomies, 28% were adnexal operations, 16% were appendectomies, and 8% were diagnostic procedures. Thirty-two percent of operations were performed in the first trimester, 54% in the second, and 13% in the third. Several principally retrospective trials comparing open and laparoscopic interventions reported no maternal and fetal outcome differences.[175,176]

Human clinical studies and clinical experience suggest that the fetal effects of the CO_2 pneumoperitoneum and increased intra-abdominal pressure are limited. In one clinical study, there were no differences in the maternal pH, $Paco_2$, or arterial to end-tidal CO_2 pressure gradients before, during, or after termination of the pneumoperitoneum during laparoscopy.[177] Steinbrook and Bhavani-Shankar[178] used thoracic electrical bioimpedance cardiography to measure changes in cardiac output in four pregnant women undergoing laparoscopic cholecystectomy. They observed hemodynamic changes similar to those that typically occur during laparoscopic surgery in nonpregnant patients (i.e., decrease in cardiac index with concurrent increases in mean arterial pressure and systemic vascular resistance).

Reported clinical experiences with laparoscopy during pregnancy generally have been favorable; complications such as intraoperative perforation of the uterus with the Veress needle have occurred rarely.[174] Nonetheless, Amos et al.[179] urged caution in a case series study in which they reported fetal death after four of seven laparoscopic procedures. Because of concerns about the fetal effects of CO_2 pneumoperitoneum, some practitioners have suggested using a gasless laparoscopic technique.[180,181]

Careful surgical and anesthetic techniques are critical to avoid problems associated with pregnancy and the special hazards of laparoscopic surgery. The surgeon should be experienced with the technique, and the anesthesia provider must be aware of the accompanying

BOX 17-3 Suggested Guidelines for Laparoscopic Surgery during Pregnancy

- Indications for laparoscopic treatment of acute abdominal processes are the same as for nonpregnant patients.
- Laparoscopy can be safely performed during any trimester of pregnancy.
- Preoperative obstetric consultation should be obtained.
- Intermittent lower extremity pneumatic compression devices should be used intraoperatively and postoperatively to prevent venous stasis (i.e., as prophylaxis for deep vein thrombosis).
- The fetal heart rate and uterine tone should be monitored both preoperatively and postoperatively.
- End-tidal CO_2 should be monitored during surgery.
- Left uterine displacement should be maintained to avoid aortocaval compression.
- An open (Hassan) technique, a Veress needle, or an optical trocar technique may be used to enter the abdomen.
- Low pneumoperitoneum pressures (between 10 and 15 mm Hg) should be used.
- Tocolytic agents should not be used prophylactically but should be considered when evidence of preterm labor is present.

Modified from Guidelines Committee of the Society of American Gastrointestinal and Endoscopic Surgeons, Yumi H. Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy. Surg Endosc 2008; 22:849-61.

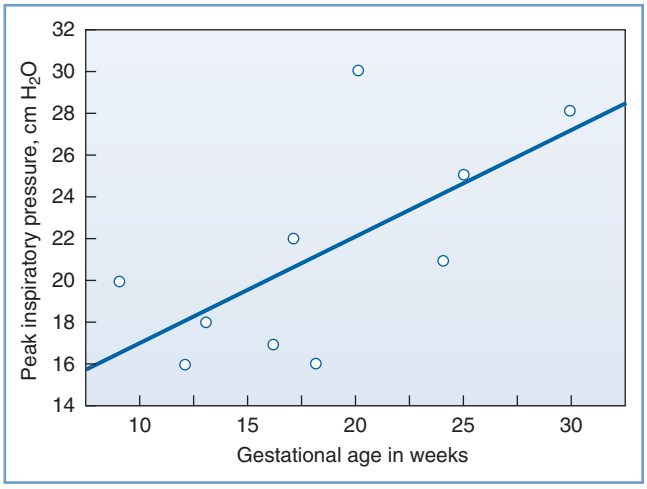

FIGURE 17-6 ■ Peak inspiratory pressure during laparoscopic cholecystectomy during pregnancy as a function of gestational age. The best-fit line by linear regression is shown ($y = 12.1 + 0.5x$; $R^2 = 0.43$). Peak inspiratory pressure tends to increase with advancing gestation. (Modified from Steinbrook RA, Brooks DC, Datta S. Laparoscopic cholecystectomy during pregnancy. Surg Endosc 1996; 10:511-5.)

cardiorespiratory changes. In 2007, the Society of American Gastrointestinal Endoscopic Surgeons[182] issued "Guidelines for Diagnosis, Treatment, and Use of Laparoscopy for Surgical Problems during Pregnancy" (Box 17-3). According to these guidelines, indications for laparoscopic surgery in pregnant patients do not differ from those for nonpregnant patients and the procedure may be performed during any trimester of pregnancy.

General anesthesia has been used in the vast majority of laparoscopic procedures, although the use of epidural anesthesia has also been described.[174] Steinbrook et al.[183] described their anesthetic technique for 10 cases of laparoscopic cholecystectomy during pregnancy. They administered general anesthesia with a rapid-sequence induction followed by tracheal intubation and positive-pressure ventilation to maintain end-tidal CO_2 between 32 and 36 mm Hg. Anesthesia was maintained with a nondepolarizing muscle relaxant, an opioid, and a volatile halogenated agent, but nitrous oxide was avoided to prevent bowel distention and to allow administration of a higher concentration of inspired oxygen. The pneumoperitoneum resulted in increased peak airway pressure (Figure 17-6) and decreased total lung compliance, changes that were progressively greater with advancing gestation.

The Trendelenburg position exacerbates decreases in FRC, and hypoxemia from airway closure may occur with this position. Hyperventilation, which may be necessary to maintain normal maternal $PaCO_2$, may reduce uteroplacental perfusion and affect fetal oxygenation. Hypotension may result from pneumoperitoneum, aortocaval compression, or use of the reverse Trendelenburg position, and a vasopressor may be needed to maintain maternal blood pressure during laparoscopy.[183] As with open surgery, fetal well-being is best preserved by maintaining maternal oxygenation, acid-base status, and hemodynamic parameters within normal pregnancy limits. The FHR and uterine tone should be monitored both before and after surgery (see later discussion).

Electroconvulsive Therapy

Psychiatric disease is an important cause of maternal morbidity and mortality during pregnancy.[9] The treatment of major psychiatric disorders during pregnancy, including electroconvulsive therapy, is discussed in Chapter 51. As with the treatment of other diseases during pregnancy, withholding treatment is rarely justified, although the benefits of the treatment should be weighed against the risk for harm to the mother and fetus.

Direct-Current Cardioversion

Direct-current (DC) cardioversion may be necessary during pregnancy (see Chapter 42). It is safe in all stages of pregnancy. The electrical current that reaches the fetus is small.[184] Careful FHR monitoring during the procedure is required, as is left uterine displacement to avoid aortocaval compression. The risk for pulmonary aspiration of gastric contents associated with sedation (with an unprotected airway) should be weighed against the risk for general anesthesia with tracheal intubation. Regardless of whether sedation or general anesthesia is selected, a nonparticulate oral antacid should be administered; administration of a histamine-2 receptor antagonist to increase gastric pH should also be considered.

Maternal Cardiac Arrest and Resuscitation

Initiation of treatment for maternal cardiac arrest differs little from that in the nonpregnant patient. Standard Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) principles apply to these patients. However, anatomic and physiologic changes of pregnancy require several specific modifications to the resuscitation protocol (see Chapters 42 and 55).[185] Left uterine displacement should be maintained during resuscitation, and hand position should be 1 to 2 cm higher on the sternum because of the upward shift of the diaphragm (see Boxes 42-11 and 55-5). Perimortem cesarean delivery is an essential aspect of maternal resuscitation for women in the second half of gestation.[186] The primary purpose of the hysterotomy is to improve the chance of maternal survival, but early delivery will also improve the likelihood of fetal survival.[185,186] Thus, if initial resuscitative efforts are unsuccessful, perimortem cesarean delivery should be initiated within 4 minutes of the arrest with the goal of delivering the fetus within 5 minutes.[185] The reversible causes of cardiac arrest during pregnancy are similar to those in nonpregnant patients. Additional causes specific to pregnancy include amniotic fluid embolism, eclampsia, placental abruption, and hemorrhage.

Fetal Monitoring during Surgery

Continuous FHR monitoring (using transabdominal Doppler ultrasonography) is feasible beginning at 18 to 20 weeks' gestation.[187] However, technical problems may limit the use of continuous FHR monitoring between 18 and 22 weeks' gestation. Transabdominal monitoring may not be possible during abdominal procedures or when the mother is very obese; thus, the intraoperative use of use of transvaginal Doppler ultrasonography may be considered in selected cases. The American College of Obstetricians and Gynecologists (ACOG) has stated that "the decision to use [intraoperative] fetal monitoring should be individualized and, if used, should be based on gestational age, type of surgery, and facilities available.[188] Responses to a survey sent to members of the Association of Professors of Gynecology and Obstetrics indicated that only 43% routinely used intraoperative FHR monitoring.[189]

FHR variability, which typically is a good indicator of fetal well-being, is present by 25 to 27 weeks' gestation. Changes in the baseline FHR and FHR variability caused by anesthetic agents or other drugs must be distinguished from changes that result from fetal hypoxia. Persistent severe fetal bradycardia typically indicates true fetal compromise.

Intraoperative FHR monitoring requires the presence of a provider who can interpret the FHR tracing. In addition, a plan should be in place that addresses how to proceed in the event of persistent nonreassuring fetal status, including whether to perform emergency cesarean delivery. The greatest value of intraoperative FHR monitoring is that it allows for the optimization of the maternal condition if the fetus shows signs of compromise. In one case, for example, decreased FHR variability was associated with maternal hypoxia, and the pattern resolved when maternal oxygenation improved (Figure 17-7).[139] An unexplained change in FHR mandates the evaluation of maternal position, blood pressure, oxygenation, and acid-base status and the inspection of the surgical site to ensure that neither surgeons nor retractors are impairing uteroplacental perfusion.

Anesthetic Management

Preoperative Management

Premedication may be necessary to allay maternal anxiety. Pregnant women are at increased risk for acid aspiration after 18 to 20 weeks' gestation (see earlier discussion). Pharmacologic precautions against acid aspiration may include preanesthetic administration of a histamine receptor antagonist, metoclopramide, and a clear nonparticulate antacid such as sodium citrate.

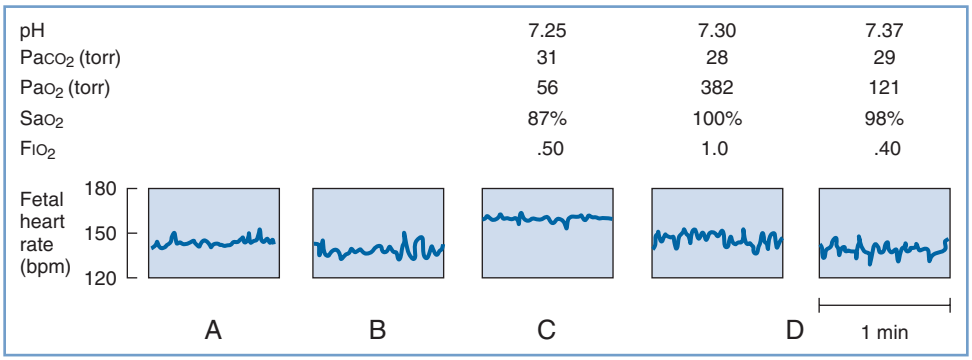

FIGURE 17-7 ■ Serial samples of the fetal heart rate tracing and corresponding maternal arterial blood gas measurements in a patient undergoing eye surgery. **A** and **B,** Baseline fetal heart rate of 140 bpm with normal variability. **C,** Fetal tachycardia and decrease in variability during inadvertent maternal hypoxemia (maternal Pao_2 = 56 mm Hg). **D,** After correction of maternal ventilation, baseline fetal heart rate and variability return. (Redrawn from Katz JD, Hook R, Barash PG. Fetal heart rate monitoring in pregnant patients undergoing surgery. Am J Obstet Gynecol 1976; 125:267.)

Choice of Anesthesia

Maternal indications and consideration of the site and nature of the surgery should guide the choice of anesthesia. No study has found an association between improved fetal outcome and any specific anesthetic technique, except for a single retrospective medical record analysis in which the use of general anesthesia was associated with a significantly lower birth weight despite similar gestational age at delivery.[190] When possible, however, local or regional anesthesia (with the exception of paracervical block) is preferred, because it permits the administration of drugs with no laboratory or clinical evidence of teratogenesis. In addition, maternal respiratory complications occur less frequently with local and regional anesthetic techniques. These techniques are suitable for cervical cerclage and urologic or extremity procedures. Most abdominal operations require general anesthesia, because the incision typically extends to the upper abdomen. This situation may create an unacceptably high risk for aspiration in a pregnant patient with an unprotected airway.

Prevention of Aortocaval Compression

Beginning at 18 to 20 weeks' gestation, the pregnant patient should be transported on her side, and the uterus should be displaced leftward when she is positioned on the operating table.

Monitoring

Maternal monitoring should include noninvasive or invasive blood pressure measurement, electrocardiography, pulse oximetry, capnography, temperature monitoring, and the use of a peripheral nerve stimulator. The FHR and uterine activity should be monitored both before and after surgery. Intraoperative FHR monitoring may be considered when technically feasible, depending on the ease of monitoring, the type and site of surgery, and gestational age (see earlier discussion).

Anesthetic Technique

General anesthesia mandates tracheal intubation beginning at 18 to 20 weeks' gestation or if the stomach is full. Denitrogenation (i.e., preoxygenation) should precede the induction of anesthesia. Although rapid-sequence induction with the application of cricoid pressure has been a long-standing practice for the induction of general anesthesia, some experts have argued that it is unnecessary in fasted pregnant women undergoing elective surgery.[191] Drugs with a history of safe use during pregnancy include thiopental, propofol, morphine, fentanyl, succinylcholine, and the nondepolarizing muscle relaxants.

A commonly used technique employs a high concentration of oxygen, a muscle relaxant, and an opioid and/or a moderate concentration of a volatile halogenated agent. Scientific evidence does not support avoidance of nitrous oxide during pregnancy,[192] particularly after the sixth week of gestation. Omission of nitrous oxide may increase fetal risk if inadequate anesthesia results or if a high dose of a volatile agent results in maternal hypotension. A cautious approach would restrict nitrous oxide administration to a concentration of 50% or less and would limit its use in extremely long operations. Hyperventilation should be avoided; rather, end-tidal CO_2 should be maintained in the normal range for pregnancy.

Rapid intravenous infusion of 500 mL of crystalloid immediately before or during the initiation of spinal or epidural anesthesia seems prudent, although the anesthesia provider should not assume that this measure will prevent maternal hypotension. Some anesthesia providers argue that colloids are more effective than crystalloids in preventing hypotension. Vasopressors should be available to treat hypotension if it occurs. Maternal hypotension should be treated aggressively. The usual precautions must be taken to guard against a high neuraxial blockade and systemic local anesthetic toxicity.

Regardless of the anesthetic technique, steps to avoid hypoxemia, hypotension, acidosis, and hyperventilation are the most critical elements of anesthetic management.

Postoperative Management

The FHR and uterine activity should be monitored during recovery from anesthesia. Adequate analgesia should be ensured with systemic or neuraxial opioids, acetaminophen, or neural blockade. Nonsteroidal inflammatory agents may be used until the second half of pregnancy, at which time they should be used with caution. Prophylaxis against venous thrombosis should be considered, especially if patients are immobilized.

KEY POINTS

- A significant number of women undergo anesthesia and surgery during pregnancy for procedures unrelated to delivery.
- Maternal risks are associated with the anatomic and physiologic changes of pregnancy (e.g., difficult intubation, aspiration) and with the underlying maternal disease.
- The diagnosis of abdominal conditions may be delayed during pregnancy, increasing the risk for maternal and fetal morbidity.
- Maternal catastrophes involving severe hypoxia, hypotension, and acidosis pose the greatest acute risk to the fetus.
- Other fetal risks associated with surgery include fetal loss, preterm labor, growth restriction, and low birth weight. Clinical studies suggest that anesthesia and surgery during pregnancy do not increase the risk for congenital anomalies.
- It is unclear whether adverse fetal outcomes result from the anesthetic, the operation, or the underlying maternal disease.

- No anesthetic agent is a proven teratogen in humans, although some anesthetic agents, specifically nitrous oxide, are teratogenic in animals under certain conditions.
- Many anesthetic agents have been used for anesthesia during pregnancy, with no demonstrable differences in maternal or fetal outcome.
- The anesthetic management of the pregnant surgical patient should focus on the avoidance of hypoxemia, hypotension, acidosis, and hyperventilation.

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PART VI

LABOR AND VAGINAL DELIVERY

Donald Caton, MD

Medical and social connotations of pain have evolved through history. Since 1847, these interpretations often influenced obstetric anesthesia. During most of the nineteenth century, patients and physicians believed that an individual's physical sensitivity to pain varied with education, social standing, and acculturation. Like the princess in Hans Christian Andersen's fairy tale who could feel a pea through 40 mattresses, refined women experienced more pain than "savages." As American suffragette Elizabeth Cady Stanton observed, "[R]efined, genteel, civilized women have worse labor pain." Commenting on her own nearly painless delivery, Stanton once quipped, "Am I not almost a savage?" Upper class women often cited their sensitivity to pain as evidence of cultural superiority, and they used this fact to justify their need for obstetric anesthesia.[1]

As the nineteenth century came to a close, the social connotations of pain also changed. Many still maintained that civilized women experienced more pain than savages. On the other hand, "sensitivity" to pain now began to signify physical deterioration rather than cultural superiority. Thus one medical book published in 1882 ascribed painful labor to "the abuses of civilization, its dissipations, and the follies of fashion." Its author, an American obstetrician named Engelmann, suggested that the idle life of upper class women led to a "relaxed condition of the uterus and abdominal walls (and) a greater tendency to malposition." He suggested that the rigorous physical life of lower class women and "savages" prepared their bodies better for childbirth.[2]

Social and cultural interpretations of childbirth pain took yet another turn in 1943, with publication of the book *Revelation of Childbirth*. Its author, Grantly Dick-Read, subsequently republished his book in the United States with the title *Childbirth Without Fear*. It marked the beginning of the natural childbirth movement.

Dick-Read combined snippets of ideas from earlier concepts to formulate his own theory. He agreed with early nineteenth-century physiologists that savages have less pain than "modern women." Unlike Engelmann, Dick-Read attributed this sensitivity to cultural rather than physical factors. According to Dick-Read, modern women had painful deliveries only because the church and culture had taught them to expect it. He said that women should be reeducated and taught that childbirth is a natural physiologic process. He opined that women would then cease to fear childbirth and thereby have less pain. Dick-Read's method, the basis for childbirth education, was a prenatal program that toughened the body with exercise and prepared the mind with facts. In yet another variation, French obstetrician Fernand Lamaze substituted Pavlovian conditioning for Dick-Read's childbirth education.[3] With Dick-Read and Lamaze, many of the social concepts of childbirth pain came full circle.[4]

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CHAPTER 18

Obstetric Management of Labor and Vaginal Delivery

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CHAPTER OUTLINE

THE PROCESS OF LABOR AND DELIVERY

Labor, which is also called *parturition*, is the process by which sufficiently frequent and strong uterine contractions cause thinning (i.e., effacement) and dilation of the cervix, thereby permitting passage of the fetus from the uterus through the birth canal.

Onset of Labor

Timing

Fewer than 10% of pregnancies end on the expected date of delivery (EDD), although the majority of births occur within 7 days of the EDD. In the United States, approximately 13% of births occur preterm (before 37 weeks' gestation), and approximately 5% to 7% of pregnancies remain undelivered at 42 weeks' gestation (14 days after the EDD, known as post-term). These rates are lower for carefully dated pregnancies.

Mechanism

The cause of the onset of labor in women—either term or preterm—remains unknown. In other mammalian species, a decrease in serum progesterone concentration in association with an increase in estrogen concentration is followed by increases in prostaglandin production, oxytocin receptors, and myometrial gap junction formation. In sheep, the fetus apparently triggers parturition through a surge in fetal cortisol production. In women, progesterone concentrations do not decline before the onset of labor and no surge in fetal cortisol secretion occurs. The laboring human uterus does manifest increases in prostaglandin production, oxytocin receptors, and myometrial gap junction formation.[1,2] As more is learned, perhaps a unifying concept of the onset of mammalian labor will emerge. Preterm and post-term deliveries both constitute important obstetric problems; and when more is understood about the mechanism of the onset of labor, new approaches to preventing the preterm and post-term onset of parturition may evolve.

Stages of Labor

By convention, labor is divided into three stages. The first stage begins with the maternal perception of regular, painful uterine contractions and ends with the complete dilation of the cervix. Complete cervical dilation is the dilation necessary to allow movement of the fetus from the uterus into the vagina. At term gestation, 10 cm approximates complete cervical dilation. Preterm fetuses require less than 10 cm of cervical dilation. The second stage of labor begins with the complete dilation of the cervix and ends with the birth of the infant. The third stage begins with the birth of the infant and ends with the delivery of the placenta. The first stage of labor can be considered the cervical stage, the second stage the pelvic stage (reflecting the descent of the fetus through the pelvis), and the third stage the placental stage. Some authorities identify a fourth stage of labor, corresponding to the first postpartum hour, during which postpartum hemorrhage is most likely to occur.

Components of Labor and Delivery

When the events that occur during labor and vaginal delivery are considered, it is helpful to think about the

TABLE 18-1 **Features Determined by Clinical Pelvimetry as Related to Pelvic Type**

	Pelvic Type			
Suboptimal Features	GYNECOID	ANDROID	ANTHROPOID	PLATYPELLOID
Promontory reached (diagonal conjugate ≤ 12 cm)	–	±	–	+
Sacrum flat/forward (versus curved)	–	+	–	+
Spines prominent (found by medical student)	–	+	+	–
Sacrosciatic notch narrow (≤ 2 fingerbreadths)	–	+	–	–
Subpubic arch narrow (acute angle)	–	+	+	–

+, Present; –, absent; ±, variable.
From Zlatnik FJ. Normal labor and delivery and its conduct. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and Gynecology. 6th edition. Philadelphia, JB Lippincott, 1990;161-88.

following three components of the process: (1) the **powers** (uterine contractions and, in the second stage, the addition of voluntary maternal expulsive efforts); (2) the **passageway** (the bony pelvis and the soft tissues contained therein); and (3) the **passenger** (the fetus). The interaction of these three components determines the success or failure of the process.

The Powers

The uterus, which is a smooth muscle organ, contracts throughout gestation with variable frequency. The parturient verifies the onset of labor when she perceives regular, uncomfortable uterine contractions. In some women, the uterus remains relatively quiescent until the abrupt onset of labor. In others, the uterus contracts several times per hour for days without causing pain or even a clear perception of uterine contractions.

During labor, the frequency, duration, and intensity of uterine contractions increase. During early labor, the contractions may occur every 5 to 7 minutes, last 30 to 40 seconds, and develop intrauterine pressures (intensity) of 20 to 30 mm Hg above basal tone (10 to 15 mm Hg). Late in the first stage of labor, contractions typically occur every 2 to 3 minutes, last 50 to 70 seconds, and are 40 to 60 mm Hg in intensity. This higher intensity reflects a more widespread propagation of the contractions, with the recruitment of more myometrial cells.

Retraction accompanies contraction as the myometrial cells shorten. The walls of the upper, contractile portion of the uterus thicken. Cervical dilation and effacement reflect the traction placed on the cervix by the contracting uterus. The passive lower uterine segment enlarges and becomes thinner as cervical tissue is pulled over the fetal presenting part by traction from the upper portion of the uterus. At the end of the first stage of labor, no cervix is palpable on vaginal examination (corresponding to complete cervical dilation). If there is no mechanical obstruction, additional uterine contractions force the fetus to descend through the birth canal. At this time, the parturient perceives an urge to defecate (reflecting pressure on the rectum). Her expulsive efforts add to the force of uterine contractions to hasten descent and shorten the second stage of labor.

The Passageway

The fetus must be of such size and conformation that there is no mechanical mismatch with the bony pelvis. At times, an ovarian or uterine tumor (e.g., leiomyoma), cervical cancer, or a vaginal septum may impede passage of the fetus through the birth canal, but these situations are unusual.

Four pelvic types have been described on the basis of the shape of the pelvic inlet (the plane bounded by the upper inner pubic symphysis, the linea terminalis of the iliac bones, and the sacral promontory) (Table 18-1).[3] The type and size of the pelvis constitute important predictors of the success of vaginal delivery.

The most common pelvic type and the one theoretically best suited for childbirth is the **gynecoid** pelvis. The flexed fetal head presents a circle to the bony pelvis; a pelvis with gynecoid features best accommodates this circle. The inlet is round or oval, with the transverse diameter only slightly greater than the anteroposterior diameter. The pelvic sidewalls are straight and do not converge, the ischial spines are not prominent, the sacrum is hollow, and the subpubic arch is wide. The absence of prominent ischial spines is an important feature, because the distance between them—the transverse diameter of the midpelvis—is the narrowest pelvic dimension. The other pelvic types are less favorable for vaginal delivery.

Radiographic pelvimetry provides much more information regarding pelvic dimensions and features than can be obtained by clinical pelvimetry alone. However, it has only a limited place in clinical management because of its poor ability to predict a successful vaginal birth. In the absence of a history of pelvic fracture or musculoskeletal disease (e.g., a dwarfing condition), there are few circumstances in which the apparent pelvic anatomy precludes a trial of labor. A pelvis with smaller-than-average dimensions may be adequate for a particular fetus if the head is well-flexed, sufficient molding (i.e., overlapping of the unfused skull bones) has occurred, and the labor is strong; thus, radiographic pelvimetry does not always predict the presence or absence of cephalopelvic disproportion.[4] Further, some risk is associated with radiographic pelvimetry. In addition to the potential for point mutations in the maternal oocytes and fetal germ cells, there is a small but apparently real increase in the incidence of malignancy and leukemia in children who were exposed to

BOX 18-1 Positions of the Occiput in Early Labor, Listed in Order of Decreasing Frequency

- Left occiput transverse (LOT)
- Right occiput transverse (ROT)
- Left occiput anterior (LOA)
- Right occiput posterior (ROP)
- Right occiput anterior (ROA)
- Left occiput posterior (LOP)
- Occiput anterior (OA)
- Occiput posterior (OP)

diagnostic radiation *in utero*. Some obstetricians use radiographic pelvimetry in cases of fetal breech presentation to assess whether fetal presentation, position, and lie are appropriate for vaginal delivery. The hope is to save a parturient from a long, futile labor and a hazardous delivery. Computed tomography and magnetic resonance imaging are associated with less or no ionizing radiation exposure, respectively; these methods are also more accurate than conventional radiographic pelvimetry. However, these methods also have limited ability to predict a successful vaginal delivery.

The Passenger

Fetal size and the relationship of the fetus to the maternal pelvis affect labor progress. The **lie** of the fetus (the relationship of the long axis of the fetus to the long axis of the mother) can be transverse, oblique, or longitudinal. In the first two, vaginal delivery is impossible unless the fetus is very immature.

The **presentation** denotes that portion of the fetus overlying the pelvic inlet. The presentation may be cephalic, breech, or shoulder. Cephalic presentations are further subdivided into vertex, brow, or face presentations, according to the degree of flexion of the neck. In more than 95% of labors at term, the presentation is cephalic and the fetal head is well flexed (i.e., vertex presentation).

The **position** of the fetus denotes the relationship of a specific presenting fetal bony point to the maternal pelvis. In vertex presentations, that bony point is the occiput. During vaginal examination, palpation of the sagittal suture and fontanels permits determination of the fetal position. Positions of the occiput in early labor are listed in Box 18-1. Other markers for position are the sacrum for breech presentation, the mentum for face presentation, and the acromion for shoulder presentation. (See Chapter 35 for a discussion of nonvertex presentations.)

The Mechanism of Labor

The *mechanism of labor* refers to the changes in fetal conformation and position (cardinal movements; Box 18-2) that occur during descent through the birth canal during the late first stage and the second stage of labor.

The first cardinal movement is **engagement,** which denotes passage of the biparietal diameter (BPD) (i.e., the widest transverse diameter of the fetal head) through the plane of the pelvic inlet. A direct clinical determination of engagement cannot be made, but obstetricians assume that engagement has occurred if the leading bony point of the fetal head is palpable at the level of the ischial spines. This is true because the distance between the leading bony point and the BPD is typically less than the distance between the ischial spines and the plane of the pelvic inlet. If the leading bony point is at the level of the spines, the vertex is said to be at zero station. If the leading bony point is 1 cm above the level of the spines, the station is designated as −1. Similarly, +1, +2, and +3 indicate that the leading bony point is 1, 2, and 3 cm below the ischial spines, respectively (Figure 18-1). At +5 station, delivery is imminent. *Station* refers to palpation of the leading bony point. Often marked edema of the scalp (i.e., caput succedaneum) occurs during labor. In such cases, the bony skull may be 2 to 3 cm higher than the scalp.

BOX 18-2 The Cardinal Movements of Labor

- Engagement
- Descent
- Flexion
- Internal rotation
- Extension
- External rotation
- Expulsion

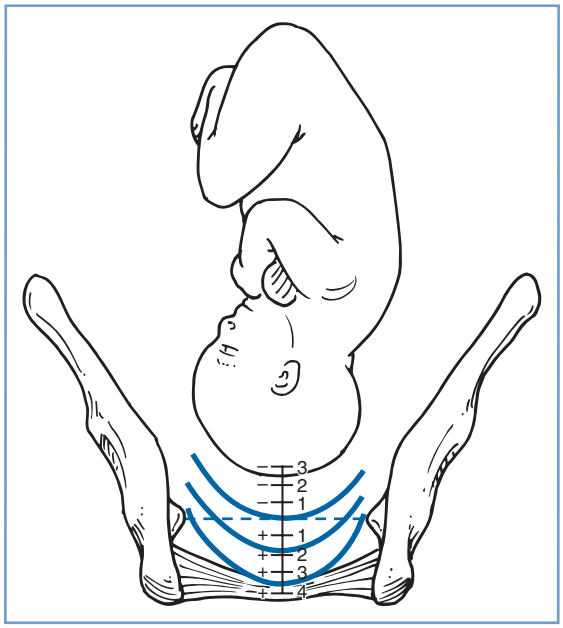

FIGURE 18-1 ■ Stations of the fetal head. (Redrawn from Zlatnik FJ. Normal labor and delivery and its conduct. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and Gynecology. 7th edition. Philadelphia, JB Lippincott, 1994:116.)

The second cardinal movement is **descent,** although it is artificial to separate descent from the other movements because descent occurs throughout the birth process. The third cardinal movement is **flexion**. A very

small fetus can negotiate the average maternal pelvis without increased flexion. However, under the usual circumstances at term, the force from above and resistance from below enhance flexion of the occiput (Figure 18-2).

The fourth cardinal movement is **internal rotation**. At the level of the midpelvis, the fetus meets the narrowest pelvic dimension, which is the transverse diameter between the ischial spines. Because the BPD of the fetal head is slightly smaller than the suboccipitobregmatic diameter, in most labors the vertex negotiates the midpelvis with the sagittal suture in an anteroposterior direction. If this did not occur, a larger-than-necessary diameter would be forced to pass through the narrowest portion of the pelvis. Internal rotation describes the change in the position of the vertex from occiput transverse or oblique to anteroposterior. The occiput tends to rotate to the roomiest part of the pelvis; thus, in gynecoid pelves, the fetus is delivered in an occiput anterior position.

The next cardinal movement is **extension,** which occurs as the fetal head delivers (Figure 18-3). Subsequently, the occiput rotates to the side of the back (**external rotation**) as the shoulders pass through the midpelvis in an oblique diameter. The anterior shoulder moves under the pubic symphysis. With gentle downward traction, it passes from the birth canal, and **expulsion** of the remainder of the fetus occurs.

This description recounts events in the typical gynecoid pelvis. Abnormalities of the pelvis affect the mechanism of labor in specific ways. In an **anthropoid** pelvis, the anteroposterior diameter of the pelvic inlet exceeds the transverse diameter. Often internal rotation to the occiput posterior position rather than the occiput anterior position occurs. Because the pelvis is narrow transversely, further descent of the vertex occurs with the occiput in the posterior position. Delivery occurs with the occiput in the posterior position, or rotation to the occiput anterior position occurs just before delivery. In cases of persistent occiput posterior position, delivery occurs by flexion rather than extension of the fetal head (see Figure 18-3).

In **platypelloid** pelves, internal rotation may not take place. The widest diameter is the transverse diameter, and descent of the vertex may occur with the occiput in the transverse position; rotation to the occiput anterior position occurs only at delivery.

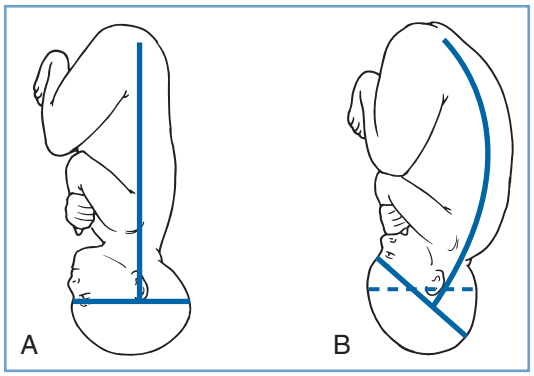

FIGURE 18-2 ■ **A,** Relation of the head to the vertebral column before flexion. **B,** Relation of the head to the vertebral column after flexion. (Redrawn from Zlatnik FJ. Normal labor and delivery and its conduct. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and Gynecology. 6th edition. Philadelphia, JB Lippincott, 1990:174.)

Clinical Course

Admission

When a patient enters the labor and delivery unit, the first question that must be asked is "why?" Did she come because of regular, painful uterine contractions; decreased fetal activity; vaginal bleeding; ruptured membranes; or some other reason? If the tentative diagnosis is labor, is she at term?

The time of the onset of labor and the presumed status of the membranes should be determined. Observation of the patient's demeanor coupled with the assessment of cervical effacement and dilation will signal whether the patient is in early or advanced labor. Examination of the cervix is deferred in patients with vaginal bleeding in the second half of pregnancy, unless placenta previa has been ruled out by ultrasonography, to avoid exacerbation of bleeding. To prevent infection, cervical examination may also be deferred in patients with premature rupture of membranes and no labor.

The obstetrician also directs attention to the second patient: the fetus. Abdominal examination or ultrasonography is used to establish presentation and an estimate of

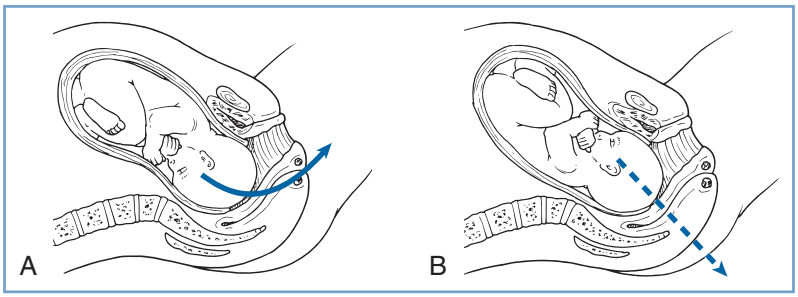

FIGURE 18-3 ■ Vertex presentations. **A,** Occiput anterior position. **B,** Occiput posterior position. (Redrawn from Zlatnik FJ. Normal labor and delivery and its conduct. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and Gynecology. 6th edition. Philadelphia, JB Lippincott, 1990:174.)

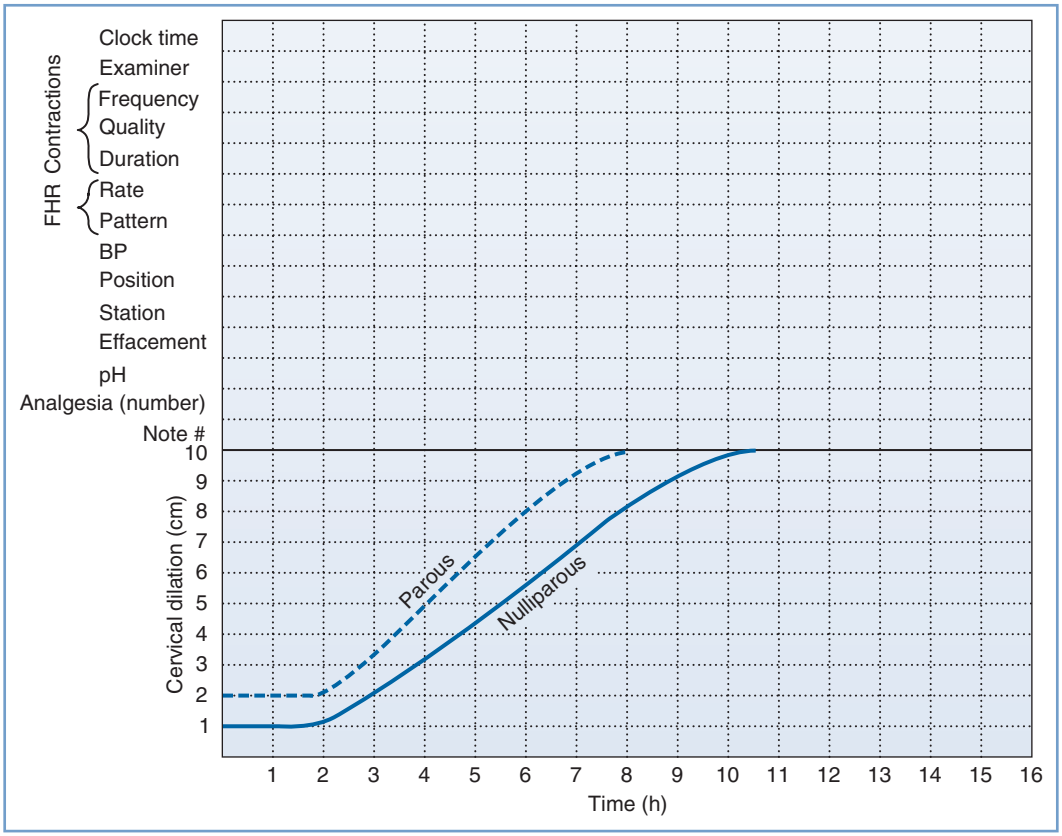

FIGURE 18-4 ■ **Flow sheet for charting labor progress.** (From Zlatnik FJ. Normal labor and delivery and its conduct. *FHR,* fetal heart rate. *BP,* blood pressure. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and Gynecology. 7th edition. Philadelphia, JB Lippincott, 1994:107.)

fetal size. With most obstetric services, external electronic fetal heart rate (FHR) monitoring is used on admission to assess fetal condition. The baseline rate and variability and the presence or absence of accelerations and decelerations are of interest.

Subsequent Care

The maternal vital signs and FHR are recorded periodically. In some obstetric services, continuous electronic FHR monitoring is used universally; with other services, it is monitored via intermittent auscultation. In low-risk patients, recording the FHR every 30 minutes in the first part of the first stage of labor, every 15 minutes in the latter part of the first stage, and every 5 minutes in the second stage is perfectly acceptable. During early labor, the patient may ambulate or assume any position of comfort on the labor bed or in a chair. During advanced labor, many women choose to lie down. Choices concerning analgesia or anesthesia are made according to the patient's wishes. Figure 18-4 shows a flow sheet (partogram) that may be useful for charting the course of labor.

During labor, those providing obstetric care must focus on the following two critical questions:

1. Is the fetus tolerating labor in a satisfactory fashion, or is there evidence of fetal compromise (see Chapter 8)?
2. Is the labor progress normal?

Labor Progress: The Labor Curve

One of the central tasks of those providing intrapartum care is to determine whether labor is progressing normally and, if not, to determine the significance of the delay and what the response should be. Parity is an important determinant of labor length. (*Parity* refers to previous pregnancies of at least 20 weeks' gestation. A pregnant woman who is gravida 2, para 1 is pregnant for the second time, and her first pregnancy resulted in delivery after 20 weeks' gestation.)

A generation of obstetricians is indebted to Emanuel Friedman, whose landmark studies of labor provide a framework for judging labor progress. Friedman's approach was straightforward: He graphed cervical dilation on the *y*-axis and elapsed time on the *x*-axis for thousands of labors. He considered nulliparous and parous patients separately, and he determined the statistical limits of normal.[5] The curve of cervical dilation over time is sigmoid shaped (Figure 18-5).

Most authorities consider Friedman's most important contribution to be his separation of the latent phase from the active phase of the first stage of labor. Many hours of regular, painful uterine contractions may take place with little appreciable change in the cervix. During this latent (or preparatory) phase, the cervix may efface and become softer. Quite abruptly, the active (or dilation) phase begins, and regular increases in cervical dilation are

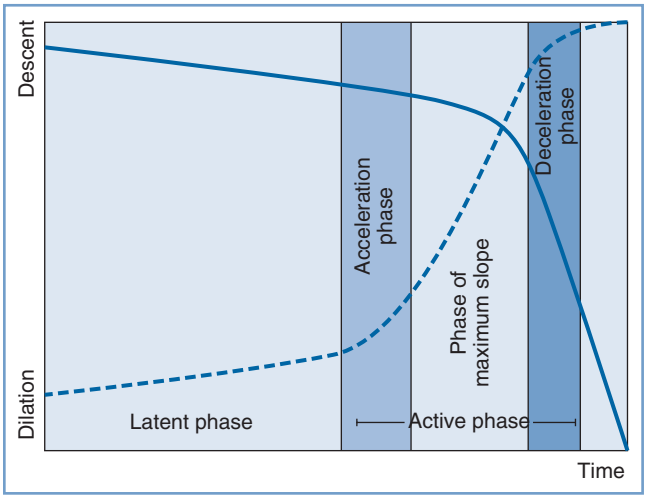

FIGURE 18-5 ■ **The Friedman curve.** (From Friedman EA. Patterns of labor as indicators of risk. Clin Obstet Gynecol 1973; 16:172-83.)

TABLE 18-2 Rate of Spontaneous Cervical Dilatation by Parity

Cervical Dilation	Nulliparous Median Time (h) (95th Percentile)	Parous Median Time (h) (95th Percentile)
First Stage		
4 to 5 cm	1.3 (6.4)	1.4 (7.1)
5 to 6 cm	0.8 (3.2)	0.8 (3.4)
6 to 7 cm	0.6 (2.2)	0.5 (1.8)
7 to 8 cm	0.5 (1.6)	0.4 (1.2)
8 to 9 cm	0.5 (1.4)	0.3 (1.0)
9 to 10 cm	0.5 (1.8)	0.3 (0.9)
Second Stage		
10 cm to delivery (epidural)	1.1 (3.6)	0.4 (2.0)
10 cm to delivery (no epidural)	0.6 (2.8)	0.2 (1.3)

Modified from Zhang J, Landy HJ, Branch DW, et al.; for the Consortium on Safe Labor. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet Gynecol 2010; 116:1281-7.

expected over time. The transition from the latent to the active phase of the first stage of labor does not occur at an arbitrary cervical dilation but rather is known—in retrospect—by change in slope of the cervical dilation curve. Peisner and Rosen[6] evaluated the progress of labor for 1060 nulliparous women and 639 parous women. After excluding women with protracted or arrested labor, these researchers noted that 60% of the women had reached the latent-active phase transition by 4 cm of cervical dilation and 89% did so by 5 cm.

A *nulliparous* woman may labor for 20 hours without achieving appreciable cervical dilation; 14 hours is the limit of the latent phase in the *parous* woman. Difficulty in assigning length to the latent phase lies not with its end (determined from the change in slope of the cervical dilation curve) but rather with its beginning. The onset of labor is self-reported by the parturient. The uterus contracts throughout gestation, and the level of prelabor uterine activity and its perception are variable. Often both the patient and the physician are uncertain as to exactly when labor started.

According to Friedman, in the active phase of the first stage of labor, a nulliparous woman's cervix should dilate at a rate of at least 1.2 cm per hour and a parous woman's cervix should dilate at least 1.5 cm per hour. (The slopes of the dilation curves in Figure 18-5 represent the lower limits of normal.) If a woman's cervix fails to dilate at the appropriate rate during the active phase of labor, she is said to have **primary dysfunctional labor**. Graphically, her cervical dilation "falls off the curve." If cervical dilation ceases during a 2-hour period in the active phase of labor, **secondary arrest of dilation** has occurred.

More recent studies have reported slower rates of cervical dilation and engendered an ongoing transition toward the use of the "contemporary labor curve."[7,8] These curves reveal that cervical dilation is particularly slow prior to 6 cm and that the deceleration phase described by Friedman is usually absent. Therefore, 6 cm rather than 4 cm of cervical dilation more accurately reflects the start of the active phase in contemporary labor curves.[8] Furthermore, in the active phase, absence of cervical change over at least 4 hours rather than 2 hours is a better definition of labor arrest. Estimates of contemporary rates of cervical dilation from 4 cm (when patients are often admitted) by parity are presented (Table 18-2). Nulliparous women have a slower cumulative rate of cervical dilation overall. However, prior to 6 cm of dilation, the times required to dilate 1 cm are similar between nulliparous and parous women.

Abnormalities of the latent phase and active phase differ in associated factors, apparent causes, and significance. A prolonged latent phase is more likely if labor begins "before the cervix is ready."[5] Just as there is a wide range of prelabor uterine activity, so too is there a wide range of cervical softness, effacement, and dilation at the start of labor. In some women, appreciable cervical softening, effacement, and dilation take place in late pregnancy; thus, when clinical labor begins, the cervix may already be 3 to 4 cm dilated and completely effaced. Alternatively, in other women, there is no cervical effacement or dilation at the start of labor. Given these differences, it is not surprising that varying amounts of uterine contractile work are needed to cause dilation of the cervix. The most common factor associated with a prolonged latent phase is an "unripe" cervix at the start of labor. Some women with a prolonged latent phase are not in true labor at all but are in "false labor"; this diagnosis is made in retrospect. After hours of regular, painful contractions, uterine activity may cease without the occurrence of appreciable cervical dilation. Several hours or days later, the patient reappears in true labor. During the latent phase of labor, it is not known with certainty whether a woman is in true or false labor.

Recent studies refute the dictum that a prolonged latent phase alone is not associated with fetal compromise or cephalopelvic disproportion.[9,10] An increased risk

for cesarean delivery, chorioamnionitis, endometritis, excessive blood loss, depressed Apgar scores, and need for neonatal resuscitation have all been associated with a prolonged latent phase. An ongoing increase in the use of labor induction may be a mediating factor. Primary dysfunctional labor and arrest of dilation during the active phase may also indicate cephalopelvic disproportion.[5,11,12] Friedman's original work suggested that an arrest of dilation during the active phase was associated with the need for cesarean delivery nearly half of the time. Later studies suggest a lower percentage, but it is clear that women who experience active-phase arrest of dilation are more likely to require abdominal delivery than women with normal labor progress during the active phase. Friedman's analysis suggested that active-phase abnormalities pose a threat to the fetus, especially if they are combined with operative vaginal delivery.[13] A later study of women who delivered in the modern era of electronic FHR monitoring and decreased frequency of mid-forceps deliveries suggested that arrest disorders by themselves do not have adverse perinatal consequences.[12]

In summary, the contemporary view is that delays in the latent phase of the first stage of labor may be associated with fetopelvic disproportion or the need for cesarean delivery, but this requires confirmation.[10] Delays in the active phase predict fetopelvic disproportion, although not with precision. Given current obstetric practice and fetal monitoring techniques, it is unclear whether first-stage labor abnormalities are intrinsically associated with neonatal depression at delivery.[14]

Amniotomy

The intact amnion serves as the vessel that contains the amniotic fluid and helps protect the uterine contents from the microbial flora of the vagina. The amniotic fluid provides mechanical protection for the fetus and umbilical cord and allows growth and movement.

In the absence of intervention, the membranes generally rupture at the onset of labor or near full cervical dilation. If the membranes are intact, should they be artificially ruptured during the course of labor? If so, when? Because there is concern about infection once the membranes are ruptured, the performance of an amniotomy commits the mother to delivery. For this reason, it should not be done during the latent phase of labor, unless (1) there is an indication for effecting delivery and/or (2) the patient is close to her EDD, the cervix is favorable, and the physician can confidently predict that labor will progress easily.

Advantages of amniotomy during the active phase of the first stage of labor are that (1) the ruptured membranes permit the placement of a fetal electrocardiographic electrode, which can provide more consistent information than external FHR monitoring; (2) the amniotic fluid can be inspected for the presence or absence of meconium; and (3) amniotomy shortens time to delivery.[15,16] Disadvantages of amniotomy during the active phase of the first stage of labor are that it may result in increased scalp edema (i.e., caput succedaneum, which has no clinical significance) and that there may be a greater likelihood of variable decelerations of the FHR. If there is a nonvertex presentation or the vertex is high in the pelvis and not well applied to the cervix, amniotomy is deferred to decrease the risk for prolapse of the umbilical cord.

Second Stage of Labor

When the cervix has been completely retracted to form the lower uterine segment and is therefore not palpable on vaginal examination, full or complete dilation has been achieved, and the second stage of labor begins. Strong uterine contractions coupled with voluntary expulsive efforts by the parturient cause the fetal presenting part to descend through the pelvis, resulting in delivery. At complete cervical dilation, there is frequently an increase in bloody show, the parturient may vomit, and, in the absence of anesthesia, she may complain that she needs to defecate. This sensation of needing to "bear down" encourages strong Valsalva maneuvers during uterine contractions. The effect of this sensation on the efficiency of "pushing" efforts during the second stage is reflected by the suggestion that the duration of the second stage of labor varies not only according to parity but also with the presence or absence of epidural analgesia.[14] A second stage longer than 2 hours may be considered prolonged for a nulliparous woman without epidural analgesia, but 3 hours are granted if the patient has epidural analgesia. For the parous woman the time limits are 1 and 2 hours, respectively.

The contemporary obstetrician, although less concerned about the elapsed time during the second stage of labor than were earlier obstetricians, continues to balance the risks of prematurely performing a cesarean delivery with the risks of adverse outcomes associated with a prolonged second stage. A generation ago, the teaching was that a long second stage meant trouble.[17] It often did, for at least two reasons. First, if cephalopelvic disproportion existed, the second stage was prolonged; this often resulted in a difficult operative vaginal delivery and serious fetal trauma. Second, umbilical cord compression may become severe with descent of the presenting part during the second stage of labor. If FHR monitoring was not performed conscientiously, considerable fetal/neonatal compromise could occur in association with delayed delivery. Cord arterial blood pH varies inversely with the length of the second stage of labor. In one large population-based cohort study, a second-stage duration longer than recommended was associated with an increase in maternal obstetric trauma, postpartum hemorrhage, infection, birth depression, and admission to the neonatal intensive care unit in both nulliparous and parous women.[18] However, the contemporary view is that the second stage of labor does not need to be terminated at any arbitrary time provided that progress in descent continues and the FHR pattern is reassuring. Clearly it is inappropriate to perform a difficult forceps delivery or vacuum extraction simply because an arbitrary time limit has elapsed.[19] Indeed, recent studies suggest that obstetricians should consider allowing a longer second-stage duration (than heretofore recommended) to decrease the cesarean delivery rate.[7,14]

If the parturient is allowed to choose her own positions during labor and delivery, she does not stay in one place.[20] Without instruction from birth attendants, the parturient frequently chooses to walk or sit in a chair during early labor. Late in the first stage, however, she often returns to the labor bed. During the second stage of labor, some women assume the squatting position, whereas others, with their legs supported by the nurse and the father of the baby, assume a semi-sitting position. The goal is to achieve a position in which the parturient's bearing-down efforts are most effective. The patient should avoid the supine position, which results in aortocaval compression. Aortocaval compression seems to be less severe with the patient in the semi-sitting position, and it is avoided altogether with the patient in the lateral position. Indeed, it is perfectly acceptable for the patient to push and deliver while remaining in the left lateral position. A vaginal examination during a contraction may provide information as to which position is best for a particular individual.

Rarely, as the fetal head distends the perineum shortly before delivery, an episiotomy may be performed. This incision extends either directly posteriorly from 6 o'clock (midline) or in a 45-degree angle to either side (mediolateral). The former causes less discomfort, is more anatomic, and is easier to repair than the latter. The mediolateral episiotomy's advantage is that extension through the anal sphincter and rectal mucosa is less likely to occur, but its major disadvantage is that it may cause more bleeding or severe postpartum pain. (If the patient has an epidural catheter, the anesthesia provider may give additional epidural local anesthetic or opioid to provide postpartum analgesia.)

The place of episiotomy in contemporary obstetrics is restricted.[21] In the past, episiotomy was advocated not only to shorten labor but also to protect the woman against the subsequent development of uterine prolapse, cystocele, and rectocele. An episiotomy hastens delivery, but only by a few minutes. Tears involving the anal sphincter (third degree) and rectal mucosa (fourth degree) are more common after midline episiotomy than if episiotomy is not performed; in the absence of an episiotomy, however, anterior periurethral lacerations are common. Although the latter rarely cause immediate problems, scientifically valid data on long-term outcome are lacking. Given the recognized association between midline episiotomies and third- and fourth-degree tears, the fact that these tears may be associated with long-term morbidity, and the failure to observe any benefits to routine episiotomy, more restrictive use of this incision is now recommended.[21,22] For example, an episiotomy may be indicated in some instances of operative vaginal delivery of a large infant, with suspected fetal compromise, or to manage shoulder dystocia.

Third Stage of Labor

The third stage of labor begins with the delivery of the infant and ends with the delivery of the placenta. The placenta typically separates from the uterine wall within a few contractions after delivery of the infant, and expulsion follows a few minutes later. Signs of placental separation are listed in Box 18-3.

BOX 18-3 Signs of Placental Separation

- The uterus rises in the maternal abdomen.
- The shape of the uterus changes from discoid to globular.
- The umbilical cord lengthens.
- A gush of blood frequently occurs.

When the placenta has separated from the uterine wall, gentle traction on the umbilical cord, coupled with suprapubic pressure to elevate the uterus, serves to deliver the placenta and membranes. In the absence of excessive bleeding, the obstetrician waits for the signs of placental separation before attempting to deliver it. If traction is exerted on the umbilical cord before the placenta has separated, problems result. The least serious—but nonetheless embarrassing—complication involves separating the umbilical cord from the placenta. This tear in the cord leads to bleeding, which is of no concern because the blood is fetoplacental blood that would be discarded; however, the obstetrician's reputation for gentleness suffers because the detached segment of umbilical cord is held with the placenta remaining *in situ*. A much more serious problem is uterine inversion, which can occur in a case of fundal implantation of the placenta. If the placenta has not separated and the umbilical cord does not break, excessive traction turns the uterus inside out, resulting in severe hemorrhage (see Chapter 38).

If the placenta does not separate in a timely fashion after delivery (prolonged third stage) or if significant bleeding occurs, manual removal of the placenta is indicated. Although some obstetricians advocate performing this procedure with sedation or systemic analgesia, neuraxial or general anesthesia is ideal. The obstetrician's hand is then passed into the uterine cavity, and the edge of the placenta is identified. The hand is used as a trowel to separate the placenta from the uterine wall. If the obstetrician cannot easily develop a plane between the placenta and the uterine wall, the diagnosis of **placenta accreta** should be considered. Placenta accreta typically results in severe hemorrhage, which frequently mandates emergency hysterectomy (see Chapter 38). Classically, a duration of 30 minutes has been used to define a prolonged third stage. However, in the absence of significant bleeding more time may be allowed for placental separation, particularly at earlier gestational ages when it may be difficult to access the uterus.

After delivery, and either before or after the placenta has been removed, uterotonic agents are administered to reduce bleeding. **Oxytocin** is given intravenously in a dilute solution (e.g., starting at an infusion rate of 20 to 80 units/h), or 10 units are given intramuscularly. Bolus intravenous injection of oxytocin can cause hypotension and should be avoided (see Chapter 38).[23]

If the uterus does not respond to oxytocin, other ecbolic agents can be tried. **Methylergonovine** (Methergine, 0.2 mg) has long been available for intramuscular administration. It contracts vascular smooth muscle and may cause hypertension. Methylergonovine should not be given intravenously except in cases of

severe, life-threatening hemorrhage. In such cases, the physician should give the drug slowly and carefully monitor the maternal blood pressure.

15-Methylprostaglandin $F_{2\alpha}$ (carboprost, Hemabate) is a newer ecbolic agent. Given intramuscularly, 0.25 mg of 15-methylprostaglandin $F_{2\alpha}$ has been demonstrated to be an effective uterotonic agent when other drugs have failed.[24] It can also cause hypertension, but the hypertension is typically not as severe as that associated with administration of methylergonovine. More important, 15-methylprostaglandin $F_{2\alpha}$ may cause bronchospasm and is relatively contraindicated in patients with asthma.

Most obstetricians in the United States do not use ecbolic agents until the placenta has been delivered, whereas European obstetricians typically administer an ecbolic agent immediately after delivery of the infant or even with delivery of the anterior shoulder. The timing probably does not matter.[25] Immediately after the delivery of the placenta, if the obstetrician suspects an abnormality, the hand can be passed into the uterine cavity. Within several minutes, however, the cervix and birth canal contract. Subsequent uterine exploration typically requires the administration of anesthesia.

Fourth Stage of Labor

Many obstetricians consider the first 60 minutes after delivery of the placenta to be the fourth stage of labor. Labor is completed, but this designation emphasizes that the patient must be watched carefully for bleeding. More than 90% of cases of postpartum hemorrhage result from uterine atony. If uterine atony is not identified during the first hour after delivery, it is unlikely to occur subsequently. The patient should be evaluated frequently to be certain that excessive bleeding is not occurring and that the uterus remains contracted. Considerable blood loss can occur in the presence of "normal" vital signs; a modest increment in additional blood loss can then be followed by profound shock. Uterine relaxation and excessive bleeding after delivery are initially treated with uterine massage and further ecbolic drug administration (see Chapter 38). Management options for persistent hemorrhage include uterine tamponade, surgery, and vascular embolization.

LABOR PROGRESS: FIVE MANAGEMENT QUESTIONS

The purpose of this section is to provide a step-by-step approach to the management of the laboring woman by serially posing and answering the following five critical questions:

1. *Is the patient in labor?* If the answer is "Yes," certain factors must be considered before proceeding. Is the patient at term? If she is preterm, is she a candidate for antenatal corticosteroids and tocolytic therapy? If the patient is at term, are there medical or obstetric conditions that affect management? Abnormal fetal size or presentation, twin gestation, preeclampsia, and vaginal bleeding are obstetric factors that may alter management of labor from the outset. If a singleton vertex presentation is identified in a patient without complications, the physician proceeds to the following question.
2. *Is the labor progress abnormal?* If progress is normal according to the labor curve, no problem exists. If progress is abnormal, the physician proceeds to the following question.
3. *Is the abnormality in the active phase?* An apparent prolongation of the latent phase may represent false labor. In the absence of some other indication for effecting delivery, the obstetrician should not administer oxytocin or perform amniotomy, which would involve committing the patient to a long labor with the risk for failure and the potential need for an unnecessary cesarean delivery. Long latent phases do increase patient anxiety and fatigue; reassurance is essential. At this point, ambulation and sedation are alternatives that may be selected on an individual basis, with input from the woman. If false labor has occurred, contractions will cease over time, or the patient will enter the active phase. Specifically, a diagnosis of failed induction in the latent phase should require at least 12 to 24 hours after rupture of membranes. If primary dysfunctional labor is the diagnosis or if a secondary arrest of dilation has occurred during the active phase, the physician is faced with an abnormality that may indicate cephalopelvic disproportion, a mechanical obstruction to delivery. The next question can then be asked.
4. *Is the fetus tolerating labor?* Although the FHR pattern should be monitored from admission until delivery, a delay in the active phase of labor calls for a reassessment. If the FHR pattern is nonreassuring, the physician should effect delivery. If not, the next question is asked.
5. *Does the pelvis appear to be adequate for the infant?* An active-phase delay indicates either insufficient uterine contractile effort to dilate the cervix or a mechanical obstruction to delivery. Obviously this is a critical issue, because the therapeutic alternatives are very different. If the pelvis is clinically small and/or the fetus is large and the labor seems strong (e.g., intense uterine contractions occurring every 2 minutes), the choice is cesarean delivery. If the fetopelvic relationship is favorable for vaginal delivery and the contractions are infrequent, the choice is intravenous oxytocin, amniotomy, or both. In the vast majority of cases, however, the obstetrician is uncertain as to whether oxytocin augmentation will result in successful vaginal delivery or whether cesarean delivery will ultimately be required despite oxytocin augmentation. Given the uncertainty about whether mechanical obstruction or insufficient uterine activity is the problem, the proper choice typically is to administer oxytocin to correct the latter, a decision that recognizes that, if the former is present, the attempt will ultimately fail. Data support longer periods of oxytocin augmentation for nonprogressive active-phase labor (at least 4 to 6 hours) provided the FHR pattern is reassuring.[26]

The benefit of intravenous oxytocin administration for labor arrest during the active phase of the first stage of labor is that the majority of the time it succeeds and cesarean delivery is avoided.[11] The risks of oxytocin stimulation are both maternal and fetal. If mechanical obstruction to delivery exists, greater uterine activity predisposes the patient to uterine rupture, which is one of the gravest obstetric complications. Multiparity and a scarred uterus are additional predisposing factors to uterine rupture. Oxytocin has an antidiuretic effect, and in the past there were reports of water intoxication with seizures and even coma and death as iatrogenic complications of its use. In these cases, oxytocin was administered over many hours (often days) in electrolyte-free solutions, with little attention paid to maternal urine output; infusion of electrolyte-containing solutions and close attention to the parturient's fluid balance should make this a theoretical rather than a practical concern. However, *uterine tachysystole with FHR decelerations* is a real concern when infusing oxytocin. The force generated during uterine contractions interrupts blood flow through the intervillous space because placental perfusion occurs during periods of uterine relaxation, and uterine contractions can be regarded as episodes of "fetal breath-holding." If the contractions are occurring very frequently (e.g., at intervals less than 2 minutes apart, defined as uterine tachysystole), there may be insufficient time between contractions for placental gas exchange, the fetus may become hypoxemic, and fetal compromise may result. Continuous observation permits a timely diagnosis of uterine tachysystole. Decreasing the infusion rate, temporarily stopping the infusion, or, rarely, giving terbutaline promptly corrects the problem.

Currently, in the United States, oxytocin for inducing or augmenting labor is given intravenously, typically by infusion pump. Continuous electronic FHR monitoring is used, and a physician or nurse constantly monitors the FHR pattern. Although the foregoing procedures are quite uniform from service to service, the selected doses of oxytocin are not.

The variability in protocols for oxytocin induction or augmentation of labor reflects confusion in the literature.[27-31] The goal is to increase uterine activity efficiently to dilate the cervix without causing fetal compromise as a result of uterine tachysystole. However, the best way to do this is unclear. Recommended starting doses of oxytocin vary from 1 to 6 mU/min, and additional drug is administered until a satisfactory labor pattern is achieved. Dosage increments typically vary from 1 to 6 mU at intervals of 15 to 40 minutes. High-dose oxytocin regimens involve the use of higher starting doses and incremental doses of 4 mU/min or greater. A systematic review of available trials suggests that the use of a higher dose regimen for labor augmentation is associated with shortened labor and a decrease in the incidence of cesarean delivery.[32,33]

The Active Management of Labor

Dystocia, which is also called abnormal labor progress, both directly and indirectly (through subsequent repeat cesarean deliveries) is the single most important reason for the high rate of abdominal delivery in the United States. Concern for the high cesarean delivery rate has created interest in the remarkable results achieved in the 1980s with the use of active management of labor at the National Maternity Hospital in Dublin, Ireland.[27,34] Components of the active management of labor include (1) a rigorous definition of labor, (2) early amniotomy, (3) constant nursing attendance, (4) the demand for continued progress in cervical dilation (1 cm or more per hour), (5) vigorous oxytocin stimulation for lack of progress, and (6) a "guarantee" that the parturient's stay in the labor unit will last no longer than 12 hours. In Dublin, these practices were associated with a cesarean birth rate of less than 5%; however, the rate has been higher in more recent years.

The introduction of the active management of labor in other obstetric services has been associated with lower cesarean delivery rates than those among historic controls. One randomized trial indicated that active management shortened labor, reduced the incidence of cesarean delivery for dystocia, and resulted in fewer maternal infectious complications without increasing maternal or neonatal morbidity.[35] However, data from other clinical trials and a Cochrane review suggest that active labor management is associated with little or no decrease in the cesarean delivery rate.[36,37]

SPECIAL SITUATIONS

Premature Rupture of Membranes

Premature rupture of the membranes (PROM) is defined as a rupture of the fetal membranes (i.e., the chorioamnion) before the onset of labor. It may occur preterm (before 37 weeks' gestation) or at term.

Preterm Premature Rupture of Membranes

The most significant complication of preterm PROM is preterm birth.[38] Although the length of the *latent period* (the interval between membrane rupture and the onset of labor) is inversely related to gestational age, only one in five women with preterm PROM have latent periods exceeding 1 week. Indeed, PROM is the precipitating factor in nearly one third of preterm deliveries. Other risks of preterm PROM include chorioamnionitis and prolapse of the umbilical cord. If membrane rupture occurs during the second trimester and if the fetus experiences a long exposure to oligohydramnios, there is risk for pulmonary hypoplasia, perinatal death, neonatal sepsis, and orthopedic deformities.

Current management of preterm PROM is conservative. After the diagnosis is confirmed by inspection and nitrazine and fern testing (or rarely by ultrasound-guided instillation of dye into the amniotic fluid and observation of its passage vaginally),[39] electronic FHR monitoring is used to identify variable FHR decelerations that signal umbilical cord compression. The mother is also evaluated for fever and uterine tenderness, which may indicate chorioamnionitis. If these are absent, the clinician awaits the onset of labor or the subsequent development of infection. The adjunctive use of maternally administered

TABLE 18-3 Natural History of Premature Rupture of the Membranes at Term

Element	Percentage
Prevalence	10
Spontaneous labor within 24 hours	90
If cervix is unfavorable and no labor at 6 hours, percent laboring by 24 hours	60
Chorioamnionitis:	
Latent period < 24 hours	1-2
Latent period > 24 hours	5-10
Significant neonatal infection if chorioamnionitis is present	10

Modified from Zlatnik FJ. Management of premature rupture of membranes at term. Obstet Gynecol Clin North Am 1992; 19:353-64.

corticosteroids to enhance fetal pulmonary maturity and/or antibiotics to prevent chorioamnionitis and delay the onset of labor is indicated.[39-42] Current evidence does not support the long-term use of tocolytic therapy to prolong pregnancy.[43] On many obstetric services, delivery is effected routinely at 34 weeks (a point beyond which the rate of severe neonatal morbidity and mortality is very low) or after documentation of fetal pulmonary maturity.

Term Premature Rupture of Membranes

Approximately 10% of term pregnancies are complicated by PROM; the natural history is summarized in Table 18-3.[44]

Although chorioamnionitis is more likely to occur preterm than at term with PROM, no clear relationship exists between the length of the latent period and chorioamnionitis in the preterm patient.[45] By contrast, chorioamnionitis at term is more likely if the latent period exceeds 24 hours. The relationship between prolonged latency and chorioamnionitis accounts for the usual practice in the United States of oxytocin induction of labor if the woman with PROM at term is not in labor by 6 to 12 hours after membrane rupture. Hannah et al.[46] conducted a trial comparing induction with expectant management in more than 5000 women with PROM at term; these investigators found similar rates of cesarean delivery and neonatal infection in the two groups. Oxytocin induction led to a lower rate of maternal infection than expectant management.

Chorioamnionitis

If chorioamnionitis develops, the uterus must be emptied. Intrapartum antibiotic administration improves the outcome for both mother and infant.[47] Ampicillin and gentamicin are often chosen to combat group B streptococcus and *Escherichia coli*, which are important neonatal pathogens. Because no relationship exists between the number of hours that chorioamnionitis has been present and perinatal outcome,[48-50] chorioamnionitis alone is not an indication for abdominal delivery. Antibiotics, oxytocin, and close observation of the mother and fetus are indicated.

TABLE 18-4 The Bishop Cervix Score

	Score			
Component	0	1	2	3
Dilation (cm)	0	1-2	3-4	5+
Effacement (%)	0-30	40-50	60-70	80+
Station	–3	–2	–1/0	+1
Consistency	Firm	Medium	Soft	
Position	Posterior	Mid	Anterior	

From Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964; 24:266-8.

Induction of Labor

Induction of labor can be defined as a surgical or medical intervention that leads to uterine contractions that progressively dilate the cervix. Because elective and indicated inductions differ in terms of eligibility criteria and the methods used, they are considered separately.

Elective Induction

The rationale for elective induction of labor is convenience, both for the patient and for the physician. Because it is elective, the delivery should be easily accomplished and the risks should approach zero. Factors associated with the success of elective induction of labor include (1) a parous patient, (2) a singleton vertex presentation, (3) a certain gestation of at least 39 weeks, (4) a favorable cervix, and (5) no contraindications to labor and vaginal delivery. The Bishop score (Table 18-4) helps quantitate the favorability of the cervix; the higher the score, the shorter the labor and the less likely induction will fail.[51] Bishop[51] observed that a score of 9 or greater was not associated with failure. Friedman et al.[52] determined that the Bishop score primarily predicts the latent phase of labor. This finding is not surprising, because a high Bishop score indicates that the cervix is ready to dilate with uterine contractions (i.e., the cervix will soon enter the active phase). By contrast, a low score suggests that many hours of uterine contractions may be needed to soften and efface the cervix. When the components of the Bishop score are considered separately in terms of their effects on the latent phase, dilation is most critical. Effacement, station, and consistency are each half as important, and position has little effect.[52]

With a favorable cervix, elective induction is begun by performance of an amniotomy with or without concomitant oxytocin administration, which some obstetricians reserve for the patient who is not experiencing uterine contractions 4 to 6 hours after amniotomy. Amniotomy is typically performed early in the morning and is followed by delivery in the afternoon. Elective inductions have been criticized by some physicians because of the possibilities of induction failure and iatrogenic

prematurity.[53] If candidates are selected with careful attention to the previously listed requirements, elective induction is both convenient and safe.

Indicated Induction

Indicated induction of labor is performed when delivery is indicated for maternal or fetal reasons and both mother and fetus can tolerate labor and vaginal delivery. An indicated induction of labor often arises in the setting of a medical or obstetric complication such as diabetes mellitus, preeclampsia, fetal growth restriction (also known as intrauterine growth restriction), or the post-term pregnancy. By definition, the physician is dealing with a complicated pregnancy when performing an indicated induction of labor; therefore, close maternal and fetal monitoring is indicated. When considering the critical question whether induction should be undertaken, the obstetrician must weigh the perinatal risks of continued intrauterine versus extrauterine existence and must also consider the potential adverse maternal consequences of induction, including a higher risk for infection and/or cesarean delivery.

If the Bishop score is favorable, amniotomy alone suffices as a means of inducing labor. Often, however, the cervix is not favorable, and induction is typically accomplished with oxytocin administration combined with amniotomy. In some cases, if the cervix is unfavorable, oxytocin may be infused for one day, with the membranes intact. The infusion is stopped in the evening, and the patient is permitted to eat. The membranes are ruptured, and the oxytocin infusion is started again the following morning. Some obstetricians have advocated vaginal or cervical prostaglandins for the induction of labor; however, it is unclear that these agents offer an advantage over intravenous oxytocin for this purpose.[54]

When induction of labor is indicated in the setting of an unfavorable cervix, the obstetrician may attempt to raise the Bishop score ("ripen" the cervix) before beginning the induction. Both osmotic cervical dilators and pharmacologic techniques are effective in improving the Bishop score.[55,56] Typically these adjunctive measures are instituted the evening before the planned induction. A Foley catheter bulb may also be used for mechanical dilation. A common pharmacologic method involves the topical application of prostaglandin E_2, either in the vagina or in the cervical canal. **Prostaglandin E_2** has a local effect in the initiation of softening, effacement, and dilation of the cervix, and it also has an oxytocin-like effect on the myometrium. Women treated with prostaglandin E_2 commonly experience contractions and labor before amniotomy or oxytocin administration. The same is true for **misoprostol**, a prostaglandin E_1 analogue that is now widely used for cervical ripening and labor induction.[57] Prostaglandins should not be administered to induce labor in women with a prior cesarean delivery, because their use is associated with an increased risk for uterine rupture.

Operative Vaginal Delivery

Cesarean delivery has become a too frequent solution to labor room problems. This safe operation is certainly preferable to the continuation of labor in the setting of genuine fetal compromise or to the performance of a difficult and traumatic vaginal delivery. Unfortunately, however, more traditional obstetric interventions (e.g., labor, additional labor, operative vaginal delivery) are often bypassed in favor of cesarean delivery, perhaps more for medicolegal than for medical concerns. The appropriate use of operative vaginal delivery techniques requires an accurate assessment of the situation, technical skills, and an honest and humble physician.

BOX 18-4 Classification of Forceps Delivery

Outlet Forceps Delivery

- Scalp is visible.
- Skull has reached the pelvic floor, and head is on the perineum.
- Sagittal suture is in the anteroposterior diameter or within 45 degrees (e.g., occiput anterior, left occiput anterior, right occiput posterior).

Low Forceps Delivery

- Station is +2 or greater.
- Hollow of the sacrum is filled.

Mid-forceps Delivery

- Vertex is engaged, but the station is 0 or +1.

Vertex Presentation

Carefully selected and performed forceps or vacuum-assisted delivery shortens the second stage of labor in cases of nonreassuring fetal status, maternal illness or exhaustion, and/or undue prolongation of labor with little or no progress (Box 18-4). The station of the presenting vertex is critical to the safety of the procedure for mother and infant. The current American College of Obstetricians and Gynecologists classification permits a more rational approach to operative vaginal delivery than was available previously.[58,59]

For any operative vaginal delivery, adequate anesthesia is required. Outlet operative deliveries are perfectly safe for both mother and fetus. The low station effectively rules out cephalopelvic disproportion, and little traction is required. Outlet operative deliveries shorten the second stage by only a few minutes. Sustained fetal bradycardia is a common indication for outlet operative delivery. An experienced physician may safely perform low-station operative deliveries in cases of fetal compromise or maternal illness or exhaustion. The higher the head, the harder the pull. Rotations increase the likelihood of vaginal tears.[59]

Midpelvic deliveries reflect a more complicated problem.[60,61] If the station is overestimated, the vertex may be barely engaged. The hollow of the sacrum is incompletely filled. Midpelvic deliveries should be regarded as "trials." The obstetrician must avoid excessive traction and must be willing to abandon the attempt in favor of cesarean delivery if vaginal delivery does not proceed easily.

Although operative vaginal delivery was traditionally accomplished with obstetric forceps, there has been interest in the soft plastic cup vacuum extractor.[62-65] Neither is uniformly better. The vacuum extractor is easier to apply, especially if the obstetrician is uncertain of the position of the occiput, and most likely it is associated with less maternal trauma. Forceps—but not the vacuum extractor—permits the correction of deflection or slight abnormalities of position that may impede progress. The vacuum extractor is more likely to slip off; whether this feature enhances safety is unknown. Neonatal results are comparable, but retinal hemorrhages, which are of unclear significance, are more likely with vacuum extraction. The obstetrician should be trained in both techniques and should individualize their use.

Persistent occiput-posterior positions often occur in anthropoid and android pelves. In modern obstetrics, the infants in most of these cases are delivered with the occiput posterior. Extension of the episiotomy is a common complication in this circumstance, which argues for the consideration of a mediolateral episiotomy.

Deep transverse arrests of the occiput were traditionally managed with rotation and delivery with Kielland's forceps. Current trainees typically have little experience with this instrument, and they are more likely to select the vacuum extractor in this circumstance.

Nonvertex Presentations

A persistent brow presentation or a transverse lie mandates cesarean delivery. Most face presentations and selected breech presentations can be safely delivered vaginally.[66] However, in response to a large international multicenter trial in which planned vaginal delivery was associated with worse perinatal outcomes than planned cesarean delivery,[67] the American College of Obstetricians and Gynecologists now recommends cesarean delivery for the persistent singleton breech presentation at term as the preferred mode of delivery for most physicians, particularly in light of diminishing experience in vaginal breech deliveries.[68]

Fetal Death

If fetal death has occurred, the obstetrician no longer has two patients, making maternal safety the only concern. Although placenta previa or absolute cephalopelvic disproportion may indicate cesarean delivery, the obstetrician is often more willing to choose a more complicated operative vaginal delivery than if the fetus were living.

Shoulder Dystocia

With vertex presentations, most mechanical difficulties are resolved with delivery of the head; once the head is delivered, the remainder of the fetus follows easily. In as many as 3% of vaginal deliveries, this is not the case. After the (often large) head is delivered, it seems to be "sucked" back into the perineum (the turtle sign). With maternal pushing and gentle traction, nothing happens. In this case, the anterior shoulder is trapped above the pubic symphysis. This serious complication is called *shoulder dystocia*. Recognition that shoulder dystocia exists is often followed by equanimity giving way to panic. If delivery is not accomplished soon, umbilical cord compression may result in asphyxia. Excessive traction on the fetal head may result in damage to the brachial plexus (e.g., Erb's palsy), which may be permanent or temporary. During the manipulations undertaken to effect delivery, a fracture of the clavicle or humerus may result.

BOX 18-5 Risk Factors for Shoulder Dystocia

- Fetal macrosomia
- Maternal diabetes mellitus
- Delayed active phase of labor
- Prolonged second stage of labor
- Operative vaginal delivery

Risk factors for shoulder dystocia are those that predict or reflect mechanical difficulty (Box 18-5).[69-72] Women with diabetes mellitus are predisposed to shoulder dystocia, not only because fetal macrosomia is more common but also because the fetus of a mother with diabetes has a shoulder circumference that is disproportionately large relative to the head circumference. Desultory labor may be a harbinger of mechanical mismatch, and operative vaginal delivery can exacerbate the situation.

Appropriate management of shoulder dystocia begins with the recognition that there is sufficient time to deliver the infant safely. Neuraxial anesthesia is ideal but not essential. Extension of the episiotomy should be considered. The anterior shoulder is stuck behind the pubic symphysis. Although greater posterior room does not directly permit delivery, it does permit vaginal manipulations that may be necessary to effect delivery. Table 18-5 lists a personal plan of management for shoulder dystocia, but other choices are available.[69,72,73] Emergency drills and simulation training may improve proficiency in the management of shoulder dystocia.

If suprapubic pressure (directed toward the floor) coupled with gentle traction on the head is not efficacious, the mother's thighs are removed from their

TABLE 18-5 **Management of Shoulder Dystocia**

Maneuver	Desired Result
Suprapubic pressure	Anterior shoulder dislodged from above pubic symphysis
Hyperflexion of maternal thighs alongside abdomen (McRoberts maneuver)	Cephalad rotation of pubic symphysis
Intravaginal pressure on posterior shoulder	Anteroposterior position of shoulders transformed to oblique position
Delivery of posterior arm	Once accomplished, added room permits delivery
Cephalic replacement (Zavenelli maneuver)	Cesarean delivery

supports and are hyperflexed alongside her abdomen. This maneuver (i.e., the McRoberts maneuver) elevates the symphysis in a cephalad direction and often frees the impacted shoulder and allows easy delivery. If the McRoberts maneuver is not successful, vaginal manipulations are undertaken to move the shoulders into an oblique position in the pelvis or to deliver the posterior arm. Despite previous assumptions to the contrary, vaginal delivery of the head does not necessarily commit one to vaginal birth of the infant. Cephalic replacement (i.e., the Zavanelli maneuver) must be kept in mind as a last resort. If all measures have failed, the "tape is rewound," and the mechanism of labor is reversed. The position of the vertex is rotated back to the position prior to external rotation (usually occiput anterior), flexion is achieved, and the head is elevated, which may be facilitated by tocolysis (e.g., sublingual or intravenous nitroglycerin 100 µg, subcutaneous or intravenous terbutaline 0.25 mg, or general anesthesia with a volatile anesthetic agent). After the fetal head has been placed back into the vagina, prompt cesarean delivery is performed.[73]

KEY POINTS

- The outcome of labor reflects the interaction of three components: the powers, the passageway, and the passenger.
- Assuming that the fetus is tolerating labor satisfactorily, the most important obstetric determination is whether the patient is in the latent or the active phase of the first stage of labor.
- Amniotomy shortens labor.
- Oxytocin is the most valuable obstetric drug, and judicious use of a higher dose regimen may increase vaginal birth and shorten labor.
- Expectant management is the standard choice for the very preterm patient with premature rupture of membranes; induction of labor is generally undertaken in patients exhibiting this condition at term.
- Elective induction of labor is an appropriate choice for a patient with a favorable cervix.
- The declining numbers of operative vaginal deliveries reflect medicolegal concerns rather than new scientific information.

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CHAPTER 19

Trial of Labor and Vaginal Birth after Cesarean Delivery

David H. Chestnut, MD

CHAPTER OUTLINE

In 1916, Edward Cragin[1] stated, "Once a cesarean, always a cesarean." This edict has had a profound effect on obstetric practice in the United States. The cesarean delivery rate increased from 5.5% of all deliveries in 1970 to 24.7% in 1988 (Figure 19-1). Much of the increase in the cesarean delivery rate resulted from performance of repeat cesarean deliveries. In contemporary practice, elective repeat cesarean deliveries account for one third of all cesarean deliveries. Cesarean delivery is the most frequently performed major surgery in the United States.

For many years most U.S. physicians ignored Cragin's subsequent statement, "Many exceptions occur."[1] In 1981 the National Institute of Child Health and Human Development Conference on Childbirth concluded that vaginal birth after cesarean (VBAC) is an appropriate option for many women.[2] In 1991, Rosen et al.[3] modified Cragin's original dictum as follows: "Once a cesarean, a trial of labor should precede a second cesarean except in the most unusual circumstances." In 1988 and again in 1994, the American College of Obstetricians and Gynecologists (ACOG)[4] concluded: "The concept of routine repeat cesarean birth should be replaced by a specific decision process between the patient and the physician for a subsequent mode of delivery.… In the absence of a contraindication, a woman with one previous cesarean delivery with a lower uterine segment incision should be counseled and encouraged to undergo a trial of labor in her current pregnancy."

The VBAC rate increased from 2% in 1970 to 28% in 1995. This change in practice helped reduce the overall cesarean delivery rate from 24.7% in 1988 to 20.7% in 1996 (see Figure 19-1). Subsequently the safety of a trial of labor after cesarean (TOLAC) underwent further scrutiny and criticism, and the VBAC rate sharply declined.[5] The VBAC rate in the United States dropped from 28% in 1995 to 9% in 2004. Meanwhile, in 2009, the overall cesarean delivery rate rose to 32.9%, the highest rate ever recorded in this country.[6]

PRIMARY CESAREAN DELIVERY: CHOICE OF UTERINE INCISION

Obstetric practice in 1916 hardly resembled obstetric practice today. In 1916, only 1% to 2% of all infants were delivered by cesarean delivery. Most cesarean deliveries were performed in patients with a contracted bony pelvis, and obstetricians uniformly performed a classic uterine incision (i.e., a long vertical incision in the upper portion of the uterus) (Figure 19-2). A patient with a classic uterine incision is at high risk for catastrophic uterine rupture during a subsequent pregnancy. Such uterine rupture may occur before or during labor, and it often results in maternal and perinatal morbidity or mortality.

In 1922, De Lee and Cornell[7] advocated the performance of a vertical incision in the lower uterine segment.

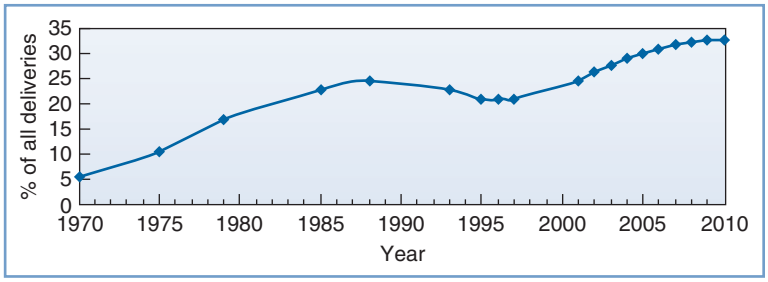

FIGURE 19-1 ■ Incidence of cesarean delivery in the United States.

Unfortunately, low-vertical incisions rarely are confined to the lower uterine segment. Such incisions often extend to the body of the uterus, which does not heal as well as the lower uterine segment. Kerr[8] later advocated the performance of a low-transverse uterine incision (see Figure 19-2). A low-transverse uterine incision results in less blood loss and is easier to repair than a classic uterine incision.[9] Further, a low-transverse uterine incision is more likely to heal satisfactorily and to maintain its integrity during a subsequent pregnancy. Thus, obstetricians prefer to make a low-transverse uterine incision during most cesarean deliveries.

Obstetricians reserve the low-vertical incision for patients whose lower uterine segment does not have enough width to allow safe delivery. Preterm parturients may have a narrow lower uterine segment. In these patients, delivery through a transverse uterine incision may cause an extension of the incision into the vessels of the broad ligament. For example, a patient with preterm labor at 26 weeks' gestation may undergo

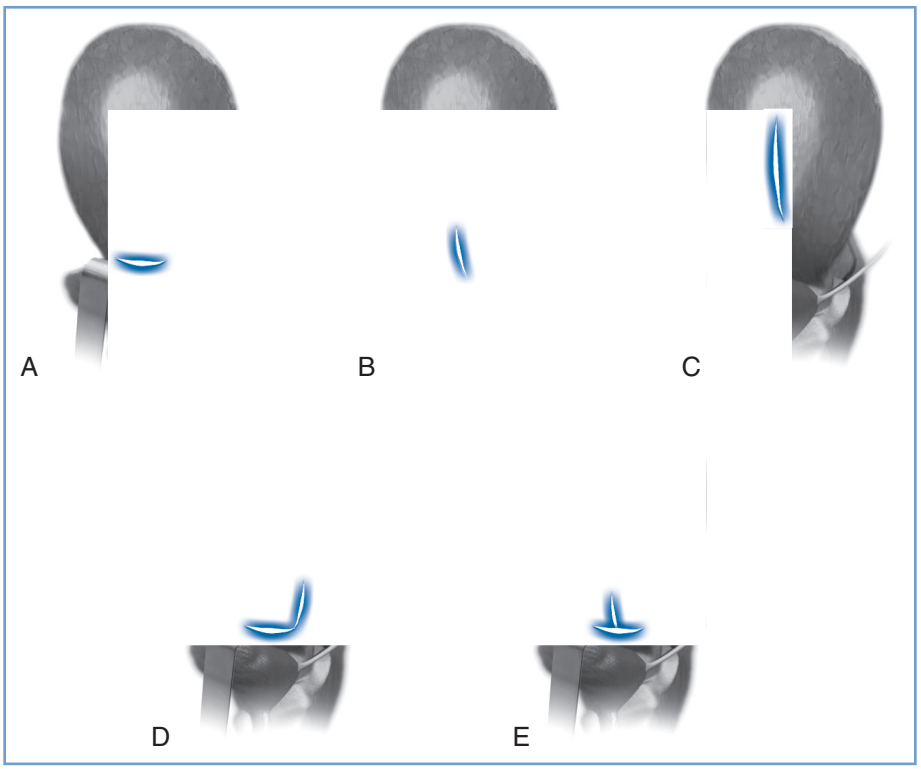

FIGURE 19-2 ■ Uterine incisions for cesarean delivery. **A,** Low-transverse incision. The bladder is retracted downward, and the incision is made in the lower uterine segment, curving gently upward. If the lower segment is poorly developed, the incision also can curve sharply upward at each end to avoid extending into the ascending branches of the uterine arteries. **B,** Low-vertical incision. The incision is made vertically in the lower uterine segment after reflection of the bladder, with avoidance of extension into the bladder below. If more room is needed, the incision can be extended upward into the upper uterine segment. **C,** Classic incision. The incision is entirely within the upper uterine segment and can be at the level shown or in the fundus. **D,** J-shaped incision. If more room is needed when an initial transverse incision has been made, either end of the incision can be extended upward into the upper uterine segment and parallel to the ascending branch of the uterine artery. **E,** T-shaped incision. More room can be obtained in a transverse incision by an upward midline extension into the upper uterine segment. (Modified from Landon MB. Cesarean delivery. In Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: Normal and Problem Pregnancies. 5th edition. Philadelphia, Churchill Livingstone Elsevier, 2007:493.)

cesarean delivery because of a breech presentation, and the obstetrician may perform a low-vertical incision to facilitate an atraumatic delivery of the fetal head.

Obstetricians rarely perform a classic uterine incision in modern obstetric practice. An obstetrician may perform a classic uterine incision when the need for extensive intrauterine manipulation of the fetus (e.g., delivery of a fetus with a transverse lie) is anticipated. Some obstetricians prefer a classic uterine incision in patients with an anterior placenta previa. In such cases, the performance of a classic incision allows the obstetrician to avoid cutting through the placenta, which might result in significant hemorrhage.

MATERNAL AND NEONATAL OUTCOMES

Multiple studies have demonstrated that TOLAC results in a successful VBAC in 60% to 80% of women in whom a low-transverse uterine incision was made for a previous cesarean delivery.[10-13] A 2010 National Institute of Health (NIH) consensus development panel[14] concluded that although the TOLAC rate has declined dramatically in recent years, the VBAC rate after TOLAC has remained constant at approximately 74%. However, the panel acknowledged that many published studies were observational and did not address issues of selection bias. The panel also noted that a history of vaginal delivery, either before or after a prior cesarean delivery, is consistently associated with an increased likelihood of successful VBAC.[14]

Maternal Outcomes

Flamm et al.[10] performed a prospective multicenter study of TOLAC. Of the 7229 patients, 5022 (70%) underwent TOLAC and 2207 underwent elective repeat cesarean delivery. Some 3746 (75%) of the women who opted for TOLAC delivered vaginally. The incidence of uterine rupture was 0.8%. The incidence of postpartum transfusion, the incidence of postpartum fever, and the duration of hospitalization were significantly lower in the TOLAC group than in the elective repeat cesarean group. Likewise, in a 1991 meta-analysis of 31 studies, Rosen et al.[3] noted that maternal febrile morbidity was significantly lower among women who attempted VBAC than among those who underwent elective repeat cesarean delivery.

In contrast, McMahon et al.[15] performed a population-based longitudinal study of 6138 women in Nova Scotia who had previously undergone cesarean delivery and who delivered a single live infant between 1986 and 1992. Some 3249 women attempted VBAC, and 2889 women chose a repeat cesarean delivery. There was no difference between the two groups in the incidence of "minor complications" (e.g., puerperal fever, transfusion, wound infection). However, "major complications" (e.g., hysterectomy, uterine rupture, operative injury) were nearly twice as common among women who attempted VBAC than among women who underwent elective repeat cesarean delivery.

Landon et al.[11] subsequently conducted a prospective 4-year observational study of all parturients with a singleton gestation and a prior cesarean delivery at 19 academic medical centers. Among the 17,898 women who attempted VBAC, 13,139 (73.4%) delivered vaginally. Symptomatic uterine rupture occurred in 124 (0.7%) women who underwent a trial of labor. The rate of endometritis was higher in women who underwent a trial of labor than in women who had an elective repeat cesarean delivery (2.9% versus 1.8%), as was the rate of blood transfusion (1.7% versus 1.0%).[15]

In a 2004 systematic review of published studies of attempted VBAC, Guise et al.[16] observed no significant difference in the incidence of maternal death or hysterectomy between women who attempted a trial of labor and those who underwent repeat cesarean delivery. Uterine rupture was more common in the women who attempted a trial of labor, but the rates of asymptomatic uterine dehiscence did not differ.

Wen et al.[17] performed a retrospective cohort comparison of outcomes after TOLAC or elective repeat cesarean delivery in 308,755 Canadian women with a history of previous cesarean delivery. These investigators observed that the rates of uterine rupture (0.65%), transfusion (0.19%), and hysterectomy (0.10%) were significantly higher in the TOLAC group. However, the maternal in-hospital death rate was significantly lower in the TOLAC group (1.6 per 100,000) than in the elective cesarean delivery group (5.6 per 100,000). Similarly, Guise et al.[18] observed a lower maternal mortality rate in women who underwent TOLAC than in women who underwent elective repeat cesarean delivery (0.004% versus 0.013%, respectively).

Cahill et al.[19] performed a multicenter cohort study in which they concluded that among TOLAC candidates who had a prior vaginal delivery, those who attempted VBAC had a lower risk for overall major maternal morbidities, as well as maternal fever and transfusion, than women who chose repeat cesarean delivery. These investigators concluded that women who have had a prior vaginal delivery have "less composite maternal morbidity if they attempt VBAC compared with [those] undergoing an elective repeat cesarean delivery." Further, they concluded that a trial of labor is "a safer overall option for women who have had a prior vaginal birth."[19]

Rossi and D'Addario[12] performed a meta-analysis of studies published in 2000-2007 that compared maternal morbidity in women who underwent TOLAC versus women who underwent elective repeat cesarean delivery. Successful VBAC occurred in 17,905 (73%) of 24,349 women who underwent TOLAC. Overall maternal morbidity did not differ between women who underwent TOLAC and women who underwent elective repeat cesarean delivery. Likewise, the incidence of blood transfusion and hysterectomy did not differ between the two groups. The incidence of uterine rupture was higher in the TOLAC group (1.3% versus 0.4%). Further, maternal morbidity, uterine rupture, blood transfusion, and hysterectomy were more common in women who had a *failed* TOLAC.

The 2010 NIH consensus development panel[14] noted that the overall benefits of TOLAC "are directly related

to having a [successful] VBAC as these women typically have the lowest morbidity." Likewise, the panel noted that the harms of TOLAC "are associated with an unsuccessful trial of labor resulting in cesarean delivery because these deliveries have the highest morbidity." However, the panel concluded that women who undergo TOLAC, regardless of the ultimate mode of delivery, are at decreased risk for maternal mortality compared with women who undergo elective repeat cesarean delivery. The panel also cited low-grade evidence of a shorter hospitalization overall for women attempting TOLAC compared with women undergoing elective repeat cesarean delivery.

Neonatal Outcomes

Lydon-Rochelle et al.[20] conducted a population-based, retrospective cohort analysis of obstetric outcomes for all 20,095 nulliparous women who gave birth to a live singleton infant by cesarean delivery in civilian hospitals in Washington between 1987 and 1996 and who subsequently delivered a second singleton child during the same period. These investigators observed that spontaneous labor was associated with a tripling of the risk for uterine rupture (i.e., a uterine rupture rate of 5.2 per 1000 women who had spontaneous onset of labor versus 1.6 per 1000 women who underwent elective repeat cesarean delivery without labor). Further, the incidence of infant death was more than 10 times higher among the 91 women who experienced uterine rupture than among the 20,004 who did not (i.e., a 5.5% incidence of infant death versus a 0.5% incidence, respectively).[20]

In the study performed by McMahon et al.[15] there was no difference between the two groups in perinatal mortality or morbidity. However, two perinatal deaths occurred after uterine rupture in the TOLAC group. Landon et al.[11] observed that hypoxic-ischemic encephalopathy occurred in no infants whose mothers underwent elective repeat cesarean delivery and in 12 infants delivered at term whose mothers underwent a trial of labor ($P < .001$).

The 2010 NIH consensus development panel[14] concluded that the perinatal mortality rate (death between 20 weeks' gestation and 28 days of life) is increased with TOLAC when compared with elective repeat cesarean delivery (i.e., 130 deaths per 100,000 infants compared with 50 deaths per 100,000 infants, respectively). Likewise, the panel concluded that the neonatal mortality rate (death in the first 28 days of life) is also increased with TOLAC when compared with elective repeat cesarean delivery (110 deaths per 100,000 infants versus 50 deaths per 100,000 infants, respectively).[14]

On the other hand, successful VBAC avoids the neonatal risks of elective cesarean delivery. Inappropriate assessment of gestational age or fetal maturity occasionally leads to the delivery of a preterm infant. Elective cesarean delivery results in some cases of iatrogenic neonatal respiratory sequelae, including respiratory distress syndrome and transient tachypnea of the newborn. Kamath et al.[21] observed that newborns born after elective repeat cesarean delivery had significantly higher rates of respiratory morbidity and neonatal intensive care unit admission—and a longer length of hospital stay—than infants whose mothers attempted VBAC. However, the 2010 NIH consensus development panel[14] concluded that there is insufficient evidence to determine whether substantial differences in respiratory outcomes occur in infants born via elective repeat cesarean delivery compared with infants born after TOLAC.

ELIGIBILITY AND SELECTION CRITERIA

Most studies suggest a high likelihood of success with TOLAC, even in women in whom the indication for previous cesarean delivery was dystocia or failure to progress in labor. Rosen and Dickinson[22] performed a meta-analysis of 29 studies of attempted VBAC. Among women whose previous cesarean deliveries were performed for dystocia or cephalopelvic disproportion, the average rate of successful VBAC was 67%. Later studies have concluded that a history of previous vaginal delivery (including previous VBAC) is the greatest predictor for successful VBAC.[23]

The highest risk for maternal morbidity and mortality is associated with unsuccessful TOLAC.[14] The ACOG[13] concluded that women with at least a 60% to 70% chance of successful VBAC have equal or less maternal morbidity when they undergo TOLAC than women who undergo elective repeat cesarean delivery. Conversely, the ACOG[13] noted that women who have a lower than 60% probability of successful VBAC have a greater likelihood of morbidity than women who undergo elective repeat cesarean delivery. Thus, the ability to identify women with a high likelihood of successful VBAC would improve the safety of TOLAC. Investigators have attempted to develop reliable scoring systems for predicting the success or failure of TOLAC, with limited success. Grobman et al.[24] developed a nomogram specifically for women undergoing TOLAC at term gestation with one previous low-transverse cesarean delivery, a singleton gestation, and a vertex fetal presentation. The nomogram incorporates six variables that may be ascertained at the first prenatal visit; those variables include maternal age, body mass index, ethnicity, prior vaginal delivery, prior VBAC, and a recurring indication for cesarean delivery. This model was validated in a subsequent study.[25]

The ACOG[13] concluded that the "preponderance of evidence suggests that most women with one previous cesarean delivery with a low-transverse incision are candidates for and should be counseled about VBAC and offered TOLAC." A history of dystocia, a need for induction of labor, and maternal obesity are associated with a lower likelihood of successful VBAC.[24,26-28]

History of More Than One Cesarean Delivery

Studies that have assessed outcomes of TOLAC in women with a history of more than one cesarean delivery have not demonstrated consistent conclusions. One large multicenter study found no increased risk for uterine rupture (0.9% versus 0.7%) in women with more than one previous cesarean delivery, when compared with

women with only one previous cesarean delivery.[29] A second large study observed that the risk for uterine rupture increased from 0.9% to 1.8% during TOLAC in women with two previous cesarean deliveries.[30] Both studies observed that TOLAC was associated with some increase in maternal morbidity in women with more than one previous cesarean delivery, although the absolute magnitude of the difference in morbidity was relatively small.[29,30] The ACOG[13] concluded that it is reasonable to consider TOLAC for women with two previous low-transverse cesarean deliveries. Data regarding the risk of TOLAC in women with more than two previous cesarean deliveries are limited.[13]

Previous Low-Vertical Incision

Some obstetricians allow a trial of labor after a previous low-vertical uterine incision, provided that there is documentation that the uterine incision was confined to the lower uterine segment. (Low-vertical uterine incisions often extend above the lower uterine segment, especially when performed in preterm patients.) Naef et al.[31] retrospectively reviewed outcomes for 174 women who attempted VBAC after a previous low-vertical cesarean delivery; 144 (83%) women delivered vaginally. Uterine rupture occurred in 2 (1.1%) of the patients. These investigators concluded that "the likelihood of successful outcome and the incidence of complications are comparable to those of published experience with a trial of labor after a previous low-segment transverse incision."[31] Adair et al.[32] made similar observations. The ACOG[13] concluded that there is no consistent evidence of an increased risk for uterine rupture in women with a previous low-vertical uterine incision, and that obstetricians and patients may choose to undergo TOLAC in the presence of a documented prior low-vertical uterine incision.

Twin Gestation

Some obstetricians believe that uterine overdistention, which occurs with twin gestation, increases the risk for uterine rupture in patients with a history of previous cesarean delivery. Early reports suggested otherwise, but these studies were limited by the small number of patients.[33,34] Cahill et al.[35] performed a retrospective cohort study of 25,005 obstetric patients with at least one previous cesarean delivery, which included 535 patients with a twin pregnancy. The investigators observed that women with a twin gestation were less likely to attempt VBAC but were no more likely to have a failed VBAC or to experience major morbidity than women with a singleton gestation.

Likewise, a report from the Maternal-Fetal Medicine Unit Cesarean Registry[36] included outcome measures for 186 women with a twin gestation who attempted VBAC. Some 120 (64.5%) women delivered vaginally. Women who attempted a trial of labor with twin gestation had no higher risk for transfusion, endometritis, intensive care unit admission, or uterine rupture than women who underwent elective repeat cesarean delivery. The investigators concluded that a trial of labor in women with a twin gestation after previous cesarean delivery does not appear to be associated with a higher risk for maternal morbidity.[36]

Ford et al.[37] subsequently examined outcomes for 6555 women with a twin gestation who delivered between 1993 and 2002. Among 1850 women who underwent a trial of labor, 836 (45.2%) delivered vaginally. The rate of uterine rupture was higher in the trial-of-labor group than in the elective cesarean delivery group (0.9% versus 0.1%), but the rate of wound complications was lower in the trial-of-labor group (0.6% versus 1.3%).

The ACOG[13] concluded that "women with one previous cesarean delivery with a low-transverse [uterine] incision, who are otherwise appropriate candidates for twin vaginal delivery, may be considered candidates for TOLAC."

Unknown Uterine Scar

For some patients, there is no documentation of the type of uterine incision performed during a previous cesarean delivery. Some obstetricians require documentation of the type of previous uterine incision before they allow a patient to attempt VBAC. At least two studies have concluded that a trial of labor does not significantly increase maternal or perinatal mortality in patients with an unknown uterine scar.[38,39] Perhaps this conclusion is true because most patients with an unknown uterine scar had a low-transverse uterine incision at previous cesarean delivery. Ultrasonography may help the obstetrician confirm the presence of a low-transverse uterine scar in the pregnant woman with an unknown uterine scar.[40] The ACOG[13] concluded that "TOLAC is not contraindicated for women with one previous cesarean delivery with an unknown uterine scar type unless there is a high clinical suspicion of a previous classical uterine incision."

Suspected Macrosomia

In 1994 the ACOG[4] concluded that an estimated fetal weight of more than 4000 g does not contraindicate TOLAC. However, in 1999, the ACOG[41] included suspected macrosomia on the list of TOLAC eligibility criteria that are controversial. In 2004, the ACOG[42] noted that macrosomia is associated with a lower likelihood of successful VBAC but did not include a specific recommendation regarding TOLAC in cases of suspected macrosomia. However, the ACOG cited one report that observed that the rate of uterine rupture appeared to be higher only in women without a previous vaginal delivery.[43] A report from the Maternal-Fetal Medicine Unit Cesarean Registry[44] concluded that for women with a history of previous cesarean delivery for dystocia, a higher birth weight in a subsequent pregnancy (relative to the first pregnancy birth weight) diminishes the chances of successful VBAC. In 2010 the ACOG[13] concluded that "suspected macrosomia alone should not preclude the possibility of TOLAC."

Gestation beyond 40 Weeks

Studies have consistently demonstrated decreased rates of successful VBAC in women who undergo TOLAC

after 40 weeks' gestation.[45-47] One study observed an increased incidence of uterine rupture in women undergoing TOLAC beyond 40 weeks' gestation,[47] but other studies (including the largest study[46] that has assessed this risk factor) have not confirmed an increased risk for uterine rupture in these patients. The ACOG[13] concluded that although the likelihood of successful VBAC may be diminished in more advanced gestations, a "gestational age of greater than 40 weeks alone should not preclude TOLAC."

Breech Presentation and External Cephalic Version

Breech presentation itself does not increase the risk for uterine rupture. In contemporary practice, most obstetricians do not allow a trial of labor in *any* patient with a breech presentation. Thus, most patients with a breech presentation undergo elective cesarean delivery, with or without a history of previous cesarean delivery. The ACOG[13] concluded that external cephalic version is not contraindicated in women with a previous low-transverse uterine incision who are at low risk for adverse maternal and neonatal outcomes from external cephalic version and TOLAC.

Size of Hospital

Most studies of VBAC have been conducted in university or tertiary care hospitals with in-house obstetricians, anesthesia providers, and operating room staff. In 1999 the ACOG[41] noted that "the safety of [a] trial of labor is less well documented in smaller community hospitals or facilities where resources may be more limited." A 2007 study[48] evaluated outcomes for women who attempted VBAC in 17 diverse hospitals, including six university hospitals, five community hospitals with an obstetrics-gynecology residency program, and six community hospitals without an obstetrics-gynecology residency program. The incidence of uterine rupture with attempted VBAC was significantly higher in community hospitals than in university hospitals (1.2% versus 0.6%, respectively). However, the rates of maternal blood transfusion and composite adverse maternal outcome were identical in community and university hospitals.[48]

Contraindications

Contraindications to planned TOLAC include[13,42]:

- Previous classic or T-shaped incision or extensive transfundal uterine surgery
- Previous uterine rupture
- Medical or obstetric complication that precludes labor and vaginal delivery
- Inability to perform emergency cesarean delivery because of unavailable surgeon, anesthesia provider, or operating room staff

Social and Economic Factors

Why do most eligible patients choose to undergo elective repeat cesarean delivery? The low frequency of TOLAC has resulted, in part, from both physician and patient preference. VBAC requires more physician effort than elective repeat cesarean delivery. In some cases, physician reimbursement is greater for elective repeat cesarean delivery than for VBAC, despite the fact that VBAC requires greater physician effort.

Stafford[49] reviewed the impact of nonclinical factors on the performance of repeat cesarean delivery in California. He observed that "proprietary hospitals, with the greatest incentive to maximize reimbursement, had the highest repeat cesarean [delivery] rates." Nonteaching hospitals and hospitals with low-volume obstetric services had lower VBAC rates than teaching hospitals and hospitals with high-volume obstetric services. Likewise, Hueston and Rudy[50] found that women who undergo elective repeat cesarean delivery are more likely to have private insurance than women who attempt VBAC. Stafford[49] concluded: "Because a cesarean [delivery] is nearly twice as costly as a vaginal birth,… the higher repeat cesarean [delivery] rates associated with proprietary hospitals, non-teaching hospitals, and low-volume hospitals contribute to increased health care expenditures."

In contrast, after assessing both the direct and indirect costs of VBAC, Clark et al.[51] concluded that "any economic savings for the healthcare system of a policy of trial of labor are at best marginal, even in a tertiary care center with a success rate for vaginal birth after cesarean of 70%." Further, they stated that "a policy of trial of labor does not result in any cost saving under most birthing circumstances encountered in the United States today."[51] The ACOG[41] had earlier acknowledged that "the difficulty in assessing the cost-benefit of VBAC is that the costs are not all incurred by one entity." In 2004 the ACOG[42] made the following conclusion:

> *A true analysis of the cost-effectiveness of VBAC should include hospital and physician costs, the method of reimbursement, potential professional liability expenses, and the probability that a woman will continue with childbearing after her first attempt at VBAC. Higher costs may be incurred by a hospital if a woman has a prolonged labor or has significant complications or if the newborn is admitted to a neonatal intensive care unit.*

Some women reject TOLAC because they have experienced prolonged, painful labor during a previous pregnancy. They fear that they will again experience a prolonged, painful labor and ultimately need a repeat cesarean delivery. This fear is more common in women who have delivered in smaller hospitals without the availability of neuraxial analgesia during labor. Other women reject TOLAC because they prefer to schedule the date of elective repeat cesarean delivery. (A scheduled, elective cesarean delivery allows the patient to arrange for a relative or friend to provide child care.) Kirk et al.[52] questioned 160 women regarding factors affecting their choice between VBAC and elective repeat cesarean delivery. These investigators concluded that "social exigencies appeared to play a more important role than an assessment of the medical risks in making these decisions." Similarly, Joseph et al.[53] observed that fear and

inconvenience are the most common deterrents to attempted VBAC. Finally, some women reject a trial of labor because of their concern about the adverse effects of labor and vaginal delivery on the maternal pelvic floor, with the risk for subsequent problems such as urinary and fecal incontinence.

Some insurance carriers previously required that eligible women with a history of previous cesarean delivery attempt VBAC in subsequent pregnancies. These carriers denied partial or full reimbursement to women who chose elective repeat cesarean delivery unless there was a medical reason to perform repeat cesarean delivery. The ACOG and others have agreed that hospitals and insurers should *not* mandate a trial of labor for pregnant women with a history of previous cesarean delivery.[54] In 2004 the ACOG[42] concluded, "After thorough counseling that weighs the individual benefits and risks of VBAC, the ultimate decision to attempt this procedure or undergo a repeat cesarean delivery should be made by the patient and her physician."

Medicolegal Factors

What is the risk for uterine rupture during VBAC? A lower uterine segment scar is relatively avascular, and massive hemorrhage rarely follows separation of a lower segment scar. In contrast, rupture of a classic uterine scar may result in massive intraperitoneal bleeding. Unfortunately, there is some inconsistency and confusion in reports of the incidence of asymptomatic uterine scar dehiscence as opposed to frank uterine rupture. **Uterine scar dehiscence** may be defined as a uterine wall defect that does not result in fetal compromise or maternal hemorrhage and that does not require emergency cesarean delivery or postpartum laparotomy. In contrast, **uterine rupture** may be accompanied by extrusion of the fetus or placenta and results in fetal compromise, maternal hemorrhage, or both, sufficient to require cesarean delivery or postpartum laparotomy.[55]

Some obstetricians have suggested that earlier studies underestimated the risks of TOLAC. Scott[56] reported 12 women from Salt Lake City, Utah, who experienced clinically significant uterine rupture during TOLAC. Some of the women did not experience optimal obstetric management. For example, Scott's series included two women whose labor occurred at home.[56] Of interest, the number of home VBACs in the United States increased from 664 in 2003 to approximately 1000 in 2008, perhaps as a result of restricted access to TOLAC in some hospitals.[57]

Obstetricians understandably fear that they will be found liable if an adverse event occurs during TOLAC. In one case, a jury awarded a verdict of $98.5 million because of a delayed diagnosis of uterine rupture.[58] Phelan[59] cited another court decision that he predicted would have a "chilling effect on the future of VBAC." In this case, the fetal heart rate (FHR) was normal until it abruptly decreased to 80 beats per minute at a cervical dilation of 9 cm. The interval between the onset of the FHR deceleration and emergency cesarean delivery was 27 minutes. At delivery, the fetal head was found in the left adnexa. The mother required transfusion, and the child suffered from developmental delay and cerebral palsy. The court found that the defendants were negligent in their failure to deliver the infant in a timely manner and to provide adequate informed consent. The court also concluded that "the ACOG 30-minute rule represented the maximum period of elapse" and did not represent the minimum standard of care. As a result of this verdict, Phelan[59] proposed the use of a VBAC consent form that includes the following statement: "I understand that if my uterus ruptures during my VBAC, there may not be sufficient time to operate and to prevent the death of or permanent brain injury to my baby." Flamm[60] responded that "widespread implementation of this or similar consent forms essentially would mean the end of VBAC."

Greene[61] wrote a sobering editorial on the risks of attempted VBAC. Observing that the study performed by Lydon-Rochelle et al.[20] was an observational study that reflected "broad experience in a wide range of clinical-practice settings," he stated that "there is no reason to believe that improvements in clinical care can substantially reduce the risks of uterine rupture and perinatal mortality." Greene[61] concluded his editorial as follows:

> *After a thorough discussion of the risks and benefits of attempting a vaginal delivery after cesarean section, a patient might ask, "But doctor, what is the safest thing for my baby?" Given the findings of Lydon-Rochelle et al., my unequivocal answer: elective repeated cesarean section.*

In an earlier editorial, Pitkin[62] made the following statement regarding VBAC: "Many women with previous cesareans can be delivered vaginally, and thereby gain substantial advantage, but neither the decision for trial [of] labor nor management during that labor should be arrived at in a cavalier or superficial manner."

PROFESSIONAL SOCIETY PRACTICE GUIDELINES

In 1999 the ACOG[41] issued guidelines stating that because uterine rupture may be catastrophic, VBAC should be attempted in institutions equipped to respond to emergencies with physicians *immediately* available to provide emergency care. The ACOG[63] defended this guideline by noting that "VBAC is a completely elective procedure that allows for reasonable precautions in assuming this small but significant risk [of uterine rupture]." In contrast, other obstetric catastrophes (e.g., placental abruption, umbilical cord prolapse) cannot be predicted. The ACOG[63] has also noted that "the operational definition of 'immediately available' personnel and facilities remains the purview of each local institution." However, this requirement for the immediate availability of physicians and other personnel clearly represents a more stringent standard than the "readily available" requirement in other published guidelines for obstetric care.

Earlier, Zlatnik[64] made the following comments regarding VBAC in a community hospital: "If a timely

cesarean [delivery] cannot be performed in a community hospital, VBAC is out of the question, but the larger question is: Should obstetrics continue to be practiced there? Timely cesarean [delivery] is an essential option for all laboring women."

In contrast, the American Academy of Family Physicians (AAFP)[65] published the following recommendations:

> *Women with one previous cesarean delivery with a low transverse incision are candidates for and should be offered a trial of labor (TOL).…Trial of labor after cesarean (TOLAC) should not be restricted only to facilities with available surgical teams present throughout labor since there is no evidence that these additional resources result in improved outcomes. At the same time, it is clinically appropriate that a management plan for uterine rupture and other potential emergencies requiring rapid cesarean section should be documented for each woman undergoing TOLAC.*

The AAFP[65] has argued that the ACOG guidelines suggest that "one rare obstetrical catastrophe (e.g., uterine rupture) merits a level of resource that has not been recommended for other rare obstetrical catastrophes that may actually be more common." The AAFP has acknowledged that these other complications are "largely not predictable," whereas a TOLAC is a "planned event that may demand a different degree of preparedness." Nonetheless, they stated that their recommendations significantly differ from ACOG guidelines because they could find "no evidence to support a different level of care for TOLAC patients."[65]

In response, Dr. Gary Hankins, Chair of the ACOG Committee on Obstetric Practice, made the following statement[66]:

> *It's very troubling when people who may not even be qualified to perform a cesarean section start issuing guidelines about the safety of this kind of thing.… Their argument is that the available data don't prove it's unsafe—they're not arguing that it is safe.…Our main concern is with having the best possible outcome for mother and baby. If women are given the true numbers about the bad outcomes that can be associated with VBAC, no woman is going to take the chance [of laboring without immediately available surgical support].*

The 2010 NIH consensus development panel[14] noted that approximately one third of hospitals and one half of obstetric physicians in the United States no longer offer TOLAC largely because of fear of liability and litigation. The panel[14] expressed concern that practice guidelines have created barriers that prevent women from choosing TOLAC. The panel concluded that TOLAC remains "a reasonable option for many pregnant women with one prior low-transverse uterine incision." The panel acknowledged that decision-making may be difficult, because the benefit of TOLAC for the woman may come at the price of increased risk for the infant. The panel stated that pregnant women should be given the opportunity to make informed decisions about the risks and benefits of TOLAC versus elective repeat cesarean delivery. The panel also urged professional societies to reassess the requirement for immediate availability of surgical and anesthesia providers.

Subsequently the ACOG[13] issued a revised practice bulletin, in which they stated that restricting access was not the intention of their "immediately available" requirement. The ACOG[13] noted that "much of the data concerning the safety of TOLAC was obtained from centers capable of performing immediate, emergency cesarean delivery." Further, they stated that "although there is reason to think that rapid availability of cesarean delivery may provide a small incremental benefit in safety, comparative data examining in detail the effect of alternate systems and response times are not available." A recent study[55] evaluated neonatal outcome after 36 cases of uterine rupture that occurred among 11,195 cases of TOLAC between 2000 and 2009. None of the 17 infants who were delivered less than 18 minutes after the identification of uterine rupture had either an umbilical arterial blood pH less than 7.0 or evidence of neurologic injury. In contrast, three infants who were delivered more than 30 minutes after the diagnosis of uterine rupture had an umbilical arterial blood pH less than 6.8 and suffered neonatal neurologic injury.[55]

The revised ACOG practice bulletin reaffirmed the earlier "immediately available" recommendation, but it also affirmed thoughtful, informed decision-making. Specifically, the ACOG[13] concluded:

> *Because of the risks associated with TOLAC and [because] uterine rupture and other complications may be unpredictable, the College recommends that TOLAC be undertaken in facilities with staff immediately available to provide emergency care. When resources for immediate cesarean delivery are not available, the College recommends that health care providers and patients considering TOLAC discuss the hospital's resources and availability of obstetric, pediatric, anesthetic, and operating staffs.…The decision to offer and pursue TOLAC in a setting in which the option of immediate cesarean delivery is more limited should be carefully considered by patients and their health care providers. In such situations the best alternative may be to refer patients to a facility with available resources.*

Further, the ACOG[13] also encouraged respect for patient autonomy, as follows:

> *Respect for patient autonomy also argues that even if a center does not offer TOLAC, such a policy cannot be used to force women to have cesarean delivery or to deny care to women in labor who decline to have a repeat cesarean delivery.…Respect for patient autonomy supports that patients should be allowed to accept increased levels of risk; however, patients should be clearly informed of such potential increase in risk and management alternatives.*

Birnbach et al.[67] reviewed the impact of anesthesia provider availability on the incidence of VBAC in the

United States. They concluded that the "immediately available" requirement necessitates having an in-hospital anesthesia provider who is not performing another simultaneous anesthetic. Their economic analysis prompted a conclusion that "the minimum requirement to provide immediate anesthesia care for all deliveries would be to have all deliveries at facilities with greater than 1500 deliveries annually."

OBSTETRIC MANAGEMENT

Intravenous Access and Availability of Blood

It seems prudent to recommend the early establishment of intravenous access in women who undergo TOLAC. Resources for transfusion of blood and blood products should be readily available.

Fetal Heart Rate Monitoring

Continuous electronic FHR monitoring represents the best means of detecting uterine rupture.[68-70] Rodriguez et al.[69] reviewed 76 cases of uterine rupture at their hospital. A nonreassuring FHR pattern occurred in 59 of the 76 patients and was the most reliable sign of uterine rupture.

Intrauterine Pressure Monitoring

The intrauterine pressure catheter provides a quantitative measurement of uterine tone both during and between contractions. In the past, some obstetricians contended that an intrauterine pressure catheter should be used in all patients who undergo TOLAC, arguing that a loss of intrauterine pressure and cessation of labor will signal the occurrence of uterine rupture. In one study,[69] 39 patients had an intrauterine pressure catheter at the time of uterine rupture. None of these patients experienced an apparent decrease in resting uterine tone or cessation of labor, but 4 patients experienced an increase in baseline uterine tone. In these 4 patients, the increase in baseline uterine tone was associated with severe variable FHR decelerations that prompted immediate cesarean delivery. The authors concluded that the information obtained from the use of the intrauterine pressure catheter did not help obstetricians make the diagnosis of uterine rupture.[69]

Use of Prostaglandins

Lydon-Rochelle et al.[20] observed a uterine rupture rate of 24.5 per 1000 women who attempted VBAC with prostaglandin-induced labor. The ACOG[13] cited evidence from small studies that observed an increased risk for uterine rupture after the use of misoprostol (prostaglandin E_1) in women who attempted VBAC. The ACOG[13,71] has concluded that "misoprostol should not be used for third trimester cervical ripening or labor induction in patients who have had a cesarean delivery or major uterine surgery."

Induction and Augmentation of Labor

Induction of labor is less likely to result in successful VBAC than spontaneous labor.[26] Studies of outcomes after the use of oxytocin augmentation of labor during TOLAC have demonstrated conflicting results.[3,20,72-74] In a 1991 meta-analysis of 31 studies of VBAC, Rosen et al.[3] noted that the use of oxytocin did not increase the risk for uterine scar dehiscence or rupture during VBAC. In contrast, in one large retrospective study of more than 20,000 women, uterine rupture was nearly five times more common among women undergoing induction of labor with oxytocin than in those who had an elective repeat cesarean delivery.[20] Zelop et al.[73] observed a higher rate of uterine rupture in women undergoing oxytocin induction of labor for attempted VBAC than in similar women attempting VBAC with spontaneous labor. Further, the rate of uterine rupture was also higher in women receiving oxytocin for augmentation of labor, but the difference was not statistically significant. The ACOG[13] has concluded that "the varying outcomes of available studies and small absolute magnitude of the risk reported in those studies support that oxytocin augmentation may be used in patients undergoing TOLAC."

ANESTHETIC MANAGEMENT

In the past, some obstetricians contended that epidural analgesia might mask the pain of uterine scar separation or rupture and thereby delay the diagnosis of uterine scar dehiscence or rupture.[75,76] Plauché et al.[75] stated, "Regional anesthesia, such as epidural anesthesia, blunts the patient's perception of symptoms and the physician's ability to elicit signs of early uterine rupture." Others have argued that the sympathectomy associated with epidural anesthesia might attenuate the maternal compensatory response to the hemorrhage associated with uterine rupture. For example, sympathectomy might prevent the compensatory tachycardia and vasoconstriction that occur during hemorrhage. However, consensus now exists that these concerns do not preclude administration of neuraxial analgesia during TOLAC, for several reasons.

First, pain, uterine tenderness, and tachycardia have low sensitivity as diagnostic symptoms and signs of lower uterine segment scar dehiscence or rupture. Some uterine scars separate painlessly. Many obstetricians have discovered an asymptomatic lower uterine segment scar dehiscence at the time of elective repeat cesarean delivery. Molloy et al.[77] reported 8 cases of uterine rupture among 1781 patients who attempted VBAC. None of these 8 patients had abdominal pain, but all had FHR abnormalities. Johnson and Oriol[70] reviewed 14 studies of VBAC published between 1980 and 1989. Among 10,967 patients who attempted VBAC, 1623 patients received epidural analgesia. Of those who experienced uterine rupture, 5 of 14 patients (35%) with epidural analgesia experienced abdominal pain, compared with 4 of 23 patients (17%) without epidural analgesia. FHR abnormalities represented the most common sign of uterine rupture among patients who did and did not

receive epidural analgesia. None of the investigators in these studies observed that epidural analgesia delayed the diagnosis of uterine rupture.

Second, pain, uterine tenderness, and tachycardia have low specificity as diagnostic symptoms and signs of lower uterine segment scar dehiscence. Case et al.[78] reported 20 patients with a history of previous cesarean delivery in whom the indication for urgent repeat cesarean delivery was severe hypogastric pain, tenderness, or both. At surgery, they confirmed the presence of scar dehiscence in only one of the 20 patients. Eckstein et al.[79] suggested that the unexpected development of pain during previously successful epidural analgesia might be indicative of uterine rupture. Crawford[80] referred to this phenomenon as the "epidural sieve." Others have described patients who received epidural analgesia and subsequently complained of pain and tenderness secondary to uterine scar rupture.[81-84] I have provided epidural analgesia for several patients in whom the first suggestion of scar separation was the sudden and unexpected development of "breakthrough pain" despite the continuous epidural infusion of local anesthetic. A recent study[85] found evidence of "epidural dose escalation immediately before uterine rupture in women who attempted VBAC, when compared with women who did not have uterine rupture." The authors concluded that "clinical suspicion for uterine rupture should be high in women who require frequent epidural dosing during a VBAC trial."[85] Thus, epidural analgesia may improve the specificity of abdominal pain as a symptom of uterine scar separation or rupture.

Third, most cases of lower uterine segment scar dehiscence do not lead to severe hemorrhage. In one report of six cases of uterine scar dehiscence or rupture, only one patient had intrapartum vaginal bleeding.[68] However, if significant bleeding should occur, epidural anesthesia may attenuate the maternal compensatory response to hemorrhage. Vincent et al.[86] observed that epidural anesthesia (median sensory level of T9) significantly worsened maternal hypotension, uterine blood flow, and fetal oxygenation during untreated hemorrhage (20 mL/kg) in gravid ewes. Intravascular volume replacement promptly eliminated the differences between groups in maternal mean arterial pressure, cardiac output, and fetal Pao_2. Maternal heart rate did not change significantly during hemorrhage in the control animals. However, there was a significant drop in maternal heart rate during hemorrhage in the animals that received epidural anesthesia.[86]

Fourth, several published series have reported the successful use of epidural analgesia in women undergoing TOLAC.[39,68,80,87-90] There is little evidence that epidural analgesia either decreases the likelihood of vaginal delivery or adversely affects maternal or neonatal outcome in women who have uterine scar separation or rupture. Flamm et al.[90] reported a multicenter study of 1776 patients who attempted VBAC. Approximately 134 (74%) of 181 women who received epidural analgesia delivered vaginally, compared with 1180 (74%) of 1595 women who did not receive epidural analgesia. Phelan et al.[87] reported that among patients who received both oxytocin augmentation and epidural analgesia, 69% delivered vaginally. This did not differ from the incidence of vaginal delivery among patients who received oxytocin without epidural analgesia. Other investigators have reported results of smaller studies suggesting a lower rate of successful VBAC among patients who received epidural analgesia.[88,89] However, this effect was limited to patients who received oxytocin for the induction or augmentation of labor. These investigators concluded that epidural analgesia does *not* decrease the likelihood of successful VBAC.

Fifth, some obstetricians favor the use of epidural analgesia because it facilitates postpartum uterine exploration to assess the integrity of the uterine scar. Meehan et al.[91] earlier supported routine postpartum palpation of the uterine scar. However, Meehan et al.[92] subsequently acknowledged that it is not necessary to repair all such defects. Many obstetricians manage asymptomatic uterine scar dehiscence with "expectant observation." Thus, they argue that routine palpation of the uterine scar is unnecessary after successful VBAC.[9]

Sixth, epidural analgesia provides rapid access to safe, surgical anesthesia if cesarean delivery or postpartum laparotomy should be required.[93]

Finally, it is inhumane to deny effective analgesia to women who undergo TOLAC. Further, the ACOG[13] has concluded that adequate pain relief may encourage more women to choose TOLAC. Thus, the availability and use of neuraxial analgesia may decrease the incidence of unnecessary repeat cesarean delivery.

The ACOG[13] has stated that good and consistent scientific evidence supports a conclusion that epidural analgesia may be used during TOLAC. In my judgment, the availability of neuraxial analgesia is an essential component of a successful VBAC program. It seems reasonable to provide analgesia—but not total anesthesia—during labor in patients attempting VBAC.

KEY POINTS

- Cesarean delivery is the most commonly performed major operation in the United States, and previous cesarean delivery is the most common indication.
- A trial of labor is successful in 60% to 80% of women in whom a low-transverse uterine incision was made during previous cesarean delivery.
- A previous vaginal delivery is the greatest predictor for successful vaginal birth after cesarean delivery (VBAC). A history of dystocia, the need for induction of labor, and/or maternal obesity are associated with a lower likelihood of successful VBAC.
- Hospitals and insurers should not mandate a trial of labor for pregnant women with a history of previous cesarean delivery.
- The American College of Obstetricians and Gynecologists has recommended that resources for performing emergency cesarean delivery should be immediately available in women attempting a trial of labor after previous cesarean

delivery (TOLAC). Other groups have argued that this guideline is too restrictive and has created barriers that prevent women from choosing TOLAC.

- Continuous electronic fetal heart rate monitoring represents the best means of detecting uterine rupture.
- Women are more likely to undergo TOLAC if they know that they will receive effective analgesia during labor.
- Epidural analgesia does not delay the diagnosis of uterine rupture or decrease the likelihood of successful VBAC.

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CHAPTER 20

The Pain of Childbirth and Its Effect on the Mother and the Fetus

Peter H. Pan, MD • James C. Eisenach, MD

CHAPTER OUTLINE

The gate control theory of pain, described more than 40 years ago by Melzack and Wall,[1] has revolutionized the understanding of the mechanisms responsible for pain and analgesia. Originally explained as the regulation of pain signals from the peripheral nerve to the spinal cord by the activity of other peripheral nerves, interneurons in the spinal cord, and central supraspinal centers (Figure 20-1), the theory has been refined with the concept of a neuromatrix, a remarkably dynamic system capable of undergoing rapid change.[2] Neural circuits and intraneural mechanisms regulate sensitivity at peripheral afferent terminals; along the conducting axons of peripheral nerves; in the spinal cord, pons, medulla, and thalamus; and at cortical sites of pain transmission and projection. For example, the peripheral application of capsaicin to the skin alters spinal gating mechanisms within 10 minutes, resulting in a light touch signal's being interpreted as burning pain.[3]

Despite extensive research (initiated by the gate control theory) into the mechanisms and treatments for chronic pain, virtually no research on the neurophysiologic basis or therapies for labor pain has been performed. This discrepancy in focus has led to vastly different approaches to the treatment of patients with chronic versus obstetric pain. A patient with chronic pain typically undergoes a sophisticated physical assessment of sensory function; is offered therapies, on the basis of the assessment, from nearly a dozen different classes of analgesics; and can benefit from the enormous resources expended by the pharmaceutical industry to introduce agents that act on novel receptors or enzymes. By contrast, a laboring woman receives no physical assessment of sensory function and is offered only a handful of systemic drugs that act primarily through the anatomic blockade of neural traffic.

In this chapter, this paradox in the approach to labor pain is examined and the basis for current therapy (anatomy), the basis for future therapy (neurophysiology), and the effects of labor pain on the mother and the infant are reviewed.

MEASUREMENT AND SEVERITY OF LABOR PAIN

The recognition and acceptance of chronic pain, which frequently lacks an obvious outward cause, contrasts to the recurrent denial of labor pain, which is accompanied by visible tissue injury. Dick-Read[4] suggested that labor is a natural process not considered painful by women in primitive cultures that should be handled with education and preparation rather than through pain medications. Lamaze[5] popularized psychoprophylaxis as a method of birth preparation; this method now forms the basis for prepared childbirth training in the developed world. Although childbirth training acknowledges the existence of pain during labor, some scientific-thought leaders still consider labor pain to be minor.

The severity of labor pain has been recognized previously. Melzack,[6] using a questionnaire developed to assess

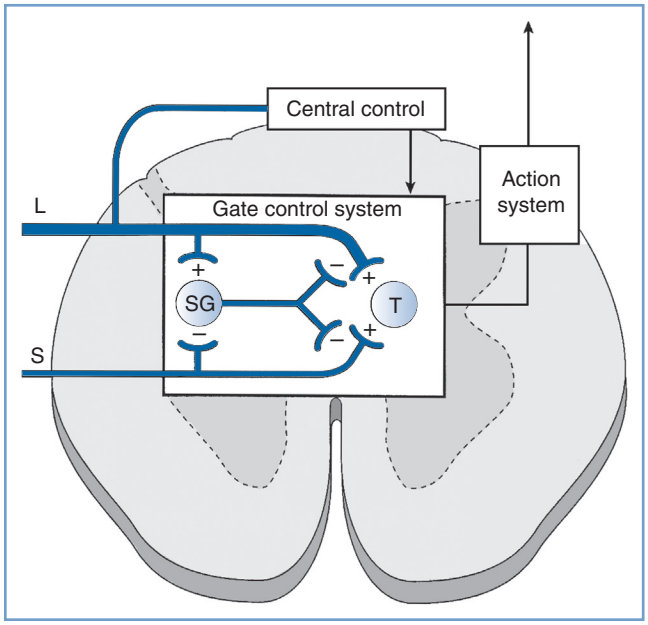

FIGURE 20-1 ■ Gate control theory of pain. Activity in small-diameter afferents (*S*) stimulates transmission cells in the spinal cord (*T*), which send signals supraspinally and results in the perception of pain. Small-diameter afferents also inhibit cells in the spinal cord substantia gelatinosa (*SG*), the activity of which reduces excitatory input to T cells. Activity in large-diameter afferents (*L*) also stimulates T cells in a manner that is perceived as nonpainful and excites SG cells to "close the gate" and reduce small-diameter afferent activation of T cells. The gate mechanism is under regulation by central sites. (From Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150:971-5.)

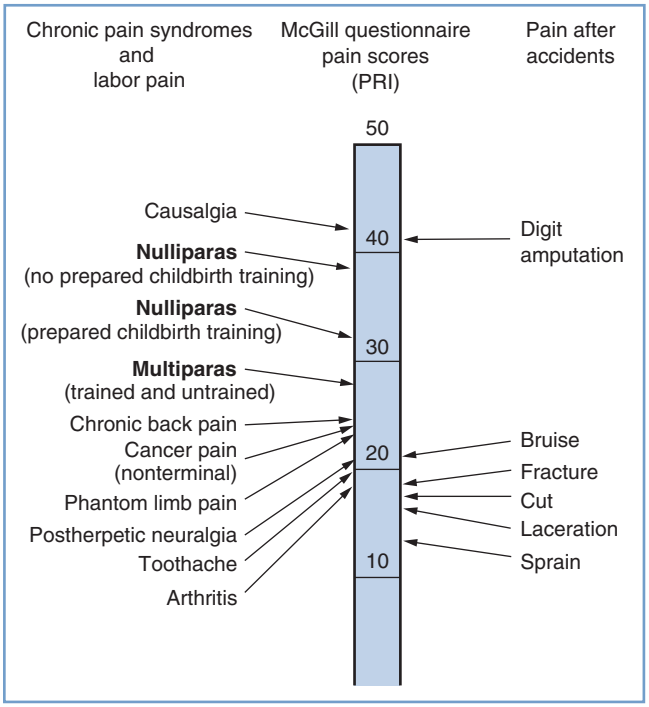

FIGURE 20-2 ■ A comparison of pain scores obtained through the McGill Pain Questionnaire. Scores were collected from women in labor, patients in a general hospital clinic, and patients in the emergency department after accidents involving traumatic injury. Note the modest difference in pain scores between nulliparous women with and without prepared childbirth training. *PRI,* Pain rating index, which represents the sum of the rank values of all the words chosen from 20 sets of pain descriptors. (Modified from Melzack R. The myth of painless childbirth [The John J. Bonica Lecture]. Pain 1984; 19:321-37.)

the intensity and emotional impact of pain, observed that nulliparous women with no prepared childbirth training rated labor pain to be as painful as a digit amputation without anesthesia (Figure 20-2).[6] More than 30 years before Melzack's quantification of pain, Javert and Hardy[7,8] trained subjects to reproduce the intensity of labor pain with the sensation of noxious heat applied to the skin from a radiant heat source. In these experiments, several women achieved "ceiling pain"—resulting in second-degree burns to the skin—when they attempted to match the intensity of uterine contraction pain.[7] Individual women also reported a close positive correlation between cervical dilation and pain intensity. Logistic regression analysis of the investigators' original data[7] indicates a high likelihood of severe pain as labor progresses, with a time course closely associated with cervical dilation (Figure 20-3). Other investigators have noted that uterine pressure during contractions accounts for more than 90% of the variability in labor pain intensity.[9] These observations are consistent with the conclusion that cervical distention is the primary cause of pain during the first stage of labor.

There is considerable variability in the rated intensity of pain during labor. Nulliparous women rate labor pain as more severe than parous women; however, the differences are small and of questionable clinical relevance.[10] There is a correlation between the intensity of menses and labor pain, especially back discomfort,[10] although the reason for this relationship is unknown. It is possible

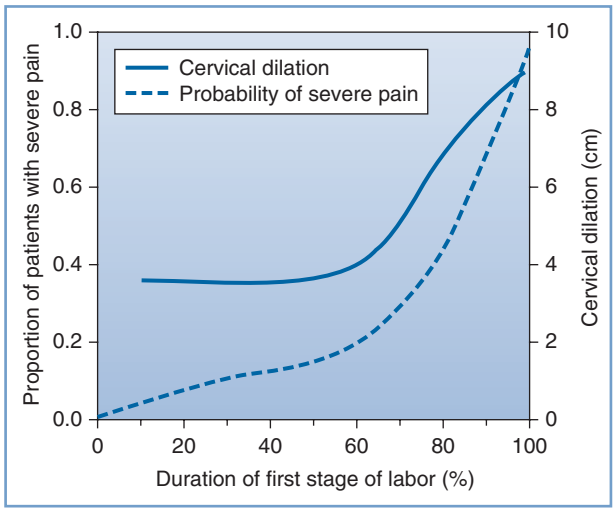

FIGURE 20-3 ■ Likelihood of severe pain during labor. A significant minority of women (approximately one third) have severe pain in early labor, and the proportion of women with severe pain increases to nearly 90% later in labor, in close relationship with cervical dilation. (Data adapted from Hardy JD, Javert CT. Studies on pain: measurements of pain intensity in childbirth. J Clin Invest 1949; 28:153-62.)

that the rated intensity of labor pain reflects individual differences in the perception of all types of pain. In a study of factors affecting labor pain, 10 of 97 subjects reported that they had never experienced pain before childbirth; these women reported significantly less pain during labor and delivery compared with women who had previously experienced pain.[11] In other studies, the variability of pain after cesarean delivery could be predicted with preoperative quantitative sensory testing (such as rating the intensity of pain with a standardized noxious thermal stimulus), psychologic constructs, and their combinations.[12,13]

The mechanism by which people perceive different levels of pain from the same stimulus remains unclear. A study involving brain imaging and a fixed acute noxious heat stimulus showed a strong correlation between verbal pain assessment and the level of activation of various cortical brain regions, especially the contralateral somatosensory cortex and anterior cingulate cortex.[14] The investigators also found that the degree of activation of the thalamus was essentially identical in all subjects, suggesting that differences in perceived pain resulted from modulation at suprathalamic levels rather than in the peripheral nerves or spinal cord. The situation in labor may be more complex. For example, a large genetic polymorphism regulates cytokine production and function as well as pregnancy outcome.[15] It is possible that interindividual differences in labor pain may partially reflect genetic differences in cytokine production or response.

In evaluating and studying labor pain and its treatment, most studies have tended to assess labor pain by using a set of discrete pain scores. However, labor pain is a complex, subjective, multidimensional, and dynamically changing experience with both sensory and affective components that are influenced by many factors. As a result, there are substantial individual differences in labor pain. Therefore, better identification of the covariates that affect labor progress and its associated pain is needed. Recently, Conell-Price et al.[16] developed and validated a dynamic model to account for labor progress in the assessment of labor pain. Subsequently, Debiec et al.,[17] at the same institution, combined a biexponential model that describes labor progress with a sigmoidal labor pain model to assess the influence of patient covariates on labor pain.[17] Both studies used retrospective patient data to develop and test their models. In the former study,[16] the prediction error for the pain scores was large, but the purpose of the model was to identify and remove variability associated with labor progress so that other factors (e.g., genetic polymorphisms) can be quantitatively studied. In this study,[16] cervical dilation accounted for only 16% to 20% of the variability in reported pain. In the latter study,[17] the covariate of ethnicity was found to have a statistically significant but clinically trivial effect on labor progress. The modeling described by these investigators provides a useful quantitative tool for future studies to identify and assess the effect—or the lack of effect—of patient and/or environmental covariates on labor progress, labor pain, and therapeutic responses. Better understanding of underlying causes of interindividual variability in labor progress, labor pain, and therapeutic responses is likely to lead to more tailored therapy.

In summary, although significant variability exists in the rated intensity of pain during labor and delivery, the majority of women experience more than minimal pain. The close correlation between cervical dilation and the rated severity of pain implies the existence of a causal relationship and increases the likelihood that a parturient will request analgesia as labor progresses.

PERSONAL SIGNIFICANCE AND MEANING

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[18] Clearly, this reflects an intensity-discriminatory component and an emotional-cognitive component, with powerful interactions between the two. The focus of current interventions is heavily weighted toward the first component and assumes that labor pain is severe and in need of pharmacologic treatment. Largely ignored are coping strategies and the personal meaning of labor pain, which varies considerably among women.[19]

Although many women rate the pain of labor and delivery as severe, the terms used to more fully describe this pain reflect an emotional meaning. In a pioneering study of the quantification of pain from experimental dilation of the cervix, Bajaj et al.[20] compared pain descriptors in women who were in labor, had experimental cervical dilation, were undergoing spontaneous abortion, or who had dysmenorrhea (Table 20-1). Women with dysmenorrhea used words that indicate suffering, such as "punishing" and "wretched," whereas those in labor did not. Some researchers have drawn parallels between the pain derived from mountain climbing, which is associated with a sense of euphoria, and the pain of labor.[19] As noted by one woman, "You mature and become a stronger personality when you've had a baby and have gone through the pain. I think that is the purpose of it, what the meaning of life is … to protect our children, to be stronger."[21] However, other women have found no deeper meaning to the pain of labor or reasons why it should not be treated. Many conditions that involve pain (e.g., trauma, severe dental disease, cancer) are considered a "normal" part of human life without a spiritual meaning, thereby making labor pain unique.

In summary, there are large interindividual differences in how women experience the personal significance or meaning of labor pain. These different perceptions can lead to a long-term sense of failure and guilt when pharmacologic pain relief is accepted or emotional trauma when it is withheld.

ANATOMIC BASIS

First Stage of Labor

Several lines of evidence suggest that the pain experienced during the first stage of labor is transduced by afferents with peripheral terminals in the cervix and

TABLE 20-1 Word Descriptors from the McGill Pain Questionnaire Used to Describe Pain from the Uterus and Cervix

Pain Descriptors	*Type/Source of Pain*			
	BALLOON DISTENTION OF THE CERVIX*	LABOR†	ABORTION‡	DYSMENORRHEA*
Sensory	Shooting, boring, sharp, hot, dull, taut	Throbbing, shooting, sharp, cramping, aching, taut	Cutting, cramping, tugging, pulling, aching	Pulsing, beating, shooting, pricking, boring, drilling, sharp, cutting, pinching, pressing, cramping, tugging, pulling, hot, stinging, dull, hurting, heavy, taut
Affective		Exhausting, tiring, frightening, grueling	Tiring	Tiring, sickening, punishing, wretched
Evaluative	Annoying		Intense	Annoying, intense
Miscellaneous	Drawing, squeezing	Tearing	Numb, squeezing	Piercing, drawing, squeezing, nagging

*Data from Bajaj P, Drewes AM, Gregersen H, et al. Controlled dilatation of the uterine cervix: an experimental visceral pain model. Pain 2002; 99:433-42.
†Data from Niven C, Gijsbers K. A study of labour pain using the McGill Pain Questionnaire. Soc Sci Med 1984; 19:1347-51.
‡Data from Wells N. Pain and distress during abortion. Health Care Women Int 1991; 12:293-302.

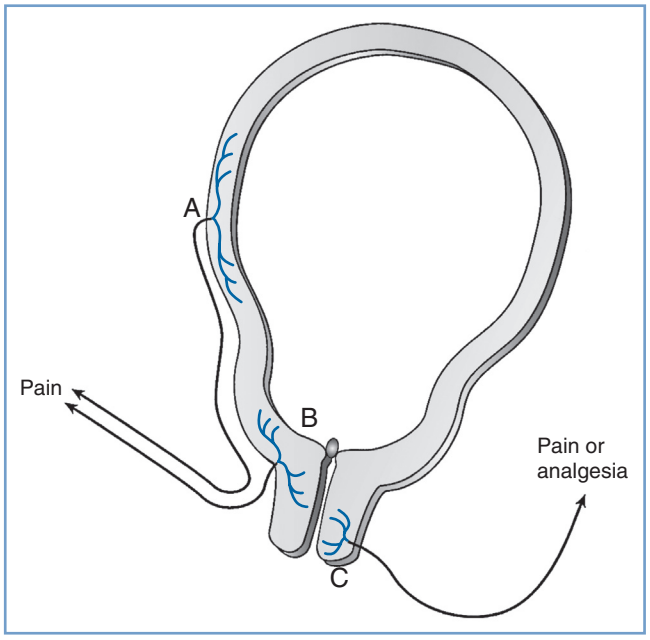

FIGURE 20-4 ■ Uterocervical afferents activated during the first stage of labor. Uterine body afferents (*A*) partially regress during pregnancy and may contribute to the pain of the first stage of labor. However, the major input is from afferents in the lower uterine segment and endocervix (*B*). By contrast, at least in animals, the activation of afferents that innervate the vaginal surface of the cervix (*C*) result in analgesia, not pain, and they enter the spinal cord in sacral areas rather than at the site of referred pain in labor.

lower uterine segment rather than the uterine body, as is often depicted (Figure 20-4). Uterine body afferents fire in response to distention, but in the absence of inflammation, uterine body distention has no or minimal effect on the behavior of laboratory animals.[22,23] These observations suggest that uterine body afferents may be an important site of chronic inflammatory disease and chronic pelvic pain but are much less relevant to acute obstetric and uterine cervical pain. In addition, afferents to the uterine body regress during normal pregnancy, whereas those to the cervix and lower uterine segment do not.[24] This denervation of the myometrium may protect against preterm labor by limiting α_1-adrenergic receptor stimulation by locally released norepinephrine. Hardy and Javert[8] reproduced the pain of uterine contractions in women during labor by manual distention of the cervix. Bonica and Chadwick[25] later confirmed that women undergoing cesarean delivery under a local anesthetic field block experience pain from cervical distention (which mimics that of labor pain) but do not experience pain from uterine distention.[25]

The uterine cervix has dual innervation; afferents innervating the endocervix and lower uterine segment have cell bodies in thoracolumbar dorsal root ganglia (DRG), whereas afferents innervating the vaginal surface of the cervix and upper vagina have cell bodies in sacral DRG.[26] These two innervations result in different sensory input and referral of pain. Pelvic afferents that innervate the vaginal surface of the cervix are almost exclusively C fibers, with the majority containing the peptides substance P and calcitonin gene–related peptide (CGRP). These afferents express alpha and beta estrogen receptors and have an innervation pattern that is not affected by pregnancy.[27-29] Stimulation of the vaginal surface of the cervix in rats results in antinociception, lordosis, ovulation, and a hormonal state of pseudopregnancy, all of which are related to mating behaviors in this species.[30] In rats, these vaginal afferent terminals are activated only during delivery and not during labor, which suggests that they are not relevant to the pain of the first stage of labor.[31] By contrast, dilation of the endocervix in rats results in the activation of afferents entering the lower thoracic spinal cord and nociception rather than antinociception. These afferents, which are mostly or exclusively C fibers,[32] are activated during the first stage of labor, suggesting that they are relevant to pain during this period.

More than 80 years ago, experiments in dogs allowed Cleland[33] to identify T11 to T12 as the segmental level of entry into the spinal cord of afferents that transmit the pain of the first stage of labor. Because dysmenorrhea could be treated through the destruction of the superior

or inferior hypogastric plexus,[34] Cleland reasoned that the sensory afferents and sympathetic efferents were likely intermingled; he subsequently demonstrated that the bilateral blockade of the lumbar paravertebral sympathetic chain could produce analgesia during the first stage of labor.[33] First-stage labor pain is transmitted by afferents that have cell bodies in T10 to L1 DRG and pass through the paracervical region, the hypogastric nerve and plexus, and the lumbar sympathetic chain.

Classical teaching states that pain-transmitting C and A-delta nerve fibers enter the spinal cord through the dorsal roots and terminate in a dense network of synapses in the ipsilateral superficial laminae (I and II) of the dorsal horn, with minimal rostrocaudal extension of fibers. Whereas this characterization is true for somatic afferents, visceral C fiber afferents enter the cord primarily—but not exclusively—through the dorsal roots and terminate in a loose network of synapses in the superficial and deep dorsal horn and the ventral horn. These afferents also cross to the contralateral dorsal horn, with extensive rostrocaudal extension of fibers. This anatomic distinction underlies the precise localization of somatic pain and the diffuse localization of visceral pain, which may cross the midline; it may also determine the potency or efficacy of drugs that must reach afferent terminals, such as intrathecal opioids.

Pain-transmitting neurons in the spinal cord dorsal horn send axons to the contralateral ventral spinothalamic tract (stimulating thalamic neurons) with further projections to the somatosensory cortex, where pain is perceived. These spinal neurons also send axons through the spinoreticular and spinomesencephalic tracts to provide signals to the areas of vigilance (locus coeruleus, reticular formation), cardiorespiratory regulation (nucleus tractus solitarius, caudal medulla), and reflex descending inhibition (periaqueductal gray, locus coeruleus and subcoeruleus, nucleus raphe magnus, rostral medial medulla, cerebellum). Thalamic activation from painful stimuli results in the activation not only of the somatosensory cortex but also areas of memory (prefrontal cortex), motor response (M1 motor cortex), and emotional response (insular cortex, anterior cingulate cortex). Supraspinal pain pathways activated by pain of the first stage of labor can be briefly described sequentially, starting with the ascending pathways projecting to the pons and the medulla, thereby activating centers of cardiorespiratory control and descending pathways as well as the thalamus, which in turn sends projections to the anterior cingulate, motor, somatosensory, and limbic regions.

The anatomic basis for pain of the first stage of labor implies that amelioration of pain should occur after blockade of peripheral afferents (by paracervical, paravertebral, lumbar sympathetic, or epidural [T10 to L1 dermatome] block) or after blockade of spinal cord transmission (by intrathecal injection of local anesthetic and/or opioid) (Figure 20-5). In addition, the widespread

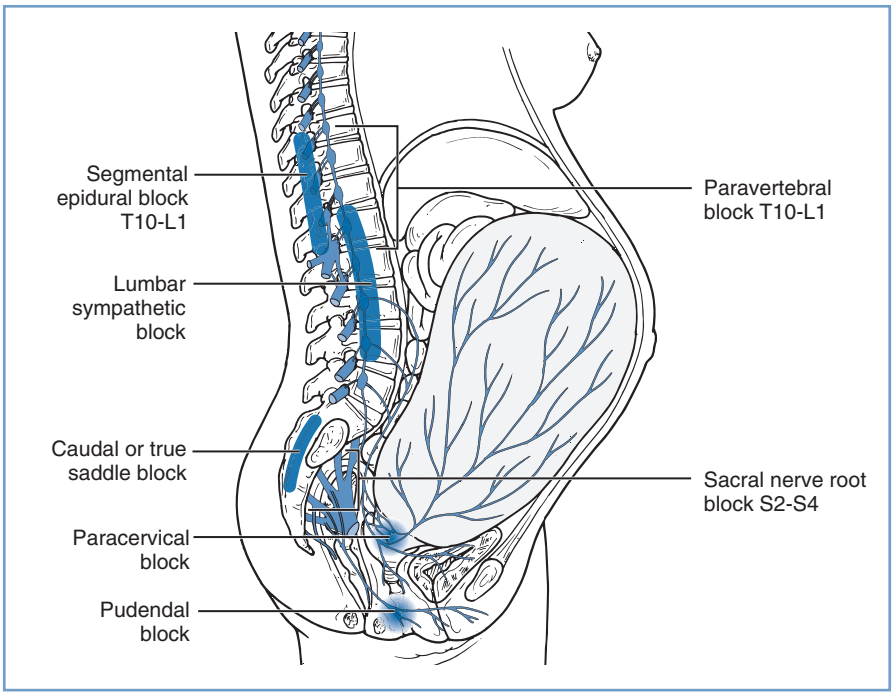

FIGURE 20-5 ■ Transmission of labor pain. Labor pain has a visceral component and a somatic component. Uterine contractions may result in myometrial ischemia, which causes the release of potassium, bradykinin, histamine, and serotonin. In addition, stretching and distention of the lower segments of the uterus and the cervix stimulate mechanoreceptors. These noxious impulses follow the sensory nerve fibers accompanying sympathetic nerve endings, travel through the paracervical region and the pelvic and hypogastric plexus, and enter the lumbar sympathetic chain. Through the white rami communicantes of the T10, T11, T12, and L1 spinal nerves, they enter the dorsal horn of the spinal cord. These pathways could be mapped successfully by demonstration that blockade at different levels along this path (sacral nerve root block of S2-4, pudendal block, paracervical block, low caudal or true saddle block, lumbar sympathetic block, segmental epidural block of T10-L1, and paravertebral block T10-L1) can alleviate the visceral component of labor pain. (From Eltzschig HK, Lieberman ES, Camann WR. Regional anesthesia and analgesia for labor and delivery. N Engl J Med 2003; 348:319-32.)

distribution of visceral synapses in the spinal cord implies that intrathecally administered drugs (e.g., opioids) must have physicochemical properties that facilitate deep penetration into the cord to reach the terminals responsible for pain transmission.

Second Stage of Labor

Pain during the second stage of labor is transmitted by the same afferents activated during the first stage of labor but with additional afferents that innervate the cervix (vaginal surface), vagina, and perineum. These additional afferents course through the pudendal nerve DRG at S2 to S4 and are somatic. Thus, the pain specific to the second stage of labor is precisely localized to the vagina and perineum and reflects distention, ischemia, and frank injury, either by stretching to the point of disruption or by surgical incision. Studies in nonpregnant women indicate a minor analgesic effect of mechanical self-stimulation of the vaginal surface of the cervix[35]; this effect may result from the stimulation of C fibers, because in women with a high oral intake of capsaicin, the activity of such fibers is reduced.[36] The relevance of this minor effect in reducing the pain of the second stage of labor is questionable and has not been examined; however, it does appear to provide evidence that noxious input during labor may activate endogenous analgesia (see later discussion).

The anatomic basis for pain of the second stage of labor implies that analgesia can be obtained through a combination of methods used to treat the pain of the first stage with a pudendal nerve block or extension of the epidural blockade from T10 to S4 (see Figure 20-5).

NEUROPHYSIOLOGIC BASIS

Peripheral Afferent Terminals

Visceral nociceptors, such as those that transduce the pain of the first stage of labor, are activated by stretching and distention. However, unlike somatic afferents, they are not activated by cutting. With each uterine contraction, pressure is transmitted to distort and stretch the uterine cervix, thereby leading to the activation of these nerve terminals. How mechanical distention results in the depolarization of the nerve terminal and the generation of an action potential is not entirely known, but the following three mechanisms are likely:

1. A variety of ion channels respond to the distortion of the cell membrane, and one of them—brain sodium channel-1 (BNC-1) or acid-sensing ion channel-2 (ASIC-2)—is exclusively expressed in sensory afferents and might directly depolarize the nerve terminal by opening its channel when the membrane is distorted (Figure 20-6).[37]
2. Mechanical distortion may result in the acute release of a short-acting neurotransmitter that directly but transiently stimulates ion channel receptors on nerve terminals. Although this process has not yet been examined in the uterine cervix, studies have observed that stretching the bladder urothelium releases adenosine triphosphate, which directly stimulates a type of ligand-gated ion channel—P2X3—on sensory afferents in the bladder wall.[38] Because P2X3 receptors are widely expressed in C fibers,[39] this mechanism might be responsible for the pain that results from the acute distention of the uterine cervix.
3. Local ischemia during contractions may result in gated or spontaneous activity of other ion channels. Some of these ion channels—the ASIC family—respond directly to the low pH that occurs during ischemia,[40] whereas other classes of ion channels may be activated to open spontaneously. For example, the vanilloid receptor type 1 (VR-1) can be stimulated by capsaicin. It is likely that VR-1 receptors (which also respond to noxious heat) are expressed on visceral afferent terminals, given that the application of capsaicin or heat to the distal esophagus in humans results in pain.[41] VR-1 receptor–gated ion channels are not normally open in the absence of high temperature or capsaicin-like ligands; however, in the presence of low pH, the temperature response of these receptors shifts so that their channels open at body temperature.[42]

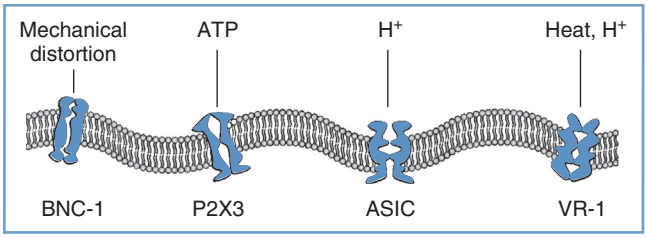

FIGURE 20-6 ■ Afferent nerve endings contain multiple excitatory ligand-gated ion channels, including those that respond to mechanical distortion: *BNC-1,* brain sodium channel-1; *ATP,* adenosine triphosphate; *P2X3,* purinergic receptor; *H*$^+$, hydrogen ion; *ASIC,* acid-sensing ion channel; *VR-1,* vanilloid receptor type 1.

Uterine cervical afferents (including the C fibers that innervate the vaginal surface of the cervix) contain substance P, CGRP, and the enzyme nitric oxide synthase.[43] C fibers can be divided into two groups: (1) those that contain substance P and CGRP and respond to nerve growth factor through actions on tyrosine kinase A receptors and (2) those that contain somatostatin, instead of substance P and CGRP, and respond to glially derived growth factor through actions on a c-ret complex.[44] Some overlap exists between these rough classifications, and further definition of C fiber subtypes will likely occur as more markers and neuropeptides are examined. Other compounds commonly contained in C fiber terminals include glutamate, vasoactive intestinal peptide, and neuropeptide Y. The variable role of C fiber subtypes in the transmission of pain is also unclear. Given that somatostatin typically inhibits substance P release and pain transmission,[45,46] the net transmission of nociception at the spinal cord level may reflect a complex interaction between excitatory and inhibitory C fiber subtypes.

The peripheral afferent neurophysiology of pain during the first stage of labor suggests that the largely unexplored multiple ion channels that transduce the mechanical signal of cervical stretching to an electrical

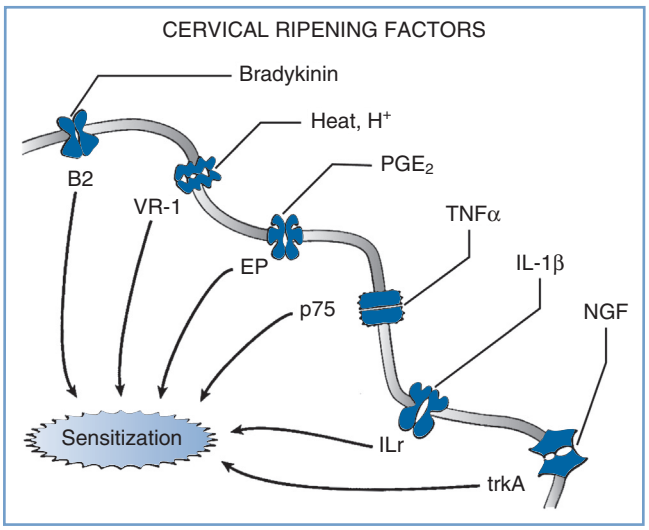

FIGURE 20-7 ■ Effects of inflammation from cervical ripening on afferent terminals. A variety of factors—including bradykinin, heat and hydrogen ions, prostaglandins (including *PGE$_2$*), tumor necrosis factor-α (*TNFα*), interleukin-1 beta (*IL-1β*), and nerve growth factor (*NGF*)—act on their cognate receptors to sensitize nerve endings and amplify the perception and severity of pain from nerve stimulation. *B2,* bradykinin-2 receptor; *EP,* prostaglandin E receptor; *ILr,* interleukin-1 receptor; *p75,* p75 tumor necrosis factor-α receptor; *trkA,* tyrosine kinase A; *VR-1,* vanilloid receptor type 1.

signal generating the perception of pain may represent important new targets for local or systemic analgesic drug delivery. In addition, the understanding of the classification, function, and relevance to pain of different C fiber subtypes remains in its infancy. Research involving endocervical C fiber subtypes may identify new targets for the treatment of labor pain.

Role of Sensitization

Peripheral afferent terminals, like other parts of the sensory system, can change their properties in response to various conditions. Afferent terminals can be directly stimulated by the low pH associated with inflammation (Figure 20-7), and selective ligand-gated ion channels on these terminals can be stimulated by the release of bradykinin.[47] In addition, peripheral inflammation sensitizes afferent terminals by changing their properties; this process can result, over a short time, in a change in gene expression by these nerve fibers, thereby leading to a large amplification of pain signaling.

Although peripheral inflammation is most commonly associated with the pain that results from acute postoperative and chronic arthritic conditions, it may also play an essential role in labor pain. The cervical ripening process and labor itself both result from local synthesis and release of a variety of inflammatory products. The clinical implications of these inflammatory pathways include the application of inflammatory mediators (e.g., prostaglandin E_2 [PGE_2]) to prepare the cervix for labor induction and the administration of inflammatory mediator inhibitors (e.g., indomethacin) to stop preterm labor.

PGE_2 is an especially important sensitizing agent for uterine cervical afferents. In most species, the onset of labor is triggered by a sudden decrease in circulating estrogen concentration. This decrease removes a tonic block on the expression of cyclooxygenase, leading to an increase in local production of prostaglandins, especially PGE_2.[48] PGE_2 is central to a variety of processes that are activated to allow ripening and dilation of the uterine cervix. During the 24 to 72 hours preceding the onset of labor, collagen in the cervix becomes disorganized owing to the activation of prostaglandin receptors and the activity of inflammatory cytokines (mostly interleukin-1-beta [IL-1β] and tumor necrosis factor-alpha [TNF-α]) and matrix metalloproteinases (especially types 2 and 9).[49,50] A series of studies in the rat paw have demonstrated that PGE_2 induces peripheral sensitization in a sex-independent manner by activation of protein kinase A[51] and nitric oxide synthase.[52]

Cytokines and growth factors are also released into the uterine cervix immediately before and during labor. The cytokine IL-1β enhances cyclooxygenase activity and substance P release in the DRG and spinal cord.[53,54] TNF-α increases the spontaneous activity of afferent fibers[55] and enhances CGRP release and VR-1 receptor expression in DRG cells in culture.[56] Nerve growth factor also induces mechanical hypersensitivity.[57] These sensitizing substances (prostaglandins, cytokines, and growth factors) signal peripheral nerves in a manner that results in a host of changes in DRG cell number, peptide expression and release, receptor and ion channel expression, and biophysical properties. For example, inflammatory mediators alter the expression of sodium (Na^+) channel subtypes,[58,59] thereby resulting in more rapid, repetitive firing capability[60] and spontaneous afferent activity.[61]

Estrogen receptor signaling can dramatically affect the structure of the uterine cervix and possibly modulate pain responses. Long-term estrogen exposure sensitizes a subset of mechanosensitive afferents innervating the uterine cervix. The hypogastric afferents that innervate the uterine cervix are polymodal and contain high-threshold (HT) and low-threshold (LT) fibers. Long-term estrogen exposure increases the spontaneous activities of both HT and LT fibers, but only HT fibers show greater responses to uterine cervical distention.[62] Long-term estrogen exposure also increases the proportion of hypogastric afferents innervating the uterine cervix, which express transient receptor potential vanilloid type 1 (TRPV-1). Capsazepine, a TRPV-1 channel antagonist, reduces the hypogastric afferent responses to cervical distention in estrogen-treated animals but not in ovariectomized animals without estrogen replacement.[63,64] These data suggest that the TRPV-1 receptor is important for estrogen-induced sensitization and amplification of pain responses to uterine cervical distention, and that it may therefore represent a potential new target for preventing or treating such enhanced pain.

Implications of the peripheral sensitization of cervical afferents during labor are as follows:

1. Braxton-Hicks contractions, prior to the onset of this inflammatory process, may be as powerful as labor contractions but are painless.
2. Pain may increase with the progress of labor as a result of sensitization.

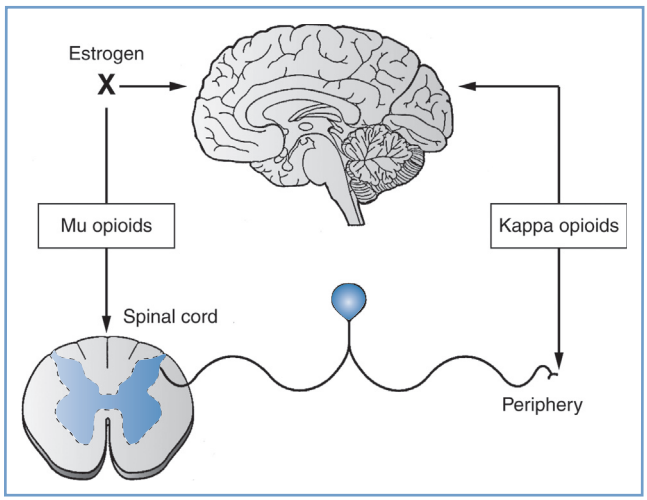

FIGURE 20-8 ■ κ-Opioid receptor agonists act primarily at visceral afferent terminals in the periphery and in the supraspinal central nervous system to provide analgesia during the first stage of labor, whereas μ-opioid receptor agonists act in the spinal cord and the supraspinal central nervous system. Estrogens block the effect of μ-opioid receptor agonists at supraspinal sites.

3. Inflammatory mediators may provide new targets to treat labor pain.

Inhibitory Receptors

Given the multiplicity of direct excitatory and sensitizing mechanisms on peripheral terminals, more plausible targets for peripheral pain treatment are the endogenous inhibitory receptors expressed on the afferent terminals (Figure 20-8). Opioid receptors have achieved the widest attention. Although μ-opioid receptors are expressed in some afferents in the setting of inflammation,[65] the efficacy of morphine provided by local instillation has proved disappointing,[66] with the exception of an intra-articular injection.[67] Similarly, μ-opioid receptor agonists produce antinociception to uterine cervical distention through actions in the central nervous system but not in the periphery.[68]

κ-Opioid receptor agonists may effectively treat visceral pain owing to the presence of these receptors in visceral, but not somatic afferents, at least in the gastrointestinal tract.[69] κ-Opioid receptor agonists can also produce antinociception in response to uterine cervical distention through actions in the peripheral nervous system.[31,68] Pharmaceutical firms are developing drugs of this class that are restricted to the periphery, have few central side effects,[70,71] and presumably express little potential for placental transfer; potentially, such agents would be useful for labor analgesia. One of these new agents has been observed to effectively treat chronic visceral pain from pancreatitis in patients receiving poor analgesia from μ-opioid receptor agonists.[72]

Estrogen and progesterone can alter the analgesic response to opioids. In most cases involving somatic stimulation, tonic estrogen treatment reduces the efficacy of μ-opioid but not κ-opioid receptor agonists.[73] Further, κ-opioid receptor agonists have greater analgesic efficacy in women than in men.[74] In animals, tonic estrogen exposure reduces the inhibitory responses to uterine cervical distention by morphine but not to the κ-opioid receptor agonist U-50488.[75] In contrast, the inhibitory action of *intrathecal* morphine against responses to uterine cervical distention is unaffected by tonic estrogen exposure,[76] which is consistent with the observation that intrathecal opioids relieve the pain of the first, but not second, stage of labor.

Implications of inhibitory receptors on afferent terminals are that κ- but not μ-opioid receptor agonists may produce pain relief through their actions in the periphery. Selective, peripherally restricted drugs are under development for the systemic treatment of visceral pain. In addition, estrogen-dependent inhibition of the supraspinal (but not the spinal) analgesic action of μ-opioid receptor agonists may underlie the limited analgesic effect produced by systemic opioids,[77] a finding that is in contrast to the efficacy of intrathecal opioids[78] in relieving the pain of the first stage of labor.

Peripheral Nerve Axons

The current approach to labor analgesia relies primarily on an understanding of the afferent axons and their level of entry into the spinal cord and on the administration of local anesthetics to block afferent traffic conduction. Traditionally, axons have been considered conduits that allow for the propagation of action potentials by the transitory opening of sodium channels. More recent investigations have confirmed the existence of a variety of sodium channel subtypes and axons that modulate transmission through other ion channels.

Although a number of voltage-gated sodium channel subtypes exist, most studies have focused on three specific subtypes that are expressed in sensory afferents.[79] Two of these, NaV1.8 and NaV1.9, are relatively resistant to blockade by tetrodotoxin (TTX-R); NaV1.9 is often referred to as "persistent," owing to its very slow inactivation kinetics.[80] Inflammation and injury to nerves decrease the TTX-R current density in afferent cell bodies.[81] Some investigators have suggested that NaV1.8 is selectively trafficked to the periphery after injury and inflammation[81] and that a reduction of its expression reduces hypersensitivity.[82] Other investigators, using sucrose gap measurements of compound action potentials, have demonstrated a shortened refractory period and a decrease in delayed depolarization after nerve injury[83,84] that are consistent with the greater expression of rapidly repriming tetrodotoxin-sensitive (TTX-S) channels and the decreased expression of kinetically slow TTX-R channels. To date, these studies have focused primarily on peripheral nerve injury models of chronic pain, and neither the subtypes nor their change during the cervical inflammation of labor has been studied.

Several pharmaceutical firms have discovery programs to produce sodium channel subtype-selective blockers that could improve both the safety and efficacy of the treatment of labor pain, because such agents would not interact with sodium channels in the brain, heart, or motor nerve fibers. Some investigators have observed that injection of the antidepressant amitriptyline, an

agent known to block the NaV1.8 sodium channel, around the peripheral nerves provides a neural blockade twofold to fivefold longer than that provided by injection of long-acting local anesthetics.[85,86]

Another subject of current research is the extension of the duration of selective antinociception with no motor or sympathetic block by manipulation of the TRPV-1 receptor, which is a nonselective ligand-gated cation channel. TRPV-1 receptors are expressed in peripheral primary afferent neurons, the nociceptive C and A-delta fibers, and the dorsal root ganglia, as well as the structures involving the endogenous antinociceptive descending pathway. TRPV-1 receptors can be activated by capsaicin, heat, and endovanilloids, leading to release of substance P, which in turn excites inhibitory neurons in laminae I, III, and IV. Further, activation of the TRPV-1 receptors causes opening of the small TRPV-1 channels on the neurons and allows entry of co-administered charged molecules of certain sizes. Permanently charged local anesthetic, when applied alone, would not be able to cross the nerve membrane to exert its effect on sodium channels in small sensory neurons, but when applied in the presence of capsaicin or other TRPV-1 agonists, the permanently charged local anesthetic would become permeant to exert its local anesthetic effect. Binshtok et al.[87] reported the inhibition of nociceptors by TRPV-1–mediated entry of impermeant sodium channel blockers. However, stimulation of TRPV-1 receptors, such as with capsaicin alone, will also result in the induction of receptor-mediated acute pain. Therefore, these investigators subsequently performed another study in rodents, and they observed that the co-application of lidocaine and its quaternary permanently charged derivative QX-314 produces a prolonged, predominantly nociceptor-selective block by allowing QX314 entry through the TRPV-1 channels without the nocifensive behavior associated with capsaicin when lidocaine is used instead to activate the TRPV-1 receptors.[88] The issues of pain elicited with administration of TRPV-1 agonists such as capsaicin and, more importantly, the neurotoxicity of permanently charged Na^+ channel blockers remain to be overcome and require further research. Additional investigations of the exploitation of new targets may allow provision of safer and prolonged selective antinociception. Should future research prove the absence of toxicity, it is conceivable that amitriptyline or other agents that interact with Na^+ channel subtypes and/or TPRV-1 receptors could be considered for single-injection techniques to produce prolonged and selective analgesia for labor pain and postoperative pain relief.

Interactions within the large number of ion channels expressed on axons can alter neural conduction. An example is the transient refractory period caused by the membrane hyperpolarization that follows a short burst of nerve firing. This phenomenon results from the activation of the Na^+/K^+ exchange pump and dampens high-frequency nerve activity. The Na^+/K^+ exchange pump activity, in turn, can be reduced by a hyperpolarization-induced current termed I_h. Drugs that block the I_h current enhance the hyperpolarization caused by the Na^+/K^+ exchange pump and ultimately serve to reduce nerve traffic[89] and provide prolonged analgesia.[90] A second example is the desensitization of VR-1 receptors present on the axons of C fibers. The perineural injection of drugs that desensitize these receptors without first stimulating them avoids the induction of receptor-mediated acute pain and instead produces very long periods of selective sensory analgesia without motor effects.[91] The mechanism by which VR-1 receptor desensitization alters the transmission of action potentials is under investigation.

Implications of the neurophysiology of axonal transmission of labor pain are that sodium channel subtype-selective agents—or those that affect other ion channels expressed on axons—may provide safer and more selective tools for regional analgesic techniques.

Spinal Cord

When action potentials invade the central terminals of C and A-delta fiber afferents in the spinal cord, voltage-gated calcium channels open and cause intracellular calcium concentration to increase; this increase triggers a multistep process of neurotransmitter docking and fusion with the plasma membrane, which results in neurotransmitter release.[92] Inhibition of these calcium channels produces analgesia. Studies in animals suggest that at least one agent that affects the calcium channels, gabapentin, produces antinociception to visceral stimulation.[93]

A nociceptive stimulus can result in the release of multiple excitatory neurotransmitters, including amino acids (glutamate, aspartate) and peptides (especially substance P, CGRP, and neurokinin A) that interact with specific receptors on spinal cord neurons. Although the stimulation of neurokinin receptors is necessary for the perception of moderate to severe pain,[94] a complex and poorly understood interplay exists among these released neurotransmitters.

Neurotransmitter release at sensory afferent terminals is controlled by presynaptic receptors that act primarily by altering the flux of intracellular calcium when an action potential arrives. Some of these neurotransmitters are excitatory; for example, the action of acetylcholine on nicotinic acetylcholine receptors amplifies further neurotransmitter release.[95] Gamma-aminobutyric acid (GABA) is the key endogenous inhibitory neurotransmitter in the nervous system, and stimulation of GABA receptors significantly reduces the afferent terminal release of other neurotransmitters.[96] Multiple compounds produce analgesia by enhancing the release of GABA at afferent terminals in the spinal cord. The existence of excitatory and inhibitory systems can make the response to a neurotransmitter or an exogenously-administered agent (such as a local anesthetic drug given intrathecally) difficult to predict. For example, acetylcholine can enhance or reduce the afferent terminal release of neurotransmitters by actions on nicotinic and muscarinic receptors, respectively.[97,98] The net effect of acetylcholine appears to be inhibitory, which is indicated by the analgesic effect of intrathecal administration of the cholinesterase inhibitor neostigmine.[99]

The primary mechanism of action of the neurotransmitter enkephalin, which is released by spinal cord interneurons, and of norepinephrine, which is released by axons descending from pontine centers, is the inhibition

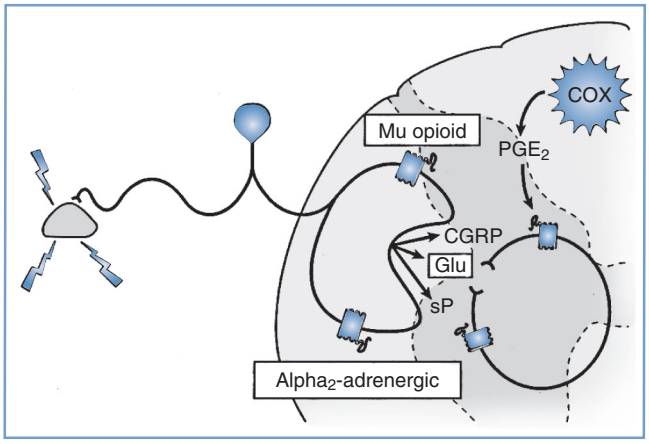

FIGURE 20-9 ■ Pain transmission in the spinal cord. Excitatory transmission occurs directly by release of amino acids such as glutamate (*Glu*) and peptides (*sP* [substance P], *CGRP* [calcitonin gene–related peptide]) and indirectly via activation of enzymes such as cyclooxygenase (*COX*) in nearby glia, which synthesize prostaglandins, including prostaglandin E_2 (PGE_2). Inhibitory mechanisms are primarily presynaptic, with μ-opioid and α_2-adrenergic receptors being the most common (or at least the most studied).

of neurotransmitter release from primary afferent terminals. These substances act on μ-opioid and α_2-adrenergic receptors, respectively,[100,101] and may produce some of the similar effects observed after the intrathecal administration of opioids and α_2-adrenergic agonists for the treatment of labor pain.

Amino acids and peptides released from sensory afferents stimulate a heterogeneous group of spinal cord neurons, including neurons that project to supraspinal structures, interneurons that modulate transmission at the afferent terminal itself (the "gate" of the control theory), and interneurons that stimulate motor and sympathetic nervous system reflexes. Large and sustained glutamate release from an intensely noxious stimulus can activate *N*-methyl-D-aspartate (NMDA) receptors, resulting in sustained depolarization and enhanced excitability of projection neurons (Figure 20-9).[102] Although the intrathecal injection of NMDA receptor antagonists (e.g., ketamine) has been restricted because of neurotoxicity concerns,[103] systemic infusion of magnesium sulfate has been observed to produce postoperative analgesia.[104] Magnesium is an endogenous inhibitory modulator of NMDA receptors, and it is conceivable that magnesium sulfate administered systemically for obstetric indications may have a minor effect on labor pain.

Prolonged and intense nociceptive stimuli can produce sensitization and amplification of pain signaling at the spinal cord level like the peripheral sensitization that occurs as a result of inflammation. Some of these processes are a direct consequence of receptors (e.g., NMDA receptors) that are activated only with highly intense and prolonged stimulation or by the long-term release of neurotransmitters that simultaneously activate the glutamate and substance P receptors on the same cell. Others reflect the synthesis and release of classic "inflammatory" substances by the spinal cord glial cells in response to prolonged afferent stimulation from nitric oxide and prostaglandins, especially PGE_2. Some non-opioid analgesic drugs produce analgesia by actions exclusively (e.g., acetaminophen) or primarily (e.g., aspirin) in the central nervous system (especially the spinal cord).[105]

Spinal sensitization processes represent a novel target for the treatment of labor pain. More than 80 years ago, Cleland[33] noted the presence of hypersensitivity to light touch on the skin of dermatomes T11 and T12 in laboring women, which likely represents the enhanced sensitivity of spinal cord neurons receiving both visceral input from the cervix and skin input at those levels.[106] When the visceral stimulation to these dermatomes was blocked by a paravertebral local anesthetic injection, Cleland[33] observed that the hypersensitivity was ablated; this observation is consistent with the later finding that ongoing C fiber input is required for hypersensitivity to occur.[107] Uterine cervical distention (UCD) results in a pattern of spinal cord neuronal activation similar to that witnessed during labor and delivery. In a study in rats reported by Tong et al.,[108] UCD significantly increased c-fos immunoreactivity in the spinal cord from T12 to L2, with most of the c-fos expression occurring in the deep dorsal horn and central canal regions. UCD-evoked c-fos expression was prevented by prior infiltration of lidocaine into the cervix or by intrathecal administration of ketorolac (a cyclooxygenase [COX] inhibitor) in a dose-dependent manner.[108] Intrathecal administration of indomethacin (a nonspecific COX inhibitor) and the selective COX-2 inhibitor SC-58238 effectively ablated UCD-induced electromyographic activity without altering the hemodynamic response to UCD. By contrast, the selective COX-1 inhibitor SC-58360 was ineffective in ablating UCD-induced electromyographic activity, as was ketorolac, an agent with higher affinity for COX-1 than COX-2.[109] Together, these data suggest that targeting COX-2 is necessary to treat the acute visceral pain often associated with brief infrequent contractions in late pregnancy; therefore, intrathecal ketorolac would be predicted to be ineffective. However, in the setting of sustained, frequent, and repetitive contractions for a prolonged period (as occurs during active labor), intrathecal ketorolac might be effective. The intrathecal injection of ketorolac has been introduced into experimental human trials[110] and warrants examination as a potential modality for selective treatment of labor pain.

The neurophysiologic basis for labor pain in the spinal cord implies that purely inhibitory mechanisms (e.g., opioid and α_2-adrenergic receptors) can be mimicked by the intrathecal injection of agonists to these receptors. However, the administration of other agents (e.g., acetylcholine) in this location has less predictable results. Central sensitization mechanisms in the spinal cord most certainly occur during labor, and future treatments may target these mechanisms.

Ascending Projections

Spinal cord neurons project to multiple brainstem sites as well as the thalamus. More than 30 years ago, it was noted that descending systems—activated primarily by stimulation of the nucleus raphe magnus, the

periaqueductal gray, and the locus coeruleus—could reduce pain transmission as described in the gate control theory.[111] Activation of descending pathways results in the spinal release of endogenous ligands for serotonergic, opioid, and α_2-adrenergic receptor–mediated analgesia. Spillover of neurotransmitters into the cerebrospinal fluid has been used as a measure of activation of these systems, and studies measuring these substances have shown no increase in enkephalin, but an increase in norepinephrine, in laboring women.[112] These descending systems can be activated by psychoprophylactic methods,[113] and agents that prolong or intensify the action of these ligands, such as enkephalinase inhibitors and blockers of monoamine reuptake, might further enhance analgesia.[114]

Brainstem activation by the pain of labor leads to other reflexes, such as increases in sympathetic nervous system activity and respiratory drive and, with prolonged activation, stimulation of descending pathways that amplify rather than reduce pain transmission at the spinal cord.[115,116] The circuitry and pharmacology of such pain-enhancing systems in the brainstem and their potential applications for treatment are under current investigation.

Our understanding of the areas of the brain activated during labor pain is limited, although studies of other types of experimental nociception in healthy volunteers indicate that visceral pain is considered more unpleasant than somatic pain; this difference reflects, in part, the greater activation of centers for negative emotions, including fear. Although distraction methods do not alter the thalamic activation from noxious stimulation, a reduction in cortical activation and the report of pain have been observed,[117] supporting a suprathalamic mechanism of psychoprophylaxis in the reduction of pain.

The neurophysiologic basis of labor pain and ascending projections suggests the activation of multiple supraspinal sites. Some of these sites stimulate potentially detrimental cardiorespiratory reflexes. Other sites, which send descending projections that either reduce or enhance pain transmission in the spinal cord, may be targeted for the provision of analgesia. In addition, suprathalamic modulation of pain signals appears to account for the interindividual differences in pain perception and for the relative efficacy of psychoprophylaxis in reducing the intensity of reported pain.

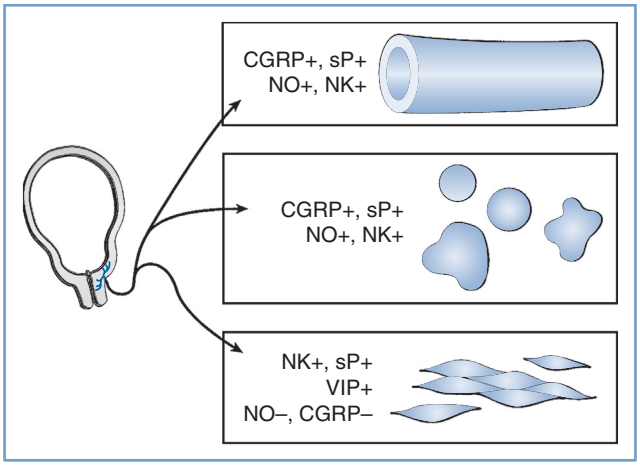

FIGURE 20-10 ■ Aspects of pain that may affect the course of labor. In addition to indirect effects (e.g., beta-adrenergic tocolysis from increased secretion of epinephrine, greater release of oxytocin via Ferguson's reflex), depolarization of afferent terminals in the lower uterine segment and cervix can directly alter aspects of labor. Substances released by nerve terminals include those that increase local blood flow (*CGRP* [calcitonin gene–related peptide], *sP* [substance P], *NO* [nitric oxide], *NK* [neurokinin]), those that stimulate immune cell function, and those that stimulate (+) or inhibit (–) myometrial smooth muscle activity, including vasoactive intestinal peptide *(VIP)*.

EFFECT ON THE MOTHER

Obstetric Course

Several aspects of labor pain can affect the course of labor and delivery (Figure 20-10). Pain-induced increases in the activity of the sympathetic nervous system lead to higher plasma concentrations of catecholamines, especially epinephrine. The provision of labor analgesia reduces the plasma concentration of epinephrine and its associated beta-adrenergic tocolytic effects on the myometrium. This process may underlie the observations by some investigators who have noted, either anecdotally or under controlled conditions, a shift from dysfunctional to normal labor patterns in some women when analgesia is achieved with paravertebral[33] or epidural[118] blocks or with systemic meperidine analgesia.[119] The abrupt reduction in plasma epinephrine concentration that follows the rapid onset of intrathecal opioid analgesia may result in an acute reduction of beta-adrenergic tocolysis and a transient period of uterine hyperstimulation; in some cases, these changes may lead to transient fetal stress and fetal heart rate abnormalities.[120,121]

Ferguson's reflex involves neural input from ascending spinal tracts (especially from sacral sensory input) to the midbrain, thereby leading to enhanced oxytocin release. Although spontaneous labor and delivery occur in women with spinal cord injury (which disrupts this tract[122]), some investigators have argued that neuraxial analgesia can inhibit this reflex and prolong labor, especially the second stage. However, strong evidence for this does not exist. Some studies have noted a reduction in plasma oxytocin concentration with epidural local anesthetic[123] or intrathecal opioid[124] analgesia, whereas others have not noted such a reduction.[125]

Papka and Shew[24] suggested that afferent terminals in the lower uterine segment and cervix might have an important secretory (efferent) function in the regulation of labor. Afferent terminals contain many substances that can *stimulate* (substance P, glutamate, vasoactive intestinal peptide) or *inhibit* (CGRP, nitric oxide) myometrial activity, and these substances can be released locally into the cervix and lower uterine segment when terminals are depolarized by contraction-related tissue distortion. In addition, depolarization of the afferent terminal can result in an action potential that, upon reaching a site of nerve branching, invades adjacent branches and travels distally to depolarize distant terminals of the same nerve. This axon reflex has long been recognized to occur in

somatic nerves; owing to the more extensive arborizations believed to exist in visceral nerves, local stimulation should result in more widespread release of these transmitters. Therefore, it is tempting to speculate that these axon reflexes are more profoundly affected when local anesthetic is administered closer to the terminals associated with cervical dilation and labor (e.g., as occurs with paracervical and paravertebral blocks) than occurs when local anesthetic is administered farther away from the terminals (e.g., with epidural block). This speculation would imply that the net effect of afferent terminal–released substances inhibits rather than accelerates labor.

In summary, neural stimulation through pain pathways leads to the release of substances that either increase (oxytocin) or inhibit (epinephrine) uterine activity and cervical dilation. Therefore, the effect of analgesia on the course of labor can vary between and within individuals. In addition, axon reflexes can result in the release of neurotransmitters from afferents into the lower uterine segment and cervix. It is hoped that future investigation will determine whether the proximity of local anesthetic deposition affects the response of cervical dilation and labor.

Cardiac, Respiratory, and Gastrointestinal Effects

Labor exerts stresses on the cardiovascular and respiratory systems. The elevated plasma catecholamine concentrations observed during labor pain can increase maternal cardiac output and peripheral vascular resistance and decrease uteroplacental perfusion. Even transient stress is associated with dramatic increases in plasma concentration of norepinephrine and subsequent decreases in uterine blood flow (Figure 20-11). Plasma epinephrine concentrations in women with painful labor are similar to those observed after intravenous administration of a bolus of epinephrine 15 μg[126]; intravenous bolus injection of 10 to 20 μg of epinephrine resulted in a significant (albeit transient) reduction in uterine blood flow in gravid ewes.[127] Effective neuraxial analgesia, provided by epidural local anesthetic[128] or intrathecal opioid administration,[129] significantly reduces (50%) maternal catecholamine concentrations. By contrast, neonatal catecholamine concentrations do not appear to be altered by maternal neuraxial anesthetic techniques; this relative independence of neonatal catecholamine responses may be important for the neonatal adaptation to extrauterine life.[130]

The intermittent pain of uterine contractions also stimulates the respiratory system and leads to periods of intermittent hyperventilation. In the absence of supplemental oxygen administration, compensatory periods of hypoventilation between contractions result in transient episodes of maternal, and even fetal, hypoxemia (Figure 20-12). Treatment of labor pain with epidural analgesia minimizes the increase in net minute ventilation and the accompanying increase in oxygen consumption.[131] In general, the cardiovascular and respiratory system changes induced by labor pain are well tolerated by healthy parturients (with normal uteroplacental perfusion) and their fetuses. Some authors have concluded that these changes

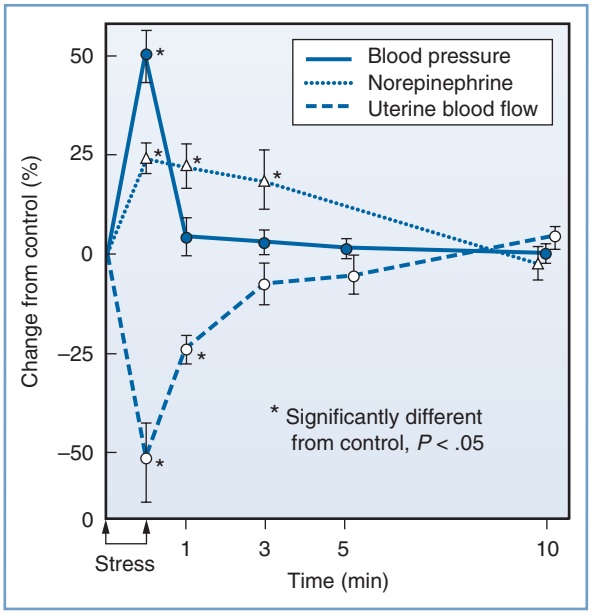

FIGURE 20-11 ■ Effect of a painful stimulus on the hind leg on maternal blood pressure, norepinephrine concentrations, and uterine blood flow in gravid ewes. The increase in blood pressure was transient, but plasma norepinephrine concentrations remained elevated for several minutes; the elevation is reflected in the slow return of uterine blood flow to normal. (From Shnider SM, Wright RG, Levinson G, et al. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology 1979; 50:524-7.)

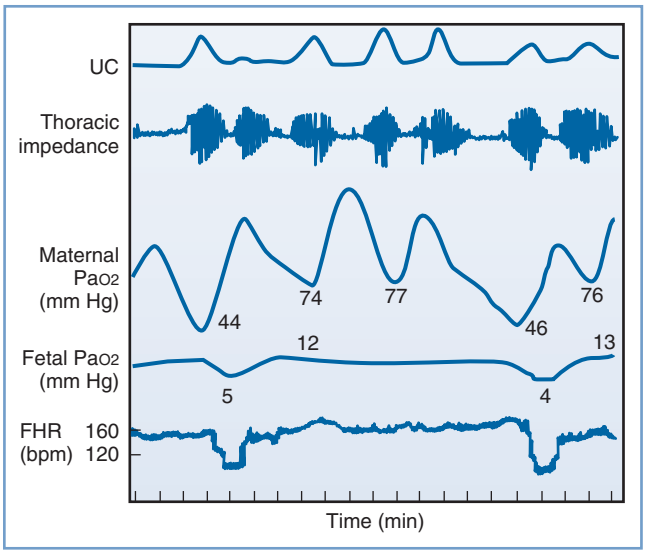

FIGURE 20-12 ■ Maternal and fetal hypoxemia during hypoventilation between uterine contractions (*UC*), which are associated with maternal hyperventilation. *FHR,* fetal heart rate. (From Bonica JJ. Labour pain. In Wall PD, Melzack R, editors. Textbook of Pain. Edinburgh, Churchill Livingstone, 1984, as redrawn from Huch A, Huch R, Schneider H, Rooth GL. Continuous transcutaneous monitoring of fetal oxygen tension during labour. Br J Obstet Gynaecol 1977; 84(Suppl):1-39.)

are of no concern or relevance in uncomplicated labor.[19] However, when maternal or fetal disease or compromise is observed, significant cardiopulmonary alterations may lead to maternal or fetal decompensation; effective analgesia may be especially important in such cases.

Labor pain, anxiety, and emotional stress increase gastrin release and inhibit the segmental and suprasegmental reflexes of gastrointestinal and urinary motility. This in turn results in an increase in gastric acidity and volume and a delay in bladder emptying.[132] These changes are further aggravated by the recumbent position, opioids, and other depressant medications (e.g., barbiturates), putting laboring parturients at risk for pulmonary aspiration of gastric contents, especially during emergency induction of general anesthesia for cesarean delivery.

In summary, pain-induced activation of the sympathetic nervous system during labor is associated with cardiovascular, respiratory, and gastrointestinal effects that may alter maternal and fetal well-being. The provision of effective neuraxial analgesia may mitigate many of these cardiopulmonary effects.

Psychological Effects

The meaning of labor pain is greatly influenced by psychosocial and environmental factors (as previously discussed) and varies considerably among women. Although the acceptance of labor analgesia has a minor overall effect on maternal satisfaction with the labor and delivery process,[133] individual women can be profoundly influenced. It has been suggested that women who understand the origin of their pain and view the labor and delivery process as positive and nonthreatening may undergo pain without suffering.[19] Billewicz-Driemel and Milne[134] reported that a small proportion (< 5%) of women who requested and received epidural labor analgesia described a sense of deprivation from having missed the natural labor experience in its entirety; some of these women may subsequently seek psychiatric counseling.[135]

By contrast, unrelieved severe labor pain can have psychological and physical consequences, including depression and negative thoughts about sexual relationships.[6,10] In a 5-year study in Sweden, 43 women requested elective cesarean delivery owing to a fear of labor and vaginal delivery.[136] Some countries (e.g., Brazil) have an extremely high elective cesarean delivery rate (> 80%) among upper-class women because of their concerns about reduced sexual function after vaginal delivery. Frank psychotic reactions resembling post-traumatic stress disorder can occur after childbirth, although the incidence is rare (< 1%).[137]

Psychological effects of labor pain can occur in a small proportion of women. Psychological harm can be experienced through the provision or withholding of labor analgesia, underscoring the tremendous variability in the meaning of labor pain for different women.

Pain after Delivery

Many women undergo delivery without negative sequelae, but some may experience significant persistent postpartum pain and even depression. Studies of acute and chronic postpartum pain have shown a 7% incidence of perineal pain at 8 weeks after vaginal delivery[138] and a 43% incidence of hyperalgesia at 48 hours and a 23% incidence of residual pain at 6 months after cesarean delivery.[139] In a multicenter, prospective, longitudinal cohort study of 1288 parturients delivering either by cesarean or vaginal delivery, Eisenach et al.[140] tested whether the mode of delivery had an independent role in persistent pain and depression at 8 weeks postpartum. The impact of mode of delivery on acute postpartum pain, persistent pain, depressive symptoms, and their interrelationships was assessed using regression analysis and propensity adjustment. They reported a 10.9% prevalence of severe acute pain within 36 hours postpartum, whereas the prevalence of persistent pain and depression at 8 weeks postpartum was 9.8% and 11.2%, respectively. The severity of acute postpartum pain, but not the mode of delivery, was independently related to risk for persistent pain and depression at 8 weeks postpartum, both of which also resulted in negative effects on activities of daily living and on sleep. Those women with severe acute postpartum pain had a 2.5- and 3.0-fold increased risk for persistent pain and depression, respectively, when compared with those with mild acute postpartum pain. These findings suggest these morbidities may not be related to degrees of physical tissue trauma but rather may be related to an individual's pain response to that injury.

Although there is significant interindividual variability with regard to acute postpartum pain,[141] the severity of acute postoperative pain in nonobstetric surgical patients has been correlated with the occurrence of chronic pain.[142] Whether the presence and severity of labor pain or the presence and severity of acute postpartum pain after either vaginal or cesarean delivery predicts the occurrence of chronic pain is under investigation. Studies in animals suggest that acute intervention at the time of tissue injury reduces the likelihood of developing chronic pain.[143] It is likely that severity of the acute pain is not just a marker of chronic pain but rather an active participatory component in the pathophysiology of transitioning from acute to chronic pain.[140] Therefore, more careful attention to pain treatment and follow-up in days after childbirth may potentially reduce long-term morbidities and improve overall outcomes.

Reports on the incidence of chronic pain after delivery vary widely in part because of the difference in the definition and the inclusion or exclusion of types of chronic pain and not critically separating new pain after delivery from preexisting pain. Long-term follow up of postpartum patients showed that the incidence of chronic pain (defined as new pain that began at the time of labor and delivery) at 6 months and 1 year was remarkably low at 3% and 0.1%, respectively, compared with nonobstetric surgeries with similar tissue injury.[144] By using a sciatic nerve injury–induced neuropathic pain model in rats, it has been observed that the birthing process plus the nursing of the pups in combination, but not individually, may be protective of the development of surgical nerve injury–induced hypersensitivity to pain. This protection is likely mediated by spinal oxytocin because the protective effect is abolished by administration of spinal atosiban, an oxytocin antagonist.[145]

Further research is needed to better define protective and/or predictive factors in patients who are at risk for developing severe acute and/or chronic postpartum pain. Persistent or chronic pain may be particularly difficult for postpartum patients owing to the multiple stresses (e.g.,

care of the neonate) and sequelae encountered. An association between pain and depression exists, and depression is the most common complication after delivery, affecting approximately 13% of postpartum women.[146] Postpartum patients with depression are among those who frequently do not disclose depression even though they desire assistance.[147,148] Immediate and effective postpartum pain management (after both vaginal and cesarean deliveries) with adequate long-term follow-up may potentially prevent long-term morbidity and improve overall outcomes.

EFFECT ON THE FETUS

Because of the absence of direct neural connections from the mother to the fetus, maternal labor pain has no direct effects on the fetus. However, maternal labor pain can affect a number of systems that determine uteroplacental perfusion, as follows: (1) uterine contraction frequency and intensity, by the effect of pain on the release of oxytocin and epinephrine; (2) uterine artery vasoconstriction, by the effect of pain on the release of norepinephrine and epinephrine; and (3) maternal oxyhemoglobin desaturation, which may result from intermittent hyperventilation followed by hypoventilation, as discussed earlier. Although these effects are well tolerated in normal circumstances and are effectively blocked by analgesia, fetal well-being may be affected in situations of limited uteroplacental reserve.

SUMMARY

Pain during the first stage of labor results from the stimulation of visceral afferents that innervate the lower uterine segment and cervix, intermingle with sympathetic efferents, and enter the spinal cord at the T10 to L1 segments. Pain during the second stage of labor results from the additional stimulation of somatic afferents that innervate the vagina and perineum, travel within the pudendal nerve, and enter the spinal cord at the S2 to S4 segments. These pain signals are processed in the spinal cord and are transmitted to brainstem, midbrain, and thalamic sites, the last with projections to the cortex, resulting in the sensory-emotional experience of pain. Current obstetric anesthesia practice relies nearly exclusively on the blocking of pain transmission by deposition of local anesthetic—with or without adjuncts—along the afferent nerves from sites near the peripheral afferent terminals to sites near their central terminals.

The neurophysiology of visceral pain, especially in relation to labor pain, is currently under investigation, with considerable academic and pharmaceutical targeting of (1) the normal ionic transduction mechanisms and processes of sensitization in peripheral afferent terminals, (2) the mechanisms of inhibition available in the spinal cord and brainstem, and (3) the processes by which conscious distraction methods can be amplified and can relieve pain. Labor pain is an intensely variable and personal experience, and it is essential that the anesthesia provider play a flexible role within this context.

KEY POINTS

- Labor pain exists and is severe in many women, with a close correlation between cervical dilation and pain during the first stage.
- The first stage of labor involves visceral pain from the lower uterine segment and endocervix, which results in hypersensitivity to convergent somatic dermatomes. This pain is most likely amplified over time as a result of the sensitization of peripheral and central pain-signaling pathways. The second stage of labor results in somatic pain from the vagina and perineum and is briefer than the first stage.
- Afferent terminals transduce a mechanical process into electrical signals, which are probably amplified by the release of prostaglandins, cytokines, and growth factors into the cervix as part of the normal disruption of collagen that allows the cervix to soften and dilate.
- Pain transmission in the spinal cord is not hardwired; it is remarkably and rapidly plastic, and it is altered by local neuronal activity that releases μ-opioid receptor agonists and descending pathways that release α_2-adrenergic and serotonergic receptor agonists.
- There are large individual differences in pain perception, which likely reflect differences at suprathalamic sites. The activation of suprathalamic sites is the primary mechanism of action for distraction methods of analgesia.
- Labor pain alters the obstetric course and the maternal cardiac and respiratory function in a complex manner that normally is well tolerated, can sometimes be detrimental to both mother and fetus, and is alleviated by analgesia.
- Labor pain carries meaning in distinction from most other causes of severe pain; the treatment of labor pain should be applied within this context.
- Acute postpartum pain after either vaginal or cesarean delivery deserves attention and treatment; the factors or mechanisms responsible for the development of persistent or chronic postpartum pain are under investigation.

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CHAPTER 21

Childbirth Preparation and Nonpharmacologic Analgesia

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CHAPTER OUTLINE

Pregnant women and their support person(s) obtain information about childbirth and analgesia from many sources. The more traditional sources of information include obstetricians, childbirth preparation classes, lay periodicals, books and pamphlets, and experiences of family and friends. Currently, the Internet has become the primary source of information for many patients. Many health care organizations provide patient access to community health libraries on site that include Internet access and librarian support to facilitate information searches. Anesthesia providers should be familiar with the information that patients in the local area are using for decision-making, because this information influences their birth experiences. Knowledge of the information and biases held by patients helps anesthesia providers in their interactions with pregnant women.

Prepared childbirth training provides undeniable benefits to the pregnant woman and her support person. However, prepared childbirth training should not be equated with nonpharmacologic analgesia.[1] Some childbirth preparation instructors discourage the use of medications during labor and delivery, whereas others make a nonbiased presentation of the advantages and disadvantages of various analgesic techniques. The information contained in this chapter provides a basis for informed discussion of pain relief options among patients, nurses, obstetricians, and anesthesia providers.

PAIN PERCEPTION

Anesthesia providers are indebted to John Bonica and Ronald Melzack for their studies of the pain of childbirth. Investigators have used sophisticated questionnaires[2,3] and visual analog scales[4] to evaluate the maternal perception of pain during parturition. Melzack et al.[5,6] developed the McGill Pain Questionnaire to measure the intensity of labor pain for various conditions. They noted that labor pain is one of the most intense types of pain among those studied (see Figure 20-2). Parous women had lower pain scores than nulliparous women, but responses varied widely (Figures 21-1 and 21-2). Prepared childbirth training resulted in a modest decrease in the average pain score among nulliparous women, but it clearly did not eliminate pain in these women.[5,6]

CHILDBIRTH PREPARATION

History

The history of modern childbirth preparation began in the first half of the 20th century; however, it is important to review earlier changes in obstetric practice to understand the perceived need for a new approach. Before the mid-19th century, childbirth occurred at home in the company of family and friends. The specialty of obstetrics developed in an effort to decrease maternal mortality. Interventions initially developed for the management of complications became accepted and practiced as routine obstetric care. Physicians first administered anesthesia for childbirth during this period. The 1848 meeting of the American Medical Association included reports of the use of ether and chloroform in approximately 2000 obstetric cases.[7] The combination of morphine and scopolamine (i.e., twilight sleep) was introduced in the early 20th

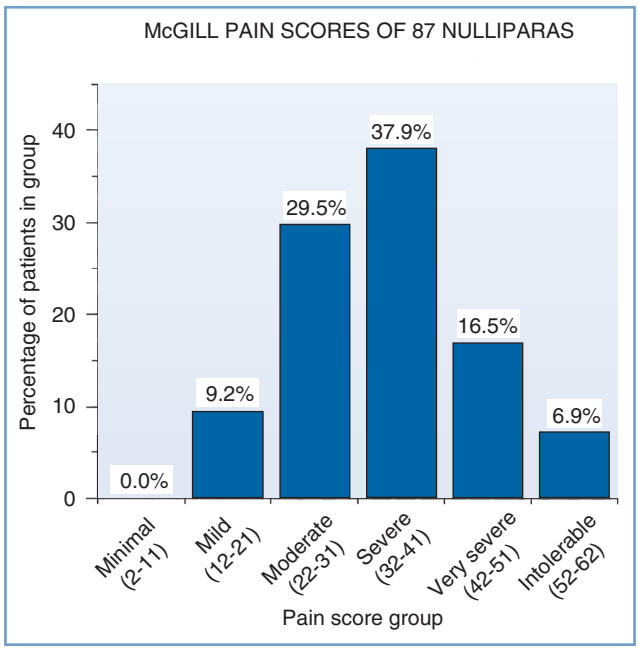

FIGURE 21-1 ■ The severity of pain during labor as assessed by the McGill Pain Questionnaire for 87 nulliparous women. (Modified from Melzack R, Taezner P, Feldman P, Kinch RA. Labour is still painful after prepared childbirth training. Can Med Assoc J 1981; 125:357-63.)

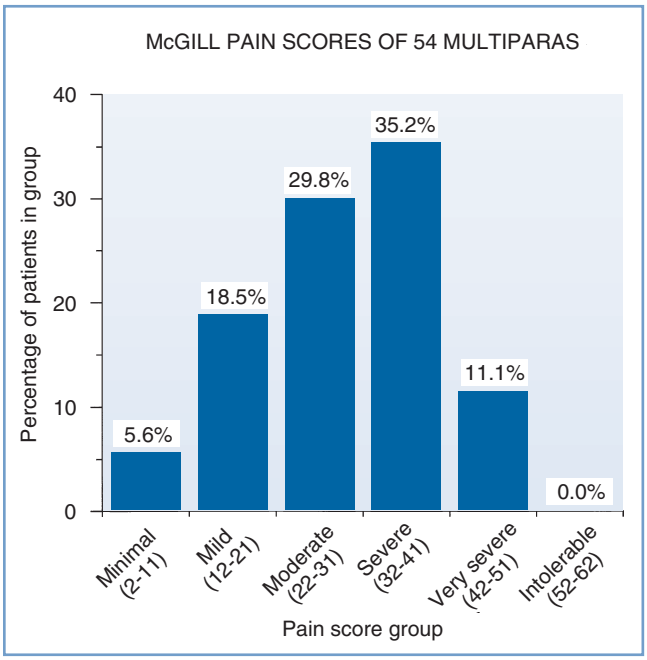

FIGURE 21-2 ■ The severity of pain during labor as assessed by the McGill Pain Questionnaire for 54 parous women. (Modified from Melzack R, Taezner P, Feldman P, Kinch RA. Labour is still painful after prepared childbirth training. Can Med Assoc J 1981; 125:357-63.)

century. These techniques were widely used, and influential women demanded that they be made available to all parturients.[8] Together, these developments moved childbirth from the home and family unit to the hospital environment.[9] Despite their desire for analgesia/anesthesia for labor and delivery, women began to resent the fact that they were not active participants in childbirth.

Beck et al.[10] wrote a detailed history of childbirth preparation. Dick-Read[11,12] reported the earliest method in his books, *Natural Childbirth* and *Childbirth Without Fear*. In his original publication, he asserted his belief that childbirth was not inherently painful. He opined that the pain of childbirth results from a "fear-tension-pain syndrome." He believed—and taught—that antepartum instruction about muscle relaxation and elimination of fear would prevent labor pain. He later established antenatal classes that included groups of mothers and fathers. Some readers incorrectly concluded that he advocated a return to primitive obstetrics, but this was not the case. Review of his practice reveals that he used the available obstetric techniques—including analgesia, anesthesia, episiotomy, forceps, and abdominal delivery—as appropriate for the individual patient. However, he cautioned against the routine use of these procedures, and he encouraged active participation of mothers in the delivery of their infants. Unfortunately, he did not use the scientific method to validate his beliefs.

Although Dick-Read was the earliest proponent of natural childbirth, it was Fernand Lamaze[13] who introduced the Western world to psychoprophylaxis. His publications were based on techniques that he observed while traveling in Russia. Although his theories ostensibly were translations of teachings later published in the West by Velvovsky et al.,[14] they contained substantial differences and modifications. The "Lamaze method" became popular in the United States after Marjorie Karmel[15] wrote about her childbirth experience under the care of Dr. Lamaze. Within a year of the publication of her book *Thank You, Dr. Lamaze: A Mother's Experiences in Painless Childbirth*, the American Society for Psychoprophylaxis in Obstetrics was born. Lamaze and Karmel published their experience at a time when organizations such as the International Childbirth Education Association and the La Leche League were formed.[16] These organizations actively and aggressively encouraged a renewed emphasis on family-centered maternity care, and society was ripe for the ideas and theories promoted by these organizations. Women were ready to actively participate in childbirth and to have input in decisions about obstetric and anesthetic interventions. Childbirth preparation methods were taught and used extensively, despite a lack of scientific validation of their efficacy.

In 1975, Leboyer[17] described a modification of natural childbirth in his book *Birth Without Violence*. He advocated childbirth in a dark, quiet room; gentle massage of the newborn without routine suctioning; and a warm bath soon after birth. He opined that these maneuvers result in a less shocking first-separation experience and a healthier, happier infancy and childhood. Although there are few controlled studies of this method, published observations do not support his claim of superiority.[18,19]

Physicians were the initial advocates of the various natural childbirth methods. Obstetricians had become increasingly aware that analgesic and anesthetic techniques were not harmless, and they supported the use of

natural childbirth methods.[10] Subsequently, natural childbirth, like the methods of obstetric analgesia introduced earlier in the century, was actively promoted by lay groups rather than physicians.[20] Lay publications, national advocacy groups, and formal instruction of patients accounted for the greater interest in psychoprophylaxis and other techniques associated with natural childbirth.

Goals and Advantages

The major goals of childbirth education that were initially promoted by Dick-Read are taught with little modification in formal childbirth preparation classes today. Most current classes credit Lamaze with the major components of childbirth preparation, even though Dick-Read was the first to promote patient education, relaxation training, breathing exercises, and paternal participation.[10] Box 21-1 describes the goals of current childbirth preparation classes. In addition, some instructors and training manuals claim other benefits of childbirth preparation (Box 21-2). Reviews by Beck and Hall[21] and Lindell[22] concluded that much of the research on the efficacy of childbirth education does not meet the fundamental requirements of the scientific method. Despite these shortcomings, childbirth preparation classes are widely available and attended.

Socioeconomic disparities exist in childbirth education class attendance.[23] In addition, the effect of childbirth education on attitude and childbirth experience depends in part on the social class to which the mother belongs. Most investigators have found that childbirth classes have a positive effect on the attitudes of both parents in all social classes, but this effect is more pronounced among "working class"[24] and indigent women[25]; this latter finding probably reflects the greater availability and use of other educational materials by middle- and upper-class women. Childbirth classes often are the only—or at least the primary—source of information for working class and indigent women.

BOX 21-1 Goals of Childbirth Preparation

- Patient education about pregnancy, labor, and delivery
- Relaxation training
- Instruction in breathing techniques
- Participation of father/support person
- Early parental bonding

BOX 21-2 Purported Benefits of Childbirth Preparation

- Greater maternal control and cooperation
- Decreased maternal anxiety
- Reduced maternal pain
- Decreased maternal need for analgesia/anesthesia
- Shorter labor
- Diminished maternal morbidity
- Less fetal stress/distress
- Strengthened family relationships as a result of the shared birth experience

Limitations

Limitations of the widespread application of psychoprophylaxis and other childbirth preparation methods remain. Proponents assume that these techniques are easily used during labor and delivery; however, Copstick et al.[26] concluded that this assumption is not valid. They found that patients were able to use the coping techniques in the early first stage of labor but that the successful use of the coping skills became less and less common as labor progressed. By the onset of the second stage, less than one third of mothers were able to use any of the breathing or postural techniques taught during their childbirth classes.[26] The method of preparation influences the ability of the pregnant woman to use the breathing and relaxation techniques. Bernardini et al.[27] observed that self-taught pregnant women are less likely to practice the techniques during the prenatal period or to use the techniques during labor.

Childbirth preparation classes may create false expectations. If a woman does not enjoy the "normal" delivery discussed during classes, she may experience a sense of failure or inferiority. Both Stewart[28] and Guzman Sanchez et al.[29] have discussed the psychological reactions of women who were unable to use psychoprophylaxis successfully during labor and delivery. In addition, several women have written about their disappointment with the dogmatic approach of their childbirth instructors; these women described instructors who rigidly defined the "correct" way to have a "proper" birth experience.[30,31]

Effects on Labor Pain and Use of Analgesics

Little scientific evidence supports the efficacy of childbirth preparation in mitigating labor pain. Psychology, nursing, obstetric, anesthesia, and lay journals provide extensive discussions of childbirth preparation, but most articles describe uncontrolled clinical experiences. Outcome studies often do not include a group of women who were randomly assigned to an untreated or a placebo-control group, and statistical analysis is often incomplete. Despite these shortcomings, supporters of childbirth preparation assume that it offers benefits for mother and child. Table 21-1 summarizes a few of the studies of Lamaze and other childbirth preparation techniques and their association with labor outcomes. The findings are not consistent. Some researchers have reported a *decreased* use of analgesics[32-35] or regional anesthesia,[32-36] shorter labor,[37] reduced performance of instrumental[32,34,36] and cesarean delivery,[36] and a lower incidence of nonreassuring fetal status,[36] whereas others have reported *no change* in the use of analgesics[36-40] or neuraxial analgesia,[38,39] length of labor,[34-36,38-41] performance of instrumental[38-40] and cesarean delivery,[34,38-40] or incidence of nonreassuring fetal status.[33,34,37,39] These diverse findings may reflect different patient populations, poor study design, or researcher bias.

TABLE 21-1 Effects of Childbirth Preparation

Study	Analgesic Use	Neuraxial Anesthesia	Length of Labor	Cesarean Delivery Rate	Instrumental Delivery Rate	Fetal Distress	Oxytocin Use
Patton et al.[39]	NC	NC	NC	NC	NC	NC	↑
Hetherington[32]	↓	↓	—	—	↓	—	—
Zax et al.[35]	↓	↓	NC	—	—	—	—
Scott & Rose[34]	↓	↓	NC	NC	↓	NC	NC
Hughey et al.[36]	NC	↓	NC	↓	↓	↓	NC
Sturrock & Johnson[40]	NC	—	NC	NC	NC	—	—
Brewin & Bradley[38]	NC	NC	NC	NC	NC	—	—
Delke et al.[37]	NC	—	↓	—	—	NC	NC
Rogers[33]	↓	—	—	—		NC	—

NC, No change; ↑, increased; ↓, decreased; —, not studied/reported.

BOX 21-3 Nonpharmacologic Analgesic Techniques

Minimal Training/Equipment

- Emotional support
- Touch and massage
- Therapeutic use of heat and cold
- Hydrotherapy
- Vertical position

Specialized Training/Equipment

- Biofeedback
- Intradermal water injection
- Transcutaneous electrical nerve stimulation
- Acupuncture
- Hypnosis

To elucidate the effect of the coping techniques taught in childbirth classes, several investigators have attempted to quantify changes in pain threshold, pain perception, anxiety levels, and physiologic responses to standardized stimuli. Several studies have evaluated nonpregnant and nulliparous women in laboratory settings,[42-45] and another study evaluated pregnant women in the antepartum, intrapartum, and postpartum periods.[46] Conclusions varied according to the stimuli applied, the coping techniques studied, and the parameters analyzed. Together, these studies suggest that *practicing* these techniques facilitates their efficacy and that newer cognitive techniques (e.g., systematic desensitization, sensory transformation) may be more effective than traditional Lamaze techniques of varied breathing patterns and relaxation. Further studies may help refine childbirth preparation to maximize the positive psychophysiologic effects.

NONPHARMACOLOGIC ANALGESIC TECHNIQUES

Nonpharmacologic analgesic techniques range from those that require minimal specialized equipment and training and are available to all patients to those that are offered only by institutions with the necessary equipment and personnel trained in their use (Box 21-3). Many studies have assessed nonpharmacologic methods of labor analgesia; however, most published studies have not fulfilled the requirements of the scientific method.[47-49] Several comprehensive reviews of alternative therapies for pain management during labor have been published,[47-49] providing a foundation for discussion with patients and obstetric providers. However, clinical evidence is insufficient to form the basis for an in-depth discussion of some of the more recent therapeutic suggestions, such as music therapy, aromatherapy, and chiropractic. These analgesic techniques may provide intangible benefits that are not easily documented by a rigorous scientific method. Parturients may consider these benefits an integral and important part of their labor experience.

Continuous Labor Support

Some techniques that require minimum equipment and specialized training are taught as integral components of childbirth preparation classes. Continuous support during labor is essential to the process of a satisfying childbirth experience; typically, the parturient's husband or friend provides this support.[50,51] This support appears most helpful for the parturient who lives in a stable family unit. At least one study noted that husband participation was associated with decreased maternal anxiety and medication requirements.[51] Others have found that emotional support provided by unfamiliar trained individuals (e.g., doulas) also has a positive effect.[52-55] Several studies have evaluated the benefits of emotional support provided by doulas or other unrelated individuals on the length of labor,[52,53,55] oxytocin use,[53] requirements for analgesia and/or anesthesia,[52,53] incidence of operative delivery,[53] and maternal morbidity.[53,54] These studies all suggested that a patient's sense of isolation adversely affects her perception of labor. Further, the companionship of another woman who is not part of the medical establishment may reduce a parturient's anxiety more effectively than the companionship provided by her husband. In one study, women randomly assigned to receive intrapartum support from a friend or female relative (who was chosen by the parturient and trained as a doula) were more likely to have positive feelings about their delivery and had a higher rate of breast-feeding 6 to 8 weeks after delivery

TABLE 21-2 **Systematic Review: Continuous Labor Support versus Usual Care**

Outcome	No. of Trials	No. of Subjects	Relative Risk*	95% Confidence Interval
Use of neuraxial analgesia	9	11,444	0.93	0.88 to 0.99
Use of any analgesia	13	12,169	0.90	0.84 to 0.97
Spontaneous vaginal delivery	18	14,005	1.08	1.04 to 1.12
Instrumental vaginal delivery	18	14,004	0.84	0.84 to 0.96
Cesarean delivery	21	15,061	0.79	0.67 to 0.92
Patient dissatisfaction with childbirth experience	11	11,133	0.69	0.59 to 0.79
Duration of labor	11	11,444	–0.58 h†	–0.86 to –0.30
Infant with a low 5-minute Apgar score	12	12,401	0.70	0.50 to 0.96

*For women who received continuous support.
†Weighted mean difference.
Data are summarized from Hodnett ED, Gates S, Hofmeyr GJ, et al. Continuous support for women during childbirth. Cochrane Database Syst Rev 2011; (2):CD003766.

than women who were randomly assigned to receive usual care.[41]

A meta-analysis evaluated results from 21 studies that included more than 15,000 women who were randomly assigned to receive either continuous childbirth support or usual care (Table 21-2).[56] The pooled data suggested that women who received one-on-one support during labor were less likely to use neuraxial analgesia or receive any type of analgesia, were more likely to have a spontaneous vaginal delivery, and reported less dissatisfaction with the childbirth experience.[56] In addition, the mean duration of labor was slightly shorter (approximately 35 minutes) in the women who received continuous support during labor. There were no differences in neonatal outcome.

These results are fascinating and have important implications for obstetric care. The patient populations studied represent special situations, and the results may not be reproduced in all populations. For example, a large randomized, controlled trial in a North American hospital (in which intrapartum medical intervention is routine) found no differences in the rate of cesarean delivery or other labor outcomes between women randomly assigned to receive continuous labor support from a specially trained nurse and women who received usual care.[57] In general, results from trials in North America do not appear as striking as those from Europe or Africa.[47] The aforementioned systematic review of continuous labor support suggested that benefits were greater when the support person was not a member of the hospital staff.[56] Further studies should compare different models of continuous childbirth support and should include outcomes such as cost analysis.[56] Meanwhile, the preponderance of evidence suggests that all parturients should have access to emotional support, whether it is provided by the husband, a family member, a labor companion (e.g., doula), or professional hospital staff.

Touch and Massage

Various touch and massage techniques are discussed with women and their support persons during childbirth preparation classes. These techniques include effleurage, counterpressure to alleviate back discomfort, light stroking, and merely a reassuring pat.[47] There has been minimal scientific study of the effects of touch and massage on labor progress and outcome[58-60]; nonetheless, touch and massage provide a comfort that is appreciated by women during labor. These measures may be used by the parturient, her support person, or the professional staff members providing intrapartum care. The techniques are easily discontinued if the parturient desires. In some cases, touch and massage may reduce discomfort. More often, touch and massage transmit a sense of caring, which fosters a sense of security and well-being.

Therapeutic Use of Heat and Cold

Another simple technique for alleviating labor pain is the therapeutic use of temperature (hot or cold) applied to various regions of the body. Warm compresses may be placed on localized areas, or a warm blanket may cover the entire body. Alternatively, ice packs may be placed on the low back or perineum to decrease pain perception. The therapeutic use of heat and cold during labor has not been studied in a rigorously scientific manner. The use of superficial heat and cold for comfort is widespread (if not completely understood), and it has no discernible risk to the mother or the fetus.[47] Cold and heat should not be applied to anesthetized skin.

Hydrotherapy

Hydrotherapy may involve a simple shower or tub bath or may include the use of a whirlpool or large tub specially equipped for pregnant women. Purported benefits of hydrotherapy include decreased anxiety and pain and greater uterine contraction efficiency.[47] Results of randomized, controlled trials comparing water baths with usual care are inconsistent. For example, some studies have found no difference between groups in the use of pharmacologic analgesia,[61,62] whereas others have demonstrated a lower use in the water bath group.[63,64] A meta-analysis of eight published trials involving almost

3000 women concluded that there was a reduction in the use of neuraxial analgesia in women randomly assigned to water immersion compared with control subjects (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.71 to 0.99).[65] There were no differences in the rate of operative delivery or neonatal outcome, including infection. In summary, bathing, showering, and other hydrotherapy maneuvers are comfort measures with little risk to the mother and the infant, provided that appropriate monitoring continues during the immersion in water that is kept at body temperature.

Vertical Position

Several investigators have studied the effects of various positions on pain perception and labor outcome. These positions are broadly categorized as *vertical* (e.g., sitting, standing, walking, squatting) or *horizontal* (e.g., supine, lateral). A systematic review summarized the results from 13 controlled trials of maternal posture during the first stage of labor.[66] In 7 trials in which women served as their own controls, women reported less pain in the standing and sitting positions than in the supine position. Six other trials randomly assigned women to either an experimental group who were encouraged to remain upright or a control group who remained supine or on their side. Women in the upright groups experienced less pain or no difference in pain when compared with the recumbent groups. A recent Cochrane review of 21 studies also found that walking and the upright position are associated with shorter labor without the need for interventions.[67]

Ambulation in the presence of neuraxial analgesia does not appear to influence the outcome of labor.[68-70] In a prospective, randomized study, Bloom et al.[68] noted that walking did not shorten the duration of the first stage of labor or reduce the requirement for oxytocin augmentation, the use of analgesia, or the requirement for operative delivery. They concluded that "walking neither enhanced nor impaired active labor and was not harmful to the mothers or their infants."[68]

A number of studies have assessed maternal position during the second stage of labor. There is renewed interest in the squatting or modified squatting position and its greater comfort for some women during childbirth. Most authorities have noted that Western women have insufficient muscular strength and stamina to maintain an unsupported squatting position for any length of time.[71-73] Squatting does not appear to alter pelvic dimensions.[74] Gardosi et al.[71] designed and studied a birth cushion that allows a modified, supported squat, which resulted in a higher incidence of spontaneous vaginal delivery and a lower incidence of perineal tears. Others have yet to substantiate the results of this trial.

Some studies have evaluated the use of a birth chair to facilitate delivery in the sitting position.[75-77] These studies noted no difference in length of the second stage of labor, mode of delivery, occurrence of perineal trauma, or Apgar scores in parturients who used a birth chair compared with those who did not. Of concern, two studies reported greater intrapartum blood loss and a higher incidence of postpartum hemorrhage in the birth-chair group.[76,77]

A systematic review of studies of maternal position in the second stage of labor in women without epidural analgesia concluded that currently published trials are generally of poor quality.[78] Tentative results suggest that less severe pain and a lower rate of perineal trauma may be associated with giving birth in the upright position; however, blood loss may be greater. Although the investigators concluded that further study is required, many obstetricians and nurses believe that ambulation and the upright posture result in a shorter labor that requires less analgesia. An alternative explanation for the observation that ambulatory parturients appear to have a less painful and shorter labor is that shorter, less painful labor *allows* continued ambulation.

Other than the possibility of greater blood loss associated with the upright position during delivery, upright positions during most of labor are not associated with any harm to the mother or newborn and may aid maternal comfort. It is unclear whether birthing cushions or stools confer any benefit to the mother or the newborn.

Biofeedback

Biofeedback is a relaxation method that is used as an adjunct to the relaxation training taught in Lamaze classes and other childbirth education programs. Two biofeedback procedures may be applicable to the laboring woman: skin-conductance (autonomic) and electromyographic (voluntary muscle) relaxation. St. James-Roberts et al.[79] demonstrated that electromyographic but not skin-conductance biofeedback techniques could be taught effectively in Lamaze classes. They noted no difference in length of the first stage of labor, use of epidural analgesia, incidence of instrumental delivery, or Apgar scores among electromyographic, skin-conductance, and control groups. In a small study, Duchene[80] reported reduced pain perception during labor and delivery and a lower rate of epidural analgesia use (40% versus 70% for a control group) with electromyographic biofeedback; there was no difference between groups in Apgar scores. A recent Cochrane review assessing the effectiveness of biofeedback found that most studies had a high risk for bias, and although some studies demonstrated reduced use of analgesics with biofeedback there was insufficient evidence to conclude that biofeedback is efficacious.[81] Biofeedback training does not appear to confer substantial benefit beyond that of traditional relaxation training taught in childbirth education classes.

Intradermal Water Injections

Intradermal or intracutaneous water injections are used to treat lower back pain, which is a common complaint during labor. The afferent nerve fibers that innervate the uterus and cervix, as well as the nerve fibers that innervate the lower back, all enter the spinal cord at the T10 through L1 spinal segments; therefore, a component of the pain may be referred pain. The technique consists of injecting 0.05 to 0.1 mL of sterile water, with an insulin or tuberculin syringe, at four sites on the lower back (i.e., over each posterior superior iliac spine, and at 1 cm medial and 3 cm caudad to the posterior superior iliac

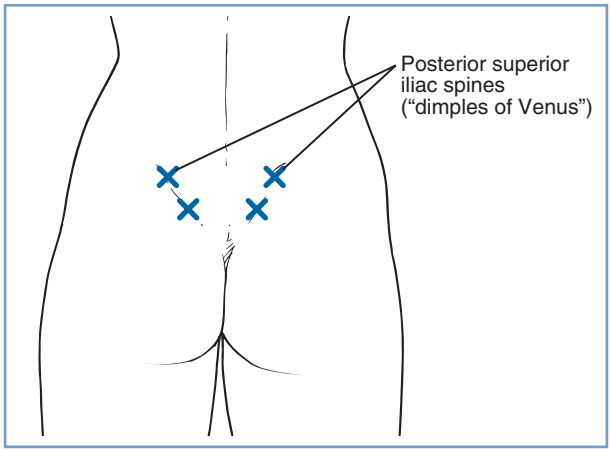

FIGURE 21-3 ■ Placement of intradermal water blocks *(x)*. Approximately 0.05 to 0.1 mL of sterile water is injected intradermally to form a small bleb over each posterior superior iliac spine and at 3 cm below and 1 cm medial to each spine on both sides of the back (i.e., for a total of four injections). The exact locations of the injections do not appear to be critical to the block success. (From Simkin P. Update on nonpharmacologic approaches to relieve labor pain and prevent suffering. J Midwifery Womens Health 2004; 49:489-504.)

spine on both sides of the back, for a total of four injections) (Figure 21-3). The injections themselves are acutely painful for 20 to 30 seconds, but as the injection pain fades, so does lower back pain.

Systematic reviews have summarized the four randomized controlled trials that compared intradermal water injections with placebo or standard care.[48,66] The results of these trials suggested that the intradermal injections are a simple method of reducing severe low back pain during labor without adverse effects on the mother and fetus. The analgesic effect appears to last for 45 to 120 minutes[47] but did reduce the rate of use of other analgesic techniques.[48,66] However, a recent Cochrane review assessing the effectiveness of water injections during labor did not find evidence that it reduced back pain or labor pain.[82]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) involves the transmission of low-voltage electrical current to the skin via surface electrodes. Advantages of TENS are that it is easy to use and discontinue, is noninvasive, and has no demonstrable harmful effects on the fetus. The only stated disadvantage is the occasional interference with electronic fetal heart rate monitoring. It is most widely used for childbirth in Scandinavia and the United Kingdom.[47] Chao et al.[83] evaluated the use of TENS at specific acupuncture points and observed a reduction in pain perception more commonly in the study group than in the control group. However, a systematic review of nine trials in more than 1000 women concluded that TENS did not reduce labor pain and did not reduce the use of additional analgesic agents.[84] There also was no effect on the duration of labor or the incidence of instrumental delivery. Patients tend to rate the device as helpful despite the fact that it does not reduce the use of additional analgesics. Widespread use of TENS does not seem warranted.

Acupuncture/Acupressure

Traditional Chinese medicine includes extensive use of acupuncture. Given that acupuncture can provide analgesia, there is interest in its use for intrapartum analgesia, although this is not a traditional use of the method. Early observational reports described conflicting results as to the efficacy of intrapartum acupuncture. Given the historic lack of use of acupuncture in obstetric patients, there is a lack of standardization of the acupuncture points to be stimulated.

Several randomized, controlled trials have compared "real" acupuncture to "false" or "minimal" acupuncture using shallow insertion of needles in non-acupuncture points,[85,86] whereas other investigators have used a control group that did not receive acupuncture.[87,88] Four randomized trials found that pain scores were lower in women randomly assigned to receive acupuncture treatment, as was the rate of use of other modes of analgesia (e.g., epidural and systemic meperidine).[85-88] These results suggest that acupuncture may hold promise for the treatment of labor pain.[85-88] Hantoushzadeh et al.[86] also observed a shorter duration of the active phase of labor and a reduction in use of oxytocin in the acupuncture group. No adverse maternal or fetal effects were identified. Other randomized studies did not find reduced pain scores with acupuncture.[89,90]

A randomized, controlled trial of acupressure (treatment) compared with touch (control) at the SP6 acupoint found lower pain scores and a shorter duration of labor in the acupressure group.[91] A meta-analysis of 13 acupuncture trials including 1986 women concluded that acupuncture may hold promise for labor analgesia; however, larger studies are required for definitive conclusions.[92] All of the randomized, controlled acupuncture studies were performed outside the United States, in countries (primarily Scandinavian) in which the use of neuraxial labor analgesia is less widespread than in the United States. Also, the use of acupuncture requires trained personnel. (Scandinavian midwives have been trained to administer acupuncture.) For these reasons it is unlikely that either acupuncture or acupressure will gain widespread acceptance in the United States for intrapartum analgesia.

Hypnosis

The use of hypnosis for obstetric analgesia is not new.[93] Early proponents touted safety for the mother and the fetus, lower analgesic requirements, and shorter labor as the major advantages of intrapartum hypnosis. Whether hypnosis differs substantially from other childbirth preparation techniques is an unresolved controversy. Fee and Reilley[94] concluded that the breathing and relaxation exercises used in childbirth preparation do not represent a hypnotic trance; support for their conclusion is provided by the successful teaching of childbirth preparation

exercises to women who are not susceptible to hypnosis. However, women susceptible to hypnosis may achieve a state much like a hypnotic trance when using the same exercises.

Instruction in the techniques of self-hypnosis occurs before the onset of labor and may entail visits to the hypnotist or involvement in a childbirth education program such as HypnoBirthing. Proponents previously suggested that successful hypnosis training should begin early in the third trimester. Rock et al.[95] found that hypnosis could be introduced to untrained, nonvolunteer patients during labor. On average, this maneuver added approximately 45 minutes of care; however, all but 3 of 22 patients in the experimental group required additional analgesia. Some studies found that hypnosis did not decrease analgesic requirements,[96] but a recent review of 13 separate studies noted that hypnosis resulted in lower analgesic requirements and a shorter duration of the first stage of labor. The authors do not believe their findings are conclusive since most studies were not randomized.[97]

Childbirth preparation and hypnosis seem to have similar effects on obstetric outcome. Harmon et al.[98] combined hypnosis and skill mastery with childbirth education. Experimental patients with a high susceptibility to hypnosis demonstrated less use of opioid, tranquilizer, and oxytocic medications; shorter first and second stages of labor; and a higher incidence of spontaneous vaginal delivery. Patients with a low susceptibility to hypnosis did not gain substantial advantage from the addition of hypnosis to the routine childbirth education provided for the control group.

In summary, hypnosis has at least the following three limitations: (1) antepartum training sessions are required, (2) trained hypnotherapists must be available during labor, and (3) it offers no clear benefit. Therefore, hypnosis is unlikely to attain widespread use during childbirth.

IMPLICATIONS FOR ANESTHESIA PROVIDERS

Childbirth preparation classes and nonpharmacologic analgesic techniques are not comparable to neuraxial analgesia/anesthesia for the relief of labor pain. Thus, some might wonder whether it is important or useful for anesthesia providers to have knowledge of these techniques. If our only obligation to the obstetric patient is a technical one (i.e., to eliminate pain safely with the use of neuraxial analgesia), knowledge of these techniques is perhaps superfluous. However, the practice of obstetric anesthesia should not be limited to the performance of pain-relieving procedures; our contributions to the care of the obstetric patient and her family should extend beyond the administration of neuraxial analgesia.

Much has been written in professional and lay journals concerning the "proper" childbirth experience. Each patient's expectations of labor influence her childbirth experience. Yarrow[99] described the results of a nonscientific poll of 72,000 readers of *Parents Magazine*, which revealed that there is an undeniable movement toward more family-centered maternity care. Women currently view childbirth from the perspective of educated consumers; they expect to have choices and a level of control during childbirth. We may not always be comfortable with this situation, but it is a reality for modern obstetric practice. Our challenge is to provide safe, effective analgesia in a nonthreatening, "homelike" environment. We are not solely responsible for a patient's childbirth experience, but our interactions with the patient, her family, and her obstetrician will influence her perception of childbirth.

Anesthesia providers must become effective educators as well as health care providers. Patients should have realistic expectations about the pain of labor and the variability of individual labor patterns. They should be encouraged to define "success" as a positive childbirth experience regardless of the mode of delivery, use of analgesia and anesthesia, or other arbitrary definitions. An obstetrician advised prospective mothers[100]:

> *If you do end up choosing some form of pain relief during labor, do not feel inadequate if a friend had her baby without assistance. Some labors are more intense than others. Ultimately, holding your baby in your arms is more important than the method you used to bring her into the world.*

Anesthesia providers may effectively provide similar advice. Unfortunately, anesthesia providers usually have little involvement in prenatal education classes. Our active participation in childbirth education classes may help patients receive more accurate information about the risks and benefits of analgesia/anesthesia for labor, vaginal delivery, and cesarean delivery. Anesthesia providers can encourage childbirth instructors to prepare patients for the unexpected and to acknowledge that the commonly described "typical" labor may, in fact, be atypical. Well-informed patients are more likely to accept the interventions that may become necessary during labor. Women with medical or obstetric diseases that may increase anesthetic risk should be encouraged to discuss these problems with an anesthesia provider before the onset of labor; thus, we must develop procedures to facilitate antepartum consultation. Beilin et al.[101] found in a survey study that most women would prefer a pre-labor visit with their anesthesiologist. In summary, the active participation of the anesthesia provider in childbirth education will lead women to perceive the anesthesia provider as an integral part of the obstetric care team.

Some nonpharmacologic analgesic techniques may have benefits other than decreased pain perception. For example, some obstetricians and nurses believe that ambulation and subsequent squatting (or use of a birth cushion) shortens labor and increases the rate of spontaneous vaginal delivery. Even if this belief proves not to be true, many women prefer to be mobile during labor and, at a minimum, to retain the ability to walk to the bathroom. We should attempt to develop and use analgesic techniques that take advantage of these relatively simple maneuvers. For example, the use of intrathecal opioids during early labor allows for continued ambulation and the use of showers and/or tubs. Some techniques

of epidural analgesia allow sitting with support. Finally, epidural analgesia/anesthesia does not eliminate the beneficial effects of other comfort measures, such as massage, and continued emotional support from family and friends.

Whenever possible, anesthesia providers should provide safe anesthetic care that is compatible with reasonable patient expectations. Future studies on the efficacy of childbirth education, nonpharmacologic analgesic techniques, and neuraxial analgesic techniques should evaluate the patient's overall experience and satisfaction rather than limit assessment to the usual measures of obstetric outcome.[102] In an editorial that accompanied the study by Bloom et al.,[68] Cefalo and Bowes[103] commented, "In the end, the nurses, midwives, and physicians who attend a woman with compassion, understanding, and professionalism are the most important factors in the management of any labor."

KEY POINTS

- Childbirth preparation does not eliminate the pain of labor or substantially reduce the use of analgesia/anesthesia, but it does decrease the anxiety associated with labor.
- Emotional support provided by doulas reduces the use of analgesics, the length of labor, and the incidence of operative deliveries in selected patient populations.
- Biofeedback, transcutaneous electrical nerve stimulation, acupuncture, and hypnosis may provide mild to moderate analgesic benefits for some patients.
- Intradermal water injections may provide effective treatment of low back pain during labor.
- Anesthesia providers should become active participants in childbirth education. We should encourage and facilitate the honest discussion of the risks and benefits of the analgesic/anesthetic techniques available at our hospitals.
- No nonpharmacologic technique consistently provides the quality of intrapartum pain relief that is provided by neuraxial analgesia.

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CHAPTER 22

Systemic Analgesia: Parenteral and Inhalational Agents

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CHAPTER OUTLINE

Systemic drugs have been used to decrease the pain of childbirth since 1847, when James Young Simpson used diethyl ether to anesthetize a parturient with a deformed pelvis. Since that time, the provision of labor analgesia has advanced significantly owing to a heightened awareness of the neonatal effects of heavy sedation or general anesthesia administered during vaginal delivery and a greater desire of women to actively participate in childbirth.

Neuraxial (i.e., epidural, spinal, combined spinal-epidural [CSE]) analgesic techniques have replaced systemic drug administration as the preferred method for intrapartum analgesia in both the United States and Canada (Table 22-1).[1,2] By contrast, in the United Kingdom, fewer than one third of parturients received a neuraxial analgesic technique during labor and vaginal delivery in 2011.[3]

Despite the increased use of neuraxial analgesia for labor, the use of systemic analgesia remains a common practice in many institutions worldwide for several reasons. Many women labor and deliver in an environment where the provision of safe neuraxial analgesia is not available. Some parturients decline neuraxial analgesia or choose to receive systemic analgesia during early labor. Finally, some women may have a medical condition that contraindicates a neuraxial procedure (e.g., coagulopathy) or presents technical challenges (e.g., severe scoliosis, the presence of spinal hardware).

PARENTERAL OPIOID ANALGESIA

Opioids are the most widely used systemic medications for labor analgesia. These compounds are agonists at opioid receptors (Table 22-2). Their popularity lies in their low cost, ease of use, and the lack of need for specialized equipment and personnel. Although these drugs provide moderate pain relief, parturients commonly report dissociation from the reality of pain rather than complete analgesia. Since neuraxial labor analgesia has become more accessible, systemic opioids have become less popular, owing to the frequency of maternal side effects (e.g., nausea, vomiting, delayed gastric emptying, dysphoria, drowsiness, hypoventilation) and the potential for adverse neonatal effects. However, a renewed interest in opioid administration during labor has occurred owing to the growing use of patient-controlled delivery systems.

Although systemic opioids have long been used for labor analgesia, there is little scientific evidence to suggest that one drug is superior to another; most often, drug selection is based on local policy or personal preference

TABLE 22-1 Types of Labor Analgesia at Hospitals Providing Obstetric Care by Number of Births

	Stratum 1 (≥1500 births)			Stratum 2 (500-1500 births)			Stratum 3 (100-500 births)		
Labor Analgesia	1981	1992	2001	1981	1992	2001	1981	1992	2001
None	27	11	6	33	14	10	45	33	12
Parenteral	52	48	34	53	60	42	37	48	37
Epidural	22	51	61	13	33	42	9	17	35

Note: Data are presented as percentages.
Modified from Bucklin BA, Hawkins JL, Anderson JR, Ulrich FA. Obstetric anesthesia workforce survey: twenty-year update. Anesthesiology 2005; 103:645-53.

TABLE 22-2 Classification of Opioid Receptors

Current Classification	Previous Classification	Effects
μ or MOP	OP_3	Analgesia, meiosis, euphoria, respiratory depression, bradycardia
κ or KOP	OP_2	Analgesia, sedation, meiosis
δ or DOP	OP_1	Analgesia, respiratory depression
Nociception or NOP	OP_4	Inhibition of opioid analgesia* May cause hyperalgesia*

OP, opioid peptide.
*Modified from the International Union of Basic and Clinical Pharmacology (IUPHAR) database. Available at http://www.iuphar-db.org. Accessed March 9, 2013.

TABLE 22-3 Systemic Opioids for Labor Analgesia

Drug	Usual Dose (IV/IM)	Time to Peak Effect (IV/IM)	Duration of Action	Comments
Meperidine	25-50 mg IV 50-100 mg IM	5-10 min IV 45 min IM	2-3 h	Maximal neonatal depression 3-5 hours after dose Has an active metabolite with a long half-life
Morphine	2-5 mg IV 5-10 mg IM	10 min IV 30 min IM	3-4 h	More neonatal respiratory depression than with meperidine Has an active metabolite
Diamorphine	5-10 mg IV 5-10 mg IM	2-5 min IV 5-10 min IM	90 min	Morphine prodrug More euphoria, less nausea than with morphine
Fentanyl	25-50 μg IV	2-4 min IV	30-60 min	Usually administered as an infusion or by PCA Accumulates during an infusion Less neonatal depression than with meperidine
Nalbuphine	10-20 mg IV 10-20 mg IM/SQ	2-3 min IV 15 min IM/SQ	3-6 h	Opioid agonist/antagonist Ceiling effect on respiratory depression Lower neonatal neurobehavioral scores than with meperidine
Butorphanol	1-2 mg IV 1-2 mg IM	5-10 min IV 30-60 min IM	4-6 h	Opioid agonist/antagonist Ceiling effect on respiratory depression
Meptazinol	50-100 mg IM	30 min IM	2-3 h	Partial opioid agonist Less sedation and respiratory depression than with other opioids
Pentazocine	30-60 mg IV 30-60 mg IM	2-3 min IV 20 min IM	3-4 h	Opioid agonist/antagonist Psychomimetic effects possible
Tramadol	50-100 mg IV 50-100 mg IM	10 min IM	2-4 h	Lower efficacy and more side effects than with meperidine

IM, Intramuscular; *IV,* intravenous; *PCA,* patient-controlled analgesia; *SQ,* subcutaneous.

(Table 22-3). The efficacy of systemic opioid analgesia and the incidence of side effects are largely dose dependent rather than drug dependent.

As a result of their high lipid solubility and low molecular weight (< 500 Da), all opioids readily cross the placenta by diffusion and are associated with the risks of neonatal respiratory depression and neurobehavioral changes. Opioids may also affect the fetus *in utero*. The fetus and neonate are particularly susceptible to opioid-induced side effects for several reasons. The metabolism and elimination of these drugs are prolonged compared with adults, and the blood-brain barrier is less well developed, allowing for greater central effects. Opioids may result in decreased variability of the fetal heart rate

(FHR), although this change usually does not reflect a worsening of fetal oxygenation or acid-base status. The likelihood of neonatal respiratory depression depends on the dose and timing of opioid administration. Even in the absence of obvious neonatal depression at birth, there may be subtle changes in neonatal behavior for several days. Reynolds et al.[4] performed a meta-analysis of studies that compared epidural analgesia with systemic opioid analgesia using meperidine, butorphanol, or fentanyl. The authors concluded that lumbar epidural analgesia was associated with improved neonatal acid-base status at delivery. Similarly, in a multicenter randomized trial, Halpern et al.[5] compared patient-controlled epidural analgesia using a local anesthetic combined with an opioid to patient-controlled analgesia (PCA) using a parenteral opioid; the investigators demonstrated an increased need for active neonatal resuscitation in the parenteral opioid group (52% versus 31%).

Opioids may be administered as intermittent bolus doses or by PCA. Bolus doses are used more commonly, but the newer synthetic opioids are increasingly used with patient-controlled devices. Because the mode of delivery influences a drug's pharmacologic profile, the opioids will be discussed by route of administration.

INTERMITTENT BOLUS PARENTERAL OPIOID ANALGESIA

Opioids may be given intermittently by subcutaneous, intramuscular, or intravenous injection. The route and timing of administration influence maternal uptake and placental transfer to the fetus. Subcutaneous and intramuscular routes have the advantage of ease of administration but are painful. Absorption varies with the site of injection and depends on local and regional blood flow; consequently, the onset, quality, and duration of analgesia are highly variable.

Intravenous administration offers several advantages. The onset of analgesia is faster, and the timing and magnitude of the peak plasma concentration of drug are more predictable. It is also possible to titrate dose to effect. For these reasons the intravenous route is generally preferred when available.

Meperidine

In 1947, meperidine (pethidine) became the first synthetic opioid to be used for intrapartum analgesia. More extensively studied than newer drugs, meperidine is the most common opioid given for labor analgesia in the United Kingdom.[6] The usual dose is 50 to 100 mg intramuscularly, which can be repeated every 4 hours. The onset of analgesia occurs in 10 to 15 minutes, but 45 minutes may be required to reach peak effect. The duration of action is typically 2 to 3 hours.

Meperidine is highly lipid soluble, readily crosses the placenta, and equilibrates between the maternal and fetal compartments within 6 minutes. Meperidine is metabolized in the liver to produce normeperidine, a pharmacologically active metabolite that is a potent respiratory depressant. Normeperidine also crosses the placenta and is largely responsible for the neonatal side effects encountered with meperidine use.[7]

Maternal administration of meperidine may reduce fetal aortic blood flow, fetal muscle activity, and FHR variability.[7] Sosa et al.[8] demonstrated that intravenous meperidine 100 mg, given during the first stage of labor, resulted in an increased incidence of umbilical cord arterial blood acidemia at delivery when compared with a placebo. Normeperidine may result in neonatal respiratory depression. After maternal intramuscular administration of meperidine, the greatest risk for neonatal respiratory depression occurs if meperidine is given to the mother 3 to 5 hours before delivery, whereas the risk is least if it is given within 1 hour before delivery.[7] Normeperidine accumulation is associated with altered neonatal behavior, manifesting as reduced duration of wakefulness and attentiveness and impaired breastfeeding.[9] Meperidine administration is associated with lower Apgar scores and muscle tone in the neonate. Maternal side effects are of less clinical concern, although there is a high incidence of nausea, vomiting, and dysphoria.

The maternal half-life of meperidine is 2.5 to 3 hours, whereas that of normeperidine is 14 to 21 hours.[10] The half-life of both compounds is increased by up to three times in the neonate as a result of reduced clearance.[10] Consequently, the adverse effects may be seen in the neonate up to 72 hours after delivery. The action of meperidine is reversed by naloxone; however, the action of normeperidine is not. This is important because antagonism with naloxone may exacerbate normeperidine-induced seizures owing to suppression of the anticonvulsant effect of meperidine.

The quality of labor analgesia with meperidine has been questioned, with some reports indicating that less than 20% of laboring women obtain satisfactory pain relief with its use. The analgesic benefit of intravenous meperidine 50 mg has been observed to be comparable with that of intravenous acetaminophen 1000 mg, but with a greater incidence of adverse effects (64% versus none).[11]

A randomized, double blind, placebo-controlled trial of intramuscular meperidine 100 mg versus 0.9% normal saline for labor analgesia was terminated after an interim analysis of 50 patients, which revealed a significantly greater reduction in pain scores with meperidine.[12] However, the analgesic effect of meperidine was modest, with a median change in visual analog pain scores (VAPS) of 11 mm at 30 minutes; 68% of women required additional analgesia during labor.

The effect of meperidine on the progress of labor is unclear. Historically, meperidine has been given to decrease the length of the first stage of labor in cases of dystocia; however, recent studies have not demonstrated such an effect, and investigators have concluded that meperidine should not be given for this purpose.[8]

Despite the concerns just highlighted, meperidine continues to be the most common opioid given for labor analgesia worldwide; this is most likely the result of its familiarity, ease of administration, availability, and low cost.

Morphine

Several decades ago, morphine was administered in combination with scopolamine to provide "twilight sleep" during labor and delivery. Analgesia was obtained at the expense of excessive maternal sedation and neonatal depression. Morphine is infrequently used during labor, but it can be given every 4 hours intravenously (0.05 to 0.1 mg/kg) or intramuscularly (0.1 to 0.2 mg/kg), with a peak effect observed in 10 and 30 minutes, respectively. The duration of action when given intravenously or intramuscularly is 3 to 4 hours.[10]

Morphine is principally metabolized by conjugation in the liver, with up to 70% being transformed into the largely inactive morphine-3-glucuronide. The remainder is transformed into the active metabolite morphine-6-glucuronide, which is 13 times more potent than morphine and has significant analgesic properties.[10] Both metabolites are excreted in the urine and have elimination half-lives of up to 4.5 hours in the presence of normal renal function.[13] Morphine rapidly crosses the placenta, and a fetal-to-maternal blood concentration ratio of 0.96 is observed at 5 minutes. The elimination half-life of morphine is longer in neonates than in adults.

Maternal side effects include respiratory depression and histamine release, which may result in a rash and pruritus. Like many opioids, morphine is emetogenic and is associated with sedation and dysphoria with increasing doses.[10]

The greatest neonatal concern is that of respiratory depression. Way et al.[14] observed that intramuscular morphine given to newborns caused greater respiratory depression than an equipotent dose of meperidine when response to carbon dioxide was measured. This finding was attributed to an increased permeability of the neonatal brain to morphine.

Pregnancy alters the pharmacokinetics of morphine. Greater plasma clearance, shorter elimination half-life, and earlier peak metabolite levels occur in pregnant women than in nonpregnant women. In theory, these characteristics should reduce fetal exposure. One study observed no cases of neonatal depression after morphine administration during labor, prompting the researchers to suggest that morphine use in labor should be reevaluated.[15] Subsequently, Oloffson et. al.[16] assessed the analgesic efficacy of intravenous morphine during labor (0.05 mg/kg every third contraction, to a maximum dose of 0.2 mg/kg) and observed clinically insignificant reductions in pain intensity. These investigators also compared intravenous morphine (up to 0.15 mg/kg) with intravenous meperidine (up to 1.5 mg/kg) and found that high pain scores were maintained in both groups despite high levels of maternal sedation.[17]

Diamorphine

Diamorphine (3,6-diacetylmorphine, heroin) is a synthetic morphine derivative in common use in the United Kingdom, with 34% of obstetric units reporting its use for labor analgesia.[6] Diamorphine is twice as potent as morphine. As a prodrug, diamorphine has no direct affinity for opioid receptors, but it is rapidly hydrolyzed by plasma esterases to active metabolites, which are responsible for its clinical effect.[10] The metabolite 6-monoacetylmorphine is responsible for a significant proportion of analgesic activity, and it is further metabolized to morphine.[13]

Typical parenteral doses (intravenous or intramuscular) are 5 to 10 mg. The most common route of administration is intramuscular and results in labor analgesia with a duration of approximately 90 minutes. Both diamorphine and its active metabolite 6-monoacetylmorphine are more lipid soluble than morphine, resulting in a faster onset of analgesia with more euphoria but less nausea and vomiting. These pharmacokinetic properties may also predispose to maternal respiratory depression. Neonatal respiratory depression may also occur due to rapid placental transfer, although this has mainly been reported with high doses.[18]

Rawal et al.[18] investigated the relationship between the dose-delivery interval (following intramuscular administration of a single dose of diamorphine 7.5 mg) and the concentration of free morphine in umbilical cord blood and neonatal outcome. The negative correlation between the dose-delivery interval and umbilical cord blood morphine levels was significant. The correlation between higher free morphine concentrations and lower 1-minute Apgar scores (and the need for neonatal resuscitation) was nonsignificant. Their findings suggest that infants born shortly after interval diamorphine administration are at greater risk for respiratory depression.

Fairlie et al.[19] randomized 133 pregnant women to receive intramuscular meperidine 150 mg or diamorphine 7.5 mg and found that significantly more women in the meperidine group reported poor or no pain relief at 60 minutes. However, approximately 40% of women in the two groups requested second-line analgesia, suggesting that both drugs had poor analgesic efficacy. The incidence of maternal sedation was comparable, but vomiting occurred much less frequently and neonatal Apgar scores were higher at 1 minute in the diamorphine group. The trial was small, but the results suggested that at the administered doses, diamorphine conferred some benefit over meperidine with regard to maternal side effects and initial neonatal condition. Currently, a much larger trial of the two drugs, at the same dose and with the same route of administration, is underway in the United Kingdom.

Fentanyl

Fentanyl is a highly lipid-soluble, highly protein-bound synthetic opioid that is highly selective for the μ-opioid receptor, resulting in an analgesic potency 100 times that of morphine and 800 times that of meperidine. Its rapid onset (peak effect, 2 to 4 minutes), short duration of action (30 to 60 minutes), and lack of active metabolites make it attractive for labor analgesia. Although it can be administered intramuscularly, fentanyl is most commonly given intravenously and is titrated to effect; frequently it is administered with a patient-controlled device.

Although small doses of fentanyl undergo rapid redistribution, large or repeated doses may accumulate.[10] Importantly, clearance of fentanyl by elimination

represents only 20% of that occurring by redistribution, resulting in a rapid increase in context sensitive half-life with an increased duration of infusion.[10] Fentanyl has a longer elimination half-life than morphine, but it is metabolized to inactive metabolites in the liver that are excreted in the urine.

Fentanyl readily crosses the placenta; however, the average umbilical vein/maternal vein ratio remains low, most likely owing to a significant degree of maternal protein binding and drug redistribution. In a chronically instrumented sheep model, Craft et al.[20] detected fentanyl in fetal plasma as early as 1 minute after maternal administration; however, maternal plasma levels were approximately 2.5 times greater than fetal plasma levels.

Rayburn et al.[21] compared responses in women who received intravenous fentanyl (50 to 100 μg as often as once per hour at maternal request) with the experience of women who did not receive analgesia. The mean dose of fentanyl administered was 140 μg (range, 50 to 600 μg). All patients who received fentanyl experienced brief analgesia (mean duration, 45 minutes), sedation, and a transient reduction in FHR variability (30 minutes). There was no difference between groups in neonatal Apgar scores, respiratory status, or Neurologic and Adaptive Capacity Scores (NACS). Rayburn et al.[22] also compared intravenous fentanyl (50 to 100 μg every hour) with an equi-analgesic dose of meperidine (25 to 50 mg every 2 to 3 hours). The researchers observed less sedation, vomiting, and neonatal naloxone administration with fentanyl, but they observed no difference between groups in NACS. The two groups had similarly high pain scores, suggesting that both drugs have poor analgesic efficacy.

Nalbuphine

Nalbuphine is a mixed agonist-antagonist opioid analgesic with agonist activity at κ-opioid receptors, thereby producing analgesia, and partial agonist activity at μ-opioid receptors, thus resulting in less respiratory depression.[13] A partial agonist is a drug that has receptor affinity but produces a submaximal effect compared with a full agonist, even when given at very high doses.[10]

Nalbuphine can be administered by intramuscular, intravenous, or subcutaneous injection, with a usual dose of 10 to 20 mg every 4 to 6 hours. The onset of analgesia occurs within 2 to 3 minutes of intravenous administration and within 15 minutes of intramuscular or subcutaneous administration. The drug is metabolized in the liver to inactive compounds that are then secreted into bile and excreted in feces.[13]

Nalbuphine and morphine are of equal analgesic potency and result in sedation and respiratory depression at similar doses. However, because of its mixed receptor affinity, nalbuphine demonstrates a ceiling effect for respiratory depression at a dose of 0.5 mg/kg.[13] Nalbuphine causes less nausea, vomiting, and dysphoria than morphine. Concerns that it may have an antianalgesic effect, particularly in men, led to the withdrawal of nalbuphine in the United Kingdom in 2003.[13]

Wilson et al.[23] performed a randomized, double-blind comparison of intramuscular nalbuphine 20 mg and meperidine 100 mg for labor analgesia. Nalbuphine was associated with less nausea and vomiting but more maternal sedation. Analgesia was comparable between the groups. Neonatal neurobehavioral scores were lower in the nalbuphine group at 2 to 4 hours, but there was no difference between groups at 24 hours. The umbilical vein-to-maternal vein concentration ratio was higher with nalbuphine (mean ± SEM, 0.78 ± 0.03) than with meperidine (0.61 ± 0.02). A subsequent study failed to demonstrate an analgesic advantage with either drug but again reported transient neonatal neurologic depression with nalbuphine.[24]

Amin et al.[25] compared the neonatal outcome for women who received either nalbuphine or saline-control before elective cesarean delivery. They found lower 1-minute Apgar scores and a significantly longer time to sustained respiration in the nalbuphine group. However, 5-minute Apgar scores and umbilical cord blood gas measurements were similar between groups.

Nicolle et al.[26] evaluated the transplacental transfer and neonatal pharmacokinetics of nalbuphine in 28 women who received the drug either intramuscularly or intravenously during labor. The investigators found a high umbilical vein-to-maternal vein concentration ratio of 0.74, which did not correlate with the administered dose. The estimated neonatal half-life was 4.1 hours, which is greater than the adult half-life and, more importantly, longer than the half-life of naloxone. There was a transient reduction in FHR variability in 54% of the fetuses, which was not associated with the plasma concentration of nalbuphine. Analgesia was rated as effective by 54% of parturients.

Giannina et al.[27] compared the effects of intravenous nalbuphine and meperidine on intrapartum FHR tracings. Nalbuphine significantly reduced both the number of FHR accelerations and FHR variability, whereas meperidine had little effect.

A recent prospective pilot study of 302 nulliparous parturients (57 women who received nalbuphine, and a control group of 245 women who received neither nalbuphine nor epidural analgesia) reported a marked reduction in duration of the active phase of the first stage of labor in the nalbuphine group (75 minutes versus 160 minutes in the control group); this effect appeared to be independent of oxytocin use.[28] Additional investigations are needed to verify this finding.

Butorphanol

Butorphanol is an opioid with agonist-antagonist properties that resemble those of nalbuphine. It is 5 times as potent as morphine and 40 times more potent than meperidine.[29] The typical dose during labor is 1 to 2 mg intravenously or intramuscularly. Butorphanol is 95% metabolized in the liver to inactive metabolites. Excretion is primarily renal. A plateau effect for respiratory depression is noted, where butorphanol 2 mg produces respiratory depression similar to that of morphine 10 mg or meperidine 70 mg. However, butorphanol 4 mg results in less respiratory depression than morphine 20 mg or meperidine 140 mg.[29]

Maduska and Hajghassemali[30] compared intramuscular butorphanol (1 to 2 mg) with meperidine (40 to

80 mg) and found similar efficacy of labor analgesia. Butorphanol and meperidine exhibited rapid placental transfer with similar umbilical vein-to-maternal vein concentration ratios (0.84 and 0.89, respectively) and no differences in FHR tracings, Apgar scores, time to sustained respiration, or umbilical cord blood gas measurements at delivery.

Hodgkinson et al.[31] performed a similar study comparing the intravenous administration of butorphanol (1 or 2 mg) and meperidine (40 or 80 mg) for labor analgesia. Maternal pain relief was found to be adequate and comparable, but there were fewer maternal side effects (e.g., nausea, vomiting, dizziness) in the women who received butorphanol. There was no difference between groups in neonatal Apgar or neurobehavioral scores.

Conversely, in a double-blind comparison of intravenous butorphanol (1 or 2 mg) and meperidine (40 or 80 mg) during labor, Quilligan et al.[32] noted lower pain scores at 30 minutes and 1 hour after the administration of butorphanol. There was no significant difference in Apgar scores between the two groups of infants; however, the mean FHR was noted to be higher among those fetuses whose mothers received butorphanol.

Nelson and Eisenach[33] investigated the possible synergistic effect of giving both intravenous butorphanol and meperidine; they compared the administration of both drugs with the administration of either drug alone. Women received intravenous butorphanol 1 mg, meperidine 50 mg, or butorphanol 0.5 mg with meperidine 25 mg. All three groups reported a similar reduction in pain intensity; however, only 29% of the women achieved clinically significant pain relief. There was no difference among groups in maternal side effects or neonatal Apgar scores. The investigators concluded that there was no therapeutic benefit to combining the two drugs.

Atkinson et al.[34] performed a double-blind trial of intravenous butorphanol (1 to 2 mg) and fentanyl (50 to 100 μg) administered hourly on maternal request. The investigators found that butorphanol provided better analgesia initially, with fewer requests for additional drug doses or progression to epidural analgesia. There was no difference in adverse maternal or neonatal effects between the two groups.

Meptazinol

Meptazinol is a partial opioid agonist specific to μ-opioid receptors with a rapid onset of action (i.e., 15 minutes after intramuscular administration). The intramuscular dose (50 to 100 mg) and duration of action for labor analgesia are similar to those for meperidine. Its partial agonist activity is thought to result in less sedation, respiratory depression, and risk for dependence than occurs with other opioid agonists.

Meptazinol is metabolized by glucuronidation in the liver and then excreted in the urine. This process is more mature in the neonate than is the metabolic pathway of meperidine. The adult half-life is 2.2 hours, and the neonatal half-life is 3.4 hours.[35]

Theoretically, this rapid elimination should confer a lower incidence of adverse neonatal effects than occurs with meperidine. In a single-blind study, Jackson and Robson[36] compared intramuscular meptazinol with meperidine at the same doses (100 mg if maternal weight was ≤ 60 kg, 125 mg if 61 to 70 kg, and 150 mg if ≥ 70 kg). Meptazinol provided significantly better analgesia than meperidine but resulted in a similar frequency of maternal side effects.

Nicholas and Robson[37] subsequently compared intramuscular meptazinol 100 mg with meperidine 100 mg in a randomized, double-blind trial in 358 parturients. Meptazinol provided significantly better pain relief at 45 and 60 minutes, but the two drugs provided a similar duration of analgesia, and there was no significant difference between groups in maternal side effects. Neonatal outcomes were similar between groups, except significantly more infants whose mothers had received meptazinol had an Apgar score of 8 or higher at 1 minute.

Other investigators have reported little difference in analgesic efficacy, maternal side effects, or neonatal outcomes between meptazinol and meperidine. In a study of 1100 patients, Morrison et al.[38] found that neither drug given at equal doses (150 mg in patients weighing > 70 kg, 100 mg in those weighing ≤ 70 kg) was effective at relieving pain. Maternal drowsiness was significantly less pronounced with meptazinol, but the incidence of vomiting was higher. FHR changes and neonatal outcomes, including Apgar scores, need for resuscitation, and suckling ability, were comparable. The overall use of naloxone was similar in the two groups, but if the dose-delivery interval exceeded 180 minutes, significantly more neonates in the meperidine group required naloxone.

De Boer et al.[39] assessed neonatal blood gas and acid-base measurements after maternal intramuscular administration of meptazinol (1.5 mg/kg) or meperidine (1.5 mg/kg) during labor. Capillary blood gas measurements at 10 minutes of life showed a significantly lower pH and a higher $Paco_2$ in the meperidine group, although this difference resolved by 60 minutes. These findings suggest that meptazinol causes less neonatal respiratory depression.

Meptazinol may confer some benefits over meperidine in early neonatal outcome, but it is not widely used. A recent survey indicated that it is the intramuscular labor analgesic of choice in only 14% of obstetric units in the United Kingdom.[6] The cost of meptazinol is considerably higher than that of meperidine. Meptazinol is not available in the United States.

Pentazocine

Pentazocine is a selective κ-opioid receptor agonist with some weak antagonist activity at μ-opioid receptors.[13] It may be given orally or systemically by intramuscular or intravenous injection. The typical parenteral adult dose is 30 to 60 mg, which is equivalent to morphine 10 mg. Onset of action occurs within 2 minutes when given intravenously and within 20 minutes if given by the intramuscular route. Metabolism occurs in the liver by oxidation and glucuronidation; metabolites are then excreted in the urine.

Pentazocine causes similar respiratory depression to that seen with equipotent doses of morphine and

meperidine, but it exhibits a ceiling effect with doses in excess of 60 mg. Psychomimetic effects (e.g., dysphoria, hallucinations) may complicate its use, particularly with increasing doses.

In a double-blind study of 94 laboring women who received intramuscular administration of pentazocine (up to 60 mg) and meperidine (up to 150 mg), Mowat and Garrey[40] observed equivalent and adequate analgesia for approximately 40% of women in each group. The incidence of sedation was comparable between groups, and fewer women in the pentazocine group complained of nausea and vomiting.

In a randomized study comparing intramuscular administration of pentazocine 30 mg with tramadol 100 mg in 100 laboring women, Kuti et al.[41] observed greater analgesia in the pentazocine group at 1 hour, with a longer time to subsequent request for additional analgesia (181 minutes versus 113 minutes, $P < .05$). The overall analgesic effect of both drugs was modest, with only 30% to 50% of women reporting satisfactory pain relief. More women in the pentazocine group were drowsy, but the result did not achieve statistical significance. There were no cases of maternal respiratory depression, and there was no difference between groups in neonatal outcomes. The investigators concluded that pentazocine provides better labor analgesia than tramadol.

Tramadol

Tramadol is an atypical, weak, synthetic opioid that has affinity for all opioid receptors, but particularly the μ-opioid subtype. Tramadol also inhibits neuronal reuptake of norepinephrine and serotonin, and it directly stimulates presynaptic serotonin release, which may account for some of its analgesic effects.[13] Tramadol can be administered orally or by intramuscular or intravenous injection at a dose of 50 to 100 mg every 4 to 6 hours in adults. Although the initial bioavailability after oral administration is only 70% owing to a significant first-pass effect, this increases to almost 100% with repeated doses.[10,13]

The analgesic potency of tramadol is equal to that of meperidine and one fifth to one tenth that of morphine. In equi-analgesic doses, tramadol causes less respiratory depression than morphine; at usual doses, no clinically significant respiratory depression occurs. The onset of analgesia is within 10 minutes of intramuscular administration, with an effective duration of 2 to 4 hours. Tramadol is metabolized by demethylation and glucuronidation in the liver to several metabolites, one of which has independent analgesic activity (M1). The metabolites are almost entirely excreted in the urine. The elimination half-life is 5 to 6 hours, whereas that of the active metabolite is 9 hours.

Tramadol readily crosses the placenta, and an umbilical vein-to-maternal vein ratio of 0.94 has been observed at delivery.[42] Neonates possess complete hepatic capacity for metabolism of tramadol to its active metabolite M1. The elimination profile of M1 suggests a terminal half-life of 85 hours because of its requirement for renal elimination, which is an immature process in neonates. Claahsen-van der Grinten et al.[42] reported that intrapartum tramadol (initial dose of 100 mg, then subsequent doses of 50 to 100 mg, up to a maximum dose of 250 mg) resulted in normal Apgar scores and NACS, with no correlation to tramadol or M1 concentrations. However, the single neonate who required naloxone had the highest plasma concentration of tramadol.

The analgesic efficacy of tramadol in labor has been questioned. Keskin et al.[43] compared intramuscular tramadol 100 mg and meperidine 100 mg for labor analgesia; they observed greater pain relief and a lower incidence of nausea and fatigue with meperidine. There was no significant difference between groups in neonatal outcome, but more infants in the tramadol group required supplemental oxygen for respiratory distress and hypoxemia. The investigators concluded that meperidine provided superior analgesia and was associated with a better side-effect profile.

By contrast, Viegas et al.[44] conducted a randomized, double-blind trial to compare intramuscular administration of tramadol 50 mg, tramadol 100 mg, and meperidine 75 mg during labor. Tramadol 100 mg and meperidine 75 mg provided similar labor analgesia; however, a higher incidence of maternal and neonatal adverse effects was observed with meperidine.

Kooshideh and Shahriari[45] evaluated the intramuscular administration of tramadol 100 mg or meperidine 50 mg on labor duration and analgesic efficacy in 160 parturients. The investigators observed that tramadol was associated with a reduced duration of both the first stage (140 versus 190 minutes, $P < .001$) and the second stage of labor (25 versus 33 minutes, $P = .001$). There was no difference in median and maximum pain scores between groups 1 hour after drug administration; however, lower pain scores were observed during the second stage of labor in the meperidine group. Nausea, vomiting, and drowsiness occurred less frequently in the tramadol group.

PATIENT-CONTROLLED ANALGESIA

Patient-controlled analgesia has been used to control postoperative pain for several decades and for the provision of labor analgesia in more recent years. First described in women with thrombocytopenia who were unable to undergo a neuraxial analgesia procedure, its use has grown in availability and popularity. A 2007 survey demonstrated that 49% of obstetric units in the United Kingdom offered PCA for labor analgesia.[46] Purported advantages of PCA include (1) superior pain relief with lower doses of drug, (2) less risk for maternal respiratory depression compared with bolus intravenous administration, (3) less placental transfer of drug, (4) less need for antiemetic agents, and (5) greater patient satisfaction.[47] The smaller, more frequent dosing used with this mode of analgesia may result in a more stable plasma drug concentration and a more consistent analgesic effect when compared with that of intermittent bolus administration regimens.[47]

PCA represents an alternative method of labor analgesia when neuraxial analgesia is not requested or is

TABLE 22-4 **Opioids Used for Intravenous Patient-Controlled Analgesia in Labor**

Drug	Bolus Dose	Lockout Interval (min)
Meperidine	5-15 mg	10-20
Nalbuphine	1-3 mg	6-10
Fentanyl	10-25 μg	5-12
Alfentanil	200 μg (+ 200 μg/h infusion)	5
Remifentanil (bolus only)	0.2-0.8 μg/kg (low dose initially, then titrated to effect)	2-3
Remifentanil (background infusion with bolus dose)	Infusion rate: 0.025-0.1 μg/kg/min Bolus dose: 0.25 μg/kg	2-3

unavailable, contraindicated, or unsuccessful. The parturient can tailor the administration of analgesia according to her individual needs, and with some regimens the bolus dose can be altered to allow further titration of analgesia as labor progresses.

However, PCA for labor is not without limitations. Despite the frequency of dose administration, the coordination of peak opioid concentrations with uterine contractions can be difficult and result in suboptimal analgesia. In addition, the relatively small doses of opioid may be less effective at controlling pain as labor progresses. Finally, a number of maternal and fetal side effects have been described (see later discussion). A variety of drugs, doses, and regimens have been studied, including comparisons of PCA with and without a continuous intravenous infusion (Table 22-4).

Meperidine

Meperidine was the first opioid to be used for PCA during labor. Isenor and Penny-McGillivray[48] compared PCA meperidine (background infusion 60 mg/h with bolus doses of 25 mg, up to a maximum dose of 200 mg) with intermittent intramuscular meperidine (50 to 100 mg every 2 hours). Women in the PCA group reported lower pain scores than women in the intramuscular group, even when adjustment was made for the increased total amount of meperidine used.[48] There was no difference in maternal side effects, FHR abnormalities, or neonatal Apgar scores between groups.

More recent studies have indicated that when administered by PCA, meperidine appears to be less effective than the shorter-acting opioids. Douma et al.[49] randomized parturients in labor to receive either meperidine (49.5 mg loading dose, 5 mg bolus dose with 10 min lockout, maximum total dose 200 mg), fentanyl (50 μg loading dose, 20 μg bolus dose with 5 min lockout, maximum dose 240 μg/h), or remifentanil (40 μg loading dose, 40 μg bolus dose with 2 min lockout, maximum dose 1200 μg/h). Meperidine provided the least effective analgesia, with no change in pain scores from baseline at 2 hours after administration and the highest rate of conversion to epidural analgesia.

Morphine and Diamorphine

When administered by PCA, morphine and diamorphine are rarely used for labor analgesia in parturients with a live fetus, but they represent an option for women with intrauterine fetal demise.[46] The accumulation of the active metabolite morphine-6-glucuronide, which is a potent respiratory depressant, is a concern in mothers with a live fetus. No studies have compared the analgesic efficacy of morphine administered by PCA versus intermittent bolus administration during labor. In a single study of diamorphine, administered by either PCA or intermittent intramuscular bolus doses, less effective analgesia and lower satisfaction scores were observed in the PCA group.[50]

Fentanyl

The pharmacokinetic profile for fentanyl (i.e., rapid onset, high potency, short duration of action, absence of active metabolites) has resulted in its selection as one of the most commonly used opioids for PCA during labor and delivery. In the United Kingdom, it is used in 26% of the units that offer PCA during labor.[46]

Nikkola et al.[51] observed that fentanyl PCA (50 μg loading dose, 20 μg bolus, 5 minute lockout) provided a moderate reduction in labor pain in 50% of the parturients receiving this mode of analgesia; however, less overall pain relief was experienced when compared with a group that received epidural analgesia. The use of fentanyl was also associated with a higher incidence of maternal dizziness and sedation.

Rayburn et al.[52] compared fentanyl PCA (bolus 10 μg, lockout interval 12 minutes) to intermittent intravenous nurse-administered fentanyl boluses (50 to 100 μg every hour, on demand). The degree of analgesia, adverse maternal effects, and neonatal outcomes (e.g., neonatal Apgar scores, naloxone requirements, neurobehavioral scores) were similar between the two groups. The two groups used a similar total amount of fentanyl, had comparable umbilical serum concentrations of fentanyl, and had incomplete analgesia during late labor.

Morley-Forster and Weberpals[53] observed a 44% incidence of moderate neonatal depression (1 minute Apgar < 6) in a retrospective review of 32 neonates whose mothers had received fentanyl PCA (at various initial doses, basal infusion rates, and lockout intervals) during labor. A total of 9.4% of the neonates required naloxone; the total dose of fentanyl was significantly higher in the mothers of neonates who required naloxone than in those who did not (mean ± SD, 770 ± 233 μg versus 298 ± 287 μg, respectively). By contrast, in a retrospective evaluation of fentanyl PCA (loading 50 μg, bolus 20 μg, lockout interval 5 minutes) compared with no analgesia during labor, Hosokawa et al.[54] observed lower mean umbilical arterial blood pH measurements, but comparable Apgar scores and no requirement for naloxone or bag-and-mask ventilation in the 129 neonates whose mothers received fentanyl.

Alfentanil

Alfentanil is a highly selective μ-opioid receptor agonist that is administered by the intravenous route only.[13] Although infrequently used during labor, it is typically administered by PCA. A fentanyl derivative, it is approximately 10 times less potent than fentanyl. It is less lipophilic and more protein bound than its parent compound, resulting in a smaller volume of distribution. Its low volume of distribution and low pKa result in a rapid onset (within 1 minute), a short duration of action, and rapid clearance (elimination half-life of 90 minutes). Furthermore, its context-sensitive half-life is shorter than that of fentanyl. Metabolism of alfentanil occurs by demethylation in the liver to noralfentanil, which is then conjugated and excreted in the urine. Importantly, alfentanil is a potent respiratory depressant, and consequently there are concerns regarding potential adverse neonatal effects.

Morley-Forster et al.[55] compared alfentanil PCA (bolus 200 μg, lockout interval 5 minutes, background infusion 200 μg/h) to fentanyl PCA (bolus 20 μg, lockout interval 5 minutes, background infusion 20 μg/h). The two drugs appeared equally effective in early labor, up to a cervical dilation of 6 cm. Subsequently, fentanyl was associated with a greater reduction in pain scores compared with alfentanil. There were no significant differences in maternal side effects or neonatal outcomes.

Pentazocine

The use of pentazocine is uncommon in the western world, and there has been little evaluation of its use via PCA. One study in South Africa compared pentazocine PCA with meperidine PCA and reported acceptable maternal analgesia and neonatal outcomes with both, but a higher incidence of maternal nausea and sedation with meperidine.[56]

Tramadol

Tramadol is not commonly used via PCA. Long and Yue[57] compared tramadol PCA with CSE analgesia and found that both forms of pain relief resulted in a significant decrease in pain scores compared with a third group not receiving analgesia; however, the CSE technique provided the best analgesia. The tramadol group experienced a higher incidence of adverse maternal events (including one case of cardiovascular collapse) and neonatal depression.

Nalbuphine

Few studies have evaluated nalbuphine PCA in labor. In one study, maternal satisfaction was higher with nalbuphine PCA (bolus 1 mg, lockout interval 6 to 10 minutes) compared with intermittent intravenous administration (bolus 10 to 20 mg every 4 to 6 hours).[58] Analgesia and Apgar scores were similar between groups, and no neonates required naloxone.

Frank et al.[59] concluded that nalbuphine PCA (bolus 3 mg, lockout interval 10 minutes) provided better analgesia in nulliparous women than meperidine PCA (bolus 15 mg, lockout interval 10 minutes). Maternal sedation scores were similar, and there was no difference in neonatal outcome as assessed by Apgar scores, time to sustained respiration, or neurobehavioral assessment at 6 to 10 hours after delivery.

Remifentanil

Remifentanil is a synthetic anilidopiperidine derivative with selective activity at the μ-opioid receptor, low lipid solubility, and a low volume of distribution (0.39 L/kg). Functional brain magnetic resonance imaging reveals an onset time of 20 to 30 seconds, peak concentration within 80 to 90 seconds at the cortical loci, and a blood-brain equilibration time of 1.2 to 1.4 minutes.[60] Remifentanil undergoes rapid hydrolysis by nonspecific plasma and tissue esterases to an inactive metabolite, resulting in a short elimination half-life of approximately 9.5 minutes.[61] The context sensitive half-life is 3.5 minutes, irrespective of duration of infusion. The effective analgesic half-life is 6 minutes, thus allowing effective analgesia for consecutive uterine contractions.[61] Plasma concentrations of remifentanil in pregnant patients are approximately half those found in nonpregnant patients.[62] This difference may be due to the greater volume of distribution (increased blood volume and reduced protein binding), greater clearance (increased cardiac output and renal perfusion), and higher esterase activity during pregnancy.

Remifentanil readily crosses the placenta, resulting in a fetal-to-maternal blood ratio of 0.88; however, the lower umbilical artery-to-vein concentration ratio of 0.29 demonstrates that the drug is either extensively redistributed or metabolized by the fetus.[62] These pharmacokinetic properties are ideal for labor analgesia[63]; moreover, remifentanil is rapidly titratable, allowing dose adjustments with labor progress or in response to side effects. For example, termination of a continuous remifentanil infusion results in a 50% recovery in minute ventilation within 5.4 minutes. The rapid elimination of remifentanil also reduces the propensity for neonatal respiratory depression compared to that with longer-acting opioids. Kan et al.[62] found no adverse neonatal effects after a remifentanil infusion during cesarean delivery.

Comparison with Other Forms of Labor Analgesia

The efficacy of remifentanil PCA has been compared with that of other labor analgesic agents and regimens (Table 22-5).

Remifentanil versus Meperidine. Thurlow et al.[64] conducted a randomized unblinded study comparing remifentanil PCA (bolus 20 μg, lockout interval 3 minutes) with intramuscular meperidine 100 mg. The remifentanil group experienced significantly lower pain scores (median maximum pain score 66.5/100 versus 82.5/100, $P = .009$) within the first 2 hours of commencing analgesia. Parturients in the remifentanil group experienced more sedation and episodes of Sao_2 less than 94% but less nausea and vomiting. No significant difference in neonatal Apgar scores was found. Patient and midwife satisfaction were both higher in the remifentanil group.

TABLE 22-5 Trials Comparing Remifentanil Patient-Controlled Analgesia with Alternative Labor Analgesia

Reference	No. Subjects	Study Design	Groups; Drugs; Doses	Primary Data	Comments
Thurlow et al.[64]	36	Unblinded, randomized	n = 18; M 100 mg IM n = 18; R PCA 20 μg b, 3 min l/o	VAPS at 1 h after analgesia Maximum VAPS at 2 h after analgesia	Lower VAPS in group R at 1 h (48 mm versus 72 mm; $P = .0004$) Lower max VAPS in group R during first 2 h (66.5 mm versus 82.5 mm; P = .009)
Ng et al.[65]	68	Double-blind, randomized	n = 34; M 50 mg IM < 60 kg, 75 mg ≥ 60 kg n = 34; R PCA 25 μg b < 60 kg, 30 μg b ≥ 60 kg, 3.75-4.5 min l/o	VAPS hourly	Lower mean VAPS in group R ($P = .001$). Lowest VAPS in group R at 2 hours after analgesia (44% relative reduction from baseline).
Evron et al.[66]	88	Double-blind, randomized	n = 45; M 75-200 mg IV n = 43; R PCA increasing b dose in 5-μg increments, range 20-70 μg, 3 min l/o	VAPS at 1 hour after analgesia VAPS at end of first stage of labor	Lower VAPS in group R at 1 hour (35.8 mm versus 58.8 mm, $P < .001$). Lower VAPS at end of first stage (32.6 mm versus 53.5 mm, P < .001).
Volikas et al.[67]	17	Double-blind, randomized	n = 8; M PCA 10 mg b, 5 min l/o n = 9 R PCA 0.5 μg/kg b, 2 min l/o	VAPS hourly VAPS after delivery	Lower mean VAPS hourly in group R ($P = .0496$) Lower mean VAPS after delivery in group R (P = .03)
Blair et al.[68]	39	Double-blind, randomized	n = 19; M PCA 15 mg b, 10 min l/o n = 20; R PCA 40 μg b, 2 min l/o	VAPS every 30 min VAPS "overall" at 2 hours after delivery	Similar VAPS in labor and overall between groups (overall pain score 63.6 mm R versus 68.6 mm M (P = NS)
Douma et al.[49]	159	Double-blind, randomized	n = 53; M PCA 49.5 mg load, 5 mg b, 10 min l/o n = 52; R PCA 40 μg load, 40 μg b, 2 min l/o n = 54; F PCA 50 μg load, 20 μg b, 5 min l/o	VAPS hourly	Greatest reduction in VAPS observed at 1 hour in all 3 groups Lower VAPS in group R at 1 h (↓3.2 cm versus ↓1.4 cm F versus ↓0.8 cm M) Similar VAPS beyond first hour among groups
Volmanen et al.[71]	15	Double-blind, randomized, crossover	All participants had 20 min of 50% nitrous oxide or R PCA (0.4 μg/kg b, 1 min l/o) followed by 20 min washout period (no analgesia) then 20 min of the other analgesic. n = 9; Group 1 R then nitrous oxide n = 6; Group 2 Nitrous oxide then R	Pain intensity difference (PID = mean pain score with analgesia – mean pain score without analgesia)	Higher PID in group R (1.5 versus 0.5, $P = .01$).
Volmanen et al.[72]	45	Double-blind, randomized	n = 24; R PCA 0.1-0.9 μg/kg b (0.1 μg/kg increments), 1 min l/o n = 21; Epidural 20 mL of 0.625 mg/mL levobupivacaine with 2 μg/mL fentanyl	Pain after each contraction (0-10)	Higher median pain scores in group R (7.3 versus 5.2, $P = .009$)
Tveit et al.[74]	37	Unblinded, randomized	n = 17; R PCA 0.15-1.05 μg/kg b (0.15 μg/kg increments), 2 min l/o n = 20; Epidural ropivacaine 1 mg/mL with fentanyl 2 μg/mL. Loading dose 15 mL then 10 mL/h infusion.	VAPS every 15 min	Similar VAPS between groups at end of first stage and during second stage. Similar maximum reduction in VAPS between groups.

VAPS, Visual analog pain score (0-100 mm); *M,* meperidine; *R,* remifentanil; *F,* fentanyl; *b,* bolus; *l/o,* lockout; *NS,* nonsignificant.

Ng et al.[65] conducted a randomized, double-blind study in which all 69 patients used a PCA device containing either remifentanil (PCA group) or 0.9% saline (meperidine group), and also received an intramuscular injection of either saline (PCA group) or meperidine (meperidine group). The doses administered depended on patient weight; women weighing less than 60 kg or 60 kg or more were given a bolus dose of remifentanil of 25 μg or 30 μg, respectively. Similarly, the doses of meperidine were either 50 mg or 75 mg. The PCA lockout interval was 3.75 to 4.5 minutes, and a background infusion was not used. Maternal analgesia was greater (particularly in the first 2 hours after initiation), the median time to first rescue analgesic request was longer (8.0 hours versus 4.9 hours), and maternal satisfaction scores were higher in the remifentanil PCA group than in the meperidine group. There were no differences between groups in maternal sedation, nausea, or Sao_2. Neonatal outcomes were also similar.

Evron et al.[66] compared increasing doses of remifentanil PCA (0.27 to 0.93 μg/kg) with intravenous meperidine. All women receiving remifentanil started with a bolus dose of 20 μg (lockout interval 3 minutes), which was increased in 5-μg increments until effective analgesia was obtained. The meperidine group received an infusion of 75 mg over 30 minutes, followed by an additional 50 mg on request up to a maximum dose of 200 mg. Remifentanil was associated with significantly lower pain scores and higher satisfaction scores than meperidine. There was also a lower incidence of maternal sedation and oxyhemoglobin desaturation with remifentanil.

Several studies have compared the efficacy of remifentanil PCA versus meperidine PCA. In a study that compared remifentanil PCA (bolus 0.5 μg/kg, lockout interval 2 minutes) and meperidine PCA (bolus 10 mg, lockout interval 5 minutes), Volikas et al.[67] terminated the study after enrollment of 17 subjects, owing to significantly lower Apgar scores in the meperidine group. The limited data indicated that women who received remifentanil had better analgesia than those who received meperidine. Blair et al.[68] also observed that the use of remifentanil PCA (bolus 40 μg, lockout interval 2 minutes) resulted in higher maternal satisfaction scores, despite similar pain scores, when compared with meperidine PCA (bolus 15 mg, lockout interval 10 minutes). Despite similar Apgar scores, neonatal NACS at 30 minutes after delivery were significantly lower in the meperidine group.

Douma et al.[49] compared remifentanil PCA (bolus 40 μg, lockout interval 2 minutes), fentanyl PCA (bolus 20 μg, lockout interval 5 minutes), and meperidine PCA (bolus 5 mg, lockout interval 10 minutes). All women received an initial bolus of their allocated drug before commencing PCA. The remifentanil group experienced the greatest decrease in pain scores; however, the effect was transient and pain scores returned toward baseline within 3 hours. Sedation and pruritus, as well as overall satisfaction, were highest in the remifentanil group. The parturients receiving meperidine had the highest crossover rate to epidural analgesia. There were no differences in neonatal outcome among groups.

In a systematic review of seven randomized controlled trials (n = 349 parturients), Leong et al.[69] evaluated the administration of remifentanil versus meperidine provided through a variety of drug delivery methods (e.g., PCA, continuous infusion, intramuscular) for labor analgesia. Remifentanil was noted to reduce mean VAPS by 25 mm more than meperidine in the first hour. Conversion rates to epidural analgesia were less than 10% when using remifentanil. The evaluated studies were too small to make definitive conclusions regarding maternal side effects; however, the incidence of Sao_2 less than 95% and bradypnea was similar between the two drugs. None of the studies demonstrated adverse neonatal outcomes with remifentanil. A meta-analysis concluded that women who received remifentanil PCA had lower mean pain scores after 1 hour, a lower crossover rate to epidural analgesia, and higher satisfaction scores than women who received meperidine.[70]

Remifentanil versus Nitrous Oxide. Volmanen et al.[71] performed a double-blind crossover trial comparing remifentanil (bolus 0.4 μg/kg, lockout interval 1 minute) with 50% nitrous oxide during the first stage of labor. The 20 patients used both analgesics in a random order for 20 minutes, with an intervening washout period of 20 minutes. Pain relief (although modest), maternal sedation, and patient satisfaction were greater in the remifentanil group. No difference in the incidence of FHR changes was observed between the two groups.

Remifentanil versus Epidural Analgesia. In a randomized, double-blind trial, Volmanen et al.[72] compared titrated remifentanil PCA (mean effective bolus 0.5 μg/kg [range 0.3 to 0.7 μg/kg], lockout interval 1 minute) with lumbar epidural analgesia (20 mL of levobupivacaine 0.0625% with fentanyl 2 μg/mL). All patients received both an epidural technique and PCA, using a saline infusion as the control. Mean cervical dilation at initiation of analgesia was 4 cm, and the study was conducted over 1 hour. Parturients receiving epidural analgesia had a more significant and rapid reduction in pain scores than those receiving remifentanil (10 minutes versus 40 minutes to reach the individual effective dose). Median pain scores were lower in the epidural group, but median "pain relief" scores were similar between the two groups. Sedation and low Sao_2 were observed more often during remifentanil infusion. Women in the remifentanil group were given supplemental oxygen more often than those who received epidural analgesia; the need for supplemental oxygen was related to bolus doses of remifentanil of 0.5 μg/kg or greater. There was no difference between groups in neonatal outcomes. Although the investigators concluded that epidural analgesia is superior to remifentanil PCA, they also postulated that high maternal satisfaction with intravenous PCA may be the result of factors other than the degree of analgesia produced. Other studies appear to corroborate this suggestion.[71,73,74]

Tveit et al.[74] conducted a similar study with remifentanil PCA (titrated bolus dose 0.3 to 1.05 μg/kg, lockout interval 2 minutes) compared with lumbar epidural analgesia (10 mL of ropivacaine 0.1% with fentanyl 2 μg/mL). Both treatments provided effective analgesia, and the two groups had similar pain scores at the end of the first stage and during the second stage of labor.

Maternal satisfaction was similar, although the incidence of sedation, oxyhemoglobin desaturation (Sao_2 < 92%), and the need for supplemental oxygen were higher with remifentanil.

Efficacy and Optimal Regimen

Remifentanil can be given as a PCA bolus, as a continuous infusion, or as a combination of the two. Although a number of studies have compared remifentanil to other opioids using fixed, nontitratable PCA doses, Volmanen et al.[75] attempted to determine the minimum effective dose of remifentanil for labor analgesia by titration to effect. Using a starting bolus dose of 0.2 μg/kg, and dose increases of 0.2 μg/kg (lockout interval 1 minute) over a 1-hour study period, the median effective bolus dose was observed to be 0.4 μg/kg (range, 0.2 to 0.8 μg/kg). However, frequent episodes of Sao_2 below 94% (in 10 of 17 subjects), maternal sedation, and reduced FHR variability were observed.

Starting with a remifentanil PCA bolus dose of 0.25 μg/kg (lockout interval 2 minutes) without a background infusion, Blair et al.[76] titrated the bolus and infusion doses to a maximum of 1 μg/kg and 0.05 μg/kg/min, respectively. In 17 of 21 participants, satisfactory analgesia was achieved with a PCA bolus dose of 0.25 μg/kg or 0.5 μg/kg with no background infusion; adding a background infusion resulted in no further improvement of analgesia but an increased incidence of adverse effects.

D'Onofrio et al.[77] conducted an observational study of 205 parturients in whom a continuous infusion of remifentanil was titrated (initial to maximum dose range, 0.025 to 0.15 μg/kg/min) with a goal of achieving pain scores less than or equal to 4 during contractions. Adequate analgesia was achieved within 30 minutes but required a median remifentanil infusion dose of 0.075 μg/kg/min. The Sao_2 remained above 95% in all patients without supplemental oxygen, and there were no reported neonatal side effects.

Balki et al.[78] compared the effect of a fixed remifentanil bolus dose with a titratable background infusion versus a fixed background infusion with a titratable bolus dose. Both groups started with a remifentanil bolus dose of 0.25 μg/kg (lockout interval 2 minutes) and a background infusion rate of 0.025 μg/kg/min. If analgesia was inadequate, either the background infusion or bolus dose was increased in a stepwise manner to a maximum of 0.1 μg/kg/min or 1 μg/kg, respectively. The mean pain scores, satisfaction scores, and cumulative remifentanil doses were similar in the two groups; only one patient eventually requested epidural analgesia. The incidence of maternal side effects was higher in the escalating bolus dose group, including drowsiness (100% versus 30%) and frequency of Sao_2 less than 95% (60% versus 40%). There was no difference in the incidence of adverse neonatal effects. The investigators advocated the use of a titrated background infusion (range, 0.025 to 0.1 μg/kg/min) with a constant PCA bolus dose (0.25 μg/kg, lockout interval 2 minutes).

Balcioglu et al.[79] compared two remifentanil background infusion rates (0.1 and 0.15 μg/kg/min) with a constant PCA bolus dose (15 μg, lockout interval 5 minutes). During the study period of 90 minutes, pain scores were significantly lower in the group receiving the higher infusion dose, but there was no difference between groups in patient satisfaction, FHR abnormalities, or neonatal Apgar scores.

Altogether, these studies suggest that fixed-dose remifentanil PCA protocols are less effective than titratable regimens, with the potential for low and high doses resulting in poor analgesia or adverse effects, respectively. Evidence is conflicting as to whether the use of a background infusion confers additional benefits, particularly given the greater risk for maternal sedation and respiratory depression; one parturient became apneic within 3 minutes of increasing a background infusion from 0.05 to 0.1 μg/kg/min.[80] Furthermore, a continuous remifentanil infusion regimen may not take advantage of the drug's intrinsic onset and offset characteristics in targeting the episodic nature of uterine contraction pain.[73]

The analgesic benefit of remifentanil may be optimized by training parturients to press the PCA button with the first perception of a contraction, given that the peak analgesic effect occurs within 1 to 3 minutes.[13] A novel delivery system (preemptive remifentanil analgesia modality [PRAM]) is in development; this system uses a mathematical analysis of the previous three contractions to deliver a bolus dose 45 seconds before the next predicted contraction to coordinate the peak action of remifentanil with uterine contractions.[81]

Side Effects

Remifentanil can cause significant respiratory depression through reductions in the ventilatory rate and tidal volume.[13] Although the safety profile of remifentanil PCA in labor has been specifically evaluated, the data are conflicting.[77,82] Volikas et al.[82] investigated the maternal and neonatal effects of remifentanil PCA (bolus dose 0.5 μg/kg, lockout interval 2 minutes) in 50 women. Effective analgesia was reported in 86% of study participants, and 44% experienced slight drowsiness (but were arousable to voice and maintained Sao_2 > 93%). Mild itching and FHR changes occurred in the first 20 minutes of remifentanil PCA but did not require treatment. Umbilical cord blood gas measurements and neonatal Apgar scores and neurologic examinations were all within normal limits.

Several theories have attempted to explain the relatively high incidence of sedation and respiratory depression with the use of remifentanil PCA in laboring women. Despite the rapid onset of remifentanil, administration of a bolus dose of remifentanil may result in an onset of analgesia after the cessation of uterine contractions (which have an average duration of 60 to 70 seconds). Thurlow et al.[64] have encouraged parturients to request a bolus dose at the very first detection of a contraction. Some investigators have suggested that administration of a PCA bolus between contractions might reduce the risk for sedation and improve the efficacy of analgesia; however, a report by Volmanen et al.[83] does not support this hypothesis. After administration of a remifentanil bolus, the onset of electroencephalographic depression occurs before the onset of respiratory depression and the

peak respiratory depression occurs approximately 2.5 minutes after bolus injection.[84]

Studies of remifentanil PCA during labor have reported a wide range in the incidence of nausea (0% to 60%).[77,78] Pruritus occurs in approximately 16% of parturients.[49] Nausea and emesis can occur through an opioid-induced increase in vagal activity, which may result in a decrease in mean arterial pressure and heart rate; however, this has not been reported in laboring women receiving remifentanil PCA, perhaps reflecting the doses administered and/or the high maternal sympathetic activity during labor.

Maternal administration of remifentanil PCA during labor appears to have minimal effect on FHR abnormalities, umbilical cord blood gas measurements, and Apgar scores.[73] Comparison studies have reported a lower incidence of FHR abnormalities with remifentanil than with meperidine.[68] Neonatal depression has been observed after general anesthesia that includes remifentanil; however, any contribution from remifentanil is likely minor given its rapid neonatal metabolism.[73] This last characteristic has led to the use of remifentanil for sedation in neonatal intensive care units.

Remifentanil is the most commonly used opioid for PCA during labor in the United Kingdom.[46] However, it is not specifically approved for this use in the United Kingdom or the United States, and strict adherence to local guidelines is required for safe practice (Box 22-1). Labor nurses and midwives should undergo a period of training and supervised practice with remifentanil PCA until they are deemed competent. Women must not have received other opioids in the previous 4 hours and should be fully informed of the potential side effects, including the possibility of requiring supplemental oxygen and needing increased levels of monitoring. Continuous pulse oximetry is advocated, and supplemental oxygen should be readily available and administered if Sao_2 consistently falls below 95% (see Box 22-1). The PCA infusion should be given via a dedicated intravenous catheter and infusion set with anti-syphon valves. Sedation scores and respiratory rate should be recorded every 30 minutes, and orders should specify clear triggers for contacting the anesthesia service. Continuous FHR monitoring is essential.

In summary, the analgesic efficacy of remifentanil, particularly in early labor, has been demonstrated. Optimal labor analgesia may require titration of remifentanil PCA with labor progression; however, clinicians should remain vigilant for the common side effects (i.e., maternal sedation, respiratory depression) and comply with local protocols to ensure safe drug use. To date, the studies of remifentanil administration for labor analgesia have included only healthy parturients with low-risk singleton pregnancies. Therefore, the information may not be applicable to all laboring women, and analgesia must be administered on an individual patient basis.

BOX 22-1 Guidelines for Patient-Controlled Anesthesia with Remifentanil*

Eligibility
- Informed consent
- No opioids in the previous 4 hours
- Dedicated intravenous cannula for remifentanil administration

Protocol
- Bolus: 40 μg
- Lockout interval: 2 min

Continuous Observations
- Sao_2 (pulse oximetry)
- Nursing supervision: one-on-one

30-Minute Observations
- Respiratory rate
- Sedation score
- Pain score

Indications for Contacting the Anesthesia Provider
- Excessive sedation score (not arousable to voice)
- Respiratory rate < 8 breaths/min
- Sao_2 < 90% while breathing room air

*Sample guidelines adapted from those used by the Ulster Community and Hospitals Trust, Ulster, United Kingdom. Labor nurses must establish competency in the use of remifentanil patient-controlled analgesia before providing care.

OPIOID ANTAGONISTS

Naloxone is a pure opioid antagonist at the μ-, κ-, and δ-opioid receptors, although it has the greatest affinity for the μ-opioid receptor.[10,13] It is the drug of choice to treat adverse opioid effects in both the mother and the newborn, and it may be given intravenously, subcutaneously, or intramuscularly. The onset of action after an intravenous dose (1 to 4 μg/kg) is 2 minutes, with a duration of action of 30 to 40 minutes; this duration may be less than that of the opioid whose action it antagonizes, and repeated doses or an infusion may be necessary.

The administration of naloxone during labor or before delivery may reverse the quality of analgesia and confer only a limited reduction in maternal side effects; however, some neonatal benefit may be obtained. Hodgkinson et al.[85] reported significantly higher neurobehavioral scores in neonates born to mothers who had received an intrapartum combination of meperidine and naloxone compared with meperidine alone. However, this difference did not persist beyond 2 hours after birth. Clark et al.[86] reported minimal differences in the neurologic and acid-base status of neonates born to mothers who had received both meperidine and naloxone compared with no-analgesia controls, although there was some evidence that high-dose naloxone may have resulted in beneficial neonatal effects.[86] When neonatal depression is anticipated due to maternal opioid administration, it is best to administer naloxone directly to the infant. Naloxone reverses neonatal respiratory depression by increasing both minute ventilation and the gradient of the CO_2 response curve.

Studies have evaluated prophylactic neonatal naloxone administration immediately after delivery of infants whose mothers received opioids during labor. When

compared with saline administration, Weiner et al.[87] observed that intravenous naloxone resulted in a short-lived (30 minutes) improvement in neurobehavioral scores, whereas intramuscular naloxone resulted in similar improvements for the duration of the study period (48 hours).

The recommended neonatal dose of naloxone is 0.1 μg/kg (1 μg/mL solution). Administration of naloxone is not recommended during the primary steps of neonatal resuscitation; however, it may be given after positive-pressure ventilation has restored normal heart rate and Sao_2, if maternal opioid administration occurred during the 4 hours before delivery.[88] The preferred route of naloxone administration is intravenous; intramuscular administration is acceptable, although absorption may be delayed with this route. Endotracheal administration of naloxone is not recommended. Naloxone should not be given to the neonate of a mother who is opioid dependent or on methadone maintenance therapy; this action may result in withdrawal activity and seizures.[88]

OPIOID ADJUNCTS AND SEDATIVES

Historically, many drugs have been used as adjuncts to parenteral opioid analgesia. Most of them cause maternal sedation and neonatal depression and are now used infrequently, particularly because neuraxial and opioid PCA techniques achieve satisfactory analgesia more safely.

Barbiturates are sedative agents with no analgesic effect. They are lipid soluble, rapidly cross the placenta, are detectable in fetal blood, and can result in neonatal depression, especially if combined with systemic opioid administration.

Phenothiazines (e.g., chlorpromazine, promethazine, propiomazine) are dopamine antagonists that have sedative, antiemetic, and antipsychotic properties. They rapidly cross the placenta and reduce FHR variability. Neurobehavioral outcomes after the maternal administration of these agents have not been studied carefully, but there is no evidence that they cause neonatal respiratory depression. Phenothiazines (particularly chlorpromazine) may cause hypotension from alpha-adrenergic receptor blockade, and they may produce unwanted extrapyramidal movements.[13] Parenterally administered promethazine (25 to 50 mg) has an onset of 15 minutes and a duration of action of up to 20 hours; it rapidly crosses the placenta, resulting in detectable fetal levels within 1 to 2 minutes of maternal intravenous administration.[13] Propiomazine is a mild respiratory depressant that may further depress maternal ventilation when co-administered with opioids. It has a faster onset and shorter duration of action than promethazine.

Metoclopramide is a procainamide derivative that can increase gastric motility and reduce nausea and vomiting. As an antagonist at central dopamine receptors, it can also cause drowsiness.[13] After meperidine administration for labor analgesia, Vella et al.[89] found metoclopramide as effective as promethazine for reducing the incidence of nausea and vomiting. Reduced pain scores and nitrous oxide use were observed in women who received metoclopramide compared with those who received promethazine or placebo; this may reflect either an antianalgesic effect of promethazine or a possible analgesic effect of metoclopramide.

Benzodiazepines (e.g., diazepam, lorazepam, midazolam) have been used for sedation in labor but are associated with significant side effects. Diazepam rapidly crosses the placenta and accumulates in the fetus at concentrations that may exceed maternal concentrations. The elimination half-life of the parent drug is 24 to 48 hours, but active metabolites may persist for up to 120 hours. Diazepam may cause maternal and neonatal respiratory depression, as well as neonatal hypotonicity, impaired thermoregulation, and an abnormal stress response. These effects may be dose related. Lorazepam has a half-life of 12 hours and is metabolized to an inactive glucuronide. McAuley et al.[90] gave lorazepam 2 mg or placebo prior to the intramuscular administration of meperidine 100 mg for labor analgesia. Analgesia was better in the lorazepam group, but lorazepam administration was associated with a nonsignificant increase in neonatal respiratory depression. Neonatal neurobehavioral scores were similar in the two groups. Amnesia was common with lorazepam.

Midazolam has a rapid onset of action and an elimination half-life of 1 to 4 hours.[13] It is metabolized in the liver to one major and several minor pharmacologically active compounds, which may persist in patients with critical illnesses accompanied by hepatic and/or renal impairment. Midazolam readily crosses the placenta and when used at high doses (e.g., induction of general anesthesia) can result in neonatal hypotonia. Midazolam causes potent anterograde amnesia, a characteristic that may be undesirable for the childbirth experience.

Ketamine is a phencyclidine derivative that acts as a noncompetitive antagonist at the NMDA receptor and, at high doses, as an agonist at μ-opioid receptors. Most commonly given by intravenous or intramuscular injection, ketamine in small doses (0.2 to 0.5 mg/kg intravenously) can provide dissociative analgesia whereas larger doses (1 to 2 mg/kg intravenously, 5 to 10 mg/kg intramuscularly) can be used to induce general anesthesia.

When given intravenously, ketamine has an onset within 30 seconds and a duration of action of 5 to 10 minutes; intramuscular administration has an onset of 2 to 8 minutes with a duration of 10 to 20 minutes.[13] Ketamine is hepatically metabolized to active metabolites, which are excreted in the urine.

Ketamine's sympathomimetic properties cause an increase in heart rate, systolic pressure, and cardiac output, which should be avoided in preeclamptic and hypertensive patients; however, these effects may be valuable during the induction of anesthesia in hypovolemic patients. In addition, given its bronchodilatory effects, ketamine has long been considered the intravenous induction agent of choice for asthmatic subjects.

Ketamine may be used for labor analgesia. Joselyn et al.[91] reported acceptable labor analgesia with an intravenous infusion of ketamine (bolus 0.1 mg/kg with an infusion of 0.2 mg/kg/h, titrated to effect). The average ketamine infusion rate was 0.17 mg/kg/h, yielding an average total dose of 57 mg (range, 18 to 160 mg). No unpleasant hallucinations were experienced; however,

with the initial dose, emesis and transient light-headedness and nystagmus occurred. All neonates had a 5-minute Apgar score of 9 or 10.

Ketamine may also provide effective analgesia just before vaginal delivery in parturients without neuraxial anesthesia, or it may be used as an adjunctive agent in parturients with unsatisfactory neuraxial analgesia/anesthesia. Using incremental doses of intravenous ketamine (0.2 to 0.4 mg/kg, up to a maximum dose of 100 mg) immediately before delivery, Akamatsu et al.[92] reported that 78 of 80 women experienced complete analgesia with no adverse maternal or neonatal effects. The occurrence of amnesia and a dreamlike state was high, but only one woman found this unpleasant.

Administration of small doses of ketamine (10- to 20-mg doses, repeated at intervals of 2 to 5 minutes, while not exceeding a total dose of 1 mg/kg during a 30-minute period) is associated with a low incidence of maternal hallucinations; however, amnesia is common. In these settings, the anesthesia provider must maintain continual verbal contact with the patient and must ensure that the patient remains sufficiently awake to maintain adequate ventilation and protect her airway.

INHALATIONAL ANALGESIA

The use of inhalational analgesia for labor varies by country. Although many of the anesthetic agents used in surgery have been administered for pain relief during childbirth, only nitrous oxide has achieved wide clinical use.

Nitrous Oxide

Globally, nitrous oxide is the most common inhalational agent used for labor analgesia.[93] Typically it is administered as 50% nitrous oxide in oxygen using a blender device (e.g., Nitronox in the United States) or premixed in a single cylinder (e.g., Entonox in the United Kingdom). The availability and use of nitrous oxide for labor analgesia varies greatly between countries; when provided alone or in combination with other forms of analgesia, the incidence of its use during labor is 1% (or less) in the United States, 43% in Canada, and 62% in the United Kingdom.[93]

The mechanism of action of nitrous oxide is not fully understood, although it is believed to enhance the release of endogenous opioid peptides in the midbrain and modulate descending spinal pain pathways.[94] Because of its low solubility, it has a very rapid onset and offset, and it undergoes minimal metabolism. Although nitrous oxide has limited cardiovascular effects, it can cause depression of ventilation through a reduction in tidal volume; partial compensation of this ventilatory effect is achieved by an increase in respiratory rate. Nitrous oxide is nonirritating to the airway and does not interfere with uterine activity.

Nitrous oxide readily crosses the placenta, and a fetal-to-maternal concentration ratio of 0.8 occurs within 15 minutes; however, no apparent detrimental effects on FHR, Apgar scores, or umbilical cord blood gas measurements have been reported.[94] Even when used immediately prior to delivery, there is no evidence that nitrous oxide causes neonatal respiratory depression or altered neurobehavioral scores. The neonate rapidly eliminates nitrous oxide by respiration, resulting in a half-life of less than 3 minutes.[94]

A systematic review of 16 studies concluded that nitrous oxide is not a potent labor analgesic, but it appears to confer benefit and high levels of satisfaction for some women.[94] In one observational study in laboring women, nitrous oxide was rated as being more effective than systemic meperidine, although it was less effective than epidural analgesia.[95]

To achieve optimal analgesia from nitrous oxide, inhalation should ideally begin in anticipation of the next contraction; however, the timing of uterine contractions is not always predictable. Therefore the patient is encouraged to breathe the mixture of nitrous oxide in oxygen from the very beginning of the contraction until the end of the contraction.

Although a low incidence of serious adverse events (3 per 10,000 administrations of 50% nitrous oxide in oxygen) has been reported, suitable equipment must be available to ensure the safe administration of nitrous oxide. An apparatus that limits the concentration of nitrous oxide (e.g., a nitrous oxide/oxygen blender or a premixed 1 : 1 cylinder) is required and should be checked periodically for correct delivery concentrations. The constituent gases separate at approximately 7° C (19.4 F), which is not usually of practical concern.[13] Inhalation may occur through a mask or mouthpiece containing a one-way demand valve, which opens only when negative inspiratory pressure is applied. This is a safety feature that limits gas delivery in a drowsy patient, and it also helps limit pollution of the environment with unscavenged gases.

Environmental pollution from unscavenged gases may be significant, and it remains unclear whether regular occupational exposure to subanesthetic concentrations of nitrous oxide results in significant health risks for health care workers. Overall, epidemiologic data do not suggest the presence of higher reproductive risks in health care workers exposed to nitrous oxide in the work environment (see Chapter 17).

The most common side effects of nitrous oxide are nausea and vomiting (occurring in up to 33% of parturients), drowsiness, dizziness, and the presence of paresthesias, which may be related to maternal hyperventilation during contractions.[94] There is a potential risk for oxyhemoglobin desaturation due to diffusion hypoxia, although this appears to occur very rarely. It is unclear whether the incidence of intrapartum maternal hypoxemia differs among women who use nitrous oxide when compared with women who receive no analgesia during labor. However, the risk for maternal hypoxemia with nitrous oxide may be more common with the concomitant administration of opioids or other sedatives[96]; the entire obstetric care team should be aware of this possibility.

Although the intrapartum use of nitrous oxide has plateaued or slightly declined in the United Kingdom, some anesthesiologists, obstetricians, and midwives in the

United States have expressed a renewed interest in the use of nitrous oxide for intrapartum analgesia.[93,97] Nitrous oxide clearly does not provide analgesia comparable with that provided by neuraxial techniques, but it has other benefits, including its lower cost and "less invasive nature."[97] In 2012, the United States Agency for Healthcare Research and Quality (AHRQ)[97] published a review of the effectiveness of nitrous oxide for analgesia during labor. The report included a systematic review of 58 publications. The authors concluded that inhalation of nitrous oxide provides less effective intrapartum pain relief than epidural analgesia, but the quality of the published studies was predominantly poor. Apgar scores in newborn infants whose mothers used nitrous oxide were similar to those of newborns whose mothers used other methods of analgesia or received no analgesia. The report concluded that additional research is needed to address all of the following key questions: efficacy, patient satisfaction, effect on the route of delivery, adverse effects, and health system factors affecting the use of nitrous oxide.[97]

Volatile Halogenated Agents

All volatile halogenated agents cause dose-dependent relaxation of uterine smooth muscle. Yoo et al.[98] observed that the minimum alveolar concentration (MAC) of volatile agents required to decrease the spontaneous myometrial contractility of isolated uterine muscle from pregnant women by 50% (ED_{50}) was similar for halothane, sevoflurane, and desflurane (1.72, 1.44, and 1.66 MAC, respectively). Other *in vitro* studies demonstrated that the ED_{50} for sevoflurane varied from 0.8 to 1.0 MAC and that the ED_{50} for desflurane varied from 0.9 to 1.4 MAC.[99,100] In contrast, Yoo et al.[98] observed that the ED_{50} of isoflurane was significantly higher (2.35 MAC) than that for sevoflurane, desflurane, and halothane; an additional unique feature observed with isoflurane was its ability to modulate K_{ATP} channels.[98] Whether these findings suggest that isoflurane is less likely to be associated with uterine atony in clinical practice requires further study. In general, when uterine tone is desirable (e.g., after delivery), volatile anesthetic concentrations higher than 0.5 MAC are not recommended and intravenous oxytocin should be administered concurrently.

A number of studies have examined the use of volatile agents for labor analgesia; most of these investigations used special breathing equipment and did not fully address the issue of unscavenged gases, which may limit their clinical application.

Enflurane

Abboud et al.[101] compared the analgesic effects of 0.25% to 1.25% enflurane with the administration of 30% to 60% nitrous oxide, both given in oxygen during the second stage of labor in 105 women. Satisfactory pain relief was reported in approximately 89% of women in the enflurane group and 76% of women in the nitrous oxide group; this outcome was achieved most frequently with the use of 0.5% enflurane and 40% nitrous oxide, respectively. Amnesia rates were less than 10% in both groups, and there were no differences observed in maternal blood loss, Apgar scores, or umbilical cord blood gas measurements. The mean umbilical cord concentrations of fluoride ions in the enflurane group were below that associated with nephrotoxicity. A subsequent study that compared administration of 1% enflurane in air to 50% nitrous oxide in oxygen during the first stage of labor observed lower pain scores, but higher levels of drowsiness, with enflurane.[102]

Isoflurane

McLeod et al.[103] observed improved labor analgesia with the self-administration of 0.75% isoflurane in oxygen compared with Entonox. Subsequent studies observed satisfactory pain relief with minimal levels of drowsiness with various concentrations of an isoflurane-Entonox mixture.[104,105] Ross et al.[106] evaluated the use of a 0.25% isoflurane-Entonox mixture in 221 parturients in whom Entonox alone provided inadequate analgesia. No mothers became unduly sedated or lost consciousness, and there was no adverse effect on Apgar scores, neonatal respiratory status, or maternal blood loss. The requirement for neonatal resuscitation was greater in mothers who had received systemic opioids within 5 hours of birth in addition to the inhaled mixture. The same investigators verified clinically acceptable performance and safety of premixed isoflurane-Entonox cylinders.[107]

Desflurane

Because of its low blood-gas partition coefficient, desflurane has a rapid onset and offset; however, it is also highly irritating to the airway, making it a less attractive option for inhalation analgesia. Abboud et al.[108] compared inhalation of 1% to 4.5% desflurane versus 30% to 60% nitrous oxide, both in oxygen, and found similar analgesia scores and neonatal outcomes between groups. The incidence of amnesia was significantly greater with desflurane than with nitrous oxide (23% versus 0%).

Sevoflurane

Sevoflurane is the volatile halogenated agent most commonly used for inhalation induction of general anesthesia. It has a short onset and offset of action, but it is less irritating and has a less unpleasant odor than the other volatile agents.

Toscano et al.[109] conducted a safety and feasibility pilot study of 50 parturients breathing 2% to 3% sevoflurane in an oxygen/air mixture via a compact anesthesia delivery system. They aimed for an end-tidal sevoflurane concentration of 1.2% to 1.4% (0.8 to 0.9 MAC during pregnancy) at the peak of uterine contractions. The mean (± SD) pain score was significantly lower during the times when parturients inhaled sevoflurane compared with times when they did not inhale sevoflurane (3.3 ± 1.5 versus 8.7 ± 1.0, respectively, on a scale of 0 to 10). Four women became drowsy, but there were no episodes of oxyhemoglobin desaturation or loss of consciousness, and there were no unexpected increases in blood loss. In addition, there were no reported adverse effects on FHR or neonatal Apgar scores.

In an escalating dose study, Yeo et al.[110] determined that 0.8% sevoflurane was the optimal concentration for labor analgesia, beyond which an increased level of sedation with no additional analgesic benefit was observed. The same investigators subsequently compared 0.8% sevoflurane with Entonox in 32 parturients, using a double-crossover study design.[111] Median with interquartile range (IQR) pain relief scores (100 mm scale) were significantly higher for sevoflurane (67 mm, 55 to 74 mm IQR) than Entonox (51 mm, 41 to 70 mm IQR). There was an increased incidence of nausea and vomiting in the Entonox group, while sedation was increased in the sevoflurane group. The investigators observed no other adverse events, such as Sao_2 less than 98%, apnea, or changes in end-tidal CO_2, although two subjects could not tolerate the odor of sevoflurane. Five parturients requested epidural analgesia during the Entonox phase. All 29 women who completed the study preferred sevoflurane. The investigators concluded that self-administered sevoflurane can provide useful labor analgesia and is superior to Entonox.

Routine use of inhalational labor analgesia may be limited by the need for specialized equipment, concern for environmental pollution, and the potential for maternal amnesia and the loss of protective airway reflexes. Although sedation occurs during intermittent inhalation of volatile anesthetic agents, profound sedation to the extent that airway reflexes are jeopardized has not been reported. Further research and refinement of inhalational labor analgesia may allow the use of this technique for women in whom neuraxial anesthesia is contraindicated.

KEY POINTS

- Systemic analgesia is commonly used in laboring women worldwide.
- All opioid analgesic drugs rapidly cross the placenta and cause a transient reduction in fetal heart rate variability.
- Meperidine is most commonly administered as an intermittent bolus. Its active metabolite is associated with neonatal respiratory depression and neurobehavioral changes.
- There is little evidence that any individual opioid confers significant benefit over meperidine when administered as a bolus.
- Neonates whose mothers received systemic opioid analgesia are more likely to exhibit neonatal depression than those whose mothers who received no analgesia or epidural analgesia.
- Patient-controlled analgesia (PCA) with remifentanil provides good analgesia with minimal effect on neonatal outcome. However, remifentanil PCA requires intensive monitoring because of the risk for maternal sedation and respiratory depression.
- The optimal remifentanil PCA regimen has not yet been determined, but titrated bolus dose regimens seem to confer an advantage as labor progresses. The use of a background infusion warrants extreme caution with respect to potential maternal adverse effects.
- Use of inhalation analgesia is less common in the United States than in other countries, but its use may increase with further study and advances in equipment and scavenging systems.
- Nitrous oxide may be used alone or with other systemic or inhaled agents. Inhalation of nitrous oxide provides some analgesia, particularly in early labor. When used alone, it does not appear to be associated with adverse effects on the fetus or neonate.
- Intermittent inhalation of volatile anesthetic agents appears to provide good analgesia with few maternal or neonatal side effects, but larger studies are needed to assess the safety of these agents.

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CHAPTER 23

Epidural and Spinal Analgesia/ Anesthesia for Labor and Vaginal Delivery

Cynthia A. Wong, MD

CHAPTER OUTLINE

Epidural analgesia and spinal analgesia are the most effective methods of intrapartum pain relief in contemporary clinical practice.[1,2] During the first stage of labor, pain results primarily from distention of the lower uterine segment and cervix (see Chapter 20). Painful impulses are transmitted by means of visceral afferent nerve fibers, which accompany sympathetic nerve fibers and enter the spinal cord at the 10th, 11th, and 12th thoracic and 1st lumbar spinal segments. As labor progresses and the fetus descends in the birth canal, distention of the vagina and perineum results in painful impulses that are transmitted via the pudendal nerve to the 2nd, 3rd, and 4th sacral spinal segments. Neuraxial analgesia is the only form of analgesia that provides complete analgesia for both stages of labor. During the first stage of labor, visceral pain impulses entering the spinal cord at T10 to L1 must be blocked. During the late first stage of labor and the second stage of labor, somatic impulses entering the spinal cord from S2 to S4 must also be blocked (see Chapter 20).

In a survey of 1000 consecutive women who chose a variety of analgesic techniques for labor and vaginal

delivery (including nonpharmacologic methods, transcutaneous electrical nerve stimulation, intramuscular meperidine, inhalation of nitrous oxide, epidural analgesia, and a combination of these techniques), pain relief and overall satisfaction with the birth experience were greater in patients who received epidural analgesia.[2] Similarly, randomized studies that have compared epidural analgesia with systemic opioids and/or inhalation analgesia (i.e., nitrous oxide) have shown that pain scores are lower and patients are more satisfied with neuraxial analgesia.[3]

The provision of analgesia for labor may result in other benefits. Effective epidural analgesia reduces maternal plasma concentrations of catecholamines (Figure 23-1).[4] Decreased alpha- and beta-adrenergic receptor stimulation may result in better uteroplacental perfusion and more effective uterine activity.[5,6] Painful uterine contractions result in maternal hyperventilation. The hyperventilation, in turn, leads to maternal respiratory alkalosis, a leftward shift of the oxyhemoglobin dissociation curve, increased maternal hemoglobin affinity for oxygen, and reduced oxygen delivery to the fetus.[7] Hypocarbia also leads to hypoventilation between contractions, which may cause a decrease in maternal Pao_2. Effective epidural analgesia blunts this "hyperventilation-hypoventilation" cycle.[8] Additionally, one study showed that paternal anxiety levels were lower, and both paternal involvement in the childbirth process and paternal satisfaction were greater, in men whose partners received epidural analgesia than in those whose partners did not.[9] Finally, the presence of an epidural catheter and effective epidural *analgesia* facilitate the rapid initiation of epidural *anesthesia* for emergency cesarean delivery. Neuraxial anesthesia for cesarean delivery is associated with greater overall maternal safety than emergency administration of general anesthesia (see Chapter 26).[10]

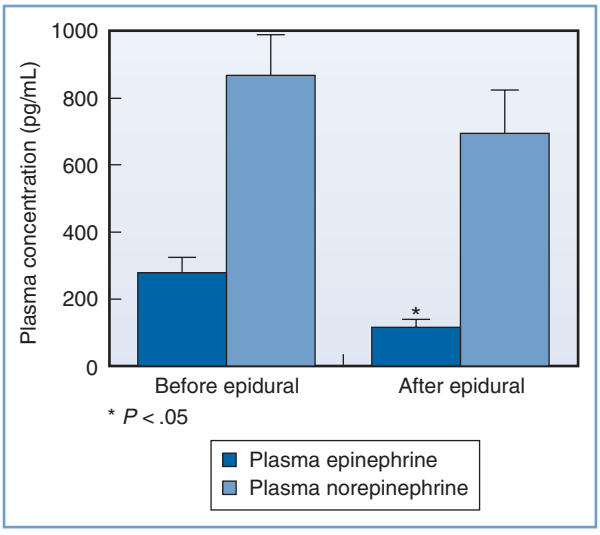


FIGURE 23-1 ■ Influence of epidural analgesia on maternal plasma concentrations of catecholamines during labor. *$P < .05$ compared with before initiation of epidural analgesia. (Modified from Shnider SM, Abboud TK, Artal R, et al. Maternal catecholamines decrease during labor after lumbar epidural anesthesia. Am J Obstet Gynecol 1983; 147:13-5.)

Neuraxial analgesia is not used by all laboring women, although surveys of obstetric anesthesia practice in the United States have shown that the use of neuraxial analgesia has grown over the past three decades.[11] Data collected from the U.S. Standard Certificate of Live Birth in 27 states in 2008 indicated that 61% of women who had a singleton vaginal delivery received neuraxial analgesia.[12] The rate was higher among white women than in women of other races/ethnicities, and it was also higher in larger maternal units than in smaller units.[11,12] In the United Kingdom, the National Health Service Maternity Statistics for 2010-2011 indicated that approximately one third of parturients chose to receive neuraxial analgesia during childbirth.[13]

The availability of skilled anesthesia providers influences the neuraxial analgesia rate.[11] Other factors include the information and advice provided to pregnant women by obstetricians, nurses, and childbirth education instructors. The personal and cultural expectations of a laboring woman, as well as obstetric complications,[2] also affect the childbirth experience and the use of neuraxial analgesia (see Chapters 20 and 21).

In contemporary clinical practice, health care costs have assumed significant importance. Studies using 1998 data estimated that the incremental cost to society for providing epidural labor analgesia was $260 to $340 per parturient (approximately $367 to $481 in 2012 dollars).[14,15] A major problem with such analyses is the difficulty of determining the total value of neuraxial analgesia. For example, the ability to rapidly convert epidural analgesia to surgical anesthesia may also have value.

Ideally, the anesthesia provider should tailor the analgesic technique to meet the individual parturient's needs. Factors that should be considered in formulating an analgesic plan for individual parturients include coexisting maternal disease, the airway examination, fetal status, spontaneous versus induced labor, stage of labor, and anticipated risk for operative delivery. The risks and benefits of the various epidural and spinal analgesic techniques should be assessed for each parturient. Good technique requires thoughtful preparation and meticulous attention to detail to ensure maternal and fetal safety.

The ideal labor analgesic technique is safe for both the mother and the infant, does not interfere with the progress of labor and delivery, and provides flexibility in response to changing conditions. In addition, the ideal technique provides consistent pain relief, has a long duration of action, minimizes undesirable side effects (e.g., motor block), and minimizes ongoing demands on the anesthesia provider's time. No single technique or anesthetic agent is ideal for all parturients during labor. The American Society of Anesthesiologists (ASA) has published practice guidelines for obstetric anesthesia (see Appendix B),[16] as well as guidelines for neuraxial anesthesia in obstetric patients (see Appendix A). Guidelines promulgated by professional organizations in other countries also address obstetric anesthesia care. All obstetric anesthesia providers should review their country's respective guidelines. Specific neuraxial techniques for labor analgesia, including their advantages, disadvantages, side effects, and complications, are considered in this chapter.

PREPARATION FOR NEURAXIAL ANALGESIA

Indications and Contraindications

Epidural analgesia is indicated to treat the pain experienced by a woman in labor. In 2008 and 2010, respectively, the American College of Obstetricians and Gynecologists (ACOG)[17] and the ASA[18] reaffirmed an earlier, jointly published opinion that stated that "in the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor." Furthermore, the ACOG[19] has stated that "decisions regarding analgesia should be closely coordinated among the obstetrician, the anesthesiologist, the patient, and skilled support personnel." Neuraxial analgesia is an appropriate treatment for the pain of labor, including early labor (defined as regular uterine contractions that cause progressive effacement and dilation of the uterine cervix). Randomized controlled trials[20-24] and a meta-analysis[25] have confirmed that initiation of neuraxial analgesia in early labor does not increase the risk for cesarean delivery (see later discussion).

Epidural analgesia may facilitate an atraumatic vaginal breech delivery, the vaginal delivery of twin infants, and vaginal delivery of a preterm infant (see Chapters 34 and 35). By providing effective pain relief, epidural analgesia facilitates blood pressure control in preeclamptic women (see Chapter 36). Epidural analgesia also blunts the hemodynamic effects of uterine contractions (e.g., sudden increase in cardiac preload) and the associated pain response (tachycardia, increased systemic vascular resistance, hypertension, hyperventilation) in patients with other medical complications (e.g., mitral stenosis, spinal cord injury, intracranial neurovascular disease, asthma; see Chapters 42, 49, and 53).

Box 23-1 lists the contraindications to administration of epidural or spinal analgesia. Some anesthesiologists have suggested that systemic maternal infection, preexisting neurologic disease, or severe stenotic heart lesions are relative contraindications to neuraxial analgesia. However, most cases of systemic infection (especially if properly treated), or neurologic or cardiac disease, do not contraindicate the administration of neuraxial analgesia (see Chapters 37, 42, and 49). It is also controversial whether mild or isolated abnormalities in tests of blood coagulation preclude the use of neuraxial analgesia. The dose and timing of administration of drugs administered for thromboprophylaxis must also be considered (see Chapter 44).[26] The anesthesia provider should consider the risks and benefits of neuraxial analgesia for each patient individually.

Thorough preparation for neuraxial labor analgesia involves several steps (Box 23-2). These include (1) a review of the parturient's obstetric history; (2) a focused preanesthetic evaluation that includes maternal obstetric, anesthetic, and health history; and (3) a brief physical examination (i.e., vital signs, airway, heart, lungs, and back).[16] Routine measurement of the platelet count is not necessary; however, assessment of the platelet count and other laboratory measurements may be indicated in selected patients.[16] Similarly, routine intrapartum blood typing and screening or crossmatching is not necessary in healthy parturients, although consideration should be given to sending a blood sample to the blood bank (to facilitate the rapid availability of blood products in case of emergency need).[16] For parturients at increased risk for hemorrhage, intrapartum typing, and screening or crossmatching should be performed. Fetal well-being should be assessed by a skilled provider, and equipment (including resuscitation equipment) should be checked by the anesthesia provider (see Box 12-1). Informed consent should be obtained (see Chapters 12 and 33). Early and ongoing communication among the obstetric and anesthesia providers, nursing staff, and other members of the multidisciplinary team is encouraged.

Types of Neuraxial Analgesia

The technical aspects of neuraxial analgesic/anesthetic techniques are discussed in detail in Chapter 12. These

BOX 23-1 Contraindications to Epidural and Spinal Analgesia

- Patient refusal or inability to cooperate
- Increased intracranial pressure secondary to a mass lesion
- Skin or soft tissue infection at the site of needle placement
- Frank coagulopathy
- Recent pharmacologic anticoagulation*
- Uncorrected maternal hypovolemia (e.g., hemorrhage)
- Inadequate training in or experience with the technique
- Inadequate resources (e.g., staff, equipment) for monitoring and resuscitation

*Safety depends on specific drug and timing and dose of the most recent drug administration (see Chapters 39 and 44).

BOX 23-2 Checklist: Preparation for Neuraxial Labor Analgesia

1. Communicate (early) with the obstetric provider:
   - Review parturient's obstetric history.
2. Perform focused preanesthetic evaluation:
   - Review maternal obstetric, anesthetic, and health history.
   - Perform targeted physical examination (vital signs, airway, heart, lungs, back).
3. Review relevant laboratory measurements and imaging studies.
4. Consider need for blood typing and screening or crossmatching.
5. Formulate analgesia plan.
6. Obtain informed consent.
7. Perform equipment check:
   - Check routine equipment.
   - Check emergency resuscitation equipment.
8. Obtain peripheral intravenous access.
9. Apply maternal monitors (blood pressure, heart rate, pulse oximetry).
10. Monitor fetal heart rate.
11. Perform a team time-out.

TABLE 23-1 **Advantages and Disadvantages of Neuraxial Techniques in Labor**

Neuraxial Technique	Advantages	Disadvantages
Continuous epidural	Continuous analgesia No dural puncture required Ability to extend analgesia to anesthesia for cesarean delivery	Slow onset of analgesia Larger drug doses required when compared with spinal techniques Greater risk for maternal systemic toxicity Greater fetal drug exposure
Combined spinal-epidural	Continuous analgesia Low doses of local anesthetic and opioid Rapid onset of analgesia Rapid onset of sacral analgesia Ability to extend analgesia to anesthesia for cesarean delivery Complete analgesia with opioid alone Decreased incidence of failed epidural analgesia	Delayed verification of correctly placed and functioning epidural catheter Increased incidence of pruritus Possible higher risk for fetal bradycardia
Continuous spinal	Continuous analgesia Low doses of local anesthetic and opioid Rapid onset of analgesia Ability to extend analgesia to anesthesia for cesarean delivery	Large dural puncture increases risk for post–dural puncture headache Possibility of overdose and total spinal anesthesia if the spinal catheter is mistaken for an epidural catheter
Continuous caudal	Continuous analgesia Avoids need to access neuraxial canal through lumbar interspace in patients with previous lumbar spine surgery	Requires large volumes/doses of drugs May be technically more difficult than other neuraxial techniques Possible higher risk for infection than with other neuraxial techniques Risk for inadvertent fetal injection
Single-shot spinal	Technically simple Rapid onset of analgesia Immediate sacral analgesia Low drug doses	Limited duration of analgesia

techniques include continuous epidural, combined spinal-epidural, and caudal analgesia and continuous and single-shot spinal analgesia. Continuous epidural and combined spinal-epidural analgesia are the most common techniques used for neuraxial labor analgesia. There are advantages and disadvantages to each technique (Table 23-1).

Epidural Analgesia

Continuous lumbar epidural analgesia has been the mainstay of neuraxial labor analgesia for several decades. Placement of an epidural catheter allows analgesia to be maintained until after delivery. No dural puncture is required. The presence of a catheter and effective analgesia allow the conversion to epidural anesthesia should cesarean delivery be necessary. Injection of a local anesthetic in the lumbar epidural space allows both cephalad and caudad spread of the anesthetic solution.

Analgesia is initiated by bolus injection of drug(s) through the epidural needle, catheter, or both. Analgesia is maintained with anesthesia provider- or patient-administered intermittent bolus injections or a continuous epidural infusion, or both. The catheter is removed after delivery when there is no further need for analgesia or anesthesia.

Combined Spinal-Epidural Analgesia

Combined spinal-epidural (CSE) analgesia has become increasingly popular in the past 15 years. Onset of complete analgesia is significantly faster than with epidural techniques (2 to 5 minutes versus 10 to 15 minutes, respectively).[27] In a meta-analysis of the onset time of CSE compared with low-dose epidural analgesia,[27] the mean difference in onset was −5.4 minutes (95% confidence interval [CI], −7.3 to −3.6). More women with spinal analgesia than with epidural analgesia had effective analgesia at 10 minutes (relative risk [RR], 1.9; 95% CI, 1.5 to 2.5). In particular, the onset of sacral analgesia is significantly slower after the initiation of lumbar epidural analgesia than with spinal analgesia. It may take several hours of lumbar epidural infusion, or several bolus injections of local anesthetic into the lumbar epidural space, to achieve sacral analgesia. Rapid onset of sacral analgesia is advantageous in the parturient in whom analgesia is initiated late in the first stage of labor or in a parous parturient with rapid progress of labor. Spinal analgesia requires significantly lower drug doses to attain effective analgesia than does epidural analgesia; therefore, the risk for local anesthetic systemic toxicity is decreased. In addition, there is less systemic absorption of spinal anesthetic agents into the maternal circulation, so maternal and fetal plasma drug concentrations are lower with spinal than with epidural analgesia.

An additional advantage of spinal analgesia is that complete analgesia for early labor can be accomplished with the intrathecal injection of a lipid-soluble opioid without the addition of a local anesthetic. Thus, motor blockade is avoided and the risk for hypotension is lower.[28] This method is ideal for patients who wish to ambulate or for

those with preload-dependent cardiac conditions such as stenotic heart lesions. Finally, use of the CSE technique may lower the incidence of failure of epidural analgesia (e.g., a nonfunctioning epidural catheter).[29,30] The likelihood of an epidural catheter placed for labor analgesia failing to provide satisfactory anesthesia for a subsequent cesarean delivery was more than five times higher for catheters placed as part of an epidural technique than for catheters placed as part of a CSE technique.[31]

Cappiello et al.[32] have described a technique in which a dural puncture is made with a small-gauge spinal needle but no drug is injected into the subarachnoid space. After injection of epidural local anesthetic and opioid, blockade of sacral dermatomes occurred more frequently in parturients with a dural puncture than in those without, presumably because of enhanced anesthetic solution migration across the dural puncture site.

CSE analgesia has several possible undesirable side effects. Dural puncture is required to initiate CSE analgesia, although puncture with a small-gauge pencil-point needle does not appear to increase the risk for post–dural puncture headache.[27] A more serious concern, however, is that dural puncture during labor may be a risk factor for postpartum neuraxial infection, a rare but potentially life-threatening complication (see Chapter 32).

The incidence of pruritus is higher with intrathecal opioid administration than with epidural opioid administration.[27] Another potential drawback of CSE analgesia is that it is not clear for 1 to 2 hours after initiation of analgesia whether the epidural catheter is properly sited in the epidural space. Thus, CSE analgesia may not be the technique of choice if a functioning epidural catheter is critical to the safe care of the patient (e.g., a mother with an anticipated difficult airway or a worrisome fetal heart rate [FHR] tracing).

The most common CSE technique for labor analgesia is the needle-through-needle technique in a midlumbar interspinous space (see Chapter 12). Analgesia is maintained via the epidural catheter, as with traditional epidural analgesia.

Continuous Spinal Analgesia

Continuous spinal analgesia is used occasionally for labor analgesia but is not practical for most parturients. Because the available catheters require dural puncture with a large-gauge introducer needle, the technique is associated with an unacceptably high incidence of post–dural puncture headache. However, continuous spinal analgesia is a management option in patients with unintentional dural puncture. Continuous spinal analgesia can readily be converted to surgical anesthesia if necessary.

Caudal Analgesia

Continuous caudal epidural analgesia is used infrequently in modern obstetric anesthesia practice. It is technically more difficult to place a caudal catheter than a lumbar epidural catheter. Large volumes of anesthetic solution are required to extend neuroblockade to the low thoracic spinal segments, resulting in higher maternal plasma concentrations of drug. There is a risk for needle/catheter misplacement and direct injection into the fetus. However, this technique is useful for parturients in whom access to the lumbar spinal canal is not possible (e.g., because of a fused lumbar spine).

Single-Shot Techniques

In general, single-shot techniques (spinal, lumbar epidural, or caudal) are not useful for most laboring women because of their limited duration of action. These techniques may be indicated for parturients who require analgesia or anesthesia shortly before anticipated vaginal delivery or in settings in which continuous epidural analgesia is not possible.[33]

Informed Consent

Informed consent is an important aspect of preparation for neuraxial labor analgesia (see Chapters 12 and 33). The preanesthetic evaluation and informed consent process allow the physician to allay the patient's concerns and to demonstrate a commitment to her care. Most laboring women understand the need for informed consent and appreciate the opportunity to participate in decisions about their care.

Equipment and Monitors

Resuscitation equipment, drugs, and supplies must be immediately available for the management of serious complications of neuraxial analgesia (e.g., hypotension, total spinal anesthesia, systemic local anesthetic toxicity) (see Box 12-1).[16] Emergency airway equipment should be checked before the administration of neuraxial analgesia.

During the initiation of neuraxial analgesia, the parturient's oxygen saturation is measured continuously and the blood pressure is assessed every 2 to 3 minutes for 15 to 20 minutes after the neuraxial anesthetic administration, or until the mother is hemodynamically stable (see Chapter 12). The FHR should be monitored before and after the initiation of neuraxial analgesia; it may be difficult to monitor the FHR during the actual procedure.[16] During maintenance of neuraxial analgesia, maternal blood pressure is measured every 15 to 30 minutes, or more frequently if hypotension ensues. The sensory level of analgesia and the intensity of motor block (Box 23-3) are assessed after the administration of the test and therapeutic doses of local anesthetics. Subsequently, sensory level, motor block, and pain control are assessed at regular intervals.

BOX 23-3 Assessment of Motor Block

- Complete: patient unable to move feet or knees
- Almost complete: patient able to move feet only
- Partial: patient just able to move knees
- None: patient capable of full flexion of knees and feet

Adapted from Bromage PR. Epidural Analgesia. Philadelphia, WB Saunders, 1978:144.

Prior to the initiation of neuraxial analgesia, ultrasonographic imaging of the back may be helpful, especially in parturients whose landmarks are difficult to palpate.

Intravenous Hydration

Placement of an intravenous catheter (preferably 18-gauge or larger) and correction of hypovolemia with intravenous hydration are necessary before the initiation of neuraxial analgesia to mitigate hypotension that can result from sympathetic blockade. Data from small studies are conflicting as to whether a fluid bolus administered immediately before the initiation of analgesia decreases the risk for nonreassuring FHR patterns.[34-36] Most anesthesia providers administer approximately 500 mL of lactated Ringer's solution (without dextrose), although the ASA Task Force on Obstetric Anesthesia has stated that a fixed volume of intravenous fluid is not required before neuraxial analgesia is initiated.[16] Severe hypotension is less likely with the contemporary practice of administering a dilute solution of local anesthetic for epidural analgesia or an intrathecal opioid for spinal analgesia.

Studies of intravenous hydration and spinal anesthesia for cesarean delivery suggest that there is no advantage to administering the fluid before the initiation of anesthesia (preload) compared with administering the fluid at the time of initiation of anesthesia (co-load).[37] Rarely, hydration should be guided by serial assessment of intravascular fluid volume (e.g., central venous pressure, transthoracic echocardiography). Fluid administration should be judicious in parturients at risk for pulmonary edema (e.g., women with severe preeclampsia).

A balanced electrolyte solution (e.g., lactated Ringer's solution) without dextrose is the most commonly used intravenous fluid for bolus administration. Data are conflicting as to whether the maintenance intravenous infusion of dextrose-containing fluid during labor is associated with a lower incidence of umbilical cord blood acidemia.[38,39] One randomized controlled trial demonstrated shorter labor in women who received an intravenous solution of normal saline with dextrose compared with saline without dextrose.[40] However, anesthesia and obstetric providers should avoid the bolus administration of dextrose-containing solutions in laboring women.

Maternal Positioning

Either the lateral decubitus or the sitting position can be used during initiation of neuraxial analgesia (see Chapter 12). Factors to consider when positioning the parturient for the procedure include patient comfort, avoidance of aortocaval compression, ability to monitor the FHR, provider comfort and experience, and optimal positioning of the spine and palpation of landmarks. Patient position relative to the baricity of the anesthetic solution should be considered during initiation of spinal analgesia/anesthesia. There is little evidence that patient position influences the extent of neuroblockade during initiation of epidural analgesia/anesthesia. After completion of the procedure, parturients should be assisted to the lateral position for the first 15 to 30 minutes after the neuraxial injection to alleviate aortocaval compression.

BOX 23-4 Suggested Procedure for Initiation of Epidural Labor Analgesia

1. Complete preparation for neuraxial analgesia checklist (see Box 23-2).
2. Position patient with the help of an assistant (lateral decubitus or sitting).
3. Initiate maternal blood pressure and pulse oximetry monitoring and fetal heart rate monitoring.
4. Initiate an intravenous fluid bolus (500 mL of lactated Ringer's solution).
5. Site epidural catheter in epidural space using sterile technique.
6. Administer an epidural test dose (see Table 12-2).
7. If the test dose is negative, secure epidural catheter and position patient in the lateral position.
8. Administer 5 to 15 mL of epidural local anesthetic, in 5-mL increments (usually low concentration of local anesthetic combined with a lipid-soluble opioid [see Table 23-2]).
9. Monitor maternal blood pressure every 2 to 3 minutes for 15 to 20 minutes, or until parturient is hemodynamically stable.
10. Assess pain score and extent of sensory blockade (cephalad and caudad).
11. Initiate maintenance epidural analgesia (see Table 23-5).

INITIATION OF EPIDURAL ANALGESIA

A procedure for initiating epidural labor analgesia is outlined in Box 23-4. Commonly, after siting the epidural catheter in the epidural space, a test dose is administered to rule out intrathecal or intravascular placement of the epidural catheter. After a negative test, epidural analgesia is established with the incremental injection of a local anesthetic, usually in combination with a lipid-soluble opioid. Maternal vital signs are monitored and clinical analgesia is verified.

Epidural Test Dose

The purpose of the test dose is to help identify unintentional cannulation of a vein or the subarachnoid space. The test dose should contain a dose of local anesthetic and/or another marker sufficient to allow the recognition of intravenous or subarachnoid injection but not so large as to cause systemic toxicity or total spinal anesthesia. The most common *intravascular* test dose contains epinephrine (see Chapter 12).

The use of the epinephrine test dose in obstetrics is not without detractors. Some anesthesia providers fear that intravenous injection of epinephrine may decrease uteroplacental perfusion and precipitate fetal compromise. However, there has been no report of adverse neonatal outcome after intravenous injection of an epinephrine-containing test dose. Another argument against routine use of a test dose is that aspiration of multi-orifice catheters is 98% sensitive in identifying their intravascular location.[41] (The sensitivity of aspiration is significantly lower for single-orifice catheters.) The epidural test dose contributes to undesirable motor

blockade.[42,43] Finally, because modern epidural labor analgesia involves the infusion of a low concentration of local anesthetic solution, unintentional intravascular or intrathecal administration is not likely to result in cardiovascular collapse or total spinal anesthesia.

Others argue that the test dose still has a role in obstetric anesthesia practice.[44] Large volumes of a concentrated local anesthetic solution are still routinely administered for emergency cesarean delivery. Although not a safety issue, it is easier for the parturient and anesthesia provider to identify a misplaced catheter at the time of initial placement and to replace the catheter at that time rather than identify the misplaced catheter after the sterile field has been breached and the parturient repositioned.

The epinephrine test dose is less specific in laboring women because cyclic changes in maternal heart rate complicate interpretation of its effects.[45] For this reason, if used, the test dose should be given immediately after a uterine contraction so there is less confusion as to whether tachycardia is caused by pain or intravenous epinephrine. Other methods of detecting intravascular injection are discussed in Chapter 12.

No matter whether a formal test dose is used or not, it is imperative that the anesthesia provider take the time to look for evidence of unintentional intrathecal injection of local anesthetic. Finally, every anesthesia provider should remember that no single test dose regimen can exclude every case of unintentional intravenous or subarachnoid injection. Box 12-3 summarizes steps that may be taken to decrease the risk for unintentional intravenous or subarachnoid injection of local anesthetic.

Choice of Drugs

The ideal analgesic drug for labor would provide rapid onset of effective analgesia with minimal motor blockade, minimal risk for maternal toxicity, and negligible effect on uterine activity and uteroplacental perfusion. It would undergo limited transplacental transfer and thus have minimal direct effect on the fetus. Finally, this ideal agent would have a long duration of action. Although this perfect analgesic drug does not exist, the combination of a local anesthetic with an opioid allows us to approach this goal.

Traditionally, local anesthetics were administered to block both the visceral pain of labor (lower uterine segment distention and cervical dilation) and the somatic pain (descent of the fetus in the birth canal). Almost 40 years ago, investigators identified dense concentrations of opioid receptors in the dorsal horn of the spinal cord.[46] The application of small doses of an opioid to these receptor sites generates a specific and profound opioid response.[46] The introduction of neuraxial opioids to the armamentarium of the obstetric anesthesia provider moved us closer to the prediction made by Benjamin Rush in 1805: "A medicine would be discovered which should suspend sensibility altogether and leave irritability or powers of motion unimpaired."[47] Intrathecal opioids effectively relieve the visceral pain of the early first stage of labor, although they must be combined with a local anesthetic to effectively relieve the somatic pain of the late first stage and the second stage of labor. The combination of a local anesthetic with a lipid-soluble opioid allows for the use of lower doses of each agent, thus minimizing undesirable side effects. For example, when used alone without an opioid, the local anesthetic dose required for effective epidural analgesia is associated with an unacceptably high incidence of motor blockade. Similarly, used alone, high doses of epidural opioid are required for satisfactory analgesia during early labor, and such doses are associated with significant systemic absorption and systemic side effects. The addition of an opioid to the local anesthetic also shortens latency,[48] an important aspect of labor analgesia, especially with the use of long-acting (and therefore, long-latency) local anesthetics. Thus, contemporary epidural labor analgesia practice most often incorporates low doses of a long-acting local anesthetic combined with a lipid-soluble opioid.

Local Anesthetics

Bupivacaine. Traditionally, the amide local anesthetic bupivacaine has been the most commonly used agent for epidural labor analgesia. Bupivacaine is highly protein-bound, a feature that limits transplacental transfer. The umbilical vein–to–maternal vein concentration ratio is approximately 0.3.[49] After epidural administration of bupivacaine (without opioid) during labor, the patient first perceives pain relief within 8 to 10 minutes,[50] but approximately 20 minutes is required to achieve the peak effect. Duration of analgesia is approximately 90 minutes. Bupivacaine 6.25 to 12.5 mg (e.g., 10 to 20 mL of a 0.0625% solution, or 5 to 10 mL of a 0.125% solution) combined with fentanyl or sufentanil is adequate to initiate labor analgesia in most parturients (Table 23-2).

The potency of local anesthetics for neuraxial labor analgesia is often assessed by determining the median effective concentration of local anesthetic solution when administered as a 20-mL epidural bolus (this concentration is often referred to as the minimum local anesthetic concentration [MLAC]). It is lower for women in early labor than in late labor,[51] and it is also lower when the local anesthetic is combined with a lipid-soluble opioid.[52]

It is important to consider both the local anesthetic *dose* and *concentration* for initiation and maintenance of epidural analgesia. Christiaens et al.[53] randomly assigned parturients to receive epidural bupivacaine 20 mg diluted in 4 mL, 10 mL, or 20 mL (0.5%, 0.2%, and 0.1% solutions, respectively). Analgesia in the 10-mL and 20-mL groups was superior to that in the 4-mL group, and duration of analgesia was longest in the 20-mL group. Lyons et al.[54] compared the minimum local anesthetic volume (MLAV) and minimum local anesthetic dose (MLAD) for 0.125% and 0.25% bupivacaine for epidural labor analgesia. Bupivacaine 0.125% produced analgesia equivalent to that provided by bupivacaine 0.25%, with a 50% increase in required volume and a 25% reduction in dose (Table 23-3). Stated differently, a dose-sparing effect is achieved by administering a 0.125% solution of bupivacaine rather than a 0.25% solution. Ginosar et al.[55] randomized parturients to receive maintenance of analgesia with an epidural infusion of either bupivacaine 0.25% at 5 mL/h or bupivacaine 0.0625% at 20 mL/h (10 mg/h in both groups). The median bupivacaine dose was lower and patient

TABLE 23-2 Drugs Used for Initiation of Epidural and Spinal Labor Analgesia

Drug	Epidural Analgesia*	Spinal Analgesia
Local Anesthetics†		
Bupivacaine	0.0625%-0.125%	1.25-2.5 mg
Ropivacaine	0.08%-0.2%	2.0-3.5 mg
Levobupivacaine	0.0625%-0.125%	2.0-3.5 mg
Lidocaine‡	0.75%-1.0%	NA
Opioids†		
Fentanyl	50-100 μg	15-25 μg§
Sufentanil	5-10 μg	1.5-5 μg§
Morphine‡	NA	125-250 μg§
Meperidine‡	NA	10-20 mg

Note: The suggested doses are based on clinical studies, potency ratios, and clinical experience.
NA, not applicable.
*The volume required to initiate epidural labor analgesia is 10 to 15 mL of local anesthetic solution.
†The local anesthetic dose/concentration and the fentanyl or sufentanil dose are reduced if the drugs are combined or if a local anesthetic-containing epidural test dose is administered before the initial therapeutic dose. The dose of opioid should be reduced or the opioid omitted if the parturient has recently received systemic opioid analgesia.
‡Lidocaine, morphine, and meperidine are not commonly used for labor analgesia because of their short duration of action (lidocaine), long latency (morphine), and high incidence of nausea and vomiting (morphine and meperidine).
§Opioids may be administered without local anesthetics when spinal analgesia is induced in early labor. Women in active labor require a higher dose than women in latent labor.

TABLE 23-3 Comparison of Epidural Bupivacaine 0.25% and 0.125%: Median Effective Volume and Dose

	Bupivacaine 0.125%‡	Bupivacaine 0.25%‡
Median Effective Volume*		
Up-down analysis (mL)	13.6 (12.4-14.8)	9.2 (6.9-11.5)
Probit analysis (mL)	13.5 (11.4-15.9)	8.6 (7.2-10.3)
Median Effective Dose†		
Up-down analysis (mg)	17.0 (15.5-18.5)	23.1 (17.2-28.9)
Probit analysis (mg)	16.8 (14.2-19.9)	21.5 (17.9-25.7)

*Median effective volume at a fixed local anesthetic concentration.
†Median effective dose at a fixed local anesthetic concentration.
‡95% confidence intervals shown in parentheses, which were calculated using up-down sequential and probit analysis.
Modified from Lyons GR, Kocarev MG, Wilson RC, Columb MO. A comparison of minimum local anesthetic volumes and doses of epidural bupivacaine (0.125% w/v and 0.25% w/v) for analgesia in labor. Anesth Analg 2007; 104:412-5.)

satisfaction was greater with bupivacaine 0.0625% than with bupivacaine 0.25%. Together, these data suggest that epidural analgesia and safety are improved with the use of low concentration–high volume local anesthetic solutions.

Ropivacaine. Ropivacaine, a relatively newer amide local anesthetic, is similar to bupivacaine in structure and pharmacodynamics.[56] It is a homologue of bupivacaine and mepivacaine, but unlike these other local anesthetics it is formulated as a single-levorotary enantiomer rather than a racemic mixture (see Chapter 13). Studies of pregnant sheep have demonstrated that clinically relevant plasma concentrations of ropivacaine do not adversely affect uterine blood flow.[57]

Studies *in vitro* and *in vivo* have shown that ropivacaine is less cardiodepressant and arrhythmogenic than bupivacaine when doses of equal *mass* are compared.[58,59] Ropivacaine is cleared more rapidly than bupivacaine after intravenous administration in both pregnant and nonpregnant sheep. Consequently, a larger dose of drug—but not a higher plasma concentration—is required to produce systemic toxicity.[60] These findings suggest that ropivacaine may have a greater margin of safety than bupivacaine if unintentional intravenous injection occurs in pregnant women. However, many early investigations assumed that ropivacaine and bupivacaine are equipotent; subsequent studies have demonstrated that ropivacaine is 25% to 40% less potent than bupivacaine.[61-63] In one study that characterized the full dose-response curves, the slope of the bupivacaine and ropivacaine curves were similar, suggesting that the nature of the drug-receptor interaction is not different between the two drugs.[63] When ropivacaine concentrations are adjusted for this difference in potency, there is a less clear advantage for ropivacaine in terms of the risk for systemic toxicity.[61] In reality, systemic toxicity is not a major concern with the contemporary administration of a dilute solution of local anesthetic for epidural labor analgesia.

Several studies that compared equal concentrations of ropivacaine and bupivacaine given by patient-controlled epidural analgesia (PCEA) have not found any significant difference in clinical efficacy between the two local anesthetics.[64-68] Other studies that adjusted for the potency difference and compared equipotent concentrations (e.g., 0.0625% bupivacaine versus 0.1% ropivacaine) also found no difference in clinical efficacy.[69,70] It is important to recognize that potency is an unchanging property of a drug, whereas clinical efficacy is influenced by multiple variables. For example, ropivacaine has a longer duration of analgesia than bupivacaine,[61] which may offset its lesser potency when it is administered by continuous epidural infusion.

Early clinical studies suggested that ropivacaine is associated with less motor block than bupivacaine[71,72]; avoidance of motor blockade is a desirable characteristic of a local anesthetic used for epidural analgesia during labor. However, these studies also compared equal concentrations of ropivacaine and bupivacaine, and the observed lower degree of motor blockade may reflect the lesser potency of ropivacaine. A study of the relative motor-blocking potencies of epidural ropivacaine and bupivacaine showed that ropivacaine was less potent than bupivacaine in terms of motor blockade,[73] a finding that corresponded to the relative analgesic potencies of the two drugs.[61,62] The differences in potency of motor blockade may not be relevant with the use of low concentrations of local anesthetic. Several clinical studies[64,66,74] and a well-conducted meta-analysis of studies that compared epidural ropivacaine and bupivacaine[75] did not demonstrate an

advantage for ropivacaine in terms of outcome of labor (see later discussion), although the incidence of motor blockade was less in the ropivacaine groups.[66,74,75]

There is no clear evidence of greater patient safety, lower risk for instrumental vaginal delivery, or other improved outcomes when ropivacaine is used to provide epidural labor analgesia.[74,76] A 2010 review concluded that there is no advantage to the routine use of ropivacaine compared with bupivacaine for labor analgesia.[76] In contrast, ropivacaine offers greater patient safety in settings in which high concentrations and greater volumes of drugs are administered (e.g., brachial plexus blockade or epidural anesthesia for cesarean delivery).[77]

Like bupivacaine, ropivacaine is often combined with fentanyl or sufentanil for labor analgesia. Ropivacaine concentrations used to initiate epidural analgesia range from 0.08% to 0.2% (see Table 23-2). Higher concentrations are used if the drug is administered without an opioid.

Levobupivacaine. Levobupivacaine is the levorotary enantiomer of bupivacaine (which is a racemic mixture). It is not available in the United States. Both preclinical and clinical studies have suggested that, like ropivacaine, levobupivacaine has less potential for cardiotoxicity than bupivacaine when equal doses of the two drugs are compared.[78,79] One study found that levobupivacaine was essentially equipotent to bupivacaine with a potency ratio of 0.98; however, the 95% CI was wide (0.67 to 1.41).[80] Other studies have suggested that levobupivacaine and ropivacaine have similar potency.[81,82] In an MLAC study that compared the motor blocking potency of bupivacaine and levobupivacaine,[83] levobupivacaine was less potent than bupivacaine (potency ratio, 0.87; 95% CI, 0.77 to 0.98).[83] Beilin et al.[66] compared epidural bupivacaine, ropivacaine, and levobupivacaine (0.0625% with fentanyl 2 μg/mL) for labor analgesia. There were no differences among groups in obstetric outcomes, although the incidence of motor blockade was lower in the ropivacaine and levobupivacaine groups. Therefore, although epidural bupivacaine is more potent than ropivacaine for both sensory and motor blockade during labor, and may be more potent than levobupivacaine, there do not appear to be any clinical advantages of one drug over the other two drugs for epidural labor analgesia.

Lidocaine. Lidocaine is an amide local anesthetic with a duration of action intermediate between those of bupivacaine and 2-chloroprocaine. During labor, the administration of a 0.75% to 1.0% solution of lidocaine typically provides satisfactory analgesia. Lidocaine is not commonly used for initiation or maintenance of epidural labor analgesia, in part because of its shorter duration of action in comparison with bupivacaine, ropivacaine, and levobupivacaine. Lidocaine is less protein-bound than these other amide local anesthetics, and at delivery, the umbilical vein–to–maternal vein lidocaine concentration ratio is approximately twice that of bupivacaine.[84] Early studies discouraged the epidural administration of lidocaine in pregnant women because epidural lidocaine was associated with abnormal neonatal neurobehavioral findings.[85] Subsequently, larger, more carefully controlled studies have demonstrated that the epidural administration of lidocaine, bupivacaine, and 2-chloroprocaine have similar neonatal outcomes.[86,87] Although some investigators have observed subtle differences in neurobehavior between infants exposed to lidocaine and those exposed to other local anesthetics, these differences are within the inherent variability of the examinations and are not clinically significant. Other factors (e.g., mode of delivery) appear to be much more important determinants of neonatal condition.

2-Chloroprocaine. An ester local anesthetic, 2-chloroprocaine has a rapid onset of action. Epidural administration of 10 mL of 2% 2-chloroprocaine provides effective analgesia for approximately 40 minutes. The short duration of action limits its usefulness during labor. In addition, the epidural administration of 2-chloroprocaine may adversely affect the efficacy of subsequently administered epidural bupivacaine and opioids,[88,89] although it is unclear whether the mechanism is related to pharmacokinetic or pharmacodynamic properties of the drug.[90,91] In obstetric practice, 2-chloroprocaine is most commonly used for extension of epidural labor analgesia for instrumental vaginal delivery (see later discussion) or emergency cesarean delivery (see Chapter 26).

Opioids

Lipid-Soluble Opioids: Fentanyl and Sufentanil. Morphine was one of the first opioids to be studied for labor analgesia. However, because of its long latency, side effects, and inconsistent analgesia, morphine has largely been replaced by the lipid-soluble opioids fentanyl and sufentanil (see Chapter 13). The lipid-soluble agents have a rapid onset of action. Permeability (of the dura-arachnoid) is not a rate-limiting factor, and increasing the concentration gradient (by administration of a larger dose) facilitates faster entry into the spinal cord. The high lipid solubility of these agents also results in a shorter duration of action and greater systemic absorption than occurs with water-soluble drugs.

Some investigators have suggested that the improved analgesia results from a supraspinal action rather than a primary spinal action. However, several studies have refuted this theory, including studies of epidural opioid administration by bolus[92] and continuous infusion.[93] Vella et al.[92] observed that the initiation of epidural analgesia with 0.25% bupivacaine with *epidural* fentanyl 80 μg*

*The Institute of Safe Medicine Practices (ISMP) has recommended that health care providers never use μg as an abbreviation for micrograms, but rather they should use mcg (http://www.ismp.org/tools/errorproneabbreviations.pdf, accessed February 2013). The use of the symbol μg is frequently misinterpreted and involved in harmful medication errors. The abbreviation may be mistaken for mg (milligrams), which would result in a 1000-fold overdose. The symbol μg should never be used when communicating medical information, including pharmacy and prescriber computer order entry screens, computer-generated labels, labels for drug storage bins, and medication administration records. However, most scholarly publications have continued to use the abbreviation μg. The editors have chosen to retain the use of the abbreviation μg throughout this text. However, the editors recommend the use of the abbreviation mcg in clinical practice.

resulted in more rapid, complete, and prolonged analgesia than *intravenous* fentanyl 80 µg, even though plasma fentanyl concentrations were higher in the intravenous group. Similarly, D'Angelo et al.[93] demonstrated that a continuous epidural infusion but not an intravenous infusion of fentanyl reduced epidural bupivacaine requirements in laboring women. Polley et al.[94] determined that the MLAC of epidural bupivacaine administered as a 20-mL bolus in laboring women was reduced from 0.064% to 0.034% when epidural rather than intravenous fentanyl was co-administered with bupivacaine. Ginosar et al.[95] determined that the MLAC of bupivacaine administered by *continuous epidural infusion* during labor was lower by a factor of three when it was co-administered with an epidural (rather than intravenous) fentanyl infusion. Finally, in a volunteer study,[96] lumbar epidural administration of fentanyl resulted in tolerance to experimental pain at a lumbar but not a cranial dermatome, whereas intravenous fentanyl administration resulted in pain tolerance at both dermatomes. These studies strongly suggest that during labor, epidural fentanyl provides analgesia primarily through a spinal site of action.

Epidural fentanyl alone provides *moderate* analgesia in early labor,[48] but the dose needed to provide complete analgesia is accompanied by significant side effects (e.g., pruritus, nausea, maternal sedation, perhaps neonatal depression). In addition, epidural administration of an opioid alone provides inadequate analgesia during the late first stage as well as the second stage of labor. In a study comparing sufentanil alone, sufentanil with bupivacaine, and bupivacaine alone,[97] women randomly assigned to the sufentanil-alone (30 µg) group experienced satisfactory analgesia after the initial dose but not after subsequent doses. However, the initial dose was administered after an epidural test dose that contained lidocaine 60 mg. In clinical practice, epidural fentanyl and sufentanil are usually administered with a local anesthetic for the initiation of analgesia (at a minimum, with a local anesthetic–containing epidural test dose).

In clinical practice, either fentanyl or sufentanil is frequently combined with a low-concentration, long-acting amide local anesthetic to initiate epidural labor analgesia. Epidural opioid administration allows the anesthesia provider to use a more dilute solution of local anesthetic to provide epidural labor analgesia.[98] Epidural fentanyl and sufentanil decrease epidural bupivacaine requirements during labor in a dose-dependent fashion (Figure 23-2).[52,99] The reduction in MLAC by the addition of fentanyl or sufentanil is observed with levobupivacaine,[100,101] ropivacaine,[101,102] and 2-chloroprocaine[103] as well as bupivacaine.

The addition of a lipid-soluble opioid to a local anesthetic for neuraxial labor analgesia decreases latency, prolongs the duration of analgesia, and improves the quality of analgesia. For example, Reynolds and O'Sullivan[104] showed that epidural bupivacaine 10 mg combined with fentanyl 100 µg was more effective for the treatment of breakthrough pain and had a faster onset and longer duration of action than either bupivacaine 25 mg or fentanyl 100 µg administered alone. Van Steenberge et al.[105] observed that the mean (± SD) onset of analgesia was 10.3 ± 3.8 minutes in women randomly assigned to receive bupivacaine 12.5 mg without sufentanil, whereas it was 8.7 ± 2.6 minutes in women who received bupivacaine combined with sufentanil 7.5 µg. Duration of analgesia was longer in the sufentanil group (131 minutes versus 86 minutes without sufentanil).[105] In another study,[106] the addition of fentanyl 100 µg to 0.125% bupivacaine prolonged the mean duration of analgesia from 55 minutes to 106 minutes.

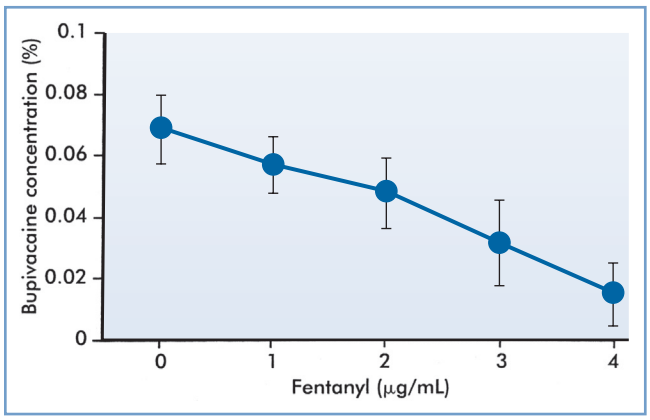


FIGURE 23-2 ■ The effect of epidural fentanyl on the minimum local anesthetic concentration (defined as the effective concentration in 50% of subjects [EC_{50}]) for epidural bupivacaine analgesia during labor. Data are expressed as median concentrations with 95% confidence intervals. (Data from Lyons G, Columb M, Hawthorne L, Dresner M. Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. Br J Anaesth 1997; 78:493-6.)

The quality of analgesia is also better with the addition of an opioid to the local anesthetic. For example, 86% of women rated their analgesia as excellent after epidural analgesia was initiated with bupivacaine combined with sufentanil, compared with 50% of those who received bupivacaine without sufentanil.[105] The percentage of women who experienced no or short periods of pain during the first stage of labor was 94% in women who received sufentanil and 76% in women who did not.[107] After initiation of analgesia with 0.125% bupivacaine with epinephrine 1.25 µg/mL, 43% of women randomly assigned to receive epidural fentanyl 100 µg rated their analgesia as excellent, compared with 6% in a control group that did not receive fentanyl.[106]

The dose-sparing effects of fentanyl and sufentanil are also evident when the drugs are combined with a low-concentration solution of bupivacaine used for the maintenance of analgesia throughout labor. For example, the total bupivacaine dose (mean ± SD) was 34 ± 17 mg in laboring women who received 0.125% bupivacaine/epinephrine 1.25 µg/mL with sufentanil, compared with 42 ± 19 mg in those who received bupivacaine/epinephrine without sufentanil.[107] Similarly, in women randomly assigned to receive bupivacaine/epinephrine with or without fentanyl 100 µg, the total bupivacaine dose was 55 mg or 110 mg, respectively.[106] Advantages of a lower total dose of local anesthetic include (1) decreased risk for local anesthetic systemic toxicity, (2) decreased risk for high or total spinal anesthesia, (3) decreased plasma concentrations of local anesthetic

in the fetus and neonate, and (4) decreased intensity of motor blockade.

Several studies have directly compared the administration of epidural fentanyl or sufentanil combined with a local anesthetic for the initiation of labor analgesia. There were no differences in analgesia in women in early labor randomly assigned to receive either fentanyl 100 μg or sufentanil 20 μg immediately after a lidocaine 45-mg/epinephrine 15-μg test dose.[108] In contrast, a second study demonstrated slightly better analgesia 20 minutes after injection of 0.125% bupivacaine (15 mg) with sufentanil 15 μg than after the same dose of bupivacaine with fentanyl 75 μg.[109]

In the United States, fentanyl is more commonly used because historically it has had a lower acquisition cost than sufentanil. Additionally, the concentration of the commercially available sufentanil preparation (50 μg/mL) may make drug errors more likely with sufentanil than with fentanyl because sufentanil doses significantly lower than 50 μg are used for initiation of epidural analgesia.

There are few rigorous *dose-response* studies of epidural fentanyl or sufentanil combined with bupivacaine for initiation of epidural labor analgesia. Herman et al.[110] randomly assigned 100 laboring women with a cervical dilation of 5 cm or less to receive 0.125% bupivacaine 10 mL, combined with fentanyl 0 to 100 μg (in 25-μg increments) or sufentanil 0 to 25 μg (in 5-μg increments), injected after a negative epidural test dose (bupivacaine 7.5 mg with epinephrine 15 μg). Using a probit dose-response analysis, these researchers calculated the effective dose in 95% of subjects (ED_{95}) to be 50 μg for fentanyl and 8 μg for sufentanil; these figures equate to a sufentanil-to-fentanyl potency ratio of 6.3 : 1. Capogna et al.[111] sought to determine the median effective analgesic dose (ED_{50}) of epidural fentanyl and sufentanil alone (no local anesthetic) for the initiation of epidural analgesia in nulliparous women with a cervical dilation between 2 and 4 cm. The ED_{50} of fentanyl was 124 μg (95% CI, 118 to 131) and the ED_{50} of sufentanil was 21 μg (95% CI, 20 to 22), with a potency ratio of 5.9 : 1. The potency ratio in volunteers subjected to an electrical stimulus was approximately 5 : 1.[112] Taken together, these data suggest that the potency ratio of sufentanil to fentanyl administered into the epidural space is approximately 6 : 1.

Several studies have compared bupivacaine combined with fentanyl 50 μg and 100 μg. No differences in the onset, duration, and quality of analgesia were noted in Asian women randomly assigned to receive 0.125% bupivacaine (10 mg) combined with either 50 or 100 μg of fentanyl.[113] In contrast, when 0.125% bupivacaine (15 mg) with epinephrine 15 μg was administered to laboring Italian women with either 50 or 100 μg of fentanyl, there was no difference in the onset or duration of analgesia, but more women in the 100-μg group had excellent analgesia.[106]

There were no differences in latency, duration of analgesia, and quality of analgesia when analgesia was induced with 0.125% bupivacaine (12.5 mg)/epinephrine 12.5 μg and either 7.5 or 15 μg of sufentanil.[105] Similarly, after injection of a lidocaine 60-mg/epinephrine 15-μg test dose, another study found no differences in latency and quality of analgesia among epidural sufentanil doses of 5, 10, 20, 30, 40, and 50 μg.[114] However, the duration of analgesia was longer after the higher doses of sufentanil.

The range of fentanyl and sufentanil doses used for the initiation of epidural labor analgesia is shown in Table 23-2. Pain and analgesic requirements vary depending on several factors, including parity, stage of labor, presence of ruptured membranes, oxytocin augmentation, and whether the opioid is administered in combination with a local anesthetic. One study reported that the ED_{50} of epidural sufentanil was higher in women undergoing prostaglandin induction of labor than in women with spontaneous labor.[115] Conell-Price et al.[116] developed a model of labor pain in nulliparous women and found that the use of oxytocin was associated with 48% more pain at the start of labor. Preliminary evidence suggests that pharmacogenetics may also play a role in dose requirements. Camorcia et al.[117] reported that nulliparous women who were heterozygous or homozygous for the single nucleotide polymorphism (SNP) A118G (substitution of adenine for guanine at position 118) of the gene encoding the μ-opioid receptor (*OPRM1*) had a lower ED_{50} for epidural sufentanil administered for labor analgesia.

Several early studies suggested that the duration of epidural and spinal analgesia may exhibit circadian rhythm (chronobiology), possibly secondary to human biologic rhythms.[118] More recently, however, in a secondary analysis of data from a large study, Scavone et al.[119] found no evidence of a circadian response to intrathecal fentanyl or intravenous opioid labor analgesia. In a detailed analysis of data from a study designed to test whether parturient response to intrathecal bupivacaine exhibited a circadian rhythm, Shafer et al.[120] demonstrated that external daily rhythms, such as nursing shifts, may contribute to the appearance of biologic rhythm. Thus, whether a circadian response to neuraxial local anesthetic or opioid exists, or is clinically significant, requires further study.

Current evidence supports the administration of epidural opioid doses at the lower end of the dose range for nulliparous women, for women in early labor, or when the opioid is co-administered with a local anesthetic. Higher doses are associated with a higher incidence of maternal side effects and the potential for neonatal depression (see later discussion). The major maternal side effect of epidural fentanyl and sufentanil for labor analgesia is pruritus. Neonatal outcomes do not appear to be adversely affected by the addition of fentanyl or sufentanil to a local anesthetic for epidural analgesia (see later discussion). In fact, the combination of drugs allows lower doses of both drugs to be administered, resulting in lower concentrations of both drugs in the neonate.

Two studies found that the diluent volume (2 to 20 mL) did not affect the onset and duration of epidural labor analgesia when fentanyl was injected into the epidural space after the injection of a local anesthetic solution.[121,122]

Other Opioids. Morphine was one of the first opioids used for labor analgesia. Hughes et al.[123] compared

analgesia using epidural administration of morphine (2.0, 5.0, and 7.5 mg) with that using epidural bupivacaine 0.5%. Morphine was effective in 7 of 11 parturients until the end of the first stage of labor, but all parturients required bupivacaine for adequate analgesia during the second stage of labor. Subsequently, investigators combined morphine with bupivacaine and observed a longer duration of analgesia compared with that for bupivacaine alone.[124] However, the inconsistent analgesia, long latency (30 to 60 minutes), and high incidence of side effects of morphine (which continued after delivery), along with the introduction of lipid-soluble opioids and epidural infusion pumps into clinical practice, have made the use of epidural morphine for labor analgesia largely obsolete.

Several studies described the use of **alfentanil** with bupivacaine for labor analgesia.[125,126] Alfentanil has lower lipid solubility than both fentanyl and sufentanil. Only a few small studies have compared alfentanil with other opioids for labor analgesia.

Several groups of investigators have reported the use of epidural **hydromorphone** for labor analgesia.[127-129] The lipid solubility of hydromorphone lies between those of morphine and fentanyl, but is closer to that of morphine.[130] In a large prospective observational study, effective labor analgesia was obtained by initiating analgesia with 0.25% bupivacaine (20 to 25 mg) with epinephrine (40 to 50 μg), followed by hydromorphone 100 μg.[127] However, Mhyre[129] observed that effective labor analgesia could not be provided by 0.035% bupivacaine (7 mg) with hydromorphone 100 to 110 μg. In another trial, parturients were randomly assigned to receive either epidural hydromorphone 300 μg or saline-control immediately after the initiation of analgesia with lidocaine 45 mg, epinephrine 15 μg, and fentanyl 100 μg.[128] Duration of analgesia and side effects were similar in the two groups. At the current time, further investigation is required before hydromorphone can be recommended for epidural labor analgesia.

Meperidine may be used effectively alone (without a local anesthetic), in part because it possesses local anesthetic properties.[131] When given during labor, epidural meperidine 100 mg provides analgesia similar to that provided by 0.25% bupivacaine, with less motor blockade. However, this dose of epidural meperidine produces more sedation, nausea, and pruritus than epidural bupivacaine. Handley and Perkins[132] observed that the addition of meperidine 25 mg to 0.125%, 0.187%, or 0.25% bupivacaine (10 mL) provided adequate analgesia for the first stage of labor. The use of the more concentrated solutions (i.e., 0.187% and 0.25% bupivacaine) did not enhance the quality or duration of analgesia but did shorten latency (10 to 20 minutes versus 20 to 30 minutes for the less concentrated solution). Epidural administration of meperidine effectively prevents or treats the shivering that often occurs during labor.[133] Investigators from Saudi Arabia randomly allocated women to receive 0.1% bupivacaine with either meperidine 1 mg/mL or fentanyl 2 μg/mL.[134] No differences were noted between groups in analgesic characteristics, except that women in the meperidine group had a higher incidence of nausea and vomiting. Currently there is no evidence that meperidine alone or in combination with bupivacaine has any advantages over a combination of a long-acting amide local anesthetic and a lipid-soluble opioid.

Butorphanol is a lipid-soluble opioid agonist-antagonist, with weak μ-receptor and strong κ-receptor activity. Because κ-opioid receptors appear to be involved in the modulation of visceral pain, κ-receptor agonists should be useful agents for the relief of labor pain, which has a significant visceral component (see Chapter 20).[124,135,136] Somnolence is the most prominent side effect of epidural butorphanol. The addition of butorphanol 1, 2, or 3 mg to 0.25% bupivacaine (25 mg) shortened latency and prolonged the duration of analgesia in comparison with epidural bupivacaine alone in one study.[135] The investigators concluded that the optimal dose of butorphanol was 2 mg. Of concern was the observation of a transient sinusoidal FHR pattern in the 3-mg group that was not unlike that seen after the intravenous administration of butorphanol.[136] However, there was no difference among groups in Apgar scores, umbilical cord blood gas and pH measurements, or neurobehavioral scores. Similarly, Abboud et al.[124] observed that the addition of butorphanol 1 or 2 mg to 0.25% bupivacaine resulted in better quality and longer duration of analgesia than the epidural administration of bupivacaine alone, without maternal or neonatal side effects. However, some anesthesia providers have noted that the epidural administration of butorphanol results in somnolence and occasional dysphoria, which are side effects of κ-receptor stimulation.

Diamorphine (heroin) is available for epidural analgesia in the United Kingdom. Using isobolographic analysis, McLeod et al.[137] concluded that the combination of diamorphine and levobupivacaine is additive when used for first-stage labor analgesia. Several studies from the United Kingdom have reported diamorphine doses between 250 and 500 μg/h (i.e., diamorphine 25 to 50 μg/mL combined with a low concentration of bupivacaine).[125,138] Whether diamorphine offers any advantages over fentanyl or sufentanil has not been studied. It is not available for clinical administration in the United States.

Adjuvants

Although the contemporary mainstay of epidural labor analgesia includes administration of a long-acting amide local anesthetic combined with a lipid-soluble opioid, other drugs may be added as adjuvants. Adjuvants may prolong the duration of analgesia or decrease the required anesthetic dose, thus reducing the risk for specific side effects.

Epinephrine. Some anesthesia providers add a low dose of epinephrine (1.25 to 5 μg/mL [1:800,000 to 1:200,000]) to the local anesthetic solution (Table 23-4). The addition of epinephrine shortens the latency and prolongs the duration of epidural bupivacaine analgesia.[50,139] The MLAC of bupivacaine with epinephrine (66 μg) is 29% lower than that of bupivacaine without epinephrine,[140] perhaps as a result of the stimulation of alpha-adrenergic receptors in the spinal cord.

TABLE 23-4 Adjuncts to Neuraxial Labor Analgesia

Adjunct Drug	*Epidural Analgesia*		*Spinal Analgesia*
	INITIATION BOLUS DOSE*	MAINTENANCE INFUSION DOSE*	INITIATION BOLUS DOSE
Epinephrine	25-75 μg†	25-50 μg/h†	2.25-200 μg
Clonidine	75-100 μg	10-30 μg/h‡	15-30 μg
Neostigmine	500-750 μg	25-75 μg/h§	NR
Morphine	NA	NA	100-250 μg (0.1-0.25 mg)

NA, not applicable; *NR,* not recommended.
*Adjuncts are usually co-administered with a low-concentration local anesthetic solution (e.g., bupivacaine < 0.08%), often with a lipid-soluble opioid. There is extensive experience with epidural clonidine for labor analgesia in some European countries but less overall experience with epidural neostigmine.
†Usually administered in a 1:800,000 to 1:200,000 solution (1.25-5 μg/mL).
‡Administered in a concentration of 0.75-1.5 μg/mL.
§Administered in a concentration of 4 μg/mL.

The addition of epinephrine to the local anesthetic has a variable effect on the systemic uptake of the local anesthetic in obstetric patients.[141-143] The systemic absorption of epinephrine may increase maternal heart rate and transiently decrease uterine activity as a result of beta-adrenergic receptor stimulation.[50,144,145] However, some studies have shown that the addition of epinephrine to bupivacaine, lidocaine, or levobupivacaine does not result in longer labor than the epidural administration of bupivacaine or lidocaine without epinephrine[144,146] or levobupivacaine-sufentanil without epinephrine.[147] Epidural administration of an epinephrine-containing local anesthetic solution does not adversely affect intervillous blood flow[148] or neonatal outcome.[139,141,147] One disadvantage of the use of epinephrine is that it increases the intensity of motor blockade.[146,147] The addition of epinephrine may improve the efficacy of epidural opioids,[149] but the enhanced effect is insufficient to make use of epidural opioids (without local anesthetic) an attractive regimen for the duration of labor. Finally, the addition of a third drug to the local anesthetic/opioid solution may increase the risk for drug error and contamination. For these reasons, at our institution my colleagues and I do not routinely administer epinephrine-containing local anesthetic solutions during labor. However, other anesthesia providers have a different view, and some consider epinephrine a useful adjuvant, especially when added to a very dilute solution of local anesthetic with an opioid.

Clonidine. Analgesia is enhanced by the direct stimulation of α_2-adrenergic receptors and the inhibition of neurotransmitter release in the dorsal horn of the spinal cord (see Chapter 20). Epidural administration of clonidine alone provides modest analgesia. Studies have evaluated the epidural administration of clonidine as an adjuvant to a local anesthetic alone,[150-153] to local anesthetic and opioid combinations,[154-158] to fentanyl,[159] and to neostigmine (see later discussion).[160,161] In an MLAC study,[162] clonidine 60 μg, but not 30 μg, decreased the MLAC of ropivacaine by approximately two thirds. In another study,[152] clonidine 75 μg and sufentanil 5 μg both reduced the MLAC of ropivacaine by about two thirds.[152] Unlike epinephrine, clonidine does not increase the motor blockade that results from the epidural administration of a local anesthetic, but it does potentiate both the quality and duration of analgesia.[150,151,154-158] However, in a "black box" warning on the package insert, the manufacturer of Duraclon (the epidural clonidine formulation approved by the U.S. Food and Drug Administration) recommends against its use in obstetric patients because of the risk for hypotension[153-155,158,162] and bradycardia. Most studies, however, have found that the hypotension is readily amenable to treatment. An additional side effect is maternal sedation.[155,156,162] High doses (> 150 μg) may be associated with FHR changes,[154] although no adverse fetal affects have been observed with lower doses.

Clonidine is rarely used for labor analgesia in North America, but it is more widely used in some European countries. It may be particularly useful in women in whom other epidural analgesics are contraindicated or in those who have breakthrough pain with standard local anesthetic/opioid solutions, despite a functioning epidural catheter. In this circumstance, additional local anesthetic will result in motor block but clonidine will not.

Neostigmine. Neostigmine prevents the breakdown of acetylcholine within the spinal cord. Acetylcholine binds to muscarinic receptors, leading to a reduction in neurotransmitter release and subsequent analgesia. Roelants et al.[163] randomly assigned parturients to receive either epidural ropivacaine (20 mg) alone or epidural neostigmine (4 μg/kg) combined with ropivacaine 10 mg, with or without sufentanil 10 μg. The magnitude and duration of analgesia in the ropivacaine/neostigmine group was similar to that of the plain ropivacaine group but less than in the ropivacaine/sufentanil group. Neostigmine is hydrophilic, and the researchers hypothesized that only a small portion of the epidural dose penetrates the spinal cord.[163] In a subsequent study, the same researchers compared epidural sufentanil 20 μg with sufentanil 10 μg combined with neostigmine 250, 500, or 750 μg.[164] Neostigmine 250 μg with sufentanil was ineffective, but both 500 and 750 μg of neostigmine produced effective analgesia similar in duration to that obtained with sufentanil alone.

Because a synergistic antinociceptive effect of spinal α_2-adrenergic agonists and cholinesterase inhibitors is suggested by animal studies,[165] researchers have also investigated epidural neostigmine combined with clonidine.[160] The combination of clonidine 75 μg with neostigmine 500 or 750 μg provided acceptable analgesia (visual analog scale pain score < 30/100 mm in 30 minutes) in approximately 80% of parturients. Epidural neostigmine 500 μg combined with clonidine 75 μg prolonged labor analgesia initiated with spinal ropivacaine and sufentanil.[161]

In another study, maintenance of epidural analgesia with a solution of neostigmine 4 μg/mL combined with bupivacaine 0.125% resulted in a 19% reduction in bupivacaine consumption compared with administration of bupivacaine alone.[166] However, maternal sedation was

noted in the neostigmine group in the first 5 to 20 minutes after initiation of epidural analgesia with bupivacaine and neostigmine 60 μg. Although no significant adverse maternal or neonatal effects were observed in any of the studies, further studies are required to determine the role of epidural neostigmine for routine labor analgesia.[167] Neostigmine is not approved for neuraxial injection in the United States.

Summary

Epidural labor analgesia is usually initiated with the bolus injection of a local anesthetic combined with a lipid-soluble opioid. The advantages of the addition of an opioid to an epidural solution of local anesthetic include (1) lower total dose of anesthetic, (2) decreased motor blockade, (3) reduced shivering, and (4) greater patient satisfaction. Some anesthesia providers contend that local anesthetic–opioid techniques result in a lower risk for hypotension, but this belief is unproven. There are no clinically significant differences among the three commonly used, long-acting amide local anesthetics (bupivacaine, ropivacaine, levobupivacaine), nor between fentanyl and sufentanil. Other adjuvants (e.g., epinephrine, clonidine) may prove useful in selected patients, but they currently do not offer any significant advantages to low-dose local anesthetic/lipid-soluble opioid combinations. High-volume/low-concentration local anesthetic solutions compared with low-volume/high-concentration solutions are associated with lower dose requirements and better analgesia.

INITIATION OF SPINAL ANALGESIA

Initiation of neuraxial analgesia with the intrathecal injection of an opioid, or an opioid combined with a local anesthetic, usually performed as part of a CSE technique, results in a rapid onset of analgesia with a low dose of drug(s) (see Table 23-2). The onset of effective spinal analgesia occurs faster than epidural analgesia, and more women have effective analgesia at 10 minutes.[27] Intrathecal opioids can provide complete analgesia during early labor when the pain stimuli are primarily visceral. An intrathecal local anesthetic without an opioid is not commonly used for labor analgesia. Doses high enough to provide analgesia are associated with significant motor blockade, and lower doses either do not provide satisfactory analgesia or are associated with an unacceptably short duration of analgesia.[168,169] A lipid-soluble opioid is combined with a local anesthetic (bupivacaine, ropivacaine, or levobupivacaine) when sacral analgesia is necessary for complete analgesia (e.g., initiation of analgesia during the active first stage or the second stage of labor). Studies in animal models support a synergistic interaction between spinal local anesthetics and opioids.[170,171] Like the combination of an epidural local anesthetic with an opioid, the combination of an intrathecal opioid with a local anesthetic results in better quality and longer duration of analgesia,[172,173] as well as a lower dose requirement for both drugs, compared with either drug used alone.[168,169,174]

Choice of Drugs

Opioids

Fentanyl and Sufentanil. The two opioids most commonly used for initiation of spinal labor analgesia are fentanyl and sufentanil. When administered alone in early labor, intrathecal fentanyl and sufentanil provide complete analgesia without a sympathectomy or motor blockade. This is a particularly useful technique for patients in whom a sudden decrease in preload (secondary to neuraxial local anesthetic–induced sympathectomy) might not be well tolerated (e.g., patient with a stenotic heart lesion).

Studies suggest that the ED_{50} of intrathecal fentanyl varies from 5.5 to 18 μg.[175-177] The wide range of published values may be explained by differences in patient population (e.g., parity), cervical dilation at initiation of analgesia, and definition of successful analgesia. Nelson et al.[178] hypothesized that acute mixing of fentanyl in cerebrospinal fluid (CSF) may explain the large interindividual variability observed after the injection of intrathecal opioid. In an elegant study, the investigators determined CSF fentanyl concentration at the site of the lumbar injection 60 seconds after the fentanyl injection. CSF fentanyl concentration did not correlate with onset, sensory level, or duration of analgesia. Instead, decreased diastolic and increased systolic blood pressure correlated with duration of analgesia. The authors hypothesized that hemodynamic characteristics may influence the distribution of drug in the CSF and, hence, block characteristics.

Herman et al.[177] determined that the ED_{95} of intrathecal fentanyl for parturients of mixed parity in early labor (cervical dilation ≤ 5 cm) was 17.4 μg (95% CI, 13.8 to 27.1) (Figure 23-3). The duration of analgesia is dose dependent but plateaus at 80 to 90 minutes after administration of 15 to 25 μg of fentanyl (Figure 23-4).[175] There does not appear to be any reason to administer doses higher than 25 μg, because side effects (e.g., pruritus, respiratory depression) are also dose dependent.[168,175,177]

The reported ED_{50} of intrathecal sufentanil varies from 1.8 to 4.1 μg,[179-182] and the ED_{95} is 8 to 10 μg.[179,182] A comparison of the potencies of fentanyl and sufentanil using ED_{50} estimates from different studies is difficult because of differences in patient populations and the definition of efficacy. In a single-center study, the relative potency ratio of intrathecal sufentanil to fentanyl for labor analgesia was estimated to be 4.4:1.[176] When the drugs were administered at twice the ED_{50} (fentanyl 36 μg, sufentanil 8 μg), the duration of sufentanil analgesia was 25 minutes longer than that of fentanyl analgesia (104 versus 79 minutes), although the incidence of side effects was not different.[176]

Landau et al.[183] investigated the influence of genetic variability of *OPRM1* on the ED_{50} of intrathecal fentanyl for labor analgesia. Nulliparous women who were heterozygous or homozygous for A118G had a lower ED_{50} for intrathecal fentanyl (18 μg, 95% CI, 13 to 22) than women homozygous for the wild-type allele (A118) (27 μg, 95% CI, 23 to 31). Additionally, women in the group with the A118G allele requested analgesia at a

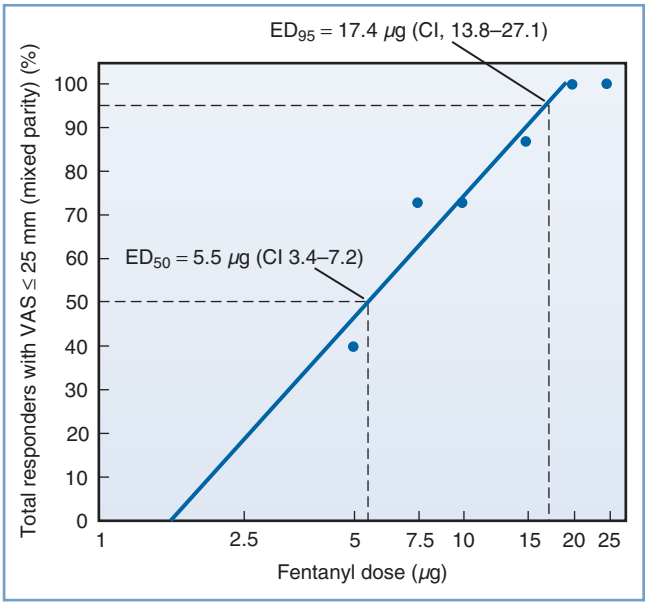


FIGURE 23-3 ■ Dose-response relationship of intrathecal fentanyl in parturients in early labor (≤ 5 cm cervical dilation). The percent response for each dose (plotted on a common log scale) reflects the number of patients with adequate analgesia (visual analog scale [VAS] pain score ≤ 25/100 mm). The intrathecal fentanyl doses, 5, 7.5, 10, 15, and 20 μg, fell on the steep slope of the dose-response curve (between 40% and 100% responders). These data were used to construct the regression line to derive the 50% and 95% effective doses (ED_{50} and ED_{95}, respectively) by observation. Each data point represents n = 15. *CI,* 95% confidence interval. (From Herman NL, Choi KC, Affleck AJ, et al. Analgesia, pruritus, and ventilation exhibit a dose-response relationship in parturients receiving intrathecal fentanyl during labor. Anesth Analg 1999; 89:378-83.)

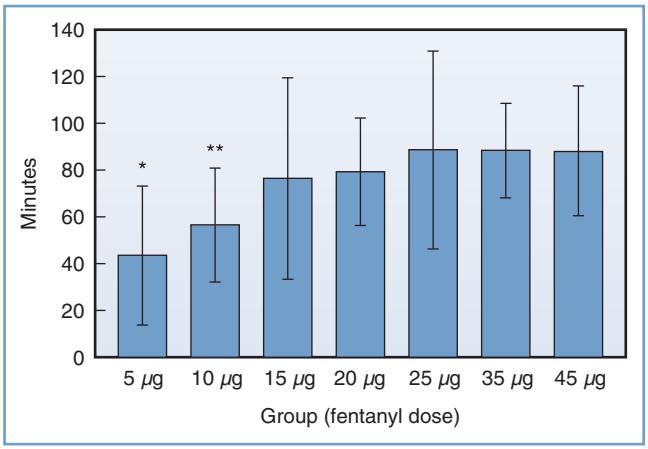


FIGURE 23-4 ■ Duration of intrathecal fentanyl analgesia (mean ± SD) among nulliparous women in active labor who received 5, 10, 15, 20, 25, 35, or 45 μg. Duration of analgesia (time from intrathecal dose to first request for additional analgesia) differed significantly among the groups (analysis of variance [ANOVA], $P < .005$). *$P < .05$ versus groups 15 through 45 μg; **$P < .05$ versus groups 25 through 45 μg. (From Palmer CM, Cork RC, Hays R, et al. The dose-response relationship of intrathecal fentanyl for labor analgesia. Anesthesiology 1998; 88:355-61.)

more advanced cervical dilation. However, in a second study,[184] there was no difference in the duration of intrathecal fentanyl analgesia in women with the A118G allele compared with women who were homozygous for the wild-type allele. Thus, the clinical implications of genetic polymorphisms of *OPRM1* on labor analgesia remain unclear.[185]

Typically, an intrathecal opioid injection for labor analgesia is administered as part of a CSE technique. Maintenance epidural analgesia is usually initiated soon after initiation of spinal analgesia. Therefore, the duration of intrathecal analgesia is relatively less important. Nelson et al.[176] concluded, and we concur, that the longer duration of sufentanil analgesia in comparison with fentanyl analgesia does not necessarily justify the former's use. Other factors, such as cost and the greater risk for a drug dose error with sufentanil (because of its greater potency), should be considered. In some European countries sufentanil is available in a dilute concentration (5 μg/mL), possibly making it easier and safer to use.

Intrathecal fentanyl (or sufentanil) is often co-administered with an amide local anesthetic (see later discussion), most commonly bupivacaine (see Table 23-2). The addition of a local anesthetic to intrathecal fentanyl or sufentanil markedly decreases the dose of opioid necessary to produce analgesia. Wong et al.[168] randomly assigned parous women to receive intrathecal bupivacaine 2.5 mg and intrathecal sufentanil 0, 2.5, 5, 7.5, or 10 μg, followed by a standard epidural test dose. There were no differences among the sufentanil groups in quality and duration of analgesia. These results suggest that a sufentanil dose as small as 2.5 μg is effective when combined with bupivacaine 2.5 mg. In current clinical practice, it is common to combine bupivacaine 2.5 mg with sufentanil 1.5 to 2 μg.[186] Stocks at al.[173] demonstrated that three different doses of intrathecal fentanyl (5, 15, and 25 μg) led to similar reductions in the ED_{50} of intrathecal bupivacaine, although both the duration of analgesia and the incidence of pruritus were dose dependent. As with sufentanil, the dose of intrathecal fentanyl is usually reduced when combined with bupivacaine.[169] Intrathecal fentanyl 10 to 15 μg, combined with bupivacaine 2.5 mg, provides effective analgesia for most parturients.

Other Opioids. Early studies demonstrated that the intrathecal administration of 0.5 to 2 mg of **morphine** reliably produced analgesia during the first stage of labor, but the analgesia was less reliable during the second stage of labor and during instrumental vaginal delivery.[187,188] However, intrathecal administration of these relatively large doses of morphine resulted in a high incidence of side effects, including somnolence, nausea and vomiting, pruritus, and respiratory depression. In addition, the onset of analgesia is slower with intrathecal morphine than with lipid-soluble opioids, and the long duration of action may be a disadvantage (i.e., the parturient may deliver before the regression of side effects). Abouleish[189] reported a case of life-threatening respiratory depression 1 hour after delivery and 7 hours after the administration of 1 mg of hyperbaric intrathecal morphine.

In several studies,[190-192] *low-dose* morphine (0.1 to 0.25 mg) was successfully combined with intrathecal bupivacaine (2 to 2.5 mg) and fentanyl (12.5 to 25 µg); the combination resulted in short latency of onset and a prolonged duration of analgesia. In contrast, a single study from Sweden[193] found no advantage to adding morphine 0.05 or 0.1 mg to bupivacaine 1.25 mg and sufentanil 5 µg. The addition of low-dose morphine to intrathecal bupivacaine and a lipid-soluble opioid may be useful in low-resource settings in which continuous epidural infusion techniques are impractical.[33] When used as part of a CSE technique, the addition of intrathecal morphine to bupivacaine and fentanyl has been shown to result in less breakthrough pain during labor[190-192] as well as decreased analgesic use in the first 24 hours postpartum, compared with intrathecal bupivacaine and fentanyl without morphine.[190,191] The incidence of intrapartum side effects was similar[190,192]; however, the morphine group had a higher incidence of postpartum nausea (17% versus 0% for no morphine).[190]

An alternative drug is **meperidine**. Meperidine is unique among the opioids in that it possesses weak local anesthetic properties,[131] and it has been used in large doses (e.g., 1 mg/kg) as the sole agent to provide spinal anesthesia for surgical procedures.[194] Intrathecal administration of meperidine (10 to 20 mg) results in effective labor analgesia within 2 to 12 minutes, with a duration of 1 to 3 hours. Honet et al.[195] compared the efficacy of intrathecal meperidine 10 mg, fentanyl 10 µg, and sufentanil 5 µg in 65 laboring women. The three drugs were similar in onset of analgesia (< 5 minutes) and duration of effective analgesia (80 to 100 minutes). However, the meperidine group had significantly lower pain scores after cervical dilation had progressed beyond 6 cm. As labor advances, the nature of pain becomes increasingly somatic; only meperidine also functions as a local anesthetic. This fact helps explain why meperidine provided more effective analgesia during advanced labor, including the second stage. Booth et al.[196] observed that intrathecal meperidine was associated with a significantly higher incidence of nausea and vomiting than a combination of fentanyl and bupivacaine for labor analgesia. Therefore, intrathecal meperidine does not seem to offer any advantages over bupivacaine-fentanyl for routine intrathecal analgesia, although it may be useful for the rare patient with a contraindication to bupivacaine-fentanyl administration.

In the United Kingdom, some anesthesia providers have advocated the intrathecal administration of **diamorphine** (heroin) for labor analgesia, although it is not commonly used for this purpose. This drug is not available for clinical use in the United States. Kestin et al.[197] observed that the intrathecal administration of diamorphine (0.2 to 0.5 mg) provided good to excellent analgesia in 90% of laboring women. The mean duration of analgesia was approximately 100 minutes. However, 75% of patients had pruritus, nausea, and vomiting. In contrast, Vaughan et al.[198] randomly assigned parturients to receive intrathecal bupivacaine 2.5 mg with either fentanyl 25 µg or diamorphine 0.25 mg. Duration of analgesia was longer in the diamorphine group, but the incidence of side effects was low in both groups.

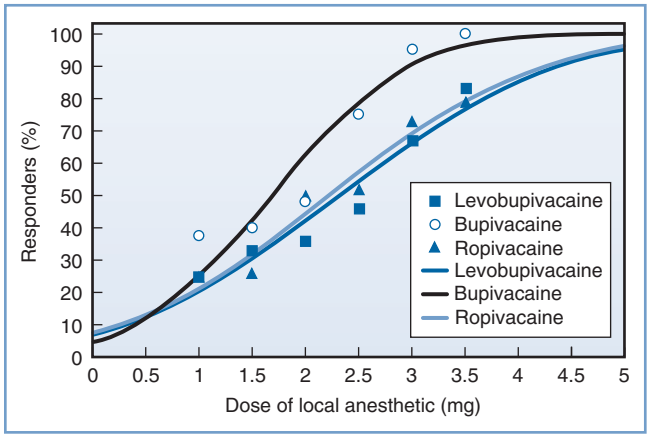


FIGURE 23-5 ■ Predicted (*lines*) and observed (*symbols*) dose-response of intrathecal bupivacaine, levobupivacaine, and ropivacaine combined with sufentanil 1.5 µg in 450 laboring women. The dose-response curves were constructed with the use of a probit regression model. The curves were compared with use of likelihood ratio tests. No difference was observed between ropivacaine and levobupivacaine. Significant differences were observed between bupivacaine and ropivacaine ($P = .003$) and bupivacaine and levobupivacaine ($P < .001$). (From Van de Velde M, Dreelinck R, Dubois J, et al. Determination of the full dose-response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. Anesthesiology 2007; 106:149-56.)

Local Anesthetics

In the late first stage and the second stage of labor, a local anesthetic must be added to the spinal opioid to block somatic stimuli from the vagina and perineum caused by descent of the fetus. The local anesthetic works synergistically with the opioid, so lower doses of both drugs can be used.[168,169,173,199] **Bupivacaine** is most commonly combined with fentanyl or sufentanil. The ED_{95} of bupivacaine was 3.3 mg when combined with sufentanil 1.5 µg[186] and 1.7 mg when combined with fentanyl 15 µg.[200] Intrathecal bupivacaine doses between 1.25 and 2.5 mg are commonly used (see Table 23-2). Levobupivacaine and ropivacaine are not usually used for intrathecal injection in the United States. They are less potent than bupivacaine for intrathecal labor analgesia (Figure 23-5).[186,201] Spinal lidocaine has not been studied for use in labor analgesia, but it is unlikely to have any advantages compared with other, longer-acting amide local anesthetics. Common doses of spinal local anesthetics are shown in Table 23-2.

Controversy exists as to whether the lower incidence and degree of motor blockade associated with ropivacaine and levobupivacaine[66,201] are a result of their inherent difference in potency or of greater sensory-motor separation with the S(–)-enantiomer drugs.[186] Camorcia et al.[201] have suggested that, especially during intrathecal use, ropivacaine may be associated with less motor blockade than bupivacaine, even when equipotent doses (e.g., 3.6 mg ropivacaine and 2.4 mg bupivacaine) are administered. However, this difference, even if it exists, is unlikely to have any clinical significance during spinal labor analgesia because all local anesthetics administered for this purpose are administered in low doses that lead to minimal motor blockade.

Baricity of the Intrathecal Solution. The local anesthetic/opioid solutions commonly injected for intrathecal labor analgesia have lower specific gravity relative to that of CSF and hence are hypobaric.[202] The extent of cephalad sensory blockade is higher for spinal analgesia initiated with the parturient in the sitting position than in the lateral position.[203] Adding dextrose to the solution (opioid alone or opioid with local anesthetic) to make the solution hyperbaric results in less extensive sensory blockade but also in inadequate analgesia.[204-206] It is probably necessary for the opioid to penetrate the spinal cord rather than just the nerve roots; therefore, injection of a hyperbaric solution of opioid and local anesthetic below the level of the spinal cord may lead to inadequate analgesia, even though the local anesthetic provides sensory blockade to the T10 dermatome.

Intrathecal Adjuvants

Several drugs have been investigated as adjuvants to local anesthetics, opioids, or combinations of local anesthetics and opioids for intrathecal labor analgesia (see Table 23-4). In one study, the addition of **clonidine** 30 µg to sufentanil (2.5 to 5 µg) prolonged the duration of analgesia from 104 to 145 minutes without motor block.[207] Other investigators have had similar results when clonidine was combined with sufentanil,[208] bupivacaine/ropivacaine and sufentanil,[209,210] and neostigmine.[211] Intrathecal clonidine alone also provides analgesia.[212] Unfortunately, a disadvantage of clonidine is the high incidence of maternal hypotension and sedation as well as FHR abnormalities. The slightly longer duration of analgesia provided by the addition of clonidine to bupivacaine and sufentanil is not an advantage when maintenance analgesia is provided by a continuous epidural infusion. Therefore, at present, intrathecal clonidine cannot be recommended for routine spinal labor analgesia, although it might be considered in parturients with contraindications to the use of other drugs.[167]

Adding intrathecal **neostigmine** to sufentanil, bupivacaine/sufentanil, or clonidine has been found to potentiate the analgesia and prolong its duration.[211,213] However, intrathecal neostigmine was associated with a markedly higher incidence of severe nausea that was unresponsive to standard antiemetics.[211,213] Therefore, neostigmine cannot be recommended as an adjuvant for intrathecal labor analgesia.

Analgesia is prolonged by 15 to 40 minutes when **epinephrine** is added to intrathecal bupivacaine-opioid.[214-216] Even an epinephrine dose as low as 2.25 µg prolonged analgesia by 15 minutes.[215] However, epinephrine 200 µg combined with bupivacaine 2.5 mg and sufentanil 10 µg resulted in a significant incidence of motor blockade[214]; epinephrine doses between 12.5 and 100 µg prolonged analgesia without any difference in the quality of analgesia.[216]

In summary, no adjuvant studied to date prolongs the duration of fentanyl or sufentanil/bupivacaine analgesia long enough to avoid the use of maintenance epidural analgesia for most parturients, and no adjuvant reduces or eliminates the side effects associated with the analgesic drugs used clinically. Therefore, it makes little sense to routinely add adjuvant drugs, because they are associated with higher cost, higher rate or severity of side effects, and probably an increased risk for drug error.

MAINTENANCE OF ANALGESIA

Epidural Analgesia

Painful labor lasts several hours in most parturients; therefore, a single intrathecal or epidural injection of local anesthetic and/or opioid typically does not provide adequate analgesia for the duration of labor. Supplemental doses are needed to maintain analgesia in most women. Neuraxial analgesia is maintained with the intermittent or continuous administration of analgesics, usually a combination of a long-acting amide local anesthetic and a lipid-soluble opioid. By far the most common technique is administration of drugs via a catheter into the epidural space. It is occasionally advantageous to administer drugs via a catheter into the subarachnoid space.

Drugs for the Maintenance of Epidural Analgesia

In the past, epidural labor analgesia was maintained with the intermittent injection or continuous infusion of a neuraxial local anesthetic alone. Currently, most anesthesia providers maintain analgesia with a combination of a low-dose, long-acting amide local anesthetic and a lipid-soluble opioid (Table 23-5). In practice, neither lidocaine nor 2-chloroprocaine is used for maintenance of analgesia. Both have a short duration of action, and tachyphylaxis may develop more quickly with either of these local anesthetics than occurs with the longer-acting local anesthetics. Lidocaine crosses the placenta to a greater extent than bupivacaine, and there is less differentiation between the dose required for sensory and motor blockade.[217] There is no evidence that any one of the three long-acting local anesthetics (bupivacaine, ropivacaine,

TABLE 23-5 **Anesthetic Solutions for Maintenance of Epidural Analgesia: Continuous Infusion or Patient-Controlled Epidural Analgesia***

Drug†	Concentration
Local Anesthetics	
Bupivacaine	0.05-0.125%
Ropivacaine	0.08-0.2%
Levobupivacaine	0.05-0.125%
Lidocaine‡	0.5%-1.0%
Opioids	
Fentanyl	1.5-3 µg/mL
Sufentanil	0.2-0.4 µg/mL

*Local anesthetic is most often combined with an opioid.
†Continuous infusions are usually administered at a rate of 8-15 mL/h into the lumbar epidural space.
‡Lidocaine is not usually used for maintenance of epidural analgesia because it crosses the placenta to a greater extent than the other amide local anesthetics and may be associated with greater tachyphylaxis.

levobupivacaine) has any advantages in terms of clinical outcomes over the other two.[66,75,76] Fentanyl is more often detected in umbilical artery blood samples than sufentanil (as discussed earlier)[109]; however, neonatal outcomes are good after maintenance epidural analgesia with either drug.

As with the induction dose, the combination of a local anesthetic with a lipid-soluble opioid allows administration of a lower concentration and a smaller total dose of local anesthetic for maintenance of analgesia. This approach improves safety and leads to less motor blockade and greater patient satisfaction. Chestnut et al.[98] demonstrated that maintenance of epidural analgesia by a continuous infusion of 0.0625% bupivacaine with fentanyl 2 μg/mL resulted in comparable maternal and neonatal outcomes, with a lower incidence of motor blockade, compared with maintenance of analgesia by a continuous epidural infusion of 0.125% bupivacaine alone. When administered as intermittent epidural boluses for the maintenance of analgesia, the addition of sufentanil to bupivacaine resulted in better quality analgesia and decreased motor blockade at delivery.[105]

In contemporary clinical practice, the bupivacaine concentration of maintenance bupivacaine/opioid solutions ranges from 0.05% to 0.125%. Hess et al.[218] retrospectively analyzed the use of three solutions at their institution: bupivacaine 0.125% and bupivacaine 0.0625%, both with fentanyl 2 μg/mL, administered at 8 to 12 mL/h, and bupivacaine 0.04% with fentanyl 1.7 μg/mL and epinephrine 1.7 μg/mL, administered at 15 mL/h. There were more interventions for breakthrough pain in the two low-concentration groups and more interventions for hypotension and motor blockade in the high-concentration group. Beilin et al.[219] initiated analgesia with intrathecal bupivacaine/fentanyl and an epidural test dose, and then randomly assigned women to receive maintenance epidural analgesia with one of four solutions: bupivacaine 0.125%, bupivacaine 0.0625%, or bupivacaine 0.04% with epinephrine 1.7 μg/mL (all with fentanyl 2 μg/mL) or placebo (saline) at 10 mL/h. The time to request for supplemental analgesia was longest in the bupivacaine 0.125% group; however, this group also had a higher incidence of motor blockade than the other groups. Therefore, to avoid motor blockade, it would seem reasonable to use a bupivacaine concentration less than 0.125%, especially if it is administered via continuous epidural infusion (see later discussion).

The dose-response relationships for fentanyl and sufentanil combined with a local anesthetic for the maintenance of epidural analgesia have not been well studied. The concentration range of fentanyl used in clinical practice is 1.5 to 3 μg/mL, and that of sufentanil, 0.2 to 0.33 μg/mL. The optimal opioid concentration probably varies according to the local anesthetic concentration, the mode of drug delivery (i.e., bolus versus infusion), presence of epinephrine, and the stage of labor, among other factors. Bader et al.[220] infused epidural bupivacaine 0.125% with fentanyl 2 μg/mL at 10 mL/h for 1 to 15 hours. Maternal and neonatal fentanyl concentrations, and their ratio, remained constant over the infusion period, and no adverse maternal or neonatal outcomes were noted. Porter et al.[221] compared neonatal outcomes in women randomly assigned to receive epidural bupivacaine with fentanyl 2.5 μg/mL or bupivacaine alone to maintain analgesia. There were no differences between groups in measures of neonatal well-being at birth or 24 hours after delivery.

Bernard et al.[222] combined sufentanil 0, 0.078, 0.156, 0.312, or 0.468 μg/mL with bupivacaine 0.125% and epinephrine 1.25 μg/mL. Each solution was administered as a 12-mL bolus via PCEA. Sufentanil concentrations lower than 0.156 μg/mL did not provide adequate analgesia for the second stage of labor, and higher doses were associated with an increased incidence of pruritus. Loftus et al.[109] compared bupivacaine with sufentanil 0.25 μg/mL or fentanyl 1.5 μg/mL as a continuous epidural infusion at 10 mL/h. Neonates in the fentanyl group had slightly lower 24-hour neuroadaptive capacity scores (NACS) than the sufentanil group.

Administration Techniques

Intermittent Bolus. Before the introduction of infusion pumps, epidural analgesia was routinely maintained by the intermittent administration of an additional therapeutic bolus dose of local anesthetic when analgesia began to wane. When the patient began to experience recurrent pain, the anesthesia provider assessed the pain relative to the stage of labor and the extent of sensory blockade and then administered another epidural bolus of local anesthetic. Analgesia was usually reestablished with the bolus injection of 8 to 12 mL of a local anesthetic/opioid solution.

The spread and quality of analgesia may change with repeated lumbar epidural injections of local anesthetic. After several injections, blockade of the sacral segments, intense motor blockade, or both may develop.[146] The sensory level and the intensity of motor blockade should be assessed and recorded before and after each bolus injection of local anesthetic.

This intermittent bolus technique has several disadvantages, the most salient of which is that pain relief is constantly interrupted by the regression of analgesia. The patient must notify the labor nurse or midwife that she is again uncomfortable and request additional analgesia. In the United States, labor nurses are not allowed to administer additional epidural analgesic drugs[223]; therefore, the nurse must call the anesthesia provider, resulting in unavoidable delays in administration of additional analgesic drugs and additional pain for the patient.

Continuous Infusion. Administration of a continuous epidural infusion of a dilute solution of local anesthetic combined with an opioid is a popular technique for the maintenance of epidural analgesia during labor. The potential benefits of a continuous epidural infusion include the maintenance of a stable level of analgesia and a less-frequent need for bolus doses of local anesthetic, which may reduce the risk for systemic local anesthetic toxicity. An additional advantage is a decreased workload for the anesthesia provider.

Published studies, however, have suggested that the continuous epidural infusion and intermittent bolus injection techniques have a comparable safety record.

Studies comparing intermittent bolus injections with continuous infusion were performed before the era of neuraxial opioid administration; thus, the studies used concentrations of bupivacaine (0.125% to 0.25%) higher than those typically used in contemporary practice. In theory, maintenance of a constant level of anesthesia should promote maternal hemodynamic stability and improve fetal and neonatal outcome. Only one published study has suggested a trend toward less frequent hypotension and a lower incidence of abnormal FHR patterns during the continuous epidural infusion of bupivacaine than with intermittent bolus injections of bupivacaine; however, neonatal outcomes were similar with the two techniques.[224]

Randomized trials of intrapartum epidural analgesia maintained by either intermittent bolus injection or continuous infusion of bupivacaine have consistently demonstrated that women require fewer bolus injections administered by the anesthesia provider (i.e., fewer episodes of breakthrough pain) with the continuous infusion technique.[224-226] The continuous infusion technique lengthens the time between bolus injections and leads to greater patient satisfaction.[226,227] This is advantageous in a busy obstetric anesthesia practice, in which an anesthesia provider may not always be available to give an additional bolus dose of local anesthetic immediately after the onset of recurrent pain.

Most studies suggest that the continuous epidural infusion technique leads to the administration of a larger total dose of bupivacaine,[225-228] but such a dose does not seem to result in higher maternal venous or umbilical venous bupivacaine concentrations at delivery.[226,228] The continuous epidural infusion of bupivacaine often achieves satisfactory perineal analgesia, obviating the need for a bolus dose of local anesthetic at delivery. Unfortunately, a prolonged epidural infusion of 0.125% bupivacaine at 10 to 14 mL/h may cause significant motor blockade.[86,224,225,227,228] Titrating the dose of bupivacaine to meet the individual needs of each patient (rather than administering the same dose to all patients), as well as reducing the total mass of bupivacaine by lowering the local anesthetic concentration and adding an opioid, helps minimize motor blockade while providing effective analgesia.

Migration of the epidural catheter into the subarachnoid, subdural, or intravenous space may occur with either the intermittent bolus injection or continuous infusion technique. If the epidural catheter should migrate into a vein during the continuous epidural infusion of a dilute solution of local anesthetic, it is unlikely that the patient will have symptoms of local anesthetic toxicity; rather, the level of anesthesia will regress. For this reason, the anesthesia provider should suspect the intravenous migration of an epidural catheter when a patient unexpectedly complains of pain during maintenance of analgesia during a continuous epidural infusion.

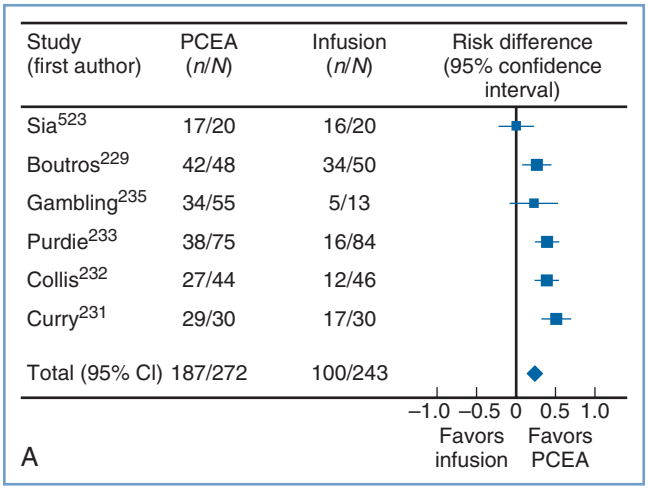
Migration of the epidural catheter into the subdural or subarachnoid space during an infusion should result in the slow ascent of the level of anesthesia and a greater density of motor blockade. These observations apply to the epidural infusion of a 0.125% solution of bupivacaine at a modest rate (e.g., 5 to 8 mL/h). The continuous infusion of a more concentrated solution or the use of a more rapid rate of infusion most likely narrows the margin of safety.

Patient-Controlled Epidural Analgesia. The method of delivering the anesthetic solution into the epidural space influences the density of neuroblockade. Given the same concentration of local anesthetic, analgesia maintained by infusion results in greater drug use, a higher degree of motor blockade,[225,229] and a higher incidence of instrumental vaginal delivery than intermittent boluses.[228] However, intermittent manual bolus administration by the anesthesia provider results in more breakthrough pain, less patient satisfaction, and more work for the anesthesia provider. PCEA is a method of delivering anesthetic solution to the epidural space that overcomes these disadvantages. Since its first description in 1988 by Gambling et al.,[230] many studies have consistently found that the analgesia with PCEA is comparable to that with continuous infusion techniques.[229,231-237]

Van der Vyver et al.[238] reported a meta-analysis of nine randomized controlled trials (n = 640) comparing PCEA (without a background infusion) with continuous epidural infusion analgesia. There were fewer anesthetic interventions in the PCEA group, and the total bupivacaine dose was lower, as was the incidence of motor blockade (Figure 23-6). There were no differences in pain scores, patient satisfaction, and maternal and neonatal outcomes between groups.

Data are conflicting as to whether PCEA should include a background infusion.[237,239-247] Most studies have reported background infusions of 3 to 4 mL/h. Bupivacaine consumption is higher in PCEA with a background infusion than in a pure PCEA technique without a background infusion.[238] A meta-analysis of five studies[237,240,241,243,244] reported in the ASA Practice Guidelines for Obstetric Anesthesia[16] concluded that a background infusion provides better analgesia than pure PCEA without a background infusion. In a 2009 review, Halpern and Carvalho[248] concluded that a background infusion improves analgesia and results in fewer unscheduled interventions by the anesthesia provider. There is no evidence that the higher local anesthetic dose associated with a background infusion increases motor blockade or has adverse effects on obstetric outcome when low-concentration infusion solutions are used. A typical background infusion provides one third to one half of the total hourly dose.[248] Sng et al.[249] described a novel PCEA system in which they used a computer-integrated infusion pump to modify the background infusion rate based on the previous hour's requirement for patient-administered bolus doses.

A wide variety of PCEA regimens have been described (Table 23-6). The anesthesia provider can manipulate the infusion solution (local anesthesia/opioid concentration), patient-controlled bolus volume, lockout interval, background infusion rate, and maximum allowable dose per hour. Patient-controlled bolus doses from 2 to 20 mL and lockout intervals from 5 to 30 minutes have been reported[235,245-247,250-253]; most studies have evaluated patient-controlled bolus doses of 5 to 12 mL. No study has found any differences in unscheduled provider interventions when investigators manipulated the



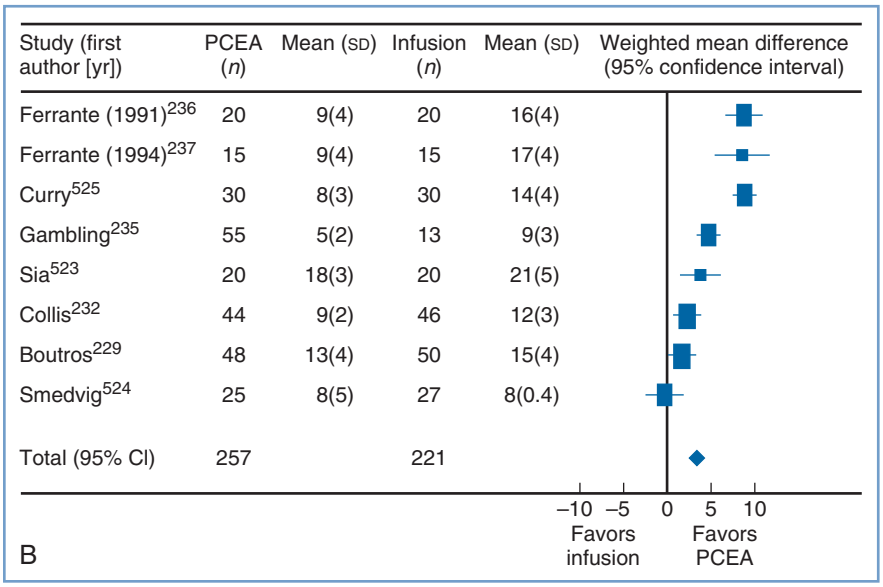


FIGURE 23-6 ■ Meta-analysis of patient-controlled epidural analgesia (PCEA) without background infusion compared with continuous epidural infusion for maintenance of analgesia. **A,** The number of patients requiring no unscheduled interventions by the anesthesia provider was lower in the PCEA group (risk difference 27%; 95% confidence interval [CI], 18 to 36). **B,** The dose of local anesthetic (mg/h) was lower in the PCEA group (weighted mean difference, –3.9 mg; 95% CI, –5.4 to –2.4). (From van der Vyver M, Halpern S, Joseph G. Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. Br J Anaesth 2002; 89:459-65.)

TABLE 23-6 Sample Patient-Controlled Epidural Analgesia (PCEA) Settings*

PCEA Technique	Basal Infusion Rate (mL/h)	Bolus Dose (mL)	Lockout Interval (min)
Without background infusion	0	8-12	10-20
With background infusion	4-8	5-8	10-15

*Anesthetic solutions are shown in Table 23-5.

patient-controlled bolus dose and lockout interval. There are no published reports of toxicity with larger bolus volumes, although the study populations were too small to allow determination of safety. Taken together, these studies suggest that there is no ideal bolus dose/volume or lockout interval for labor PCEA.

Various local anesthetic concentrations also have been studied. No studies have reported any differences in analgesia efficacy. Use of more-concentrated local anesthetic solutions results in higher local anesthetic consumption[241,254-256] and greater motor blockade than use of less-concentrated solutions.[245,254,257] Thus, as with continuous infusion epidural analgesia, administration of a dilute local anesthetic solution combined with an opioid results in less local anesthetic consumption and motor blockade without a reduction in analgesia efficacy.

In summary, solutions used for PCEA are identical to those used for continuous epidural infusion analgesia (see Table 23-5). It is suggested that larger bolus volumes be used if PCEA is administered without a background infusion. Early PCEA studies investigated higher-concentration local anesthetic solutions (i.e., 0.125% to 0.25% bupivacaine), smaller bolus volumes (≤ 5 mL), and low background infusion rates (3 to 5 mL/h). Given the more recent data supporting the efficacy of epidural administration of higher volumes of more dilute solutions of local anesthetic, it appears reasonable to apply this principle to PCEA. The safety of large-volume boluses (> 10 mL) has not been determined.

Timed Intermittent Bolus Injection. Bolus administration of a local anesthetic into the epidural space results in better analgesia than continuous epidural infusion.

Likewise, larger volumes of a less concentrated anesthetic solution provide better analgesia than smaller volumes of a more concentrated solution. Presumably, distribution of anesthetic solution in the epidural space is better when larger volumes are administered under high injection pressure.[258] Several studies have demonstrated that timed (automated) intermittent boluses (5 to 10 mL every 30 to 60 minutes) administered via a programmable pump result in improved patient satisfaction, less drug use, longer duration of analgesia, and less breakthrough pain than a continuous infusion of the same mass of drug per unit of time.[259-263] For example, Wong et al.[259] randomly assigned patients to receive either a continuous epidural infusion of a dilute bupivacaine/fentanyl solution at 12 mL/h or 6 mL of the same solution delivered as an automated bolus every 30 minutes. Similarly, Sia et al.[263] randomly assigned patients to receive either a continuous epidural infusion of a ropivacaine/fentanyl solution at 5 mL/h or 5 mL of the same solution delivered as an automated bolus every hour. All patients in both studies were allowed PCEA for the treatment of breakthrough pain. The total dose of local anesthetic was smaller in the automated bolus groups than in the continuous infusion groups.

Capogna et al.[264] compared motor block and mode of delivery in women randomized to receive an automated timed bolus of levobupivacaine 0.0625% with sufentanil 0.5 μg/mL (10 mL every 60 minutes) or the same solution as a continuous infusion (10 mL/h). Women were able to treat breakthrough pain with PCEA using levobupivacaine 0.125% (5-mL bolus). The incidence of motor block was greater in the continuous infusion group. Of interest, the rate of instrumental vaginal delivery was also higher in the continuous infusion group (7% versus 20%; risk ratio, 2.9; 95% CI, 1.1 to 7.9).

In a systematic review and meta-analysis of nine studies (n = 344), George et al.[265] concluded that the intermittent programmed bolus technique was associated with a small decrease in total anesthetic consumption and improved patient satisfaction. Although no difference was found in the need for anesthesia provider intervention and other outcomes, the confidence intervals were wide. The authors concluded that further study is needed to ascertain whether this technique impacts clinically significant anesthetic and obstetric outcomes. Infusion pumps with the ability to deliver this mode of analgesia are now coming on the market.

Patient Monitoring during Maintenance Epidural Analgesia

The use of a continuous epidural infusion technique or PCEA does not abolish the need for frequent assessment of the patient by the anesthesia provider at regular intervals. Assessment should involve determining the quality of analgesia and progress of labor, recording the sensory level and intensity of motor block, and reviewing maternal vital signs and FHR tracings for the previous hour. An inappropriately high level of anesthesia signals the administration of an excessive dose of local anesthetic or subdural or subarachnoid migration of the catheter. A low level of anesthesia may signal intravenous migration of the catheter, movement of the catheter outside the epidural space, or administration of an inadequate dose of local anesthetic.

Equipment

Anesthesia providers should consider the safety of their equipment when choosing a maintenance technique. The use of an infusion pump identical to that used for the intravenous administration of other drugs increases the chance that a nurse or physician will inject oxytocin, magnesium sulfate, or another drug into the epidural space unintentionally. Thus, the use of an infusion pump that is used exclusively for epidural analgesia and that differs from the pumps used for intravenous drug and fluid administration is recommended. The pump should be easy to use, reliable, adjustable, and sturdy. PCEA pumps should differ from patient-controlled *intravenous* analgesia (PCIA) pumps. The PCEA "buttons" should be labeled with instructions that only the patient (not medical providers or family members) should push the button. If possible, pumps should be preprogrammed with maximum safe limits to prevent errors in pump programming.

The anesthesia provider should use infusion tubing (which connects the pump to the epidural catheter) that is unique for the epidural administration of drugs. Some tubing is color coded (yellow). The presence of an injection side-port increases the likelihood of unintentional epidural administration of the wrong drug; thus, use of tubing that does not have an injection side-port is recommended. The epidural catheter and tubing should be clearly labeled with the word "epidural." Patient safety experts[266] and the U.K. National Patient Safety Agency (NPSA)[267] have recommended that syringes, needles, and catheters used for neuraxial injections be modified so that it is not possible to use this equipment for intravenous injections, thus making the possibility of drug administration error less likely.

Each labor unit must have a clear policy as to who may administer and adjust epidural infusion parameters. Anesthesia personnel should be responsible for changes in the content or rate of the infusion and the volume of bolus doses or develop protocols that allow nurses to make changes within the guidelines of the protocol or by order of the anesthesia provider. In the presence of maternal distress or fetal bradycardia, the nurse or obstetrician may discontinue the epidural infusion, but the anesthesia provider should be notified immediately.

Solutions for maintenance of neuraxial analgesia, consisting of dilute local anesthetic and opioid, require careful preparation, because these solutions are not commercially available. A hospital pharmacist or compounding pharmacy should prepare the solution in a clean or sterile environment. Preservative-free drugs and saline should be used to prepare the solutions. Solution contents should always be double-checked for content and expiration date by the anesthesia provider before analgesia is initiated.

Spinal Analgesia

Placement of a catheter in the subarachnoid space allows the anesthesia provider to administer continuous spinal

analgesia by intermittent bolus injection or continuous infusion of a local anesthetic combined with an opioid. Continuous spinal analgesia is an option when unintentional dural puncture has occurred (see later discussion). The technique has also been described for use in patients in whom placement of an epidural catheter is difficult (e.g., in patients with morbid obesity or abnormal vertebral anatomy, such as kyphoscoliosis, or in patients with severe cardiac disease who require careful titration of analgesia.)[268]

Reports of this technique usually describe the use of a standard epidural catheter placed through an 18- or 19-gauge epidural needle. To reduce the risk for post–dural puncture headache, very small (e.g., 28- to 32-gauge) catheters were developed for insertion through small (e.g., 22- to 26-gauge) spinal needles. Unfortunately, several cases of cauda equina syndrome (associated with the use of spinal microcatheters during surgery in nonpregnant patients) prompted the U.S. Food and Drug Administration to remove these microcatheters from the market in 1992.[269] The etiology of these neurologic deficits is unclear. Some anesthesiologists have suggested that neurologic injury may result from the maldistribution of local anesthetic within the subarachnoid space.[270] The very slow rate of injection through a caudally directed microcatheter may lead to pooling of local anesthetic solution in the terminal part of the dural sac. If the local anesthetic solution is hyperbaric, the neighboring elements of the cauda equina experience prolonged exposure to a high concentration of local anesthetic and a hyperglycemic, hyperosmotic marinade (e.g., 550 to 800 mOsm/L). Permanent neural damage may occur from the combination of tissue dehydration and a toxic concentration of local anesthetic. It is unclear whether this complication is unique to the use of microcatheters.

Arkoosh et al.[271] reported a randomized multicenter study comparing continuous spinal labor analgesia (via a 28-gauge catheter) with continuous epidural analgesia. The incidence of neurologic complications was not different between the two groups, and patients in the spinal group had better early analgesia, less motor blockade, and better patient satisfaction. The incidence of post–dural puncture headache also was not different between the two groups (spinal 9%, epidural 4%; $P = .10$), although a type II statistical error is possible given the size of the study and the low incidence of this outcome. The spinal catheter was associated with a higher incidence of technical difficulties and catheter failures. The researchers concluded that larger studies are needed to determine the safety of the spinal catheter, which is not marketed in the United States.

Continuous spinal analgesia can be initiated with the same drug combination and dose used to initiate CSE analgesia (see Table 23-2).[268] For maintenance of analgesia, my colleagues and I administer our standard epidural solution (0.06% bupivacaine with fentanyl 2 μg/mL) at an initial rate of 2 mL/h. The infusion is then titrated to patient needs. We prefer to use our standard PCEA pumps for the continuous infusion, with the PCEA function disabled. This approach allows the anesthesia provider to administer a small (1 to 3 mL) bolus from the infusion bag without disconnecting the spinal catheter from the infusion tubing. Opening the infusion system to air may increase the risk for contamination and drug error. The catheter and pump should be clearly labeled so that all care providers know that the catheter is a spinal, not an epidural, catheter.

Patient-controlled spinal analgesia for labor has been described.[272] Continuous spinal analgesia with opioids has also been described for patients with obstructive cardiac lesions.[273,274] If intrathecal local anesthetics are used for intrapartum analgesia, the sensory level and the intensity of motor blockade should be monitored. Moreover, the anesthesia provider must be prepared to treat hypotension and other complications associated with high spinal anesthesia.

Ambulatory "Walking" Neuraxial Analgesia

The term "walking" or "mobile" epidural analgesia was first coined to describe low-dose CSE opioid analgesia because motor function was maintained and the ability to walk was not impaired.[275] However, the term is more accurately applied to any neuraxial analgesic technique that allows safe ambulation. Initial studies using clinical testing to assess sensory and motor impairment and dorsal column function produced conflicting results. After initiation of epidural analgesia with 15 mL of 0.1% bupivacaine/fentanyl 2 μg/mL, Buggy et al.[276] demonstrated that 66% of women had altered proprioception and 38% had impaired vibration sense. In contrast, Parry et al.[277] found that dorsal column function was impaired in only 7% of laboring women who received low-dose epidural or CSE analgesia. The same group of investigators then used computerized dynamic posturography to assess balance in nonpregnant women, term pregnant women not in labor, and laboring women after initiation of CSE analgesia with bupivacaine 2.5 mg and fentanyl 5 μg.[278] Pregnancy significantly affected balance function, but initiation of CSE analgesia did not further impair function. However, further supplementation of analgesia with the epidural injection of 10 mL of 0.1% bupivacaine/fentanyl 2 μg/mL in a subgroup of patients resulted in impaired balance function. The investigators concluded that the results support the safety of allowing ambulation after low-dose CSE analgesia, but further studies are required to understand the relative contributions of dorsal column function, proprioception, and lower limb motor strength to overall balance and ability to ambulate.[278]

Several studies have shown that an epidural test dose containing lidocaine 45 mg and epinephrine 15 μg adversely affects the ability to ambulate after initiation of CSE or low-dose epidural analgesia.[42,43]

The concept of the "walking epidural" is popular in the lay press; however, many women, once comfortable, prefer to rest rather than ambulate. The ability to walk to the toilet or sit in a chair at the bedside, however, remains desirable to many laboring women. In a small study, the ability to walk to the toilet to void resulted in lower postvoid residual volume than voiding on a bedpan.[279] Although ambulation per se has not been

BOX 23-5 Criteria for Ambulation during Labor with Neuraxial Analgesia

- Reassuring fetal status
- Engagement of fetal presenting part
- Stable orthostatic vital signs (asymptomatic and within 10% of baseline)
- Ability to perform bilateral straight-leg raises in bed against resistance
- Ability to step up on a step stool with either leg taking the first step, without assistance
- Satisfactory trial of walking accompanied by a nurse or midwife
- Patient must be accompanied by a companion at all times
- Intermittent fetal heart rate monitoring (every 15 minutes)

BOX 23-6 Anesthesia for Vaginal Delivery

Lumbar Epidural Catheter

- Supplement existing analgesia with 5 to 10 mL of 1% or 2% lidocaine or with 5 to 10 mL of 2% or 3% 2-chloroprocaine.

Spinal Anesthesia

- Intrathecal injection of hyperbaric bupivacaine 6 to 8 mg or hyperbaric lidocaine 25 to 50 mg.
- Administer a larger dose for a "trial of forceps" in case cesarean delivery is necessary.

Combined Spinal-Epidural Anesthesia

- Intrathecal injection of bupivacaine 2.5 to 5 mg with fentanyl 15 to 25 μg.
- Follow with administration of additional drug(s) via epidural catheter if anesthesia is inadequate.

shown to affect the progress or outcome of labor positively or negatively, dense motor blockade may adversely affect the spontaneous vaginal delivery rate (see later discussion). Thus, the intent of the "walking epidural"—minimization of motor blockade—should be the goal of the anesthesia provider, whether or not the patient wishes to ambulate.

Safe ambulation during labor requires several safeguards (Box 23-5). Prior to ambulation, orthostatic blood pressure and heart rate should be measured and motor function and balance must be assessed. The patient should not ambulate alone.

ANALGESIA/ANESTHESIA FOR VAGINAL DELIVERY

During the second stage of labor, pain results from distention of the pelvic floor, vagina, and perineum. Pain impulses are transmitted to the spinal cord by means of somatic nerve fibers that enter the cord at S2 to S4. These somatic nerve fibers are larger than the visceral afferent nerve fibers that transmit the pain of the first stage of labor. Blockade of these larger nerve fibers may require administration of a more concentrated solution and/or a greater volume of local anesthetic than is required during the first stage of labor[51]; this need often creates a dilemma for the anesthesia provider. Administration of a more concentrated solution of local anesthetic results in more intense motor blockade at a time when maternal expulsive efforts are helpful.

The continuous epidural infusion of bupivacaine often leads to the gradual development of sacral analgesia. Likewise, several lumbar epidural injections of local anesthetic (given every 60 to 90 minutes) may result in sacral analgesia.[146] If analgesia is not adequate for the second stage of labor and delivery, the anesthesia provider can give additional doses of local anesthetic to augment perineal analgesia (Box 23-6). Some anesthesia providers contend that the use of the sitting position helps facilitate the onset of perineal analgesia. Published studies suggest that maternal position does not consistently affect the spread of local anesthetic in the epidural space[280,281]; rather, the administration of a larger volume of local anesthetic solution facilitates the onset of sacral analgesia.[282] Unfortunately, the larger volume also results in a higher (i.e., more cephalad) sensory level of analgesia, so the patient should be observed for evidence of hemodynamic or respiratory compromise.

Dense anesthesia is often required for delivery, especially if the obstetrician performs an episiotomy or a forceps or vacuum-extraction delivery. After administration of a test dose (3 mL of the local anesthetic solution), at our institution my colleagues and I administer 5 to 10 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine. We inject this "delivery dose" when the fetal head is visible on the perineum during pushing or when the obstetrician has decided to proceed with instrumental vaginal delivery. The anesthesia provider should monitor the maternal blood pressure carefully, especially if excessive blood loss occurs in a patient with extensive anesthesia.

Occasionally a parturient tolerates the pain of labor until late in the first stage (i.e., more than 8 cm cervical dilation) and then requests analgesia. Advanced labor does not preclude initiation of neuraxial analgesia, especially in a nulliparous woman, in whom the second stage of labor may last 2 to 3 hours. However, initiation of lumbar epidural analgesia in the late first stage of labor often results in inadequate sacral analgesia unless large volumes of a concentrated local anesthetic solution are administered. This leads to higher cephalad sensory blockade than necessary and dense motor blockade. Another option is to administer CSE analgesia. The advantages of this technique are that it provides a rapid onset of spinal analgesia with sacral coverage for advanced labor and that it includes the placement of an epidural catheter. Additional local anesthetic can be administered through the epidural catheter if the extent or duration of spinal analgesia is inadequate. One disadvantage is that the correct placement of the epidural catheter in the epidural space cannot be verified until intrathecal analgesia regresses.

A caudal epidural catheter, which facilitates the onset of sacral analgesia, is an option for analgesia late in labor. Caudal analgesia was the first form of neuraxial analgesia

used during labor. However, caudal analgesia is used rarely in modern obstetric anesthesia practice. Sacral analgesia adequate for labor and delivery can be achieved with an injection of 12 to 15 mL of 0.25% bupivacaine, 1.0% to 1.5% lidocaine, or 2% 2-chloroprocaine.

Single-shot spinal anesthesia for vaginal delivery may be indicated in a parturient who does not have epidural anesthesia and who requires perineal anesthesia. A so-called saddle block can be administered to achieve blockade of the sacral spinal segments; a small dose of a hyperbaric local anesthetic solution is adequate for this purpose. A saddle block may be advantageous in the patient with a preterm fetus or a vaginal breech presentation. In these cases, dense perineal relaxation may facilitate an atraumatic vaginal delivery. A saddle block performed with the patient in the sitting position with hyperbaric local anesthetic solution provides excellent anesthesia for an outlet/low forceps delivery. A higher level (T10) of anesthesia often is required for a midforceps delivery.

Clear communication between the obstetrician and anesthesia provider is essential. If the obstetrician is certain that the application of forceps (or vacuum extraction) will result in a successful delivery, a saddle block will likely provide satisfactory anesthesia. However, in some cases, the obstetrician will perform a *trial* of forceps. We alter our technique when giving spinal anesthesia for a trial of forceps. If the trial fails, cesarean delivery must follow. In some cases, we give a dose of local anesthetic appropriate for cesarean delivery. Alternatively, a saddle block can be administered via the CSE technique. If spinal anesthesia is inadequate for the planned procedure, additional local anesthetic can be given through the epidural catheter.

SIDE EFFECTS OF NEURAXIAL ANALGESIA

Hypotension

Neuraxial anesthesia–induced sympathetic blockade leads to peripheral vasodilation and increased venous capacitance. Recent data from women undergoing spinal anesthesia for cesarean delivery suggests that the hypotension that occurs after extensive neuroblockade primarily reflects decreased systemic vascular resistance.[283] Hypotension is often defined as a 20% to 30% decrease in systolic blood pressure (compared with baseline) or a systolic blood pressure less than 100 mm Hg. Modest hypotension rarely has adverse consequences in young, nonpregnant patients. However, placental circulation has limited autoregulation; thus, maintenance of uteroplacental perfusion largely depends on maintenance of maternal blood pressure (see Chapter 3). Uncorrected hypotension results in decreased uteroplacental perfusion. If hypotension is severe and prolonged, hypoxia and acidosis will develop in the fetus. Blood pressure should be monitored frequently (every 2 to 3 minutes) after initiation of analgesia, until stable blood pressure is ascertained.

The incidence of hypotension after initiation of neuraxial analgesia *during labor* is approximately 14%.[27] Kinsella and Black[284] reported that maternal position and the position of the blood pressure cuff markedly influence the measured blood pressure. With laboring patients in the full lateral position, the mean difference in systolic blood pressure between the dependent and upper arm was 10 mm Hg; the mean difference in diastolic pressure was 14 mm Hg. Therefore, the incidence of hypotension may vary with the position of both the patient and the blood pressure cuff.

A meta-analysis of studies comparing low-dose epidural analgesia with CSE analgesia found no difference in the incidence of hypotension between the two techniques.[27]

The prevention of hypotension includes avoidance of aortocaval compression. Preston et al.[285] noted a higher incidence of severe FHR decelerations in women placed in the supine-lateral tilt position than in those in the full lateral position after initiation of epidural analgesia. In contrast, Beilin et al.[286] found no difference in maternal blood pressure and FHR decelerations between the two positions.

Traditionally, intravenous "preload" (also known as "prehydration") with 0.5 to 1.5 L of crystalloid solution has been used to reduce the incidence and severity of hypotension after the initiation of neuraxial labor analgesia. However, several randomized controlled trials have shown that the incidence of hypotension after preload with 0.5 to 1.0 L of fluid is no lower than that after no preload.[34,287] In women undergoing spinal anesthesia for cesarean delivery there is no difference in the incidence of hypotension when crystalloid is administered as a rapid bolus prior to the initiation of neuroblockade (preload) compared with administration concurrently with the initiation of anesthesia (co-load).[37] Data are inconsistent as to whether a fluid bolus decreases the risk for nonreassuring FHR changes associated with the initiation of neuraxial analgesia (see earlier discussion). Many anesthesia providers omit a fluid bolus. In our practice, my colleagues and I usually administer approximately 500 mL of intravenous crystalloid (co-load) at the time of initiation of neuraxial labor analgesia.

The hypotension associated with neuraxial analgesia is usually easily treated. Treatment includes the administration of additional intravenous crystalloid, placement of the mother in the full lateral and Trendelenburg position, and administration of an intravenous vasopressor. Traditionally, ephedrine 5 to 10 mg has been administered; however, studies in women undergoing spinal anesthesia for elective cesarean delivery have shown that phenylephrine is equally efficacious in restoring blood pressure and is associated with higher umbilical arterial blood pH measurements at birth.[288] No differences in neonatal outcome have been noted. Because there is no evidence that the choice of vasopressor influences maternal or neonatal outcome, the use of either drug is acceptable. The FHR should be monitored continuously, and treatment should be more aggressive if nonreassuring FHR patterns are noted or if the mother is symptomatic (e.g., presence of presyncope or nausea). Ephedrine crosses the placenta and may increase both FHR and FHR variability (e.g., saltatory FHR pattern).[289,290]

Data are conflicting as to whether there is a dose-response relationship between hypotension and intrathecal local anesthetics when these drugs are administered

in low doses for labor analgesia. Palmer et al.[291] found no difference in blood pressure in women randomly assigned to receive intrathecal fentanyl combined with either 1.25 or 2.5 mg of bupivacaine. In contrast, Lee et al.[292] noted a greater decrease in blood pressure at 10 minutes in women who received bupivacaine 2.5 mg than in women who received 1.25 mg. Because 1.25 mg is less than the ED_{95} for bupivacaine (when combined with fentanyl)[200] and there is no apparent advantage to combining bupivacaine 1.25 mg with fentanyl over using fentanyl alone,[293] there is little reason to manipulate the dose of intrathecal bupivacaine with the goal of decreasing the incidence and severity of hypotension when low doses are used for labor analgesia.

Pruritus

Pruritus is the most common side effect of epidural or intrathecal opioid administration.[294] Intrathecal opioid administration is associated with a higher incidence and severity of pruritus than epidural opioid administration (41.4% versus 1.3% in one study[295]).[27] The incidence of pruritus after intrathecal opioid administration is close to 100% in some studies, although the need for treatment is much lower.[168] The incidence and severity of pruritus are dose dependent for both epidural[99] and spinal[168,177] opioid administration. The co-administration of local anesthetic decreases the incidence of pruritus,[199] whereas the co-administration of epinephrine may worsen pruritus.[296]

The cause of the neuraxial opioid-induced pruritus is poorly understood, but it appears to be unrelated to histamine release. The pruritus appears to be mediated through central μ-opioid receptors, given that μ-opioid receptor antagonists relieve itching.[297,298] The pruritus may be caused by a perturbation of sensory input that results from rostral spread of the opioid within the CSF to the level of the trigeminal nucleus in the medullary dorsal horn.[297] A disruption of sensory modulation is consistent with the observation that a similar pattern of pruritus is seen in medical conditions in which sensory modulation is disturbed (e.g., diabetic neuropathy, multiple sclerosis).[299]

Few studies have addressed the *treatment* of established pruritus (see Chapter 28). The most effective treatment is a centrally acting μ-opioid antagonist (e.g., naloxone or naltrexone) or a partial agonist-antagonist such as nalbuphine (Table 23-7). However, the use of these agents in a bolus or continuous infusion may reverse the analgesia. Antihistamines (e.g., diphenhydramine) are often prescribed but are usually ineffective because the mechanism of pruritus is not related to histamine release. Any observed effect of diphenhydramine is probably related to its sedating effects. Although propofol 10 to 20 mg was found effective for the treatment of pruritus in several studies in nonobstetric patients, its efficacy was no different than placebo in an obstetric study.[300] Charuluxananan et al.[301] found that the 5-HT_3 receptor antagonist ondansetron was more efficacious than placebo for the treatment of established pruritus; however, a second study that compared ondansetron 4 mg to pentazocine (a κ-opioid and partial μ-opioid receptor agonist) 15 mg found that pentazocine was superior to ondansetron.[302] Another group of investigators found that ondansetron was no more effective than diphenhydramine.[303]

TABLE 23-7 Treatment of Neuraxial Opioid-Induced Pruritus

Drug	Dose
Naloxone	40-80 μg intravenous bolus 1-2 μg/kg/h continuous intravenous infusion
Nalbuphine	2.5-5 mg intravenous bolus
Naltrexone	6 mg orally

A number of drugs have been investigated for *prophylaxis* against neuraxial opioid–induced pruritus, primarily coincident with neuraxial morphine administration. In a meta-analysis of nine studies, the incidence of pruritus was not reduced with prophylactic 5-HT_3 receptor antagonists compared with placebo, although the incidence of severe pruritus requiring treatment was lower.[304] Similarly, prophylactic dexamethasone was also not associated with a lower incidence of pruritus after intrathecal morphine administration.[305]

We do not routinely administer prophylaxis for the pruritus associated with neuraxial administration of opioids for labor analgesia. The pruritus is typically self-limiting; the severity of pruritus usually diminishes markedly in the first hour after opioid administration, and most women do not require treatment. For moderate to severe pruritus that requires treatment, we usually administer **nalbuphine** 2.5 mg and repeat the dose in 10 to 15 minutes if no improvement is noted. The advantage of nalbuphine is that it is less likely to reverse the intrathecal or epidural opioid analgesia.[306]

Nausea and Vomiting

Nausea and vomiting occur frequently during labor. It is difficult to determine the incidence of nausea and vomiting directly related to epidural and intrathecal opioid administration. Nausea and vomiting may also be secondary to neuraxial analgesia–induced hypotension. Maternal blood pressure should be measured when the patient complains of nausea in the presence of neuroblockade. Other causes of nausea and vomiting during labor are pregnancy itself, pain, opioid-induced delay of gastric emptying (see later discussion), and systemic opioids, which are sometimes administered before intrathecal or epidural opioids. In one study, the incidences of nausea (7% versus 44%) and vomiting (2% versus 17%) were significantly lower in women randomly assigned to receive intrathecal fentanyl than in those assigned to receive systemic hydromorphone analgesia in early labor.[21]

The etiology of neuraxial opioid-associated nausea is unclear, but it may be caused by the modulation of afferent input at the area postrema (i.e., the chemoreceptor trigger zone) or at the nucleus of the tractus solitarius, which is a key relay station in the visceral sensory network.[307] Of interest, nausea is less common after epidural or intrathecal opioid administration during labor than after the administration of the same drugs for post–cesarean delivery analgesia. Norris et al.[295] noted that women who received epidural or intrathecal opioid

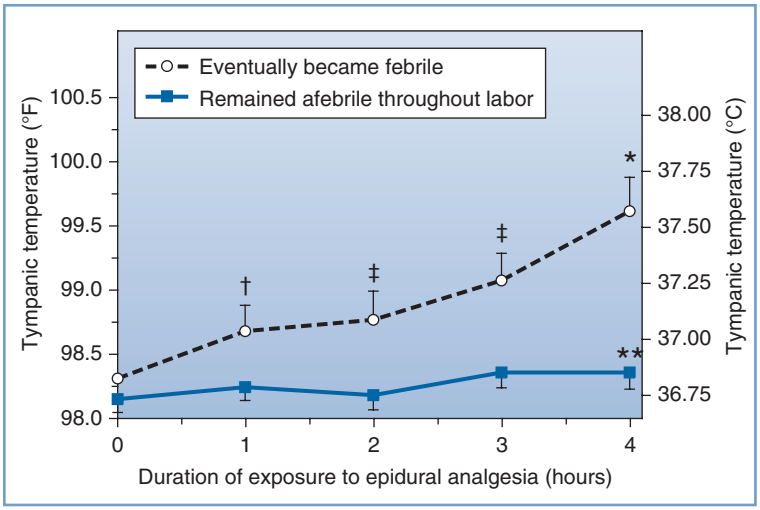


FIGURE 23-7 ■ Maternal tympanic temperature in the 4 hours immediately after initiation of epidural analgesia, stratified by ultimate intrapartum fever status (febrile ≥ 38.0° C or afebrile < 38° C). *P < .001; †P < .05; ‡P < .01 (repeated measures analysis, febrile versus afebrile); **P = .26 (repeated measures analysis, afebrile group temperature change over time). (Modified from Goetzl L, Rivers J, Zighelboim I, et al. Intrapartum epidural analgesia and maternal temperature regulation. Obstet Gynecol 2007; 109:687-90.)

analgesia during labor had an incidence of nausea of only 1.0% or 2.4%, respectively.

Although the incidence of nausea is low, treatment should be available. No studies, however, have specifically addressed the *treatment* of neuraxial analgesia-associated nausea and vomiting during labor. **Metoclopramide, ondansetron,** and **droperidol** have been used *prophylactically* in women who received neuraxial morphine for analgesia after cesarean delivery or nonobstetric surgery (see Chapter 28). Used in low doses, these agents have few significant side effects. When administered intravenously, metoclopramide should be administered slowly over 1 to 2 minutes to minimize feelings of restlessness and anxiety that may accompany rapid intravenous administration.[308] A partial explanation for metoclopramide's efficacy may be its action in promoting gastric emptying. The package insert for droperidol contains a "black box" warning because of concern that the administration of this agent may increase the risk for severe cardiac dysrhythmias (secondary to prolongation of the QT interval and *torsades de pointes*). The warning suggests that patients be monitored for dysrhythmias for several hours after droperidol administration. Because maternal electrocardiographic monitoring is rarely undertaken in healthy parturients, the drug is now rarely used in the United States by obstetric anesthesia providers.

Fever

Both observational and randomized controlled trials have consistently noted a gradual rise in core temperature over several hours in laboring women receiving epidural analgesia that was not observed in women receiving no analgesia, inhaled nitrous oxide, or parenteral opioids.[309] The mean increase in core temperature is typically small (< 1.0° C); however, women with epidural analgesia are more likely to have clinical fever (usually defined as core temperature ≥ 38° C) than those without epidural analgesia (risk ratio, 3.34; 95% CI, 2.63 to 4.23).[3] In a retrospective study, Herbst et al.[310] identified the use of epidural analgesia as a risk factor for intrapartum fever, along with prolonged labor and a prolonged interval between rupture of membranes and delivery. The incidence of clinical fever ranges from 20% to 30% in women randomized to receive epidural analgesia compared with 5% to 7% in women in the control groups.[309]

Newer evidence suggests that the slow increase in mean temperature observed in women with epidural analgesia may be an averaging artifact.[311] In a prospective observational study of women with epidural analgesia, Goetzl et al.[311] observed the incidence of fever was 22.2%. The mean temperature increase over 8 hours was 0.72° C, similar to that observed in earlier studies. However, the investigators noted that temperature increased in only a subset of women; the remaining cohort had no temperature increase (Figure 23-7). In the small subset of women who eventually developed clinical fever, core temperature began to rise within an hour of initiation of epidural analgesia. The researchers concluded that most women do not become febrile after epidural analgesia, and therefore it is unlikely that a perturbation in thermoregulation induced by epidural analgesia is the cause of epidural analgesia–associated fever.

The mechanism of temperature elevation in some women who receive epidural labor analgesia is incompletely understood but likely reflects an inflammatory process. Several lines of evidence support this mechanism.[309] Risk factors for intrapartum fever are similar to factors that are associated with the request for epidural analgesia, including nulliparity, prolonged rupture of membranes, and prolonged labor. In an observational study in women who self-selected the type of analgesia, the histologic diagnosis of placental inflammation was more common in women with epidural analgesia.[312] However, the incidence of maternal fever was not different between women with and without epidural analgesia in the absence of placental inflammation. Additionally, Goetz et al.[313] noted higher baseline maternal serum levels of interleukin-6 (IL-6), a marker of inflammation, in laboring women who eventually developed fever; final IL-6 levels were directly related to the duration of epidural analgesia.[313] In a subsequent study, women with epidural analgesia randomized to receive maternal methylprednisolone (100 mg) had a lower rate of fever than those who received placebo, again suggesting that an inflammatory mechanism is involved.[314]

The significance of the temperature changes during labor is unclear. Maternal fever is associated with mode of delivery; the rate of instrumental and cesarean delivery is higher in women with intrapartum fever.[315] Epidural analgesia during labor is associated with more neonatal sepsis evaluations but not with a higher incidence of neonatal sepsis.[316,317] This link likely exists because the diagnosis of intrapartum chorioamnionitis is based on the presence of fever and usually one or two additional criteria (i.e., maternal leukocytosis, maternal tachycardia, uterine tenderness, foul-smelling amniotic fluid).[318] Because maternal fever from any cause leads to maternal and fetal tachycardia, it may be difficult to differentiate women with actual infection (based on postpartum histologic placental examination) from women with fever associated with epidural analgesia. In the interests of maternal and fetal safety, intrapartum maternal fever typically prompts an intrapartum diagnosis of clinical chorioamnionitis. Revised 2010 guidelines from the U.S. Centers for Disease Control and Prevention stipulate that even well-appearing newborns whose mothers carry the diagnosis of suspected chorioamnionitis should undergo a limited evaluation (complete blood count [CBC] with differential cell count and blood culture) and antibiotic therapy pending the culture results.[319]

Of greater concern is the association between maternal or neonatal fever and serious adverse outcomes (i.e., neonatal seizures and encephalopathy, development of cerebral palsy).[309] Evidence suggests that the mechanism of neonatal brain injury is inflammatory rather than fever per se.[309,320] Whether epidural analgesia plays any role in these outcomes requires further research. However, because of the growing evidence that maternal inflammation and infection, which manifest as fever, can be detrimental to the fetal brain, anesthesia providers should not dismiss this apparent physiologic effect as a mere curiosity. When maternal fever occurs, good clinical practice dictates that efforts be made to lower maternal temperature and identify and treat a presumed maternal infection. (See Chapter 37 for a more complete discussion of this subject.)

Shivering

A number of factors, including hormonal factors, likely influence thermoregulatory response during labor and delivery. Shivering is frequently observed during labor and may occur more commonly after epidural analgesia.[321] Panzer et al.[322] performed an observational study of shivering during labor. Before delivery, 18% of women shivered, and 15% of these episodes were associated with normothermia and vasodilation, suggesting a nonthermoregulatory cause of the shivering. After delivery, shivering was observed in 16% of women, and in 28% of them, it was nonthermoregulatory. There was no difference in the incidence of shivering between women who chose epidural (bupivacaine/fentanyl) analgesia and those who chose systemic meperidine analgesia. The addition of an opioid to the local anesthetic solution may affect the shivering response.[133,323] At least one study has suggested that the epidural administration of epinephrine increases shivering[323]; the etiology of this response is unknown.

Urinary Retention

Urinary retention is a troublesome side effect of neuraxial anesthesia/analgesia. The bladder and urethral sphincters receive sympathetic innervation from the low thoracic/high lumbar sympathetic fibers and parasympathetic innervation from sacral fibers. Neuraxial local anesthetics cause urinary retention through blockade of sacral nerve roots. Efferent and afferent nerve traffic via the S2, S3, and S4 nerve roots controls the detrusor muscle (responsible for urine storage and micturition) and internal and external sphincter function. Intrathecal opioids cause dose-dependent suppression of detrusor muscle contractility and decreased urge sensation via inhibition of sacral parasympathetic nervous system outflow.[307,324] The onset of urinary retention appears to parallel the onset of analgesia.

It is difficult to determine the magnitude of this problem during labor, because parturients often require catheterization for other reasons. Postpartum bladder dysfunction was observed in 14% of women who had a normal spontaneous vaginal delivery and in 38% of women who underwent instrumental vaginal delivery, all without epidural analgesia.[325]

Several observational studies suggest that there is a higher risk for intrapartum and postpartum urinary retention in women who receive epidural labor analgesia than in those who receive nonepidural or no analgesia.[326,327] Similarly, a meta-analysis of three small randomized controlled trials comparing neuraxial with systemic opioid analgesia, in which urinary retention was reported as a secondary outcome, also identified this association.[3] Whether this higher risk reflects a cause-and-effect relationship or patient selection bias is not clear. Wilson et al.[328] found that women randomized to receive neuraxial labor analgesia with low-concentration bupivacaine with opioid more often retained the ability to void spontaneously than women who received epidural analgesia with 0.25% bupivacaine (approximately 31% versus 11%), which suggests a dose-response relationship.

Any difference in bladder function appears to be short-lived; differences between groups in one study had resolved by postpartum day 1.[326] In two studies, patients were randomly assigned to receive epidural analgesia with or without an opioid; there was no difference between groups in the incidence of intrapartum[329] or postpartum[327] urinary retention.

Parturients should be regularly observed during labor for evidence of bladder distention, especially if they complain of suprapubic pain during contractions. The differential diagnosis of breakthrough pain during neuraxial labor analgesia should include bladder distention. Personal observation suggests that many women can void in the presence of low-dose neuroblockade if placed on a bedpan or escorted to the toilet, even if they do not perceive a full bladder. Inability to void and bladder distention should prompt catheterization to empty the bladder.

Recrudescence of Herpes Simplex Virus

The seroprevalence of herpes simplex virus (HSV) among pregnant women was 72% in the period 1999 to 2002.[330]

HSV type 1 (HSV-1) is typically found in the trigeminal ganglia and causes orofacial lesions, whereas HSV-2 is more commonly found in the lumbosacral ganglia. However, either of these viruses can infect any region of the body.

The common cold sore or fever blister is a manifestation of the reactivation of latent infection. Reactivation can occur after exposure to ultraviolet light, fever, immunosuppression, or trauma. Prospective randomized studies have demonstrated a higher incidence of postpartum *oral* HSV reactivation in women randomly assigned to receive neuraxial (epidural,[331,332] intrathecal[333]) morphine than among women assigned to receive systemic morphine for post–cesarean delivery analgesia. Case reports have associated intraspinal administration of meperidine and fentanyl with the subsequent recurrence of HSV infection.[334,335]

To our knowledge, postcesarean reactivation of HSV infection after neuraxial opioid administration has not resulted in clinically significant maternal or neonatal complications.[336] In addition, we are unaware of any study that has investigated whether epidural or intrathecal opioid administration during labor increases the incidence of recurrent oral HSV infection after vaginal delivery. Therefore, we do not withhold neuraxial opioids during labor in women with a history of oral herpes.

Delayed Gastric Emptying

Labor may result in delayed gastric emptying, which may be exacerbated by opioid administration (see Chapter 29).[337,338] Intravenous or intramuscular opioid administration results in delayed gastric emptying in laboring women. Studies suggest that epidural fentanyl combined with bupivacaine and administered as part of a continuous epidural infusion does not result in delayed gastric emptying compared with infusion of bupivacaine alone[339,340]; however, delayed gastric emptying may occur with epidural fentanyl administered as a bolus (50 to 100 μg)[341,342] or with a *prolonged* infusion.[339] In another study, intrathecal fentanyl 25 μg resulted in delayed gastric emptying compared with epidural fentanyl 50 μg plus bupivacaine or bupivacaine alone.[343] Delayed gastric emptying may predispose a patient to nausea and vomiting. In addition, it may result in a greater volume of gastric contents, which—in theory—might be problematic in patients who require induction of general anesthesia for emergency cesarean delivery.

COMPLICATIONS OF NEURAXIAL ANALGESIA

Inadequate Analgesia

The reported failure rate for neuraxial analgesia varies according to the definition of "failure."[30,344,345] In survey studies the rate of epidural catheter replacement has ranged from 5% to 13%.[30,344,345] Successful location of the epidural space is not always possible, and satisfactory analgesia does not always occur, even when the epidural space has been identified correctly. Factors such as patient age and weight, the specific technique, the type of epidural catheter, and the skill of the anesthesia provider are associated with the rate of failure of neuraxial analgesia.[30,345] Failure to provide adequate analgesia not only results in a dissatisfying experience for the patient but also may lead to litigation.[346] The risk for failed anesthesia and the potential need to place a second epidural catheter should be discussed with the patient during the preanesthetic evaluation, before placement of the first epidural catheter.

Pan et al.[30] used quality assurance data to retrospectively assess the failure rate among more than 12,000 neuraxial procedures performed for labor analgesia over a 3-year period (Table 23-8). The overall failure rate of 12% included procedures that resulted in no or

TABLE 23-8 **Characteristics of Neuraxial Analgesia Failures***

Characteristic	*Rate According to Type of Analgesia (%)*			*P* Value
	EPIDURAL (n = 7849)	COMBINED SPINAL-EPIDURAL (n = 4741)	TOTAL (n = 12,590)	
Overall Failure Rate	14	10	12	< .001
Initial Catheter Failure				
Intravenous catheter	7	5	6	< .001
Recognized dural puncture†	1.4	0.8	1.2	< .002
Other Failure				
No cerebrospinal fluid or spinal analgesia	NA	2.4	NA	
Inadequate analgesia with epidural catheter	8.4	4.2	6.8	< .001
Catheter replacement for inadequate analgesia‡	7.1	3.2	5.6	< .001
Multiple replacements of epidural catheter	1.9	0.7	1.5	< .001

NA, not applicable.
*Retrospective audit of all neuraxial analgesic procedures for labor analgesia at a single teaching institution over a 3-year period. Most of the procedures were performed by residents.
†Dural puncture with epidural needle or catheter.
‡Epidural catheter initially functional but was replaced during the course of labor.
Modified from Pan PH, Bogard TD, Owen MD. Incidence and characteristics of failures in obstetric neuraxial analgesia and anesthesia: a retrospective analysis of 19,259 deliveries. Int J Obstet Anesth 2004; 13:227-33.

inadequate analgesia, unintentional dural puncture with an epidural needle or catheter, intravenous cannulation with the epidural catheter, or replacement of the catheter for any reason. After initial adequate analgesia, 6.8% of the catheters were replaced, although eventually 98.8% of women received adequate pain relief. The rate of failed analgesia was significantly lower after CSE than after epidural analgesia (10% versus 14%, respectively; $P < .001$).

Typically, failed analgesia after injection of intrathecal or epidural anesthetics results in no neuroblockade, unilateral blockade or missed segments, or inadequate density of neuroblockade. Patient complaints of pain should prompt timely evaluation and treatment (Box 23-7). The progress of labor should be assessed, and the patient should be queried as to the nature of the pain. Typically, pain becomes more intense as labor progresses. An epidural block that was adequate at 4-cm cervical dilation may not be adequate at 8-cm cervical dilation. Expectations and treatment may be different for women in latent versus active or second-stage labor. The bladder should be checked and emptied if distended. The position of the epidural catheter at the skin should be assessed to exclude the possibility of catheter migration out of the epidural space. Inadequate analgesia may also result from migration of the epidural catheter into a vein or movement of the catheter outside of the epidural space. Before giving a bolus dose of local anesthetic, the anesthesia provider should give a test dose to exclude intravenous migration of the catheter.

BOX 23-7 Assessment and Management of Inadequate Neuraxial Analgesia

- Assess progress of labor:
  - Rule out other causes of pain (distended bladder, ruptured uterus).
- Perform an honest evaluation of the anesthetic:
  - Is the catheter really in the epidural space?
  - If in doubt, replace the catheter.
- If the catheter is in the epidural space, but the extent of neuroblockade is inadequate (does not extend from T10 to S4, as is required for late labor):
  - Inject a dilute solution of local anesthetic (5 to 15 mL), with or without an opioid.
  - Alter maintenance technique (e.g., increase volume, decrease concentration).
  - If this maneuver is unsuccessful, replace the catheter.
- If catheter is in the epidural space, but the block is asymmetric:
  - Inject a dilute solution of local anesthetic (5 to 15 mL), with or without an opioid.
  - Alter maintenance technique (e.g., increase volume, decrease concentration).
  - Place the less-blocked side in the dependent position.
  - If this maneuver is unsuccessful, replace the catheter.
- If the catheter is in the epidural space, but the patient has breakthrough pain despite adequate extent of neuroblockade:
  - Inject a more concentrated solution of local anesthetic, with or without an opioid.
  - Alter maintenance technique (e.g., increase concentration of local anesthetic).

The extent of neuroblockade should be assessed with a cold or sharp stimulus that starts over the lateral thighs (the dermatomal level at which the tip of the epidural catheter is sited) and moves both *cephalad* and *caudad* on both sides. Inexperienced anesthesia providers often fail to check for the presence of sacral blockade. In the case of no sensory blockade, the epidural catheter should be replaced. If the extent of neuroblockade is inadequate (in either the cephalad or caudad direction), or if there is unilateral blockade or missed segments, the injection of a large volume (10 to 15 mL) of a dilute local anesthetic solution (e.g., 0.0625% to 0.125% bupivacaine) may result in satisfactory analgesia. An advantage of using a more dilute solution of local anesthetic is the ability to increase the administered volume to ensure adequate spread of analgesia.

Some women appear to have adequate *extent* of sensory blockade but still complain of pain. These women may require more dense analgesia; a larger dose of local anesthetic (10- to 15-mL bolus of 0.125% bupivacaine or a 5- to 10-mL bolus of 0.25% bupivacaine) often successfully reestablishes analgesia. Alternatively, a lipid-soluble opioid (e.g., fentanyl 50 μg) may be added to the solution. The opioid is especially helpful if the parturient is experiencing back pain because the fetus is in the occiput posterior position. In some European practices, epidural clonidine (75 μg) is used to treat breakthrough pain that occurs during/after epidural administration of the standard local anesthetic-opioid solution.

Some anesthesia providers advocate pulling the epidural catheter 1 to 2 cm out of the epidural space before administering the bolus injection. Beilin et al.[347] investigated this practice by randomly assigning women with incomplete analgesia to one of two treatments: (1) immediate injection of 0.25% bupivacaine 5 mL or (2) withdrawal of the (multi-orifice) epidural catheter 1 cm followed by injection of the same dose of bupivacaine. There was no difference in the ability to rescue analgesia between the two treatments (74% versus 77%, respectively).

Although available data are inconsistent, maternal position has little effect on the development of an asymmetric block after a *bolus* dose of anesthetic solution into the epidural space.[348,349] Husemeyer and White[348] administered 10 mL of epidural 1.5% lidocaine to pregnant women who were in the lateral position; they observed greater spread (two to three spinal segments) of anesthesia on the dependent side. In contrast, others have observed that posture has little influence on the spread of local anesthetic within the epidural space.[281,350] It is likely that the position of the epidural catheter in relation to other epidural space structures (e.g., connective tissue, fatty tissue, blood vessels) affects the spread and quality of analgesia to a greater extent than maternal position. Anatomic barriers (e.g., a longitudinal connective tissue band between the dura and ligamentum flavum) or placement of the catheter tip in the anterior epidural space or paravertebral space may explain some cases of single nerve root, unilateral, or asymmetric blockade.[351-354]

The response to the bolus dose should be assessed in a timely fashion, and the epidural catheter should be

replaced (with the patient's consent) if satisfactory analgesia is not obtained.

Unintentional Dural Puncture

In a meta-analysis of 13 studies that involved more than 300,000 obstetric patients, Choi et al.[355] determined that the rate of unintentional dural puncture with an epidural needle or catheter was 1.5% (95% CI, 1.5% to 1.5%) (see Chapter 31). Dural puncture may be detected at the time of insertion of the epidural needle or after placement of the catheter. If dural puncture is detected with the epidural needle, the anesthesia provider has two primary options. He or she may elect to remove the needle and place an epidural catheter at another interspace; if CSE analgesia was planned, the intrathecal dose may be injected through the epidural needle before it is removed and re-sited at a different interspace. Alternatively, the anesthesia provider may place a catheter in the subarachnoid space and administer continuous spinal analgesia for labor and delivery. This latter technique is particularly advantageous for patients at high risk for repeat dural puncture on a second attempt or in cases in which it may be difficult to enter either the epidural or subarachnoid space successfully at an alternative interspace (e.g., in obese women or in patients with abnormal anatomy of the lumbar spine). It is very important to append a label that clearly identifies the catheter as a spinal catheter to decrease the risk for injecting an epidural dose of local anesthetic into the subarachnoid space. The parturient and all providers on the labor and delivery unit, including nurses, midwives, and other anesthesia providers, must be made aware of the intrathecal catheter, and this information must be communicated during any hand-off of care to another provider.

Re-siting the epidural catheter in a different interspace eliminates the problem of mistaking an intrathecal catheter for an epidural catheter. However, local anesthetic or opioid injected through the epidural catheter may pass through the dural puncture site and into the subarachnoid space, resulting in unexpectedly high neuroblockade.[356] This complication is more likely to occur with the bolus injection of local anesthetic than with an epidural infusion of local anesthetic.

If dural puncture is not recognized until CSF is aspirated from the catheter, or if administration of the test dose results in spinal anesthesia, the anesthesia provider has the following two options: (1) replace the epidural catheter at an alternative interspace or (2) provide continuous spinal analgesia through the existing catheter.

Respiratory Depression

The administration of opioids by any route entails risk for respiratory depression. Factors that affect the risk for respiratory depression after neuraxial opioid administration include the choice and dose of drug and its interaction with systemically administered opioids and other central nervous system depressants (see Chapter 13). The most important factor affecting the onset of respiratory depression is the lipid solubility of the drug.[307] In general, if respiratory depression is going to occur, it will do so within 2 hours of the injection of a lipid-soluble opioid such as fentanyl or sufentanil. When a lipid-soluble opioid gains access to the CSF, it is quickly absorbed by lipophilic body tissues. Subsequent clearance and elimination are similar to those associated with intravenous injection of the same drug. Thus, with spinal or epidural injection of a lipid-soluble opioid, the "time window" for respiratory depression is short. Conversely, with a hydrophilic drug such as morphine, the onset of respiratory depression is delayed. Once a hydrophilic drug such as morphine enters the CSF, it tends to stay in the CSF. Rostral migration and absorption into the respiratory centers occur over several hours, so respiratory depression may not occur until 6 to 12 hours after injection of the drug (see Figure 13-13).

The dose of opioid is a major determinant of the risk for respiratory depression.[177] Herman et al.[177] observed an increase in end-tidal CO_2 concentration with intrathecal fentanyl doses of 15 μg or higher. The time of maximum end-tidal CO_2 was approximately 30 minutes after the intrathecal injection. A risk factor for respiratory depression is previous parenteral opioid administration. Several reports have implicated prior intravenous opioid administration as a contributing factor to the respiratory arrest that occurred after intrathecal sufentanil 10 μg administration in laboring women.[357,358] (This dose is higher than the currently recommended intrathecal dose range.) For this reason, we refrain from administering a bolus dose of epidural or spinal opioid to women who have recently received systemic opioid analgesia.

Intravascular Injection of Local Anesthetic

The incidence of fatal local anesthetic systemic toxicity (LAST) appears to have declined in the past quarter century.[359] In a prospective audit from the United Kingdom of more than 145,000 obstetric epidural procedures, the incidence of intravascular injection was 1 in 5000 (Table 23-9). Bupivacaine 0.75% is no longer used

TABLE 23-9 **Incidence of Unintentional Intravascular, Intrathecal, and Subdural Injections during Attempted Epidural Labor Analgesia***

Event	Incidence	Rate (%)†
Intravascular injection	1:5000	0.020 (0.014-0.029)
Intrathecal injection	1:2900	0.035 (0.027-0.046)
Subdural injection	1:4200	0.025 (0.017-0.033)
High/total spinal anesthesia	1:16,200	0.006 (0.003-0.012)

*Prospective data collection of 145,550 epidural procedures for obstetric patients in 14 maternity units in the South West Thames Region (United Kingdom) over a 17-year period.
†*95% confidence intervals shown in parentheses.*
Modified from Jenkins JG. Some immediate serious complications of obstetric analgesia and anaesthesia: a prospective study of 145,550 epidurals. Int J Obstet Anesth 2005; 14:37-42.

for epidural anesthesia in obstetric patients. In the United States, lidocaine or 2-chloroprocaine is most often used when a high-concentration local anesthetic is required for operative epidural anesthesia, and low concentrations of local anesthetic are now routinely used for labor analgesia. Nonetheless, local anesthetic systemic toxicity remains a serious potential complication during the administration of epidural anesthesia in obstetric patients.

Intravenous injection of a large dose of local anesthetic causes central nervous system symptoms (e.g., restlessness, dizziness, tinnitus, perioral paresthesia, difficulty speaking, seizures, loss of consciousness) (see Chapter 13). Cardiovascular effects may progress from increased blood pressure (as a result of sympathetic stimulation) to bradycardia, depressed ventricular function, and ventricular tachycardia and fibrillation. Bupivacaine cardiotoxicity may be fatal in pregnant women.[360]

Steps for the management of the unintentional intravascular injection of local anesthetic are listed in Box 23-8. They include treatment of convulsions, supporting oxygenation and ventilation, and initiating advanced cardiac life support, if indicated. Lidocaine should not be administered for the treatment of life-threatening ventricular arrhythmias. Early delivery of the infant should be considered, because it may improve the likelihood of successful resuscitation.

In its 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,[361] the American Heart Association recommended that providers consider the administration of lipid emulsion in cases of suspected LAST. Both the American Society of Regional Anesthesia and Pain Medicine[362] and the Association of Anaesthetists of Great Britain and Ireland[363] have incorporated the administration of lipid emulsion into their guidelines for managing LAST. At least one case report describes the successful resuscitation of a parturient who developed LAST after the epidural injection of bupivacaine using lipid emulsion.[364]

BOX 23-8 Management of Unintentional Intravenous Injection of Local Anesthetic

- Call for help.
- Position patient with left uterine displacement.
- Prepare for emergency delivery. Consider delivery of the infant if mother is not resuscitated within several minutes, because this may facilitate successful resuscitation of the mother.
- Administer 100% oxygen to maintain maternal oxygenation.
- Use positive-pressure ventilation if necessary. Tracheal intubation will facilitate support of ventilation and help protect the airway, but do not delay administration of oxygen to intubate the trachea.
- Stop the seizure with a benzodiazepine. Be aware that hypoxemia and acidosis develop rapidly during a seizure.
- Alert the nearest facility capable of cardiopulmonary bypass.
- Monitor maternal vital signs and fetal heart rate.
- Support maternal blood pressure with fluids and vasopressors.
- Initiate advanced cardiac life support if necessary, including modifications for pregnancy (see Chapter 55).
- Avoid vasopressin, calcium entry-blocking agents, beta-adrenergic blockers, and local anesthetics.*
- Administer individual epinephrine doses at less than 1 μg/kg.*
- Administer 20% intravenous lipid emulsion.*
  - Bolus dose: 1.5 mL/kg over 1 min (approximately 100 mL)
  - Continuous infusion: 0.25 mL/kg/min for at least 10 min after attaining circulatory stability
  - Repeat bolus dose once or twice for persistent cardiovascular collapse.
  - Double the infusion rate if blood pressure remains low.
  - Recommended maximum dose: 10 mL/kg over 30 min

*From Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine Checklist for Managing Local Anesthetic Toxicity: 2012 Version. Reg Anesth Pain Med 2012; 37:16-8.

High Neuroblockade and Total Spinal Anesthesia

An unexpectedly high level of anesthesia may result in one of several situations. High (or total) spinal blockade may occur after the unintentional and unrecognized injection of local anesthetic (via a needle or catheter) into either the subarachnoid or subdural space during the planned initiation of epidural analgesia/anesthesia. Alternatively, the epidural catheter may migrate into the subarachnoid or subdural space during the course of labor and delivery. Finally, high spinal blockade may result from an overdose of local anesthetic in the epidural space. Crawford[356] reported 6 cases of high or total spinal anesthesia in a series of nearly 27,000 cases of lumbar epidural anesthesia administered during labor (an incidence of approximately 1 in 4500). Paech et al.[344] reported 8 cases of unexpectedly high neuroblockade in a series of 10,995 epidural blocks in obstetric patients (an incidence of approximately 1 in 1400). Two patients required tracheal intubation and mechanical ventilation. Jenkins[365] reported an incidence of 1 in 16,200 procedures (see Table 23-9).

Aspiration alone, particularly through a single-orifice catheter, is a not completely reliable method of excluding subarachnoid placement of the catheter. Administration of an appropriate test dose and careful assessment of the patient's response to the test dose should minimize the chance of unintentional injection of a large dose of local anesthetic into the subarachnoid space.

High or total spinal anesthesia results in agitation, profound hypotension, dyspnea, the inability to speak, and loss of consciousness. Loss of consciousness usually results from hypoperfusion of the brain and brainstem, not from brain anesthesia. Evidence of spinal anesthesia may be apparent shortly after intrathecal injection of a local anesthetic, but the maximal spread may not be evident for several minutes. This delay underscores the need for the anesthesia provider to carefully assess the effects of both the test and therapeutic doses of local anesthetic. If total spinal anesthesia should occur, the

anesthesia provider must be prepared to maintain oxygenation, ventilation, and circulation (Box 23-9). Immediate management consists of avoidance of aortocaval compression, ventilation with 100% oxygen, tracheal intubation, and administration of intravenous fluids and vasopressors to support the blood pressure as needed. The FHR should be monitored continuously.

Extensive neuroblockade may also result from subdural injection of a local anesthetic.[366-368] A subdural injection may be difficult to diagnose because onset is later than that with an intrathecal injection and more closely resembles that associated with epidural neuroblockade.

The subdural space is a potential space between the dura mater and the arachnoid mater. A retrospective review of 2182 lumbar epidural injections for pain management found that clinical signs of subdural catheter placement occurred in approximately 0.82% of patients[366]; the true incidence is not known, but may be as high as 10%.[369] Subdural injection of local anesthetic typically results in unexpectedly high (but patchy) blockade with an onset time that is intermediate between that of spinal anesthesia and epidural anesthesia (i.e., 10 to 20 minutes) (Table 23-10).[369] Cranial spread is more extensive than caudal spread of the local anesthetic, so sacral analgesia typically is absent. The block may involve the cranial nerves. (The subdural space, unlike the epidural space, extends intracranially.) Thus, apnea and unconsciousness can occur during a subdural block. Horner's syndrome has been reported.[367] A subdural block usually results in less intense motor blockade than the blockade that occurs with high or total spinal anesthesia. This difference may reflect the limited spread of the local anesthetic within the subdural space, which helps spare the anterior motor fibers.[368] Subdural block results in less severe hypotension than that with high or total spinal anesthesia, most likely because subdural injection leads to less sympathetic blockade than spinal anesthesia. The unpredictable spread of local anesthetic, the slower onset of maximal spread (in comparison with spinal anesthesia), the patchy nature of the block, and the sacral sparing make it difficult to use a subdural catheter safely during labor and delivery. If it is suspected that a catheter is positioned within the subdural space, it should be replaced with an epidural catheter.

Unexpectedly high neuroblockade may result from the migration of an epidural catheter into the subdural or subarachnoid space.[368] The mechanism by which a soft epidural catheter penetrates the dura or dura-arachnoid is unclear. Disposable epidural needles are sharp, and insertion of the needle into the epidural space may result in an unrecognized nick in the dura, which may create a site for delayed migration of the catheter into the subdural or subarachnoid space. Subdural or subarachnoid injection of local anesthetic also may occur if a multi-orifice catheter is used, and one orifice is located within the epidural space while another is located within the subdural or subarachnoid space. In this situation, the force of injection determines the ultimate destination of the local anesthetic. Thus, each bolus injection of local anesthetic should serve as a test dose. During the continuous infusion of a local anesthetic, a gradual increase in the level of anesthesia and intensity of motor blockade may indicate the intrathecal infusion of the local anesthetic solution.

BOX 23-9 Management of High and Total Spinal Anesthesia

- High spinal anesthesia may occur several minutes after the unintentional intrathecal injection of local anesthetic or as a result of overdose of epidural local anesthetic. Communication with the patient is important. Agitation, dyspnea, difficulty speaking, and profound hypotension may herald the onset of total spinal anesthesia.
- Avoid aortocaval compression.
- Administer 100% oxygen.
- Provide positive-pressure ventilation, preferably through an endotracheal tube.
- Monitor maternal vital signs, electrocardiogram, and fetal heart rate.
- Support maternal circulation with intravenous fluids and vasopressors as needed. Do not hesitate to give epinephrine if needed.
- Maintain verbal communication with the mother, or administer sedative-hypnotic (after treating any hypotension and hypoxemia) because total spinal anesthesia does not signal brain anesthesia. Patients may lose consciousness and stop breathing because of central nervous system hypoperfusion, not brain anesthesia.

Extensive Motor Blockade

Clinically significant motor block may occur after repeated bolus doses[146] or after many hours of a continuous infusion of local anesthetic into the epidural space.[370]

TABLE 23-10 **Clinical Features of Epidural, Subdural, and Spinal Blocks**

	Epidural Block	Subdural Block	Spinal Block
Onset Time	Slow	Intermediate	Rapid
Spread	As expected	Higher than expected; may extend intracranially, but sacral sparing is common	Higher than expected; may extend intracranially, and a sacral block is typically present
Nature of Block	Segmental	Patchy	Dense
Motor Block	Minimal	Minimal	Dense
Hypotension	Less than spinal, and dependent on the extent of the block	Intermediate between spinal and epidural, and dependent on the extent of the block	Likely

The administration of bupivacaine with epinephrine may result in a greater likelihood of motor blockade than the administration of bupivacaine alone.[146,371] Extensive motor blockade is often bothersome for the patient, and it may impair maternal expulsive efforts during the second stage of labor and increase the likelihood of instrumental vaginal delivery (see later discussion). Some obstetricians argue that pelvic floor relaxation prevents rotation of the fetal head and increases the likelihood of an abnormal position of the vertex at delivery.

If intense motor blockade develops during the continuous epidural infusion of local anesthetic, the infusion can be discontinued for a short period (e.g., 30 minutes). Subsequently, the infusion can be restarted at a reduced rate or with a more dilute solution of local anesthetic. Extensive motor blockade does not occur with administration of a very dilute solution of local anesthetic combined with an opioid.

Prolonged Neuroblockade

Rarely, the duration of neuraxial analgesia/anesthesia exceeds the time expected. Most cases of unexpectedly prolonged neuroblockade follow the epidural administration of a high concentration of local anesthetic with epinephrine.[372] Abnormal neurologic findings after the administration of neuraxial anesthesia should prompt the anesthesia provider to look for evidence of peripheral nerve injury or an epidural hematoma (see Chapter 32). Factors that argue against the presence of an epidural hematoma include (1) the absence of back pain, (2) a unilateral block, and (3) regression (rather than progression) of the symptoms. Peripheral nerve injuries typically result in a neurologic deficit in the distribution of a specific peripheral nerve. Neurologic or neurosurgical consultation and immediate imaging studies should be obtained if there is any question about the etiology of prolonged anesthesia. Avoiding the use of a high concentration of local anesthetic should help minimize the incidence of prolonged neuroblockade during and after labor and vaginal delivery.

Sensory Changes

In one of the early studies of intrathecal opioid administration during labor, Cohen et al.[294] observed sensory changes in women who received intrathecal sufentanil. Subsequent studies have demonstrated that these sensory changes do not result from a local anesthetic effect of sufentanil. Sensory changes do not predict the quality or duration of analgesia or the extent of hemodynamic change.[373] Further, intrathecal sufentanil does not cause a sympathectomy.[374] Wang et al.[375] have provided the best explanation for these sensory changes. They showed that intrathecal opioids block the afferent information from A-delta and C fibers to the spinal cord but that efferent nerve impulses are unaffected. These sensory changes can be clinically significant, especially when they extend to the cervical dermatomes. In such cases, patients may feel that they cannot breathe or swallow, a sensation that can be quite distressing. Fortunately, neither intrathecal sufentanil nor fentanyl affects the efferent limb of the nervous system and so does not impair motor function. Affected patients should be reassured that respiratory efforts are not compromised and that these symptoms will subside in 30 to 60 minutes.[376,377]

In addition to sensory changes, case reports have described mental status changes, aphasia, and automatisms after the intrathecal injection of fentanyl[378] and sufentanil.[379] These symptoms seem to be related to an opioid effect. In one case, the symptoms were partially reversed by naloxone.[378]

Back Pain

Approximately 50% of women complain of back pain during pregnancy and the puerperium.[380,381] The most significant risk factors for postpartum back pain are antepartum back pain and inability to reduce weight to prepregnancy levels.[380,382,383] Early retrospective studies identified an association between epidural anesthesia and an increased risk for postpartum back pain.[384,385] However, retrospective studies suffer not only from patient recall bias (i.e., patients with a problem are much more likely to complete and return the questionnaire) but also from selection bias in the epidural and nonepidural groups. Patients who select epidural analgesia for labor may have obstetric, orthopedic, social, or other unidentified factors that predispose them to postpartum back pain.

In an attempt to assess anesthetic factors that might contribute to postpartum backache (e.g., motor blockade), Russell et al.[383] randomly assigned laboring women requesting epidural analgesia to receive either bupivacaine alone or bupivacaine plus an opioid. Despite the expected differences in motor blockade, the incidence of backache did not differ between the two anesthetic groups (bupivacaine alone, 39%; bupivacaine plus an opioid, 30%). In addition, the incidence of backache in both epidural groups was similar to that found in a nonrandomized control group of women who labored without epidural analgesia (31%).

Prospective reports have not shown a significant relationship between the use of epidural analgesia and long-term backache. Breen et al.[382] observed no difference in the incidence of postpartum backache among women who delivered vaginally with or without epidural analgesia. A prospective Canadian study assessed the relationship between postpartum backache and patient-selected intrapartum analgesia.[386] The rate of low back pain was greater in the epidural group (53%) than in the nonepidural group (43%) on the first postpartum day, but the rates were similar on postpartum day 7 and at 6 weeks and 1 year.[386] These investigators suggested that the higher incidence of backache immediately after delivery may have resulted from tissue trauma during epidural needle placement. Finally, Loughnan et al.[387] enrolled 310 women in a randomized controlled trial that compared epidural bupivacaine with systemic meperidine analgesia. The primary outcome was back pain 6 months after delivery. There was no difference between the two groups in the incidence of backache (epidural 48%, meperidine 50%). Similarly, another randomized controlled trial of epidural versus nonepidural analgesia found

no difference in the incidence of backache at 3 and 12 months[388] and several years[389] after delivery.

In summary, prospective studies have consistently shown that no causal relationship exists between epidural analgesia and the development of long-term postpartum backache. Short-term backache (several days) may be related to local tissue trauma at the site of skin puncture.

Pelvic Floor Injury

Few studies have evaluated the possible effects of epidural analgesia on postpartum pelvic floor function. In a case-control study, Christianson et al.[390] did not identify epidural analgesia as a risk factor for third- or fourth-degree perineal lacerations. Similarly, Sartore et al.[391] observed no significant difference in the incidence of stress urinary incontinence, anal incontinence, or vaginal prolapse 3 months after vaginal delivery between those women who did and those who did not receive epidural analgesia. In a small randomized trial that compared epidural with systemic administration of meperidine, there was no difference in the rate of perineal trauma between groups.[388]

Any factor that increases the likelihood of instrumental vaginal delivery might be expected to increase the risk for pelvic floor injury and subsequent pelvic floor dysfunction (see later discussion). However, to our knowledge, there is no evidence that epidural analgesia per se predisposes to pelvic floor injury.

EFFECTS OF NEURAXIAL ANALGESIA ON THE PROGRESS OF LABOR

Neuraxial analgesia during labor is associated with a prolonged labor and operative delivery. (The term *operative delivery* refers to both cesarean delivery and instrumental vaginal delivery [e.g., forceps delivery or vacuum extraction]). Controversy exists as to whether there is a cause-and-effect relationship between the use of these analgesic techniques and prolonged labor or operative delivery. The understanding of this subject has been limited by the difficulty of performing controlled trials in which parturients are randomly assigned to neuraxial analgesia or a control group. Ideally, if one wants to study the effect of neuraxial analgesia on the progress and outcome of labor, the control group would receive no analgesia. However, such a study is not ethical, and even if it were and women volunteered to participate in it, the crossover rate would probably be high and the data consequently would not be interpretable. Therefore, controlled trials have randomly assigned parturients to receive neuraxial analgesia or an alternative form of pain relief, usually systemic opioid analgesia. However, even when the control group receives some type of analgesia, the crossover rate may be high because the quality of neuraxial analgesia is markedly superior to that of all other modes of labor analgesia.[392]

The difficulty in performing and interpreting the results of labor analgesia trials was aptly described by Noble et al.,[393] who assessed obstetric outcome in 245 patients randomly assigned to receive either epidural analgesia or "conventional" analgesia (i.e., meperidine, nitrous oxide, or no analgesia). The investigators made the following comments[393]:

> *Of 245 selected patients, 43 had to be removed from the trial after labour ensued.…Most of the patients removed from the non-epidural group were apparently experiencing severe pain; they were usually primigravidae whose baby presented in the occipito-posterior position.… The majority of patients removed from the epidural group were apparently normal and usually multigravidas; their labours were so rapid it was not possible to arrange for an epidural block.*

In other words, patients at low risk for operative delivery were excluded from the epidural group, and patients at high risk were excluded from the nonepidural group. The investigators' candid comments illustrate that, even when a prospective, randomized study is performed, it is difficult to maintain conditions that allow for the comparison of women at equal risk for abnormal labor and operative delivery.

Another concern is the external validity of these studies. Women who agree to participate in research trials may be inherently different from women who refuse to participate. Many women make a decision regarding labor analgesia well before the onset of labor and are unwilling to let chance randomization determine the type of labor analgesia. Thus, the study results may not be generalizable to the general obstetric population.

Ironically, the effect of systemic opioids on the progress and outcome of labor has not been well studied. Furthermore, there may be differences among the opioids.[394] Finally, neuraxial analgesia is not a generic procedure. Conclusions about the effect of one technique on the progress of labor may not be applicable to other techniques (see later discussion).

Additional factors prevent rigorous scientific study of this issue. Ideally, a randomized controlled trial should be double blinded. This is not possible for studies that compare neuraxial analgesia with another mode of analgesia, because of the marked difference in the quality of analgesia. Therefore, the potential for bias on the part of the parturient, nurses, and anesthesia and obstetric providers is substantial. Additionally, a number of factors are known to affect or to be associated with the progress and outcome of labor, including parity, artificial rupture of membranes, use of oxytocin, and payer status; these factors should be controlled in well-conducted studies.

One factor known to markedly influence the outcome of labor is the obstetric provider. Neuhoff et al.[395] retrospectively reviewed the records of 607 nulliparous women at term gestation and compared the mode of delivery in "clinic" patients (whose care was given primarily by residents) and private patients (whose care was provided primarily by private obstetricians). Approximately 42% of patients received epidural analgesia during labor. Five percent of patients in the clinic group and 17% of patients in the private group underwent cesarean delivery ($P < .001$). More striking was the difference between groups in the incidence of cesarean delivery for dystocia (0.5% versus 13.7%, respectively; $P < .001$). Similarly, Guillemette and Fraser[396] observed marked obstetrician

variation in cesarean delivery rates, despite similarities in the use of oxytocin and epidural analgesia.

Several groups of investigators have noted that the timing of cesarean delivery conforms to a "circadian" rhythm.[397,398] For example, investigators in Japan noted a delivery time rhythm in hospitals, but not birthing centers, suggesting that obstetric intervention, not biologic rhythm, partly determines the timing of delivery.[399]

Retrospective studies are difficult to interpret because they suffer from selection bias. In some cases, distinguishing between anesthesia administered for pain relief during labor and anesthesia administered in preparation for operative delivery is difficult. Moreover, women at higher risk for prolonged labor and operative delivery are more likely to request and receive epidural analgesia during labor than women who have a rapid, uncomplicated labor.[400] Wuitchik et al.[400] observed a relationship between pain and cognitive activity during early labor and the subsequent progress of labor in 115 healthy nulliparous women. During the latent phase, higher levels of pain were predictive of longer latent and active phases of labor. Those women who reported "horrible" or "excruciating" pain during the latent phase were more than twice as likely to require instrumental delivery as women who only had "discomfort." In addition, women who reported "distress" rather than "coping" had a fivefold higher incidence of abnormal FHR patterns and a fourfold higher requirement for assistance from pediatricians during neonatal resuscitation.

Greater pain intensity during labor appears to be a risk factor for operative delivery. This fact will significantly bias observational studies of labor analgesia because women with greater pain intensity request analgesia, specifically neuraxial analgesia, at a higher rate than women with less intense pain. Alexander et al.[401] performed a secondary analysis of data from a randomized controlled trial in which one group of laboring women received patient-controlled intravenous meperidine analgesia. The rate of cesarean delivery for dystocia was 14% in women who self-administered 50 mg/h or more of meperidine, compared with 1.4% in women who self-administered less than 50 mg/h. In a retrospective study of factors that predict operative delivery in laboring women, Hess et al.[402] found that the cesarean delivery rate in women who had significant breakthrough pain during low-dose bupivacaine/fentanyl epidural analgesia was more than twice as high as the rate in women with less breakthrough pain (odds ratio, 2.62; 95% CI, 2.01 to 3.43).

Taken together, these studies suggest that the early onset of severe pain and the requirement of high doses of analgesic agents predict higher risks for abnormal labor, FHR abnormalities, and operative delivery. These findings may explain the observed association between neuraxial analgesia and operative delivery.

Cesarean Delivery Rate

Randomized Controlled Trials

A number of randomized controlled trials have studied the effect of neuraxial (primarily epidural) and systemic opioid (primarily meperidine) analgesia on the cesarean delivery rate.[388,392,403-427] These trials differ in a number of ways, including (1) the population studied (e.g., nulliparous women or women of mixed parity); (2) onset of labor (spontaneous labor alone or a mix of spontaneous and induced labors); (3) type of neuraxial analgesia; (4) density of neuraxial analgesia; (5) route of administration of systemic analgesia (although all the studies included meperidine with or without an adjuvant); (6) the crossover rate; and (7) management of labor (e.g., active management of labor, including electronic FHR monitoring, artificial rupture of membranes, and oxytocin infusion). All but one of these studies found no difference in the rate of cesarean delivery between women randomly assigned to receive either neuraxial or systemic opioid analgesia.

Four prospective, randomized trials were performed at the University of Texas Southwestern Medical Center, Parkland Hospital, in Dallas.[392,408,422,423] This institution is unique among many others that have performed randomized trials, in that the population is composed largely of indigent women whose labor is managed by the same group of resident physicians and midwives, supervised by the same core group of attending obstetricians. In the first study, 1330 women of mixed parity were randomly assigned to receive either epidural bupivacaine/fentanyl or intravenous meperidine for labor analgesia.[392] Approximately one third of the women did not receive the assigned treatment. The cesarean delivery rates were 9.0% in women who received epidural analgesia and 3.9% in women who received intravenous meperidine. However, the investigators did not report an intent-to-treat analysis of these data; thus, it was unclear whether there was a higher incidence of cesarean delivery in the women randomly assigned to the epidural analgesia group. Subsequently, the investigators published a reanalysis of the data that included an intent-to-treat analysis (Table 23-11).[428] The cesarean delivery rate in both groups was 6%. These analyses support the conclusion that women

TABLE 23-11 Parkland Hospital Randomized Controlled Trial of Epidural Versus Systemic Opioid Analgesia and Rate of Cesarean Delivery: Actual Treatment Versus Intent-to-Treat Analysis*

Type of Analysis	*Cesarean Delivery Rate (%)*	
	Epidural Analgesia (n = 664)	Systemic Opioid Analgesia (n = 666)
Actual treatment†	9.0	3.9‡
Intent-to-treat	6	6

*In the systemic opioid group, 103 women requested and received epidural analgesia because opioid analgesia was inadequate. The initial analysis was published in 1995. The intent-to-treat analysis of the same data was published in 2000.
†The protocol violation rate was 35%.
‡$P < .05$ compared with epidural analgesia group.
Data from Ramin SM, Gambling DR, Lucas MJ, et al. Randomized trial of epidural versus intravenous analgesia during labor. Obstet Gynecol 1995; 86:783-9; and Sharma SK, Leveno KJ. Update: Epidural analgesia does not increase cesarean births. Curr Anesthesiol Rep 2000; 2:18-24.

who choose epidural analgesia have an inherent risk factor(s) for cesarean delivery and that the administration of neuraxial analgesia per se does not alter this risk.

In an attempt to lower the rate of crossover by providing better analgesia to the control (meperidine) group, the Parkland Hospital investigators performed another study in which meperidine was administered by PCIA.[422] A significant number of women in both groups did not receive their assigned treatment, although the reason in all cases was rapid labor. Only 5 of 357 women randomly assigned to the meperidine group crossed over to receive epidural analgesia. Using an intent-to-treat analysis, the investigators observed no difference between the groups in the incidence of cesarean delivery (4% in the epidural group and 5% in the PCIA group). There was no difference between the two groups in neonatal outcome, except that more neonates of women in the PCIA group received naloxone to reverse respiratory depression at birth.

Only one randomized trial has compared CSE and systemic opioid analgesia.[408] In this large study (n = 1223), patients of mixed parity were randomly assigned to receive CSE analgesia (intrathecal sufentanil 10 μg, followed by epidural bupivacaine with fentanyl at the second request for analgesia) or intravenous meperidine (50 mg every hour on request). Approximately 60% of patients complied with the protocol. An intent-to-treat analysis showed that there was no difference between groups in the rate of cesarean delivery (CSE 6%, systemic opioid 5.5%).

The studies comparing neuraxial with systemic opioid analgesia have been systematically reviewed in several meta-analyses.[3,429] The latest meta-analysis covered outcomes for 8417 women randomized to receive neuraxial or no neuraxial/no analgesia (control) from 27 trials (Figure 23-8).[3] The risk ratio for cesarean delivery in women randomly assigned to receive neuraxial analgesia compared with those assigned to the control group was

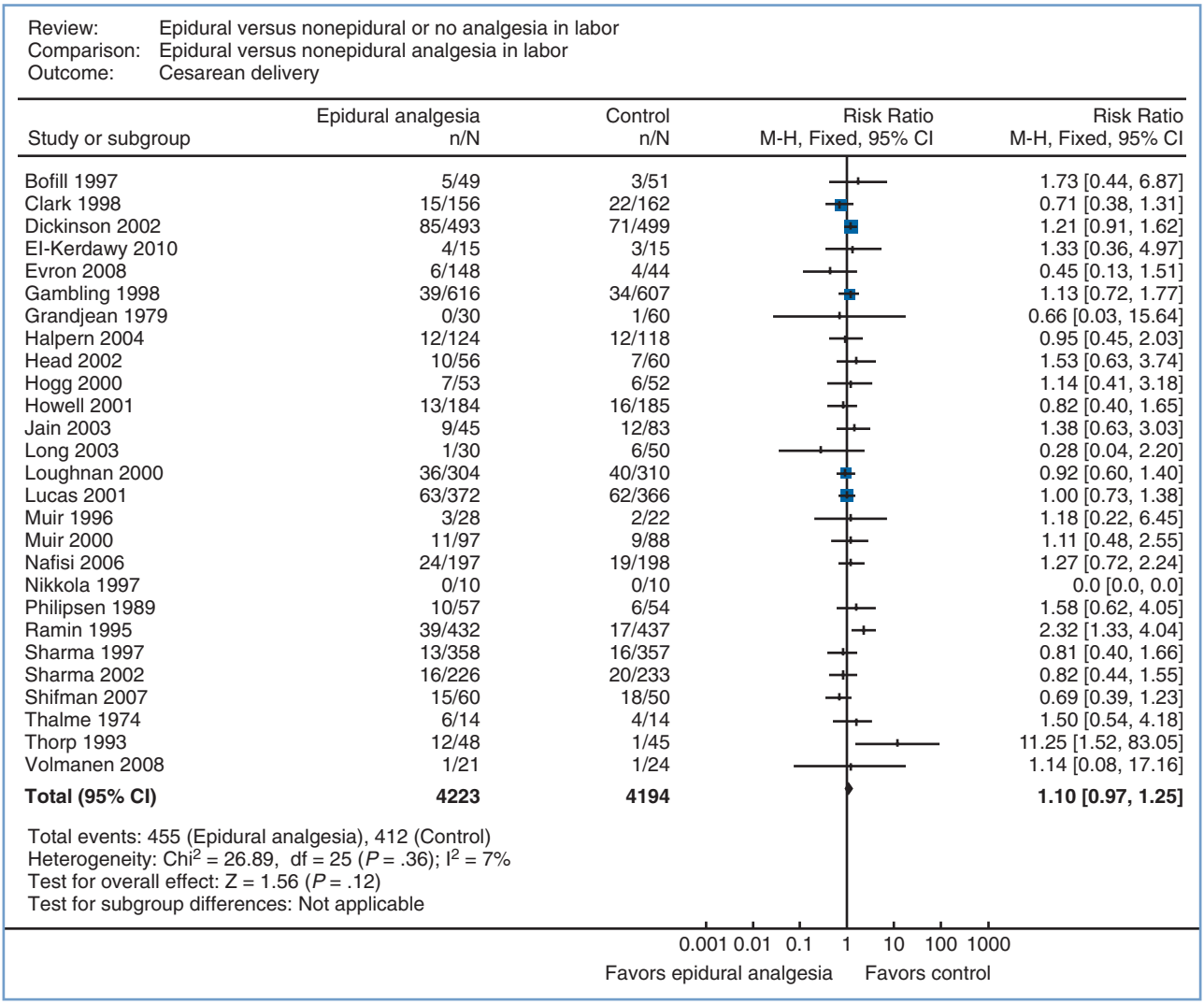


FIGURE 23-8 ■ Meta-analysis of cesarean delivery rate in women randomized to neuraxial or non-neuraxial labor analgesia. The number of women who had a cesarean delivery, the risk ratio, and 95% confidence interval (CI) of the risk ratio (fixed effect model) are shown for each study. For studies with no cesarean deliveries the risk ratio could not be calculated. Control, nonepidural analgesia. *n,* number of events (cesarean delivery) in the neuraxial or non-neuraxial group; *N,* total number of subjects in the neuraxial or non-neuraxial group. The scale is logarithmic. (Modified from Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev 2011; [12]:CD000331.)

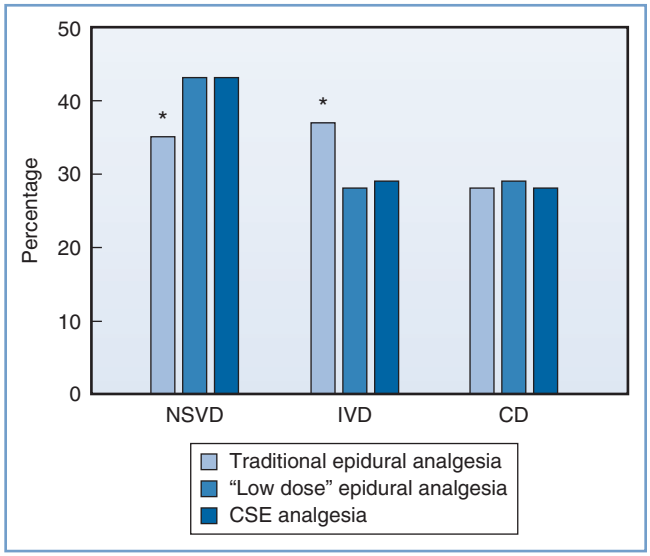


FIGURE 23-9 ■ Outcome of labor in the COMET study. Parturients were randomly assigned to traditional epidural analgesia or to one of two "low-dose" neuraxial techniques (see text). There was no difference among groups in the cesarean delivery (*CD*) rate. *Women who received traditional epidural analgesia had a higher rate of instrumental vaginal delivery (IVD) than those who received either "low-dose" technique ($P = .04$). *CSE,* combined spinal-epidural; *NSVD,* normal spontaneous vaginal delivery. (Data from Comparative Obstetric Mobile Epidural Trial Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. Lancet 2001; 358:19-23.)

1.10 (95% CI, 0.97 to 1.25).[3] In an individual patient meta-analysis of the studies performed at Parkland Hospital (n=4465),[429] the odds ratio was 1.04 (95% CI, 0.81 to 1.34).

Mode and Density of Neuraxial Analgesia and Effect on Cesarean Delivery Rate. If neuraxial analgesia adversely affects the outcome of labor, one would expect to observe a dose-response effect. The COMET study randomly assigned more than 1000 parturients to one of three groups: (1) "high-dose" epidural analgesia (traditional epidural analgesia with bupivacaine 0.25%); (2) "low-dose" epidural analgesia (bupivacaine 0.1%/fentanyl 2 µg/mL bolus, followed by a continuous epidural infusion); and (3) "low-dose" CSE analgesia (intrathecal bupivacaine/fentanyl followed by intermittent boluses of epidural bupivacaine 0.1%/fentanyl 2 µg/mL).[430] There was no difference in cesarean delivery rates among groups (Figure 23-9). Similarly, several other studies that compared traditional epidural analgesia (using bupivacaine 0.25%) and low-dose CSE techniques found no difference between groups in the cesarean delivery rate.[431-433] The results of these studies suggest that "high-dose" neuraxial analgesia does not entail a higher risk for cesarean delivery than "low-dose" techniques; in other words, no dose-response effect has been observed.

There is no evidence that CSE analgesia influences the mode of delivery, when compared with epidural analgesia alone. Large randomized controlled trials comparing CSE analgesia with epidural analgesia alone have found no difference between groups in the rate of cesarean delivery.[430-432,434]

Impact Studies

Some physicians have questioned whether prospective, randomized studies provide an accurate representation of the effect of neuraxial analgesia on the mode of delivery in actual clinical practice. They have suggested the possibility that prospective studies may introduce a Hawthorne effect (which may be defined as the appearance or disappearance of a phenomenon on initiation of a study to confirm or exclude its existence). An alternative study design is to assess obstetric outcome immediately before and after a sentinel event, such as the introduction of an epidural analgesia service in a given hospital. The results of these studies may be generalizable to the general population because patients have not chosen to participate in a study. It also eliminates the problem of treatment group crossover because epidural analgesia was not available in the control period. One limitation of this study design is that it assumes that there were no other changes in obstetric management in the "after" period.

In 1999, Yancey et al.[435] published an impact study using data from the Tripler Army Medical Center in Hawaii. Because of relative homogeneity in socioeconomic status, universal access to health care, and the availability of dedicated health care providers in the population served by this hospital, its rate of cesarean delivery may not be subject to influences common to other hospitals. Prior to 1993 the rate of epidural analgesia was less than 1% at Tripler Army Medical Center. In 1993 a policy change within the U.S. Department of Defense mandated on-demand availability of neuraxial labor analgesia in military hospitals. In nulliparous women in spontaneous labor with a singleton infant with a vertex presentation, the rate of epidural labor analgesia rose from less than 1% to approximately 80% in a 1-year period.[436] The rate of cesarean delivery was unchanged during the same period (14.4% versus 12.1%, respectively; adjusted RR, 0.8; 95% CI, 0.6 to 1.2).

In another impact study, Impey et al.[437] compared obstetric outcome for the first 1000 nulliparous women (term gestation, singleton fetus, cephalic presentation, spontaneous labor) who delivered at the National Maternity Hospital in 1987 with the outcome for a similar group of women who delivered in 1992 and 1994. The epidural analgesia rate rose from 10% in 1987 to 45% in 1992 and 57% in 1994. In each of these 3 years, 82% of women underwent spontaneous vaginal delivery. The cesarean delivery rate was 4% in 1987, 5% in 1992, and 4% in 1994 (P = NS) (Figure 23-10). The investigators concluded that the consistency of the operative delivery rates in each of 3 years with very different epidural rates suggests that epidural analgesia does not increase the cesarean delivery rate.

Socol et al.[438] evaluated the impact of three initiatives to reduce the cesarean delivery rate in their hospital. First, they strongly encouraged a trial of labor and vaginal birth after cesarean delivery. Second, after the 1988 calendar year, they circulated data showing the cesarean delivery rate of every obstetrician to all obstetricians. Third, they recommended the active management of labor as the preferred method of labor management for term nulliparous women. The rates of total, primary, and repeat cesarean

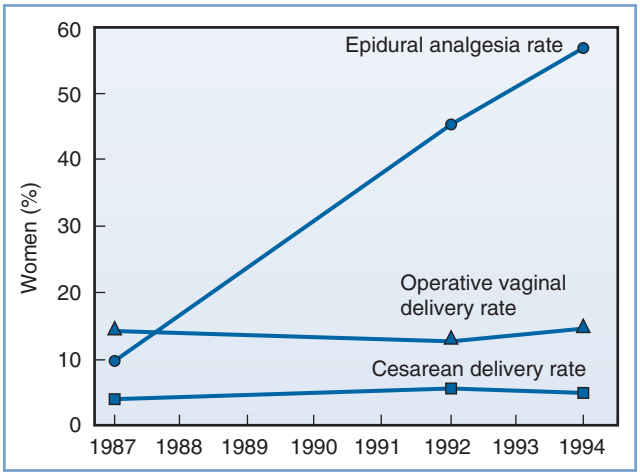


FIGURE 23-10 ■ Epidural analgesia and cesarean and instrumental vaginal delivery rates for 1000 consecutive nulliparous women in spontaneous labor at term during 3 different years at the National Maternity Hospital in Dublin, Ireland. (Modified from Impey L, MacQuillan K, Robson M. Epidural analgesia need not increase operative delivery rates. Am J Obstet Gynecol 2000; 182:358-63.)

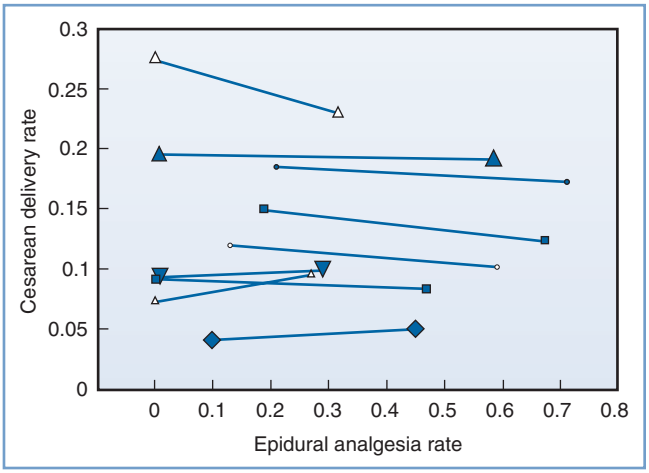


FIGURE 23-11 ■ Rates of cesarean delivery during periods of higher and lower availability of epidural analgesia in nine studies (n = 37,753) subjected to meta-analysis. Each pair of symbols shows data from one investigation (the left symbol is the epidural analgesia rate and cesarean delivery rate during the period of low epidural analgesia availability, and the right symbol is the epidural analgesia rate and cesarean delivery rate during the period of high epidural availability). The size of the plot symbol is proportional to the number of patients in the analysis. (Modified from Segal S, Su M, Gilbert P. The effect of a rapid change in availability of epidural analgesia on the cesarean delivery rate: a meta-analysis. Am J Obstet Gynecol 2000; 183:974-8.)

deliveries dropped from 27%, 18%, and 9% in 1986 to 17%, 11%, and 6%, respectively, in 1991 ($P < .001$ for all three comparisons). Meanwhile, the use of epidural analgesia rose from 28% in 1986 to 48% in 1991 ($P < .001$). There was no change in the incidence of instrumental vaginal delivery (13% in 1986 versus 13% in 1991).

In a meta-analysis, Segal et al.[439] identified nine impact studies involving a total of 37,753 patients. These researchers found no increase in the rate of cesarean delivery with the increase in availability of epidural analgesia (Figure 23-11). Thus, the before-after impact studies support the results of randomized controlled trials—namely, that neuraxial analgesia does not cause an increase in the cesarean delivery rate.

Several studies have assessed whether there is a relationship between an individual obstetrician's cesarean delivery rate and the rate of epidural analgesia for his or her patients.[440,441] For example, Lagrew et al.[440] divided obstetricians into two groups according to whether their individual cesarean delivery rates were more than 15% (the control group) or less than 15% (the target group). Obstetricians in the target group used epidural analgesia more often than obstetricians in the control group. In other words, the target group of obstetricians was able to achieve a lower cesarean delivery rate despite their greater use of epidural analgesia.

Timing of Initiation of Neuraxial Analgesia

Review of observational data suggests an association between cesarean delivery and the initiation of neuraxial analgesia during early labor (often defined as a cervical dilation < 4 to 5 cm).[426,432,442] For example, in a retrospective study of 1917 nulliparous women, the rate of cesarean delivery was twice as high in women who received neuraxial analgesia at a cervical dilation less than 4 cm than in those in whom neuraxial analgesia was initiated at a cervical dilation of 4 cm or more (18.9% versus 8.9%, respectively).[442] As a result of these data, for many years the ACOG suggested that women delay requesting epidural analgesia "when feasible, until the cervix is dilated to 4 to 5 cm."[443] However, as with the cause-and-effect question raised by the association of neuraxial labor analgesia and cesarean delivery, the question arises as to whether the early initiation of neuraxial labor analgesia *causes* a higher risk for cesarean delivery or whether the request for early labor analgesia is a marker for some other risk factor(s) for cesarean delivery.

A number of randomized controlled trials have addressed the question of whether initiation of neuraxial analgesia during early labor adversely affects the mode of delivery.[20-24,444,445] All except one small study[444] compared early labor neuraxial analgesia with systemic opioid analgesia, which was followed by neuraxial analgesia when cervical dilation reached 4 to 5 cm (the control group in the Luxman et al.[444] study received no analgesia). In 1994, Chestnut et al.[20,23] reported two trials in which nulliparous women were randomly assigned to receive early epidural analgesia or early intravenous nalbuphine analgesia followed by epidural analgesia when cervical dilation reached 5 cm. The median cervical dilation at the time of initiation of analgesia was 3.5 cm[23] and 4 cm[20] in the two studies. There was no difference between groups in the cesarean delivery rate.

Subsequently, Wong et al.[21] and Ohel et al.[22] reported randomized trials that compared early labor neuraxial analgesia with systemic opioid analgesia; the median cervical dilation at initiation of analgesia was 2 cm. As in the previous studies, there was no difference between the two groups in rate of cesarean delivery or in rate of instrumental vaginal delivery. The study protocols differed in that the treatment group in one study received *CSE* analgesia in early labor,[21] whereas the treatment group in the

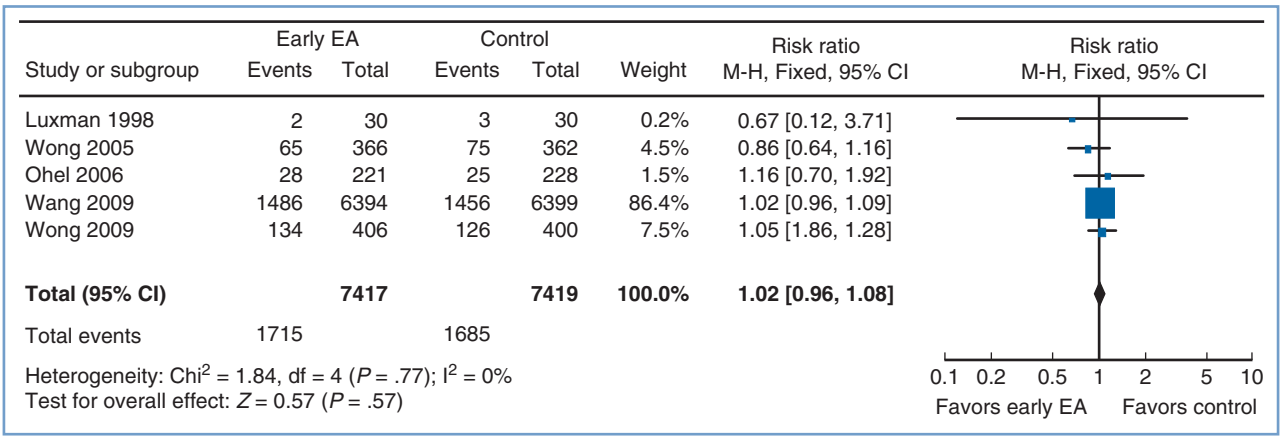


FIGURE 23-12 ■ Meta-analysis of cesarean delivery in women randomized to receive early labor initiation of neuraxial analgesia (cervical dilation < 4 cm) or late initiation (cervical dilation ≥ 4 cm). The size of the box at the point estimate for each study is proportional to the number of patients in the study. The diamond represents the point estimate of the pooled risk ratio, and the length of the diamond is proportional to the confidence interval. *Control,* late epidural analgesia; *EA,* epidural analgesia; *n,* number of events (cesarean delivery) in the treatment or control group; *N,* total number of patients in the treatment or control group. (Modified from Wassen MM, Zuijlen J, Roumen FJ, et al. Early versus late epidural analgesia and risk of instrumental delivery in nulliparous women: a systematic review. BJOG 2011; 118:655-61.)

second study received *epidural* analgesia alone.[22] The use of oxytocin augmentation was markedly different in the two studies (94%[21] and 29%[22]).

Subsequent to the publication of the later studies, the ACOG[446] published an updated Committee Opinion entitled *Analgesia and Cesarean Delivery Rates.* This revised opinion includes the following statement:

> *Neuraxial analgesia techniques are the most effective and least depressant treatments for labor pain. The American College of Obstetricians and Gynecologists previously recommended that practitioners delay initiating epidural analgesia in nulliparous women until the cervical dilation reached 4-5 cm. However, more recent studies have shown that epidural analgesia does not increase the risks of cesarean delivery. The choice of analgesic technique, agent, and dosage is based on many factors, including patient preference, medical status, and contraindications. The fear of unnecessary cesarean delivery should not influence the method of pain relief that women can choose during labor.*

Later randomized trials in nulliparous women in both spontaneous[24] and induced[445] labor, as well as a 2011 meta-analysis (five randomized controlled trials; n = 14,836),[25] replicated these results. The researchers concluded that early initiation of neuraxial analgesia does not increase the rate of cesarean delivery (RR, 1.02 ; 95% CI, 0.96 to 1.08) (Figure 23-12).[25]

Instrumental Vaginal Delivery Rate

Observational data associate neuraxial labor analgesia with a higher rate of instrumental (forceps or vacuum extraction) vaginal delivery. The effect of neuraxial analgesia on mode of vaginal delivery has not been assessed as a primary outcome in randomized controlled trials, although it has been assessed as a secondary outcome in multiple trials. Interpretation of these results is clouded by the fact that most studies have not assessed the quality of analgesia during the second stage of labor. Further, most investigators did not define the criteria for the performance of instrumental vaginal delivery. In clinical practice, and in study interpretation, it is often difficult to distinguish "indicated" instrumental deliveries from elective instrumental deliveries. Indeed, we have observed that indications for instrumental vaginal delivery vary markedly among obstetricians. An obstetrician is more likely to perform an elective instrumental delivery in a patient with satisfactory anesthesia than in a patient without analgesia. In addition, most randomized controlled trials are conducted in teaching institutions that have an obligation to teach obstetric residents how to perform instrumental vaginal delivery. Instrumental vaginal deliveries performed for the purpose of teaching are more likely to be done in women with adequate analgesia.

Multiple randomized, controlled studies comparing epidural analgesia with systemic opioid analgesia have assessed the rate of instrumental vaginal delivery as a secondary outcome variable.* Most systematic reviews have concluded that epidural analgesia is associated with a higher risk for instrumental vaginal delivery than systemic analgesia.[3,429] For example, in a 2011 meta-analysis of 23 studies (n = 7935),[3] the risk ratio for instrumental vaginal delivery in women randomly assigned to receive epidural analgesia or nonepidural/no analgesia was 1.42 (95% CI, 1.28 to 1.57) (Figure 23-13). Similarly, in the individual patient meta-analysis reported by Sharma et al.,[429] the adjusted odds ratio was 1.86 (95% CI, 1.43 to 2.40).

In contrast to these studies, many of the impact studies observed no difference in the instrumental vaginal delivery rate between the control and study periods.[435-437,447] For example, despite a rise in the epidural analgesia rate from 1% to almost 80% at Tripler Army Medical Center, the rate of instrumental vaginal delivery did not change (11.1% versus 11.9%).[435] Similarly, despite a more than fivefold increase in the epidural analgesia rate at the National Maternity Hospital in Dublin (see earlier

*References 388, 392, 403-411, 413, 415-417, 419-423, 425-427.

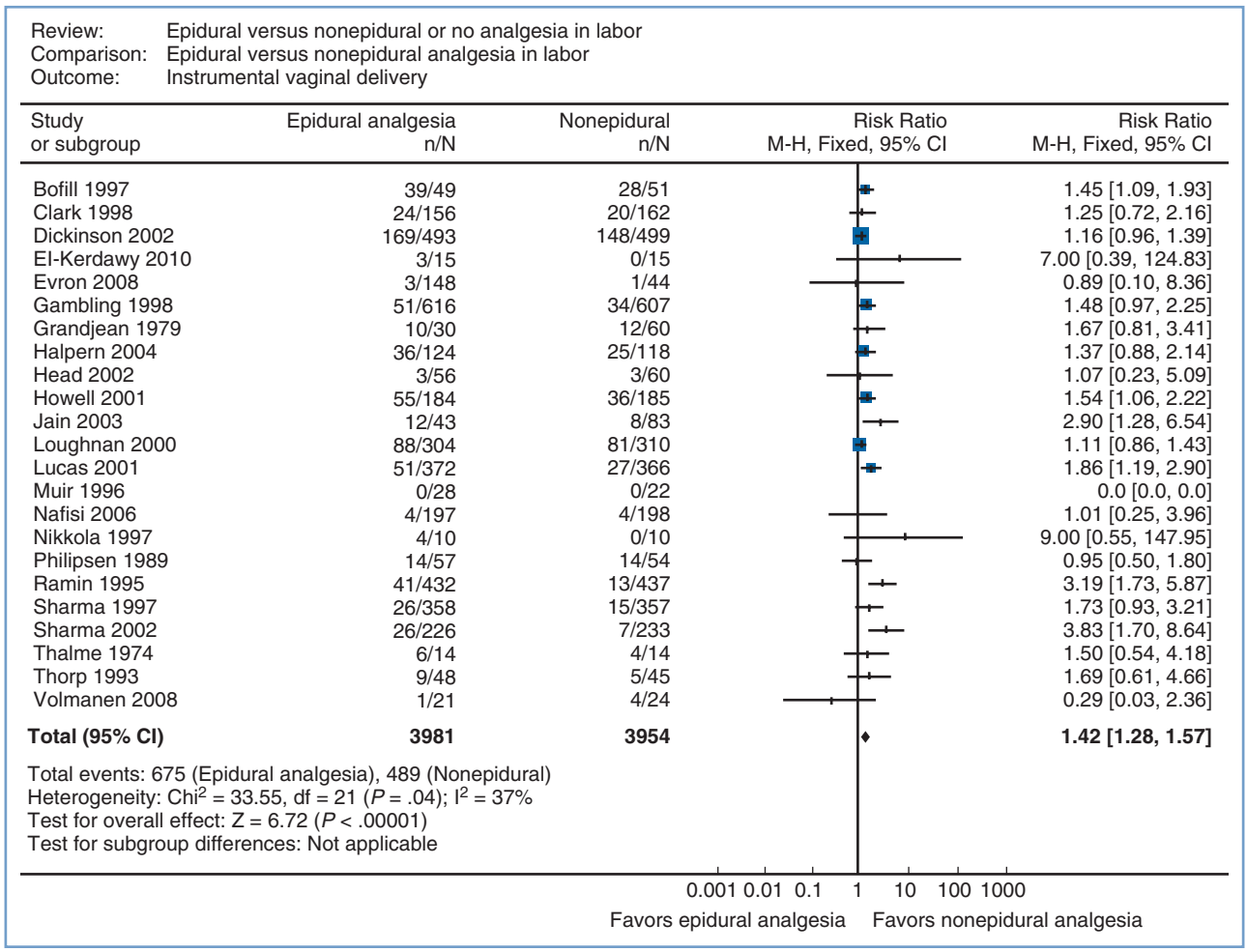


FIGURE 23-13 ■ Meta-analysis of instrumental vaginal delivery rate in women randomized to neuraxial or non-neuraxial labor analgesia. The number of women who had an instrumental vaginal delivery, the risk ratio, and 95% confidence interval *(CI)* of the risk ratio (fixed effect model) are shown for each study. For studies with no instrumental vaginal deliveries the risk ratio could not be calculated. *n,* number of events (instrumental vaginal delivery) in the neuraxial or non-neuraxial group; *N,* total number of subjects in the neuraxial or non-neuraxial group. The scale is logarithmic. (Modified from Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev 2011; [12]:CD000331.)

discussion), the instrumental vaginal delivery rate remained unchanged (see Figure 23-10). A systematic review of seven impact studies[439] involving more than 28,000 patients did not identify a difference in instrumental vaginal delivery rates between periods of low and periods of high epidural analgesia rates (mean change, 0.76%; 95% CI, –1.2 to 2.8).

Studies of early versus late initiation of neuraxial labor analgesia have not identified an increased risk for instrumental vaginal delivery in the early analgesia group.[21,22,24,445]

Obstetricians and anesthesiologists have suggested that multiple factors (e.g., station and position of the fetal vertex, maternal pain and the urge to bear down, and neuraxial analgesia–induced motor blockade) may contribute to the outcome of the second stage of labor. The contribution of these factors to the mode of vaginal delivery, and their interactions, are not well understood and these factors have not been well controlled in many studies.

Several studies have specifically assessed the effect of maintenance of neuraxial analgesia until delivery with regard to the duration and outcome of the second stage of labor.[370,448-452] Chestnut et al.[370] randomly assigned women already receiving epidural analgesia at 8 cm of cervical dilation to receive a continuous epidural infusion of 0.75% lidocaine or saline until delivery. There was no difference between groups in the rate of instrumental vaginal delivery, but women in the lidocaine group as well as the saline group had inadequate second-stage analgesia. In a similar study in which patients were randomly assigned to receive epidural bupivacaine 0.125% or saline (control),[449] second-stage analgesia was clearly better in the bupivacaine group than in the control group, but the rate of instrumental vaginal delivery was nearly double (52% versus 27%, respectively; $P < .05$), and the duration of the second stage was longer. In a third study, second-stage analgesia was maintained with 0.0625% bupivacaine with fentanyl 2 μg/mL or saline-placebo.[448] There was no difference between groups in the instrumental vaginal delivery rate, but analgesia was only marginally better in the treatment group.

The effect of neuraxial analgesia on the outcome of the second stage of labor may be influenced by the density of neuraxial analgesia. High concentrations of epidural local anesthetic may cause maternal motor blockade, leading to relaxation of pelvic floor musculature, which in turn may interfere with fetal rotation during descent. Abdominal muscle relaxation may decrease the effectiveness of maternal expulsive efforts. The effects of specific analgesic techniques, concentration of local anesthetic, total dose of local anesthetic, and degree of motor blockade on the risk for instrumental vaginal delivery are overlapping and difficult to study. For example, some studies suggest that administration of epidural analgesia using higher concentrations of bupivacaine is associated with a higher risk for instrumental vaginal delivery compared with use of lower concentrations.[430,432,433,453] James et al.[453] randomly assigned parturients to receive intermittent epidural bupivacaine 0.25% or bupivacaine 0.1% with fentanyl 2 μg/mL. The severity of motor blockade and the incidence of instrumental vaginal delivery were less in the low-dose group than in the high-dose group (6% versus 24%, respectively; $P = .03$). Similarly, in a much larger study that compared CSE (low-dose) with traditional high-dose epidural analgesia, the rate of instrumental vaginal delivery was lower in the CSE group.[432] In another large study, Olofsson et al.[433] noted a lower instrumental vaginal delivery rate in women randomly assigned to "low-dose" bupivacaine 0.125% with sufentanil than in those receiving "high-dose" bupivacaine 0.25% with epinephrine.

In contrast, Collis et al.[431] observed no difference in mode of delivery between women randomly assigned to receive either a high-dose or a low-dose neuraxial technique. Even more confusing, the COMET investigators reported a lower rate of instrumental vaginal delivery in the two groups of women randomly assigned to receive either the low-dose epidural or CSE technique than in the group that received 0.25% bupivacaine (see earlier discussion and Figure 23-9).[430] However, the total bupivacaine dose in the traditional "high-dose" epidural group did not actually differ from that in the "low-dose" epidural group because the former was administered by intermittent injection and the latter by continuous infusion. In contrast, the total bupivacaine dose was significantly lower in the CSE group. Finally, in a meta-analysis of studies that compared CSE and epidural analgesia,[27] the instrumental vaginal delivery rate was lower in the CSE group than in the traditional "high-dose" epidural analgesia groups (risk ratio 0.80; 95% CI, 0.65 to 0.98), but there was no difference between "low-dose" epidural and CSE analgesia (risk ratio 1.06; 95% CI, 0.87 to 1.30). Together, these data suggest that the specific analgesia technique may influence the risk for instrumental vaginal delivery.

In general, the dose of bupivacaine is significantly lower if epidural analgesia is maintained with an intermittent bolus technique rather than a continuous infusion technique (see earlier discussion). Most investigators have noted a difference in motor blockade between the two techniques; higher total bupivacaine doses (i.e., continuous infusion techniques) are associated with a greater degree of motor blockade. However, the relationship between motor blockade and instrumental vaginal delivery is inconsistent. Smedstad and Morison[228] reported a higher incidence of instrumental vaginal delivery when bupivacaine 0.25% was administered as a continuous epidural infusion than as intermittent bolus injections. In contrast, the COMET investigators observed no difference in the instrumental vaginal delivery rate in the two groups who received "low-dose" bupivacaine/fentanyl, one by infusion and the other by intermittent bolus.[430] Similarly, in a meta-analysis of PCEA (without background infusion) compared with continuous epidural infusion analgesia,[238] the dose of bupivacaine and degree of motor blockade were significantly lower in the PCEA group, but the rates of instrumental vaginal delivery did not differ.

It is possible that the inconsistent results can be explained by the actual absolute differences in bupivacaine dose and motor blockade. For example, the differences in dose and motor blockade may have clinically significant adverse effects on the outcome of the second stage of labor if bupivacaine 0.25% is compared with bupivacaine 0.125% but not if bupivacaine 0.125% is compared with bupivacaine 0.0625%. Many of the randomized controlled trials included in the meta-analysis that compared epidural with systemic opioid analgesia used concentrated solutions of bupivacaine for both the loading and infusion doses (e.g., bupivacaine 0.25% for the loading dose, bupivacaine 0.125% by continuous infusion for maintenance of analgesia.)[3]

Motor blockade may increase the risk for malrotation of the fetal vertex. Robinson et al.[454] and Le Ray et al.[455] observed a higher incidence of occiput malposition at delivery in patients who received epidural analgesia before engagement of the fetal head. In contrast, Yancey et al.[456] and Sheiner et al.[457] noted that the administration of on-demand epidural analgesia did not increase the frequency of malposition of the fetal head at delivery; the incidence of instrumental vaginal delivery was not related to fetal station at initiation of analgesia. In a prospective cohort study using ultrasonography, Lieberman et al.[458] reported that fetal position changed frequently during labor but that epidural analgesia was associated with a higher incidence of occiput posterior position at delivery (13% versus 3%, $P < .002$). However, these results should be interpreted with caution as women were not randomly assigned to the treatment group. Factors that cause women to request analgesia when the fetal head is high may also be independent risk factors for instrumental vaginal delivery. A study from Italy[459] in which ultrasonography was used to assess fetal head position found no association between use of early labor neuraxial analgesia and fetal head position at delivery.

In an editorial, Chestnut[460] concluded that *effective* second-stage analgesia increases the risk for instrumental vaginal delivery. However, effective analgesia is a spectrum that ranges from complete absence of sensory input (dense analgesia) to perception of uterine contraction "pressure" without pain (less dense analgesia). Minimizing the risk for instrumental vaginal delivery while maximizing analgesia is both an art and a science and requires the attention of the anesthesia provider to the individual needs of the patient. A single analgesic technique or

single dose/concentration of drug(s) is not likely to have optimal results for everyone. I believe the best technique incorporates the use of PCEA with a low-rate background infusion (4 to 8 mL/h) using a dilute solution of local anesthetic combined with an opioid. Use of a dilute local anesthetic solution without PCEA leads to inadequate analgesia for many women. Increasing the infusion dose improves analgesia and reduces the workload for the anesthesia provider but will result in overly dense analgesia for some patients, thus potentially increasing the risk for instrumental vaginal delivery. In the future, new pump technology may allow timed bolus and/or closed feedback-loop anesthetic administration that will better tailor anesthetic dose to patient need.

Why should anesthesia providers give attention to the effects of analgesia on the method of vaginal delivery? Lack of effective maternal effort associated with inadequate progress of labor (descent of the fetus) is an indication for operative vaginal delivery.[461] Studies suggest that vacuum extraction is associated with a higher neonatal risk for cephalohematoma, subgaleal hemorrhage, and intraventricular hemorrhage than spontaneous vaginal or forceps delivery, whereas forceps delivery is associated with an increased risk for facial trauma.[462] However, there is no evidence of adverse long-term outcome with operative vaginal compared with spontaneous vaginal delivery.[463]

The risk for maternal trauma is also greater with operative vaginal delivery (e.g., third- and fourth-degree vaginal lacerations, which are associated with a small but not negligible risk for rectovaginal fistula). Robinson et al.[464] observed that epidural analgesia was associated with an increased rate of severe perineal trauma because of the more frequent use of instrumental vaginal delivery and episiotomy in nulliparous women who received epidural analgesia. In contrast, several large observational studies suggest that epidural analgesia is associated with a decreased risk for anal sphincter laceration in nulliparous women.[465,466] Regardless of the presence or magnitude of the risks of maternal or neonatal injury, many women want to minimize the likelihood of operative delivery and they perceive that a higher risk for instrumental vaginal delivery is undesirable. Of concern is a decline in the number of obstetricians skilled at operative vaginal delivery.[467] The concern is that loss of these skills will lead to an increase in second-stage cesarean delivery rates.

Duration of Labor

First Stage of Labor

The effect of neuraxial labor analgesia on the duration of the first stage of labor was addressed as a secondary outcome variable in many of the randomized controlled trials. A 2011 meta-analysis[3] of 11 studies found no difference in the duration of the first stage of labor between women who were randomly assigned to receive epidural analgesia and those assigned to receive systemic opioid analgesia, although the confidence interval was wide, indicating significant heterogeneity among studies (Table 23-12). There was significant heterogeneity in the outcome because of the mixed parity of the patient populations and differences among studies in the definition of the duration of the first stage of labor. In contrast, the individual meta-analysis of the Parkland Hospital data showed a significant prolongation of the first stage of labor (approximately 30 minutes) in nulliparous women who were randomly assigned to receive epidural analgesia.[429]

Wong et al.[21] and Ohel et al.[22] assessed duration of labor as a secondary outcome in their randomized controlled trials of the initiation of neuraxial analgesia during early labor. Both groups of investigators determined that the duration of the first stage of labor, and thus consequently the overall duration of labor, were significantly shorter in women randomly assigned to receive early labor neuraxial analgesia than in those assigned to receive systemic opioid analgesia. In the Wong et al. study,[21] the median difference in the overall duration of labor between the early and late neuraxial analgesia groups was 81 minutes (95% CI, 28 to 123).

Determining the duration of labor requires that investigators document start and end times. The definition of the start time varies among studies but is usually consistent between groups within a study. The end of the first stage of labor is defined as the time of full (10 cm) cervical dilation. This point can be determined only with manual cervical examination. Most studies do not mandate regular cervical examinations by study protocol, or if they do, the intervals are fairly long (e.g., 1 to 2 hours). Clinically, full cervical dilation is diagnosed when a cervical examination is performed because the patient complains of rectal pressure. It is likely that women with effective epidural analgesia will complain of rectal pressure at a

TABLE 23-12 **Meta-Analyses of Duration of First and Second Stages of Labor**

Meta-analysis	N	*First Stage of Labor*			*Second Stage of Labor*		
		NEURAXIAL	SYSTEMIC OPIOID	*P* VALUE	NEURAXIAL	SYSTEMIC OPIOID	*P* VALUE
Anim-Somuah, 2011[3]	2981* 4233†	WMD 19 min (95% CI, –13-50)		.25	WMD 14 min (95% CI, 7-21)		<.001
Sharma, 2004[429]	2703	8.1 ± 5 h	7.5 ± 5 h	.01	60 ± 56 min	47 ± 57 min	<.001

CI, confidence interval; *WMD,* weighted mean difference
*First stage of labor.
†Second stage of labor.
Data are from Anim-Somuah M, Smyth R, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev 2011; [12]:CD000331 and Sharma SK, McIntire DD, Wiley J, Leveno KJ. Labor analgesia and cesarean delivery: an individual meta-analysis of nulliparous women. Anesthesiology 2004; 100:142-8.

later time (and lower fetal station) than women with systemic opioid analgesia. In other words, the patient may be fully dilated for a significant time before cervical examination verifies full cervical dilation. This difference serves to artificially prolong the duration of the first stage of labor in the epidural group, although it shortens the apparent duration of the second stage of labor.

Other factors may also influence the duration of the first stage of labor. Some clinicians have noted enhanced uterine activity in some patients for approximately 30 minutes after the initiation of neuraxial analgesia, whereas uterine activity appears to be reduced in other patients. Schellenberg[468] suggested that aortocaval compression is responsible for the transient decrease in uterine activity that occurs after the administration of epidural analgesia in some patients. He concluded that this effect does not occur if aortocaval compression is avoided. Cheek et al.[469] noted that uterine activity decreased after the intravenous infusion of 1 L of crystalloid solution, but not after infusion of 0.5 L or maintenance fluid alone. There was no decrease in uterine activity after the administration of epidural analgesia. Zamora et al.[36] made similar observations. Miller et al.[470] hypothesized that a fluid bolus might inhibit antidiuretic hormone (vasopressin) release from the posterior pituitary gland. Because this organ also releases oxytocin, the production of that hormone might also be transiently suppressed; this possible decrease in oxytocin release may partially explain the transient changes in uterine contractility observed in association with epidural analgesia.

In a prospective but nonrandomized study, Rahm et al.[471] observed that epidural analgesia (bupivacaine with sufentanil) was associated with lower plasma oxytocin levels at 60 minutes after initiation of analgesia than in healthy controls who did not receive epidural analgesia. Behrens et al.[472] noted that epidural analgesia during the first stage of labor significantly reduced the release of prostaglandin $F_{2\alpha}$ and "impede[d] the normal progressive increase in uterine activity." In contrast, Nielsen et al.[473] measured upper and lower uterine segment intrauterine pressures for 50 minutes before and after the administration of epidural bupivacaine analgesia in 11 nulliparous women during spontaneous labor. No significant difference in the number of contractions before and after epidural analgesia was observed. There was greater intrauterine pressure in the upper uterine segment than in the lower segment (consistent with fundal dominance) both before and after initiation of epidural analgesia. Further, fundal dominance was higher after epidural analgesia than in the preanalgesia period.

Increased uterine activity after the initiation of neuraxial analgesia has been hypothesized to be an indirect effect of neuraxial analgesia (see later discussion).[474] Initiation of neuraxial analgesia is associated with an acute decrease in the maternal plasma concentration of circulating epinephrine.[4] Epinephrine is a tocolytic, and the acute decrease in maternal concentration may result in greater uterine activity. This may be an explanation for the salutary effect on the progress of labor that is observed in some women with dysfunctional labor after the initiation of neuraxial analgesia[475] or in women who are extremely anxious.[476]

The epidural administration of a local anesthetic with epinephrine is followed by systemic absorption of both drugs. Some physicians have expressed concern that the epinephrine may exert a systemic beta-adrenergic tocolytic effect and slow labor. Early studies, which used large doses of epinephrine, suggested that the caudal epidural administration of local anesthetic with epinephrine prolonged the first stage of labor and increased the number of patients who required oxytocin augmentation of labor.[477] Subsequently, most studies have suggested that the addition of epinephrine 1.25 to 5 μg/mL (1:800,000 to 1:200,000) to the local anesthetic solution does not affect the progress of labor or method of delivery.*

There is no evidence that the specific local anesthetic or opioid used for neuraxial analgesia directly or indirectly affects the duration of labor.[86,479] In a randomized controlled trial, Tsen et al.[480] observed a higher rate of cervical dilation in women who received CSE analgesia than in those who received epidural analgesia. However, randomized controlled trials that compared CSE and epidural analgesia have not found a difference in the duration of labor between the two techniques.[430-432,434,481]

New evidence suggests that genetic polymorphism in the oxytocin receptor, catechol-O-methyltransferase (*COMT*), and β_2-adrenergic receptor (*ADRB2*) genes affect the progress of labor.[482,483] Whether these genotypes interact with neuraxial analgesia to affect the progress of labor requires further study with large numbers of parturients.

In summary, neuraxial analgesia appears to have a variable effect on the duration of the first stage of labor. It may shorten labor in some women and lengthen it in others. However, analgesia-related prolongation of the first stage of labor, if it occurs, is short, has not been shown to have adverse maternal or neonatal effects, and is probably of minimal clinical significance.

Second Stage of Labor

There is little doubt that effective neuraxial analgesia prolongs the second stage of labor. Meta-analyses of randomized controlled trials that compared neuraxial with systemic opioid analgesia support this clinical observation (see Table 23-12).[3,429] The mean duration of the second stage was 15 to 20 minutes longer in women randomly assigned to receive neuraxial analgesia than in women assigned to receive systemic opioid analgesia.[3,429]

The ACOG has defined a prolonged second stage in nulliparous women as lasting more than 3 hours with neuraxial analgesia and more than 2 hours without neuraxial analgesia; for parous women, it is more than 2 hours in those with neuraxial analgesia and more than 1 hour in those without neuraxial analgesia.[484] Zhang et al.[485] performed a secondary analysis of data from the Consortium on Safe Labor, a large, multicenter study from 19 hospitals across the United States, to characterize the duration of labor in a contemporary cohort of American women. Data were abstracted for term parturients in spontaneous labor with a singleton gestation in the vertex presentation and with normal perinatal outcome. The

*References 50, 88, 139, 141, 144, 478.

TABLE 23-13 Duration of Second Stage of Labor by Parity

	Parity 0 (n = 25,624)	Parity 1 (n = 16,755)	Parity ≥ 2 (n = 16,219)
Epidural Analgesia (h)	1.1 (3.6)	0.4 (2.0)	0.3 (1.6)
No Epidural Analgesia (h)	0.6 (2.8)	0.2 (1.3)	0.1 (1.1)

Data are median (95th percentile) duration of the second stage of labor in spontaneous laboring women.

Data from Zhang J, Landy HJ, Branch DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet Gynecol 2010; 116:1281-7.

95th percentiles for duration of the second stage of were 3.6 and 2.8 hours for nulliparous women with and without epidural analgesia, respectively (Table 23-13). Thus, these contemporary data suggest that a significant proportion of women will have a "prolonged" second stage, as defined by the ACOG criteria.

Rouse et al.[486] studied the relationship between second-stage duration and maternal and neonatal outcomes in nulliparous women by performing a secondary analysis of data collected as part of a multicenter study between 2002 and 2005. The rate of spontaneous vaginal delivery declined as the duration of the second stage of labor increased; however, over 55% of women whose second-stage duration was 3 hours or longer still went on to deliver vaginally.[486] The risk for chorioamnionitis, third- or fourth-degree perineal laceration, and uterine atony was greater in women with a prolonged second stage duration; however, after adjusting for mode of delivery, adverse neonatal outcomes did not differ in women whose second stage duration was 3 hours or longer, compared with those women with a shorter second-stage labor duration. The authors concluded that the second stage of labor does not need to be terminated based on duration alone. Extending the duration of the second stage will allow a significant number of women to deliver vaginally.

Other studies have confirmed that a delay in delivery is not harmful to the infant or mother provided that (1) electronic FHR monitoring confirms the absence of nonreassuring fetal status, (2) the mother is well hydrated and has adequate analgesia, and (3) there is ongoing progress in the descent of the fetal head.[484] The ACOG has stated that if progress is being made, the duration of the second stage alone does not mandate intervention.[484] A 2012 workshop was convened by the National Institute of Child Health and Human Development, the Society for Maternal-Fetal Medicine, and the ACOG with the goal of recommending practices that prevent primary cesarean delivery. The group concluded that a cesarean delivery for second-stage arrest in nulliparous women with epidural analgesia should not be considered unless there is no progress (descent or rotation) for more than 4 hours (Box 23-10).[487] Thus, the decision as to whether to perform an operative delivery in the second stage or allow continued observation should be made on the basis of clinical assessment of the woman and the fetus and the skill and training of the obstetrician.

BOX 23-10 Definition of Second-Stage Arrest

No progress (descent or rotation) for:

- Four hours or more in nulliparous women with epidural analgesia
- Three hours or more in nulliparous women without epidural analgesia
- Three hours or more in parous women with epidural analgesia
- Two hours or more in parous women without epidural analgesia

Definitions from Spong CY, Berghella V, Wenstrom KD, et al. Preventing the first cesarean delivery. Summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists Workshop. Obstet Gynecol 2012; 120:1181-93.

Second-Stage Management: Immediate versus "Delayed" Pushing. Many women are asked to begin "pushing" as soon as full cervical dilation has been confirmed, regardless of the fetal station. Some practitioners have suggested that "delayed" pushing might result in less maternal exhaustion and better maternal and fetal outcomes. Several studies have sought to determine whether immediate or delayed pushing for women with epidural analgesia during the second stage of labor affects labor duration and outcome.[488-498] Data are conflicting. A 2012 meta-analysis of studies that compared early and delayed pushing included nine high-quality and three low-quality randomized controlled trials involving approximately 3000 women.[499] Analysis of only the high-quality studies showed that delayed pushing did not influence the rate of spontaneous vaginal delivery (59.0% versus 54.9%; pooled RR, 1.07; 95% CI, 0.98 to 1.26) (Figure 23-14) or the rate of second-stage cesarean delivery. The total duration of the second stage was longer with delayed pushing (weighted mean difference, 57 min; 95% CI, 42 to 72), although duration of pushing was shorter. Heterogeneity in the reporting of neonatal outcomes among the trials precluded meta-analysis. One large study reported a higher incidence of low (< 7.10) umbilical arterial blood pH in the delayed pushing group[491]; however, other studies found no difference between groups in this outcome or in Apgar scores. The authors concluded that there are few clinical differences in outcomes between early and delayed pushing but that effects on maternal and neonatal outcomes remain unclear.

Although there do not appear to be any major advantages to delayed pushing, it does not seem reasonable to ask the mother to push from a high fetal station. It is common for anesthesia providers to be asked to decrease or discontinue neuraxial analgesia because the mother does not feel the urge to push when she is fully dilated. However, women with effective neuraxial analgesia do not feel the urge to push at a high fetal station. The density of neuraxial analgesia should not be decreased until the fetus has descended. If evaluation at this point determines that the mother still does not feel the urge to push, the maintenance dose may be reduced. Discontinuing the maintenance of analgesia is rarely indicated

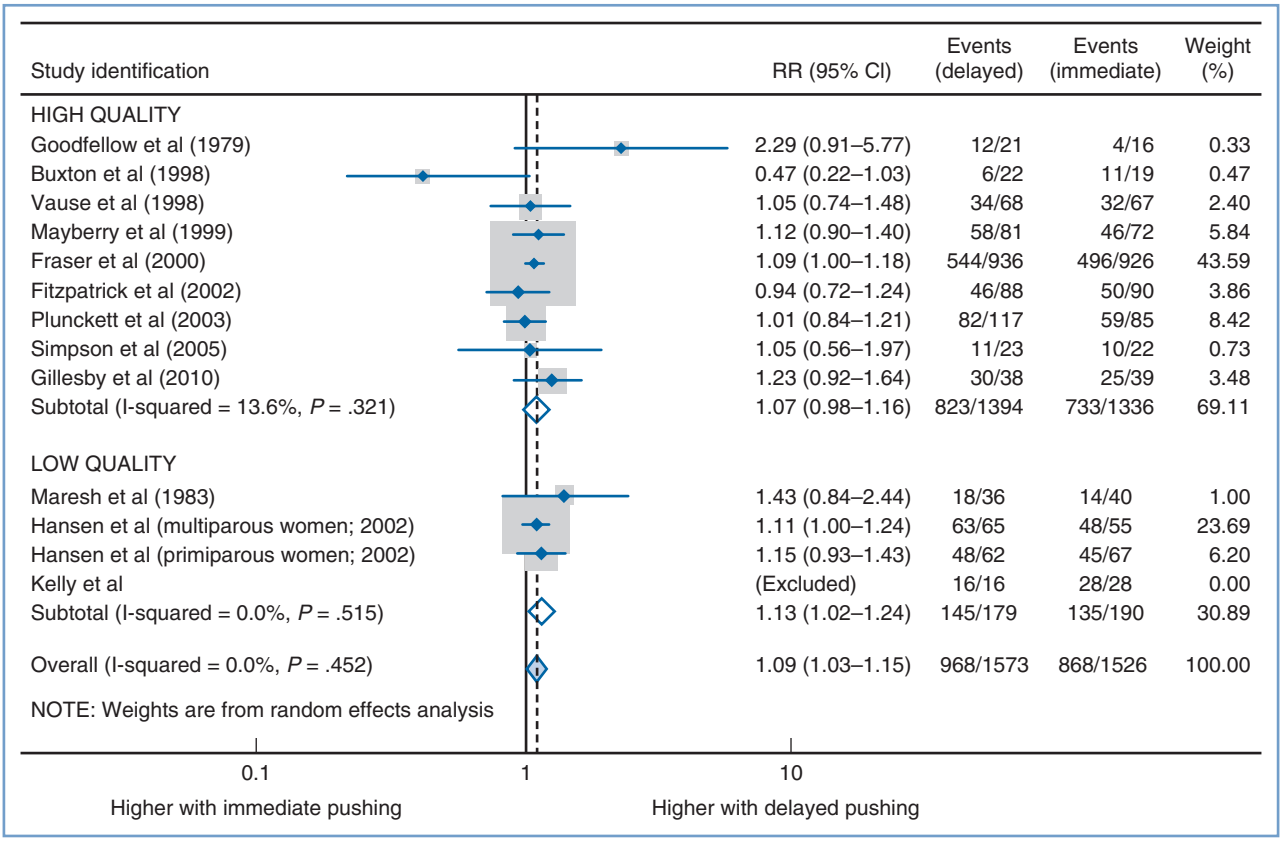


FIGURE 23-14 ■ Meta-analysis of delayed versus immediate pushing on the rate of spontaneous vaginal delivery, stratified by quality of study. The circle represents the point estimate and the diamond is the point estimate for the pooled risk ratio. The number of events is the number of spontaneous vaginal deliveries. *RR,* risk ratio; *CI,* confidence interval. (Modified from Tuuli M, Frey HA, Odibo AO, et al. Immediate compared with delayed pushing in the second stage of labor: a systematic review and meta-analysis. Obstet Gynecol 2012; 120:660-8.)

because analgesia/anesthesia may be difficult to reestablish if the need for operative delivery arises.

Third Stage

Rosaeg et al.[500] retrospectively reviewed the outcomes of 7468 women who underwent vaginal delivery at their hospital between 1996 and 1999. Epidural analgesia was not associated with a prolonged third stage of labor. The duration of the third stage of labor was shorter in women who received epidural analgesia and subsequently required manual removal of the placenta. The researchers suggested that epidural analgesia "provided a 'permissive' role"—in other words, epidural analgesia likely facilitated and/or encouraged earlier intervention by the obstetrician.

Other Factors and Progress of Labor

Oxytocin

Active management of labor is a concept that consists of a disciplined, standardized labor management protocol that includes early amniotomy and oxytocin augmentation if the cervix fails to dilate at a minimum rate (usually 1 cm/h in nulliparous women). Early studies suggested that this type of labor management decreased the rate of cesarean delivery.[501] More recently, meta-analysis of a number of randomized controlled trials suggests that active management of labor may have little effect on the cesarean delivery rate.[502] Although randomized trials of neuraxial compared with systemic opioid analgesia have consistently found that neuraxial analgesia does not cause an increase in the rate of cesarean delivery (see earlier discussion), Kotaska et al.[503] questioned the external validity of these trials because of oxytocin management. In a search of the medical literature, they identified 16 randomized controlled trials; 8 of the 16 trials included descriptions of labor management and these trials were included in the analysis. Seven of the eight trials described active management of labor and found no difference in the mode of delivery between groups. Only one of eight trials described the use of low-dose oxytocin and reported a markedly higher rate of cesarean delivery in the neuraxial analgesia group. Kotaska et al.[503] concluded that epidural analgesia in the setting of low-dose oxytocin probably increases the rate of cesarean delivery. The researchers were correct in stating that the role of oxytocin in neuraxial analgesia outcome studies has not been well controlled. However, their conclusion that epidural analgesia in the setting of low-dose oxytocin probably causes an increase in the rate of cesarean delivery is highly flawed because, in their analysis, the researchers did not include the eight studies that did not describe the management of labor. In all

probability the management of labor in these studies was not active (e.g., did not include high-dose oxytocin administration), or this would have been described.

In randomized controlled trials that compared the effects of neuraxial and systemic opioid analgesia on the outcome of labor, women who received neuraxial opioids had a higher rate of oxytocin augmentation.[3,429] In a meta-analysis that included 13 randomized trials, the risk ratio was 1.19 (95% CI, 1.03 to 1.39).[3] The reason(s) for this observation are not clear.

Randomized controlled trials that compared early and late initiation of neuraxial analgesia have used markedly different oxytocin protocols, yet all have concluded that early initiation of neuraxial analgesia does not have an adverse effect on the outcome of labor. In the study of early CSE analgesia by Wong et al.,[21] the rate of oxytocin use was high in both groups (approximately 93%). However, the maximum oxytocin infusion rate in the control (early systemic opioid) group was significantly higher than that in the early CSE group even though the median duration of labor was 81 minutes shorter in the CSE group. In the study of early epidural analgesia by Ohel et al.,[22] the rate of oxytocin use in both groups was much lower (approximately 29%); however, as in the study by Wong et al.,[21] the duration of labor was significantly shorter in the early neuraxial analgesia group. Taken together, the results of these studies do not support the hypothesis that oxytocin played a major role in the outcomes.

The ACOG supports the use of oxytocin for the treatment of dystocia or arrest of labor in the first or second stage, whether or not the patient is receiving neuraxial analgesia.[484]

Ambulation

Observational studies suggest that ambulation may be associated with less pain and a shorter duration of labor.[504] However, randomized controlled trials that compared ambulation and bed rest during the first stage of labor in women with neuraxial analgesia have not demonstrated any advantages of ambulation with regard to the progress or outcome of labor. Nageotte et al.[432] randomly assigned 505 nulliparous women to receive CSE analgesia either with or without ambulation. There was no difference between groups in the mode of delivery or duration of labor. These results agree with those of a meta-analysis of five randomized controlled trials involving 1161 women.[505] In addition, there were no differences between groups in the use of oxytocin augmentation, satisfaction with analgesia, or Apgar scores. No adverse effects were reported. These results are similar to those of trials that compared ambulation and bed rest in women without neuraxial analgesia.[506]

EFFECTS OF NEURAXIAL ANALGESIA ON THE FETUS AND NEONATE

Neuraxial analgesia may affect the fetus directly, indirectly, or both. First, systemic absorption of the anesthetic agents may be followed by transplacental transfer of the drug, which has a direct effect on the fetus. Second, the effects of neuraxial blockade on the mother may affect the fetus indirectly. Effects of local anesthetics and opioids on the fetus and neonate are discussed in detail in Chapter 13.

Direct Effects

Direct fetal effects include intrapartum drug effects on the FHR as well as possible respiratory depression after delivery. The determinants of maternal plasma drug concentration, transfer across the placenta, and effects on the neonate are discussed in Chapters 4 and 13. Determinants of maternal plasma drug concentration include dose, site of administration, metabolism and excretion of the drug, and the presence of adjuvants (e.g., epinephrine). Factors that influence placental transfer include maternal and fetal placental perfusion, the physicochemical characteristics of the drug, concentration of the free drug in maternal plasma, and permeability of the placenta. Most anesthetic and analgesic drugs, including local anesthetics and opioids, readily cross the placenta.

Fetal Heart Rate

Effects of local anesthetics and opioids on FHR may be direct and indirect (see earlier discussion)[474,479]; however, there is little evidence for a direct effect when these drugs are administered as components of neuraxial analgesia. Transient changes in FHR variability and periodic decelerations have been observed during epidural labor analgesia with bupivacaine and other local anesthetics.[479,507,508] These FHR decelerations were not associated with maternal hypotension. However, Loftus et al.[509] did not observe FHR decelerations in women who received epidural bupivacaine for elective cesarean delivery, despite the use of larger doses of bupivacaine and the occurrence of more extensive sympathetic blockade in comparison with epidural labor analgesia. Of interest, one study noted that the administration of either epidural bupivacaine or intrathecal sufentanil was followed by a similar incidence of FHR decelerations (23% and 22%, respectively) in laboring women.[510] Other studies have not observed a higher incidence of FHR decelerations associated with epidural administration of bupivacaine during labor.[511] Further, the reports of FHR decelerations after bupivacaine did not demonstrate adverse neonatal outcome; thus, the significance of these decelerations is unclear. There are no published data on the relationship between the concentration of bupivacaine used for intrapartum epidural analgesia and the incidence of FHR decelerations. Altogether, these data suggest that epidural local anesthetics have minimal, if any, direct effect on FHR.

Similarly, neuraxial opioid administration has little direct effect on the FHR.[109,512,513] In contrast, systemic meperidine analgesia was associated with a greater reduction of FHR variability and fewer FHR accelerations than epidural bupivacaine analgesia.[514] Spinal administration of local anesthetics and opioids results in lower maternal plasma concentrations of drug(s) than epidural administration and is therefore even less likely to cause a direct fetal effect.

Neonatal Depression

Systemic absorption of local anesthetic or opioid may have neonatal effects. This occurs more often after the systemic administration of opioid for labor analgesia.[21,515] The neonatal depressant effects of drugs administered to the mother in the intrapartum period are usually assessed with neurobehavioral testing. Unfortunately, these tests are quite subjective and lack specificity. Additionally, scientifically rigorous studies are lacking, and most of the local anesthetic studies were performed in the era when high-dose epidural analgesia was common; these observational studies found that local anesthetics administered as components of epidural analgesia were sometimes associated with minor, transient effects on neonatal behavior.[86,479,516]

When given by continuous epidural infusion, epidural opioid administration rarely results in accumulation of the drug and subsequent neonatal respiratory depression.* Bader et al.[220] noted that a continuous epidural infusion of 0.125% bupivacaine with fentanyl 2 μg/mL over a period of 1 to 15 hours did not result in significant fetal drug accumulation or adverse neonatal effects (in this study, the maximal cumulative dose of fentanyl was 300 μg). Porter et al.[221] reported no adverse effect of fentanyl on neurobehavioral scores or other indices of fetal welfare when patients received an epidural infusion of 0.0625% bupivacaine with or without fentanyl 2.5 μg/mL. The mean ± SD maternal dose of fentanyl was 183 ± 75 μg (range, 53 to 400 μg). Loftus et al.[109] observed only a modest reduction in NACS at 24 hours in neonates whose mothers had received epidural fentanyl during labor; neonates exposed to sufentanil during labor had a somewhat higher NACS at 24 hours, and sufentanil was detected in the umbilical arterial blood in only one of nine samples. Vertommen et al.[107] observed no difference in Apgar scores or NACS in neonates whose mothers were randomly assigned to receive epidural sufentanil (up to 30 μg) during the course of labor and a control group that did not receive sufentanil.[107] Maternal sufentanil levels were below the sensitivity of the assay (0.1 ng/mL) after an epidural bolus of 10 μg.[114]

Intrathecal administration of an opioid during labor would be expected to have even fewer direct effects on the fetus than epidural administration. Smaller doses of opioid are administered, and less drug is absorbed systemically.

Indirect Effects

The indirect fetal effects of epidural and intrathecal opioids may be more significant than the direct effects. Obviously, if the mother has severe respiratory depression and hypoxemia, fetal hypoxemia and hypoxia will follow.[357] More common is the occurrence of fetal bradycardia after initiation of neuraxial analgesia. The presumed cause is that the rapid onset of analgesia results in decreased plasma concentrations of catecholamines.[474] Epinephrine causes uterine relaxation by stimulating β_2-adrenergic uterine receptors. A reduced circulating concentration of epinephrine may result in increased uterine tone. Because uteroplacental perfusion occurs during periods of uterine diastole (i.e., uterine relaxation), uterine tachysystole may result in decreased uteroplacental perfusion and fetal hypoxia.

Published observations suggest that uterine tachysystole and fetal bradycardia may follow the administration of either intrathecal or epidural analgesia during labor. Abrão et al.[518] randomized 72 laboring women to receive either CSE or epidural analgesia, and they observed the incidence of FHR abnormalities (prolonged deceleration or bradycardia) and an elevation in uterine tone (defined as an increase of 10 mm Hg or more in basal uterine pressure). The incidences of FHR abnormalities (32% versus 6%), and FHR abnormalities combined with an increase in uterine pressure (27% versus 3%), were significantly higher in the CSE group than in the epidural group. However, a significant limitation of this study is that the outcomes were assessed for only 15 minutes after the initiation of analgesia and the analgesic techniques were not equipotent.[519] The overall high incidence of FHR abnormalities noted in the study may have been due to the initiation of analgesia in women in advanced labor.

Fortunately, fetal bradycardia after labor analgesia does not appear to increase the overall risk for adverse outcome. Albright and Forster[520] retrospectively reviewed outcomes for 2560 women who delivered at their hospital between March 1995 and April 1996. Approximately half of the patients received CSE analgesia (10 to 15 μg of intrathecal sufentanil), and the other half received either systemic opioids or no medication. There was no difference between the two groups in the incidence of emergency cesarean delivery (1.3% versus 1.4%, respectively). Mardirosoff et al.[521] performed a systematic review of reports of randomized comparisons of intrathecal opioid analgesia with any nonintrathecal opioid regimen in laboring women. The investigators noted that intrathecal opioid analgesia was associated with a significant increase in the risk for fetal bradycardia (OR, 1.8; 95% CI, 1.0 to 3.1). However, the risk for cesarean delivery for FHR abnormalities was similar in the two groups (6.0% versus 7.8%, respectively). Van de Velde et al.[522] randomly assigned laboring women to one of the following three treatment regimens: intrathecal sufentanil 7.5 μg, intrathecal sufentanil 1.5 μg/bupivacaine 2.5 mg/epinephrine 2.5 μg, and epidural bupivacaine 12.5 mg/sufentanil 7.5 μg/epinephrine 12.5 μg. Although the incidence of FHR abnormalities was higher in the high-dose intrathecal sufentanil group, there was no difference among groups in the need for emergency cesarean delivery.

Given the risk for fetal bradycardia with neuraxial analgesia in laboring women, the FHR should be monitored during and after the administration of either epidural or intrathecal analgesia. Treatment of fetal bradycardia includes (1) relief of aortocaval compression; (2) discontinuation of intravenous oxytocin; (3) administration of supplemental oxygen; (4) treatment of maternal hypotension, if present; and (5) fetal scalp stimulation. Persistent uterine tachysystole should also prompt the administration of a tocolytic drug (e.g., terbutaline or nitroglycerin).

*References 107, 109, 114, 220, 221, 517.

CONCLUSIONS AND RECOMMENDATIONS

Philosophy of Labor Analgesia

An unacceptably high number of women involuntarily experience severe pain during labor. As noted by the ASA and the ACOG, "There is no other circumstance where it is considered acceptable for a person to experience severe pain, amenable to safe intervention, while under a physician's care."[18,19] Unfortunately, labor represents one of the few circumstances in which the provision of effective analgesia is alleged to interfere with the parturient's and obstetrician's goal (e.g., spontaneous vaginal delivery). Dense neuraxial anesthesia may adversely affect the progress of labor in some patients. Indeed, given the complicated neurohumoral and mechanical processes involved in childbirth, it would be unreasonable to expect that neuroblockade of the lower half of the body would *not* have an effect on this process, whether positive or negative. However, maternal-fetal factors and obstetric management—not the use of neuraxial analgesia—are the most important determinants of the outcome of labor. Anesthesia providers should identify those methods of analgesia that provide the most effective pain relief without unduly increasing the risk for obstetric intervention. Operative delivery increases the risk for maternal morbidity and mortality and is more expensive than spontaneous vaginal delivery. Randomized trials suggest that the use of neuraxial analgesia does not increase the cesarean delivery rate but may adversely influence the instrumental vaginal delivery rate.[3] Further, neuraxial analgesia may occasionally, either directly or indirectly, have adverse—usually temporary—effects on the fetus.

Despite these risks, many women opt for neuraxial analgesia because no other method of labor analgesia provides its benefits (almost complete analgesia), and the risks are acceptably low. Even no analgesia may be more hazardous to some women than neuraxial analgesia (e.g., patients with an anticipated difficult airway or those at high risk for emergency cesarean delivery). Therefore, it is the duty of the anesthesia provider to provide appropriate (albeit not always total) pain relief during the first and second stages of labor. Analgesia should be tailored to the individual patient's labor, medical condition, preferences, and goals. Most women strongly dislike dense motor blockade, and many prefer to maintain some sensation of uterine contractions and perineal pressure, especially during the second stage of labor. However, a few women may accept the probable increase in risk for instrumental vaginal delivery in exchange for dense analgesia.

A Practical Guide to Neuraxial Labor Analgesia

Initiation of Analgesia

Neuraxial labor analgesia may be initiated with either the intrathecal (CSE) or the epidural injection of analgesic/anesthetic agents. The decision regarding the specific technique and choice of drugs and doses is individualized for each parturient. Parity, stage and phase of labor, use of intravenous oxytocin, and the presence of any coexisting disease(s), as well as the status of the fetus, are all considered in the decision.

In healthy *nulliparous* women in *early* labor (< 4 to 5 cm cervical dilation), my colleagues and I often initiate CSE analgesia with an intrathecal opioid alone (e.g., fentanyl 25 μg or sufentanil 5 μg), followed by placement of an epidural catheter and administration of a standard lidocaine 45 mg/epinephrine 15 μg epidural test dose. Some anesthesia providers initiate intrathecal analgesia with both an opioid and a local anesthetic. The addition of a local anesthetic is unnecessary for achieving complete spinal analgesia during early labor; it may increase the risk for hypotension and result in motor blockade in some patients, particularly if it is followed by injection of an epidural test dose that contains a local anesthetic. However, the intrathecal administration of both an opioid and a local anesthetic achieves a longer duration of analgesia and lower incidence and severity of pruritus than intrathecal injection of an opioid alone.

Alternatively, epidural analgesia can be initiated with injection of a low-concentration local anesthetic solution (bupivacaine 0.0625% to 0.125%) combined with an opioid (fentanyl 50 to 100 μg). The epidural catheter is sited and a standard epidural test dose is injected, followed by administration of 5 to 15 mL of the local anesthetic/opioid solution, injected in 5-mL increments. Ten to 15 mL provides satisfactory analgesia for most nulliparous women in early labor; injection of 20 mL may be necessary if a dilute solution (e.g., 0.0625% bupivacaine) is used. A smaller dose is necessary if administered after a standard test dose.

We typically give an epinephrine-containing test dose before initiation of epidural analgesia in laboring women. Some anesthesia providers elect to omit the epidural test dose when initiating epidural labor analgesia, particularly if a woman wishes to ambulate in early labor. The omission of the epidural test dose requires that the therapeutic dose of local anesthetic be injected slowly, incrementally, and cautiously, because the therapeutic dose functions as the test dose. These precautions should be followed with all bolus injections of local anesthetic through an epidural catheter.

For *nulliparous* women in the active phase of the first stage of labor, CSE analgesia is usually initiated with the intrathecal injection of an opioid combined with a local anesthetic (fentanyl 15 μg and bupivacaine 2.5 mg). Alternatively, epidural analgesia can be initiated with a local anesthetic (bupivacaine 0.125%) combined with an opioid (fentanyl 100 μg). Women in active labor may require a higher total volume of epidural local anesthetic solution (15 to 20 mL) than women in early labor (10 to 15 mL) as well as a higher local anesthetic concentration (e.g., 0.125% rather than 0.0625% bupivacaine).

Labor typically progresses at a faster rate in *parous* women, who often require a more rapid onset of analgesia and more extensive neuroblockade than nulliparous women when neuraxial analgesia is initiated at the same cervical dilation. Therefore, in healthy parous women CSE analgesia is usually initiated with an intrathecal

opioid combined with a local anesthetic, regardless of the stage and phase of labor. Alternatively, epidural analgesia is initiated with bupivacaine 0.125% combined with fentanyl 100 μg.

CSE analgesia with both a local anesthetic and an opioid is particularly advantageous for parous women in the late active phase of the first stage of labor and in all women in whom neuraxial analgesia is initiated in the second stage of labor. Sacral neuroblockade is required for complete analgesia during the second stage of labor; this neuroblockade is difficult to accomplish in a timely fashion with an initial (*de novo*) lumbar epidural injection of analgesic/anesthetic agents. (For initiation of lumbar epidural anesthesia in late labor, the injection of a large volume [≥ 20 mL] of local anesthetic solution may be required to achieve sacral analgesia, and this injection often results in a mid- or high-thoracic neuroblockade that is more extensive than desired. Therefore, when initiating neuraxial analgesia in late labor, a CSE technique is preferred).

Maintenance epidural analgesia is typically initiated soon after the initiation of analgesia (within 15 to 30 minutes) rather than waiting for the neuroblockade to regress. There are several advantages to this technique. Most women experience seamless analgesia (i.e., there is no window of pain as the initial block regresses). The workload for the anesthesia provider is lessened, because he or she can set up and initiate the epidural infusion while monitoring the patient for hypotension after initiation of neuroblockade. Finally, an epidural bolus of local anesthetic is not required to reestablish or extend neuroblockade, possibly enhancing safety.

Analgesia is typically maintained with a dilute solution of an amide local anesthetic and an opioid, administered by continuous infusion or PCEA. My colleagues and I prefer PCEA because it allows patient titration of neuroblockade and entails less risk for breakthrough pain. Patient satisfaction is better and the workload for the anesthesia provider is decreased. At our institution, the PCEA infusion pump parameters are the same for all laboring women, so there are fewer errors in pump setup. However, when a continuous infusion is used without PCEA to maintain analgesia, it may be necessary to titrate the continuous infusion rate to individual patient needs. For example, women in early labor require less drug to maintain analgesia (6 to 10 mL/h), whereas women in more advanced labor may require a higher infusion rate (8 to 15 mL/h). Similarly, a parous patient may require a higher infusion rate than a nulliparous patient, even though analgesia is initiated at the same stage of labor.

Some parturients experience breakthrough pain. After evaluating the nature of the pain, the extent of neuroblockade, and the progress of labor, we usually treat breakthrough pain with a bolus epidural injection of bupivacaine 0.125%, 10 to 15 mL, administered in 5-mL increments. The patient may benefit from additional instruction about the optimal use of PCEA. Occasionally, we may elect to use a more concentrated local anesthetic solution (e.g., bupivacaine 0.25%), particularly in the presence of an abnormal fetal position or dysfunctional labor. In this case, the concentration of the maintenance solution may also need to be increased.

This maintenance technique usually results in satisfactory perineal analgesia for delivery. Occasionally, women with epidural analgesia require additional (more dense) analgesia for delivery, particularly if an instrumental vaginal delivery is planned. In this case, we often administer 5 to 12 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine. This usually results in satisfactory sacral anesthesia in a patient with preexisting epidural labor analgesia.

There is no single correct way to provide neuraxial labor analgesia, although for particular patients and specific clinical conditions some methods may have advantages over others. Frequent communication among members of the anesthesia, obstetric, and nursing teams is essential to the safe and satisfactory provision of neuraxial labor analgesia. In addition, within each labor and delivery unit, consistency among anesthesia providers in their choice of techniques, specific drugs, and drug doses/concentrations is likely to result in fewer errors and higher satisfaction among other caregivers and patients.

KEY POINTS

- Neuraxial analgesia is the most effective form of intrapartum analgesia currently available.
- In most cases, maternal request for pain relief represents a sufficient indication for the administration of neuraxial analgesia.
- The safe administration of neuraxial analgesia requires a thorough (albeit directed) preanesthetic evaluation and the immediate availability of appropriate resuscitation equipment.
- Neuraxial labor analgesia is not a generic procedure. The procedure should be tailored to individual patient needs.
- The administration of the epidural test dose should allow the anesthesia provider to recognize most cases of unintentional intravascular or intrathecal placement of the epidural catheter. All therapeutic doses of local anesthetic should be administered incrementally.
- Bupivacaine is the local anesthetic most often used for epidural analgesia during labor. Ropivacaine and levobupivacaine are satisfactory alternatives. Most anesthesia providers reserve 2-chloroprocaine and lidocaine for cases that require the rapid extension of epidural anesthesia for vaginal or cesarean delivery.
- The addition of a lipid-soluble opioid to a neuraxial local anesthetic allows the anesthesia provider to provide excellent analgesia while reducing the total dose of local anesthetic and minimizing the side effects of each agent. Perhaps the major advantage of this technique is that the severity of motor block can be minimized during labor.

- Intrathecal opioids alone may provide complete analgesia during the early first stage of labor. Epidural opioids without local anesthetics do not provide complete analgesia during labor.
- Administration of a local anesthetic (with or without an opioid) is necessary to provide complete neuraxial analgesia for the late first stage and the second stage of labor. Although a neuraxial local anesthetic alone can provide complete analgesia, the required dose is often associated with an undesirably dense degree of motor blockade.
- Hypotension is a common side effect of neuraxial analgesia. Prophylaxis and treatment involve the avoidance of aortocaval compression and the administration of a vasopressor as needed. The administration of an intravenous fluid "preload" does not significantly decrease the incidence of hypotension in euvolemic patients.
- Other potential side effects of neuraxial analgesia include pruritus, shivering, urinary retention, delayed gastric emptying, maternal fever, and fetal heart rate changes.
- Complications of neuraxial analgesia include inadequate analgesia, unintentional dural puncture, respiratory depression, unintentional intravenous injection, and extensive or total spinal anesthesia.
- The presence of severe pain during early labor—and/or an increase in local anesthetic/opioid dose requirement—may signal a higher risk for prolonged labor and operative delivery.
- Neuraxial labor analgesia is not associated with a higher rate of cesarean delivery than systemic opioid analgesia.
- Initiation of neuraxial analgesia in early labor (cervical dilation < 4 to 5 cm) does not increase the rate of cesarean delivery or prolong the duration of labor.
- Effective neuraxial analgesia likely results in a modest prolongation of the second stage of labor.
- Controversy exists as to whether there is a cause-and-effect relationship between neuraxial labor analgesia and risk for instrumental vaginal delivery. Dense neuroblockade (e.g., presence of significant motor blockade) and complete analgesia during the second stage of labor probably increase the rate of instrumental vaginal delivery. Use of a dilute solution of local anesthetic and opioid is less likely to adversely affect the progress of labor.
- Maternal-fetal factors and obstetric management—not the use of neuraxial analgesia—are the most important determinants of the cesarean delivery rate.

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CHAPTER 24

Alternative Regional Analgesic Techniques for Labor and Vaginal Delivery

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Neuraxial analgesic techniques are the most flexible analgesic techniques available for obstetric patients. The anesthesia provider may use an epidural or a spinal technique to provide effective analgesia during the first and/or second stage of labor. Subsequently, the epidural or spinal technique may be used to achieve anesthesia for either vaginal or cesarean delivery. Unfortunately, some maternal conditions (e.g., coagulopathy, hemorrhage) contraindicate the administration of neuraxial analgesia. Many parturients do not have access to neuraxial analgesia, and others do not want it. The purpose of this chapter is to discuss alternative regional analgesic techniques for labor and vaginal delivery.

PARACERVICAL BLOCK

During the first stage of labor, pain results primarily from dilation of the cervix and distention of the lower uterine segment and upper vagina. Pain impulses are transmitted from the upper vagina, cervix, and lower uterine segment by visceral afferent nerve fibers that join the sympathetic chain at L2 to L3 and enter the spinal cord at T10 to L1. Some obstetricians perform paracervical block to provide analgesia during the first stage of labor. The goal is to block transmission through the paracervical ganglion—also known as *Frankenhäuser's ganglion*—which lies immediately lateral and posterior to the cervicouterine junction.

Paracervical block does not adversely affect the progress of labor. Further, it provides analgesia without the annoying sensory and motor blockade that may result from neuraxial analgesia. The paracervical technique does not block somatic sensory fibers from the lower vagina, vulva, and perineum. Thus, it does not relieve the pain caused by distention of these structures during the late first stage and second stage of labor. Contemporary experience suggests that paracervical block results in satisfactory analgesia during the first stage of labor in 50% to 75% of parturients. One study noted that paracervical block provided better analgesia in nulliparous women than in parous women, probably because paracervical block does not provide effective analgesia for the sudden and rapid descent of the presenting part that often occurs in parous women.[1]

In 1981, approximately 5% of laboring women in the United States received paracervical block,[2] and 2% to 3% of parturients in the United States received paracervical block during labor in 2001.[3] Paracervical block remains more popular in Scandinavian countries. Approximately 17% of Finnish parturients received paracervical block during labor in 2004-2005.[4] In the United States, the decline in the popularity of paracervical block has resulted from both fear of fetal complications and the greater popularity of neuraxial analgesic techniques.

Jensen et al.[5] randomly assigned 117 nulliparous women to receive either bupivacaine paracervical block

or intramuscular meperidine 75 mg. Women in the paracervical block group had significantly better analgesia than women in the meperidine group at 20, 40, and 60 minutes. During the first 60 minutes, pain relief was complete or acceptable in 78% of the women in the paracervical block group but in only 31% of the women in the meperidine group. Two fetuses in the paracervical block group and one in the meperidine group had transient bradycardia. A total of 6 infants in the paracervical block group and 16 infants in the meperidine group ($P < .05$) had fetal/neonatal depression, which the investigators defined as an umbilical arterial blood pH of 7.15 or less and/or a 1-minute Apgar score of 7 or less.[5] A 2012 Cochrane Review cited this study as evidence that paracervical block provides more effective analgesia during labor than intramuscular meperidine.[6]

In a recent study, Junttila et al.[4] randomly assigned 122 parous women to receive either bupivacaine paracervical block or single-shot spinal bupivacaine with sufentanil. Single-injection spinal analgesia was superior to that provided by paracervical block (Figure 24-1), although paracervical block resulted in a pain score of 3 or less in 43% of the study subjects, and over half of the women in the paracervical block group indicated that they would be happy to receive this method of analgesia during labor in a future pregnancy. There was no difference between the two groups in the incidence of fetal heart rate (FHR) abnormalities, and there were no cases of fetal bradycardia in either group.[4]

Kangas-Saarela et al.[7] compared neonatal neurobehavioral responses in 10 infants whose mothers received bupivacaine paracervical block with those in 12 infants whose mothers received no analgesia. The investigators performed paracervical block while each patient lay in a left lateral position, and they limited the depth of the injection into the vaginal mucosa to 3 mm or less. They observed no significant differences between groups in neurobehavioral responses at 3 hours, 1 day, 2 days, or 4 to 5 days after delivery. These investigators concluded that properly performed paracervical block does not adversely affect newborn infant behavior or neurologic function.[7]

Technique

Paracervical block is performed with the patient in a modified lithotomy position. The uterus should be displaced leftward during performance of the block; this displacement may be accomplished by placing a folded pillow beneath the patient's right buttock. The physician uses a needle guide to define and limit the depth of the injection and to reduce the risk for vaginal or fetal injury. The physician introduces the needle and needle guide into the vagina with the left hand for the left side of the pelvis and with the right hand for the right side (Figure 24-2). The needle and needle guide are introduced into the left or right lateral vaginal fornix, near the cervix, at the 4-o'clock or the 8-o'clock position. The needle is

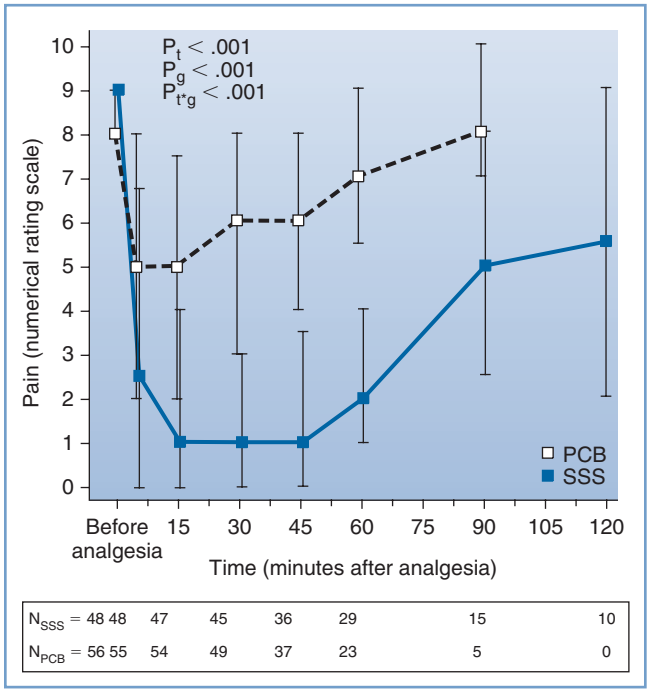

FIGURE 24-1 ■ Pain scores over time before and after paracervical block (10 mL of 0.25% bupivacaine) or single-shot spinal (intrathecal) injection of bupivacaine 2.5 mg and sufentanil 2.5 μg. Data are median pain scores with the 25th and 75th percentiles. *PCB,* paracervical block; *SSS,* single-shot spinal analgesia; P_t, P-time; P_g, P-groups; P_{t*g}, P-time*group. *N,* number of parturients at the measurement time points. (From Junttilla EK, Karjalainen PK, Ohtonen PP, et al. A comparison of paracervical block with single-shot spinal for labour analgesia in multiparous women: a randomized controlled trial. Int J Obstet Anesth 2009; 18:15-21.)

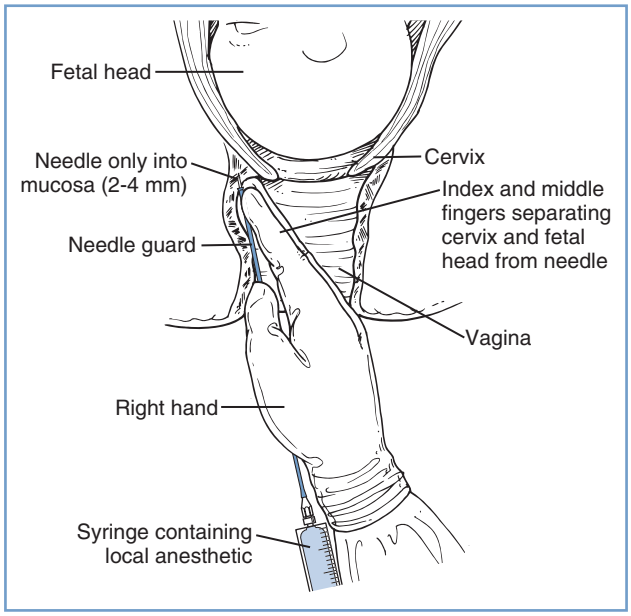

FIGURE 24-2 ■ Technique of paracervical block. Notice the position of the hand and fingers in relation to the cervix and fetal head. No undue pressure is applied at the vaginal fornix by the fingers or the needle guide, and the needle is inserted to a shallow depth. (Redrawn from Abouleish E. Pain Control in Obstetrics. New York, JB Lippincott, 1977:344.)

advanced through the vaginal mucosa to a depth of 2 to 3 mm.[8] The physician should aspirate before each injection of local anesthetic. A total of 5 to 10 mL of local anesthetic, without epinephrine, is injected on each side.[9] Some obstetricians recommend giving incremental doses of local anesthetic on each side (e.g., 2.5 to 5 mL of local anesthetic between the 3-o'clock and 4-o'clock positions, followed by 2.5 to 5 mL between the 4-o'clock and 5-o'clock positions).[8,10,11]

After injecting the local anesthetic in either the left or right lateral vaginal fornix, the physician should wait 5 to 10 minutes and observe the FHR before injecting the local anesthetic on the other side.[11] Some obstetricians do not endorse this recommendation. Van Dorsten et al.[12] randomly assigned 42 healthy parturients at term to either of two methods of paracervical block. The study group experienced a 10-minute interval between injections of local anesthetic on the left and right sides of the vagina. The control group had almost simultaneous injections on the left and right sides. No cases of fetal bradycardia occurred in either group. The investigators concluded that patient selection and lateral positioning after the block have a more important role in the prevention of post–paracervical block fetal bradycardia than spacing the injections of local anesthetic. However, because they studied only 42 patients and had no cases of fetal bradycardia in either group, they could not exclude the possibility that incremental injection might reduce the incidence of fetal bradycardia in a larger series of patients.

Choice of Local Anesthetic

The physician should administer small volumes of a dilute solution of local anesthetic. There is no reason to inject more than 10 mL of local anesthetic on each side. Further, there is no indication for the use of concentrated solutions, such as 2% lidocaine, 0.5% bupivacaine, or 3% 2-chloroprocaine. Nieminen and Puolakka[13] observed that paracervical block with 10 mL of 0.125% bupivacaine (5 mL on each side) provided analgesia similar to that provided by 10 mL of 0.25% bupivacaine.

The choice of local anesthetic is controversial. The North American manufacturers of bupivacaine have stated that bupivacaine is contraindicated for the performance of paracervical block. In contrast, many European obstetricians—especially those in Finland—have expressed a preference for bupivacaine for this procedure. Bupivacaine has greater cardiotoxicity than other local anesthetic agents, and some investigators have suggested that its use leads to a higher incidence of fetal bradycardia or adverse outcome than use of other local anesthetics for paracervical block. In a review of 50 cases of perinatal death associated with paracervical block, Teramo[14] found that the local anesthetic was bupivacaine in at least 29 of the 50 cases.

Palomäki et al.[15] hypothesized that levobupivacaine might result in a lower incidence of post–paracervical block fetal bradycardia than racemic bupivacaine. In a randomized double-blind study of 397 laboring women, paracervical block was performed with 10 mL of either 0.25% levobupivacaine or 0.25% racemic bupivacaine. The incidence of transient FHR abnormalities was 10.4% in the levobupivacaine group and 12.8% in the racemic bupivacaine group, and that of fetal bradycardia was 2.6% in the levobupivacaine group and 3.8% in the racemic bupivacaine group (P = NS).

Some physicians have suggested that 2-chloroprocaine is the local anesthetic of choice for paracervical block. Published studies suggest but do not prove that post–paracervical block fetal bradycardia occurs less frequently with 2-chloroprocaine than with amide local anesthetics.[10,16-18] Weiss et al.[16] performed a double-blind study in which 60 patients were randomly assigned to receive 20 mL of either 2% 2-chloroprocaine or 1% lidocaine for paracervical block. Bradycardia occurred in 1 of the 29 fetuses in the 2-chloroprocaine group, compared with 5 of 31 fetuses in the lidocaine group (P = .14). LeFevre[18] retrospectively observed that fetal bradycardia occurred after 2 (6%) of 33 paracervical blocks performed with 2-chloroprocaine versus 44 (12%) of 361 paracervical blocks performed with mepivacaine (P = .29).

2-Chloroprocaine undergoes rapid enzymatic hydrolysis. Thus it has the shortest intravascular half-life among the local anesthetics used clinically. This rapid metabolism seems advantageous in the event of unintentional intravascular or fetal injection. Philipson et al.[17] performed paracervical block with 10 mL of 1% 2-chloroprocaine in 16 healthy parturients. At delivery, only trace concentrations of 2-chloroprocaine were detected in one (6%) of the maternal blood samples and four (25%) of the umbilical cord venous blood samples. The investigators concluded[17]:

> *In all of the studies of paracervical block with 2-chloroprocaine, there were no cases in which the abnormal fetal heart rate patterns were associated with depressed neonates. This is in contrast to the studies with amide local anesthetics and may be explained by the rapid enzymatic inactivation of 2-chloroprocaine.*

Some obstetricians dislike 2-chloroprocaine because of its relatively short duration of action. However, in one study the mean duration of analgesia was 40 minutes after paracervical administration of either 2-chloroprocaine or lidocaine.[16] A 2012 Cochrane Review concluded that the choice of local anesthetic agent did not affect maternal satisfaction with pain relief after paracervical block.[6]

Maternal Complications

Maternal complications of paracervical block are uncommon but may be serious (Box 24-1).[19-22] Systemic local anesthetic toxicity may result from direct intravascular injection or rapid systemic absorption of the local anesthetic. Postpartum neuropathy may follow direct sacral plexus trauma, or it may result from hematoma formation. Retropsoal and subgluteal abscesses are rare but may result in maternal morbidity or mortality.[21,22]

Fetal Complications

In some cases, fetal injury results from direct injection of local anesthetic into the fetal scalp during paracervical

BOX 24-1 Maternal Complications of Paracervical Block

- Vasovagal syncope
- Laceration of the vaginal mucosa
- Systemic local anesthetic toxicity
- Parametrial hematoma
- Postpartum neuropathy
- Paracervical, retropsoal, or subgluteal abscess

block.[23] Fetal scalp injection of 10 or 20 mL of local anesthetic undoubtedly causes systemic local anesthetic toxicity, which may result in fetal death. Fetal scalp injection seems more likely to occur when the obstetrician performs paracervical block in the presence of advanced (i.e., > 8 cm) cervical dilation.

Bradycardia is the most common fetal complication. Fetal bradycardia typically develops within 2 to 10 minutes after the injection of local anesthetic. Most cases resolve within 5 to 10 minutes, but some cases of bradycardia persist for as long as 30 minutes. Published studies have noted an incidence of bradycardia that varies between 0% and 70%.[4,11,18,24-31] These figures represent extremes on either side of the true incidence of this complication. Some studies have overstated the problem by defining bradycardia as a baseline FHR of less than 120 bpm. (A baseline FHR of 110 bpm does not necessarily indicate fetal compromise.) Experienced obstetricians clearly do not encounter clinically significant fetal bradycardia after 70% of their paracervical blocks. It is equally clear that the incidence of clinically significant fetal bradycardia is not zero, and it is difficult to teach this technique without placing some fetuses at risk.

Shnider et al.[26] reported that fetal bradycardia occurred after 24% of 845 paracervical blocks administered to 705 patients with either 1% mepivacaine, 1% lidocaine, or 1% propitocaine (prilocaine). Neonatal depression occurred significantly more often in infants who had FHR changes after paracervical block than in a control group or in a group of infants with no FHR changes after paracervical block. In contrast, Carlsson et al.[27] performed 523 paracervical blocks with 0.125% or 0.25% bupivacaine in 469 women. Of the total, nine (1.9%) fetuses had bradycardia, but at delivery all nine of the newborns had a 5-minute Apgar score of 9 or 10.

Goins[28] observed fetal bradycardia in 24 (13%) of 182 patients who received paracervical block with 20 mL of 1% mepivacaine. He compared neonatal outcome for these patients with neonatal outcome for 343 patients who received other analgesic/anesthetic techniques. There was a slightly higher incidence of low Apgar scores at 1 minute and 5 minutes in the paracervical block group, but the difference was not statistically significant. LeFevre[18] observed fetal bradycardia after 46 (11%) of 408 paracervical blocks. Fetal bradycardia was more common in those patients with a nonreassuring FHR tracing before the performance of paracervical block.

In a review of four randomized controlled trials published between 1975 and 2000, Rosen[30] estimated that the incidence of post–paracervical block fetal bradycardia is 15%. More recently, Volmanen et al.[31] reviewed four studies of paracervical block that had adequate sample size (n > 200), used the superficial injection technique, and administered 0.125% or 0.25% bupivacaine. Among the 1361 patients in these four studies, the incidence of fetal bradycardia was 2.2%. The observed episodes of fetal bradycardia were transient and did not require emergency cesarean delivery.[31]

Etiology of Fetal Bradycardia

The etiology of fetal bradycardia after paracervical block is unclear. Investigators have offered at least four theories that might explain the etiology of fetal bradycardia, as discussed here.

Reflex Bradycardia. Manipulation of the fetal head, the uterus, or the uterine blood vessels during performance of the block may cause reflex fetal bradycardia.[25]

Direct Fetal Central Nervous System and Myocardial Depression. The performance of paracervical block results in the injection of large volumes of local anesthetic close to the uteroplacental circulation. Local anesthetic rapidly crosses the placenta[32] and may cause fetal central nervous system (CNS) depression, myocardial depression, and/or umbilical vasoconstriction. Puolakka et al.[33] observed that the most common abnormality after paracervical block was the disappearance of FHR accelerations. They speculated that FHR changes result from rapid transplacental passage of local anesthetic into the fetal circulation, followed by a direct toxic effect of the local anesthetic on the FHR regulatory centers.

Some investigators have suggested that fetal bradycardia results from a direct toxic effect of the local anesthetic on the fetal heart.[34,35] Shnider et al.[34] reported that in four cases of fetal bradycardia, mepivacaine concentrations in fetal scalp blood were higher than peak concentrations in maternal arterial blood. Asling et al.[35] made similar observations in six of seven cases of fetal bradycardia. They suggested that local anesthetic reaches the fetus by a more direct route than maternal systemic absorption, and they speculated that high fetal concentrations of local anesthetic result from local anesthetic diffusion across the uterine arteries. This would lead to local anesthetic concentrations in intervillous blood that are higher than concentrations in maternal brachial arterial blood. High fetal concentrations would then occur from the passive diffusion of local anesthetic across the placenta.

High fetal concentrations of local anesthetic also may result from fetal acidosis and ion trapping.[36,37] Local anesthetics are weak bases, and if acidosis develops in a fetus, increasing amounts of local anesthetic will cross the placenta regardless of the site of maternal injection. It is also possible that the obstetrician may directly inject local anesthetic into uterine blood vessels.

Most studies have noted that local anesthetic concentrations in the fetus are consistently lower than those in the mother after paracervical block.[9] Further, fetal bradycardia has not consistently occurred in documented cases of fetal local anesthetic toxicity. Freeman et al.[38] injected 300 mg of mepivacaine directly into the scalp of

two anencephalic fetuses. The QRS complex widened, the PR interval lengthened, and both fetuses died, but fetal bradycardia did not occur before fetal death. In contrast, the investigators observed no widening of the QRS complex or lengthening of the PR interval in normal fetuses demonstrating bradycardia after paracervical block. Rather, the fetal electrocardiogram (ECG) changes were consistent with sinoatrial node suppression with a wandering atrial pacemaker. The investigators concluded that a mechanism other than direct fetal myocardial depression is responsible for fetal bradycardia after paracervical block.

Increased Uterine Activity. Increased uterine activity results in decreased uteroplacental perfusion. Fishburne et al.[39] noted that direct uterine arterial injection of bupivacaine consistently caused a significant increase in uterine tone in gravid ewes. Uterine arterial injection of 2-chloroprocaine did not affect myometrial tone, whereas injection of lidocaine had an intermediate effect.

Myometrial injection of a local anesthetic also may cause greater uterine activity. Morishima et al.[40] performed paracervical block with either lidocaine or 2-chloroprocaine in pregnant baboons with normal and acidotic fetuses. A transient increase in uterine activity and a significant reduction in uterine blood flow occurred after paracervical block in 73% of the mothers. Approximately 33% of the normal fetuses and all of the acidotic fetuses had bradycardia after paracervical block. The acidotic fetuses had more severe bradycardia, greater hypoxemia, and slower recovery of oxygenation compared with fetuses that were well oxygenated before paracervical block. The researchers concluded that post–paracervical block fetal bradycardia is in part a result of greater uterine activity, diminished uteroplacental perfusion, and decreased oxygen delivery to the fetus. They also concluded that paracervical block should be avoided in the presence of fetal compromise.

Uterine and/or Umbilical Artery Vasoconstriction. The deposition of local anesthetic in close proximity to the uterine arteries may cause uterine artery vasoconstriction, with a subsequent drop in uteroplacental perfusion. At least two studies noted that lidocaine and mepivacaine caused vasoconstriction of human uterine arteries *in vitro*.[41,42] (These studies were performed before recognition of the importance of intact endothelium during investigation of vascular smooth muscle response.) Similarly, Norén et al.[43,44] noted that bupivacaine caused concentration-dependent contraction of uterine arterial smooth muscle from rats and pregnant women. The calcium entry–blocking drugs verapamil and nifedipine decreased the vascular smooth muscle contraction caused by bupivacaine. The researchers concluded that the use of bupivacaine for paracervical block may cause uterine artery vasoconstriction, especially when the bupivacaine is injected close to the uterine arteries. Further, they suggested that the administration of a calcium entry–blocking drug may successfully eliminate this vasoconstrictive effect of bupivacaine. (Although these studies were performed in 1991, the researchers did not mention whether they preserved, removed, or even observed the presence of the vascular endothelium. The presence of vascular endothelium may alter the response of vascular smooth muscle to local anesthetics.[45])

Greiss et al.[46] observed that intra-aortic injection of lidocaine or mepivacaine led to decreased uterine blood flow in gravid ewes. Similarly, Fishburne et al.[39] noted that direct uterine arterial injection of lidocaine, bupivacaine, or 2-chloroprocaine reduced uterine blood flow in gravid ewes. They concluded that only paracervical block "would be expected to produce the high, sustained uterine arterial concentrations of anesthetic drugs that cause the significant reductions in uterine blood flow which we now feel are the etiology of fetal bradycardia."[39] In a later study, Manninen et al.[47] observed that paracervical injection of 10 mL of 0.25% bupivacaine led to an increase in the uterine artery pulsatility index—an estimate of uterine vascular resistance—in healthy nulliparous women, suggesting that paracervical block may result in uterine artery vasoconstriction.

In contrast, Puolakka et al.[33] used ^{133}Xe to measure intervillous blood flow before and after the performance of paracervical block with 10 mL of 0.25% bupivacaine in 10 parturients. They observed no decrease in mean intervillous blood flow in these patients. Further, they noted minimal change in intervillous blood flow in the three patients who had fetal bradycardia after paracervical block. Using Doppler ultrasonography, Räsänen and Jouppila[48] observed no significant change in either uterine or umbilical artery pulsatility index after the performance of paracervical block with 10 mL of 0.25% bupivacaine in 12 healthy parturients. However, fetal bradycardia occurred in two patients, and in those two cases, a marked increase in umbilical artery pulsatility index occurred.

Baxi et al.[49] performed paracervical block with 20 mL of 1% lidocaine in 10 pregnant women. They observed a decrease in fetal transcutaneous Po_2 5 minutes after injecting lidocaine in each of the 10 patients. There was a maximum decline in transcutaneous Po_2 at 11.5 minutes, and transcutaneous Po_2 returned to baseline by approximately 31 minutes. Some of the patients had increased uterine activity after paracervical block. In contrast, Jacobs et al.[50] observed a consistent, sustained decrease in fetal transcutaneous Po_2 after only 1 of 10 paracervical blocks performed with 10 mL of 0.25% bupivacaine. These investigators attributed their good results to the following precautions: (1) performance of paracervical block only in healthy mothers with normal pregnancies; (2) administration of a small dose of bupivacaine; (3) a limited depth of injection; (4) administration of bupivacaine in four incremental injections (i.e., two injections on each side); and (5) use of the left lateral position immediately after performance of the block. In a later study, Kaita et al.[51] observed that paracervical injection of 10 mL of 0.25% bupivacaine in 10 healthy parturients resulted in a slight (clinically insignificant) increase in fetal Sao_2 as measured by fetal pulse oximetry.

Summary

Most observers currently believe that post–paracervical block bradycardia results from reduced uteroplacental and/or fetoplacental perfusion. Reduction in

uteroplacental perfusion may occur because of increased uterine activity and/or a direct vasoconstrictive effect of the local anesthetic. Likewise, decreased umbilical cord blood flow may result from increased uterine activity and/or umbilical cord vasoconstriction. Regardless of the etiology, the severity and duration of fetal bradycardia correlate with the incidence of fetal acidosis and subsequent neonatal depression. Freeman et al.[38] reported a significant drop in pH and a rise in base deficit only in fetuses with bradycardia of longer than 10 minutes' duration. In an observational study of paracervical block and nalbuphine analgesia during labor, Levy et al.[52] observed no association between paracervical block and low umbilical arterial blood pH at delivery.

Physician Complications

The performance of paracervical block requires the physician to make several blind needle punctures within the vagina. The needle guide does not consistently protect the physician from a needle-stick injury. Thus, the performance of paracervical block may entail the risk for physician exposure to human immunodeficiency virus (HIV) or another infectious agent.

Recommendations

It is difficult for me to offer enthusiasm for the performance of paracervical block in contemporary obstetric practice. Nonetheless, paracervical block may be an appropriate technique in circumstances in which neuraxial analgesia is contraindicated or unavailable. The following recommendations seem reasonable:

1. Perform paracervical block only in healthy parturients at term who have no evidence of uteroplacental insufficiency or fetal compromise.
2. Continuously monitor the FHR and uterine activity before, during, and after performance of paracervical block. Perform paracervical block only in patients with a reassuring FHR tracing. An obvious exception would be a patient whose fetus has an anomaly incompatible with life (e.g., anencephaly).
3. Do not perform paracervical block when the cervix is dilated 8 cm or more.
4. Establish intravenous access before performing paracervical block.
5. Maintain left uterine displacement while performing the block.
6. Limit the depth of injection to approximately 3 mm.
7. Aspirate before each injection of local anesthetic.
8. After injecting the local anesthetic on one side, wait 5 to 10 minutes and observe the FHR before injecting the local anesthetic on the other side.
9. Administer small volumes of a dilute solution of local anesthetic; 2-chloroprocaine is the agent of choice.
10. Avoid the administration of epinephrine-containing local anesthetic solutions.
11. Monitor the mother's blood pressure and watch for signs of local anesthetic toxicity after performance of the block. Maintain normal maternal blood pressure.
12. If fetal bradycardia should occur, try to achieve fetal resuscitation *in utero*. Discontinue oxytocin, administer supplemental oxygen, and ensure that the patient is on her left side. Perform operative delivery if the fetal bradycardia persists beyond 10 minutes.

LUMBAR SYMPATHETIC BLOCK

In 1933, Cleland[53] demonstrated that lower uterine and cervical visceral afferent sensory fibers join the sympathetic chain at L2 to L3. Subsequently, lumbar sympathetic block was used as an effective—if not popular—method of first-stage analgesia in some hospitals.[54-57] Like paracervical block, paravertebral lumbar sympathetic block interrupts the transmission of pain impulses from the cervix and lower uterine segment to the spinal cord. Lumbar sympathetic block provides analgesia during the first stage of labor but does not relieve pain during the second stage. It provides analgesia comparable to that provided by paracervical block but with less risk for fetal bradycardia.

Lumbar sympathetic block may have a favorable effect on the progress of labor. Hunter[58] reported that lumbar sympathetic block accelerated labor in 20 of 39 patients with a normal uterine contractile pattern before performance of the block. (Indeed, some of the patients in that study had a 5- to 15-minute period of uterine hypertonus after the block.) Further, he observed that lumbar sympathetic block converted an abnormal uterine contractile pattern to a normal pattern in 14 of 19 patients. He concluded that lumbar sympathetic block represents "one of the most reliable methods reported to actively convert an abnormal labor pattern to a normal pattern."[58] In a later study, Leighton et al.[59] randomly assigned 39 healthy nulliparous women at term to receive either epidural analgesia or lumbar sympathetic block. The women who received lumbar sympathetic block had a more rapid rate of cervical dilation during the first 2 hours of analgesia, a shorter second stage of labor, and a nonsignificant trend toward a lower incidence of cesarean delivery for dystocia. However, there was no difference between the groups in the rate of cervical dilation during the active phase of the first stage of labor.

Anesthesiologists may successfully perform lumbar sympathetic block when a history of previous back surgery precludes the successful administration of epidural analgesia.[60] Some anesthesiologists offer lumbar sympathetic block to prepared childbirth enthusiasts who desire first-stage analgesia without any motor block or loss of perineal sensation. Meguiar and Wheeler[61] stated that the primary usefulness of lumbar sympathetic block is "in cases where continuous lumbar epidural analgesia is refused or contraindicated." They administered 20 mL of 0.5% bupivacaine with 1:200,000 epinephrine to 40 nulliparous women. Among these women, 38 experienced good analgesia, and 28 delivered before resolution of the block. Pain recurred before delivery in the remaining 12 women; the mean duration of analgesia was 283 ±

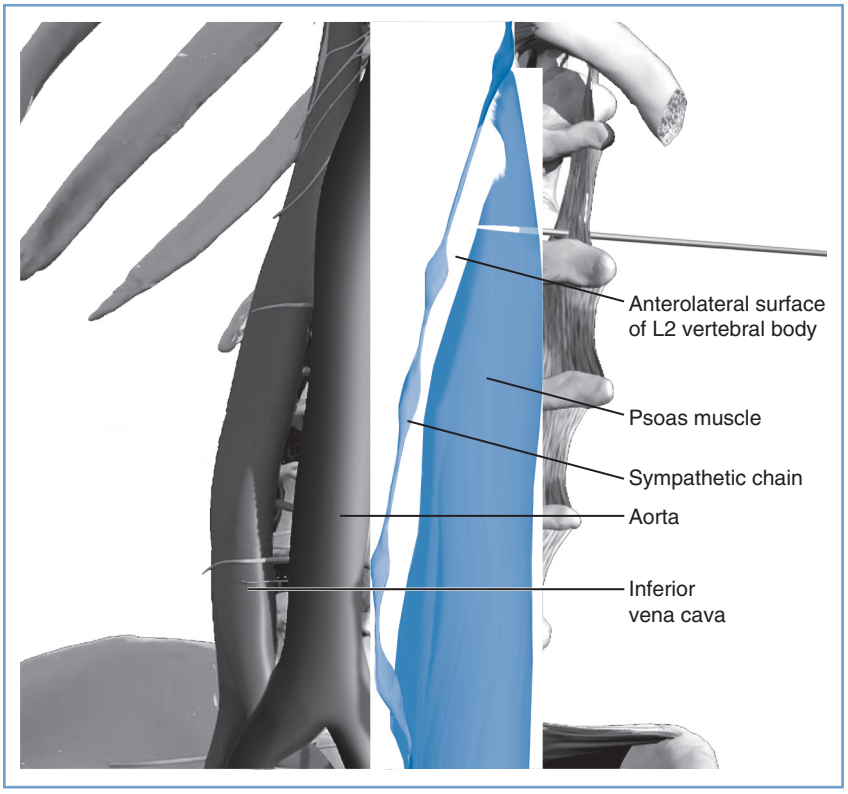

FIGURE 24-3 ■ Lateral view of needle placement for lumbar sympathetic block. The needle has been advanced so that the tip of the needle is near the anterolateral surface of the L2 vertebral body. The figure illustrates the proximity of the aorta. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

103 minutes among these patients.[61] Leighton et al.[59] administered the same dose of bupivacaine, but they observed a shorter duration of analgesia than that observed by Meguiar and Wheeler.[61]

During the last three decades, lumbar sympathetic block has all but disappeared from obstetric anesthesia practice in the United States, for several reasons. Anesthesiologists may minimize motor block during epidural analgesia by giving a dilute solution of local anesthetic, with or without an opioid. For those few patients who want to retain full perineal sensation, anesthesiologists may give an opioid alone, either intrathecally or epidurally. Thus, there are few patients for whom lumbar sympathetic block holds unique advantages. Further, the procedure often is painful, and few anesthesiologists have acquired and maintained proficiency in performing lumbar sympathetic block in obstetric patients.

Lumbar sympathetic block remains an attractive technique in a small number of patients.[60] Alternatively, two recent reports have described the performance of bilateral lower thoracic paravertebral block in a total of five laboring women in whom epidural analgesia was contraindicated.[62,63] As anesthesiologists gain greater proficiency with thoracic paravertebral block for patients undergoing breast surgery, perhaps this technique will be used more often in parturients for whom neuraxial analgesia is contraindicated.

Technique

With the patient in the sitting position, a 10-cm, 22-gauge needle is used to identify the transverse process on one side of the second lumbar vertebra. The needle is then withdrawn, redirected, and advanced another 5 cm so that the tip of the needle is at the anterolateral surface of the vertebral column, just anterior to the medial attachment of the psoas muscle (Figure 24-3). It is possible to place the needle within a blood vessel or the subarachnoid space; thus, the anesthesiologist must aspirate before injecting the local anesthetic. Two 5-mL increments of a dilute solution of local anesthetic (with or without epinephrine) are then injected, and the procedure is repeated on the opposite side of the vertebral column.

Complications

Modest hypotension occurs in 5% to 15% of patients.[58,59,61] The risk for hypotension may be reduced by giving 500 mL of lactated Ringer's solution intravenously before performing the block. Less common maternal complications are systemic local anesthetic toxicity, total spinal anesthesia, retroperitoneal hematoma, Horner's syndrome,[64] and post–dural puncture headache.[65]

Fetal complications are unlikely unless hypotension or increased uterine activity results in decreased uteroplacental perfusion.

PUDENDAL NERVE BLOCK

During the second stage of labor, pain results from distention of the lower vagina, vulva, and perineum. The pudendal nerve, which includes somatic nerve fibers from the anterior primary divisions of the second, third, and fourth sacral nerves, represents the primary source of sensory innervation for the lower vagina, vulva, and

perineum. The pudendal nerve also provides motor innervation to the perineal muscles and to the external anal sphincter.

In 1916, King[66] reported the use of pudendal nerve block for vaginal delivery. This procedure did not become popular until 1953 and 1954, when Klink[67] and Kohl[68] described the anatomy and reported modified techniques. Obstetricians often perform pudendal nerve block in patients without epidural or spinal analgesia. The goal is to block the pudendal nerve distal to its formation by the anterior divisions of S2 to S4 but proximal to its division into its terminal branches (i.e., dorsal nerve of the clitoris, perineal nerve, and inferior hemorrhoidal nerve). Pudendal nerve block may provide satisfactory anesthesia for spontaneous vaginal delivery and perhaps for outlet-forceps delivery, but it provides inadequate anesthesia for mid-forceps delivery, postpartum examination and repair of the upper vagina and cervix, and manual exploration of the uterine cavity.[69]

Efficacy and Timing

The efficacy of pudendal nerve block varies according to the experience of the obstetrician. Unilateral or bilateral failure is common. Thus, obstetricians typically perform simultaneous infiltration of the perineum, especially if the performance of pudendal nerve block is delayed until delivery. Scudamore and Yates[70] reported bilateral success rates of approximately 50% after use of the transvaginal route and of approximately 25% after use of the transperineal route. They concluded[70]:

> *The term "pudendal block" is often a misnomer.… If this limitation were more widely appreciated, then many mothers would be spared the unnecessary pain which is caused when relatively complicated procedures are attempted under inadequate anesthesia.*

In the United States, most obstetricians perform pudendal nerve block immediately before delivery. This practice reflects their concern that perineal anesthesia prolongs the second stage of labor. An advantage to early pudendal nerve block is that the obstetrician may repeat the block on one or both sides if it should fail, provided that the maximum safe dose of local anesthetic is not exceeded. European obstetricians seem more willing to perform pudendal nerve block at the onset of the second stage of labor. Langhoff-Roos and Lindmark[71] administered pudendal nerve block before or just after complete cervical dilation in 551 (64%) of 865 women. In a nonrandomized study, Zador et al.[72] evaluated obstetric outcome in 24 patients who received pudendal nerve block when the cervix was completely dilated and in 24 patients who did not receive pudendal block. Pudendal nerve block slightly prolonged the second stage of labor, but it did not increase the incidence of instrumental vaginal delivery.[72]

It is barbaric to withhold analgesia during the second stage of labor. Obstetricians need not delay the administration of pudendal nerve block until delivery. Rather, for those patients without epidural or spinal analgesia, it seems appropriate to perform pudendal nerve block when the patient complains of vaginal and perineal pain. A 2004 study suggested that pudendal nerve block does not provide reliable analgesia during the second stage of labor but has greater efficacy for episiotomy and repair.[73] In a randomized, double-blind, placebo-controlled study, Aissaoui et al.[74] observed that unilateral, nerve stimulator–guided pudendal nerve block with ropivacaine was associated with decreased pain and less need for supplemental analgesia during the first 48 hours after performance of mediolateral episiotomy at vaginal delivery.

Technique

The transvaginal approach is more popular than the transperineal approach in the United States. The obstetrician uses a needle guide (either the Iowa trumpet or the Kobak needle guide) to prevent injury to the vagina and fetus. In contrast to the technique for paracervical block, the needle must protrude 1.0 to 1.5 cm beyond the needle guide to allow adequate penetration for injection of the local anesthetic. The obstetrician introduces the needle and needle guide into the vagina with the left hand for the left side of the pelvis and with the right hand for the right side (Figure 24-4). The needle is introduced through the vaginal mucosa and sacrospinous ligament, just medial and posterior to the ischial spine. The pudendal artery lies in close proximity to the pudendal nerve; thus, the obstetrician must aspirate before and during the injection of local anesthetic. The obstetrician typically injects 7 to 10 mL of local anesthetic solution on each side. (Some obstetricians inject 3 mL of local anesthetic just above the ischial spine on each side.[75]) The obstetrician should pay attention to the total dose of local anesthetic given, especially when repetitive pudendal nerve blocks or both pudendal nerve block and perineal infiltration are performed.

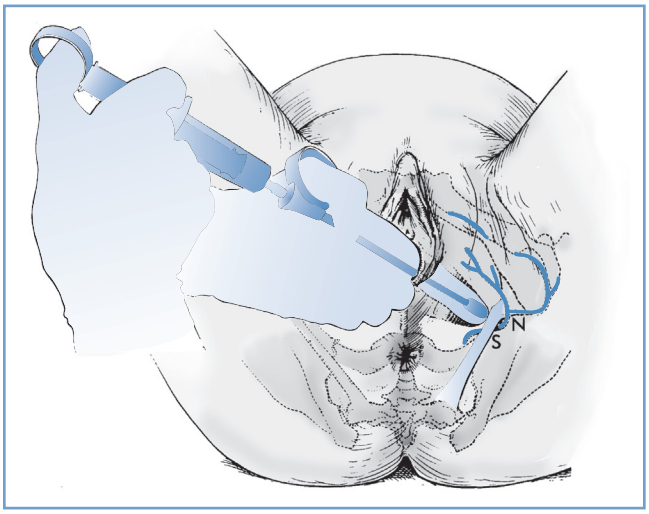

FIGURE 24-4 ■ Local infiltration of the pudendal nerve. Transvaginal technique showing the needle extended beyond the needle guard and passing through the sacrospinous ligament (*S*) to reach the pudendal nerve (*N*). (From Cunningham FG, MacDonald PC, Gant NF, et al. Williams Obstetrics. 20th edition. Stamford, CT, Appleton & Lange, 1997:389.)

Choice of Local Anesthetic

Rapid maternal absorption of the local anesthetic occurs after the performance of pudendal nerve block.[72,75] Zador et al.[72] detected measurable concentrations of lidocaine in maternal venous and fetal scalp capillary blood samples within 5 minutes of the injection of 20 mL of 1% lidocaine. They detected peak concentrations between 10 and 20 minutes after injection. Kuhnert et al.[76] reported that after pudendal nerve block, neonatal urine concentrations of lidocaine and its metabolites were similar to those measured in neonatal urine after epidural administration of lidocaine.

Some physicians favor the administration of 2-chloroprocaine. Its rapid onset of action provides an advantage when pudendal nerve block is performed immediately before delivery. Its rapid metabolism and short intravascular half-life lower the likelihood of maternal or fetal systemic toxicity. 2-Chloroprocaine has the disadvantage of a short duration of action. However, if the obstetrician performs pudendal nerve block with 2-chloroprocaine at the onset of the second stage of labor, the block can be repeated as needed. When the block is performed immediately before delivery, the brief duration of action of 2-chloroprocaine is not a disadvantage for the experienced obstetrician.

Merkow et al.[77] evaluated neonatal neurobehavior in infants whose mothers received 30 mL of 0.5% bupivacaine, 1% mepivacaine, or 3% 2-chloroprocaine for pudendal nerve block and perineal infiltration before delivery. Neonatal response to pinprick at 4 hours was better in the mepivacaine group; otherwise, there were no significant differences among groups in neurobehavioral scores at 4 and 24 hours after delivery.

Regardless of the choice of local anesthetic, there is no indication for the administration of a concentrated solution. For example, it is unnecessary, and perhaps dangerous, to give 0.5% bupivacaine, 2% lidocaine, or 3% 2-chloroprocaine. Rather, the obstetrician should use 2% 2-chloroprocaine or 1% lidocaine.

Some obstetricians contend that the addition of epinephrine to the local anesthetic solution improves the quality of pudendal nerve block. Langhoff-Roos and Lindmark[71] reported a randomized, double-blind study of 865 patients who received pudendal nerve block with 16 mL of 1% mepivacaine, 1% mepivacaine with epinephrine, or 0.25% bupivacaine. Mepivacaine with epinephrine provided effective anesthesia more often and also caused a greater "loss of the urge to bear down" than did the other two local anesthetic solutions. However, there was no significant difference among groups in the duration of the second stage of labor or the incidence of instrumental vaginal delivery. Schierup et al.[78] randomly assigned 151 patients to receive pudendal nerve block with 20 mL of 1% mepivacaine either with or without epinephrine. The addition of epinephrine did not improve the quality of anesthesia, but it slightly prolonged the interval between pudendal nerve block administration and delivery. Maternal venous blood mepivacaine concentrations were slightly higher in the no-epinephrine group, but there was no difference between groups in umbilical cord blood concentrations of mepivacaine.

BOX 24-2 Maternal Complications of Pudendal Nerve Block

- Laceration of the vaginal mucosa
- Systemic local anesthetic toxicity
- Vaginal, ischiorectal, or retroperitoneal hematoma
- Retropsoal or subgluteal abscess

Complications

Maternal complications of pudendal nerve block are uncommon but may be serious (Box 24-2). Systemic local anesthetic toxicity may result from either direct intravascular injection or systemic absorption of an excessive dose of local anesthetic. Toxicity may occur if the obstetrician exceeds the safe dose of local anesthetic during repetitive injections performed to obtain a successful block. Vaginal, ischiorectal, and retroperitoneal hematomas may result from trauma to the pudendal artery.[79] These hematomas are typically small and rarely require operative intervention. Subgluteal and retropsoal abscesses are rare but can result in significant morbidity or mortality.[21,22]

Fetal complications are rare. The primary fetal complications result from fetal trauma and/or direct fetal injection of local anesthetic.

As with paracervical block, the performance of pudendal nerve block requires the obstetrician to make several blind needle punctures within the vagina. The needle guide does not uniformly protect the physician from a needle-stick injury. Thus, performance of pudendal nerve block may entail a risk for physician exposure to HIV or another infectious agent.

PERINEAL INFILTRATION

Perineal infiltration is perhaps the most common local anesthetic technique used for vaginal delivery. Given the frequent failure of pudendal nerve block, obstetricians often perform pudendal nerve block and perineal infiltration simultaneously. Perineal infiltration also may be required in patients with incomplete neuraxial anesthesia. The obstetrician injects several milliliters of local anesthetic solution into the posterior fourchette. There are no large nerve fibers to be blocked, so the onset of anesthesia is rapid. However, perineal infiltration provides anesthesia only for episiotomy and repair. Anesthesia is often inadequate even for these limited procedures. Moreover, perineal infiltration provides no muscle relaxation. In a prospective randomized trial, perineal infiltration of saline-placebo provided postpartum analgesia that was equivalent to that provided by infiltration of either ropivacaine or lidocaine in women who underwent mediolateral episiotomy at vaginal delivery.[80]

Choice of Local Anesthetic

Philipson et al.[81] evaluated the pharmacokinetics of lidocaine after perineal infiltration. They gave 1% or 2% lidocaine without epinephrine during the crowning phase

of the second stage of labor in 15 healthy parturients. The mean ± SD dose of lidocaine was 79 ± 3 mg, and the mean drug-to-delivery interval was 7.8 ± 7.0 minutes. The investigators detected lidocaine in maternal plasma as early as 1 minute after injection. Peak maternal plasma concentrations of lidocaine occurred between 3 and 15 minutes after injection. Despite the administration of small doses of lidocaine and the short drug-to-delivery intervals, there was rapid placental transfer of significant amounts of lidocaine. The mean fetal-to-maternal lidocaine concentration ratio of 1.32 was significantly higher than the ratio reported after administration of lidocaine for paracervical block, pudendal nerve block, or epidural anesthesia for vaginal or cesarean delivery. There was a significant correlation between the fetal-to-maternal lidocaine concentration ratio and the length of the second stage of labor. These investigators speculated that fetal tissue acidosis increased the fetal-to-maternal lidocaine ratio after perineal infiltration in this study. Finally, they noted the persistence of lidocaine and its pharmacologically active metabolites for at least 48 hours after delivery.[81]

Subsequently, Philipson et al.[82] evaluated the placental transfer of 2-chloroprocaine after perineal administration of 1% or 2% 2-chloroprocaine to 17 women shortly before delivery. The mean ± SD dose of 2-chloroprocaine was 81.8 ± 27.0 mg, and the mean drug-to-delivery interval was 6.7 ± 4.3 minutes. Perineal infiltration of 2-chloroprocaine provided adequate anesthesia for episiotomy repair except in two patients who required additional local anesthetic for repair of fourth-degree lacerations. The investigators did not detect 2-chloroprocaine in maternal plasma after infiltration or at delivery. Further, they detected 2-chloroprocaine at delivery in only one umbilical cord venous blood sample and no 2-chloroprocaine in neonatal plasma. In contrast, they consistently detected the drug's metabolite, chloroaminobenzoic acid, in maternal plasma, umbilical cord venous plasma, and neonatal urine. The fetal-to-maternal ratio of chloroaminobenzoic acid (0.80) was similar to that reported after the administration of 2-chloroprocaine for paracervical block and epidural anesthesia for cesarean delivery. The investigators suggested that very little, if any, unchanged 2-chloroprocaine reaches the fetus after perineal infiltration. They concluded that 2-chloroprocaine may be preferable to lidocaine for antepartum perineal infiltration.[82]

Complications

The obstetrician must take care to avoid injecting the local anesthetic into the fetal scalp. Kim et al.[83] reported a case of newborn lidocaine toxicity after maternal perineal infiltration of 6 mL of 1% lidocaine before vaginal delivery. Similarly, DePraeter et al.[84] reported a case of lidocaine toxicity in a newborn whose mother received perineal infiltration with 10 mL of 2% lidocaine 4 minutes before delivery. In both cases, the infants were initially vigorous but required endotracheal intubation 15 minutes after delivery. No lidocaine was detected in umbilical cord blood, but neonatal blood samples revealed concentrations of 14 μg/mL at 2 hours and 13.8 μg/mL at 6.5 hours. Small scalp puncture wounds suggested that the lidocaine toxicity resulted from direct fetal scalp injection. Pignotti et al.[85] reported two cases of neonatal local anesthetic toxicity. In one case, lidocaine and prilocaine cream had been applied to the maternal perineum. In the second case, 10 mL of 2% mepivacaine had been injected into the perineum. Both infants required endotracheal intubation and mechanical ventilation, but in both cases, neurodevelopmental outcome was normal at 12 months of age. Kim et al.[83] suggested that the presence of a molded head in the occiput posterior position may predispose to unintentional direct injection of the fetal scalp. These cases support the recommendation for use of 2-chloroprocaine for perineal infiltration.

KEY POINTS

- Paracervical block and lumbar sympathetic block may provide effective analgesia for the first stage of labor. Neither technique relieves pain during the second stage.
- Fetal bradycardia is the most worrisome complication of paracervical block.
- Paracervical block is contraindicated in patients with uteroplacental insufficiency or preexisting fetal compromise.
- For patients without epidural or spinal analgesia, it is appropriate to perform pudendal nerve block when the patient complains of pelvic floor pain.
- Pudendal nerve block may provide satisfactory anesthesia for spontaneous vaginal delivery and outlet-forceps delivery, but it provides inadequate anesthesia for mid-forceps delivery, postpartum repair of the cervix, and manual exploration of the uterine cavity.
- Perineal infiltration provides anesthesia only for episiotomy and repair.
- It is unnecessary—and perhaps dangerous—to give concentrated solutions of local anesthetic for paracervical block, pudendal nerve block, or perineal infiltration.
- Some cases of fetal injury result from direct fetal scalp injection of local anesthetic during attempted paracervical block, pudendal nerve block, or perineal infiltration.
- 2-Chloroprocaine is most likely the safest choice of local anesthetic for paracervical block, pudendal nerve block, and perineal infiltration.
- The performance of either paracervical block or pudendal nerve block requires the obstetrician to make several blind needle punctures within the vagina. Thus, there is a risk for physician needlestick injury during the performance of either procedure.

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CHAPTER 25

Postpartum Tubal Sterilization

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CHAPTER OUTLINE

Many parous women choose tubal ligation for permanent contraception. Half are performed postpartum (over 350,000 annually in the United States) and half as ambulatory interval procedures.[1] Although the interval sterilization rate has declined by 12% in the United States, the postpartum sterilization rate remains stable, and postpartum sterilization is performed after 8% to 9% of all live births.[1] The considerations and controversies regarding the administration of anesthesia for postpartum tubal sterilization are discussed in this chapter.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS GUIDELINES

The American Society of Anesthesiologists (ASA) has published "Practice Guidelines for Obstetric Anesthesia,"[2] which includes a discussion of postpartum tubal ligation. (See Appendix B.) The Task Force recommendations can be summarized as follows:

1. For postpartum tubal ligation, the patient should have no oral intake of solid foods within 6 to 8 hours of the surgery, depending on the type of food ingested (e.g., fat content).
2. Aspiration prophylaxis should be considered.
3. Both the timing of the procedure and the decision to use a specific anesthetic technique (i.e., neuraxial versus general) should be individualized, based on anesthetic risk factors, obstetric risk factors (e.g., blood loss at delivery), and patient preferences.
4. Neuraxial techniques are preferred to general anesthesia for most postpartum tubal ligations. The anesthesia provider should be aware that gastric emptying will be delayed in patients who have received opioids during labor and that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals.
5. If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care on the labor and delivery unit.

SURGICAL CONSIDERATIONS

Tubal sterilization can be performed satisfactorily at any time, but the early postpartum period has several advantages for women who have had an uncomplicated vaginal delivery.[3] The patient avoids the cost and inconvenience of a second hospital visit. The uterine fundus remains near the umbilicus for several days postpartum, which allows easy access to the fallopian tubes. Minilaparotomy and laparoscopy have similar rates of serious complications (e.g., bowel laceration, vascular injury).[4]

There are at least two potential disadvantages to immediate postpartum sterilization. First, parous women are at increased risk for uterine atony and postpartum hemorrhage. This risk decreases substantially 12 hours after delivery. Second, immediate surgery results in sterilization before assessment of the newborn is complete. Postpartum tubal ligation is not wise if the patient is ambivalent regarding permanent sterilization. However, women who undergo postpartum sterilization have a similar probability of regret within 1 year of delivery (23.7%) as women who undergo interval sterilization (22.3%), although the risk is markedly increased when the woman is younger than 25 years of age.[5]

Several techniques are used for postpartum tubal sterilization (Figure 25-1).[6] Puerperal sterilization has a failure rate that is lower than most interval procedures, and the failure rate is lowest (approximately 0.75%) if some form of tubal resection occurs.[7] With the Irving procedure, the obstetrician buries the cut ends of the

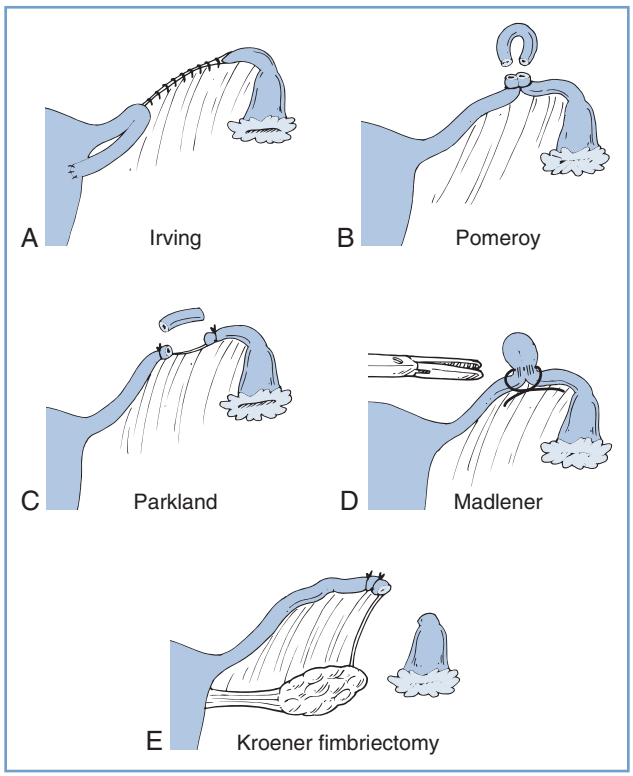

FIGURE 25-1 ■ Techniques for tubal sterilization. **A**, Irving procedure. The medial cut end of the oviduct is buried in the myometrium posteriorly, and the distal cut end is buried in the mesosalpinx. **B**, Pomeroy procedure. A loop of oviduct is ligated, and the knuckle of tube above the ligature is excised. **C**, Parkland procedure. A midsegment of tube is separated from the mesosalpinx at an avascular site, and the separated tubal segment is ligated proximally and distally and then excised. **D**, Madlener procedure. A knuckle of oviduct is crushed and then ligated without resection; this technique has an unacceptably high failure rate of approximately 7%. **E**, Kroener procedure. The tube is ligated across the ampulla, and the distal portion of the ampulla, including all of the fimbria, is resected; some studies have reported an unacceptably high failure rate with this technique. (From Cunningham FG, MacDonald PC, Gant NF, et al. Williams Obstetrics, 20th edition. Stamford, CT, Appleton & Lange, 1997:1376.)

tubes in the myometrium and mesosalpinx. This technique is least likely to fail, but it requires more extensive exposure and increases the risk for hemorrhage. The Pomeroy procedure is simplest. The surgeon ligates a loop of oviduct and excises the loop above the suture. With the Parkland procedure, the obstetrician ligates the tube proximally and distally and then excises the midsegment. The last two methods are most commonly performed during postpartum tubal ligations. Regardless of the technique, the obstetrician should document that fimbriae are present to preclude ligation of another structure such as the round ligament. The excised portions typically are sent to a pathologist for verification.

A randomized clinical trial found a significantly increased risk for pregnancy at 24 months after use of the titanium clip for postpartum tubal occlusion (i.e., a cumulative pregnancy rate of 1.7 pregnancies per 1000 women who had titanium tubal occlusion versus 0.04 pregnancies per 1000 women in whom the Pomeroy technique was used).[8] Therefore, evidence does not support routine use of the titanium clip for postpartum sterilization.[8]

NONMEDICAL ISSUES

Nonmedical issues affect decisions regarding the timing of tubal sterilization. The obstetrician must obtain and document informed consent for surgery.[5] Tubal ligation should be considered an irreversible procedure. Therefore, most obstetricians require a discussion with the patient before labor and delivery. Postpartum partial salpingectomy has 5-year and 10-year failure rates of 6.3 and 7.5 per 1000 patients, respectively, the lowest of all sterilization procedures.[5] Physicians should be aware of state laws or insurance regulations that may require a specific interval between obtaining consent and performance of sterilization procedures. Regulations often do not allow the woman to give consent while in labor or immediately after delivery. For example, the Medicaid reimbursement program includes the following requirements for sterilization[8]:

- The patient must be at least 21 years of age and mentally competent when consent is obtained.
- Informed consent may not be obtained while the patient is in labor or during childbirth.
- Consent may not be obtained while the patient is undergoing an abortion or under the influence of alcohol or other substances.
- A total of 30 days must pass between the date the consent is signed and the date the procedure is performed. (Exceptions to the 30-day waiting period can be made for preterm delivery or emergency abdominal surgery.)
- Consent is valid for only 180 days.

In some cases the obstetrician may schedule a patient for a postpartum tubal ligation because of a fear that the patient will not return for interval tubal sterilization 6 weeks after delivery. Concerns regarding patient compliance should not prompt the performance of postpartum tubal ligation in patients with significant medical or obstetric complications. However, women who request postpartum tubal sterilization but do not receive it are more likely to become pregnant within 1 year of delivery (46.7%) than are women who did not request the procedure (22.3%).[9]

PREOPERATIVE EVALUATION

The patient scheduled for postpartum tubal ligation requires a thorough preoperative evaluation, and a reevaluation should be performed even if the patient is known to the anesthesia provider as a result of the provision of labor analgesia. A cursory evaluation should not be performed simply because the patient is young and healthy. Patients with pregnancy-induced hypertension may safely receive neuraxial or general anesthesia for postpartum tubal ligation provided that there is no evidence of pulmonary edema, oliguria, or thrombocytopenia.[10]

Physicians and nurses often underestimate blood loss during delivery.[11] Excessive blood loss from uterine atony is not uncommon in parous women. Orthostatic changes in blood pressure and heart rate should be excluded, especially if an immediate postpartum procedure is to be performed. At the University of Colorado, for surgery performed the day after delivery, the patient's hematocrit is determined several hours after delivery (to allow for equilibration) and compared with the antepartum measurement. A hematocrit is not obtained before an immediate postpartum tubal sterilization (performed < 8 hours after delivery), provided that the antepartum hematocrit was acceptable, there are no orthostatic vital sign changes, and there was no evidence of excessive blood loss during delivery.

No absolute value of hematocrit requires a delay of surgery, but physical signs of hemodynamic instability or laboratory evidence of excessive blood loss should prompt postponement of the procedure until 6 to 8 weeks postpartum. Fever may signal the presence of endometritis or urinary tract infection and also may require postponement of surgery until a later date. Finally, the condition of the neonate should be confirmed before surgery to exclude any unexpected problems.

Mothers may be concerned that medications administered during surgery might affect their ability to breast-feed or that these medications might harm the newborn. Any drug present in the mother's blood will be present in breast milk, with the concentration dependent on factors such as protein binding, lipid solubility, and degree of ionization.[12] Typically, the amount of drug present in breast milk is small. Opioids, barbiturates, and propofol administered during anesthesia are excreted in insignificant amounts. (See Chapter 14 for a detailed discussion of interactions between drugs and breast-feeding.)

RISK FOR ASPIRATION

Historically, anesthesiologists have considered maternal aspiration the major risk associated with anesthesia for postpartum tubal ligation, although the evidence for this is scant and conflicting. A review of anesthesia-related maternal mortality found no maternal deaths associated with aspiration during postpartum tubal ligation, despite tracking deaths for 1 year after delivery.[13] However, several factors may place the pregnant woman at increased risk for aspiration. Some but not all of these factors are resolved at delivery. The placenta is the primary site of progesterone production, and progesterone concentrations fall rapidly after delivery of the placenta (Figure 25-2).[14,15] Typically, progesterone concentrations decline within 2 hours of delivery; and by 24 hours postpartum, progesterone concentrations are similar to those found during the luteal phase of the menstrual cycle.

Two important questions to address during the preanesthetic evaluation are (1) What is the duration of the fast for solids? (2) Were parenteral opioids administered during labor?

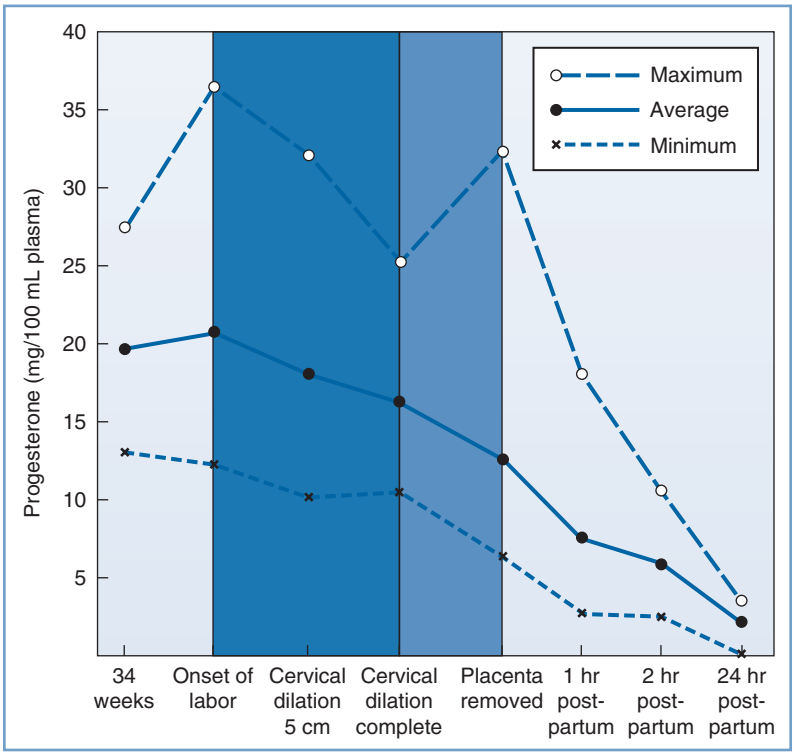

FIGURE 25-2 ■ Average progesterone concentrations with the highest and lowest measurements of 13 pregnant women at given time intervals. (From Llauro JL, Runnebaum B, Zander J. Progesterone in human peripheral blood before, during and after labor. Am J Obstet Gynecol 1968; 101:871.)

Gastric Emptying

Several studies have assessed gastric emptying in pregnant and postpartum women. In summary, the preponderance of evidence suggests that (1) administration of an opioid during labor increases the likelihood of delayed gastric emptying during the early postpartum period, (2) gastric emptying of *solids* is delayed during labor in all parturients, and (3) gastric emptying of clear liquids is probably not delayed unless parenteral opioids were administered. However, there are few data on gastric emptying during the first 8 hours postpartum.

O'Sullivan et al.[16] used an epigastric impedance technique to compare gastric emptying times for solids and liquids in women during the third trimester of pregnancy, in women during the first hour postpartum, and in nonpregnant controls. The investigators observed that the overall rate of gastric emptying was lower in the postpartum patients than in pregnant or nonpregnant patients. When patients who had received parenteral opioids in labor were separated from those who had not, rates of gastric emptying for women who had not received opioids were similar to those for nonpregnant controls. The investigators concluded that the rate of gastric emptying in postpartum women is delayed only if opioids have been administered during labor.

Other studies have used the acetaminophen (paracetamol) absorption technique to assess gastric emptying. Gin et al.[17] studied women on the first and third days after delivery and at 6 weeks postpartum. They found comparable times to peak concentration of acetaminophen in all three groups. They concluded that gastric emptying was no different in the immediate postpartum period than 6 weeks later, and they recommended that "the approach to prophylaxis against acid aspiration should be more consistent between nonpregnant and postpartum patients." Whitehead et al.[18] observed no significant delay in gastric emptying during the first, second, or third trimesters of pregnancy or between 18 and 48 hours postpartum when compared with gastric emptying in nonpregnant controls. They observed that gastric emptying was significantly delayed during the first 2 hours after vaginal delivery, but at least 4 of the 17 women studied received intramuscular meperidine during labor. The researchers did not measure gastric emptying between 2 and 18 hours postpartum. Despite the confounding use of opioids, they concluded, "The presence of delayed gastric emptying in the immediate (within 2 hours) postpartum period confirms that strict precautions against acid aspiration should be provided to mothers who are newly delivered and requiring anaesthesia."[19]

Sandhar et al.[19] used applied potential tomography to measure gastric emptying in 10 patients at term gestation, 2 to 3 days postpartum, and 6 weeks postpartum. The 6-week measurement served as each woman's control value. All measurements were made after administration of an H_2-receptor antagonist. The times to 50% emptying after ingestion of 400 mL of water were not different among the three periods of testing (Figure 25-3).

Wong et al.[20] assessed gastric emptying in nonlaboring pregnant women at term gestation, after ingestion of either 50 or 300 mL of water, by using two techniques:

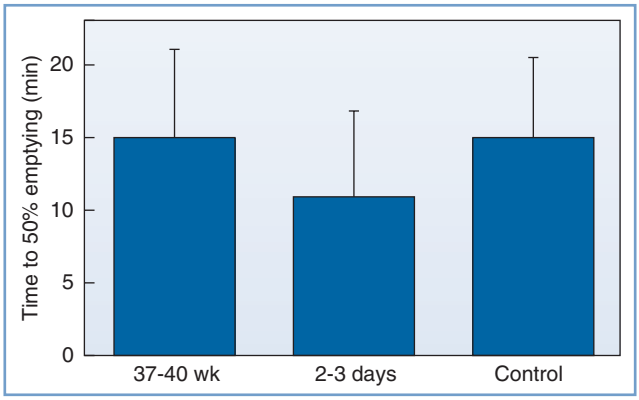

FIGURE 25-3 ■ Mean (SEM) times to 50% gastric emptying (min). No significant differences were noted between term pregnant, postpartum, and nonpregnant control women. (From Sandhar BK, Elliott RH, Windram I, Rowbotham DJ. Peripartum changes in gastric emptying. Anaesthesia 1992; 47:197.)

(1) serial assessment of acetaminophen absorption and (2) use of ultrasonography to determine gastric antrum cross-sectional areas. Gastric emptying was significantly faster after ingestion of 300 mL of water, consistent with the observation that a liquid meal may actually accelerate gastric emptying. Repeating the study in obese women showed similar results.[21] Kubli et al.[22] compared the effects of isotonic "sport drinks" versus water on residual gastric volume in women in early labor. Women who received isotonic "sports drinks" had similar gastric volumes and a similar incidence of vomiting as compared with those who received water, but the ingestion of "sport drinks" prevented the increase in ketone production that occurred in the control (water) group. Altogether, these studies suggest that gastric emptying of clear liquids is not delayed during pregnancy, early labor, or the postpartum period unless an opioid has been administered.

In contrast, Jayaram et al.[23] found that 39% of postpartum patients, but not nonpregnant patients presenting for gynecologic surgery, had solid food particles in the stomach, as demonstrated by ultrasonography. Four hours after a standardized meal, 95% of postpartum women—compared with only 19% of nonpregnant subjects—still had solid food particles in the stomach. Prior administration of an opioid did not seem to be a risk factor in this study. Scrutton et al.[24] randomized 94 women presenting in early labor to receive either a light diet or water only during labor. The mothers who ate a light diet had significantly larger gastric antrum cross-sectional areas (determined by ultrasonography) and were twice as likely to vomit at or around delivery as those who had water only. Also, the volumes vomited were significantly larger in the women who ate a light diet.

During the preoperative assessment of any woman scheduled for postpartum tubal ligation, the anesthesia provider should determine when the patient last consumed solids and whether opioids were administered by any route. Systemic absorption of an opioid occurs after epidural administration. However, published studies have provided conflicting results regarding the effect of epidural opioid administration on gastric emptying. Wright

et al.[25] observed that epidural administration of 10 mL of 0.375% bupivacaine with fentanyl 100 µg caused a modest prolongation of gastric emptying during labor when compared with epidural administration of bupivacaine alone. However, Kelly et al.[26] found that intrathecal, but not epidural, fentanyl delayed gastric emptying. Metoclopramide may not accelerate gastric emptying in patients who have received an opioid.

Gastric Volume and pH

There is little evidence that postpartum women are at greater risk for sequelae of aspiration than patients undergoing elective surgery based solely on pregnancy-induced changes in gastric pH and volume. The conventional wisdom is that a gastric volume of more than 25 mL and a gastric pH of less than 2.5 are risk factors for aspiration pneumonitis. Coté[27] noted that this dogma was derived from unpublished animal studies and that it assumes that every milliliter of gastric fluid is directed into the trachea. A marked disparity exists between the incidence of patients labeled "at risk" and the incidence of patients with clinically significant aspiration pneumonitis.

Blouw et al.[28] measured gastric volume and pH in nonpregnant women undergoing gynecologic surgery and postpartum women 9 to 42 hours after delivery. They found no significant difference between the groups. Approximately 75% of women in both groups had a gastric pH of less than 2.5. When the combination of volume and pH was used to determine the risk for aspiration, 64% of the control patients but only 33% of postpartum patients were at risk. The researchers concluded that 8 hours after delivery, postpartum patients are not at greater risk than nonpregnant patients undergoing elective surgery. They did not examine patients earlier than 8 hours after delivery. In addition, they acknowledged that a large number of patients in both groups are at risk.

James et al.[29] attempted to determine the "safe" interval after delivery. They compared gastric pH and gastric volume in postpartum women 1 to 8 hours, 9 to 23 hours, and 24 to 45 hours after delivery with a control group of nonpregnant women undergoing elective surgery. There were no significant differences in either parameter between the group of patients undergoing elective surgery and any of the postpartum groups (Table 25-1). Approximately 60% of all patients were considered "at risk" for aspiration pneumonitis. The investigators concluded that there was no difference in the risk for sequelae if aspiration should occur, but they speculated that hormonal changes or mechanical factors might make aspiration more likely during the postpartum period.

Finally, Lam et al.[30] administered 150 mL of water to 50 women 2 to 3 hours before tubal ligation that was performed 1 to 5 days postpartum. Another 50 postpartum and 50 nonpregnant women fasted after midnight. The authors found no differences in gastric pH or volume among the postpartum-water group, the postpartum-fasted group, and the group of nonpregnant controls undergoing elective surgery.

TABLE 25-1 **Gastric Volume and pH at Intervals after Delivery**

	Volume > 25 mL (%)	pH < 2.5 (%)	At Risk* (%)
Group 1 (1-8 h)	73	100	73
Group 2 (9-23 h)	40	100	40
Group 3 (24-45 h)	73	80	67
Group 4 (control)	67	80	60

*Gastric contents with pH < 2.5 and volume > 25 mL.
From James CF, Gibbs CP, Banner T. Postpartum perioperative risk of aspiration pneumonia. Anesthesiology 1984; 61:756-9.

Gastroesophageal Reflux

Women in the third trimester of pregnancy have decreased lower esophageal barrier pressures as compared with nonpregnant controls.[31] Those with symptoms of heartburn have even lower pressures and a higher incidence of gastric reflux. Vanner and Goodman[32] asked parturients to swallow a pH electrode to measure lower esophageal pH at term and on the second postpartum day. Patients were placed in four positions: supine with tilt, left lateral, right lateral, and lithotomy, and were then asked to perform a Valsalva and other maneuvers to promote reflux. A total of 17 of 25 patients had reflux at term, whereas only 5 of 25 had reflux after delivery. The investigators concluded that the incidence of reflux returns toward normal by the second day after delivery. However, this conclusion is arguable given the fact that they did not determine *normal* by defining the incidence of reflux before or 6 to 8 weeks after pregnancy.

Summary

No data indicate that the postpartum patient's safety is enhanced by delaying surgery or is compromised by proceeding with surgery immediately after delivery. This situation has led to confusion and inconsistency in the development of policies for the performance of postpartum tubal ligation.[33] No waiting interval guarantees that the postpartum patient is free of risk for aspiration. It is probably prudent to use some form of aspiration prophylaxis in all patients undergoing postpartum tubal ligation. However, significant aspiration pneumonitis is so rare that it will be difficult to document cost-effectiveness and decreased rates of morbidity and mortality from the use of these measures. H_2-receptor antagonists and antacids do not reduce the possibility of regurgitation and aspiration, but they may make the consequences less severe. Metoclopramide (a prokinetic agent) may decrease the incidence of reflux by increasing lower esophageal sphincter tone and hastening gastric emptying.[32] None of these medications can guarantee that gastric contents will not enter the lungs. Aspiration is best prevented by an experienced anesthesia provider using careful airway management and/or by use of a neuraxial anesthetic technique.

Performance of an immediate postpartum tubal ligation (within 8 hours of delivery) may decrease both the length of the hospital stay and hospital costs. In this era of health care cost-containment, any decision to postpone surgery that requires an extra day of hospitalization must be evaluated carefully. Anesthesia providers and obstetricians have questioned the need to wait 8 or more hours after delivery if gastric emptying time and gastric volume and pH are no different in the postpartum patient from those in nonpregnant women. Possible reasons to consider an 8-hour delay are as follows. First, women may remain at increased risk for gastroesophageal reflux immediately after delivery. Second, delays in gastric emptying due to the antepartum administration of opioids will resolve during this period. Third, an 8-hour delay allows the administration of aspiration prophylaxis drugs, although they might also be given during labor. Fourth, maximal hemodynamic stress and potential instability occur immediately postpartum when central blood volume suddenly increases because of contraction of the evacuated uterus, relief of aortocaval compression, and loss of the low-resistance placental circuit; indeed, the patient with cardiovascular disease is at greatest risk for hemodynamic decompensation immediately postpartum. Fifth, if there are concerns about excessive blood loss at delivery, an 8-hour delay allows the physician to assess serial hemodynamic measurements (including the presence or absence of orthostatic changes), obtain an equilibrated postpartum hematocrit, and, if necessary, restore intravascular volume. Sixth, delay allows a more thorough evaluation of the infant. Finally, delay allows the woman more time to assess her decision.

In summary, at the University of Colorado, immediate postpartum tubal ligation is performed in patients who have a functioning epidural catheter in place. These patients are given an H_2-receptor antagonist and metoclopramide intravenously during labor, and a clear (nonparticulate) antacid is administered just before taking the patient to the operating room. In other patients who do not want (or are unable to receive) epidural analgesia for labor, an H_2-receptor antagonist and metoclopramide are given intravenously after delivery followed by a wait of at least 1 hour for a therapeutic effect. This is an elective procedure, and patients should not consume solid food for 6 to 8 hours preoperatively. (NPO policies for postpartum tubal sterilization should not differ from those used for elective surgery in the main operating rooms.) Before surgery, estimated blood loss is reviewed and orthostatic vital signs are assessed. A clear antacid is given just before the patient goes to the operating room. Most of these patients (without preexisting epidural analgesia) receive spinal anesthesia for postpartum tubal ligation. However, general anesthesia can be provided using rapid-sequence induction with cricoid pressure.

ANESTHETIC MANAGEMENT

Local, general, or neuraxial anesthesia may be used successfully for postpartum tubal sterilization. Physiology remains altered in the postpartum patient and requires some modification in anesthetic technique. It seems reasonable to give all postpartum patients some form of aspiration prophylaxis. This may include a clear (nonparticulate) antacid, an H_2-receptor antagonist, and/or metoclopramide to increase lower esophageal sphincter tone and hasten gastric emptying. Metoclopramide also may prevent emesis during and after surgery. Patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes mellitus) warrant prophylaxis with all three classes of drugs. Tubal sterilization does not require administration of preoperative antibiotics.[34]

Local Anesthesia

Local anesthesia is used for more than 75% of tubal sterilizations worldwide, although neuraxial anesthesia is most often administered for postpartum tubal sterilization in the United States.[3] Several reports have documented the efficacy and safety of local anesthesia for postpartum or laparoscopic tubal ligation in the hospital operating room or a free-standing outpatient facility. Cruikshank et al.[35] described the use of intraperitoneal lidocaine for postpartum tubal ligation. After intravenous administration of diazepam, lidocaine 100 mg was used to infiltrate the skin and subcutaneous tissue. The peritoneum was entered, and 400 mg of lidocaine (80 mL of 0.5% solution) was instilled into the peritoneal cavity. A Pomeroy tubal ligation was performed 5 minutes later. All patients had complete peritoneal anesthesia, and all patients stated they would have the same procedure again. None recalled any pain or discomfort 24 hours later. There were no signs of lidocaine toxicity in any patient, and the maximum lidocaine blood level obtained was 5.3 μg/mL. Surgeons rated the conditions excellent. This study was published in 1973 when anesthesiologists may or may not have been involved and before ASA monitoring standards such as pulse oximetry existed.

Poindexter et al.[36] described almost 3000 laparoscopic tubal sterilization procedures performed with local anesthesia in an ambulatory surgical facility. After intravenous sedation with midazolam (5 to 10 mg) and fentanyl (50 to 100 μg), the skin was infiltrated with 10 mL of 0.5% bupivacaine. After insertion of the trocar, the abdomen was insufflated with nitrous oxide. Each tube was sprayed with 5 mL of 0.5% bupivacaine, and a Silastic ring was applied. Patients were discharged home after approximately 1 hour in the postanesthesia care unit. The authors reported a technical failure rate of 0.14% and no unintended laparotomies or intraoperative complications. They reported that this technique reduced surgical time by 33% and cost by 68% to 85% when compared with general anesthesia. The investigators presented no data regarding patient satisfaction, and they made no comment on the use of pulse oximetry or blood pressure monitors. Four percent of patients, however, required oxygen therapy for "adequate tissue perfusion." This study was done in the 1980s, before many ambulatory surgery facilities had institutional guidelines for sedation.

General Anesthesia

Much of the impetus for performing sterilization procedures under local anesthesia came from two reports

in 1983 indicating that morbidity and mortality were much higher when general anesthesia was used. The first report involved 3500 interval (not postpartum) laparoscopic tubal sterilizations at nine university medical centers.[37] Among all patients, the risk for intraoperative or postoperative complications was 1.75%, but the risk was five times higher with general anesthesia than with local anesthesia. (In this report, local anesthesia included local, epidural, and spinal anesthesia.) The reason(s) for the difference was unclear. In the second report, the U.S. Centers for Disease Control and Prevention examined deaths attributed to tubal sterilization procedures from 1977 to 1981.[38] Both immediate postpartum laparotomies and interval laparoscopic procedures were included. Of the 29 deaths, 11 followed complications of general anesthesia and were caused by hypoventilation or cardiorespiratory arrest. Aspiration was not reported as a cause of death. Of the six patients whose deaths were definitely attributed to hypoventilation, none had undergone tracheal intubation. Five of the 11 deaths attributed to general anesthesia occurred during postpartum laparotomy. Of these, only one woman had undergone tracheal intubation; all others underwent mask ventilation. The investigators concluded, "It appears that for tubal sterilization, like abortion, the greatest risk for death is that associated with the anesthesia used during the procedure."[39]

These reports preceded the mandatory use of pulse oximetry and capnography and do not reflect modern anesthesia care. In the 30 years since those reports, appropriate airway management with tracheal intubation has become standard practice. Thorough adherence to ASA standards for basic anesthesia monitoring (including use of pulse oximetry and capnography to monitor oxygenation and ventilation) should help prevent morbidity and mortality associated with general anesthesia. At the University of Colorado, rapid-sequence induction (with cricoid pressure) is performed and all patients undergo tracheal intubation during administration of general anesthesia for postpartum tubal ligation.

Volatile anesthetic agents cause uterine relaxation and could potentially increase the risk for postpartum hemorrhage if administered to women in the immediate postpartum period. Therefore, the question arises as to whether the anesthesia provider should use an inhalation or an intravenous technique to maintain general anesthesia for postpartum tubal ligation. Marx et al.[39] measured postpartum uterine activity and the response to oxytocin with different concentrations of halothane or enflurane (Figure 25-4). Impairment of spontaneous uterine activity occurred at 0.5 minimum alveolar concentration (MAC) of both agents, and loss of the response to oxytocin occurred near 1.0 MAC. Spontaneous contractions reappeared when anesthetic concentrations were reduced below these levels. Parous women are at risk for postpartum uterine atony, and administration of a high concentration of a volatile halogenated agent may precipitate postpartum hemorrhage.

Two studies have determined the MAC of isoflurane during the postpartum period. Chan et al.[40] found a positive correlation between MAC and the length of time after delivery, with nonpregnant values achieved by 72 hours postpartum. Zhou et al.[41] determined that MAC of isoflurane was approximately 0.75% in the first 12 hours postpartum and 1.04% in patients who were 12 to 24 hours postpartum. No significant difference in MAC existed between the latter group and a control group of nonpregnant gynecologic patients. Together these results demonstrate that the reduced MAC observed during pregnancy persists for a variable period between 12 and 36 hours postpartum.

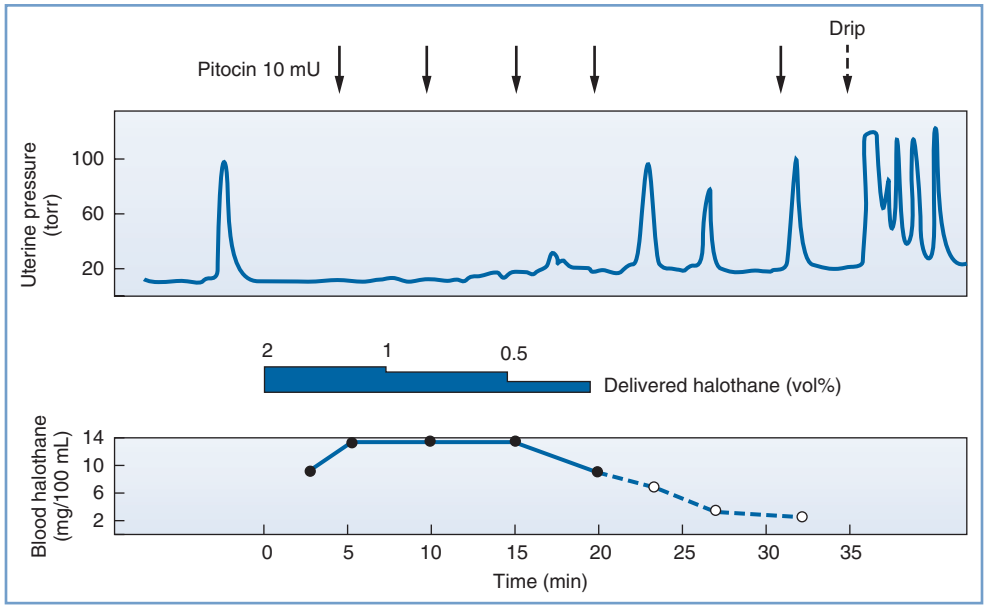

FIGURE 25-4 ■ Halothane anesthesia blocked the normal response to oxytocin when arterial blood levels exceeded 10.5 mg/100 mL or approximately 0.8 MAC. (From Marx GF, Kim YI, Lin CC, et al. Postpartum uterine pressures under halothane or enflurane anesthesia. Obstet Gynecol 1978; 51:697.)

Propofol has some advantages (e.g., rapid awakening, decreased incidence of emesis) that make it attractive as an induction agent for short sterilization procedures. When propofol was used for induction and maintenance of anesthesia for cesarean delivery, breast milk samples obtained at 4 and 8 hours postpartum had a low concentration of the drug, which suggested a negligible newborn exposure to propofol.[42] Use of sodium thiopental for induction of anesthesia also results in negligible newborn exposure during subsequent breast-feeding.

Alterations occur in the activity of both depolarizing and nondepolarizing muscle relaxants during the postpartum period. Evans and Wroe[43] described the changes in plasma cholinesterase activity during pregnancy. A rapid decline in activity occurred during the first trimester. This low level of activity was maintained until delivery and was followed by an even lower level of activity during the first week postpartum. Ganga et al.[44] found that a lower dose of succinylcholine was required to achieve 80% twitch suppression in postpartum women than in nonpregnant women. Time to recovery also was prolonged and correlated with lower cholinesterase activity in the postpartum patients. Leighton et al.[45] studied four groups of patients: nonpregnant, nonpregnant using oral contraceptives, term pregnant, and postpartum women. Cholinesterase activity was significantly lower in both term pregnant and postpartum women. Recovery time was 25% longer in the postpartum patients than in other groups (685 seconds versus approximately 500 seconds). Although a 3-minute prolongation of paralysis may not seem clinically significant, it could be important if airway difficulties occur.[46] Metoclopramide prolongs neuromuscular block with succinylcholine by 135% to 228% because of its inhibition of plasma cholinesterase.[46] Ranitidine does not affect either plasma cholinesterase activity or the duration of action of succinylcholine.[47]

Several studies have evaluated the use of the nondepolarizing muscle relaxants rocuronium, mivacurium, vecuronium, atracurium, and cisatracurium in postpartum patients. Rocuronium's duration of action is prolonged by approximately 25% in postpartum patients,[48] and mivacurium's duration of action is prolonged by approximately 20%.[49] In postpartum patients, the duration of action of vecuronium is prolonged by more than 50%.[50] In contrast, the duration of action for atracurium is unchanged[51] (Figure 25-5) and that of cisatracurium is significantly shorter in the postpartum period.[52] Prolongation of neuromuscular block could be clinically significant during a short procedure. Khuenl-Brady et al.[52] suggested that a relative decrease in hepatic blood flow and/or competition between vecuronium and steroid hormones for hepatic uptake may interfere with the hepatic clearance of vecuronium in postpartum women. Alternatively, Gin et al.[53] concluded that the duration of action for rocuronium is not prolonged in postpartum women if lean body mass—rather than total body weight—is used to calculate dose. These researchers speculated that the prolonged duration noted earlier[49] might be explained by relative drug overdose if the dose of rocuronium is based on the patient's temporarily increased body weight.[54]

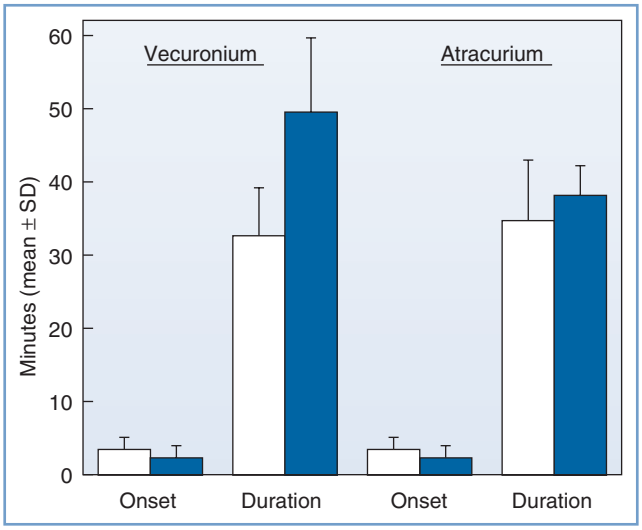

FIGURE 25-5 ■ Onset and duration of action of vecuronium (0.1 mg/kg) and atracurium (0.5 mg/kg) in postpartum (solid bar) and nonpregnant control (open bar) patients. $P < .001$ for duration of vecuronium in postpartum compared with nonpregnant patients. (From Khuenl-Brady KS, Koller J, Mair P, et al. Comparison of vecuronium- and atracurium-induced neuromuscular blockade in postpartum and nonpregnant patients. Anesth Analg 1991; 72:112.)

Neuraxial Anesthesia

Spinal and epidural anesthesia both provide excellent operating conditions for postpartum tubal ligation. Airway obstruction, hypoventilation, and aspiration are much less likely during and after neuraxial anesthesia. A sensory level of T4 is needed to block visceral pain during exposure and manipulation of the fallopian tubes. The choice between spinal and epidural anesthesia is a matter of personal preference for the patient and the anesthesia provider.

Epidural Anesthesia

When the performance of postpartum tubal ligation is anticipated in a parous patient, I encourage administration of epidural analgesia for labor and delivery. The epidural anesthetic can be extended for immediate postpartum tubal ligation if appropriate. I avoid administration of parenteral opioids during labor if immediate postpartum tubal ligation is planned. Immediate postpartum tubal ligation may save the patient the cost and inconvenience of an extra day in the hospital, allow her to eat shortly after delivery (and surgery), and enable her to avoid the apprehension of undergoing a surgical procedure the following day. The avoidance of opioids helps maintain normal gastric emptying, which should decrease any risk for aspiration during postpartum surgery. If the patient is stable and personnel are available, the procedure may be performed immediately after delivery, once the patient is moved to the operating room. The obstetrician must exclude excessive intrapartum blood loss and document that the patient has given informed consent.[5] The patient should also be asked whether the epidural catheter provided adequate analgesia for her delivery. A

catheter that was inadequate for labor analgesia is unlikely to provide adequate surgical anesthesia.

Additional intravenous crystalloid may be administered, an epidural test dose is given to rule out intrathecal or intravascular migration of the epidural catheter, and the sensory level is extended with a concentration of local anesthetic suitable for surgical anesthesia. A short-acting local anesthetic (e.g., 3% 2-chloroprocaine) is usually appropriate because the procedure is quite short. An alternative choice is 2% lidocaine with epinephrine 1:200,000. Appropriate sedative drugs also may be given, if the patient requests. The anesthesia provider should be cautious about giving sedative drugs that may cause prolonged postpartum amnesia. Women want to remember the first several hours of contact with their newborn. In some cases, peripartum administration of a benzodiazepine may cause retrograde amnesia, and the patient may not recall childbirth.[54]

If surgery is not performed immediately, the catheter may be left in place for later postpartum tubal ligation. Several studies have evaluated the efficacy of using a previously placed epidural catheter for a tubal ligation performed several hours after delivery. Vincent and Reid[55] found that the mean delivery-to-surgery interval was shorter in those patients who had adequate epidural anesthesia than in those without adequate anesthesia (10.6 versus 14.8 hours). The chance of successful epidural anesthesia was greatest if the catheter was used within 4 hours of delivery. Lawlor et al.[56] reported an 87% success rate using an indwelling epidural catheter for postpartum tubal ligation, and they observed no difference in the catheter placement-to-surgery interval between the successful epidural and failed epidural groups (21.4 versus 20.5 hours). In this study, each epidural catheter was threaded 4 to 7.5 cm into the epidural space. Similarly, Goodman and Dumas[57] reported an overall success rate of 92% with the use of an indwelling epidural catheter for postpartum tubal ligation. The success rate was 93% among patients who underwent surgery less than 24 hours after delivery and 80% among the 10 patients who underwent surgery more than 24 hours after delivery (Figure 25-6). This difference was not significant; however, this study lacked sufficient power to identify a difference of this magnitude. Clinical experience suggests that if the anesthesia provider uses an epidural catheter placed for labor, the risk for anesthesia failure may be greater if surgery is delayed more than 10 hours after delivery. To ensure maximal success when using a multi-orifice catheter, the anesthesia provider should thread the catheter 4 to 6 cm into the epidural space and have the patient assume a deflexed position before taping the catheter to the skin.[58,59]

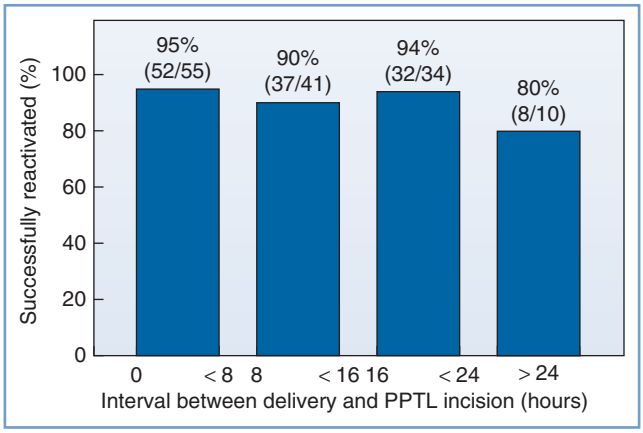

FIGURE 25-6 ■ Rate of successful reactivation of epidural catheters for various intervals between delivery and the incision for postpartum tubal ligation (PPTL). There was no difference among groups in the success rate. (From Goodman EJ, Dumas SD. The rate of successful reactivation of labor epidural catheters for postpartum tubal ligation surgery. Reg Anesth Pain Med 1998; 23:260.)

Spinal Anesthesia

Spinal anesthesia for postpartum tubal ligation has several advantages over epidural anesthesia. Epidural anesthesia requires the use of a large volume of concentrated local anesthetic and thereby introduces the risk for intravascular injection and cardiotoxicity.[60] Epidural anesthesia also is time consuming; the induction of epidural anesthesia may require more time than the tubal ligation itself. Spinal anesthesia is simple to perform, is rapid in onset, and provides dense sensory and motor block. In one study, spinal anesthesia for postpartum tubal ligation was associated with lower professional fees and operating room charges than attempted reactivation of an epidural catheter placed during labor.[61] The ability to reinject a catheter intraoperatively is not necessary for a short procedure such as postpartum tubal ligation, and there is no need for prolonged postoperative analgesia. The risk for post–dural puncture headache is low if a small-gauge (25- or 27-gauge) pencil-point or non-cutting spinal needle is used. Indeed, some anesthesiologists have suggested that the incidence of post–dural puncture headache in obstetric patients is no different after spinal anesthesia with a 25-gauge Whitacre needle from that after planned epidural anesthesia (Table 25-2).

Local anesthetic requirements for spinal and epidural anesthesia are decreased during pregnancy, but studies have demonstrated a return to nonpregnant requirements by 36 hours postpartum. Assali and Prystowsky[62] demonstrated a return to nonpregnant requirements by 36 to 48 hours postpartum. Abouleish[63] prospectively compared the dose of spinal bupivacaine required for cesarean delivery with that required for postpartum tubal ligation. He noted that 30% more bupivacaine was required to achieve a T4 dermatomal level in women who were 8 to 24 hours postpartum. The reason for the rapid decrease in sensitivity to local anesthetics is unclear but may be related to the rapid fall in progesterone levels after delivery of the placenta.

Datta et al.[64] examined plasma and cerebrospinal fluid (CSF) progesterone concentrations and spinal lidocaine requirements in nonpregnant, term pregnant, and postpartum women 12 to 18 hours after delivery. Plasma progesterone levels in pregnant women were 60 times higher than in nonpregnant women but only seven times higher than those in postpartum women. CSF progesterone concentrations were eight times higher in term pregnant women and three times higher in postpartum women

TABLE 25-2 Risk of Post–Dural Puncture Headache (PDPH) after Spinal and Epidural Anesthesia in Obstetric Patients

Needle Used*	No. of Anesthetics	Incidence of PDPH (%)	Patients with PDPH Who Required Epidural Blood Patch (%)
Quincke 26-gauge	2,256	5.2	33
Quincke 27-gauge	852	2.7	39
Whitacre 25-gauge	1,000	1.2	13
Epidural 17-gauge	21,578	1.3	75

Quincke needles have a cutting bevel. Whitacre needles have a pencil-point tip.

*There was a significant difference in the incidence of post–dural puncture headache between the 26-gauge Quincke needle and the epidural needle ($P < .05$), but not between the Whitacre needle or the 27-gauge Quincke needle and the epidural needle.

Data from Lambert DH, Hurley RJ, Hertwig L, Datta S. Role of needle gauge and tip configuration in the production of lumbar puncture headache. Reg Anesth 1997; 22:66-72.

than in nonpregnant women. Intrathecal lidocaine requirements were similar in pregnant and postpartum patients, even though plasma and CSF progesterone concentrations were lower in the postpartum women. The authors suggested "that a minimum level of progesterone in the CSF and/or plasma is necessary for this heightened local anesthetic activity" associated with progesterone. Together these studies suggest that local anesthetic requirements return to nonpregnant requirements 12 to 36 hours after delivery.[63-65]

Huffnagle et al.[65] gave hyperbaric intrathecal lidocaine 75 mg to postpartum women to determine whether age, weight, height, body mass index, vertebral column length, or time from delivery to placement of the block correlated with the spread of sensory block. Only patient height had a weak positive correlation, and it accounted for less than 15% of the variance in height of the block. Because of the large variation in the spread of sensory block among patients of the same height, the investigators concluded that there was little use in adjusting the dose of local anesthetic on the basis of height.

Many anesthesia providers have discontinued the use of hyperbaric lidocaine for spinal anesthesia because of concern about transient neurologic symptoms or transient radicular irritation, but obstetric patients may be at lower risk for this complication. A prospective nonrandomized study of 303 obstetric patients who received spinal anesthesia during a 9-month period observed a 0% incidence of transient radicular irritation (95% confidence interval 0% to 4.5%).[66] Patients underwent a variety of procedures, including cesarean delivery, postpartum tubal ligation, cerclage, and other cases. The number of patients was too small to determine the true incidence of transient radicular irritation in obstetric patients, but the investigators concluded that the true incidence is likely less than 5%. In a randomized controlled trial, Philip et al.[67] compared spinal administration of hyperbaric 5% lidocaine with that of hyperbaric 0.75% bupivacaine for postpartum tubal ligation. They observed a 3% incidence of transient neurologic symptoms with the use of lidocaine, compared with a 7% incidence with bupivacaine, a nonsignificant difference. In an editorial accompanying their report, Schneider and Birnbach[68] acknowledged that "there are no very short-acting hyperbaric spinal local anesthetics that have taken the place of lidocaine for these short procedures and many believe that spinal bupivacaine lasts too long to be a reasonable choice of anesthetic for a procedure that will last less than 20 minutes." However, they concluded, "Because pregnant patients represent a population that lies to the extreme in terms of the criteria for safety and lack of morbidity, we believe that for the present, there is still insufficient safety evidence to suggest that spinal hyperbaric 5% lidocaine be routinely used in obstetrics." At the University of Colorado, some of the anesthesia providers use 5% lidocaine because of its short duration of action, whereas others prefer to avoid spinal lidocaine despite the low risk for transient neurologic symptoms in obstetric patients.

Postpartum women seem to be at lower risk for hypotension during spinal anesthesia than pregnant women, and maintenance of uteroplacental perfusion is not a concern after delivery. Abouleish[64] gave ephedrine to correct maternal hypotension in 83% of pregnant women who received spinal bupivacaine anesthesia for cesarean delivery. In contrast, only 7% of postpartum women who received spinal anesthesia for tubal ligation required ephedrine. An autotransfusion of blood occurs immediately after delivery. The greater intravascular volume and the lack of aortocaval compression may help protect postpartum patients from hypotension during spinal anesthesia. Sharma et al.[69] compared the use of crystalloid with the use of 6% hetastarch for the prevention of hypotension during spinal anesthesia for postpartum tubal ligation. They observed a 52% incidence of hypotension in the crystalloid group and a 16% incidence in the hetastarch group. However, they acknowledged that the greater expense of colloid, as well as the risk for an allergic reaction, might not be justifiable. Suelto et al.[70] compared normotensive and hypertensive patients receiving hyperbaric lidocaine for postpartum tubal ligation and found no difference in the use or dose of ephedrine for treatment of hypotension.

Preservative-free intrathecal meperidine can be used as an alternative to local anesthetic for postpartum tubal ligation. The typical dose is 1 mg per kilogram prepregnant weight (50 to 80 mg) for cesarean delivery or tubal ligation. With an onset time of 3 to 5 minutes and a duration of 30 to 60 minutes, intrathecal meperidine compares favorably with 5% lidocaine. In a study that compared intrathecal lidocaine 70 mg with intrathecal meperidine 60 mg for postpartum tubal ligation, patients who received meperidine had more pruritus but longer postoperative analgesia (448 versus 83 minutes, respectively).[71] There was no difference between groups

in rates of nausea, hemoglobin desaturation, or patient satisfaction. Intrathecal meperidine may be an alternative to lidocaine for postpartum tubal ligation.

Box 25-1 summarizes a personal approach to anesthetic management for postpartum tubal ligation.

BOX 25-1 Anesthetic Management for Postpartum Tubal Ligation

Management during Labor

- Encourage use of epidural analgesia.
- Avoid administration of parenteral opioids.
- Keep patient on *nil per os* (NPO) status except for clear liquids.
- Give aspiration prophylaxis if the procedure is to be performed immediately after delivery.

Timing of Surgery

- Consider performing surgery immediately postpartum if the patient is hemodynamically stable and has received aspiration prophylaxis.
- An epidural catheter placed for labor may provide more reliable anesthesia if used within 10 hours of delivery.

General Anesthesia

- Perform a rapid-sequence induction with cricoid pressure.
- Intubate the trachea and control ventilation.
- Avoid high concentrations (> 0.5 minimum alveolar concentration [MAC]) of a volatile anesthetic agent.
- Monitor neuromuscular blockade if a nondepolarizing muscle relaxant is used.

Epidural Anesthesia

- Requires a T4 sensory level of anesthesia.
- After a negative test dose result, consider using 3% 2-chloroprocaine unless a longer procedure is planned.
- If a catheter placed during labor is used, beware of a higher risk of failure if the delivery-to-surgery interval is prolonged more than 10 hours.
- Give fentanyl 50 to 100 µg via the epidural catheter for intraoperative and postoperative analgesia.

Spinal Anesthesia

- Requires a T4 sensory level of anesthesia.
- It is the preferred technique for delayed postpartum tubal ligation, or for immediate surgery in patients who did not have epidural labor analgesia, or in whom epidural analgesia during labor and delivery was ineffective.
- Use a small-gauge, non-cutting, pencil-point spinal needle.
- Give lidocaine 75 mg with fentanyl 10 to 25 µg or bupivacaine 10 to 12 mg with fentanyl 10 to 25 µg.

Postoperative Pain Management

- Consider infiltration of the skin and the mesosalpinx with bupivacaine.
- Administer a nonsteroidal anti-inflammatory drug such as ketorolac or ibuprofen perioperatively.
- Begin oral analgesics before complete block regression after spinal or epidural anesthesia.

POSTOPERATIVE ANALGESIA

Postpartum tubal ligation produces modest postoperative pain of short duration. Patients may receive one dose of parenteral opioid postoperatively, followed by oral analgesics. Optimal analgesia encourages early ambulation, interaction with the newborn, and early discharge from the hospital. An oral nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen may be given to supplement other analgesics. When epinephrine 0.2 mg was added to lidocaine with fentanyl 10 µg for spinal anesthesia, the duration of complete and effective analgesia was prolonged and the incidence of pruritus was decreased, but the time to complete motor recovery was also prolonged.[72] Habib et al.[73] reported that adding intrathecal morphine 0.05 mg to intrathecal bupivacaine and fentanyl for postpartum tubal ligation resulted in less intense pain at rest and with movement at 4 hours after surgery than with saline control. However, patients who received morphine had more vomiting and pruritus. Despite side effects, patients who received morphine were significantly more satisfied. Similarly, Marcus et al.[74] found that epidural morphine 2 mg provided better analgesia without increasing the need to treat side effects, in comparison with a regimen of oral opioids and NSAIDs without epidural morphine. Although effective, spinal and epidural morphine analgesia should be used with caution because these patients could be discharged soon after postpartum tubal ligation, before the risk for delayed respiratory depression has lapsed. The method of postoperative analgesia chosen should not delay patient discharge because of side effects or the need for postoperative respiratory monitoring.

Local anesthetic infiltration of the mesosalpinx with bupivacaine or topical application of a local anesthetic to the fallopian tubes significantly decreases opioid requirements postoperatively.[75] These are simple, rapid techniques that can be used by the obstetrician. Wittels et al.[76] reported that use of multimodal therapy with spinal or epidural anesthesia consisting of intravenous ketorolac 60 mg, intravenous metoclopramide 10 mg, and infiltration of the incised skin, fallopian tubes, and mesosalpinx with 0.5% bupivacaine prevented pain, nausea, and painful uterine cramping in both the immediate postoperative period and for 7 days after postpartum tubal ligation in 9 of 10 patients. The manufacturer of ketorolac has stated that ketorolac is contraindicated in nursing mothers because of the possible adverse effects of prostaglandin synthetase inhibitors on neonates. In contrast, the American Academy of Pediatrics considers ketorolac to be compatible with breast-feeding.[77]

KEY POINTS

- Postpartum tubal sterilization is an elective procedure. No data indicate that the postpartum patient's safety is enhanced by a delay of surgery or compromised by the performance of tubal ligation immediately after delivery.

- Postpartum sterilization offers the advantages of convenience for the patient and technical simplicity for the surgeon.
- Postpartum patients do not have lower gastric pH or higher gastric volumes than nonpregnant patients undergoing elective surgery. Some studies suggest that gastric emptying is delayed postpartum only if the patient has received an opioid analgesic during labor.
- The incidence of gastroesophageal reflux returns toward normal by the second postpartum day.
- Modern anesthetic drugs do not appear in breast milk in amounts that affect the newborn.
- The duration of succinylcholine-, rocuronium-, mivacurium-, and vecuronium-induced neuromuscular blockade is prolonged during the postpartum period. In contrast, the duration of action for atracurium is unchanged and that of cisatracurium is shorter.
- An epidural catheter placed for labor may be used for postpartum tubal ligation, but the risk for anesthesia failure may be greater if surgery is delayed more than 10 hours after delivery.
- Spinal anesthesia is preferred for delayed postpartum tubal ligation (>10 hours after delivery), regardless of whether an epidural catheter was placed for labor analgesia.
- The local anesthetic dose for spinal anesthesia returns to nonpregnant requirements by 12 to 36 hours postpartum.
- Postoperative multimodal analgesia improves maternal mobilization and infant bonding and may facilitate earlier hospital discharge.

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PART VII

CESAREAN DELIVERY

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During most of the nineteenth century, physicians performed very few cesarean deliveries because the mortality rate was so high. For example, in his case books, John Snow mentions more than 90 patients anesthetized for vaginal delivery, but not one cesarean delivery.[1] The procedure was reserved for desperate situations. One physician quipped that a woman had a better chance of surviving an abdominal delivery if she performed the surgery herself, or if her abdomen were accidentally ripped open by the horn of a bull.[2]

Hemorrhage and infection caused most deaths. The use of anesthesia allowed surgeons to develop techniques to deal with these problems. Italian surgeon Eduardo Porro made the first important innovation in 1876. To limit hemorrhage, he excised the uterus after delivering the child. Others had left the uterine incision open in the belief that it would heal better. In 1882, German surgeon Max Sänger advised closing the uterus with sutures, thereby obviating the need for a hysterectomy. Sänger, benefiting from the advances in bacteriology, also devised techniques to limit the risk of infection.[3]

In 1910, J. Whitridge Williams of Johns Hopkins still called cesarean delivery a "dangerous procedure" despite the fact that the maternal mortality rate had fallen to 10%. He performed it only for the most severe cases of contracted pelvis.[2,4] In fact, Williams warned that a cesarean delivery "should never be performed when the child is dead or in serious danger." Even in 1970, cesarean delivery rates remained below 7% in the United States, and at less than 2% in many European countries.[5]

With few agents to choose from, anesthetic techniques for cesarean delivery also evolved slowly. Regional anesthesia was not available before 1900. Ether and chloroform were the only two potent agents available for general anesthesia until the addition of cyclopropane. Until curare was introduced to clinical practice, use of these agents necessitated achieving an anesthetic depth sufficient to obtain abdominal relaxation.

Only in the past five decades have there been incentives to develop better anesthetic techniques for cesarean delivery. First, obstetricians began to perform cesarean delivery more often to deal with fetal and maternal problems. Second, physicians developed a better understanding of the physiology of pregnancy, especially the nature of risks associated with anesthesia. Third, anesthesiologists and obstetricians began to place greater emphasis on the well-being of the neonate, a change that required the development of anesthetic techniques that would protect the mother but have the least possible effect on the child.

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CHAPTER 26

Anesthesia for Cesarean Delivery

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CHAPTER OUTLINE

HISTORY

Cesarean delivery is defined as the birth of an infant through incisions in the abdomen (laparotomy) and uterus (hysterotomy). Although the technique is commonly associated with the birth of the Roman Emperor Julius Caesar, medical historians question this possibility, given his birth in an era in which such operations were invariably fatal (100 BC) and the acknowledged presence of Caesar's mother in his later life.[1] Although the term *cesarean section* is commonly used, the Latin words *caedere* and *sectio* both imply "to cut," and modern linguists argue that use of both words is redundant. Consequently, *cesarean delivery* is the preferred term.

Morbidity and mortality, most often associated with hemorrhage and infection, limited the use of cesarean delivery until the 20th century, when advances in aseptic, surgical, and anesthetic techniques improved the safety for both mother and baby. Today, cesarean delivery is the most common major surgical procedure performed in the United States, accounting for more than 30% of all births and 1 million procedures each year.[2] Globally, the incidence of cesarean delivery has progressively increased; however, the rate varies dramatically by country, ranging from 0.4% to 45.9% (Figure 26-1).[3] Maternal, obstetric, fetal, medicolegal, and social factors are largely responsible for this variability, resulting in significant differences in cesarean delivery rates even among individual obstetricians and institutions (Box 26-1).[4]

BOX 26-1 Factors Contributing to the Increasing Cesarean Delivery Rate

Maternal

- Increasing proportion of deliveries in nulliparous women
- Delayed childbearing and increasing maternal age
- Increasing prevalence of obesity

Obstetric

- Increasing use of labor induction
- Fewer vaginal breech deliveries
- Fewer instrumental vaginal deliveries
- Fewer attempts at trial of labor after cesarean delivery
- Increasing availability of cesarean delivery in developing nations

Fetal

- Increasing incidence of fetal macrosomia
- Increasing incidence of multiple gestation
- *Ex utero* intrapartum treatment (EXIT) procedures

Practice Environment

- Concern for malpractice litigation
- Increased use of electronic fetal heart rate monitoring
- Concern for pelvic floor injury associated with vaginal birth
- Desire for scheduled procedures (convenience)

BOX 26-2 Indications for Cesarean Delivery

Maternal

- Antepartum or intrapartum hemorrhage
- Arrest of labor
- Breech presentation
- Chorioamnionitis
- Deteriorating maternal condition (e.g., severe preeclampsia)
- Dystocia
- Failure of induction of labor
- Genital herpes (active lesions)
- High-order multiple gestation (or twin gestation in which twin A has a breech presentation)
- Maternal request
- Placenta previa
- Placental abruption
- Previous myomectomy
- Prior classic uterine incision
- Uterine rupture

Fetal

- Breech presentation or other malpresentation
- Fetal intolerance of labor
- Suspected macrosomia
- Nonreassuring fetal status
- Prolapsed umbilical cord

Obstetrician

- Desire to avoid difficult forceps or vacuum delivery

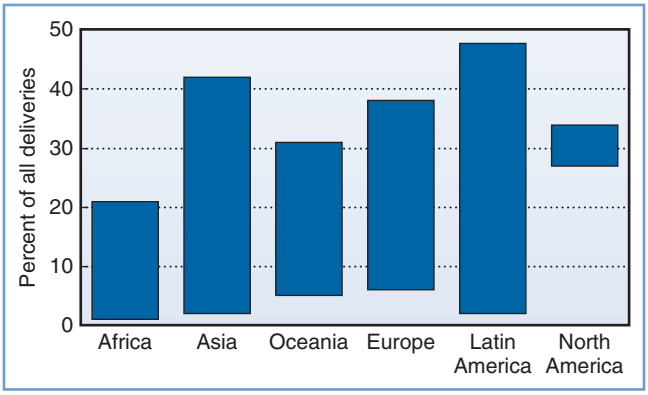

FIGURE 26-1 ■ The range of cesarean delivery rates by world region as collected in surveys or vital registration system reports. (Data modified from Gibbons L, Belizan JM, Lauer JA, et al. Inequities in the use of cesarean section deliveries in the world. Am J Obstet Gynecol 2012; 206:331.e1-19.)

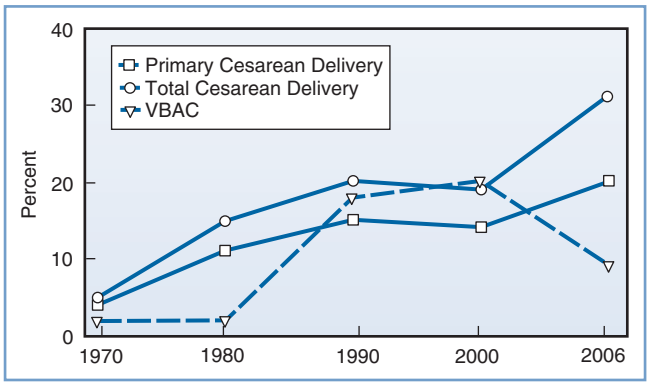

FIGURE 26-2 ■ Rates of primary cesarean delivery, total cesarean delivery, and vaginal birth after cesarean delivery (*VBAC*) in the United States, 1970 to 2006. (Data for 1970-1988 from the National Hospital Discharge Survey; data for 1989-2006 from the National Vital Statistics System, Centers for Disease Control and Prevention. Available at http://www.cdc.gov.)

INDICATIONS

The common indications for cesarean delivery include dystocia, malpresentation, nonreassuring fetal status, and previous cesarean delivery (Box 26-2). An *elective* cesarean delivery can be performed for obstetric or medical indications or at the request of a pregnant patient, and it is typically planned and performed *prior to* the onset of labor.[5] A cesarean delivery performed during labor for a planned vaginal delivery can also occur for a wide range of maternal and fetal indications but may need to be conducted in an urgent or emergent manner. A prior cesarean delivery does not necessitate cesarean delivery in a subsequent pregnancy. A trial of labor after cesarean (TOLAC), which if successful is called a vaginal birth after cesarean (VBAC), is an alternative option; the use of TOLAC, once growing in popularity, has declined in recent years for a variety of reasons (Figure 26-2) (see Chapter 19).

OPERATIVE TECHNIQUE

The technical aspects of performing a cesarean delivery are comparable worldwide, with minor variations. A midline vertical *abdominal* incision allows rapid access and greater surgical exposure; however, the horizontal suprapubic (Pfannenstiel) incision offers better cosmesis and wound strength. Similarly, a low transverse *uterine* incision, in comparison with a vertical incision, allows for a lower incidence of uterine dehiscence or rupture in subsequent pregnancies, as well as a reduction in the risks of infection, blood loss, and bowel and omental adhesions. Vertical uterine incisions are most often used in the following situations: (1) when the lower uterine segment is underdeveloped (before 34 weeks' gestation), (2) in delivery of a preterm infant in a woman who has not labored, and (3) in selected patients with multiple gestation and/or malpresentation. In some cases, a vertical uterine incision is performed high on the anterior uterine wall (i.e., classic incision), especially in the patient with a low-lying anterior placenta previa or when a cesarean hysterectomy is planned.

Uterine exteriorization following delivery facilitates visualization and repair of the uterine incision, particularly when the incision has been extended laterally. Although the effect of exteriorization on blood loss and febrile morbidity remains controversial,[6] higher rates of intraoperative nausea, emesis, and venous air embolism as well as postoperative pain have been observed.[7,8]

MORBIDITY AND MORTALITY

Complications of cesarean delivery include hemorrhage, infection, thromboembolism, ureteral and bladder injury, abdominal pain, uterine rupture in subsequent pregnancies, and death (Box 26-3).[9] Nonelective cesarean delivery is associated with a greater risk for maternal morbidity than elective cesarean delivery; a 2008 study of all deliveries in Finland indicated that the rates of severe maternal morbidity were 5.2, 12.1, and 27.2 per 1000 vaginal, elective cesarean, and nonelective cesarean deliveries, respectively.[10]

Maternal mortality has decreased during the past 75 years (see Chapter 40). Since 1937, when the maternal mortality rate for nulliparous women undergoing cesarean delivery in the United States was 6%, the risk for death associated with the procedure has decreased by a factor of nearly 1000 owing to the availability of blood transfusions, antibiotics, safer anesthetic techniques, and critical care units.[11] Maternal morbidity and mortality vary widely from country to country. In most developed nations, the rate of maternal death associated with all cesarean deliveries remains higher than that associated with vaginal deliveries.[3,12] The risk for maternal death for a planned, elective primary cesarean delivery may not differ from that associated with a planned vaginal delivery, but performance of cesarean delivery places the mother at higher risk for morbidity (and perhaps mortality) in subsequent pregnancies and cesarean deliveries.[13]

BOX 26-3 Complications of Cesarean Delivery

Intraoperative Complications

Hemorrhage

- Uterine atony
- Uterine lacerations
- Broad ligament hematoma

Infection

- Endometritis
- Wound infection

Postoperative Complications

- Cardiovascular: venous thromboembolism
- Gastrointestinal: ileus, adhesions, injury
- Genitourinary: bladder or ureteral injury
- Respiratory: atelectasis, aspiration pneumonia
- Chronic pain

Future Pregnancy Risks

- Placenta previa
- Placenta accreta
- Uterine rupture
- Obstetric hysterectomy

Clark et al.[12] identified the causes of maternal death in a retrospective study of 1.5 million deliveries that occurred between 2000 and 2006 within a health care network composed of primary, secondary, and tertiary care hospitals in 20 states (Table 26-1). Only 15% of maternal deaths were related to preexisting medical conditions; most deaths occurred in women classified as being at low risk at the beginning of pregnancy. The investigators concluded that 17 deaths (18%) could have been prevented by provision of more appropriate medical care. (Causality was determined by evaluating whether the maternal death could have been avoided with the use of an alternative route of delivery, with the assumption that all other details remained the same prior to delivery.) The preventable deaths were associated with postpartum hemorrhage (8), preeclampsia (5), medication error (3), and infection (1). Cesarean delivery was determined to be directly responsible for maternal death in four cases, including hemorrhage from surgical vascular injury in three cases and sepsis from surgical injury to the bowel in the fourth. Deaths associated with, but not directly caused by, cesarean delivery were associated with perimortem procedures or caused by thromboembolic phenomena; of the nine patients who died of thromboembolic phenomena, none had received peripartum mechanical or pharmacologic thromboprophylaxis. The investigators concluded that cesarean delivery *per se* was only rarely the causative factor in maternal death; in the majority of cases, death was related to the indication for the cesarean delivery rather than the operative procedure. Nonetheless, these investigators also concluded that the risk for death caused by cesarean delivery is approximately 10 times higher than that for

TABLE 26-1 **Relationship between Route of Delivery and Maternal Death**

Delivery Type	No. of Procedures	Association of Delivery Route with Maternal Death*		Causal Relationship of Delivery Route with Maternal Death†	
		NO. OF DEATHS	FREQUENCY OF DEATH (PER 100,000 PROCEDURES)	NO. OF DEATHS	FREQUENCY OF DEATH (PER 100,000 PROCEDURES)
Vaginal	1,003,173	17	1.7	2	0.2
Primary cesarean	282,632	46	16.3	7	2.5
Repeat cesarean	175,465	12	7.4	2	1.1
Total cesarean	458,097	58	12.7	9	2.0
Not delivered/dilation and curettage	NA	20	NA	NA	NA
TOTAL	1,461,270	95	6.5‡	20	1.4‡

NA, not applicable.
**Association relationships:* For vaginal birth versus total cesarean, vaginal birth versus primary cesarean, and vaginal birth versus repeat cesarean, $P < .001$. For primary cesarean versus repeat cesarean, $P = .01$.
†*Causal relationships:* For vaginal birth versus total cesarean and vaginal birth versus primary cesarean, $P < .001$. For vaginal birth versus repeat cesarean, $P = .12$. For primary cesarean versus repeat cesarean, $P = .50$. For vaginal birth versus primary, repeat, and total cesarean delivery, excluding pulmonary embolism deaths preventable with universal prophylaxis, $P = .07$, $P = .38$, and $P = .08$, respectively.
‡Deaths per 100,000 pregnancies.
Modified from data in Clark SL, Belfort MA, Dildy GA, et al. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol 2008; 199:36.e1-5.

vaginal birth and likely could be reduced with the implementation of universal perioperative thromboprophylaxis (see later discussion).

Neonatal morbidity, in particular respiratory system morbidity (thus potentially resulting in the anesthesia provider's involvement in neonatal resuscitation), is greater with elective cesarean delivery than with vaginal delivery.[14] Patterns and rates of neonatal mortality are similar to those of maternal mortality; the higher neonatal mortality rates observed after cesarean delivery most likely reflect the conditions that prompt nonelective cesarean delivery.[15]

PREVENTION OF CESAREAN DELIVERY

Neuraxial labor analgesia was earlier thought to increase the cesarean delivery rate compared with nonmedicated labor or other analgesic techniques; however, randomized controlled trials and sentinel event studies indicate that neuraxial analgesia is not associated with a higher cesarean delivery rate than systemic opioid analgesia (see Chapter 23).[16,17] Moreover, the combined spinal-epidural (CSE) technique for labor analgesia, despite its association with fetal bradycardia, does not result in an increase in the total cesarean delivery rate.[18,19] Some cesarean deliveries may be avoided through the provision of (1) adequate labor analgesia, including analgesia for trial of labor after cesarean delivery and instrumental vaginal delivery; (2) analgesia for external cephalic version (see Chapter 35); and (3) intrauterine resuscitation, including pharmacologic uterine relaxation in cases of uterine tachysystole.

Maternal Labor Analgesia

The National Institutes of Health consensus statement on cesarean delivery on maternal request emphatically concluded that "maternal request for cesarean delivery should not be motivated by unavailability of effective [labor] pain management."[5] It is of concern that a survey of 1300 hospitals indicated that as recently as 2001, 6% to 12% of hospitals in the United States did not provide any form of labor analgesia.[20] Although the availability of labor analgesia, especially in the form of neuraxial techniques, has increased during the past three decades,[20] there are still institutions, predominantly smaller ones, where cesarean deliveries are likely performed because of nonexistent or inadequate labor analgesia.

Adequate maternal analgesia and perineal relaxation are also important for instrumental (forceps, vacuum) vaginal deliveries. Neuraxial techniques can optimize anesthetic conditions for these obstetric procedures (see Chapter 23).

External Cephalic Version

Singleton breech presentations occur in 3% to 4% of term pregnancies. The Royal College of Obstetricians and Gynaecologists[21] and the American College of Obstetricians and Gynecologists (ACOG)[22] caution against a vaginal breech delivery, given the increased risk for emergency cesarean delivery and neonatal injury. External cephalic version (ECV), a procedure by which manual external pressure is applied to the maternal abdomen to change the fetal presentation from breech to cephalic, remains a viable option. ECV is usually performed between 36 and 39 weeks' gestation.[22]

Neuraxial analgesia or anesthesia has been observed to increase the success of an ECV of a fetus with a breech presentation (see Chapter 35). Two recent, independent meta-analyses both concluded that the use of neuraxial blockade resulted in a significant improvement in the ECV success rate.[23,24] Both randomized and nonrandomized studies have indicated that the use of neuraxial blockade improves the overall success rate by 13% to 50%. Moreover, in these studies, the use of neuraxial blockade did not appear to compromise maternal and fetal safety, and specifically it did not increase the incidence of fetal bradycardia, placental abruption, or fetal death.

Intrauterine Resuscitation

Evidence of intrapartum fetal compromise (nonreassuring fetal status) should prompt the obstetric team (including obstetric and anesthesia providers and nurses) to attempt intrauterine fetal resuscitation (Box 26-4).

In cases of uterine tachysystole, the administration of nitroglycerin (50 to 100 µg intravenously) may provide rapid onset (40 to 50 seconds) uterine relaxation.[25] Higher doses of intravenous nitroglycerin (200 to 500 µg) have been described for uterine relaxation in other settings (e.g., internal podalic version, ECV, uterine prolapse)[26]; to date, a nitroglycerin dose-response study evaluating uterine tone as well as side effects (e.g., hypotension) has not been performed. Nitroglycerin may also be administered via other routes (e.g., sublingual, topical), but the bioavailability associated with the use of these routes is different and highly variable. For example, three sprays of sublingual nitroglycerin (400 µg/spray) have been used for uterine tocolysis[27]; however, the bioavailability of nitroglycerin by this route is approximately 38%. Nitroglycerin relaxes the uterus through the production of nitric oxide in uterine smooth muscle.[28] Although the use of nitroglycerin has not been uniformly demonstrated to be superior to placebo for the promotion of uterine relaxation,[29] a number of reports have indicated its value in cases requiring acute tocolysis.[30] Nitroglycerin does not provide total relaxation of the cervix because the majority (85%) of cervical fibers are fibrous in origin.[31]

BOX 26-4 Obstetric Management of Nonreassuring Fetal Status

- Optimize maternal position:
  - To avoid or relieve aortocaval compression.
  - To relieve umbilical cord compression.
- Administer supplemental oxygen.
- Maintain maternal circulation:
  - Perform rapid intravenous administration of a non–dextrose-containing balanced salt solution.
  - Treat hypotension with either ephedrine or phenylephrine.
- Discontinue oxytocin.
- Consider administration of a tocolytic agent for treatment of uterine tachysystole.

PREPARATION FOR ANESTHESIA

The anesthetic management of cesarean delivery may depend in part on the obstetric indications for operative delivery. The anesthesia provider should consider the patient's medical, surgical, and obstetric history, the presence or absence of labor, the urgency of the delivery, and the resources available in preparing for a cesarean delivery.

Preanesthetic Evaluation

All women admitted for labor and delivery are potential candidates for the emergency administration of anesthesia, and an anesthesia provider ideally should evaluate every woman shortly after admission. Optimally, for high-risk patients, preanesthesia consultation should occur in the late second or early third trimester, even if a vaginal delivery is planned. This practice offers the opportunity to provide patients with information, solicit further consultations, optimize medical conditions, and discuss plans and preparations for the upcoming delivery.[32,33] Early communication among the members of the multidisciplinary team is encouraged.[34] In some cases, the urgent nature of the situation allows limited time for evaluation before induction of anesthesia and commencement of surgery; nonetheless, essential information must be obtained and risks and benefits of alternative anesthetic management decisions should be considered.

A focused preanesthetic history and physical examination includes (1) a review of maternal health and anesthetic history, relevant obstetric history, allergies, and baseline blood pressure and heart rate measurements; and (2) performance of an airway, heart, and lung examination consistent with the American Society of Anesthesiologists (ASA) guidelines (see Appendix B).[34,35]

Informed Consent

Recognized by the courts as early as the 18th century, the concept of *informed medical consent* was defined in 1957 as a requirement that the physician explain to the patient the "risks, benefits, and alternatives" of a procedure.[36] The ethical issues in obtaining consent from the obstetric patient can be challenging because of the clinical situations encountered, such as (1) the pain and stress of labor; (2) birth plans (in which the patient dictates in advance those interventions that are "acceptable" and "not acceptable"); (3) rapidly changing maternal and fetal status, often requiring emergency care; and (4) fetal considerations, which may involve consideration of extrauterine viability and the definition of independent moral status (i.e., the existence of fetal rights equal to those of the mother). Discussion of this last issue may invoke theological, moral, ethical, and philosophical arguments (see Chapter 33).

Informed consent has the following three elements: threshold, information, and consent (Box 26-5).[37]

BOX 26-5 Elements of Informed Consent

Threshold Elements

- Patient is competent to provide consent (i.e., refers to the patient's legal authority to make decisions regarding her health care).

Information Elements

- Provider discloses information about material risks.
- Patient understands information.

Consent Elements

- Provider offers information in a noncoercive manner.
- Patient gives authorization voluntarily.

Information from Barkham M, Peters G, Pace N. Ethical and medico-legal aspects of obstetric anaesthesia. Anaesth Intensive Care Med 2005; 6:127-129.

Threshold Elements

Threshold elements include the ability of the patient to meet the basic definition of **competence**, which refers to the patient's legal authority to make a decision about her health care. Although some cognitive functions may be compromised by the effects of pain, exhaustion, and analgesic drugs,[38] evidence suggests that most laboring women retain the **capacity** to hear and comprehend information during the consent process.[36]

Information Elements

The premise that a patient should be informed about the risks of a planned procedure in a language that she understands is the basis for the information elements of the consent process. In part, the difficulty with obtaining informed consent for anesthesia lies in determining the incidence of anesthesia-related morbidity and mortality. Jenkins and Baker[39] surveyed the risks associated with anesthesia and compared them with risks inherent in daily living to provide contextual comparisons for patients. The investigators concluded that the perceptions regarding anesthesia risks held by anesthesia providers, surgeons, and the public are somewhat optimistic and that the consent process should include a more realistic and comprehensive disclosure.

A second difficulty is determining what risks require disclosure. White and Baldwin[40] stated:

> *Anesthesia is by nature a practical specialty; every procedure [is] performed carrying a range of risks, which may be minor or major in consequence, common or rare in incidence, causal or incidental to the harm sustained (if any), convenient or inconvenient in timing, expected or unexpected, relative or absolute, operator-dependent or any combination of the above. In addition, there are significant difficulties in communicating risk, caused by patient perceptions, anaesthetist perceptions and the doctor-patient interaction, and complicated by the range of communication methods (numerical, verbal, or descriptive).*

A survey conducted among obstetric anesthesia providers in the United Kingdom and Ireland found a consensus that the following neuraxial anesthetic risk factors should be disclosed: (1) the possibility of intraoperative discomfort and a failed/partial blockade, (2) the potential need to convert to general anesthesia, (3) the presence of weak legs, (4) hypotension, and (5) the occurrence of an unintentional dural puncture (with the use of an epidural technique).[41] Backache and urinary retention were considered "optional" for discussion, and the risk for paraplegia was considered unworthy of mention unless the patient specifically asked about it.[41]

Among obstetric patients, the desire for risk disclosure varies. In a study from Australia, Bethune et al.[42] reported a significant range (between 1:1 and 1:1 billion) in the level of risk for complications of epidural analgesia at which pregnant women wished to be informed. In a similar study from the United Kingdom in which the risks associated with general anesthesia were discussed, Jackson et al.[43] found that 50% of pregnant women wished to know all risks that occurred at a frequency of greater than 1:1000. Overall, pregnant women appear to want more rather than less information regarding the risks of anesthetic interventions.[44]

Consent Elements

In obtaining consent, care must be taken to preserve patient autonomy by providing information in a noncoercive, nonmanipulative manner (i.e., avoiding a paternalistic or maternalistic approach). Barkham et al.[37] observed that there are occasions when noncoercive forms of influence may be appropriate and that reasoned argument can be used to persuade patients of the merits of a particular course of action. For example, a woman with anatomy consistent with a difficult airway who is requesting general anesthesia for an elective cesarean delivery may reconsider her choice after rational persuasion.

In many cases, the course of action most appropriate for maternal health is also beneficial to the fetus. In some cases, however, the best interests of the mother may conflict with those of the fetus. For example, emergency cesarean delivery with general anesthesia is often performed primarily for the benefit of the fetus but may involve higher risk to the mother than a nonemergency procedure performed with neuraxial anesthesia. This conflict in relative risks and benefits will most likely intensify in the future as intrauterine fetal surgery becomes more common.

Informed Refusal

The National Institute of Clinical Excellence (NICE) is a part of the National Health Service in the United Kingdom. The NICE guidelines for cesarean delivery state that "after providing the pregnant woman with evidence-based information and in a manner that respects the woman's dignity, privacy, views, and culture whilst taking into consideration the clinical situation … a competent pregnant woman is entitled to refuse treatment, even when the treatment would clearly benefit her or her

BOX 26-6 Selected Risk Factors for Peripartum Hemorrhage

- Abnormal placentation
- Advanced maternal age
- Anticoagulation
- Bleeding disorder
- Chorioamnionitis
- Fetal demise
- Fetal malpresentation
- General anesthesia
- Increased parity/grand multiparity
- Instrumental vaginal delivery
- Internal trauma (e.g., curettage, internal version)
- Oxytocin augmentation of labor
- Placental abruption
- Precipitous delivery
- Preeclampsia (thrombocytopenia, coagulopathy)
- Premature rupture of membranes
- Previous uterine surgery (cesarean delivery, myomectomy)
- Prolonged labor
- Retained placenta
- Tocolytic therapy
- Trauma (blunt or penetrating)
- Uterine distention (e.g., macrosomia, multiple gestation, polyhydramnios)
- Uterine leiomyoma

baby's health. Refusal of treatment needs to be one of the woman's options."[45] Although compliance with maternal requests is the usual course of action, a court-based decision is sometimes made on behalf of the unborn infant (see Chapter 33).

The anesthesia provider is not obliged to honor a patient's or obstetrician's request (e.g., general anesthesia in a morbidly obese patient with a difficult airway), particularly when it conflicts with the clinician's experience and knowledge of acceptable risks and benefits.[46]

Overall, anesthesia providers are encouraged to (1) engage in, rather than withhold, a discussion of anesthetic risks; (2) recognize that their own biases may influence the presentation of risks; (3) understand how the perception of risks is modified by the situation; and (4) provide contextual explanation of risks, to help place potential complications in perspective.[39] When recognized as an opportunity to foster a closer patient-physician relationship and greater involvement of the patient in her care, rather than simply as a tool to avoid litigation, informed consent can help guide the decision-making associated with anesthesia care.

Blood Products

Peripartum hemorrhage remains a leading cause of maternal mortality worldwide (see Chapters 38 and 40).[47] There is little difference in blood loss between an uncomplicated elective cesarean delivery and an uncomplicated planned vaginal birth[48]; however, a cesarean delivery performed during labor is associated with greater blood loss.[49] Risk factors for peripartum hemorrhage are listed in Box 26-6.

Preparation for obstetric hemorrhage includes (1) reviewing the patient's history for anemia or risk factors for hemorrhage (e.g., placenta previa, prior uterine surgery, possible placenta accreta); (2) consulting with the obstetric team regarding the presence of risk factors; (3) reviewing reports of ultrasonographic or magnetic resonance images of placentation; (4) obtaining a blood sample for a type and screen or crossmatch; (5) contacting the blood bank to ensure the availability of blood products; (6) obtaining and checking the necessary equipment (blood filters and warmers, infusion pumps and tubing, compatible fluids and medications, and standard clinical laboratory collection tubes [to check hemoglobin, platelets, electrolytes, and coagulation factors]); and (7) consulting with a blood bank pathologist, hematologist, and/or interventional radiologist in selected cases (Box 26-7).

Currently, there is a lack of consensus as to which patients require a blood type and screen and which patients require a crossmatch.[34] The maternal history (previous transfusion, existence of known red blood cell antibodies) and anticipated hemorrhagic complications, as well as local institutional policies, should guide decision-making. In certain high-risk cases (e.g., suspected placenta accreta), blood products (i.e., 2 to 4 units of packed red blood cells) should be physically present near or in the operating room before making the surgical incision, if possible.

If an interventional radiologist plans to place prophylactic intravascular balloon occlusion catheters before surgery, and if neuraxial anesthesia is planned, the anesthesia provider should place an epidural catheter prior to placement of the balloon catheters (see later discussion).[50]

Monitoring

Attention should be given to the availability and proper functioning of equipment and monitors for the provision of anesthesia and the management of potential complications (e.g., failed intubation, cardiopulmonary arrest).[34] Equipment should be checked on a daily basis and serviced at recommended intervals. The equipment and facilities available in the labor and delivery operating room suite should be comparable to those available in the main operating room.[34]

The ASA standards for basic monitoring apply to the provision of anesthesia for all patients.[51] Within obstetrics, basic monitoring consists of maternal pulse oximetry, electrocardiogram (ECG), and noninvasive blood pressure monitoring,* as well as fetal heart rate (FHR) monitoring.

*Outside the operating room, and before the onset of labor, maternal blood pressure is ideally measured (using an appropriately sized cuff with a bladder length that is 80% and a width that is at least 46% of the arm circumference) after a rest period of 10 minutes or more, with the pregnant woman sitting or lying on her left side with her arm at the level of the right atrium. The onset (phase 1) and disappearance (phase 5) of Korotkoff sounds correspond to systolic and diastolic pressures, respectively.[52]

BOX 26-7 Suggested Resources for Obstetric Anesthesia

Monitors

- Electrocardiogram
- Noninvasive blood pressure
- Pulse oximetry
- Capnography
- Oxygen and volatile agent analyzers
- Ventilator (with appropriate pressure and disconnection sensors/alarms)
- Peripheral nerve stimulator

For Hemorrhage

- Large-bore intravenous catheters
- Fluid warmer
- Forced-air body warmer
- Availability of blood bank resources
- Equipment for infusing intravenous fluids and blood products rapidly (e.g., hand-squeezed fluid chambers, hand-inflated pressure bags, automatic infusion devices)

For Routine Airway Management

- Laryngoscope and assorted blades
- Oral airways of assorted sizes
- Endotracheal tubes of assorted sizes (6.5 and 7.0 mm) with stylets
- Oxygen source
- Suction source with tubing and catheters
- Self-inflating bag and mask for positive-pressure ventilation
- Medications for blood pressure support, hypnosis, and muscle relaxation
- Carbon dioxide detector
- Pulse oximeter

For Difficult Airway Management

- Rigid laryngoscope blades of alternative design and size from those routinely used
- Supraglottic airway devices (e.g., laryngeal mask airway)
- Endotracheal tube guides (e.g., semirigid stylets with or without hollow cores for jet ventilation, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube)
- Retrograde intubation equipment
- At least one device suitable for emergency nonsurgical airway ventilation (e.g., hollow jet ventilation stylet with a transtracheal jet ventilator; supraglottic airway device, such as a Combitube [Sheridan Catheter Corporation, Argyle, NY] or intubating LMA [Fastrach LMA, LMA North America, San Diego, CA])
- Fiberoptic intubation equipment
- Equipment suitable for emergency surgical airway access (e.g., cricothyrotomy)
- Topical anesthetics and vasoconstrictors

Modified from the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Practice guidelines for obstetric anesthesia. Anesthesiology 2007; 106:843-63. (The full text of the practice guidelines is published as Appendix B at the end of this textbook.)

Automated blood pressure monitors that use oscillometric methods indicate lower systolic and diastolic blood pressures than auscultatory methods between 11% to 22% of the time in normotensive pregnant women.[53] Forearm, wrist, and finger blood pressure monitors have been developed but have not yet undergone adequate validation. In general, blood pressure measurements at locations distal to the heart tend to reflect higher systolic and lower diastolic blood pressures, respectively, relative to central aortic pressure.[52] Invasive hemodynamic monitoring should be considered in women with severe cardiac disease, refractory hypertension or hypotension, pulmonary edema, or unexplained oliguria.

ECG abnormalities are often observed in late pregnancy and are believed to be due to hyperdynamic circulation, circulating catecholamines, and/or altered estrogen and progesterone concentration ratios (see Chapter 2). During cesarean delivery with neuraxial anesthesia, ECG changes have a reported incidence of 25% to 60%[54,55]; in this setting, administration of droperidol, ondansetron, and oxytocin may be associated with prolongation of the QTc interval,[56,57] and oxytocin administration may be associated with ST-segment depression.[58] The significance of these ECG findings as an indicator of cardiac pathology remains controversial, because only a small minority of parturients experience myocardial ischemia as measured by elevated serum cardiac troponin levels.[59] The placement of five ECG leads improves the sensitivity of detecting ischemic events; combining leads II, V_4, and V_5 resulted in a sensitivity of 96% in detecting ST-segment changes in a nonobstetric population.[60] In a prospective study of 254 healthy women undergoing cesarean delivery with spinal anesthesia, Shen et al.[61] determined the incidence of first- and second-degree atrioventricular block (3.5% for each), severe bradycardia (< 50 beats/min; 6.7%), and multiple premature ventricular contractions (1.2%). The investigators speculated that a relative increase in parasympathetic activity occurred as a result of spinal blockade of cardiac sympathetic activity. Most of the dysrhythmias were transient and resolved spontaneously.

Monitors that process the electroencephalogram to indicate the depth of anesthesia have received only limited evaluation in women undergoing cesarean delivery.[62] Whether routine use of these monitors can reduce the incidence of intraoperative awareness during general anesthesia for cesarean delivery is unclear (see later discussion).

An indwelling urinary catheter is used in almost all women undergoing cesarean delivery.[63] A urinary catheter helps avoid overdistention of the bladder during and after surgery. In cases associated with hypovolemia and/or oliguria, or anticipated significant blood loss, a collection system that allows precise measurement of urine volume is helpful.

An evaluation of the FHR tracing by a qualified individual may be useful before and after administration of anesthesia.[34] Whether FHR evaluation should be performed before every cesarean delivery is controversial. The ACOG[64] has stated that the decision to monitor the fetus either by electronic FHR monitoring or by ultrasonography before a *scheduled (elective)* cesarean delivery should be individualized, because data are insufficient to determine the value of FHR monitoring before elective cesarean delivery in patients without risk factors. In contrast, the National Collaboration Centre for Women's and Children's Health in the United Kingdom has stated that the FHR should be monitored during the initiation

of the neuraxial technique and until the abdominal skin preparation for cesarean delivery has begun.[45]

In most cases of *emergency* cesarean delivery, a previously placed fetal scalp (or buttock) ECG electrode can be used to monitor the FHR before, during, and after the initiation of anesthesia. Typically, the fetal scalp electrode is removed when the surgical drapes are applied to the abdomen, but in some cases the scalp electrode may be left in place until just before delivery, when the circulating nurse reaches under the drapes to disconnect the electrode.

In cases of emergency cesarean delivery, continuous FHR monitoring is useful for at least three reasons. First, the FHR abnormality often resolves; in some cases, the obstetrician will then elect to forgo the performance of a cesarean delivery. In other cases, the obstetrician may continue with plans to perform a cesarean delivery but continuous FHR monitoring may facilitate the administration of neuraxial anesthesia. For example, an improved FHR tracing allows time for extension of adequate epidural anesthesia or administration of spinal anesthesia. Second, continuous FHR monitoring may guide management in cases of failed tracheal intubation. If intubation fails and there is no evidence of fetal compromise, both the anesthesia provider and the obstetrician will have greater confidence in a decision to awaken the patient and proceed with an alternative anesthetic technique. By contrast, if there is evidence of ongoing fetal compromise, the anesthesia provider may decide to provide general anesthesia by means of a face mask or supraglottic airway (e.g., laryngeal mask airway [LMA]), and the obstetrician may proceed with cesarean delivery (see Chapter 30). Third, intraoperative FHR monitoring allows the obstetrician to modify the surgical technique according to the urgency of delivery.

Medication Availability and Storage

The drugs used for the provision of general and neuraxial anesthesia, including vasopressors and emergency medications, should be readily available. The Joint Commission[65] mandates that all medications should be secured. Currently, only Schedule II controlled substances as classified by the Drug Enforcement Agency[66] need to be secured in a "substantially constructed locked cabinet."[67] Other drugs and products, including anesthetic medications, should be "reasonably secure" but not necessarily locked. These drugs include the Schedule III drug thiopental, as well as succinylcholine and vasopressor agents. The Joint Commission has defined "reasonably secure" as storage in areas not readily accessible or easily removed by the public. Federal law requires that all hospitals receiving Medicare funding adhere to conditions of participation, which state that "drugs and biologicals must be kept in a secure area, and locked when appropriate."[67] This rule applies to noncontrolled substances.

Equipment

Labor and delivery units may be adjacent to or remote from the operating rooms. In some facilities, the unit is located on a separate floor but shares a common operating room facility (used for other surgical procedures), whereas in others it is a geographically separate, self-contained unit with its own operating room facilities. Regardless of location, the equipment, facilities, and support personnel available in the labor and delivery operating room should be comparable to those available in the main operating room.[34] In addition, personnel and equipment should be available to care for obstetric patients recovering from major neuraxial or general anesthesia.

Resources for the conduct and support of neuraxial anesthesia and general anesthesia should include those necessary for the basic delivery of anesthesia and airway management as well as those required to manage complications (e.g., failed tracheal intubation). The *immediate* availability of these resources is particularly important, given the frequency and urgency of anesthesia care. Consideration should be given to having some of the equipment and supplies immediately available in one location or in a cart (e.g., difficult airway cart, massive hemorrhage cart, malignant hyperthermia box) specifically located on the labor and delivery unit. Equipment and supplies should be checked on a frequent and regular basis. Securing special-situation equipment and supplies in a cart with a single-use breakthrough plastic tie helps ensure that the cart is kept in a fully stocked state.

Aspiration Prophylaxis

The patient should be asked about oral intake, although insufficient evidence exists regarding the relationship between recent ingestion and subsequent aspiration pneumonitis (see Chapter 29). Gastric emptying of clear liquids during pregnancy occurs relatively quickly; the residual content of the stomach (as measured by the cross-sectional area of the gastric antrum 60 minutes after the ingestion of 300 mL of water) does not appear to be different from baseline fasting levels in either lean or obese nonlaboring pregnant women.[68,69] Moreover, when measured by serial gastric ultrasonographic examinations and acetaminophen absorption, the gastric emptying half-time of 300 mL of water is shorter than that of 50 mL of water in healthy, nonlaboring, nonobese pregnant women (24 ± 6 versus 33 ± 8 minutes, respectively).[68]

The healthy patient undergoing *elective* cesarean delivery may drink modest amounts of clear liquids up to 2 hours before induction of anesthesia.[34] Examples of clear liquids are water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sports drinks. The volume of liquid ingested is less important than the absence of particulate matter. Patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway) or laboring patients at increased risk for cesarean delivery (e.g., nonreassuring FHR pattern) may have further restrictions of oral intake, determined on a case-by-case basis.[34]

Ingestion of solid foods should be avoided in laboring patients and patients undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation). A fasting period for solids of 6 to 8 hours,

depending on the fat content of the food, has been recommended.[34]

A reduction in gastric content acidity and volume is believed to decrease the risk for damage to the respiratory epithelium if aspiration should occur. Oral administration of a nonparticulate antacid (0.3 M **sodium citrate**, pH 8.4) causes the mean gastric pH to increase to greater than 6 for 1 hour; it does not affect gastric volume.[70,71] **H_2-receptor antagonists (ranitidine, famotidine)**, **proton pump inhibitors (omeprazole),** and **metoclopramide** reduce gastric acid secretion and volume but require at least 30 to 40 minutes to exert their effects.[72] In a systematic review of interventions used to reduce the risk for aspiration pneumonitis in women undergoing cesarean delivery, Paranjothy et al.[73] found a significant reduction in the risk for gastric pH less than 2.5 with antacids (relative risk [RR], 0.17; 95% confidence interval [CI], 0.09 to 0.32), H_2-receptor antagonists (RR, 0.09; 95% CI, 0.05 to 0.18), and proton-pump antagonists (RR, 0.26; 95% CI, 0.14 to 0.46), compared with no treatment or placebo. The combined use of an antacid and an H_2-receptor antagonist was found to be more effective in reducing pH less than 2.5 than administration of placebo or an antacid alone.[73] Sodium citrate was associated with a higher incidence and severity of nausea than an H_2-receptor antagonist (famotidine).[74] **Metoclopramide** is a promotility agent that hastens gastric emptying, increases lower esophageal sphincter tone, and decreases nausea and vomiting.[75,76] Prior to surgical procedures, the timely administration of a nonparticulate antacid, an H_2-receptor antagonist, and metoclopramide should be considered, especially for nonelective procedures.[34]

Prophylactic Antibiotics

With both elective (nonlaboring) and nonelective (laboring) cesarean deliveries, a 60% decrease in the incidence of endometritis, a 25% to 65% decrease in the incidence of wound infection, and fewer episodes of fever and urinary tract infections have been demonstrated after prophylactic antibiotic administration.[77] The ACOG[78] has recommended the prophylactic administration of a narrow-spectrum antibiotic, such as a first-generation cephalosporin, within 1 hour of the start of cesarean delivery.

Antibiotics with efficacy against gram-positive, gram-negative, and some anaerobic bacteria are commonly used for prophylaxis for cesarean delivery. Appropriate coverage includes intravenous ampicillin 2 g, cefazolin 1 g, or ceftriaxone 1 g. Appropriate antibiotic coverage should last for 3 to 4 hours; therefore, ampicillin may be less appropriate owing to a shorter half-life.[78,79] In parturients with a significant allergy to beta-lactam antibiotics (e.g., history of anaphylaxis, angioedema, respiratory distress, or urticaria), intravenous clindamycin with gentamicin is a reasonable alternative.

Because of the greater volume of distribution, higher doses of antibiotics should be considered in women with a body mass index (BMI) greater than 30 kg/m^2 or an absolute weight greater than 100 kg.[78,80] After administration of cephazolin 2 g, Pevzner et al.[80] observed that the minimum inhibitory tissue concentration for gram-negative rods was not achieved at the time of skin incision or closure in 20% of obese women and 33% of morbidly obese women.

The optimal timing of antibiotic administration (before skin incision versus after clamping of the umbilical cord) and the potential value of more broad-spectrum antibiotics remain controversial. In the past, prophylactic antibiotics typically have been administered after umbilical cord clamping, because of concern that fetal antibiotic exposure might mask a nascent infection and/or increase the likelihood of a neonatal sepsis evaluation. However, in a meta-analysis, Costantine et al.[81] concluded that preincision antibiotic prophylaxis reduces the incidence of postcesarean endometritis and total maternal infectious morbidity, without evidence of adverse neonatal effects. Although earlier studies suggested that ampicillin and first-generation cephalosporins are similar in efficacy to more broad-spectrum agents,[77] more recent trials have suggested that there is benefit associated with extended-spectrum antibiotic prophylaxis that includes the addition of an agent that covers other organisms such as *Ureaplasma*.[79,82] Further investigation is necessary to determine whether more broad-spectrum prophylactic antibiotic coverage improves maternal and fetal outcomes in mothers with active or presumed infection (e.g., chorioamnionitis).

Aseptic Technique

In the early 19th century, Ignác Semmelweis observed that puerperal fever, known as "childbed fever," was most likely transmitted when the first stage of labor was prolonged and multiple individuals performed vaginal examinations with contaminated hands. Since that time, the practice of hand hygiene has caused a significant reduction in maternal and neonatal infectious morbidity.

Epidural abscess and meningitis have been reported as complications of neuraxial procedures in obstetric patients (see Chapter 32). These cases have prompted questions regarding the best antiseptic solution for disinfecting the skin,[83] provider attire, and the appropriate dressing for the neuraxial catheter insertion site (see Chapters 12 and 32). There is wide variation in aseptic practices. Regrettably, some anesthesia providers do not wear a face mask, whereas others wear a gown, face mask, and hat.[84] "Rapid-sequence spinal" has been described for cases of emergency cesarean delivery in which the use of draping is omitted and a single-wipe skin preparation is used[85]; however, many obstetric anesthesia providers would argue that this practice is unwise.

Subtle changes in circulating immunoglobulin levels induced by pregnancy may affect the risk associated with exposure to infectious pathogens.[86] As a consequence, obstetric anesthesia providers should always give careful attention to aseptic technique, especially during performance of a neuraxial technique. Proper sterile technique consists of wearing a face mask, giving careful attention to hand hygiene, and donning sterile gloves before initiating neuraxial blockade.[87]

Attention should also be given to the careful preparation of anesthetic drugs during administration of either

general or neuraxial anesthesia. Although many local anesthetics have bactericidal properties that appear concentration dependent,[88] propofol and other anesthetic agents can support bacterial growth.[89] An increasing number of institutions are using premixed solutions of local anesthetic and opioid (prepared under aseptic conditions in a hospital or compounding pharmacy) to limit breaches in aseptic technique during the administration of neuraxial anesthesia.

Intravenous Access and Fluid Management

The establishment of functional intravenous access is of critical importance to the successful outcome of many clinical situations in obstetric anesthesia practice. According to the Hagen-Poiseuille equation, the infusion rate of fluid through a catheter is directly related to the pressure gradient of the fluid and the fourth power of the catheter's radius, and inversely related to the viscosity of the fluid and the catheter's length. Because the size of the catheter, more than the size of the vein, dictates the flow rate, the use of a short, large-diameter catheter (e.g., 16- or 18-gauge) is associated with the best flow.[90]

In general, a smaller but functional catheter is more important than a larger catheter that is unreliable or requires frequent manipulation. Smaller catheters may be acceptable in an emergency; volume and blood resuscitation can be satisfactorily achieved using 20- and 22-gauge catheters (without evidence of greater red blood cell destruction) with the use of dilution, pressurization, or both.[91] However, when large-bore peripheral venous access is problematic, especially when large blood loss is anticipated, or administration of multiple blood products is required, the anesthesia provider may choose to insert a central venous catheter.

Although the administration of intravenous fluids may decrease the incidence of neuraxial anesthesia–associated hypotension, initiation of anesthesia should not be delayed to administer a fixed volume of fluid,[34] particularly in the case of an emergency cesarean delivery, in which the life and health of the mother and the infant are best preserved with timely delivery. Vasopressors can be used for both prophylaxis and treatment of hypotension. The type of fluid (crystalloid, colloid) and the volume, rate, and timing of administration are relevant factors in the prevention and treatment of hypotension.[92,93] In most situations, a balanced salt solution such as lactated Ringer's solution is acceptable. Blood products are most often administered with normal saline. Crystalloid or colloid solutions that contain calcium or glucose should not be administered with blood products, owing to the risks for clotting (due to reversal of the citrate anticoagulant) and clumping of red blood cells, respectively.

Traditionally, approximately 1 L of crystalloid solution has been administered intravenously (as "prehydration" or "preload") to prevent or reduce the incidence and severity of hypotension during neuraxial anesthesia for cesarean delivery. However, prehydration, even with large volumes (30 mL/kg), is minimally effective in preventing neuraxial anesthesia–induced hypotension. Although an initial study found that administering crystalloid solution at the time of the intrathecal injection ("co-load") was more efficacious than prehydration in preventing hypotension,[94] later studies did not support this finding,[95] likely because the infusion rate was too slow.[93] Colloid, administered before or at the time of the intrathecal injection, is more effective than crystalloid for preventing hypotension.[96] Colloid administered before the intrathecal injection (preload) is equally efficacious to administration at the time of injection (co-load).[95]

In healthy patients, we rapidly administer approximately 1 L of crystalloid at the time of initiation of neuraxial anesthesia. For patients at high risk for hypotension or the consequences of hypotension, colloid may be administered before or at the time of initiation of neuroblockade.[93] Hypotension despite fluid administration is treated with vasopressors (see later discussion).

Supplemental Medications for Anxiety

The administration of benzodiazepines, even low doses (e.g., midazolam 0.02 mg/kg), may result in amnesia[97,98]; as a consequence, benzodiazepines are typically avoided during awake cesarean delivery. However, on occasion, particularly in women with severe anxiety or undergoing an emergency cesarean delivery, the use of low doses of intravenous midazolam or an opioid may facilitate performance of a neuraxial technique, awake tracheal intubation, or the induction of general anesthesia. Anxiolytics may also assist in mitigating the feelings of distress during the birthing experience, which may lessen the risk for developing post-traumatic stress disorder.[99] The use of low doses of sedative or anxiolytic agents has minimal to no neonatal effects. Frölich et al.[100] observed no differences in neonatal Apgar scores, neurobehavioral scores, or oxygen saturation among women who were randomized to receive either intravenous midazolam (0.02 mg/kg) and fentanyl (1 μg/kg) or saline before administration of spinal anesthesia for cesarean delivery.

Positioning

After 20 weeks' gestation, all pregnant women should be positioned with left uterine displacement to minimize aortocaval compression. The **supine hypotension syndrome,** which is caused by compression of the aorta and inferior vena cava by the gravid uterus, can manifest as pallor, tachycardia, sweating, nausea, hypotension, and dizziness.[101,102] Uteroplacental blood flow is compromised by decreased venous return and cardiac output, increased uterine venous pressure, and compression of the aorta or common iliac arteries.[103]

The full lateral position minimizes aortocaval compression but does not allow performance of cesarean delivery. In an editorial, Kinsella[104] concluded that 15 degrees of **left lateral tilt (left uterine displacement)** significantly reduces the adverse hemodynamic consequences of the supine position, although both the aorta and inferior vena cava may remain partially compressed. However, most anesthesia providers underestimate the degree of lateral tilt. In a systematic review, Cluver et. al.[105] observed no differences in maternal and early neonatal outcomes among various maternal

positions for cesarean delivery, but acknowledged that the small sample size in their study was a serious shortcoming that limited the applicability of their observations. They also acknowledged that the effect of maternal position may vary with different clinical situations and that aortocaval compression may be more problematic in women with multiple gestation, fetal macrosomia, or polyhydramnios.[105] Anesthesia providers should recognize that (1) individual susceptibility to aortocaval compression varies,[106] (2) visual estimates of lateral tilt may be in error,[107] and (3) in symptomatic women, increasing the extent of left uterine displacement may be beneficial. Lateral tilt should be used in all women in mid to late pregnancy after the administration of neuraxial or general anesthesia, with greater tilt used when feasible if aortocaval compression is suspected as the cause for maternal or fetal compromise.[108]

The use of a slight (10 degrees) **head-up position** may help reduce the incidence of hypotension after initiation of hyperbaric spinal anesthesia.[109] The use of a more significant head-up position (30 degrees) has been observed to significantly increase functional residual capacity in parturients compared with the supine position, with the effect diminishing with increasing BMI.[110] In morbidly obese patients receiving general anesthesia, the 30-degree head-up position may be particularly useful to improve preoxygenation, denitrogenation, and the view of the glottis during direct laryngoscopy[111]; this can be accomplished with blankets or commercially available devices (see Chapters 30 and 50). If blankets are used to create the ramp position, they should be stacked rather than interlaced, to allow for rapid readjustment of the head and neck position if necessary. Ideal positioning leads to the horizontal alignment between the external auditory meatus and the sternal notch; this position (1) aligns the oral, pharyngeal, and tracheal axes ("sniffing position") and (2) facilitates insertion of the laryngoscope blade (see Chapter 30).[112]

Theoretically, the **Trendelenburg (head-down) position** may augment venous return and increase cardiac output. The value of this approach in *preventing* hypotension during neuraxial anesthesia has been questioned.[105] After the initiation of hyperbaric spinal anesthesia, the Trendelenburg position has been reported to result in more cephalad spread of anesthesia in one study[113] but not in others.[114,115] However, this position had no effect on the incidence of hypotension after administration of hyperbaric spinal anesthesia.[113,115]

The optimal patient position for insertion of a neuraxial needle (or catheter) may depend on clinical circumstances and the preferences and skills of the anesthesia provider. Whether the use of the **lateral** or the **sitting position** is best for routine initiation of neuraxial anesthesia is controversial.[116,117] Advocates of the lateral position cite a reduction of vagal reflexes, which can result in dizziness, diaphoresis, pallor, bradycardia, and hypotension.[118] Moreover, the lateral position may allow better uteroplacental blood flow than the sitting position. Using technetium Tc 99m–radiolabeled isotopes in pregnant women in the third trimester, Suonio et al.[119] observed a 23% reduction in uteroplacental blood flow when pregnant patients moved from the left lateral recumbent to the sitting position. In contrast, Andrews et al.[120] observed a greater decrease in cardiac output in parturients placed in the left lateral position than in those in the sitting position during initiation of epidural analgesia. Using substernal Doppler ultrasonography, Armstrong et al.[121] observed that maternal cardiac index, stroke volume index, heart rate, and systolic blood pressure were higher by approximately 8% in the right or left lateral positions than in the sitting or supine positions; however, there were no significant differences among positions in fetal heart rate, pulsatility index, or resistivity index.

Some parturients find the lateral position more comfortable during administration of neuraxial anesthesia[122]; this position may also limit side-to-side and front-to-back patient motion during needle insertion. Moreover, because uterine compression of the vena cava diverts blood into the epidural venous plexus,[123] the use of the lateral position can reduce hydrostatic pressure and return the engorged epidural venous plexus to its size in the nonpregnant state.[124] Bahar et al.[125,126] observed that fewer needle/catheter replacements occurred for needle- or catheter-induced venous trauma when epidural procedures were performed in the lateral recumbent head-down position than in either the sitting or the lateral recumbent horizontal position in both obese and nonobese parturients.

The lateral position may also be of value during epidural needle placement because it minimizes the prominence of the dural sac. On the other hand, a bulging dural sac might be preferable during administration of spinal or CSE anesthesia. Magnetic resonance imaging and computed tomography studies have indicated that the cross-sectional area and the anteroposterior diameter of the dural sac at the level of the L3-L4, L4-L5, and L5-S1 interspaces are significantly influenced by posture.[127] Lumbar cerebrospinal fluid (CSF) pressure is lower and dural sac cross-sectional area smaller in the recumbent position than in the upright position.[127] Bulging of the lumbar dural sac—particularly in the sitting position—may decrease the force required to create a dural puncture with a Tuohy epidural needle, but this possibility is unproven.

In a randomized controlled trial, Yun et al.[128] observed that the severity and duration of hypotension were greater in women randomly assigned to receive CSE anesthesia (hyperbaric spinal bupivacaine with fentanyl) in the sitting position than in those in the lateral position, despite no differences in the level of sensory blockade.

The sitting position may offer some advantages (e.g., physical landmark recognition in obese parturients, practitioner preference).[117] However, anesthesia providers should be facile with the placement of needles for neuraxial techniques in both the sitting and lateral positions, because the sitting position should not be used in some situations (e.g., fetal head entrapment, umbilical cord prolapse, footling breech presentation).[116]

Supplemental Oxygen

The routine administration of supplemental oxygen during elective cesarean delivery with neuraxial

anesthesia has been a common practice since publication of the seminal report by Fox and Houle[129]; their report demonstrated improved oxygenation, better umbilical cord blood acid-base measurements, and less time to sustained respiration in the neonate, when mothers undergoing cesarean delivery with neuraxial anesthesia breathed 100% oxygen instead of air for at least 10 minutes. However, later evidence suggested that routine oxygen administration may be unnecessary and ineffective[130] and may even be detrimental.[131] The use of a fractional inspired concentration of oxygen (F_{IO_2}) of 0.35 to 0.4 (which cannot be obtained by a nasal cannula or a simple face mask with a flow rate less than 6 L/min[132]) does not improve fetal oxygenation during labor or elective cesarean delivery. Although respiratory function can deteriorate in parturients receiving neuraxial anesthesia,[133,134] maternal or fetal hypoxemia does not normally occur when parturients breathe room air.[134] An F_{IO_2} of 0.6 in nonlaboring women undergoing elective cesarean delivery with spinal anesthesia increases the umbilical venous oxygen content by only 12%; an increase in oxygen content is not observed when the uterine incision-to-delivery (U-D) interval exceeds 180 seconds.[135]

Supplemental oxygen has both beneficial and detrimental effects. Through normal biologic processes, oxygen is converted to reactive oxygen species, including free radicals. The reactive oxygen species cause lipid peroxidation, alteration of cellular enzymatic functions, and destruction of genetic material[136]; these adverse effects occur with the restoration of perfusion after a period of ischemia (i.e., ischemia-reperfusion injury), including intermittent umbilical cord occlusion and perhaps during uterine contractions.[137] Reactive oxygen species are present during hyperoxia (causing such disorders as neonatal retinopathy and bronchopulmonary dysplasia) and in the setting of prolonged labor, oligohydramnios, intermittent umbilical cord compression, and/or fetal compromise.[137,138] Hyperoxia in these settings (i.e., during the period of reperfusion following ischemia) results in a higher level of lipid peroxidation.[131,138]

Term (but not preterm) fetuses may be able to withstand the adverse effects of these reactive oxygen species through a compensatory increase in antioxidants during labor.[139,140] Antioxidants, the defense against reactive oxygen species, consist of enzymatic inactivators (superoxide dismutase, catalase, peroxidase) and scavengers (ascorbate, glutathione, transferrin, lactoferrin, ceruloplasmin). The activity of these compensatory mechanisms and their relationships to gestational age and labor suggest that the highest risk for ischemia-reperfusion injury occurs in preterm fetuses before the onset of labor.[131,140]

The use of a very high F_{IO_2} improves oxygen delivery to hypoxic fetuses for a limited period (approximately 10 minutes); beyond this time, continued hyperoxia, especially in the setting of restored perfusion, increases reactive oxygen species, placental vasoconstriction, and fetal acidosis.[141,142] A lower F_{IO_2} may be of benefit in some situations. When asphyxiated infants are immediately resuscitated at birth with air instead of 100% oxygen, better short-term outcomes have been observed[143,144]; this finding may be a result of the shift in the balance between beneficial oxygenation and detrimental free radicals.

In summary, no significant improvement in maternal-fetal oxygen transfer occurs until very high levels of maternal F_{IO_2} are used. At these levels, the resulting hyperoxia creates reactive oxygen species. Preterm fetuses in nonlaboring mothers are the population at highest risk for hyperoxia-induced injury. Nonetheless, the emergency cesarean delivery of the compromised fetus should include maternal administration of a high F_{IO_2}. The greater maternal oxygen consumption and reduced fetal oxygen delivery associated with uterine contractions may exacerbate the fetal compromise; in these situations, supplemental oxygen may augment fetal oxygenation and, perhaps, reduce the severity of fetal hypoxia. However, diminishing fetal benefit appears to occur after 10 minutes.

All women who are at risk for requiring general anesthesia for emergency cesarean delivery should receive an F_{IO_2} of 1.0 after transfer to the operating table. Denitrogenation should always be performed; if it is not performed, the mother is at risk for hypoxemia during apnea before intubation, in turn putting the fetus at risk. When general anesthesia is administered in a patient with fetal compromise, the mother should receive an F_{IO_2} of 1.0 before and immediately after induction of anesthesia, even though the subsequent increases in umbilical venous and arterial oxygen content are not dramatic.

The value of supplemental maternal oxygen during *elective* cesarean delivery of a noncompromised fetus is questionable. The only reason some obstetric anesthesia providers place nasal cannulae in patients undergoing elective cesarean delivery with neuraxial anesthesia is to facilitate the monitoring of expired carbon dioxide (to monitor the parturient's ventilation).

ANESTHETIC TECHNIQUE

Providing anesthesia to the parturient is a dynamic, multistep process (Table 26-2). The most appropriate anesthetic technique for cesarean delivery depends on maternal, fetal, and obstetric factors (Table 26-3). The urgency and anticipated duration of the operation play an important role in the selection of an anesthetic technique.

In cases of dire fetal compromise, the anesthesia provider may need to perform a preanesthetic evaluation simultaneously with other tasks (i.e., establishing intravenous access and placing a blood pressure cuff, pulse oximeter probe, and ECG electrodes). Regardless of the urgency, the anesthesia provider should not compromise maternal safety by failing to obtain critical information about previous medical and anesthetic history, allergies, and the airway. Effective communication with the obstetric team is critical to establish the degree of urgency, which helps guide decisions regarding anesthetic management. Further, contemporary standards for patient safety require that all members of the surgical team participate in a pre–cesarean delivery "time-out" to verify (1) the correct patient identity, position, and operative site; (2) agreement on the procedure to be performed; and (3) the availability of special equipment, if needed.

TABLE 26-2 **Provision of Anesthesia for Cesarean Delivery***

Phase	Issues	Specific Concerns
Preparation	Preanesthetic evaluation	History and physical examination
		Indicated laboratory measurements
		Imaging studies
	Oral intake	No clear liquids and solid foods for 2 hours and 6-8 hours, respectively, prior to elective surgery (the presence of comorbid conditions may warrant a longer fasting interval)
	Communication with obstetric team	Indication(s) for cesarean delivery, including degree of urgency
		Anticipated surgical complications
	Informed consent	Threshold, information, and consent elements
		Informed refusal
	Blood products	Risk factors
		Baseline hematocrit
		Blood type and screen or crossmatch
		Equipment for rapid transfusion
	Monitoring	Pulse oximetry, electrocardiogram, blood pressure, fetal heart rate, urinary catheter
		Consider electroencephalographic (bispectral index) monitoring during general anesthesia (controversial)
		Invasive monitoring in selected patients
	Medication availability	Anesthetic (general and neuraxial anesthetic drugs, vasopressors)
		Obstetric (uterotonic agents)
		Emergency (advanced cardiac life support, malignant hyperthermia)
	Equipment availability	Anesthesia, airway management
	Aspiration prophylaxis	Fasting guidelines, nonparticulate antacid, H_2-receptor antagonist, metoclopramide
	Prophylactic antibiotics†	Within 60 minutes *before* incision
	Intravenous access and fluid management	Intravenous catheter: 16- or 18-gauge
		Fluid type, volume, and rate
	Supplemental medications	Consider anxiolysis for severe anxiety
	Positioning	Lateral or sitting position for neuraxial needle/catheter placement
		Left uterine displacement, slight head up for surgery
		"Sniffing" position if general anesthesia is planned
	Supplemental oxygen	Preoxygenation/denitrogenation required before general anesthesia
		Of unclear benefit during neuraxial anesthesia for elective delivery of a noncompromised fetus
Selection of anesthetic technique	Neuraxial	Adequate sacral and cephalad spread (T4) and density of neuroblockade
		Prevention or treatment of hypotension
	General	Airway management
		Prevention of awareness and recall
		Prevention of anesthesia-associated uterine atony
	Local	Usually a supplement for inadequate neuraxial anesthesia
		Can facilitate emergency delivery in absence of an anesthesia provider
		Rarely provides satisfactory anesthesia as a primary technique
Recovery	Oral intake	Fluids and foods allowed within 4 to 8 hours of surgery, in absence of complications
	Removal of urinary catheter	Typically within 24 hours
	Postoperative assessment and discharge	Hemodynamic stability
		Resolution of neuroblockade
		Effective analgesia
		Recognition and treatment of surgical and anesthetic complications

*Procedures, techniques, and drugs may need to be modified for individual patients and circumstances.
†Evidence now suggests that administration of prophylactic antibiotics *before* incision (rather than after cord clamping) reduces the incidence of postcesarean endometritis and total maternal infectious morbidity.[78]

TABLE 26-3 **Selection of Anesthetic Technique for Cesarean Delivery**

Indication(s)	Comments/Examples
For Neuraxial Anesthesia*	
Maternal desire to witness birth and/or avoid general anesthesia	Most common maternal preference
Risk factors for difficult airway or aspiration	Physical examination predicts possible difficult airway History of difficult intubation High body mass index (obesity) History of gastroesophageal reflux (common in pregnancy)
Presence of comorbid conditions	Malignant hyperthermia history Pulmonary disease
General anesthesia intolerance or failure	History of significant side effects with general anesthesia Attempted general anesthesia with failed intubation; patient awakened
Other benefits	Plan for neuraxial analgesia after surgery Less fetal drug exposure Less blood loss Allows presence of husband or support person
For General Anesthesia*	
Maternal refusal or failure to cooperate with neuraxial technique	Strong maternal preference, in the absence of factors that predict a difficult airway Severe psychiatric disorder Severe developmental delay Severe emotional immaturity or lability
Presence of comorbid conditions that contraindicate a neuraxial technique	Coagulopathy Local infection at neuraxial insertion site Sepsis Severe uncorrected hypovolemia (e.g., hemorrhage from placenta previa or uterine rupture) Intracranial mass with increased intracranial pressure Known allergy to local anesthetic (rare)
Insufficient time to induce neuraxial anesthesia for urgent delivery	Umbilical cord prolapse with persistent fetal bradycardia
Failure of neuraxial technique	Multiple needle placement failures Missed spinal segments Persistent intraoperative pain that is not treated successfully
Fetal issues	Planned *ex utero* intrapartum treatment (EXIT) procedure

*Many indications for or contraindications to specific anesthesia techniques are relative, and the choice of anesthetic must be tailored to individual circumstances.

In cases of emergency cesarean delivery, the emotional needs of the infant's mother and father are also important. Parental distress commonly occurs in this setting, and the anesthesia provider is often the best person to give reassurance. All members of the obstetric care team should remember that chaos does not need to accompany urgency.

Neuraxial versus General Anesthesia

Overall, neuraxial (epidural, spinal, CSE) techniques are the preferred method of providing anesthesia for cesarean delivery; specific benefits and risks of each technique dictate the eventual choice. In contemporary practice, neuraxial anesthesia is administered to some patients who would have received general anesthesia in the past. Umbilical cord prolapse, placenta previa, and severe preeclampsia are no longer considered absolute indications for general anesthesia. For example, in some cases a prolapsed umbilical cord can be decompressed, and if fetal status is reassuring, a neuraxial technique can be used. In an analysis of obstetric anesthesia trends in the United States between 1981 and 2001, a progressive increase was noted in the use of neuraxial anesthesia, especially spinal anesthesia, for both elective and emergency cesarean deliveries (Figure 26-3).[20] Neuraxial anesthesia has been used for more than 80% of cesarean deliveries since 1992. Similar increases have occurred in the United Kingdom and in other developed as well as developing countries.[145,146]

The greater use of neuraxial anesthesia for cesarean delivery has been attributed to several factors, including (1) the growing use of epidural techniques for labor analgesia, (2) an awareness of the possibility that an *in situ* epidural catheter (even if not used during labor) may decrease the necessity for general anesthesia in an urgent situation, (3) improvement in the quality of neuraxial anesthesia with the addition of an opioid to the local anesthetic, (4) appreciation of the risks of airway complications during general anesthesia in parturients, (5) the desire for limited neonatal drug transfer, and (6) the ability of the mother to remain awake to experience childbirth and to have a support person present in the operating room. Spinal anesthesia is considered an appropriate technique even in the most urgent settings; in a tertiary care institution with an average of 9500 cesarean deliveries annually, neuraxial anesthesia was used in more than 99% of cesarean deliveries over a 6-year period.[147]

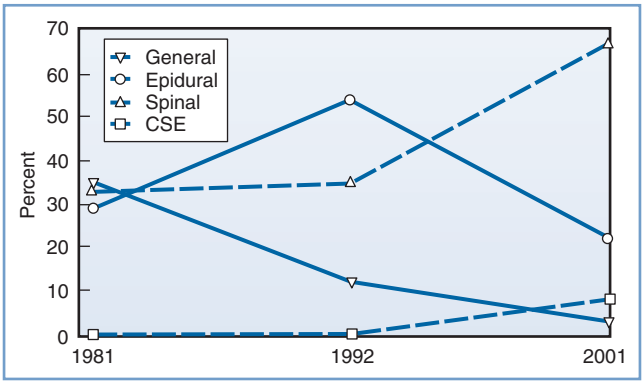

FIGURE 26-3 ■ Rates of use of different anesthesia types for cesarean delivery in the United States. Data from random sample of hospitals in the United States stratified by geographic region and number of births per year. Data shown represent hospitals in stratum I (> 1500 births/yr) and are presented as percentages of cesarean births by anesthesia type. *CSE,* combined spinal-epidural anesthesia. Data from 2001 represent anesthetic technique selected for elective cesarean delivery. (Data modified from Bucklin BA, Hawkins JL, Anderson JR, Ullrich FA. Obstetric anesthesia workforce survey: twenty-year update. Anesthesiology 2005; 103:645-53.)

In the setting of a category 1 (immediate threat to life of woman or fetus) cesarean delivery, Kinsella et al.[85] described a "rapid-sequence spinal" technique, by which skin preparation, spinal drug combinations, and the spinal technique were simplified; the median time from positioning until satisfactory neuroblockade was 8 minutes (interquartile range [IQR] 7 to 8 [range 6 to 8]). In an analysis of category 4 (elective) cesarean deliveries in a Pakistani hospital, the mean (± SD) elapsed times from initiation to completion of induction of anesthesia were 4.5 ± 1.4 minutes versus 8.1 ± 3.8 minutes for general and spinal anesthesia, respectively.[148]

Maternal *mortality* following general anesthesia has been a primary motivator for the transition toward greater use of neuraxial anesthesia for cesarean delivery. Hawkins et al.[149] compared the anesthesia-related maternal mortality rate from 1979 to 1984 with that for the period from 1985 to 1990 in the United States. The estimated case-fatality risk ratio for general versus neuraxial anesthesia was as high as 16.7 in the years 1985 to 1990; however, a similar analysis by the same group of investigators found a nonsignificant risk ratio of 1.7 in the years 1991 to 2002.[150] Of interest, these data may overstate the relative risk of general anesthesia, because this form of anesthesia is used principally when neuraxial anesthetic techniques are contraindicated for medical reasons or time constraints[147,151]; these data also suggest that the relative risk associated with neuraxial anesthesia has increased. However, this change may reflect the growing acceptance of performing neuraxial techniques in parturients with significant comorbidities (e.g., obesity, severe preeclampsia, cardiac disease).

Maternal *morbidity* is also lower with the use of neuraxial anesthetic techniques than with general anesthesia. In a systematic review of randomized and quasi-randomized controlled trials comparing major maternal and neonatal outcomes with the use of neuraxial anesthesia and general anesthesia for cesarean delivery, Afolabi et al.[152] found less maternal blood loss and shivering but more nausea in the neuraxial anesthesia group. The intraoperative "perception" of pain was greater in the neuraxial group, but the time elapsed before the first postoperative request for analgesia was longer. Prospective audits of post–cesarean delivery outcomes have indicated that in the first postoperative week, patients who received neuraxial anesthesia had less pain, gastrointestinal stasis, coughing, fever, and depression and were able to breast-feed and ambulate more quickly than patients who received general anesthesia.[153]

Neonatal outcomes associated with maternal anesthetic selection require further study. Apgar and neonatal neurobehavioral scores are relatively insensitive measures of neonatal well-being, and umbilical cord blood gas and pH measurements may reflect the reason for the cesarean delivery rather than differences in the effect of the anesthetic technique on fetal/neonatal well-being. In a meta-analysis, lower umbilical cord blood pH measurements were associated with spinal, but not epidural, anesthesia compared with general anesthesia.[154] However, the study included both randomized and nonrandomized trials and both elective and nonelective procedures, and most trials were conducted in an era when ephedrine was used to support maternal blood pressure (see later discussion). In a systematic review of randomized trials in which the indication for cesarean delivery was not urgent, no differences in umbilical cord arterial blood pH measurements were found among general and neuraxial anesthetic techniques.[152]

Overview of Neuraxial Anesthetic Techniques

Table 26-4 outlines the advantages and disadvantages of the various neuraxial anesthetic techniques for cesarean delivery. With all neuraxial techniques, an adequate sensory level of anesthesia is necessary to minimize maternal pain and avoid the urgent need for administration of general anesthesia. Because motor nerve fibers are typically larger and more difficult to block, the complete absence of hip flexion and ankle dorsiflexion most likely indicates that a functional sensory and sympathetic block is also present in a similar (primarily lumbosacral) distribution. However, because afferent nerves innervating abdominal and pelvic organs accompany sympathetic fibers that ascend and descend in the sympathetic trunk (T5 to L1), a sensory block that extends rostrally from the sacral dermatomes to T4 should be the goal for cesarean delivery anesthesia.

The manner in which the level of sensory blockade is assessed has implications for the success of a neuraxial technique. The different methods of assessing the extent of sensory blockade (i.e., sensation to light touch, pinprick, cold) may indicate levels of blockade that differ by several spinal segments. Russell[155] prospectively demonstrated differential neuraxial blockade in women undergoing cesarean delivery; pinprick evaluation identified a dermatomal level of blockade that was several segments

TABLE 26-4 **Advantages and Disadvantages of Neuraxial Anesthetic Techniques for Cesarean Delivery**

Neuraxial Technique	Advantages	Disadvantages
Epidural	No dural puncture required Can use *in situ* catheter placed for earlier administration of labor analgesia Ability to titrate extent of sensory blockade Continuous intraoperative anesthesia Continuous postoperative analgesia	Slow onset of anesthesia Larger drug doses required than for spinal techniques: • Greater risk for maternal systemic toxicity • Greater fetal drug exposure
Combined spinal-epidural	May be technically easier than spinal anesthesia in obese patients Low doses of local anesthetic and opioid Rapid onset of dense lumbosacral and thoracic anesthesia Ability to titrate extent of sensory blockade Continuous intraoperative anesthesia Continuous postoperative analgesia	Delayed verification of functioning epidural catheter
Continuous spinal	Low doses of local anesthetic and opioid Rapid onset of dense anesthesia Ability to titrate extent of sensory blockade Continuous intraoperative anesthesia	Large dural puncture increases risk for post–dural puncture headache Possibility of overdose and total spinal anesthesia if the spinal catheter is mistaken for an epidural catheter
Single-shot spinal	Technically simple Low doses of local anesthetic and opioid Rapid onset of dense lumbosacral and thoracic anesthesia	Limited duration of anesthesia Limited ability to titrate extent of sensory blockade

more cephalad than that identified by light touch. A subsequent study of spinal anesthesia in parturients undergoing cesarean delivery indicated that although sensory blockade to light touch differed from sensory blockade to pinprick or cold sensation by 0 to 11 spinal segments, no constant relationship among these levels could be determined.[156] The investigators concluded that a T6 blockade to touch would likely provide a pain-free cesarean delivery for most women.

In a survey performed in the United Kingdom, the majority of anesthesiologists used the absence of cold temperature sensation to a T4 level to indicate adequate cephalad extent of sensory blockade for cesarean delivery.[157] Sensory examination should move caudad to cephalad in the midaxillary line on the lower extremities but can be performed in the midclavicular line on the torso. The time at which an adequate block is achieved, as well as the cephalad level of the block and the presence of surgical anesthesia of the lower abdomen, should be documented on the anesthetic record.

Because the undersurface of the diaphragm (C3 to C5) and the vagus nerve may be stimulated by surgical manipulation during cesarean delivery,[158] maternal discomfort (including shoulder pain) and other symptoms (e.g., nausea and vomiting) may occur despite a T4 level of blockade. Neuraxial or systemic opioids help prevent or alleviate these symptoms (see later discussion).

Spinal Anesthesia

Spinal anesthesia is a simple and reliable technique that allows visual confirmation of correct needle placement (by visualization of CSF) and is technically easier to perform than an epidural technique. Spinal anesthesia provides rapid onset of dense neuroblockade that is typically more profound than that provided with an epidural technique, resulting in a reduced need for supplemental intravenous analgesics or conversion to general anesthesia.[159,160] Only a small amount of local anesthetic is needed to establish functional spinal blockade; therefore, spinal anesthesia is associated with negligible maternal risk for systemic local anesthetic toxicity and with minimal drug transfer to the fetus.[161,162] Given these advantages, spinal anesthesia is now the most commonly used anesthetic technique for cesarean delivery in the developed world.[20,145] Spinal anesthesia is also associated with predictable and relatively prompt recovery that enables patients to quickly transition through the postanesthesia care unit (PACU); in some settings, such a recovery may result in a cost savings to the institution.[159]

Spinal anesthesia is usually administered as a single-injection procedure ("single-shot" technique) through a non-cutting, pencil-point needle that is 24-gauge or smaller. A number of different needle designs are available (see Chapter 12)[163]; the size and design of the needle tip affect the incidence and severity of post–dural puncture headache (see Chapter 31).

The spinal technique should be performed at the L3-L4 interspace or below (see Chapter 12). This space is used to avoid the potential for spinal cord trauma; although the spinal cord ends at L1 in most adults, it extends to the L2-L3 interspace in a small minority (see Chapter 32). Additionally, anesthesia providers often misidentify the location of the needle insertion site on the spinal column, and the needle is more frequently introduced at a higher level than intended.

On occasion, a continuous spinal anesthetic technique is used, particularly in the setting of an unintentional dural puncture with an epidural needle. Intentional continuous spinal anesthesia may be desirable in certain settings, when the reliability of a spinal technique and the ability to precisely titrate the initiation and duration of

anesthesia are strongly desired (e.g., a morbidly obese patient with a difficult airway). Although microcatheters (27- to 32-gauge) were used to provide spinal analgesia and anesthesia in the 1980s, the U.S. Food and Drug Administration (FDA) removed these catheters from the market because of concerns about cauda equina syndrome; the catheters are still being used in Europe, particularly in Germany. Currently the administration of continuous spinal anesthesia in the United States requires the use of a 17- or 18-gauge epidural needle and a 19- or 20-gauge catheter; this technique is associated with a high incidence of post–dural puncture headache.

Local Anesthetic Agents

The choice of local anesthetic agent (and adjuvants) used to provide spinal anesthesia depends on the expected duration of the surgery, the postoperative analgesia plan, and the preferences of the anesthesia provider. For cesarean delivery, the local anesthetic agent of choice is typically **bupivacaine** (Table 26-5). In the United States, spinal bupivacaine is formulated as a 0.75% solution in dextrose 8.25%. Intrathecal administration of bupivacaine results in a dense block of long duration.

The dose of intrathecal bupivacaine that has been successfully used for cesarean delivery ranges from 4.5 to 15 mg. In general, pregnant patients require smaller doses of spinal local anesthetic than nonpregnant patients. Reasons include (1) a smaller CSF volume in pregnancy, (2) cephalad movement of hyperbaric local anesthetic in the supine pregnant patient, and (3) greater sensitivity of nerve fibers to the local anesthetic during pregnancy.[164] Overall, the mass of local anesthetic, rather than the concentration or volume, is thought to influence the spread of the resulting blockade[165]; however, the specific influence of the dose/concentration and baricity on the efficacy of the block is controversial. The necessary dose may be influenced by other factors, such as co-administration of neuraxial opioids and surgical technique. (Exteriorization of the uterus during closure of the uterus is more stimulating than closure *in situ*.) Carvalho et al.[166] demonstrated that the effective dose for 95% of recipients (ED_{95}) for plain bupivacaine with fentanyl 10 μg* and morphine 0.2 mg in women undergoing cesarean delivery (n = 48) was 13 mg; the effective dose for 50% of recipients (ED_{50}) was 7.25 mg. By contrast, Sarvela et al.[167] demonstrated that spinal hyperbaric or plain bupivacaine 9 mg with fentanyl 20 μg provided satisfactory anesthesia for all but one of 76 subjects. Anesthesia characteristics and hemodynamic changes were similar in the hyperbaric and plain bupivacaine groups; more than 50% of patients in both groups required vasopressor support.

Vercauteren et al.[168] demonstrated that hyperbaric bupivacaine 6.6 mg with sufentanil 3.3 μg provided better anesthesia and less hypotension than the same dose of plain bupivacaine. Ben-David et al.[169] reported that reducing the dose of plain bupivacaine from 10 to 5 mg decreased the incidence of hypotension and nausea; however, these findings were obscured by the variable use of opioids in the low-dose group. Finally, Bryson et al.[170] compared plain bupivacaine 4.5 mg with hyperbaric bupivacaine 12 mg (both with fentanyl 50 μg and morphine 0.2 mg); they observed similar cephalad sensory levels (C8), incidence of hypotension (approximately 75%), side effects, and rates of patient satisfaction with the two approaches. Five of 27 (19%) patients in the bupivacaine 4.5-mg group and 1 of 25 (4%) patients in the bupivacaine 12-mg group required supplemental analgesia; no conversions to general anesthesia occurred. Altogether, these data indicate that lower anesthetic doses *can* be used; whether they *should* be used is controversial. The anesthesia provider should consider whether adjuvant drugs will be used and whether the risks of giving supplemental analgesia or conversion to general anesthesia that are associated with low doses of bupivacaine outweigh the potential benefits (i.e., less hypotension, faster recovery).

TABLE 26-5 Drugs Used for Spinal Anesthesia for Cesarean Delivery

Drug	Dose Range	Duration (min)*
Local Anesthetics		
Lidocaine	60-80 mg	45-75
Bupivacaine	7.5-15 mg	60-120
Levobupivacaine	7.5-15 mg	60-120
Ropivacaine	15-25 mg	60-120
Opioids		
Fentanyl	10-25 μg	180-240
Sufentanil	2.5-5 μg	180-240
Morphine	100-200 μg (0.1-0.2 mg)	720-1440
Meperidine†	60-70 mg	60
Adjuvant Drugs		
Epinephrine‡	100-200 μg (0.1-0.2 mg)	

*For the local anesthetics, the duration is defined as the time to two-segment regression. For the opioids, the duration is defined as the period of analgesia (or time to first request for a supplemental analgesic drug).

†Meperidine has both local anesthetic and opioid properties and can provide surgical anesthesia without the addition of a local anesthetic. The dose indicated represents meperidine used without a local anesthetic.

‡The addition of epinephrine may augment the duration of local anesthetics by 15 to 20 minutes.

*The Institute of Safe Medicine Practices (ISMP) has recommended that health care providers never use μg as an abbreviation for micrograms, but rather they should use mcg (http://www.ismp.org/tools/errorproneabbreviations.pdf, Accessed February 2013). The use of the symbol μg is frequently misinterpreted and involved in harmful medication errors. The abbreviation may be mistaken for mg (milligrams), which would result in a 1000-fold overdose. The symbol μg should never be used when communicating medical information, including pharmacy and prescriber computer order entry screens, computer-generated labels, labels for drug storage bins, and medication administration records. However, most scholarly publications have continued to use the abbreviation μg. The editors have chosen to retain the use of the abbreviation μg throughout this text. However, the editors recommend the use of the abbreviation mcg in clinical practice.

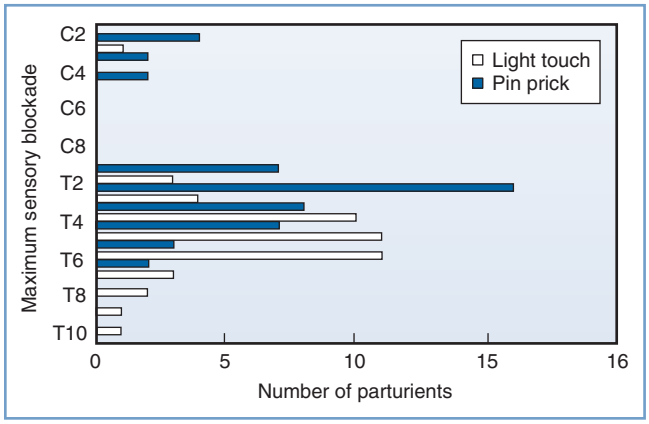

FIGURE 26-4 ■ Maximum cephalad sensory level for analgesia or anesthesia in 52 term parturients after spinal injection of hyperbaric bupivacaine 15 mg with morphine 0.15 mg. (Modified from Norris MC. Patient variables and the subarachnoid spread of hyperbaric bupivacaine in the term patient. Anesthesiology 1990; 72:478-82.)

For a single-shot spinal technique, most clinicians use a dose of bupivacaine between 10 and 15 mg, in combination with an opioid. Studies of hyperbaric bupivacaine (12 to 15 mg) have determined that the patient's age, height, weight, body mass, and vertebral column length do not affect the resulting neuraxial blockade.[171,172] The use of the larger dose (15 mg) results in a longer duration of surgical anesthesia; however, cervical sensory blockade is achieved more frequently (Figure 26-4). In patients with extremes of height (< 5 feet [152 cm], or > 6 feet [183 cm]), some anesthesia providers alter the dose of local anesthetic. The baricity of the local anesthetic *does* affect the extent of spread of blockade. When the cephalad spread of hyperbaric local anesthetic is desired, the patient can be placed in a slight head-down position.

Ropivacaine is approximately 40% less potent than bupivacaine after spinal injection in nonpregnant individuals.[173] Ogun et al.[174] assessed plain spinal ropivacaine 0.5% and bupivacaine 0.5%, both administered with morphine 0.15 mg; ropivacaine was associated with a slower onset, less hypotension, and faster recovery. Khaw et al.[175] randomly assigned 72 patients undergoing elective cesarean delivery to receive CSE anesthesia with plain spinal ropivacaine 10, 15, 20, or 25 mg; the ED_{50} and ED_{95} were 16.7 mg and 26.8 mg, respectively. Subsequently, the same investigators demonstrated that hyperbaric spinal ropivacaine 25 mg produced a more rapid block with faster recovery and fewer requirements for supplemental epidural anesthesia than the same dose of plain ropivacaine in women undergoing cesarean delivery with spinal anesthesia.[176] Gautier et al.[177] randomly assigned 90 parturients to receive bupivacaine 8 mg, levobupivacaine 8 mg, or ropivacaine 12 mg (all with sufentanil 2.5 μg); they observed effective anesthesia in 97%, 80%, and 87% of patients, respectively. The duration of levobupivacaine and ropivacaine sensory and motor blockade was shorter than that with bupivacaine blockade.[177]

For spinal anesthesia, the value of ropivacaine and levobupivacaine compared with bupivacaine is doubtful. Given the small doses administered, a reduction in risk for systemic local anesthetic toxicity is not a consideration. Further, it is not clear that ropivacaine produces spinal anesthesia of similar quality to that provided by bupivacaine. The FDA has not approved ropivacaine or levobupivacaine for intrathecal administration. Thus, in the United States, bupivacaine remains the predominant agent for spinal anesthesia for cesarean delivery.

Hyperbaric spinal **lidocaine** or **mepivacaine** (60 to 80 mg) may be used when the obstetrician can reliably perform cesarean delivery in less than 45 minutes. The use of hyperbaric lidocaine for spinal anesthesia remains controversial because of concerns about transient neurologic symptoms (see Chapter 32).

Adjuvant Agents. Adjuvant medications contribute to spinal anesthesia by different mechanisms from those of local anesthetics. For cesarean delivery, adjuvant agents improve the quality of intraoperative anesthesia, prolong postoperative analgesia, and reduce the dose, and therefore the side effects, of local anesthetics. Opioids, dextrose, and epinephrine are commonly used adjuvants; neostigmine and clonidine are two agents undergoing clinical investigation.

Opioids have been observed to improve intraoperative and postoperative comfort for patients undergoing spinal anesthesia for cesarean delivery. Intraoperatively, this effect can be observed through a reduction in local anesthetic drug doses and the need for analgesic supplementation.[178,179] In a systematic review of intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids, Dahl et al.[180] indicated that 24% of patients undergoing cesarean delivery with spinal hyperbaric bupivacaine alone required supplemental intraoperative analgesia. Opioids augment the quality and prolong the duration of local anesthetic-induced blockade, an effect most likely modulated by A-delta (pinprick) and C (cold) nerve fibers; muscle function (A-alpha nerve fibers) does not appear to be affected.[181] The mechanism for the opioid-induced prolongation of sensory block remains unclear but may include modulation of sensory input at the spinal and supraspinal level as well as an alteration of consciousness of peripheral sensations.[182]

An additional advantage of intrathecal opioid administration is its salutary effect on the incidence of *intraoperative* nausea and vomiting. During periods of visceral stimulation (i.e., exteriorization of the uterus and fascial stimulation during closure), patients often complain of nausea. The addition of spinal fentanyl in doses of 10 to 25 μg to lidocaine or bupivacaine decreases the incidence of nausea and/or vomiting during cesarean delivery.[183,184] Clinicians commonly add both a lipid- and water-soluble opioid to the local anesthetic for spinal anesthesia for cesarean delivery. This practice takes advantage of the fast onset of the lipid-soluble agent and the prolonged duration of the water-soluble agent (Figure 26-5) (see Chapter 13). Controversy exists as to whether the co-administration of a lipid-soluble agent (e.g., fentanyl, sufentanil) with a water-soluble agent (e.g., morphine) leads to diminished response to the water-soluble agent (i.e., acute opioid tolerance). Cooper et al.[185] observed that spinal fentanyl 25 μg or saline added to plain

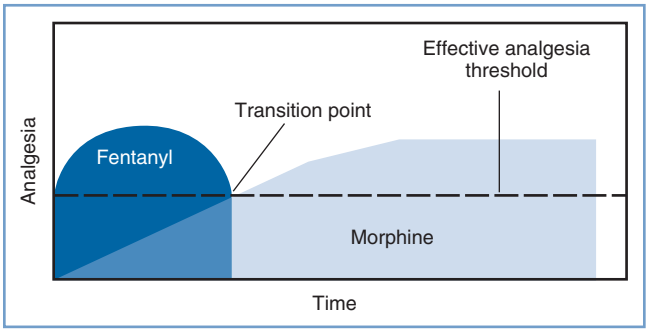

FIGURE 26-5 ■ Schematic illustration of the pharmacokinetic and pharmacodynamic activities resulting from the neuraxial administration of a lipid-soluble opioid (e.g., fentanyl) and a water-soluble opioid (e.g., morphine) for analgesia. The transition point varies according to the opioid drugs and doses administered. For most commonly used opioids, this transition point occurs in the postoperative period.

bupivacaine 10 mg resulted in no difference in intravenous patient-controlled analgesia morphine consumption within the first 6 hours after cesarean delivery; however, between 6 and 23 hours, there was a 63% increase in morphine use in the group that received fentanyl. In a study of 40 women undergoing cesarean delivery using intrathecal fentanyl (0, 5, 10, or 25 μg) combined with hyperbaric bupivacaine 12 mg and morphine 0.2 mg, Carvalho et al.[186] observed higher postoperative pain scores in the patients who received fentanyl but no differences among groups in postoperative intravenous patient-controlled analgesia morphine consumption. Women who received no fentanyl had a higher incidence of intraoperative nausea and vomiting, suggesting that fentanyl is an important adjunct for *intraoperative* anesthesia.[186] We recommend the administration of both a lipid- and a water-soluble opioid when spinal anesthesia is administered for cesarean delivery.

The optimal dose of spinal opioids is influenced by the type, dose, and baricity of the accompanying local anesthetic and the presence of other adjuvants. Dahl et al.[180] performed a systematic review of spinal **fentanyl** administered in doses ranging from 2.5 to 60 μg to augment spinal anesthesia for cesarean delivery. Studies included in the analysis were pooled into two groups based on spinal fentanyl dose (15 to 35 μg and 40 to 60 μg); there was no difference between groups in the need for supplemental intraoperative analgesia. Postoperative pruritus, nausea, and vomiting were significantly reduced with administration of doses less than 35 μg, although no meaningful postoperative analgesia was produced at these doses. Manullang et al.[187] found that spinal fentanyl 20 μg was superior to intravenous ondansetron 4 mg for the prevention of perioperative nausea (but not vomiting) during spinal anesthesia for cesarean delivery. Spinal doses of fentanyl 10 to 25 μg are commonly used for cesarean delivery anesthesia (Table 26-5).[180,188]

Spinal **sufentanil** 2.5 to 20 μg has been used with bupivacaine for cesarean delivery. In a study of 37 parturients undergoing elective cesarean delivery with sufentanil (0, 10, 15, or 20 μg) added to hyperbaric bupivacaine 10.5 mg, Courtney et al.[189] found better quality and longer duration of analgesia in all sufentanil groups than in the control group, with similar Apgar scores, umbilical cord blood gas measurements, and Early Neonatal Neurobehavioral Scale (ENNS) scores. No cases of respiratory depression occurred. Braga Ade et al.[190] randomly assigned parturients to receive hyperbaric bupivacaine 12.5 mg with sufentanil (0, 2.5, 5, or 7.5 μg). Analgesia lasted longer with sufentanil 5 and 7.5 μg, and pruritus and somnolence were more pronounced with 7.5 μg. Thus, there appears to be little justification for giving a dose of sufentanil greater than 5 μg in this setting.

Preservative-free **morphine** and **diamorphine** can improve intraoperative comfort of parturients during cesarean delivery; however, both drugs are primarily used for providing prolonged (12 to 24 hours) postcesarean analgesia (see Chapter 28). Spinal morphine has a latency of 30 to 60 minutes for onset of analgesia,[191] and it produces significant analgesia with acceptable side-effect profiles when given in doses ranging from 0.1 to 0.25 mg. Palmer et al.[192] conducted a dose-response study of morphine added to hyperbaric bupivacaine 12.75 mg; morphine 0.1 mg provided analgesia comparable to that provided by doses as high as 0.5 mg. The occurrence of pruritus, but not nausea and vomiting, appeared to be dose related.

Intrathecal **diamorphine** is used in the United Kingdom for postoperative analgesia. It is metabolized to the two active compounds 6-acetyl morphine and morphine. Diamorphine is more lipophilic than morphine, enabling a rapid onset (6 to 9 minutes, similar to fentanyl) but a potentially shorter duration of action.[193] Saravanan et al.[178] observed that intrathecal diamorphine 0.4 mg combined with bupivacaine 12.5 mg resulted in an intraoperative supplementation rate of less than 5%; however, the incidence of nausea and vomiting was 56% and the incidence of pruritus was 80%.

Neuraxial administration of water-soluble opioids such as morphine is associated with delayed respiratory depression (6 to 18 hours after administration) (see Chapter 28). Postoperative monitoring protocols should observe for respiratory depression, which although infrequent, can lead to mortality, particularly in high-risk patients (e.g., those with sleep apnea or obesity).[180,194] Many opioids, including morphine and diamorphine, may outlast the antagonism provided by naloxone (approximately 90 minutes).[195]

Most spinal local anesthetics are prepared in **dextrose** to make the agents hyperbaric. For example, commercially available hyperbaric bupivacaine contains 8.25% dextrose (82.5 mg/mL), and hyperbaric lidocaine contains 7.5% dextrose (75 mg/mL). The amount of dextrose required to make a meaningful clinical difference in a spinal technique with local anesthetic agents has not been well characterized. *Baricity* is defined as the ratio of the density of the local anesthetic solution to the density of CSF measured at the same temperature. The density of CSF is lower in women than men, particularly during pregnancy and the immediate postpartum period[196]; even so, CSF density is significantly greater than that of local anesthetics and opioids in the absence of dextrose.[196]

The intrathecal administration of an alpha-adrenergic agonist (e.g., epinephrine, clonidine) increases the density of sensory and motor blockade and may prolong the duration of blockade as well as contribute to postcesarean analgesia. Abouleish[197] observed that intrathecal **epinephrine** 0.1 to 0.2 mg, when combined with hyperbaric bupivacaine, improved the quality of intraoperative analgesia and prolonged both sensory and motor blockade by approximately 15% in comparison with bupivacaine alone. However, Randalls et al.[198] observed that the addition of epinephrine 0.3 mg to hyperbaric bupivacaine 12.5 mg for elective cesarean delivery increased the incidence of nausea.

Spinal **clonidine,** in doses of 60 to 150 µg, improves intraoperative analgesia, decreases shivering, and reduces peri-incisional hyperalgesia in women undergoing cesarean delivery; however, it has been associated with hypotension and sedation.[199] This agent is not used commonly in the United States, although it may be considered in specific circumstances (e.g., when neuraxial opioid analgesia is contraindicated). The FDA has issued a "black box" warning against its use in obstetric patients because of concerns about hemodynamic instability.

In women undergoing cesarean delivery, spinal **neostigmine** in doses up to 100 µg significantly reduced postoperative pain with no effect on FHR or Apgar scores; however, 100% of patients who received 100 µg complained of nausea.[200] Chung et al.[201] observed that 74% of parturients undergoing cesarean delivery with spinal neostigmine 25 µg with hyperbaric bupivacaine 12 mg had significant nausea and vomiting, which persisted for greater than 1 hour despite multiple antiemetic agents. In a dose-response investigation in nonpregnant healthy volunteers, spinal doses of neostigmine as low as 6.25 µg were associated with a high incidence of side effects, including prolonged motor blockade, nausea, and vomiting.[202] Collectively, these studies suggest that the high incidence of nausea associated with intrathecal neostigmine limits its clinical use.

At many institutions, the spinal agents and doses are standardized so that consistent results are obtained during the provision of spinal anesthesia for cesarean delivery. Such standardization enables the anesthesia, obstetric, and nursing staff to anticipate predictable onset and recovery characteristics and respond to physiologic responses that are outside the norm. Standardization of drugs and doses may also result in fewer errors. At our institution, spinal anesthesia for cesarean delivery is provided with 0.75% hyperbaric bupivacaine 12 mg, fentanyl 10 µg, and morphine 0.2 mg. Administration of these doses of fentanyl and morphine allows administration of the same volume (0.2 mL) of fentanyl 50 µg/mL and morphine 1 mg/mL, thereby helping to prevent dosing errors. The use of a tuberculin or insulin syringe to prepare the opioids further improves measurement accuracy.

Epidural Anesthesia

The use of epidural anesthesia for nonelective cesarean delivery has increased, primarily as a result of the greater use of epidural analgesia during labor. However, the overall use of epidural anesthesia is becoming less common for *elective* cesarean delivery when an epidural catheter is not already *in situ* (e.g., for labor analgesia or as a potential mode of anesthesia in a laboring individual at high risk for urgent cesarean delivery) (see Figure 26-3), in part because the resulting block is less reliable than that with spinal anesthesia. Initiation of CSE anesthesia offers both rapid onset and reliable spinal anesthesia coupled with the ability to augment or prolong the blockade through the epidural catheter. The dural puncture performed as part of CSE anesthesia may enhance movement of drugs injected into the epidural space across the dura-arachnoid into the subarachnoid space.[203] Epidural local anesthetic and opioid doses are generally 5 to 10 times greater than doses given intrathecally; this difference results from the requirement for penetration of nerve roots as they traverse the epidural space, the greater capacity of the epidural space, and the presence of the epidural venous plexus, which becomes progressively more engorged during pregnancy. Greater systemic absorption of anesthetic agents occurs with epidural anesthesia than with spinal anesthesia, and the risk for local anesthetic toxicity is a real possibility with local anesthetic injection for epidural anesthesia, but not for spinal anesthesia.

Possible advantages of the epidural technique include a slower onset of sympathetic blockade; this may allow compensatory mechanisms to attenuate the severity of hypotension. A catheter-based technique also allows titration of the level, density, and duration of anesthesia. Continuous postcesarean analgesia can be provided through an epidural catheter.

Local Anesthetic Agents

The most common local anesthetic used for the initiation and maintenance of epidural anesthesia for cesarean delivery is 2% **lidocaine with epinephrine** (see Table 26-6). The epidural administration of lidocaine in concentrations less than 2%, or without the addition of epinephrine (which augments the analgesia through alpha-adrenergic receptor blockade[204]), may result in anesthesia that is inadequate for surgery.[205] Hillyard et al.[206] observed a significantly lower incidence of intraoperative block supplementation with 2% lidocaine with epinephrine 1:200,000 or 0.75% ropivacaine compared with 0.5% bupivacaine or 0.5% levobupivacaine.

A 3% solution of **2-chloroprocaine** has the most rapid onset and the shortest duration of action of available local anesthetics given epidurally. These characteristics make it an excellent choice for emergency cesarean delivery (see later discussion) because the dose is administered rapidly, and even if unintentional intravenous administration of drug were to occur, the sequelae would likely be less severe than the similar administration of an amide local anesthetic agent. Administration of 2-chloroprocaine has been associated with neurologic sequelae, possibly associated with the antioxidant sodium bisulfite, and paralumbar muscle spasms and pain, believed to be a result of calcium chelation by the preservative EDTA. Current preparations of 2-chloroprocaine do not contain either an antioxidant or a preservative (see

TABLE 26-6 **Drugs Used for Epidural Anesthesia for Cesarean Delivery**

Drug	Dose Range*	Duration (min)†
Local Anesthetics		
Lidocaine 2% with epinephrine 5 μg/mL	300-500 mg	75-100
2-Chloroprocaine 3%	450-750 mg	40-50
Bupivacaine 0.5%	75-125 mg	120-180
Ropivacaine 0.5%	75-125 mg	120-180
Opioids		
Fentanyl	50-100 μg	120-240
Sufentanil	10-20 μg	120-240
Morphine	3-4 mg	720-1440
Meperidine	50-75 mg	240-720

*Both the mass and volume of local anesthetic affect the extent and quality of anesthesia. The usual volume of local anesthetic solution administered into the epidural space at the indicated concentrations is 15 to 25 mL. More mass/volume is required for initiating epidural anesthesia *de novo;* conversely, less is required if epidural labor analgesia is being extended to surgical anesthesia.

†For the local anesthetics, the duration is defined as the time to two-segment regression. For the opioids, the duration is defined as the period of analgesia (or time to first request for a supplemental analgesic drug).

Chapter 13). Epidural administration of 2-chloroprocaine may be associated with a rapid onset of hypotension and an apparent reduction in the clinical efficacy of subsequently administered epidural opioids or local anesthetics. Toledo et al.[207] observed that the analgesic effect of epidural morphine administered 30 minutes *before* 2-chloroprocaine did not appear to be mitigated; however, administration of morphine before 2-chloroprocaine in the setting of emergency cesarean delivery is not possible. These considerations limit the use of 2-chloroprocaine to those situations in which the rapid onset of anesthesia is paramount.

Surgical anesthesia can be produced with epidural administration of 0.5% **bupivacaine**; however, the slow onset of neuroblockade and the risk for cardiovascular sequelae from unintentional intravascular injection (or systemic absorption) limit the contemporary use of this agent. (The risk for cardiovascular sequelae resulted in a proscription against the epidural administration of 0.75% bupivacaine in obstetric patients by the FDA.[208]) The single-isomer, levorotatory local anesthetics 0.5% to 0.75% **ropivacaine** and 0.5% **levobupivacaine** may be preferable to racemic bupivacaine because of their better safety profiles and earlier recovery, although a significant portion of the improved safety profile is due to the lower potency of these agents (e.g., 0.5% bupivacaine is more potent than 0.5% levobupivacaine or 0.5% ropivacaine).[209] Bader et al.[210] compared 30 mL of epidural 0.5% levobupivacaine with racemic 0.5% bupivacaine in women undergoing elective cesarean delivery; they observed no differences in the block onset or resolution, signal-averaged ECG results, complications, or maternal and fetal plasma pharmacokinetic profiles between the treatment groups. After administration of 25 mL of 0.5% levobupivacaine or 0.5% racemic bupivacaine for epidural anesthesia in women undergoing cesarean delivery, Faccenda et al.[211] observed no difference in onset, spread, or duration of sensory block between the agents, although levobupivacaine produced lower limb motor blockade of longer duration but less intensity. Datta et al.[212] demonstrated that the onset, duration, and regression of sensory blockade with 0.5% ropivacaine was similar to that provided by 0.5% bupivacaine, although a faster onset and longer duration of motor blockade was observed with bupivacaine. The free concentrations of ropivacaine were approximately twice those of bupivacaine in both maternal and neonatal blood at delivery; however, these measurements were less than the concentrations shown to be toxic in animals.

Adjuvant Agents

As with spinal anesthesia, adjuvant medications are used for their intrinsic properties and to reduce the dose and side effects of local anesthetic agents. The use of epidural adjuvants can improve the quality of intraoperative anesthesia and result in less motor blockade as well as enhance postoperative analgesia (see Chapter 28).

Whereas some anesthesia providers administer an epidural opioid with the initial therapeutic dose of local anesthetic, others delay opioid administration until after the umbilical cord is clamped to prevent transfer of opioid to the fetus (see Chapter 28). The onset of analgesia is dictated by complex pharmacokinetics; however, the lipid-soluble opioids (e.g., fentanyl, sufentanil) have greater availability, more rapid onset, and more rapid clearance than the water-soluble opioids (e.g. morphine).[213]

The administration of epidural **fentanyl** (50 to 100 μg) results in activity at both spinal and supraspinal sites of action,[214] improves the intraoperative quality of anesthesia during cesarean delivery,[215,216] and does not appear to adversely affect the neonate.[217] The optimal dose of epidural fentanyl has not been determined for patients undergoing cesarean delivery; however, Eichenberger et al.[218] observed a segmental effect of epidural fentanyl 100 μg, but not 50 μg, on experimental pain in nonpregnant patients.

Epidural **sufentanil** (10 to 20 μg), when added to 0.5% bupivacaine with epinephrine 5 μg/mL, provides significantly better intraoperative anesthesia and longer postoperative analgesia than bupivacaine and epinephrine alone, with minimal maternal side effects and no adverse neonatal effects.[219] Epidural sufentanil is approximately five times as potent as epidural fentanyl, but when equipotent doses are administered, no differences between the agents in onset, quality, or duration of analgesia have been observed.[220,221]

Epidural administration of the hydrophilic drug **morphine** provides prolonged postcesarean analgesia. In a dose-response study of epidural morphine 1.25, 2.5, 3.75, and 5 mg, Palmer et al.[222] found 3.75 mg to be an optimal dose beyond which postcesarean analgesia (as measured by patient-controlled analgesia morphine demands) was no better. Extended-release epidural morphine 10 mg

provides better postoperative analgesia than epidural morphine 4 mg, with no differences in nausea, pruritus, or sedation scores.[223]

Epidural **diamorphine** (2.5 to 3 mg) is commonly used in the United Kingdom for providing prolonged postcesarean analgesia.[224] Optimal dose-finding studies of epidural diamorphine have not been performed; however, Bloor et al.[225] observed that duration and quality of analgesia from epidural diamorphine 3 mg was similar to that provided by spinal diamorphine 0.3 mg, with significantly less pruritus.

Epidural **clonidine** (75 to 200 μg) combined with morphine or fentanyl reduces the requirement for postcesarean morphine analgesia.[226] Eisenach et al.[226] demonstrated an additive rather than synergistic effect of epidural clonidine and fentanyl in producing postcesarean analgesia. Common side effects include hypotension and sedation. Currently, epidural clonidine has only one specific neuraxial indication in the United States (intractable cancer pain), and the package insert has a "black box" FDA warning stating that "epidural clonidine is not recommended for obstetrical, postpartum and perioperative pain management."

Epidural **neostigmine** produces a modest amount of postcesarean analgesia when given after umbilical cord clamping. Kaya et al.[227] investigated the administration of 75, 150, or 300 μg of epidural neostigmine in women undergoing elective cesarean delivery. An increase in intraoperative shivering and sedation was observed in the 300-μg group only; a dose-independent reduction in postoperative pain and sedation was observed in all groups.

Epinephrine is frequently added to the local anesthetic agent to minimize systemic absorption and peak blood level of local anesthetic, increase the density of sensory and motor blockade, and prolong the duration of anesthesia.[204,228,229] Bernards et al.[230] observed that the pharmacokinetic effects of epinephrine co-administered with an opioid vary with the opioid and the sampling site. In the lumbar epidural space, epinephrine lengthened the mean residence time of morphine but shortened that of fentanyl and sufentanil.

The epidural administration of epinephrine in preeclamptic women is controversial (see Chapter 36).[231] Animal and clinical studies suggest that epidural epinephrine 0.1 mg does not decrease uterine blood flow.[232,233] Alahuhta et al.[234] used maternal Doppler ultrasonography and fetal M-mode echocardiography to evaluate the hemodynamic effects of the addition of epidural epinephrine 5 μg/mL (1:200,000) to 0.5% bupivacaine for cesarean delivery; maternal diastolic pressure, but not systolic pressure or uterine blood flow, was decreased with the addition of epinephrine. By contrast, in a similar study in *hypertensive* women, Alahuhta et al.[235] observed that the addition of epidural epinephrine 5 μg/mL (1:200,000) to 0.5% bupivacaine significantly reduced uteroplacental blood flow but did not affect umbilical arterial blood flow or pH measurements at delivery.

When combined with local anesthetic for epidural anesthesia, the usual epinephrine concentration is 2.5 or 5 μg/mL (i.e., 1:400,000 or 1:200,000). The addition of epinephrine to a solution of plain local anesthetic just prior to administration results in a solution that has a higher pH than commercially prepared epinephrine-containing products, which use (low-pH) antioxidants to preserve the efficacy of the epinephrine (see Chapter 13). Thus, use of freshly prepared solutions hastens the onset of anesthesia.

The addition of **sodium bicarbonate** results in a solution with more local anesthetic molecules in a nonionized state, which hastens the onset and augments the quality of the local anesthetic blockade, particularly if sodium bicarbonate is added to a low-pH solution (see later discussion).

Combined Spinal-Epidural Anesthesia

The CSE technique incorporates the rapid and predictable onset of spinal blockade with the ability to augment anesthesia by injection of additional drug through the epidural catheter.[236,237] In 1981, Brownridge[236] reported the first use of the CSE technique for cesarean delivery through separate spinal and epidural needles introduced at different interspaces. Carrie and O'Sullivan[237] subsequently described the needle-through-needle technique via a single interspace for cesarean delivery; this has become the more popular technique. Compared with a conventional epidural anesthetic technique for cesarean delivery, Davies et al.[238] reported that the CSE technique resulted in a faster onset, greater motor blockade, and lower pain scores at delivery; moreover, no differences were observed in the incidence of maternal hypotension, nausea, or headache, the use of supplemental analgesics, or overall patient satisfaction.

Additional advantages of the CSE technique include (1) use of the epidural needle as an introducer for a longer spinal needle when attempts with a traditional introducer and spinal needle have failed and (2) use of a spinal needle (and return of CSF through the needle) to "confirm" the correct positioning of the epidural needle in the epidural space. The CSE technique also allows use of a low dose of local anesthetic to initiate spinal anesthesia (associated with a lower incidence of hypotension), followed by use of the epidural catheter to extend intraoperative anesthesia or provide postoperative analgesia.

Conventional spinal doses (e.g., 12 mg) of hyperbaric bupivacaine are most often used to provide CSE anesthesia for cesarean delivery; however, a satisfactory block has been reported with plain bupivacaine drug doses as low as 4.5 mg.[170] Although the use of lower amounts of local anesthetic is enabled by the presence of the epidural catheter (because additional agents can be administered if discomfort occurs), the block achieved with the CSE technique may be inherently different from the block achieved with a single-shot spinal technique with the same dose(s) of medication. Goy et al.[239] positioned men undergoing surgery in the right lateral position for initiation of neuraxial anesthesia and demonstrated that the median effective doses of intrathecal hyperbaric bupivacaine (to achieve a T6 sensory level of anesthesia for 60 minutes) for the CSE and spinal techniques were 9.2 mg and 11.4 mg, respectively. The investigators speculated that the use of the loss-of-resistance to air (during

introduction of the epidural needle) resulted in a reduction in lumbar CSF volume and a subsequently higher sensory blockade. Similarly, after initiating neuraxial analgesia with intrathecal bupivacaine 10 mg in parturients undergoing *elective* cesarean delivery, Ithnin et al.[240] observed median sensory levels of C6 and T3 with the CSE and spinal techniques, respectively. The CSE technique was performed with loss-of-resistance to air (2 mL); however, after administration of the spinal medications, the epidural catheter was not inserted. The investigators speculated that the loss of negative pressure in the epidural space created by the introduction of the epidural needle was responsible for the observed differences. However, when investigators from the same institution performed the same anesthetic techniques for cesarean delivery in *laboring* women, no differences in the block characteristics were observed.[241] The reasons for these different results are unclear.

The *sequential* CSE technique uses a lower dose of spinal bupivacaine (7.5 to 10 mg) followed by incremental injection of local anesthetic through the epidural catheter to achieve a T4 level of anesthesia.[242,243] The purported advantage of this approach is a lower incidence of hypotension. Thoren et al.[243] observed a more gradual onset of hypotension and a lower initial sensory level with the CSE compared with the single-shot spinal technique (T7 and T4, respectively); however, all parturients in the CSE group required additional doses of local anesthetic through the epidural catheter. The sequential CSE technique may be of particular advantage in high-risk parturients (e.g., significant cardiac disease) in whom avoidance of severe hypotension can be vitally important.

Another CSE technique is the *extradural volume extension* (EVE) technique.[242,244] Intrathecal administration of a small dose of local anesthetic is followed by the administration of saline through the epidural catheter. In a review of this technique, McNaught and Stocks[242] observed a higher cephalad spread of one to four dermatomal segments. However, the effect of EVE may depend on the initial dose and baricity of local anesthetic, the time interval between spinal and epidural injection, the volume of epidural saline, and the outcomes measured. Kucukguclu et al.[244] found no clinical differences when 10 mL of epidural saline was administered within 5 minutes of intrathecal injection of either hyperbaric or plain 0.5% bupivacaine 8 to 9 mg with fentanyl 20 μg. Similarly, Loubert et al.[245] found no difference in sensory or motor blockade when spinal hyperbaric bupivacaine 7.5 mg was administered with or without 5 mL of epidural saline injected immediately after the spinal dose.

Potential drawbacks of CSE techniques include an untested epidural catheter and hypotension. Yun et al.[128] reported greater severity and duration of hypotension when the CSE technique was administered in the sitting position than in the lateral decubitus position. The hypotension may be related to the delay in moving the patient from the sitting to the supine (with leftward tilt) position. Alternatively, greater hypotension may result from a higher level of sympathetic blockade with the CSE technique.

Extension of Epidural Labor Analgesia

The extension of epidural labor *analgesia* to surgical *anesthesia* sufficient for cesarean delivery can be accomplished with one of several local anesthetic agents. The selection of agent often depends on the urgency of the case. Extension of epidural analgesia can be initiated as preparations are being made to move the patient from the labor room to the operating room. Whether an *in situ* epidural catheter should be used for an extension attempt depends on a number of factors, including the quality of the existing labor analgesia. If obtaining satisfactory epidural labor analgesia has been problematic (e.g., one-sided or "patchy" analgesia), replacing the catheter and using a spinal or CSE technique may be a better method to attain rapid and effective anesthesia. In a systematic review and meta-analysis, Bauer et al.[246] observed that the incidence of failed conversion of labor analgesia to cesarean delivery anesthesia is greater when an increasing number of epidural boluses have been required to produce sufficient labor analgesia, a greater urgency for cesarean delivery exists, and a nonobstetric anesthesiologist is managing the case.

Specific local anesthetic and adjuvant solutions may influence whether the quality and level of epidural anesthesia is adequate for cesarean delivery. Lucas et al.[247] compared the extension of existing labor epidural analgesia among three solutions: 0.5% bupivacaine, 2% lidocaine with epinephrine 5 μg/mL (1:200,000), and a 50:50 combination of the two solutions. They observed no difference among groups in the time required to obtain a bilateral loss to cold sensation at T4. Similarly, although the study was likely underpowered, Bjornestad et al.[248] observed no significant difference in onset of anesthesia between epidural administration of 3% 2-chloroprocaine and that of 2% lidocaine with freshly added epinephrine 5 μg/mL; median onset was 8 minutes (range of 4 to 13 minutes) in the 2-chloroprocaine group and 5 minutes (range of 2 to 22 minutes) in the lidocaine group. However, given the time taken to prepare the lidocaine with epinephrine solution, the investigators concluded that use of a pre-prepared solution, such as 2-chloroprocaine, may be preferred. Of interest, 30% and 20% of patients in the 2-chloroprocaine and lidocaine groups, respectively, required intravenous alfentanil for supplementation of anesthesia.

Alkalinization of the local anesthetic solution not only increases the speed of onset but also improves the quality and prolongs the duration of neuroblockade.[249] Alkalinization shifts more of the local anesthetic molecules to the non-ionized, lipid-soluble form, which allows the local anesthetic to pass more easily through the lipid neuronal membrane surrounding the sodium channel. Although this phenomenon can be demonstrated for all local anesthetics, alkalinization is most often performed with local anesthetic agents of short and medium duration (e.g., 2-chloroprocaine, lidocaine). Typically, 1 mL of 8.4% sodium bicarbonate (1 mEq/mL) is added to 10 mL of lidocaine or 2-chloroprocaine. Longer-acting agents (e.g., bupivacaine, ropivacaine, levobupivacaine) easily precipitate with the addition of sodium bicarbonate. Precipitation occurs with the addition of less than 0.2 mEq

of bicarbonate to 20 mL of 0.5% bupivacaine.[250] Alkalinization exerts the greatest effect when it is freshly mixed with the local anesthetic solution; however, the mixture is relatively stable. Tuleu et al.[251] evaluated the stability of pH-adjusted lidocaine with epinephrine, prepared with 2 mEq of sodium bicarbonate added to 20 mL of 2% lidocaine and epinephrine 0.1 mg. Although the local anesthetic activity was unchanged, the epinephrine showed evidence of partial degradation at 6 hours.

Lam et al.[249] evaluated the extension of a T10 level of epidural labor analgesia with the addition of 1.2 mL of 8.4% sodium bicarbonate (or saline) to 12 mL of premixed 2% lidocaine with epinephrine 5 µg/mL (1:200,000) and fentanyl 75 µg (Figure 26-6). The mean times to attain a T6 anesthesia level with and without bicarbonate were 5.2 minutes and 9.7 minutes, respectively. Gaiser et al.[252] evaluated the addition of 2 mL of 8.4% sodium bicarbonate to 23 mL of either 1.5% lidocaine with epinephrine 5 µg/mL (1:200,000) or 3% 2-chloroprocaine; the mean onset time to extend the T10 analgesia level to a surgical level of anesthesia was 4.4 minutes for lidocaine and 3.1 minutes for 2-chloroprocaine. Malhotra and Yentis[253] evaluated the use of 20 mL of 0.5% levobupivacaine, with and without fentanyl 75 µg, to extend a T9 labor analgesia level to a T4 sensory level. The onset time did not differ between groups, averaging 10 to 11 minutes.

Extension of a T10 level of *analgesia* to a T4 level of *anesthesia* typically requires a volume of 15 to 20 mL of local anesthetic with one or more adjuvants. At our institution the extension of epidural labor analgesia begins with assessment of the quality of analgesia. For emergency cesarean delivery, we often initiate the extension of epidural anesthesia in the labor room by giving 5 to 10 mL of alkalinized 2% lidocaine (with epinephrine) or 3% 2-chloroprocaine. The sensory blockade is assessed after transfer of the patient to the operating room; if the blockade is bilateral and moving in a cephalad direction, an additional 5 to 10 mL is administered to bring the sensory level to T4. The use of this fractionated dosing schedule offers several advantages, including (1) greater hemodynamic stability during patient transfer; (2) assessment of the evolving sensory level before administration of the full dose of local anesthetic; (3) minimization of dural sac compression (by a large volume epidural injection),[254] which enables a less difficult and safer conversion to spinal anesthesia if extension of epidural anesthesia is not successful (see later discussion); and (4) early sensory blockade at the incision site, so that surgery can be initiated in emergency cases before establishment of a full T4 sensory level. The extension of epidural analgesia to epidural anesthesia in the labor room is controversial.[255] Some anesthesia providers delay epidural administration of additional local anesthetic until the patient has arrived in the operating room. However, this practice may increase the risk for failed epidural anesthesia, necessitating the induction of general anesthesia with its attendant risks (see later discussion).

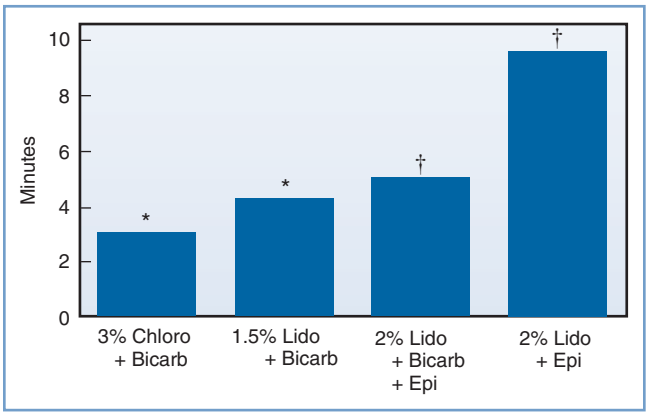

FIGURE 26-6 ■ Onset time for extension of existing labor analgesia blockade (T10 sensory level) with different local anesthetic preparations. Results between the two studies cannot be directly compared owing to differences in labor analgesia regimens, different sensory testing methods and target levels, and presence of epidural opioids. The 2% lidocaine with epinephrine solution was premixed. The epinephrine concentration was 5 µg/mL. *Chloro,* 2-chloroprocaine; *Bicarb,* bicarbonate; *Lido,* lidocaine; *Epi,* epinephrine 5 µg/mL. **To T4 sensory level.* (Data modified from Gaiser RR, Cheek TG, Gutsche BB. Epidural lidocaine versus 2-chloroprocaine for fetal distress requiring urgent cesarean section. Int J Obstet Anesth 1994; 3:208-10.) †*To T6 sensory level.* (Data modified from Lam DT, Ngan Kee WD, Khaw KS. Extension of epidural blockade in labour for emergency Caesarean section using 2% lidocaine with epinephrine and fentanyl, with or without alkalinisation. Anaesthesia 2001; 56:790-4.)

General Anesthesia

Although neuraxial techniques are typically preferred when anesthesia is provided for cesarean delivery, there are some clinical situations in which the administration of general anesthesia is considered the most appropriate option (see Table 26-3). In addition, general anesthesia offers an advantage in cases in which uterine relaxation would be beneficial (e.g., cesarean delivery as part of an *ex utero* intrapartum treatment [EXIT] procedure).

The basic elements for preparation and care of the obstetric patient undergoing cesarean delivery also apply to the patient undergoing general anesthesia (Box 26-8; see Table 26-2). The preanesthetic evaluation should focus on assessment of physical characteristics (e.g., airway) and comorbidities. The consent process should feature the risks associated with airway management, aspiration, and awareness. The importance of a careful airway evaluation cannot be overemphasized (see Chapter 30); pregnancy-induced changes in the upper airway may be exacerbated during labor. Kodali et al.[256] used acoustic reflectometry to show that soft tissue mucosal edema in both the oral (incisor teeth to oropharyngeal junction) and pharyngeal (oropharyngeal junction to the glottis) tissue increases during labor; these changes occurred over an average labor duration of 11 hours, of which 75 minutes was in the second stage, and resulted in worsening of the airway classification compared with the prelabor evaluation. Failed intubation, failed ventilation and oxygenation, and pulmonary aspiration of gastric contents remain leading anesthesia-related causes of maternal death.[150] If the airway evaluation suggests the possibility of a difficult intubation, consideration should be given to the placement of a neuraxial catheter

BOX 26-8 Steps for Initiating General Anesthesia for Cesarean Delivery*

1. Discuss the operative plan with the multidisciplinary team.
2. Perform preanesthetic assessment and obtain informed consent.
3. Prepare necessary medications and equipment.
4. Place patient supine with left uterine displacement.
5. Secure 16- or 18-gauge intravenous access. Send blood specimen for baseline laboratory measurements; consider type and screen (or crossmatch) if risk factors for peripartum hemorrhage are present.
6. Give metoclopramide 10 mg and/or ranitidine 30 mg intravenously more than 30 minutes before induction, if possible.
7. Give a nonparticulate antacid orally less than 30 minutes before induction.†
8. Administer antibiotic prophylaxis (with 60 minutes prior to incision).‡
9. Initiate monitoring.
10. Perform a team "time-out" to verify patient identity, position, and operative site; procedure to be performed; and availability of special equipment, if needed.
11. Provide 100% oxygen with a tight-fitting face mask for 3 minutes or longer, when possible, for denitrogenation/preoxygenation. Otherwise, instruct the patient to take four to eight vital-capacity breaths immediately before induction of anesthesia.
12. After the abdomen has been prepared and operative drapes are in place, verify that the surgeon and assistant are ready to begin surgery.
13. Initiate rapid-sequence induction:
    a. Cricoid pressure 10 N while awake; increase to 30 N after loss of consciousness.
    b. Thiopental 4 to 5 mg/kg or propofol 2 to 2.8 mg/kg and succinylcholine 1 to 1.5 mg/kg; wait 30 to 40 seconds.§
14. Perform tracheal intubation. Confirm correct placement of endotracheal tube.
15. Provide maintenance of anesthesia:
    a. Use isoflurane, sevoflurane, or desflurane (approximately 1 MAC) in 100% oxygen, or oxygen/nitrous oxide (up to 50%).
    b. Treat hypotension (e.g., phenylephrine, ephedrine).
    c. If additional muscle relaxant (e.g., rocuronium, vecuronium) is necessary, titrate dose according to response to peripheral nerve stimulator.
16. Observe delivery of infant.
17. Administer a bolus and/or a continuous infusion of oxytocin; consider other uterotonic agents (e.g., methylergonovine, 15-methyl prostaglandin $F_{2\alpha}$, misoprostol) if uterine tone is inadequate. Monitor blood loss and respond as necessary.
18. Adjust maintenance technique after delivery of the infant:
    a. Administer a reduced concentration of a volatile halogenated agent (0.5 to 0.75 MAC).
    b. Supplement anesthesia with nitrous oxide and an intravenous opioid.
    c. Give attention to risk for awareness and recall. Consider administration of a benzodiazepine (e.g., midazolam).
19. Perform extubation when neuromuscular blockade is fully reversed and the patient is awake and responds to commands.
20. Evaluate postoperative issues (e.g., pain, nausea).

IV, intravenously; *MAC,* minimum alveolar concentration.

*The events and sequence of events may need to be modified and tailored to individual circumstances. In an emergency, some tasks may have to be performed simultaneously.

†Some anesthesiologists suggest that sodium citrate should be administered within 20 minutes of induction of general anesthesia (see Chapter 29).

‡Recent evidence suggests that administration of prophylactic antibiotics *before* incision (rather than after umbilical cord clamping) reduces the incidence of post-cesarean endometritis and total maternal infectious morbidity.[78]

§Drugs and doses may have to be modified for individual patients and circumstances.

during early labor, even if it is not used to provide labor analgesia.[34]

Preparation

All pregnant patients requiring surgical anesthesia should be considered at risk for pulmonary aspiration of gastric contents (see Chapter 29). Attempts should be made to minimize both the risk for maternal aspiration and the risk for pulmonary injury if aspiration occurs. Fasting policies should be shared with all members of the obstetric care team. We administer metoclopramide 10 mg and ranitidine 50 mg intravenously between 30 and 60 minutes before induction of general anesthesia, to diminish gastric volume and gastric acid secretion, respectively.[73] A clear, nonparticulate antacid (sodium citrate 30 mL) should also be administered within 30 minutes of surgery to neutralize gastric acid[71]; the antacid may be particularly relevant in the emergent situation when metoclopramide and ranitidine have not had the necessary time to exert their pharmacologic effects.

If the patient has airway characteristics that herald difficult mask ventilation or intubation, preparations should be made to perform an awake tracheal intubation (see Chapter 30). Preparations include administering an antisialagogue (e.g., glycopyrrolate), judicious sedation (e.g., midazolam), and topical airway anesthesia (e.g., aerosolized lidocaine). Glossopharyngeal and laryngeal nerve blocks may also be considered.

The patient should be placed supine with left uterine displacement. The head, neck, and shoulders should be optimally positioned for airway management (i.e., the sniffing position) (see Figure 30-8). Routine monitoring should be established, including ECG, pulse oximetry, blood pressure, and capnography. Preoxygenation (denitrogenation) with 100% oxygen should be performed to delay the onset of hypoxemia during apnea; this hypoxemia occurs more rapidly due to the pregnancy-induced decrease in functional residual capacity and increase in oxygen consumption. In a computer simulation of the respiratory and cardiovascular systems during pregnancy, McClelland et al.[257] noted that the presence of labor,

high BMI, and sepsis further accelerated oxyhemoglobin desaturation during apnea; by contrast, multiple gestation and hemorrhage appeared to have minimal effects. Ideally, preoxygenation is accomplished by 3 minutes of tidal-volume breathing with a tight-fitting face mask.[258] Although four maximal deep breaths over 30 seconds with an F_{IO_2} of 1.0 can achieve a similar P_{aO_2}, the same protection against rapid oxyhemoglobin desaturation is not afforded, owing to differences in tissue and venous compartment oxygen reserves.[257,258] The method of eight deep breaths over 1 minute appears to provide better protection from oxyhemoglobin desaturation during apnea than the four deep breath over 30-second method.[259]

In contrast to most surgical procedures, the patient's abdomen is prepared and draped *before* induction of general anesthesia to minimize fetal exposure to general anesthesia. After the surgical drapes have been applied and the operating personnel are ready at the tableside, the surgeon should be instructed to delay the incision until the anesthesia provider confirms correct placement of the endotracheal tube and gives verbal instructions to proceed with surgery.

Induction

A rapid-sequence induction is initiated with denitrogenation/preoxygenation followed by administration of an induction agent, paralysis, and cricoid pressure; mask ventilation is not performed, to prevent unintentional insufflation of the stomach. Whether rapid-sequence induction should be employed, particularly in an appropriately fasted, nonlaboring patient presenting for elective cesarean delivery, has been questioned.[260] Further, the value of cricoid pressure has been challenged owing to (1) physiologic evidence demonstrating that cricoid pressure reduces lower esophageal sphincter pressure, (2) anatomic investigations showing an inability to completely occlude the esophagus, (3) a lack of clinical outcome data that confirm that cricoid pressure reduces the incidence of aspiration, and (4) the frequent misapplication of the technique itself.[261] The technique for cricoid pressure begins with an assistant applying 10 newtons (N) of force, with one N being the unit of force required to accelerate a mass of 1 kilogram 1 meter per second squared. (Force cannot be represented by mass alone, but as a practical guide to the amount of force to apply, 10 N is approximately equivalent to the downward force exerted by a weight of 1 kg.) Following loss of consciousness, the amount of force is increased to 30 N. Application of the full amount of force while the patient is still awake can provoke active retching and regurgitation. In some cases, cricoid pressure may be briefly released to enable a successful intubation; not infrequently the benefit of release outweighs the risk for regurgitation. Cricoid pressure should then be reapplied until the correct endotracheal tube position is confirmed.

Historically, **thiopental** (4 to 5 mg/kg) has been the most frequently used induction agent. Because of recent lack of availability, and also lack of familiarity, it is now rarely used in the United States, although it is still used in other countries. **Propofol** (2 to 2.8 mg/kg) is now commonly used to induce general anesthesia for cesarean delivery. Propofol, in a dose sufficient for induction and to prevent maternal awareness (2.5 mg/kg), depresses the infant more than thiopental. In the presence of hemodynamic instability, **ketamine** (1 to 1.5 mg/kg) or **etomidate** (0.3 mg/kg) should be substituted for propofol. Paralysis is achieved by **succinylcholine** (1 to 1.5 mg/kg) in 30 to 40 seconds; a peripheral nerve stimulator can be used to confirm neuromuscular blockade, because the presence of fasciculations is an unreliable sign. Administration of a defasciculating dose of a nondepolarizing muscle relaxant is *not* recommended, because it may delay the onset of neuromuscular blockade with succinylcholine. Pregnancy appears to be associated with less severe succinylcholine-induced fasciculations and muscle pain.[262]

Rocuronium (1 mg/kg) may provide intubating conditions similar to those provided with succinylcholine (1 mg/kg) for cesarean delivery[263] and is a viable alternative in situations in which succinylcholine should be avoided (e.g., malignant hyperthermia, myotonic dystrophy, spastic paraparesis). The use of a priming preinduction dose of a nondepolarizing muscle relaxant is not recommended during pregnancy, because it may result in complete paralysis and increase the risk for aspiration.[264] Enhanced activity of nondepolarizing agents may also be observed in patients receiving magnesium sulfate (e.g., for seizure prophylaxis in preeclamptic women or for fetal neuroprotection).[265] **Sugammadex,** a modified gamma-cyclodextrin, has been demonstrated to be effective in providing rapid recovery (a train-of-four ratio of greater than 0.9) without recurarization from moderate and profound rocuronium-induced neuromuscular blockade in parturients undergoing cesarean delivery.[266] Sugammadex has not been approved for use in all countries owing to concerns regarding hypersensitivity and allergic reactions.

A small-diameter cuffed endotracheal tube (i.e., 6.5 or 7.0 mm) should be used during pregnancy; the use of a flexible stylet within the endotracheal tube optimizes the first attempt at intubation. Tissue trauma and airway edema may occur with repeated attempts at intubation. Correct endotracheal tube placement should be confirmed by auscultation in both axillae and over the stomach to detect inadvertent endobronchial and esophageal intubation, respectively. Expired end-tidal carbon dioxide may be detected transiently with an esophageal intubation; thus, the anesthesia provider should observe ongoing evidence of a normal capnographic tracing and adequate maternal oxyhemoglobin saturation as well as bilateral thoracic movement and breath sounds. If doubts persist, the anesthesia provider can perform direct laryngoscopy or fiberoptic bronchoscopy to confirm the correct placement of the endotracheal tube in the trachea. If incorrect endotracheal tube placement is promptly recognized, extubation (with continued cricoid pressure) will often allow another attempt without the need for additional muscle relaxant.

Anticipation of a difficult endotracheal intubation, or a failed intubation attempt, should invoke the difficult airway algorithm and a call for assistance (see Chapter 30). Options include (1) allowing the patient to awaken, (2) using alternative techniques to place an endotracheal

tube, and (3) using alternative airway devices. The laryngeal mask airway (LMA) does not prevent pulmonary soiling with gastric contents as efficiently as an endotracheal tube, but it can be a lifesaving device in situations of failed intubation. Han et al.[267] reported clinically effective airway management with a classic LMA, which was placed successfully on the first attempt in 98% of 1067 healthy parturients undergoing elective cesarean delivery with general anesthesia. Cricoid pressure was maintained throughout the cesarean delivery, and no adverse sequelae occurred. Utilizing an LMA with a higher seal pressure than a simple LMA, and a built-in gastric draining tube, Halaseh et al.[268] reported successful placement of the LMA in 98% of 3000 healthy parturients undergoing elective cesarean delivery; they observed only one case of regurgitation without aspiration. Cricoid pressure was not maintained after confirmation of successful LMA placement. In both of these studies, patients were excluded if they had symptoms of gastropharyngeal reflux, known/predicted difficult airway, and a prepregnancy BMI greater than 30 kg/m^2. A number of variations to the classic LMA have been developed that may facilitate airway management in specific situations (see Chapter 30). Emergency airway equipment should be immediately available in all obstetric operating rooms.[34]

Maintenance

The goals for anesthetic maintenance include (1) adequate maternal and fetal oxygenation, with maintenance of normocapnia for pregnancy; (2) appropriate depth of anesthesia to promote maternal comfort and a quiescent surgical field and to prevent awareness and recall; (3) minimal effects on uterine tone after delivery; and (4) minimal adverse effects on the neonate.

Fetal oxygenation appears maximal when a maternal F_{IO_2} of 1.0 is used[269]; however, in the absence of fetal compromise, an F_{IO_2} of 0.3 appears to provide sufficient oxygenation while minimizing the production of oxygen free radicals (see earlier discussion). Although the use of a higher F_{IO_2} can increase maternal arterial and umbilical venous blood oxygen content, this action has not been observed to result in differences in 1- or 5-minute Apgar or neurobehavioral scores.[270,271] As a consequence, in the absence of fetal compromise, inspired oxygen concentrations should be guided by pulse oximetry rather than provision of an arbitrarily set level of F_{IO_2}.

Maternal ventilation should maintain normocapnia, which at term gestation is a P_{aCO_2} of 30 to 32 mm Hg. Excessive ventilation can cause uteroplacental vasoconstriction and a leftward shift of the oxyhemoglobin dissociation curve, which may result in compromised fetal oxygenation.[272] On the other hand, hypercapnia can lead to maternal tachycardia and is also undesirable.

Initially, high fresh-gas flows should be used to ensure an adequate end-tidal concentration of the volatile halogenated agent. No specific volatile halogenated agent has been demonstrated to be superior to another. The anesthetic requirements for volatile halogenated agents are diminished 25% to 40% during pregnancy.[273] End-tidal levels of halogenated agent greater than 1 to 1.5 times the minimum alveolar concentration (MAC) may reduce the effect of oxytocin on uterine tone and lead to greater blood loss after delivery.[274] A bispectral index measurement less than 60 typically requires more than 0.75 MAC of a volatile halogenated agent combined with 50% nitrous oxide and has been suggested to prevent intraoperative awareness and recall in parturients undergoing general anesthesia[275]; however, this target bispectral index value requires further study in pregnant women. Yoo et al.[276] observed lower bispectral index values with a standardized sevoflurane–50% nitrous oxide anesthetic in women with prior labor compared with women without prior labor; in addition, plasma norepinephrine concentrations were higher at both baseline and delivery in the laboring group. Similarly, Erden et al.[277] observed lower volatile agent requirements to maintain a target bispectral index value between 40 and 55 in parturients who were in labor compared with nonlaboring women; this finding could not be explained by differences in plasma concentrations of progesterone, prolactin, or cortisol.[277] Postoperative analgesia requirements for the first 24 hours were also less in the group who had labored.[276]

In clinical practice, approximately 1.0 MAC of a volatile halogenated agent is typically administered between tracheal intubation and delivery, and the concentration of the volatile agent is then reduced to 0.5 to 0.75 MAC after delivery. Nitrous oxide 50% in oxygen is often added to reduce the required concentration of volatile agent, thereby mitigating adverse effects on uterine tone. The administration of a benzodiazepine (e.g., midazolam) after delivery may reduce the risk for maternal awareness.

Intravenous opioids are often withheld until after delivery to minimize the potential for neonatal respiratory depression; however, there may be circumstances in which maternal hemodynamic stability or blunting of responses to airway manipulation and surgical stimulation favor the administration of opioids during the induction of general anesthesia. The rapid onset and efficacy of intravenous lipid-soluble agents (e.g., remifentanil, fentanyl, alfentanil) make them ideal for mitigating the responses to laryngoscopy and intubation.[278] Intraoperatively, the prolonged activity of water-soluble agents (e.g., morphine, hydromorphone) can be useful to minimize volatile anesthetic use and for the provision of intraoperative and postoperative analgesia (see Chapter 27).

Given the pregnancy-induced stretching of the abdominal wall, additional neuromuscular blockade is seldom necessary in the parturient who has an adequate depth of anesthesia (with administration of both a volatile agent and an opioid). A small dose of a short-acting nondepolarizing agent (or an infusion of succinylcholine) may be administered, with maternal response monitored with a peripheral nerve stimulator, if additional muscle relaxation is indicated.

Although differences in maternal and umbilical artery acid-base status have been observed in women who underwent elective general anesthesia compared with epidural anesthesia for cesarean delivery, similar neonatal outcomes were demonstrated.[279] With any anesthetic technique, consideration should be given to the duration of the U-D interval; in a study evaluating spinal anesthesia, when the U-D interval was longer than 180 seconds,

lower Apgar scores and greater fetal acidosis were observed.[137] (This result most likely reflects difficulty in delivering the baby rather than a direct effect of the anesthetic agents.) General anesthetic agents can redistribute from the neonatal fat to the central circulation and lead to secondary depression of neonatal ventilatory effort; thus, the presence of a pediatrician (or another neonatal provider) is advisable until a normal ventilatory pattern is observed.

Emergence and Extubation

When the patient awakens, extubation should be undertaken with the patient in a semirecumbent position. The patient should demonstrate purposeful response to verbal commands and return of protective airway reflexes before tracheal extubation. In a review of anesthesia-related maternal deaths between 1985 and 2003 in the state of Michigan, Mhyre et al.[280] observed that deaths associated with hypoventilation or airway obstruction did not occur at induction and tracheal intubation but rather during emergence, extubation, or recovery from anesthesia. Risk factors associated with mortality were obesity and African-American race, which may have delayed the visual recognition of cyanosis; medical management and medication issues were also identified. The American Society of Anesthesiologists Practice Guidelines for Postanesthetic Care suggest that pulse oximetry is associated with early detection of hypoxemia; the guidelines recommend periodic assessment of airway patency, respiratory rate, and oxygen saturation during emergence and recovery.[281] If repeated airway manipulation, massive hemorrhage, or emergency hysterectomy has occurred, delayed extubation and/or transfer to an intensive care unit (ICU) should be considered.

Pharmacology

Thiopental. Historically, the barbiturates (e.g., thiopental [thiopentone], methohexital, thiamylal) have been the induction agents most commonly used for cesarean delivery. Extensive published data have confirmed the safety and efficacy of thiopental for induction of anesthesia in patients undergoing cesarean delivery at various gestational ages. Thiopental 4 mg/kg provides a rapid and reliable induction of anesthesia. As a negative inotrope and vasodilator, thiopental can cause decreased cardiac output and blood pressure,[282] which may result in significant hypotension in hypovolemic patients. Some investigators have attempted to minimize this effect by using a lower dose of thiopental in combination with ketamine or propofol, with varying success.

Thiopental rapidly crosses the placenta. In 11 healthy subjects who underwent induction of general anesthesia with thiopental, the mean umbilical artery–to–umbilical vein ratio was 0.87 with an induction-to-delivery (I-D) interval that ranged from 8 to 22 minutes.[283] Fetal-to-maternal concentration ratios after a single thiopental dose exposure in other studies in term infants exhibited a range of 0.43 to 0.96.[284] The equilibration of thiopental occurs relatively rapidly in the fetus; however, fetal brain concentrations rarely exceed the threshold required for neonatal depression. With a maternal induction dose of 4 mg/kg, umbilical vein concentrations of thiopental are well below the arterial plasma concentrations necessary to produce anesthesia in adults.[285] However, with large induction doses (8 mg/kg), thiopental can produce significant neonatal depression.[286]

The following theories have been proposed to explain the clinical occurrence of an unconscious mother but an awake neonate: (1) preferential uptake of thiopental by the fetal liver, which is the first organ perfused by blood coming from the umbilical vein[286]; (2) the higher relative water content of the fetal brain[287]; (3) rapid redistribution of the drug into the maternal tissues, which causes a rapid reduction in the maternal-to-fetal concentration gradient; (4) nonhomogeneity of blood flow in the intervillous space; and (5) progressive dilution by admixture with the various components of the fetal circulation. Because of this rapid equilibration of thiopental and the low fetal brain concentration of thiopental, there is no advantage in delaying delivery until thiopental concentrations decline. There is no evidence that thiopental causes adverse fetal effects when the I-D time is prolonged.

Propofol. Propofol is an intravenous induction agent with a rapid onset, rapid recovery, and favorable side-effect profile, which includes a low incidence of nausea and vomiting. Induction with propofol can result in pain on injection and a reduction in maternal blood pressure and cardiac output. The pharmacokinetics of propofol are similar in pregnant and nonpregnant women, except for a more rapid clearance observed during pregnancy, which may partially reflect drug removal through blood loss and the delivery of the infant and placenta.

When given as an intravenous bolus, by continuous infusion, or both, propofol rapidly crosses the placenta and results in an umbilical vein–to–maternal vein (UV/MV) ratio of approximately 0.7.[288] In an *in vitro* human placenta study, Soares de Moura et al.[289] observed that propofol produced vasodilation of fetal placental blood vessels and decreased the effect of various vasoconstrictors, most likely through the inhibition of calcium influx through the smooth muscle sarcolemma; intralipid, the propofol carrier solution, was not responsible for these effects. Celleno et al.[290] randomly assigned 40 mothers undergoing cesarean delivery with general anesthesia to receive either propofol 2.8 mg/kg or thiopental 5 mg/kg for induction of anesthesia; they observed significantly lower Apgar and neurobehavioral scores in the propofol group. The I-D and U-D intervals in the two groups were nearly identical. Five infants exposed to propofol had profound muscular hypotonus at birth and at 5 minutes, and one newborn was somnolent. Other studies have found no effect of propofol on neurobehavioral scores or the time to sustained spontaneous respiration with induction bolus doses of propofol 2.5 mg/kg or with infusion doses less than 6 mg/kg/h.[291,292] However, higher doses of propofol (9 mg/kg/h) have been correlated with a low Neurologic and Adaptive Capacity Score (NACS).[293]

Compared with thiopental, propofol results in a greater incidence of maternal hypotension,[294] which may more effectively attenuate the response to laryngoscopy and intubation at the risk of reduced uteroplacental blood

flow. Moreover, in women undergoing cesarean delivery, Celleno et al.[295] demonstrated that propofol 2.4 mg/kg, in comparison with thiopental 5 mg/kg, resulted in electroencephalographic patterns consistent with a lighter depth of anesthesia, which was confirmed by the presence of clinical signs of light anesthesia in 50% of the patients. Other studies have not observed significant hypotension after the administration of propofol (2 to 2.8 mg/kg) or lower umbilical cord blood gas and pH measurements than after administration of thiopental (4 to 5 mg/kg)[291,296] or thiamylal (3 to 4 mg/kg).[297] However, one report noted a transient but severe episode of maternal bradycardia after administration of propofol followed by succinylcholine for rapid-sequence induction.[298] This effect has also been demonstrated in pregnant ewes; one animal experienced severe bradycardia that led to a sinus arrest.[299]

In a study of nonpregnant women, the interaction of propofol and ketamine was found to be additive at hypnotic and anesthetic endpoints; the cardiostimulant effects of ketamine appear to offset the cardiodepressant effects of propofol.[300]

Propofol provides a vehicle for bacterial growth, has undergone less investigation in pregnant women (especially preterm parturients), is painful on administration, and may lead to a higher incidence of adverse maternal and neonatal effects. Thus, propofol does not offer a significant benefit over thiopental for the induction of general anesthesia for cesarean delivery.

Ketamine. The sympathomimetic properties of ketamine make it an ideal induction agent in the setting of an urgent cesarean delivery in a patient with hypotension or an acute exacerbation of asthma.[301] Ketamine is an analgesic, hypnotic, and amnestic agent associated with minimal respiratory depression; it is often used to supplement a neuraxial technique that may not be providing optimal anesthesia. Ketamine's effect is likely related to antagonism of the *N*-methyl-D-aspartate (NMDA) receptor.

An induction dose of ketamine 1 mg/kg is associated with an increase in blood pressure immediately after induction, and a further increase is observed after laryngoscopy and intubation.[302] Such an increase can be desirable in the bleeding hypotensive patient but should be avoided in the parturient with hypertension (e.g., preeclampsia). However, in experimental animal models, ketamine was sometimes associated with direct myocardial depression, decreased cardiac output, and hypotension.[282]

Studies in pregnant ewes suggest that the use of ketamine is not associated with a reduction in uterine blood flow.[303] Ketamine is associated with dose-dependent increases in uterine tone, but a single induction dose does not increase uterine tone at term gestation.[304] Using an induction dose of ketamine 0.7 mg/kg, Craft et al.[303] observed a 39% increase in resting uterine tone with no effect on uterine blood flow in gravid ewes.

Ketamine rapidly crosses the placenta. No neonatal depression is observed with doses less than 1 mg/kg.[305] At higher doses, low Apgar scores, neonatal respiratory depression, and need for resuscitation have been reported.[305] Apgar scores and umbilical cord blood gas and pH measurements at delivery with ketamine are similar to those with thiopental.[306,307] A formulation of the purified S+ isomer of ketamine is available for clinical use in some countries outside the United States. In chronically instrumented pregnant sheep, Strumper et al.[308] found that the effects of the isomer were similar to those of the racemic mixture in terms of maternal and fetal hemodynamics and uterine perfusion; however, the S+ isomer was associated with a smaller increase in maternal and fetal Pco_2 than that seen with racemic ketamine in spontaneously breathing animals.

The emergence delirium and hallucinations experienced with ketamine, particularly in the unpremedicated patient, have limited the adoption of this drug as a routine induction agent for cesarean delivery. If ketamine is used, a benzodiazepine should be administered to decrease the incidence of these psychomimetic effects.[309] Maternal awareness may still occur after an induction dose of ketamine 1 to 1.5 mg/kg,[310] but the incidence is lower than with thiopental 4 mg/kg or a mixture of ketamine 0.5 mg/kg and thiopental 2 mg/kg.[311] The incidence of maternal awareness can also be diminished with the co-administration of a benzodiazepine.

When used to maintain general anesthesia with 50% nitrous oxide in oxygen for cesarean delivery, a continuous infusion of ketamine (70 μg/kg/minute) was followed by a higher incidence of factual recall and postoperative pain than seen with a volatile anesthetic technique.[312] Ngan Kee et al.[306] found that patients who received ketamine 1 mg/kg for induction had lower postoperative consumption of morphine than patients who received thiopental 4 mg/kg for induction (anesthesia was maintained with nitrous oxide and isoflurane). Some investigators have suggested that lower doses of ketamine (0.5 to 0.7 mg/kg) combined with thiopental or propofol may be preferable to the administration of any one individual agent. There appears to be limited advantage to this approach with thiopental in terms of maternal recall, maternal hemodynamic status, and neonatal neurobehavioral scores.[313,314] Whether ketamine, given as a bolus or infusion initiated after infant delivery, can provide postcesarean analgesia and modulate pain remains controversial (see later discussion).

Etomidate. Etomidate is an intravenous induction agent that produces rapid onset of anesthesia with minimal effects on cardiorespiratory function. This property makes it ideal for parturients who are hemodynamically unstable or who would not tolerate hemodynamic aberrations well (e.g., patients with severe cardiac disease).[315] With an induction dose of 0.2 to 0.3 mg/kg, etomidate undergoes rapid hydrolysis, thereby allowing rapid recovery.[316] Intravenous administration of etomidate may cause pain and involuntary muscle movements in unpremedicated patients; etomidate is also associated with nausea and vomiting, potential activation of seizures in patients with an epileptogenic foci, and an impaired glucocorticoid response to stress.[317]

Etomidate crosses the placenta rapidly; however, large variations in the UV/MV ratio (0.04 to 0.5) have been reported.[316] Downing et al.[318] observed that an induction

dose of etomidate 0.3 mg/kg was associated with better neonatal acid-base measurements and overall clinical condition than with thiopental 3.5 mg/kg. A transient (< 6 hours) reduction in neonatal cortisol production has been observed when an induction dose of etomidate is used for cesarean delivery[319]; however, the clinical relevance of this finding is unclear.

Midazolam. Midazolam is a short-acting, water-soluble benzodiazepine that has few adverse hemodynamic effects and provides hypnosis and amnesia. Although most commonly used as a premedicant prior to anesthesia, midazolam can be used as an induction agent for cesarean delivery. Crawford et al.[320] observed that induction with either midazolam 0.3 mg/kg or thiopental 4 mg/kg resulted in similar maternal hemodynamic responses and Apgar scores. By contrast, Bland et al.[321] reported that midazolam 0.2 mg/kg for induction of anesthesia resulted in a higher incidence of low Apgar scores and longer time to spontaneous respiration in the neonates than thiopental 3.5 mg/kg. Umbilical cord blood gas measurements did not differ between the two groups; however, the infants exposed to midazolam had lower neurobehavioral scores, body temperature, general body tone, and arm recoil. These differences did not persist at 4 hours after delivery. There are few indications for the use of midazolam for the induction of general anesthesia for cesarean delivery; it should be used only when there are relative or absolute contraindications to the use of other agents.

Muscle Relaxants. Muscle relaxants are commonly used before delivery to provide optimal intubation and operating conditions. Most muscle relaxants are highly ionized with low lipid solubility; thus, they do not undergo significant placental transfer.

The depolarizing agent **succinylcholine** (1 to 1.5 mg/kg) is the muscle relaxant of choice for most parturients undergoing rapid-sequence induction of general anesthesia. Maternal administration provides adequate intubating conditions within approximately 45 seconds of intravenous administration. Succinylcholine is a highly ionized and water-soluble molecule, and only small amounts cross the placenta. Although high doses of succinylcholine (2 to 3 mg/kg) can result in detectable levels in umbilical cord blood, very large doses (10 mg/kg) are required to lead to placental transfer sufficient to cause neonatal muscle weakness.[322]

Succinylcholine is rapidly metabolized by plasma pseudocholinesterase, the concentration of which is decreased during pregnancy; however, in most patients this effect is offset by the pregnancy-induced increase in volume of distribution. Thus, recovery from succinylcholine is not prolonged, unless the patient has extremely low levels of pseudocholinesterase or atypical pseudocholinesterase.[323] The administration of metoclopramide may also prolong succinylcholine-induced neuromuscular blockade, perhaps by inhibiting plasma pseudocholinesterase[324]; this effect is rarely (if ever) clinically significant. The return of neuromuscular function should be confirmed before additional doses of muscle relaxant are given.

Rocuronium is a suitable alternative to succinylcholine when a nondepolarizing agent is preferred for rapid-sequence induction (e.g., history of malignant hyperthermia). Abouleish et al.[325] observed that rocuronium (0.6 mg/kg) administered with an induction dose of thiopental (4 to 6 mg/kg) provided good to excellent intubating conditions in pregnant women after a mean interval of 79 seconds and maximal intubating conditions in 98 seconds. Rocuronium did not adversely affect neonatal Apgar scores, acid-base measurements, time to sustained respiration, or neurobehavioral scores. Neuromuscular blockade was reversed satisfactorily at the end of cesarean delivery. Magorian et al.[326] demonstrated that rocuronium 1.2 mg/kg resulted in an onset of paralysis similar to that provided by succinylcholine (55 seconds), but it had a significantly longer clinical duration of action.

Vecuronium 0.1 mg/kg may be administered when the use of succinylcholine is contraindicated; however, its onset of action is significantly slower than that of rocuronium (144 seconds).[326] Hawkins et al.[327] evaluated the use of two methods of vecuronium administration for rapid-sequence induction of anesthesia for elective cesarean delivery. One group of women received vecuronium 0.01 mg/kg as a priming dose before administration of 0.1 mg/kg 4 to 6 minutes later; the other group received 0.2 mg/kg as a single bolus. The mean onset time for both groups (177 seconds and 175 seconds, respectively) was much longer than that for succinylcholine; moreover, the duration of blockade was prolonged (73 minutes in the priming group and 115 minutes in the bolus group). The same group performed a separate study in women undergoing postpartum tubal ligation; the mean duration of action of vecuronium was significantly longer in these women (57 minutes) than in nonpregnant controls (35 minutes).[328] Vecuronium crosses the placenta in small amounts; however, neonatal outcome, as assessed by Apgar scores and NACS, does not appear to be adversely affected.[329]

Atracurium is a less desirable agent for rapid-sequence induction because the high dose required for a rapid onset of action may result in significant histamine release, which may cause hypotension. The isomer **cisatracurium** does not have these undesirable side effects, but its relatively slow onset makes it less optimal than other alternatives.[330]

Regardless of the choice of agent, laryngoscopy and intubation should not be attempted until adequate muscle relaxation has occurred. The use of a nerve stimulator allows an objective assessment of the onset and duration of the neuromuscular blockade. Residual neuromuscular blockade can be reversed with neostigmine and glycopyrrolate. To diminish the risk for aspiration, the anesthesia provider should confirm that the patient responds appropriately to verbal commands before tracheal extubation.

Nitrous Oxide. Nitrous oxide is an inhalational agent commonly used in the setting of a cesarean delivery because of its minimal effects on maternal blood pressure and uterine tone. The use of nitrous oxide allows for a reduction in the concentration of the volatile halogenated agent. (High concentrations of a volatile halogenated

agent decrease uterine tone.) Administration of 50% to 67% nitrous oxide in oxygen *without* another anesthetic agent does not provide complete anesthesia and can result in maternal awareness in 12% to 26% of cases.[331,332]

Nitrous oxide is transferred rapidly across the placenta, where fetal tissue uptake reduces the fetal arterial concentration for the first 20 minutes. Karasawa et al.[333] evaluated the relationship between duration of exposure to nitrous oxide 67% and the resulting UV/MA nitrous oxide concentration ratios; they observed different ratios according to duration of exposure: 2 to 9 minutes (0.37), 9 to 14 minutes (0.61), and 14 to 50 minutes (0.70). Apgar scores at 1 minute inversely correlated with duration of anesthesia, an effect observed in other studies.[334] The use of a lower concentration (e.g., 50%) of nitrous oxide may reduce but not eliminate these neonatal effects. Piggott et al.[269] randomly assigned parturients undergoing general anesthesia to receive either 100% oxygen or 50% nitrous oxide in oxygen, both supplemented by isoflurane (1.5 MAC for the first 5 minutes and 1.0 MAC thereafter). Neonates exposed to nitrous oxide required more resuscitation, although no significant differences were observed in Apgar scores.

Volatile Halogenated Agents. Volatile halogenated agents are perhaps the most commonly used agents for maintaining general anesthesia for cesarean delivery. Volatile halogenated agents produce central nervous system and cardiovascular effects in a dose-dependent manner; of particular concern for the obstetric patient are the resulting decreases in blood pressure (which may result in reduced uterine blood flow) and uterine tone. The uptake and delivery of a volatile halogenated agent is determined by inspired partial pressure, blood flow, and the blood/gas/tissue partition coefficient. The alveolar partial pressure of volatile agents during pregnancy follows known patterns of equilibration; the following commonly used agents are listed in order of more rapid to slower equilibration: nitrous oxide, desflurane, sevoflurane, and isoflurane. Volatile halogenated agents cross the placenta rapidly and equilibrate quickly with fetal tissues.[335] Neonatal depression may occur. This is typically not a clinical issue when volatile anesthetic agents are used for emergency cesarean delivery, because the delivery usually occurs before much of the volatile agent crosses the placenta (particularly if uteroplacental insufficiency is the reason for emergency delivery). Also, the maternal hemodynamic response to laryngoscopy and intubation typically offsets any hypotension that might result from administration of a volatile halogenated agent before delivery.

Munson and Embro[336] evaluated three concentrations (0.5, 1.0, and 1.5 MAC) of isoflurane, enflurane, and halothane in an *in vitro* study of gravid and nongravid uterine myometrial strips; the amount of depression of uterine contractile activity was dose related for each agent and was similar for the three agents. In a similar study, Dogru et al.[337] evaluated the effect of 0.5, 1.0, and 2.0 MAC of desflurane and sevoflurane on gravid uterine myometrial strips; a dose-dependent decrease in uterine contractions was observed. Importantly, the duration, amplitude, and frequency of oxytocin-induced uterine contractions were affected in a dose-dependent manner and were completely inhibited at 2 MAC.[337] The same group of investigators also reported that 1 MAC of desflurane inhibits the amplitude of oxytocin-induced myometrial contractions to a lesser extent than sevoflurane[338] and that pregnant myometrium is more sensitive than nonpregnant myometrium to the inhibitory effects of volatile halogenated agents.[339] These effects may influence maternal blood loss after delivery.

Lower amounts of volatile halogenated agents are required during pregnancy. Gin et al.[340] demonstrated a 28% lower MAC for isoflurane in pregnant women at 8 to 12 weeks' gestation than in nonpregnant women. The same group of investigators found a 27% and 30% decrease in MAC of halothane and enflurane, respectively.[341] These findings were correlated with an increase in progesterone level. In an animal model, Datta et al.[342] demonstrated that long-term administration of progesterone was associated with a reduction in the MAC of halothane in rabbits. Chan and Gin[343] observed that the reduction in MAC persists for 24 to 36 hours postpartum, with a gradual return to normal values by 72 hours.

Opioids. All opioids, particularly those with high lipid solubility (e.g., remifentanil, fentanyl, sufentanil), readily pass through the placenta to the fetus. As a consequence, the administration of opioids is usually avoided until after delivery to reduce the risk for neonatal depression. However, the hemodynamic stability provided by opioids during airway manipulation and surgery may be valuable in select settings, particularly in the presence of maternal cardiac disease, neurologic conditions, and preeclampsia or hypertension.

The administration of **remifentanil** has been observed to mitigate the hemodynamic responses to intubation and surgery but result in significant neonatal depression. Even with the administration of relatively low doses of remifentanil (0.5 μg/kg bolus followed by 0.15 μg/kg/min continuous infusion until peritoneal incision), Draisci et al.[344] observed that Apgar scores and umbilical cord blood pH measurements were lower in the infants exposed to remifentanil than in the infants whose mothers received fentanyl 5 μg/kg after delivery; some neonates exposed to remifentanil required tracheal intubation. There were no significant differences between groups in maternal hemodynamics or maternal plasma concentrations of catecholamines and growth hormone.

The highly lipid-soluble agent **fentanyl** rapidly crosses the placenta. Fentanyl is 60% to 80% protein bound; thus, approximately one third is available for transfer across the placenta.[345] Despite its low lipid solubility, **morphine** has a fetal-to-maternal blood concentration ratio of 0.96 at 5 minutes[346]; this rate of equilibration and the production of active metabolites are relevant considerations in the use and timing of intravenous morphine administration.

Meperidine is highly lipid soluble and is 50% to 70% protein bound; maternal administration results in a mean fetal-maternal blood concentration ratio of 0.75.[347] The production of the active metabolite normeperidine, which can accumulate in both the mother and neonate

and result in respiratory and neurobehavioral alterations, limits the use of meperidine as a principal analgesic agent during cesarean delivery; however, after delivery of the neonate, an intravenous dose of 12.5 to 25 mg is useful for treatment of shivering in the mother.

Maternal respiratory depression, as well as nausea and emesis during the intraoperative and postoperative periods, represent significant concerns in parturients given intravenous opioids.

Local Anesthesia

As a method used primarily for supplementation of neuraxial anesthesia, the infiltration of local anesthesia can also be used to facilitate an emergency cesarean delivery. This latter technique has been well described and is used predominantly in developing countries, where contemporary anesthesia techniques may not be readily available. Few contemporary obstetricians are familiar or proficient with this technique in developed countries.

The success of local infiltration depends on the obstetrician's making a midline abdominal incision, avoiding use of retractors, and not exteriorizing the uterus. In settings in which an anesthesia provider might not be readily available, the obstetrician might begin surgery with the aid of local infiltration; after delivery of the infant, the achievement of temporary hemostasis, and the arrival of the anesthesia provider, surgery may be completed once general anesthesia has been induced.

Local infiltration is performed in sequential steps as the operation progresses (Box 26-9).[348] The use of 0.5% lidocaine with epinephrine is recommended; the use of a more concentrated solution is likely to result in systemic toxicity. A 25-gauge spinal needle is used to make the intracutaneous injection; the needle is inserted just below the umbilicus and is directed in the midline toward the symphysis pubis. Approximately 10 mL of local anesthetic is required to create a skin wheal that extends from the symphysis pubis to the umbilicus. The subcutaneous injection is also performed for the full length of the planned incision with 10 to 20 mL of local anesthetic.

BOX 26-9 Steps for Initiating Local Infiltration Anesthesia for Cesarean Delivery

1. Professional support person with patient
2. Infiltration with 0.5% lidocaine with epinephrine (total dose should not exceed 500 mg)
3. Intracutaneous injection in the midline from the umbilicus to the symphysis pubis
4. Subcutaneous injection
5. Incision down to the rectus fascia
6. Rectus fascia blockade
7. Parietal peritoneum infiltration and incision
8. Visceral peritoneum infiltration and incision
9. Paracervical injection
10. Uterine incision and delivery
11. Administration of general anesthesia for uterine repair and abdominal closure, if needed

Ideally, the obstetrician should then wait for 3 to 4 minutes to allow the local anesthetic agent to exert its effect before making the skin incision.

A vertical skin incision is made between the umbilicus and the symphysis pubis and is extended down to the rectus fascia. The obstetrician then infiltrates local anesthetic into the rectus fascia and rectus muscles by making three to five laterally directed injections on each side. The needle should be passed between the rectus sheath and the transversus muscle at an angle of 10 to 15 degrees and a depth of 3 to 5 cm; aspiration is performed, and 2 to 3 mL of local anesthetic is injected at each site with an additional 1 mL injected with needle withdrawal. The obstetrician should also make oblique injections at the upper and lower poles of the incision. The local anesthetic will spread freely in the rectus sheath, but it takes 4 to 5 minutes for anesthesia to be complete. The suprapubic area must also be generously infiltrated to ensure blockade of the branches of the iliohypogastric nerve. The disadvantage of the rectus sheath block is the large volume (40 to 50 mL) of local anesthetic required; a less effective alternative that requires less volume and time is to raise a longitudinal paramedian wheal in the rectus fascia on each side of the midline and to infiltrate the suprapubic region.

The obstetrician then extends the incision through the rectus sheath, and the peritoneum is grasped with forceps clamps. If the patient has pain, the parietal peritoneum may be infiltrated with 5 to 10 mL of local anesthetic and then incised. The visceral peritoneum overlying the area of the uterine incision is injected with 10 mL of local anesthetic and is then incised and reflected appropriately. Paracervical infiltration with 5 to 10 mL of local anesthetic may block pain impulses from the uterus and cervix.

A uterine incision is made, and the infant is delivered. The surgeon must avoid forceful retraction and blunt dissection of tissue planes, and uterine manipulation should be kept to a minimum. A support person at the head of the table who can provide coaching and reassurance to the mother is invaluable.

The major disadvantages of local infiltration anesthesia are patient discomfort and the potential for systemic local anesthetic toxicity, given that as much as 100 mL of local anesthetic solution is required. The latter disadvantage may be especially problematic in the absence of a skilled anesthesia provider to assist with maternal resuscitation. Another disadvantage is the amount of time required for maximal anesthesia to develop; maternal discomfort often accompanies an urgent delivery performed with this form of anesthesia. Finally, local infiltration does not provide satisfactory operating conditions in the event of a surgical complication (e.g., uterine laceration, broad ligament hematoma).

Cesarean delivery with use of local infiltration, if successful, has the advantages of preserving maternal cardiovascular stability and a patent airway while allowing the initiation of surgery in emergency cases. However, the technique is frequently associated with incomplete maternal anesthesia, which subsequently presents significant management issues, because the surgical procedure has commenced, positioning options are limited, and the

consequences of the operative procedure (e.g., hemorrhage) may require immediate attention.

Additional peripheral nerve blockade techniques (e.g., transversus abdominis plane blockade[349]) may successfully augment local anesthesia infiltration; however, the degree to which the maternal experience is enhanced and the timing required to place these blocks deserve further investigation.

RECOVERY FROM ANESTHESIA

Cesarean delivery represents a major abdominal surgical procedure with significant anatomic, physiologic, and hormonal sequelae, even when it is performed electively without complications in a healthy parturient. The risk for adverse outcomes is greater in the presence of significant maternal comorbidity or in the setting of surgical complications (e.g., massive blood loss, cesarean hysterectomy).[350]

Cohen et al.[351] evaluated revised PACU discharge criteria in their tertiary care center for patients who received neuraxial anesthesia for cesarean delivery. They suggested that the majority of patients undergoing cesarean delivery could meet revised discharge criteria (i.e., presence of a normal level of consciousness, stable vital signs, adequate analgesia, and ability to flex the knees) within 60 minutes, a period that would shorten the average duration of PACU stay and result in cost savings. However, 26% to 36% of patients remained in the PACU for up to 180 minutes because of pain, sedation, nausea and vomiting, pruritus, prolonged neuroblockade, and/or drug treatment. In addition, 16% to 22% remained in the PACU for up to 210 minutes for cardiovascular (e.g., bleeding, hypertension, hypotension, tachycardia) or respiratory events. Moreover, the study did not include the most seriously ill or highest-risk patients, who were transferred directly to an ICU.

The 2001 National Sentinel Caesarean Section Audit in the United Kingdom reported that 10% of women undergoing cesarean delivery required admission to a high-dependency unit.[352] Moreover, 3.5% of these women required subsequent transfer to an ICU. Preexisting comorbid conditions accounted for the majority (80%) of these ICU admissions; a smaller fraction were due to the medical emergency (e.g., uterine rupture, placental abruption) that prompted the cesarean delivery.[352] Although ICU admission is uncommon in obstetric patients, it occurs more frequently (approximately 9 per 1000 patients) after cesarean delivery.[352]

Of concern, inadequate postoperative care has been cited as a recurring factor in maternal deaths (see Chapter 40). The ASA Practice Guidelines for Obstetric Anesthesia state that "appropriate equipment and personnel should be available to care for obstetric patients recovering from major neuraxial or general anesthesia."[34] Similarly, the National Obstetric Anaesthetic Service Guidelines from the United Kingdom state that postoperative care of the patient undergoing cesarean delivery should meet the same standard of care as required for any postoperative patient.[353]

Oral Intake

Mangesi and Hofmeyr[354] performed a systematic review of six randomized clinical trials comparing early with delayed oral intake of fluids and foods after cesarean delivery; they found that the early consumption (within 4 to 8 hours) was associated with a shorter time to return of bowel sounds and a shorter hospital stay. No differences were reported in nausea and vomiting, abdominal distention, time to bowel activity, paralytic ileus, or need for analgesia. The NICE guidelines state that "women who are recovering well and who do not have complications … can eat and drink when they feel hungry or thirsty."[355]

Removal of Urinary Catheter

There are no differences in the incidence of urinary retention after general anesthesia and epidural anesthesia following cesarean delivery.[356] Risk factors for postpartum urinary retention after cesarean delivery include the use of postoperative opioid analgesia (particularly when given via an epidural catheter), multiple gestation, and a low BMI.[357] Most urinary catheters are removed either immediately after cesarean delivery or within 24 hours; there are no differences between these two options in regard to postoperative urinary retention, dysuria, urgency, fever, positive microscopy, or length of hospital stay.[358] In the pregnant population, the return of bladder sensation of fullness after neuraxial techniques appears to be a function of time, rather than urinary volume.[359] The return of bladder sensation after spinal anesthesia for cesarean delivery (with hyperbaric bupivacaine and fentanyl) takes longer (mean of 374 minutes [IQR 172 to 692]) than return of sensation after patient-controlled epidural analgesia for vaginal delivery (mean of 234 minutes [IQR 95 to 382]).[359]

Postoperative Assessment and Discharge

The anesthesia provider should assess for recovery of motor and sensory function if a neuraxial technique was administered. Women should be reassured that breastfeeding is safe, even after general anesthesia, and that postoperative analgesics have a favorable safety profile. Early mobility and ambulation should be encouraged.

ANESTHETIC COMPLICATIONS

Awareness and Recall

Cesarean delivery is considered to be a high-risk procedure for the occurrence of intraoperative awareness, defined as the spontaneous postoperative recall of an event that occurred during general anesthesia.[62] The following factors contribute to the risk for maternal awareness during cesarean delivery: (1) the avoidance of sedative premedications, (2) the deliberate use of a low concentration of a volatile halogenated agent, (3) the use of muscle relaxants, (4) the reduction in dose of anesthetic agents

during hypotension or hemorrhage, (5) the presence of a partial neuraxial blockade in parturients requiring conversion to general anesthesia after failed neuraxial anesthesia, and (6) the (mistaken) assumption that high baseline sympathetic tone is responsible for intraoperative tachycardia in parturients.

Concern about neonatal depression and uterine atony associated with volatile halogenated agents has led to administration of relatively low doses of these agents. Administration of a barbiturate induction agent followed by nitrous oxide 50% in oxygen resulted in maternal awareness in 12% to 26% of cases.[331,332] Using an isolated forearm technique, King et al.[360] assessed 30 women undergoing cesarean delivery with thiopental 250 mg, succinylcholine infusion, and 0.5% halothane in 50% nitrous oxide; the majority of patients signaled pain in the first minute. The incidence of recall with this anesthetic regimen was approximately 1%.[361] The use of higher concentrations of a volatile halogenated agent has subsequently become a more common practice, leading to an incidence of maternal awareness of approximately 0.26%.[62] However, the result of increasing the depth of maternal anesthesia is that neonates born to women who receive general anesthesia tend to have lower Apgar and neurobehavioral scores, particularly when the I-D interval exceeds 8 minutes.[362]

The optimal doses and concentrations of anesthetic agents to prevent awareness remain unclear, in part because of the difficulty in assessing awareness. Studies have evaluated several tools for assessment of depth of maternal anesthesia, including the electroencephalogram, brainstem auditory evoked potentials, and the bispectral index.[62,276,311] The bispectral index is an empirically derived electroencephalographic parameter in which values less than 60 are suggested to predict a low probability of intraoperative recall and awareness.[363] With each of these monitoring devices, the threshold for awareness will need further validation, particularly during pregnancy[364]; moreover, many of these devices are not suitable for the emergency conditions under which most general anesthetics for cesarean delivery are administered.

Yeo et al.[365] evaluated 20 women undergoing cesarean delivery and noted that an end-tidal concentration of 1% sevoflurane (approximately 0.5 MAC) with 50% nitrous oxide resulted in a range of bispectral index values between 52 and 70; no patient experienced intraoperative dreams, recall, or awareness. Using a similar regimen, Yoo et al.[276] demonstrated that bispectral index values were lower during general anesthesia in women who were in labor prior to cesarean delivery than in nonlaboring women; the nonlaboring group did not reliably have values less than 60, and the mean value at tracheal intubation was 64 ± 10. Ittichaikulthol et al.[366] found that mean bispectral index values in women undergoing cesarean delivery with 3% and 4.5% desflurane in 50% nitrous oxide were 62 ± 8 and 49 ± 12, respectively. Chin et al.[275] observed that an 80% probability of maintaining bispectral index values less than 60 required a sevoflurane concentration of at least 1.2% to 1.3%.

Although pregnancy diminishes anesthetic requirements by 25% to 40%,[273] administration of 0.5 MAC of a volatile halogenated agent may not reliably provide adequate depth of anesthesia to consistently prevent maternal awareness. Robins and Lyons[62] have recommended a larger induction dose of barbiturate (e.g., thiopental 5 to 7 mg/kg instead of 3 to 4 mg/kg), an end-tidal volatile anesthetic concentration greater than 0.8 MAC, the highest concentration of nitrous oxide compatible with appropriate oxygenation, and the administration of an opioid and a benzodiazepine after delivery. Intravenous induction or infusion techniques that may reduce the risk for maternal awareness include the administration of repeat doses of thiopental,[365] the use of ketamine,[310] or a combination of thiopental and ketamine.[313] Midazolam 0.075 mg/kg provides 30 to 60 minutes of anterograde amnesia when given to women undergoing elective cesarean delivery under epidural anesthesia.[367] Induction of general anesthesia with propofol 2.4 mg/kg compared with thiopental 5 mg/kg has been associated with a significantly greater incidence (50% versus 10%) of rapid low-voltage (8-9 Hz) waves, suggestive of a light plane of anesthesia.[295] Infusion of propofol 8 mg/kg/h with 67% nitrous oxide has also been used with satisfactory amnestic effect.[368] Propofol exhibits an amnestic effect that is not dependent on the degree of sedation; however, the effect is significantly less than that with midazolam.[369]

The psychological morbidity associated with awareness should not be underestimated.[62] Further investigations into the anesthetic regimens and monitoring necessary to prevent awareness and recall in pregnant women undergoing operative procedures are needed. These studies should incorporate the growing data on gender- and pregnancy-related differences in pharmacokinetics and pharmacodynamics of drugs used for anesthesia.[370,371]

Paradoxically, the issue of recall is not limited to the administration of general anesthesia. In women undergoing cesarean delivery with a neuraxial technique who desire treatment for anxiety, the administration of anxiolytic or hypnotic agents may result in a lack of recall of delivery, which is typically undesirable.

Dyspnea

After the initiation of neuraxial anesthesia, the patient may complain of dyspnea. The most common cause of this complaint is hypotension (causing hypoperfusion of the brainstem); therefore, the complaint of difficulty in breathing should prompt immediate assessment of blood pressure and treatment, if appropriate. Other causes of dyspnea are the blunting of thoracic proprioception, the partial blockade of abdominal and intercostal muscles, and the recumbent position, which increases the pressure of the abdominal contents against the diaphragm. The sensation of dyspnea appears related to the cephalad extent of the sensory blockade and may be mitigated by using a low-dose hyperbaric spinal bupivacaine technique in women undergoing cesarean delivery.[372]

Despite these changes, significant respiratory compromise is unlikely, primarily because the neuraxial blockade rarely affects the cervical nerves that control the diaphragm. Lirk et al.[373] evaluated the effects of spinal bupivacaine 10 mg, ropivacaine 20 mg, and

levobupivacaine 10 mg, all with fentanyl 15 μg, on women undergoing cesarean delivery. Reductions in the functional vital capacity (3 to 6%) and peak expiratory flow rate (6 to 13%) were observed; however, the findings had no apparent clinical significance, were similar for all local anesthetics, and did not differ for sensory blockade that extended higher, versus no higher, than the T4 dermatome.

If the patient loses the ability to vocalize, demonstrate a strong hand grip, and/or maintain normal oxyhemoglobin saturation (e.g., symptoms suggestive of high spinal anesthesia), a rapid-sequence induction with cricoid pressure and placement of an endotracheal tube should be performed to maintain ventilation and prevent pulmonary soiling with gastrointestinal contents.

Hypotension

Hypotension is a common sequela of neuraxial anesthesia and, if severe and sustained, may lead to impairment of uteroplacental perfusion and result in fetal hypoxia, acidosis, and neonatal depression or injury.[374] Severe maternal hypotension can also have adverse maternal outcomes, including altered consciousness, pulmonary aspiration, apnea, and cardiac arrest.

Although not universally accepted, most investigators accept the following definitions for maternal hypotension: (1) a decrease in systolic blood pressure of more than 20% to 30% from baseline measurements or (2) a systolic blood pressure lower than 100 mm Hg.[375] Neuraxial anesthetic techniques produce hypotension through blockade of sympathetic nerve fibers, which control vascular smooth muscle tone. Several studies using noninvasive measures of cardiac output have demonstrated that cardiac output commonly *increases* after spinal anesthesia, even in the presence of a phenylephrine infusion and fluid administration.[376-378] These studies emphasize that spinal anesthesia–induced hypotension is principally related to a marked decrease in systemic vascular resistance, rather than decreased cardiac output. The rate and extent of the sympathetic involvement, and subsequently the severity of hypotension, are determined by the onset and spread of the neuraxial blockade[379]; hypotension may be less common with epidural anesthesia than with spinal anesthesia because of the slower onset of neuroblockade and the earlier recognition and treatment.[380]

Risk Factors for Hypotension

A number of studies have attempted to identify pregnant women at increased risk for development of hypotension. Of interest, women with severe preeclampsia[381] or in established labor appear less likely to experience hypotension during administration of spinal anesthesia for cesarean delivery.

Using a modified orthostatic challenge (i.e., "tilt test"), Kinsella and Norris[382] were unable to establish a correlation in the observed change in blood pressure or heart rate with hypotension after spinal anesthesia. Similarly, Frölich and Caton[383] could not establish a correlation between orthostatic blood pressure and heart rate changes and the hypotension that developed after spinal anesthesia; however, the investigators found that patients with a baseline heart rate higher than 90 bpm had a 83% chance (positive predictive value) of experiencing marked hypotension (decrease in blood pressure > 30%), whereas patients with a baseline heart rate lower than 90 bpm had a 75% chance (negative predictive value) of *not* experiencing marked hypotension.

Dahlgren et al.[384] hypothesized that the response of pregnant women to a preoperative *supine stress test* would predict the occurrence of maternal symptoms, a need for ephedrine, or a decrease in blood pressure below 80 mm Hg during administration of spinal anesthesia for cesarean delivery. The supine stress test was considered positive if it was associated with (1) an increase in maternal heart rate greater than 10 bpm, (2) a decrease in systolic blood pressure of more than 15 mm Hg, or (3) signs and symptoms related to the supine position (e.g., nausea, dizziness). These investigators found that the preoperative stress test had a sensitivity of 69% and a specificity of 92% in identifying those who would have hypotension.

Investigators have used other methods, including assessment of heart rate variability[385,386] and noninvasive measurements of systemic vascular resistance (e.g., thoracic impedance[387]) in an attempt to identify parturients at risk for neuraxial anesthesia–induced hypotension for cesarean delivery. Hanss et al.[385,388] suggested that the low- to high-frequency ratio of heart rate variability could identify pregnant patients at risk for severe spinal anesthesia–induced hypotension and could guide prophylactic treatment with fluid and vasopressors. To date, predicting which parturients will have hypotension after neuraxial anesthesia for cesarean delivery has not proven feasible clinically and will likely require more sophisticated studies that employ a number of different methodologies; the reason may be the myriad of factors that control the autonomic, physiologic, and hormonal changes and hemodynamic responses that occur during pregnancy.

Prevention of Hypotension

A number of strategies can mitigate hypotension after spinal anesthesia for cesarean delivery, including fluid administration, vasopressor administration, lower local anesthetic doses, leg elevation or wrapping, and left uterine displacement.

The use of **intravenous fluid** to prevent hypotension can be manipulated by (1) timing of administration, either prior to (preload) or coincident with (co-load) the intrathecal injection, and/or (2) type of fluid, either crystalloid or colloid. Rate of fluid administration may also play a role. A crystalloid preload is minimally effective, even when volumes as great as 30 mL/kg are infused.[93] By contrast, a colloid preload consistently reduces the incidence and severity of hypotension. Ueyama et al.[389] compared the administration of 1500 mL of lactated Ringer's solution and 500 mL and 1000 mL of hydroxyethyl starch solution (HES) 6% prior to spinal anesthesia for cesarean delivery; the incidence of hypotension (systolic blood pressure < 100 mm Hg and < 80% of baseline) was 75%, 58%, and 17%, respectively. Significant

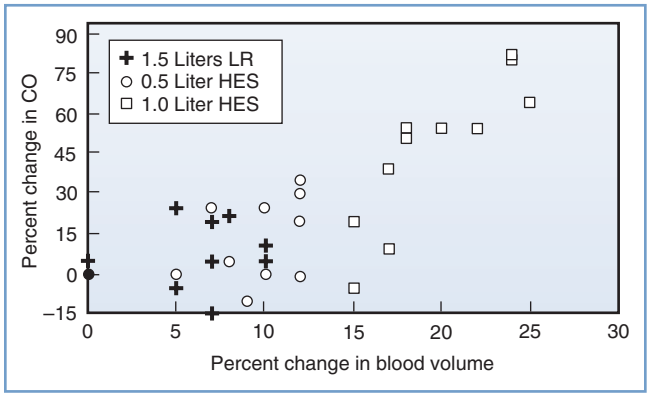

FIGURE 26-7 ■ The relationship between the changes (%) in blood volume and cardiac output after volume preload in parturients undergoing spinal anesthesia. Cardiac output (CO) was estimated with indocyanine green pulse spectrophotometry methodology. *HES,* hydroxyethyl starch solution; *LR,* lactated Ringer's solution. (Modified from Ueyama H, He Y, Tanigami H, et al. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective cesarean section. Anesthesiology 1999; 91:1571-6.)

increases in intravascular volume and cardiac output, as measured by indocyanine green spectrophotometry, were observed in the HES groups (Figure 26-7). At 30 minutes, 100% of the HES volume, versus 28% of the lactated Ringer's volume, remained within the intravascular space.

In one trial,[94] the rapid administration of a crystalloid co-load (20 mL/kg in 10 minutes, initiated immediately on induction of spinal anesthesia) was more effective than crystalloid preload in preventing hypotension; however, a meta-analysis of randomized trials comparing crystalloid preload to co-load did not find a difference in the incidence of hypotension.[95] Similarly, no difference in the incidence of hypotension is observed with a colloid preload versus co-load, likely reflecting the intravascular dwell time of colloid.[95] Additionally, co-load administration of colloid is as effective, and likely more effective, than co-load administration of crystalloid.[376]

The cost and associated pruritus, mild coagulation abnormalities, and potential for allergic reaction to colloid starch solutions, particularly with first-generation agents, have tempered their widespread use. Possible fetal and neonatal effects related to the type and timing of maternal fluid administration deserve further investigation; for example, the rapid administration of 1500 to 2000 mL of fluid can release atrial natriuretic peptide, which may result in vasodilation and reduced sensitivity to vasoconstrictors.[390] Our current practice is to administer a rapid crystalloid co-load (approximately 15 mL/kg) to healthy parturients undergoing elective cesarean delivery with spinal anesthesia. Parturients at high risk for hypotension (e.g., history of supine hypotension syndrome), or at high risk for the adverse consequences of hypotension (e.g., hypertrophic cardiomyopathy), receive a colloid preload (500 mL).

Vasopressor agents, including ephedrine and phenylephrine, can be titrated to maintain maternal blood pressure and have been observed to be more effective than crystalloid solution or placebo in preventing spinal anesthesia–induced hypotension. In a meta-analysis, Lee et al.[391] concluded that ephedrine was superior to placebo in the prevention of spinal anesthesia–induced hypotension for women undergoing cesarean delivery. Although greater doses of ephedrine provided more effective prophylaxis, hypotension was still observed and reactive hypertension and umbilical artery metabolic acidosis were more common.

Traditionally, ephedrine was used to prevent and treat the hypotension associated with neuraxial anesthesia because of fear that pure alpha-adrenergic agonists would decrease uterine blood flow. However, phenylephrine is equally efficacious to ephedrine for the prevention and treatment of hypotension, and it is less likely to depress umbilical arterial blood pH and base excess.[392] Phenylephrine crosses the placenta at a lower rate than ephedrine and undergoes greater fetal metabolism than ephedrine.[393] Presumably, fetal ephedrine contributes to stimulation of fetal metabolism, resulting in lower pH and base excess than phenylephrine.[394]

There is some controversy as to whether vasopressors should be administered as a continuous infusion or bolus, particularly for the prevention of hypotension. When administered as an infusion, phenylephrine infusion rates of 25 to 100 μg/min are usually used to prevent hypotension.[395,396] However, the number of interventions to maintain systolic blood pressure within 20% of baseline are lower for phenylephrine infusions of 25 and 50 μg/min than for infusions of 75 and 100 μg/min because of the number of interventions required to treat hypertension with the higher doses. Using an up-down sequential allocation study design, the effective phenylephrine *bolus* dose for preventing hypotension in 95% of patients (ED_{95}) was estimated at 159 μg (95% CI, 122 to 371 μg).[397] Reflex decreases in heart rate and reductions in cardiac output may occur with phenylephrine; however, this does not appear to affect umbilical cord blood gas measurements or neonatal Apgar scores in uncompromised infants delivered via elective cesarean delivery.[396] The effect on infants that have been subjected to intrauterine compromise remains unclear.

One study demonstrated a salutary effect of a prophylactic infusion of ephedrine combined with phenylephrine compared with infusion of ephedrine alone.[398] However, another study comparing infusions of different ephedrine-to-phenylephrine ratios found that as the proportion of ephedrine increased, the incidence of hypotension and nausea/vomiting also increased, whereas umbilical cord blood pH and base excess were decreased.[399]

The titration of vasopressor infusions often requires frequent infusion rate adjustments, and this mode of administration may be more cumbersome than bolus administration of the same agents. Thus, some clinicians prefer to administer a bolus dose of vasopressor to prevent or treat hypotension. Loughrey et al.[400] tested various ratios of ephedrine combined with phenylephrine, administered as a bolus, but were unable to identify a combination that reliably prevented hypotension yet avoided hypertension. Methods under investigation include a closed-loop feedback computer-controlled infusion of phenylephrine for maintaining blood pressure during spinal anesthesia.[401]

The combination of fluid and vasopressor administration may be the most effective regimen to prevent hypotension. Ngan Kee et al.[402] reduced the incidence of spinal anesthesia–associated hypotension to almost zero (1.9%) by combining a rapid crystalloid co-load with a prophylactic phenylephrine infusion (beginning at 100 μg/min); the incidence of hypotension was 28% in the women who received phenylephrine without the co-load. No difference in neonatal outcome was observed between groups.

The use of lower doses of spinal local anesthetic is associated with a lower incidence of hypotension, particularly when high and low doses are compared (e.g., hyperbaric bupivacaine 6.5 versus 9.5 mg, or 3.75 versus 9 mg; and plain bupivacaine 5 versus 10 mg combined with fentanyl 25 μg).[403] However, the desire to use a low dose of spinal local anesthetic (e.g., bupivacaine ≤ 8 mg) should be tempered by the potential for an increased requirement for intraoperative supplemental analgesia or conversion to general anesthesia.[404] The optimal local anesthetic dose is likely influenced by a number of factors, including technical factors (e.g., precision of dose, spinal level of injection, concomitant opioid use, positioning of patient during and after the block), and other factors (e.g., genetic sensitivity, patient expectations, differences in operative technique); these factors are often not controlled in studies of local anesthetic dose.[403] Anesthesia providers who administer an intermediate or low dose of local anesthetic should consider the use of a catheter-based technique (continuous spinal or CSE anesthesia), given the frequent need (up to 40%) for supplemental administration of additional local anesthetic through the catheter.[403]

Physical methods to prevent hypotension include the use of lower limb compression bandages or pneumatic compression devices, which have demonstrated some success[375] and may assist in preventing thromboembolic complications. Compared with the supine position, left uterine displacement does not consistently reduce the occurrence of maternal hypotension during cesarean delivery,[375] most likely reflecting the variable presence and significance of supine hypotension syndrome. However, in some studies, adequate left uterine displacement was associated with higher umbilical arterial blood pH measurements and better neonatal outcomes than the supine position, indicating that maternal blood pressure measured at the level of the brachial artery may not always predict uteroplacental perfusion. It is not known *a priori* who will experience hypotension; more important, diminished uterine blood flow may occur in the presence or absence of maternal hypotension. Thus, we consider the use of left uterine displacement mandatory during anesthesia for cesarean delivery.

Treatment of Hypotension

The ideal treatment of hypotension would be reliable, titratable, easy to use, and devoid of maternal and fetal side effects. Almost 40 years ago, ephedrine, a mixed alpha- and beta-adrenergic receptor agonist, emerged as the leading choice for the treatment of hypotension on the basis of studies demonstrating its efficacy and apparent superiority (over other agents) in protecting and/or restoring uterine blood flow in gravid ewes and other pregnant animal models.[405] By contrast, other agents, including metaraminol and phenylephrine, while restoring maternal blood pressure, were associated with a decrease in uterine artery blood flow and fetal pH.[405]

Contemporary animal studies have provided a mechanistic understanding of these effects. During pregnancy vasopressors appear to constrict the femoral artery more than the uterine artery, which increases blood pressure and protects uterine blood flow. This differential pressor effect is greater for ephedrine than metaraminol.[406] A second mechanism appears to be the up-regulation of nitric oxide synthase (NOS) in the uterine artery during pregnancy.[407] The presence of NOS potentially makes this artery less sensitive to vasopressors; this effect may be further augmented by ephedrine, a drug observed to independently cause the release of NOS.

In a quantitative systematic review, Lee et al.[392] noted that the use of ephedrine for treatment of maternal hypotension during administration of spinal anesthesia for cesarean delivery was associated with lower umbilical cord blood pH measurements than the use of phenylephrine. This surprising clinical result (which differs from results in animal studies) may reflect interspecies differences in vascular smooth muscle physiology, control of blood flow, and drug metabolism. Also, this result may reflect the fetal effects of ephedrine given to the mother. Cooper et al.[394] developed a measurement index by subtracting the umbilical vein Pco_2 from the umbilical artery Pco_2 to determine the amount of CO_2 generated by the fetus; the index indicated a higher metabolic production of CO_2 in fetuses whose mothers received ephedrine. Ngan Kee et al.[393] observed that the greater depression of fetal pH and base excess with ephedrine compared with phenylephrine appears related to its ability to cross the placenta to a greater extent, undergo less early metabolism or redistribution in the fetus, and consequently produce greater fetal concentrations of lactate, glucose, and catecholamines.

The NICE guidelines state that phenylephrine and ephedrine are equally effective as vasopressors.[408] Given the efficacy of phenylephrine in the treatment of hypotension and the better umbilical cord blood acid-base measurements associated with its use in clinical studies, many anesthesia providers now use phenylephrine as a first-line agent for the prevention and treatment of maternal hypotension.[409] Regardless of the vasopressor agent selected to treat hypotension, therapy should be administered as soon as the blood pressure begins to decrease, rather than after the occurrence of clinically significant hypotension.[410] In addition, vasopressor administration strategies can optimize maternal, and potentially fetal, hemodynamics and well-being by maintaining blood pressure near baseline, instead of lower target goals such as 80% or 90% of baseline measurements.[411] Ephedrine is usually administered intravenously in bolus doses of 5 to 10 mg. Phenylephrine may be administered intravenously in bolus doses of 50 to 100 μg or by continuous infusion beginning at 25 to 50 μg/min,[395] with titration to maintain maternal arterial blood

pressure at or near baseline and avoidance of maternal bradycardia.[378] Administration of ephedrine may lead to tachycardia, as well as tachyphylaxis. By contrast, phenylephrine may result in reflex maternal bradycardia, which, if treated with an anticholinergic agent in the absence of hypotension, may result in significant hypertension.

Failure of Neuraxial Blockade

"Failed" neuraxial anesthesia can be defined as neuroblockade insufficient in extent, density, or duration to provide anesthesia for cesarean delivery. Four to 13 percent of epidural anesthetics and 0.5% to 4% of spinal anesthetics fail to provide sufficient anesthesia for the initiation or completion of cesarean delivery.[412,413] Epidural techniques are more often associated with failure, given that the catheter is often placed during early labor, and over time the catheter may migrate out of the epidural space. Factors that may correlate with failed extension of labor epidural anesthesia for cesarean delivery include a higher number of bolus doses for the provision of labor analgesia (i.e., treatment of breakthrough pain), patient characteristics (e.g., obesity, distance from the skin to the epidural space), and the time elapsed between placement of the epidural catheter and cesarean delivery.[413]

The causes of failure of neuraxial techniques include anatomic, technical, and obstetric factors. Steps to reduce the likelihood of epidural block failure include meticulous attention to technical detail, the administration of a solution that contains both a local anesthetic and an opioid, and a better understanding of the characteristics of epidural versus spinal blockade. Moreover, the patient should be prepared to expect the sensation of deep pressure and movement yet be reassured that reports of discomfort or pain will be addressed promptly. Initiation of surgery should be delayed until adequate thoracic and sacral sensory blockade has been achieved; on rare occasions, in the setting of an urgent procedure for which a developing epidural block is present at T10 but has yet to achieve a T4 level, surgery can commence with the understanding that adjuvant treatments or alternative forms of anesthesia may be required.

Evaluation of intraoperative pain requires (1) determination of the location and extent of discomfort, (2) evaluation of the sensory level of anesthesia, (3) assessment of the current status of the surgery (e.g., incision, delivery, uterine repair, skin closure), and (4) assessment of the presence of confounding factors (e.g., hemorrhage, anxiety). Shoulder pain can originate from irritation of the diaphragm (usually by amniotic fluid or blood) and is mediated by the phrenic nerve (C3 to C5); prolonged abduction and extension of the arms can also cause discomfort. Additional discomfort can occur from visceral stimulation such as uterine manipulation, which often involves the greater splanchnic nerve (T5 to T10). Alternatively, the extent of the block may be adequate but the density of neuroblockade of the large nerve fibers in the lumbosacral plexus may be inadequate. Inadequate anesthesia can result from regression of the block from a cephalad or caudad direction.

Management of breakthrough pain should begin with acknowledgement of the patient's discomfort and a consideration of the fetal (e.g., presence of nonreassuring fetal status), surgical (e.g., ongoing or anticipation of prolonged surgery), and anesthetic (e.g., maternal airway examination, BMI) implications, as well as the anesthesia provider's experience. Emergent or ongoing surgery may require administration of general anesthesia. If no block exists, the surgery has not begun, and time allows, neuraxial anesthesia can be repeated; whether an epidural or spinal technique is attempted depends on the previously mentioned factors. If an inadequate, partial block exists in an elective situation, either the surgery can be postponed (to allow resolution of the partial block) or a second neuraxial technique may be performed *with caution*.

The disadvantages of replacing a failed neuraxial block with epidural anesthesia include (1) the potential for local anesthetic toxicity (particularly after epidural administration of a large dose of local anesthetic for the initial attempt), (2) the time required to establish an adequate block, and (3) the unpredictable reliability and quality of the resulting block. As a consequence, many practitioners intent on replacing a failed epidural technique suggest the *cautious* use of a technique with an intrathecal component (i.e., spinal, CSE, or continuous spinal technique).[414]

The performance of a spinal technique in the setting of a partial but failed epidural or spinal anesthetic technique is controversial. In this setting, intrathecal administration of a standard intrathecal dose of bupivacaine may result in a high spinal block.[415] Radiographic evidence suggests that the dural sac is compressed by prior epidural drug administration.[254] Thus, when performing a spinal anesthetic technique after failed epidural or spinal anesthesia, the anesthesia provider should consider (1) using a different interspace to avoid the anatomic distortions (e.g., from the loss of resistance to saline or previous needle passes) or difficulties; (2) reducing the dose of bupivacaine (with the chosen dose depending on the extent of existing neuroblockade); (3) placing the patient in a semi-sitting (Fowler's) position to limit cephalad spread of the local anesthetic; (4) using a CSE technique with a small intrathecal dose of local anesthetic, and, if necessary, titrating the sensory level with additional drugs administered through the epidural catheter; and (5) intentionally placing an epidural catheter into the intrathecal space for administration of continuous spinal anesthesia. This last strategy may be especially useful in obese patients in whom the technical difficulty of the neuraxial approach may otherwise limit success.

If discomfort is reported after the start of surgery, it is often helpful to ask the surgeons to halt the operation while an assessment is made. If an epidural catheter is in place, an alkalinized local anesthetic with an opioid (e.g., 3% 2-chloroprocaine with fentanyl) should be administered. The density of epidural anesthesia may be improved by "repainting the fence." An additional dose of local anesthetic (20% to 30% of the initial dose [e.g., 4 to 7 mL]) is administered approximately 20 minutes after the initial dose. This second dose serves to improve the density of neuroblockade without extending the sensory

level. Some anesthesia providers routinely administer this supplemental dose, without waiting for a patient's complaint of breakthrough pain.

Intravenous administration of an opioid (fentanyl), inhalation of nitrous oxide (40% to 50% in oxygen), or intravenous anxiolysis (midazolam) may be helpful for the treatment of breakthrough pain. Severe pain may require intravenous ketamine in 5- to 10-mg increments. However, care should be taken, because the administration of multiple agents can result in significant sedation, loss of consciousness, and the presence of psychomimetic and amnestic effects. The obstetrician can infiltrate the wound or instill the peritoneal cavity with local anesthetic; however, at this point, the induction of general anesthesia with tracheal intubation is often necessary.

If the anesthesia provider anticipates that the duration of the surgical procedure will be longer than the predicted duration of epidural or CSE anesthesia, additional local anesthetic (with or without an opioid) should be administered *before* anticipated regression of neuroblockade (see Table 26-6). The usual dose to maintain neuroblockade is half of the initial dose.

High Neuraxial Blockade

It is not uncommon for the parturient to report mild dyspnea or reduced ability to cough, especially if the neuraxial blockade has achieved a T2 sensory level. If impaired phonation, unconsciousness, respiratory depression, or significant impairment of ventilation occurs, administration of general anesthesia should be performed. High neuraxial blockade may also result in cardiovascular sequelae, including bradycardia and hypotension. An easy method to diagnose a clinically significant high neuraxial blockade is to ask the patient to make a fist ("squeeze your fingers"). A weak hand grasp indicates high thoracic and cervical motor blockade.

High neuraxial block can be caused by several mechanisms, including an exaggerated spread of spinal or epidural drugs and unintentional intrathecal or subdural administration of an "epidural dose" of local anesthetic. The rapid epidural administration of a large volume of local anesthetic solution in the presence of a large-bore dural puncture (e.g., after a "wet tap") may also result in high neuroblockade.

Nausea and Vomiting

Nausea and vomiting are regulated by the chemoreceptor trigger zone and the vomiting center, which are located in the area postrema and the medullary lateral reticular formation, respectively. The vomiting center receives impulses from the vagal sensory fibers in the gastrointestinal tract, the semicircular canals and ampullae (labyrinth) of the inner ear, higher cortical centers, the chemoreceptor trigger zone, and intracranial pressure receptors. Impulses from these structures are influenced by dopaminergic, muscarinic, tryptaminergic, histaminic, and opioid receptors, which are subsequently the targets for antiemetic agents. Efferent impulses from the vomiting center are transmitted through the vagus, phrenic, and spinal nerves to the abdominal muscles, which causes the physical act of vomiting.

Preoperative Nausea and Vomiting

Nausea and vomiting may occur separately or in combination and are not uncommon during pregnancy. A number of metabolic, endocrine, and anatomic changes have been implicated in the genesis of gestational nausea and vomiting, including human chorionic gonadotropin, estrogen, progesterone, prostaglandins, and immune system dysregulation.[416] When vomiting is sufficiently severe to produce weight loss, dehydration, acidosis from starvation, alkalosis from loss of hydrochloric acid in vomitus, and hypokalemia, it is referred to as *hyperemesis gravidarum* (see Chapter 16). This disorder most commonly occurs in early pregnancy, but as many as 10% of pregnant women have nausea and vomiting that persist beyond 22 weeks' gestation.[416] Severe and persistent hyperemesis may result in maternal and fetal morbidity.

The presence of delayed gastric emptying during labor and administration of opioids are risk factors for nausea and vomiting before cesarean delivery.

Intraoperative Nausea and Vomiting

Intraoperative nausea and vomiting associated with cesarean delivery can be variable in incidence and presentation, depending on preexisting symptoms, anesthetic and obstetric techniques, and preventive and therapeutic measures. The incidence of nausea may be as high as 80%, particularly when the anesthesia provider specifically assesses for the presence of intraoperative symptoms; symptoms occur frequently with exteriorization of the uterus.[7] Anesthetic causes of intraoperative nausea and vomiting include hypotension and increased vagal activity; nonanesthetic causes include surgical stimuli, bleeding, medications (e.g., uterotonic agents, antibiotics), and motion at the end of surgery.[417] Many of these elements occur simultaneously.

Hypotension is among the most common sequelae associated with the administration of neuraxial anesthesia. Centrally, hypotension may lead to cerebral and brainstem hypoperfusion, which results in stimulation of the medullary vomiting center. Peripherally, hypotension may cause gut ischemia with release of emetogenic substances (e.g., serotonin) from the intestine.[418] Strict maintenance of intraoperative blood pressure can reduce the occurrence of emesis; Datta et al.[410] observed that the incidence of intraoperative nausea and vomiting was 66% when the blood pressure decreased more than 30% from baseline, but was less than 10% when blood pressure was maintained at baseline with ephedrine. Similarly, Ngan Kee et al.[411] demonstrated progressive increases in intraoperative nausea and vomiting when blood pressure control with an infusion of phenylephrine was less aggressive; the incidence of nausea and vomiting was 4% when blood pressure was maintained at 100% of baseline, 16% when maintained at 90% of baseline, and 40% when maintained at 80% of baseline during spinal anesthesia for cesarean delivery.

Uterotonic agents may also contribute to intraoperative nausea and vomiting. Ergot alkaloids may cause nausea and vomiting by interacting with dopaminergic and serotoninergic receptors. Oxytocin causes nausea and vomiting primarily as a result of the hypotension produced through release of nitric oxide and atrial natriuretic peptide.[419] A 29% incidence of nausea and a 9% incidence of vomiting have been reported with an intravenous bolus of oxytocin 5 units during elective cesarean delivery with neuraxial anesthesia.[420] Administration of 15-methyl prostaglandin $F_{2\alpha}$ causes nausea through the stimulation of smooth muscles of the gastrointestinal tract; a 10% incidence of nausea and vomiting has been observed after administration of 250 µg intramuscularly.[417]

Surgical stimuli, including exteriorization of the uterus, intra-abdominal manipulation, and peritoneal traction, can cause visceral pain and subsequent nausea through the stimulation of vagal fibers and activation of the vomiting center; despite high levels of thoracic sensory block obtained for cesarean delivery anesthesia, visceral pain may still occur, particularly after the neuraxial administration of a local anesthetic without opioid.[421] The administration of neuraxial opioids reduces visceral pain–induced nausea and vomiting. Neuraxial fentanyl both improves the quality of neuraxial anesthesia and decreases intraoperative nausea; the minimal effective doses are 6.25 µg given intrathecally and 50 µg given epidurally, respectively.[180]

Postoperative Nausea and Vomiting

Risk factors for postoperative nausea and vomiting have not been specifically studied in obstetric patients; however, studies have identified risk factors in nonobstetric patients receiving general or neuraxial anesthesia (Box 26-10).[422,423] Apfel et al.[423] identified the following four highly predictive factors for postoperative nausea and vomiting in nonobstetric patients after general anesthesia, which may have relevance in the pregnant population: (1) female gender, (2) history of motion sickness or postoperative nausea and vomiting, (3) nonsmoking status, and (4) the use of perioperative opioids. The incidence of postoperative nausea and vomiting was 10% if the patient had no risk factors, 21% for one, 39% for two, 61% for three, and 79% for four. A subset of pregnant women may have a lower threshold for nausea and vomiting associated with motion.[416] Changes in position and transfer to and on the stretcher may stimulate afferent neural pathways that trigger emesis. Because the histamine-1 (H_1) and muscarinic cholinergic pathways play primary roles in this response, antihistamine and anticholinergic agents should be considered first-line treatments.[424] Postoperative nausea and vomiting may be related to postoperative ileus, which in turn is influenced by the effect of opioids on the gastrointestinal tract, the activation of the sympathetic nervous system, the occurrence of intestinal wall inflammation, and the presence of volume overload or edema.[416]

BOX 26-10 Risk Factors for Nausea and Vomiting

General Anesthesia–Related Factors

- Female gender
- History of motion sickness or postoperative nausea and vomiting
- Nonsmoking status
- Use of perioperative opioids

Spinal Anesthesia–Related Factors

- Block height of T5 or higher
- History of motion sickness
- Hypotension
- Omission of neuraxial opioids

Information from Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006; 102:1884-98; and Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91:693-700.

Prophylaxis and Treatment of Nausea and Vomiting

Preventing maternal hypotension may be the best means of preventing nausea and vomiting (see earlier). Several options exist for the pharmacologic prophylaxis of nausea and vomiting, and several different classes of drugs are available (Table 26-7). Although various algorithms have been developed to prevent postoperative nausea and vomiting, primarily targeting the nonpregnant patient population, none has been universally successful.[425] However, the prophylactic use of these agents either before or after umbilical cord clamping during cesarean delivery with neuraxial anesthesia has been demonstrated to be highly effective. Balki and Carvalho[417] suggested an algorithm consisting of metoclopramide as a first-line agent, dimenhydrinate as a second-line agent, and ondansetron or granisetron as a third-line agent. Multimodal therapies may eventually prove the most effective.

Metoclopramide is the agent most frequently given, owing to its favorable prokinetic effects. Common side effects include dizziness, drowsiness, and fatigue; more rare side effects include extrapyramidal reactions and acute dystonias. In a meta-analysis of 11 studies of 702 patients undergoing cesarean delivery, Mishriky and Habib[75] found that intravenous metoclopramide 10 mg, administered before neuraxial blockade, resulted in a significant reduction in intraoperative nausea (RR, 0.27; 95% CI, 0.16 to 0.45) and vomiting (RR, 0.14; 95% CI, 0.03 to 0.56) when metoclopramide, rather than placebo, was administrated before neuraxial blockade. This approach was more effective than giving metoclopramide after delivery, an approach that also resulted in a significant reduction in perioperative nausea and vomiting. Early postoperative nausea (RR, 0.47; 95% CI, 0.26 to 0.87) and vomiting (RR, 0.45; 95% CI, 0.21 to 0.93) were also reduced with metoclopramide.

Abouleish et al.[426] found that **ondansetron** was more effective than placebo for the prevention of intraoperative nausea and vomiting during cesarean delivery with spinal anesthesia. Pan and Moore[427] observed that when administered after umbilical cord clamping, ondansetron 4 mg was more effective than metoclopramide 10 mg

TABLE 26-7 **Agents for Prevention of Nausea and Vomiting in Women Undergoing Cesarean Delivery with Neuraxial Anesthesia***

Drug	Dose	Optimal or Recommended Timing	Comments
Dexamethasone	4-8 mg IV	Unknown for patients undergoing cesarean delivery†	Delayed onset of action; used infrequently in patients undergoing cesarean delivery
Dimenhydrinate‡	25-50 mg IV	Unknown for patients undergoing cesarean delivery	Antihistamine
Dolasetron	12.5 mg IV	After umbilical cord clamping	Serotonin antagonist; not effective in the single published randomized controlled trial
Droperidol	0.625-1.25 mg IV	End of surgery	Butyrophenone with a package insert that contains an FDA "black box" warning regarding prolongation of corrected QT interval on electrocardiogram
Ephedrine‡	0.5 mg/kg IM	End of surgery	Vasopressor
Granisetron	40 μg/kg IV	After umbilical cord clamping	Serotonin antagonist
Metoclopramide	10 mg IV	Prior to surgery or after umbilical cord clamping	Benzamide
Ondansetron	4 mg IV	After umbilical cord clamping	Serotonin antagonist
Scopolamine	1.5-mg transdermal patch	Unknown	Muscarinic antagonist

IM, intramuscularly; *IV,* intravenously.
*If nausea and vomiting occur despite prophylaxis, the anesthesia provider should consider administration of a drug from a different pharmacologic class. There is no evidence that a second administration of the same drug within 6 hours provides additional benefit.
†Studies in nonobstetric patients suggest that administration of dexamethasone at induction of anesthesia results in better efficacy, but the optimal timing in obstetric patients is unclear.
‡Has not been studied in patients undergoing cesarean delivery with neuraxial anesthesia; however, this drug has proved effective for prophylaxis of postoperative nausea and vomiting in studies of nonobstetric patients after administration of general anesthesia.

in preventing nausea (26% versus 51%) but not vomiting (15% versus 18%). In a systematic review, Griffiths et al.[428] concluded that the use of a serotonin antagonist (e.g., ondansetron, granisetron) in women undergoing neuraxial anesthesia for cesarean delivery was associated with a reduction in intraoperative nausea (but not vomiting) and postoperative nausea and vomiting, compared with placebo. Furthermore, serotonin antagonists were found to be more effective in reducing postoperative nausea than dopamine antagonists (e.g., metoclopramide, droperidol).[428]

In an animal toxicology study that was followed by a human clinical trial, Han et al.[429] demonstrated no histologic changes in spinal cord tissues after *epidural* administration of ondansetron in rats. Moreover, in 80 women undergoing elective cesarean delivery with CSE anesthesia, the incidence of postoperative nausea was lower in women randomized to receive an epidural infusion of ondansetron than in women who received an intravenous infusion (8 mg over 48 hours) at both 24 and 48 hours.[429] However, future investigations are needed to validate the safety of the neuraxial administration of ondansetron before this route of administration can be recommended.

In a meta-analysis, Allen et al.[430] found that a single intravenous dose of **dexamethasone** 5 to 10 mg (but not 2.5 mg) compared with placebo reduced the incidence of postoperative nausea (23% versus 41%, respectively) and vomiting (20% versus 36%, respectively) in women who received neuraxial morphine for cesarean delivery. In a subgroup analysis, the authors identified a lower incidence of postoperative nausea and vomiting in women who received epidural morphine; however, they were unable to draw definitive conclusions regarding the effect of dexamethasone on postoperative nausea and vomiting in women who received spinal morphine because of the small sample size.

Harnett et al.[431] observed that the administration of a **transdermal scopolamine** 1.5-mg patch after umbilical cord clamping was as effective as ondansetron 4 mg in the prevention of nausea and vomiting after cesarean delivery with spinal anesthesia (bupivacaine 12 mg with fentanyl 10 μg and morphine 0.2 mg); compared with placebo, both drugs resulted in a reduction in the incidence of postoperative emesis from approximately 60% to approximately 40%. The use of scopolamine may be limited by side effects, particularly dry mouth and blurry vision. The results of a systematic review suggest that the use of an anticholinergic agent (e.g., scopolamine, glycopyrrolate) in women undergoing neuraxial anesthesia for cesarean delivery results in a significant reduction in intraoperative nausea but not vomiting.[428]

Alternative therapies may play a role in preventing or treating perioperative nausea and vomiting. Several studies have found a favorable effect of **acupressure** on the P6 acupoint (on the inner aspect of the wrist). After spinal anesthesia for cesarean delivery, acupressure has been observed to result in a lower incidence of nausea (36% and 15%, respectively) and vomiting (17% and 9%, respectively), when compared with placebo.[432] Two

systematic reviews of randomized controlled trials involving a total of 649 women undergoing neuraxial anesthesia for cesarean delivery concluded that despite heterogeneity in the data, P6 stimulation (compared with placebo) appears to reduce intraoperative nausea but not intraoperative vomiting or postoperative nausea or vomiting.[428,433]

One study found that the administration of **supplemental oxygen** (F_{IO_2} of 0.7) between umbilical cord clamping and the end of cesarean delivery with neuraxial anesthesia was not associated with a lower incidence of nausea and vomiting than the administration of room air.[434] This finding is consistent with a meta-analysis[435] of randomized controlled trials in the nonobstetric population; there was no difference in the incidence of nausea and vomiting with the use of supplemental oxygen (F_{IO_2} of 0.8) compared with the use of lower oxygen concentrations (F_{IO_2} of 0.3 to 0.4).[435]

A systematic review[428] suggests that the administration of subhypnotic doses of **propofol** (0.5 to 1.5 mg/kg/h) for the reduction of intraoperative and postoperative nausea and vomiting in women undergoing neuraxial anesthesia for cesarean delivery is more effective than placebo; however, there are insufficient data to compare this method with other therapies.[428]

Perioperative Pain

In contrast to surveys performed in the general surgical patient population, in which patients have revealed a primary concern for postoperative nausea and vomiting, a survey performed in obstetric patients during their expectant parent class indicated that pain during and after cesarean delivery was their greatest concern.[436] Inadequate neuraxial anesthesia leading to pain during labor or cesarean delivery was the most frequent "damaging event" in obstetric claims (31%) against the National Health Service in the United Kingdom from 1995 to 2007.[437] Although pain during cesarean delivery was generally classified as "mild" or "moderate" (when accompanied by post-traumatic stress disorder), it represented an especially frequent cause of low-severity obstetric claims.[437] Pain due to inadequate neuraxial anesthesia is also a common cause of obstetric complaints in the American Society of Anesthesiologists Closed-Claims Project database (see Chapter 33).

A preoperative discussion about pain and discomfort can help allay patient concerns. The anesthesia provider should (1) explain that there may be some deep pressure, pain, or discomfort during cesarean delivery performed with a neuraxial technique; (2) reassure the patient that the anesthesia provider will be present throughout the operation to administer additional analgesics or general anesthesia if necessary; (3) ensure and document adequacy of neuraxial blockade before the start of surgery; (4) communicate with the patient frequently during the procedure, specifically about pain or discomfort; and (5) treat pain when it arises, in agreement with the patient's wishes. During the postoperative visit, the anesthesia provider should address any concerns that may have arisen during or after surgery.

The anesthetic technique for the cesarean delivery may be altered because of postoperative pain management considerations. For example, an epidural catheter–based technique may be optimal for the patient with a significant pain history (e.g., sickle cell vaso-occlusive crises, chronic pain syndromes, drug-seeking behavior) so that the epidural catheter may be used for postoperative pain management.

By directly activating spinal and supraspinal opioid receptors, epidurally and spinally administered opioids blunt nociceptive input and produce analgesia of greater intensity than parenterally or intramuscularly administered doses.[214] A number of opioids have been used in the epidural and spinal spaces; however, morphine has emerged as the leading agent for postcesarean analgesia, owing to its long duration of action and low cost (see Chapter 28). When morphine is administered intrathecally or epidurally, doses of 0.1 mg and 3.75 mg, respectively, appear to provide optimal analgesia after cesarean delivery.[192,222] Neuraxial morphine has a peak analgesic effect at 60 to 90 minutes but continues to provide effective analgesia for up to 24 hours.[222] Thus, intrathecal morphine is often co-administered with the local anesthetic and lipid-soluble opioid administered for spinal anesthesia, and epidural morphine is administered intraoperatively, after the umbilical cord is clamped, to allow sufficient time for the onset of epidural morphine analgesia before the regression of epidural anesthesia.

The local anesthetic selected for epidural anesthesia may influence postoperative analgesia. The epidural administration of 2-chloroprocaine has been observed to adversely affect the subsequent efficacy of epidural morphine analgesia,[438] although this remains a matter of some dispute.[439] The mechanism for this potential interaction remains unknown, however, the use of 2-chloroprocaine should be limited to emergency situations in which rapid augmentation of epidural anesthesia is desired (see earlier discussion).

Adverse effects of neuraxial morphine include pruritus, nausea and vomiting, urinary retention, and delayed respiratory depression. Frequent evaluations (hourly for the first 12 hours, and then every 2 hours for another 12 hours) should be conducted.[440] Postpartum women who are morbidly obese or have preexisting respiratory issues (sleep apnea) are at greater risk for respiratory depression.

Postoperative pain has at least two components, somatic and visceral. A multimodal approach with different agents (e.g., ketamine) and techniques (e.g., infiltration, peritoneal spraying, transversus abdominis plane [TAP] block) provides the most effective postcesarean analgesia (see Chapters 27 and 28). The administration of nonsteroidal anti-inflammatory drugs has been associated with potential adverse effects (platelet dysfunction, uterine atony), and some investigators have expressed concerns related to neonatal exposure through breast milk. However, the American Academy of Pediatrics[441] has stated that ibuprofen and ketorolac are compatible with breast-feeding.

Pruritus

The incidence of pruritus with the administration of opioids can be as high as 30% to 100%, and pruritus is

more commonly observed when opioids are administered intrathecally than epidurally. Pruritus may be generalized or localized to regions of the nose, face, and chest and is typically self-limited in duration. The particular combinations and doses of opioid and local anesthetic may influence the incidence and severity of pruritus, and the addition of epinephrine to an opioid–local anesthetic solution has been observed to worsen pruritus.[442] Pruritus does not represent an allergic reaction to the neuraxial opioid. If flushing, urticaria, rhinitis, bronchoconstriction, or cardiac symptoms also occur, an allergic reaction to another substance should be considered.

The cause of neuraxial opioid–induced pruritus is not known, although multiple theories have been proposed. They include μ-opioid receptor stimulation at the medullary dorsal horn, antagonism of inhibitory transmitters, and activation of an "itch center" in the central nervous system.[443] Pharmacologic prophylaxis or treatment of pruritus may include an opioid antagonist, an opioid agonist/antagonist, droperidol, a serotonin antagonist (e.g., ondansetron), and/or a subhypnotic dose of propofol (Table 26-8).[443] Intravenous administration of granisetron 3 mg may reduce the severity but not the incidence of intrathecal morphine–induced pruritus when compared with administration of ondansetron 8 mg.[444] Dexamethasone in doses of 2.5 to 10 mg has not been found to reduce the incidence of pruritus associated with neuraxial morphine in women undergoing cesarean delivery.[430] Although opioid antagonists, such as naltrexone and naloxone, and partial agonist/antagonists, such as nalbuphine, are currently the most effective treatments for pruritus, a single dose or continuous intravenous infusion of any of these agents may reverse analgesia. Because the primary mechanisms of opioid-induced pruritus appears unrelated to histamine release, antihistamines seldom represent a viable treatment option, although some benefit may be derived from the accompanying sedative qualities of these agents.

TABLE 26-8 Agents for Prevention or Treatment of Pruritus in Women Undergoing Cesarean Delivery

Drug Class	Drug and Dose	Comments
Opioid antagonists	Naloxone infusion 1-2 μg/kg/h IV Naltrexone 6-9 mg PO	May reverse analgesia
Opioid agonist/antagonist	Nalbuphine 2.5-5 mg IV	
Sedative/hypnotic agent	Propofol 10-20 mg IV	Subhypnotic dose with conflicting evidence regarding efficacy in treating pruritus
Serotonin antagonist	Ondansetron 0.1 mg/kg IV	Conflicting evidence regarding efficacy in treating pruritus
Butyrophenone	Droperidol 1.25 mg IV	Package insert contains an FDA "black box" warning regarding prolongation of corrected QT interval on electrocardiogram

IV, intravenously; *PO,* orally.

Hypothermia and Shivering

Perioperative hypothermia and shivering are commonly observed in women undergoing cesarean delivery, with a reported incidence of 66% and 85%, respectively.[445,446] Hypothermia has been associated with a number of adverse outcomes in nonpregnant surgical patients, including wound infection, coagulopathy, increased blood and transfusion requirements, increased oxygen consumption, decreased metabolism, and prolonged recovery.[447] In a systematic evaluation of randomized trials of normothermic and mildly hypothermic (34° C to 36° C) nonpregnant surgical patients, Rajagopalan et al.[448] observed that even hypothermia less than 1° C below normal body temperature was associated with a 16% increase in blood loss (95% CI, 4% to 26%) and a 22% increase in risk for transfusion (95% CI, 3% to 37%).

Normally, core body temperature is tightly regulated within a narrow range of 36° C to 37° C. During pregnancy, despite an increase in maternal basal metabolic rate and energy released by the developing fetal and uteroplacental unit, maternal core temperature decreases, reaching a nadir at 12 weeks postpartum (36.4° C).[449] Major causes of hypothermia during cesarean delivery are most likely related to core-to-periphery heat redistribution due to diminished vasoconstriction and shivering, particularly after neuraxial blockade, and impairment of centrally mediated thermoregulatory control.[447]

The onset and severity of hypothermia and shivering are associated with the patient's baseline thermal status, the perioperative environment, and the anesthetic technique and agents selected. Saito et al.[450] observed that spinal anesthesia reduced the initial core temperature of patients undergoing cesarean delivery more rapidly than epidural anesthesia, but the overall incidence of shivering was similar. However, the severity of shivering was significantly less in the spinal group, possibly through the induction of a lower shivering threshold or the inhibition of thermoregulatory control as a function of the number of blocked dermatomes.[451]

The effect of neuraxial opioids on thermoregulation and shivering in patients undergoing cesarean delivery is not fully understood. Intravenously administered meperidine 12.5 to 25 mg is one of the most effective antishivering drugs known and is unique among opioids in producing this effect at doses not typically associated with respiratory depression. The mechanism of this effect does not appear to be related to κ-opioid receptor activity or inhibition of cholinergic receptors; instead, central α_{2B}-adrenergic receptor stimulation may be involved.[452] The α_2-adrenergic receptor agonists clonidine (150 μg) and dexmedetomidine are effective antishivering agents that can lower the shivering threshold,[452] although both agents may have limited use during pregnancy because of the potential to cause sedation, bradycardia, and

hypotension. Other modalities have been used to prevent and treat hypothermia and shivering. Preoperative patient warming using forced air has been shown to reduce the incidence of perioperative and postoperative core hypothermia and shivering in patients undergoing cesarean delivery with *epidural* anesthesia.[453] In contrast, a subsequent study found that perioperative forced-air warming did not prevent maternal hypothermia after cesarean delivery with *spinal* anesthesia.[445] Lower limb wrapping has also been observed to have no effect on the incidence of hypothermia or shivering.[454]

OBSTETRIC COMPLICATIONS

Postpartum Hemorrhage

A leading cause of maternal and fetal morbidity and mortality worldwide, mild to moderate obstetric hemorrhage can be masked by pregnancy-related physiologic changes. Underestimation of blood loss and inadequacy of resuscitation remain common problems (see Chapter 38).

Failure of the uterus to contract (uterine atony) after delivery accounts for most cases of postpartum hemorrhage and remains a leading cause of postpartum hysterectomy and blood transfusion. Each minute, 600 to 700 mL of blood flows through the placental intervillous spaces; thus, obstetric hemorrhage can rapidly result in maternal shock. Uterine atony occurs more commonly after cesarean delivery than after vaginal delivery, perhaps as a reflection of the condition(s) that prompted the cesarean delivery or possibly because surgery disrupts the normal postpartum response to uterotonic hormones and pharmacologic agents. Risk factors for uterine atony include (1) high parity, (2) an overdistended uterus (multiple gestation, macrosomia, polyhydramnios), (3) prolonged labor (augmented by oxytocin), (4) chorioamnionitis, (5) abnormalities in placentation (placenta accreta, increta, or percreta), (6) retained placental tissue, and (7) poor perfusion of the uterine myometrium (e.g., with hypotension).

Initial efforts to control uterine atony include uterine massage and exogenous **oxytocin** administration. Postpartum oxytocin is administered in a wide range of doses, methods, and timing patterns (e.g., before or after delivery of the placenta),[455] although small doses of oxytocin are sufficient to produce adequate uterine contraction after cesarean delivery in most women.[455] The effective bolus dose necessary for adequate uterine tone in 90% (ED_{90}) of nonlaboring women undergoing cesarean delivery oxytocin is 0.35 unit[456]; in laboring women who have received approximately 10 hours of oxytocin augmentation, the ED_{90} is 2.99 units.[457] George et al.[458] estimated the ED_{90} of an oxytocin *infusion* to be 0.29 unit/min (95% CI, 0.15 to 0.43).

Women receiving oxytocin augmentation for labor have greater blood loss despite higher oxytocin doses; this appears to originate from signal attenuation and desensitization of the oxytocin receptors in a time- and concentration-dependent manner.[459-462] Continued high-dose oxytocin exposure in the postpartum period can lead to acute receptor desensitization and render the myometrium less responsive to additional oxytocin but not to other uterotonic agents.[462] Pregnancy causes a 180-fold increase in the concentration of oxytocin receptors with a significant proportion of this increase occurring just before the onset of labor[463]; this change in receptor number may have relevance to parturients who are delivering preterm infants.

Tsen and Balki[455] have suggested a "rule of 3's" (oxytocin 3 units, 3-minute evaluation intervals, 3 total doses, and oxytocin 3 units/h for maintenance) protocol for the administration of oxytocin after delivery. The oxytocin 3 units is given as a slow bolus or as an infusion (30 units oxytocin in 500 mL of normal saline [50 mL]), at a rate no faster than over a period of 15 seconds. Uterine tone is reassessed again at 3 and 6 minutes; if inadequate, an additional dose of oxytocin 3 units is given. If uterine atony persists after three total doses of oxytocin, other uterotonic agents should be employed (see later discussion). The specific timing of the initial dose of oxytocin varies by individual practitioner; insufficient data are available to determine whether oxytocin administration immediately on emergence of the infant's shoulder or body or after placental delivery makes a difference in overall blood loss during cesarean delivery. After the establishment of adequate uterine tone, an infusion of 3 units/h for up to 5 hours is recommended.[455]

The administration of oxytocin as a rapid intravenous bolus causes hypotension and may result in cardiovascular collapse[464,465]; patients with preeclampsia may have an unpredictable hemodynamic response to oxytocin administration (i.e., decrease in cardiac output).[466] Oxytocin has a direct relaxing effect on the vascular smooth muscle, which leads to decreased systemic vascular resistance, hypotension, and tachycardia.[467] Tachycardia also may result from a direct effect on specific oxytocic receptors in the myocardium and subsequently result in alterations in atrioventricular conduction and myocardial repolarization.[467] Chest pain and signs suggestive of myocardial ischemia and anaphylaxis may occur. Owing to the structural similarity of oxytocin to vasopressin, water intoxication may occur and, when severe, can lead to hyponatremia, confusion, convulsions, and coma.

If oxytocin proves ineffective, the ergot alkaloid derivative **methylergonovine** (0.2 mg) may be given intramuscularly to enhance uterine tone; onset time is within 10 minutes and the effect persists for 3 to 6 hours. Intravenous administration (in small divided doses) should be performed only *with great caution*, because intense vasoconstriction may lead to acute hypertension, seizures, cerebrovascular accident, retinal detachment, and myocardial arrest[468]; this possibility is of special concern in patients with preeclampsia or cardiac disease. Methylergonovine also has additive hemodynamic effects when given with sympathomimetic agents, such as ephedrine and phenylephrine. Nausea and vomiting are common side effects, which most likely reflect a direct central nervous system effect. The co-administration of oxytocin and ergometrine has been demonstrated to improve uterine contractions (as measured by the requirement for additional uterotonic agents) compared with the administration of oxytocin alone; however, the estimated blood loss was not different between groups, and nausea and

vomiting were more prevalent with the oxytocin-ergometrine combination.[469]

Uterine sensitivity to prostaglandins increases with advancing gestation. **15-Methyl prostaglandin $F_{2\alpha}$** causes a dose-dependent increase in the force and the frequency of uterine contractions. The initial recommended dose is 250 μg given intramuscularly; this dose can be repeated if necessary at 15- to 90-minute intervals up to a maximum of eight doses.[470] Whether 15-methylprostaglandin $F_{2\alpha}$ is more effective than oxytocin is controversial[471]; however, it clearly has a role in the treatment of refractory uterine atony.[472] In approximately 20% of women, the following side effects occur (listed in descending order of frequency): diarrhea, hypertension, vomiting, fever, flushing, and tachycardia.[472] Bronchospasm, pulmonary vasoconstriction, and oxyhemoglobin desaturation may also occur.

Rectal or sublingual administration of **prostaglandin E_1 (misoprostol)** is a uterotonic agent with a rapid onset of action. A systematic review of prophylactic misoprostol (given orally or sublingually in doses ranging from 400 to 800 μg) administered for the active management of the third stage of labor concluded that it is more effective than placebo in preventing severe postpartum hemorrhage but less effective than conventional injectable uterotonic agents.[473] Several large studies have assessed misoprostol's role in the treatment of postpartum hemorrhage. An editorial concluded that the drug was no more effective than oxytocin and was associated with more side effects.[474] These side effects include hyperthermia and severe shivering. There may be a prophylactic role for this drug in low-resource settings where oxytocin is not available.

Preparation for Blood Loss

When risk factors for hemorrhage are identified, several preparatory steps can be considered. **Iron supplementation** and use of **recombinant human erythropoietin** are effective therapies for producing red blood cells, particularly in patients with preexisting anemia, renal failure, and/or reasons for preoperative donation of autologous blood.[475] Antepartum erythropoietin administration may be of value in pregnant women at high risk for hemorrhage; however, additional investigation is needed to determine the optimal dosing, goals of therapy, and side-effect profiles. Hypertension, a problem associated with the use of erythropoietin in patients with renal failure, is a relevant concern during pregnancy. Although normal pregnancy is associated with a twofold to fourfold increase in maternal erythropoietin levels, isolated studies of the effect of erythropoietin on placental vessels suggest that dose-dependent vasoconstriction occurs.[476] Observation of high erythropoietin levels in hypertensive and preeclamptic parturients has fueled speculation that erythropoietin participates in the humoral mechanisms responsible for preeclampsia and fetal growth restriction (also known as intrauterine growth restriction).[477] A hyperglycosylated analogue of recombinant human erythropoietin (darbepoetin) has a threefold longer terminal half-life and results in a more rapid and greater erythropoietic response than recombinant human erythropoietin. This novel protein may be useful in the setting of anticipated or actual obstetric hemorrhage if concerns about its adverse effects are alleviated.[475]

The efficacy of preoperative **autologous blood donation** is limited by the maximum life span of stored blood; collection can start no sooner than 6 weeks before a planned delivery, with an average unit collection interval of 3 to 7 days. This method may be of some use in a woman with maternal antibodies to red blood cell antigens. The technique seems safe but has limited applicability and efficacy in obstetric patients (see Chapter 38).

Acute normovolemic hemodilution has the advantage of reducing the risk for administrative errors and bacterial contamination and allowing the infusion of whole blood replete with functional coagulation factors and platelets. This technique may reduce the need for transfusion in selected patients, and it may be acceptable to Jehovah's Witness patients at increased risk for blood loss during cesarean delivery.

The use of **intraoperative red blood cell salvage** in obstetric patients is gaining greater acceptance.[478] In the past, obstetric anesthesia providers have expressed concern that intraoperative cell salvage might precipitate amniotic fluid embolism. Allam et al.[478] noted that "existing cell salvage systems differ in their ability to clear contaminants and all require the addition of a leucocyte depletion filter." The cell salvage process does not remove all fetal red blood cells and hemoglobin, and maternal isoimmunization may occur.[479] Intraoperative cell salvage may be used to prevent morbidity and mortality in parturients who refuse homologous blood or in cases of intractable hemorrhage that may overwhelm blood bank supplies (see Chapter 38).[34]

Response to Blood Loss

Underestimation of blood loss and inadequate resuscitation are common problems in the management of obstetric hemorrhage. Rapid volume replacement is more important in maintaining tissue perfusion and oxygenation than the type of administered fluid. Colloids and blood products should be considered early, along with a request for assistance, establishment of a second large-bore intravenous catheter, and use of pressurized transfusion equipment. Many institutions require performance of a blood type and screen for parturients at high risk for hemorrhage undergoing a trial of labor for a planned vaginal delivery and in all parturients undergoing cesarean delivery. The immediate availability of two to four units of crossmatched packed red blood cells should be considered when the potential for significant blood loss appears imminent, such as in women suspected placenta accreta. In situations in which the need for emergency blood transfusion precedes the availability of crossmatched blood, type-specific (or type O, Rh-negative blood) should be administered. All institutions should consider the development of a massive transfusion protocol.[480] Continued blood loss and hemodynamic instability despite transfusion of packed red blood cells is often an indication for placement of an arterial line and invasive central venous pressure monitoring; however, restoration of circulating volume takes precedence. Urine output,

heart rate, blood pressure, and transthoracic or transesophageal echocardiography (TTE or TEE)[481] assessments can assist in the rapid evaluation of the adequacy of volume resuscitation.

Fortunately, most pregnant women are healthy and tolerate modest blood loss well. Also, concerns about uteroplacental perfusion and fetal oxygenation are no longer present after delivery of the infant. The ASA Task Force on Blood Component Therapy[482] has concluded that transfusion of packed red blood cells is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when the hemoglobin concentration is less than 6 g/dL. Transfusion of platelets is rarely indicated unless the platelet count is less than 100,000/mm^3 (unless platelet dysfunction and microvascular bleeding are present), and replacement of fibrinogen is rarely indicated unless the fibrinogen concentration is less than 150 mg/dL in the presence of microvascular bleeding. However, decreases in fibrinogen concentrations at levels higher than this threshold may serve as an early predictor of the severity of obstetric hemorrhage.[483]

The prophylactic placement of **intravascular balloon occlusion catheters** can facilitate the timely control of obstetric bleeding in some parturients at high risk for hemorrhage.[484] Harnett et al.[50] have recommended the placement of an epidural catheter prior to an intravascular balloon catheter for the following reasons: (1) once the balloon catheter is placed, flexion of the hips (during positioning for a neuraxial anesthetic technique) is discouraged, because it may result in balloon dislodgement or occlusion and subsequent thrombosis; (2) epidural anesthesia seems preferable to the use of local anesthesia with sedation for balloon catheter placement; (3) during balloon catheter placement, small amounts of heparin are sometimes used, and it seems preferable to have the epidural catheter in place prior to anticoagulation; and (4) should untoward events (e.g., fetal compromise, vessel rupture) occur during the procedure, the epidural catheter allows for rapid extension of anesthesia for cesarean delivery. With prior planning, operative procedures, including cesarean delivery, can be performed successfully under neuraxial anesthesia in the interventional radiology suite.[50]

When uterine bleeding occurs postpartum, the use of **uterine tamponade balloon catheters** has been demonstrated to tamponade and potentially treat intrauterine sources of bleeding and allow time to correct coagulopathy.[485] A number of balloon catheters have been used by practitioners for uterine tamponade (e.g., Sengstaken-Blakemore esophageal balloon, Foley urinary catheters). Commercial balloon catheters designed specifically for uterine tamponade are now available. Some of the catheter designs allow for uterine cavity drainage, with variable success in function and ability to identify ongoing, significant bleeding.[485] The balloons are often left in place for 24 to 48 hours, along with a vaginal pack and continued antibiotic administration. Distention of the uterus causes discomfort, and pain relief should be provided, either with systemic agents or epidural analgesia if a catheter is *in situ*. We typically provide continuous epidural analgesia, or patient-controlled epidural analgesia, with a dilute solution of local anesthetic and a lipid-soluble opioid, similar to that used for labor analgesia. The epidural catheter, regardless if used for analgesia, is typically kept in place until the uterine balloon is deflated to allow for rapid transition to surgical anesthesia if necessary.

The treatment of postpartum hemorrhage with **human recombinant factor VIIa** (rFVIIa), a vitamin K–dependent protein licensed for the treatment of bleeding episodes in patients who have hemophilia A or B with inhibitors to factor VIII or factor IX, remains controversial (see Chapter 38). Off-label administration of rFVIIa has resulted in cessation or reduction of severe bleeding refractory to standard hematologic or hemostatic support in a variety of animal and human trials and case reports or series.[486] Administration of rFVIIa promotes clotting primarily through the extrinsic (tissue factor) pathway with some activation of the intrinsic pathway and should be combined with best practice use of blood products (i.e., blood product component therapy). Administered as an intravenous dose of 60 to 100 μg/kg, rFVIIa has been observed to have a clinical effect within 10 minutes in some cases. The half-life of the drug is 2 to 6 hours, and side effects consist primarily of hypertension, hypotension, bradycardia, renal dysfunction, and thromboembolism.[486] Observational trials in the setting of traumatic injury are being performed, but to date there have been no large randomized studies of rFVIIa in obstetric patients.

Obstetric Hysterectomy

The incidence of cesarean hysterectomy and emergency postpartum hysterectomy ranges from 0.03% to 0.33% in different hospital settings and countries.[487] Over a 14-year period in the United States, the rate of peripartum hysterectomy per 100,000 deliveries increased from 71.6 (1994 to 1995) to 82.6 (2006 to 2007); this increased rate was associated with an increased rate of abnormal placentation (e.g., placenta previa, placenta accreta) from 32.9 to 40.5 and an increased rate of uterine atony from 11.2 to 25.9 per 100,000 deliveries.[488] Increasing rates of cesarean delivery, failed trial of labor, infection, intrauterine fetal death, and disseminated intravascular coagulation are other factors associated with cesarean hysterectomy. Improvements in ultrasonography, color flow Doppler ultrasonography, and magnetic resonance imaging have allowed earlier identification of some women with placenta accreta; however, limitations in diagnostic sensitivity and specificity exist.[489]

Cesarean hysterectomy is considered a high-risk procedure owing to the vascularity and size of the uterus and the distorted anatomic relationships. Bladder and ureteral injuries are common. Prior to performance of hysterectomy, various conservative medical and surgical treatment modalities may be attempted (see Chapter 38). The ligation or embolization of major and collateral uterine vessels with the assistance of an interventional radiologist is becoming more common, particularly in tertiary care settings.[484]

The amount of blood loss depends in part on whether the hysterectomy is elective or an emergency. In a

prospective review of all obstetric hysterectomies performed at five university hospitals (1984 to 1987), Chestnut et al.[490] found an average blood loss of 1319 mL and 2526 mL in 25 elective and 21 emergency cases, respectively, with an average replacement of 1.6 units and 6.6 units of blood, respectively. In a more recent study, Briery et al.[491] performed a multicenter retrospective review of operative and postoperative outcomes in 30 elective and 35 emergency cesarean hysterectomies; the mean (± SD) blood loss for elective and emergency cases was 1963 ± 1180 mL and 2597 ± 1369 mL, with 33% and 66% of the patients requiring blood transfusion, respectively.

The anesthesia provider should consult with the obstetric team to discuss risk factors and the planned course of management. Preparations for the management of potentially massive blood loss should be made, which may include the placement of an epidural catheter and prophylactic intravascular balloon catheters (see earlier discussion). An elective cesarean hysterectomy, or a cesarean delivery in which the patient is at high risk for emergency hysterectomy, is not a contraindication to a neuraxial anesthetic technique, although a catheter-based technique is recommended. Moreover, the occurrence of an emergency cesarean hysterectomy does not necessitate immediate conversion to general anesthesia. Consideration should be given to (1) maternal history (e.g., number of prior abdominal operative procedures, which may lead to more scarring and adhesions); (2) the presence of risk factors (e.g., extent of placentation abnormality, coagulation status); (3) the potential difficulty of conversion to general anesthesia if required (e.g., presence of difficult airway, level of assistance available); (4) the desires and experience of the obstetric team; and (5) the desires of the patient. Chestnut et al.[490] observed in their review that none of the 12 patients who received continuous epidural anesthesia for cesarean delivery (8 patients from the elective group and 4 from the emergency group) required intraoperative induction of general anesthesia for hysterectomy. In addition, there was no evidence that epidural anesthesia significantly affected blood loss, crystalloid replacement, or requirement for transfusion.

Given the morbidity and mortality associated with a peripartum hysterectomy, particularly if it is accompanied by significant blood loss, postoperative observation of the patient in a critical care setting should be considered. Wright et al.[492] used the Nationwide Inpatient Sample database to compare women who underwent a peripartum hysterectomy (n = 4,967) with women who had a nonobstetric hysterectomy (n = 578,179) from 1998 to 2007; women in the peripartum hysterectomy group were nine and five times more likely to have bladder and ureteral injuries, respectively, and they had greater rates of reoperation, postoperative hemorrhage, wound complications, and venous thromboembolism. Perioperative cardiovascular, pulmonary, gastrointestinal, renal, and infectious morbidities were also higher for women who had peripartum hysterectomy ($P < .001$ for all). In addition, women undergoing peripartum hysterectomy had a higher rate of blood transfusion (46% versus 4%), a longer hospital stay, and a higher rate of perioperative mortality.[492]

Thromboembolic Events

Thromboembolic events constitute a major reason for peripartum maternal mortality, and risks for the development of pregnancy-associated thrombosis include an operative delivery, physiologic changes of pregnancy, and medical history and comorbidities (e.g. obesity, hemoglobinopathies, hypertension, and smoking).[493] The risk for venous thromboembolism appears highest in the first postpartum week.[493] A number of prophylactic interventions have been evaluated; however, the trials have been small and unable to provide robust results.[494] Recommended thromboprophylaxis measures include hydration, early mobilization, pneumatic compression devices, and, in high-risk patients, pharmacologic prophylaxis (see Chapter 39).

KEY POINTS

- Cesarean delivery is the most common major surgical procedure performed in many developed countries. The rate of cesarean delivery is increasing worldwide.
- Some cesarean deliveries might be avoided through the provision of satisfactory neuraxial analgesia for labor (including a trial of labor after cesarean delivery), instrumental vaginal delivery, and external cephalic version.
- Gastric emptying is unchanged during pregnancy. The parturient without complications may drink modest amounts of clear liquids up to 2 hours before induction of anesthesia for *elective* cesarean delivery. The fasting period for solids should be 6 to 8 hours. Slower digestion is observed for foods with high fat content.
- An H_2-receptor antagonist or a proton-pump inhibitor may be given intravenously to increase gastric fluid pH, and intravenous metoclopramide may be given to both accelerate gastric emptying and increase lower esophageal sphincter tone. If possible, these agents should be administered *more than* 30 minutes before induction of anesthesia. Oral sodium citrate, which also increases gastric fluid pH, should be administered *less than* 30 minutes before induction.
- Antibiotic prophylaxis, administered within 60 minutes before abdominal incision, decreases the risk for maternal infectious complications after cesarean delivery.
- Although the use of intravenous fluids may reduce the frequency of maternal hypotension, initiation of neuraxial anesthesia should not be delayed to administer a fixed volume of fluid.
- The value of supplemental maternal oxygen during neuraxial anesthesia for the elective cesarean delivery of a noncompromised fetus is questionable.
- Left uterine displacement is essential during cesarean delivery, regardless of the anesthetic technique.

- The estimated case-fatality risk ratio for general versus neuraxial anesthesia has been as high as 16.7 in the years 1985 to 1990; however, in the latest analysis, covering the years 1991 to 2002, a nonsignificant risk ratio of 1.7 has been observed.
- Umbilical cord prolapse (without fetal bradycardia), placenta previa, and severe preeclampsia (in a patient with an acceptable platelet count) are not absolute indications for general anesthesia.
- Among women receiving general anesthesia for cesarean delivery, maternal deaths associated with hypoventilation or airway obstruction are occurring with greater frequency during emergence, tracheal extubation, or recovery, rather than during induction and tracheal intubation; attention to airway and ventilation management should focus on both of these critical time periods.
- The combined spinal-epidural technique offers the benefits of both spinal and epidural anesthesia while minimizing the disadvantages of either technique alone. Advantages include the fast onset of dense anesthesia with a small dose of local anesthetic and the ability to provide prolonged anesthesia and continuous postoperative analgesia.
- Alkalinization of the local anesthetic solution not only increases the speed of onset but also improves the quality and prolongs the duration of neuroblockade. Administration of 3% 2-chloroprocaine with 8.4% sodium bicarbonate (10 mL of 2-chloroprocaine mixed with 1 mL [1 mEq] of bicarbonate) produces the fastest onset of epidural anesthesia.
- The application of cricoid pressure to prevent passive regurgitation during induction of general anesthesia is controversial. If used, pressure should be initiated with a force of 10 newtons (N) on the cricoid cartilage and increased to 30 N once the patient loses consciousness.
- When choosing the concentration of a volatile halogenated agent to maintain general anesthesia, the anesthesia provider must consider the uterine relaxation caused by these agents as well as the reduced MAC (minimum alveolar concentration) of pregnancy and the potential for maternal awareness.
- Either phenylephrine or ephedrine may be used for the prevention and treatment of maternal hypotension during neuraxial or general anesthesia for cesarean delivery. Phenylephrine appears to exert less metabolic effect on the fetus and results in higher umbilical arterial blood pH at delivery compared with ephedrine.
- Underestimation of blood loss and inadequate intravascular volume resuscitation during peripartum hemorrhage are common occurrences that contribute to maternal morbidity and mortality.

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CHAPTER 27

Postoperative and Chronic Pain: Systemic and Regional Analgesic Techniques

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CHAPTER OUTLINE

MECHANISMS AND PREVALENCE OF PAIN

Pregnancy is associated with increased excitability of mechanosensitive afferent nerve fibers innervating the uterine cervix and lower uterine corpus. This change in sensitivity of the nerve fibers is likely due, at least in part, to elevated estrogen levels during pregnancy.[1,2] Whether skin and visceral nociception are transmitted by different nerve fiber subgroups or discharge patterns is controversial.[3] The uterine (visceral) afferent fibers stimulated by pressure and vasoconstriction primarily include C fibers and some A-delta fibers. By contrast, the majority of afferent fibers that relay nociceptive stimuli from the skin are A-delta fibers.

Postoperative pain results from **direct trauma** to tissue and subsequent **inflammation.** Local and systemic inflammatory cytokines act to sensitize the peripheral nerves and enhance pain perception.[4] Inflammation likely plays a significant role in pain after delivery because inflammatory cytokines are elevated as a part of the normal labor and delivery process.[5,6] Additionally, after cesarean delivery, cytokines are present in the wound; their concentration is positively correlated with analgesic drug consumption.[7]

Multimodal therapy has long been advocated for postoperative analgesia in nonobstetric patients, and it clearly provides benefit to obstetric patients. Local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentin, and epidural clonidine are efficacious adjuvants to opioid analgesia after cesarean delivery.[8-13]

Pain is less severe immediately after vaginal delivery than after cesarean delivery (Figure 27-1).[14] In one multicenter study, patients reported an average pain score of 3.3 of a possible 10 during the first 24 hours after vaginal delivery and an average score of 4.7 after cesarean delivery; however, there was significant variability in both groups. Forceps-assisted vaginal delivery was associated with more pain than spontaneous vaginal delivery, likely owing to local tissue damage from the forceps or factors related to the indication for forceps delivery. Mode of delivery was *not* associated with risk for persistent pain 8 weeks after delivery.[14]

Intrapartum and postpartum pain was previously considered a reality of life that was not discussed as a

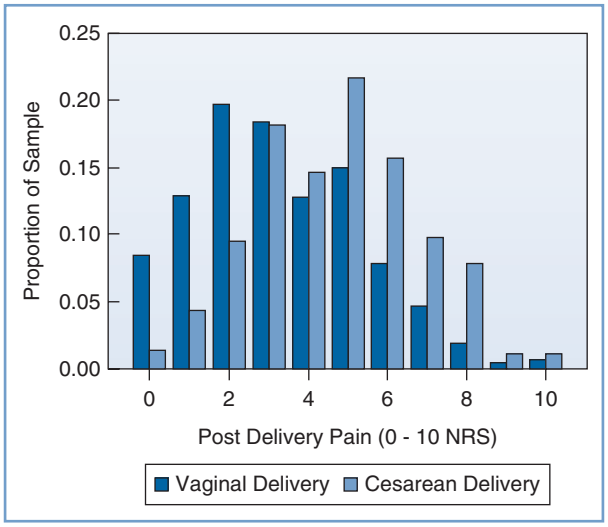

FIGURE 27-1 ■ Distribution of numerical rating scale (*NRS*) scores (0, no pain; 10, worst pain imaginable) of average pain for the first 24 hours after vaginal and cesarean delivery. (From Eisenach JC, Pan PH, Smiley R, et al. Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. Pain 2008; 140:87-94.)

complication of childbirth. The idea that acute pain during and immediately after delivery may have long-term consequences was not evaluated until the early 2000s, when investigators noted that severe pain after some types of surgery was associated with a high incidence of persistent chronic pain.[14,15]

Pain after Cesarean Delivery

In a prospective study, the prevalence of persistent pain 8 weeks after cesarean delivery was 9.2%; the risk for experiencing pain at 8 weeks was associated with the severity of acute postpartum pain.[14] In a retrospective survey, the incidence of persistent pain 1 year after delivery was 10% after vaginal delivery and 18% after cesarean delivery.[16] Another retrospective study reported a 6% incidence of daily or almost daily pain 6 to 18 months after cesarean delivery.[17] In these studies,[16,17] the incidence of persistent pain after cesarean delivery was comparable to that reported 4 months after a hysterectomy.[18] By contrast to the results of retrospective studies,[16,17] a prospective study observed that the incidence of persistent pain 1 year after either cesarean or vaginal delivery was less than 1%.[19]

Pain after Vaginal Delivery

In the absence of analgesia, almost all patients experience severe pain at some point during labor and vaginal delivery (see Chapter 20).[20,21] The severity of acute pain after vaginal delivery is highly variable.[14] Most patients experience some degree of cramping pain from uterine involution. Severe pain may result from episiotomy, perineal lacerations, and/or perineal hematoma. This pain is transmitted primarily via the pudendal and iliohypogastric nerves and the sacral and lumbar plexuses. Such pain should be treated aggressively because it significantly distracts from the activities of daily living for a new mother. First-line treatment of pain after vaginal delivery typically consists of NSAIDs, supplemented by opioids if necessary. In a prospective study, the prevalence of persistent pain 8 weeks after vaginal delivery was 10%.[14]

PREDICTORS OF PAIN

Intrinsic Patient Factors

The likelihood of developing chronic pain after childbirth may be influenced by multiple factors. There is evidence for heritability in labor pain. Studies of nonpregnant patients have shown that patients who carry a common polymorphism in the μ-opioid receptor gene (*OPRM1:* A118G [substitution of guanine for adenine at nucleotide position 118; Rs 1799971]) have an altered response to exogenous opioids.[22] Landau et al.[23] studied the ED_{50} (median effective dose) of intrathecal fentanyl for labor analgesia in women who were homozygous for the wild-type allele compared with women who carried the A118G polymorphism. Women who carried at least one copy of the G-allele had a lower ED_{50} and requested analgesia at a greater cervical dilation than women with two copies of the wild-type allele.[23] However, in another study, the duration of intrathecal fentanyl analgesia did not vary according to the *OPRM1* genotype.[24]

In contrast to the findings of Landau et al.,[23] in which women with the G-allele had a lower ED_{50} for intrathecal fentanyl for labor analgesia, Sia et al.[25] observed that women who carried the G-allele self-administered a higher dose of morphine to treat breakthrough pain after intrathecal morphine administration for postcesarean analgesia. The reasons for these seemingly disparate results have yet to be elucidated.[26]

Elevated concentrations of endorphins and enkephalins are found in the plasma and cerebrospinal fluid (CSF) of parturients, and opioid antagonists abolish pregnancy-induced analgesia to visceral stimulation in experimental animals (see Chapter 2). Given our current knowledge of the influence of genetic variability on response to exogenous opioids, it would not be surprising if some of the variability in labor pain and acute postpartum pain is a result of differing responses to endogenous and exogenous opioids. Other genes may also play a role. β_2-Adrenergic receptor polymorphisms have been associated with preterm labor[27] and labor progress.[28,29] Slower development of pain during labor may be associated with slower labor progress.[28]

Long-standing psychological factors and mental preparation for labor influence labor pain or its expression during labor. Catastrophizing (i.e., the unfounded belief that something will be worse than it is) has been associated with labor pain and request for treatment.[30,31] There is evidence that even the way that the practitioner asks about pain influences the response. When the negative word "pain" was used in a postcesarean visit, 54% of women reported pain. By comparison, when patients were asked, "Are you comfortable," only 28% reported pain directly or indirectly ($P < .001$).[32] Preexisting

depression and anxiety impact the outcome after surgery; affected patients report more severe pain and are at increased risk for analgesic drug abuse.[33]

Women who abuse illegal drugs are at increased risk for adverse pregnancy outcomes.[34] These patients have particularly high risk for inadequate treatment of intrapartum and postpartum pain. Although a large proportion of pregnant women who abuse drugs deny doing so,[35] it is important to identify these patients antenatally to devise an analgesia plan. Buprenorphine and methadone are the most common drugs used for treatment of opioid addiction during pregnancy. Both drugs are effective and are not associated with respiratory depression in the neonate, although these infants usually require treatment of opioid withdrawal.[36] Women who use opioids, cocaine, and/or amphetamines during pregnancy require more analgesia during labor than nonusers.[37] Patients on opioid maintenance programs should receive their normal maintenance dose of opioid and should receive additional medication to treat postpartum pain. A multimodal analgesia strategy that includes NSAIDs is beneficial in this setting.

Women with preexisting chronic pain syndromes may have significant anxiety regarding childbirth pain. Anxiety itself is a predictor of labor pain.[38] Patients with chronic pain syndromes who are treated with chronic opioid therapy are likely to develop opioid tolerance similar to patients who use opioids recreationally. Thus, patients with chronic pain syndromes should be maintained on their therapeutic regimen throughout the course of labor, delivery, and recovery; additional medication will likely be necessary to treat postpartum pain.

Environmental Factors

Sleep deprivation accentuates responses to noxious stimuli. Research subjects who sleep less than 6.5 hours per day have greater areas of secondary hyperalgesia in response to a heat test after capsaicin treatment. Additionally, those deprived of sleep have a lower threshold for pressure pain.[39] Sleep deprivation accentuates pain, and pain interrupts sleep. This association creates a vicious cycle that commonly accentuates pain after cesarean delivery. Prolonged labor may precede cesarean delivery. Afterward, care of the newborn requires frequent interruptions in sleep. It is important to facilitate sleep as a therapeutic intervention as much as possible by decreasing environmental stimuli and reducing light during the evening.

Stress is also an important factor that can worsen postoperative pain and can facilitate conversion to chronic pain. Antepartum stressors induced by fear of surgery, parenting, or other changes that are associated with childbirth and cesarean delivery may accentuate postoperative pain. In patients undergoing back surgery, preoperative report of worry or intrusive memories was associated with chronic preoperative pain, failed back syndrome, and chronic postoperative pain.[40] Further, biochemical evidence of preoperative stress, as measured by abnormal reactivity of the hypothalamic-pituitary-adrenal axis, was also associated with chronic pain after surgery.[40] Evidence specific to obstetric surgery is limited, but there is no reason to expect that the common stressors that accompany a significant life change such as childbirth, as well as specific individual stressors, would not have a similar impact on postcesarean pain and conversion to chronic pain.

In summary, the presence of intrinsic and extrinsic factors predicts severe acute pain after cesarean delivery. Similarly, conversion to chronic pain is associated with the presence of these factors and the presence of severe acute postoperative pain. Patients may have an intrinsic tendency toward severe pain in response to injury. This tendency may be inherited as a genetic or epigenetic phenomenon, or it may be acquired through life experiences. Assessment of these predictive factors with validated scales may identify a subset of women for whom aggressive multimodal treatment of acute postoperative pain may prevent conversion of acute to chronic pain.[41]

Depression, anxiety, sleep deprivation, and disability are also predictable *consequences* of severe pain, thus creating a positive reinforcing cycle. Interruption of this cycle by predicting and treating severe postcesarean pain may help prevent the development of chronic pain. In addition, identification and treatment of coexisting psychological distress and sleep disorders may help prevent conversion of acute pain to chronic pain.

In 2001, The Joint Commission announced new pain management standards.[42] These standards recognize the right of patients to receive appropriate assessment and management of pain. The standards require accredited organizations to screen patients for pain during the initial assessment, to reassess pain periodically, and to educate patients about pain management options. Fulfillment of these requirements in the obstetric setting is challenging because pain is expected during childbirth. Nonetheless, the mandate for pain assessment is not controversial. As occurs with all other types of surgery, obstetric patients should be assessed for postpartum pain at regular intervals and offered treatment. Multimodal pharmacologic and nonpharmacologic treatment for pain is the optimal approach and should be offered whenever feasible and medically indicated.

SYSTEMIC OPIOID ANALGESIA

Neuraxial opioid administration currently represents the "gold standard" for providing effective postcesarean analgesia. Intrathecal and epidural opioid administration provide analgesia that is superior to intramuscular opioid and intravenous opioid patient-controlled analgesia (PCA) after cesarean delivery (see Chapter 28, Figure 28-1).[43-45] A 2010 systematic review found that a single bolus dose of epidural morphine provides better analgesia than parenteral opioids after cesarean delivery.[46] In the United States, most women who undergo cesarean delivery with neuraxial anesthesia receive neuraxial opioids for postcesarean analgesia. Multimodal analgesic strategies are used to augment the analgesic effect of neuraxial opioids in this setting. Some women may have breakthrough pain using this analgesia strategy and may require augmentation with systemic opioids.

TABLE 27-1 **Management of Opioid Side Effects***

Adverse Effect(s)	Management Considerations
Allergic reaction	True immunoglobulin E–mediated allergic reactions are rare.
	Anaphylactoid-type signs and symptoms (e.g., hypotension, bronchoconstriction) are usually secondary to mast cell activation and subsequent histamine release.
	Selection of another opioid class is usually necessary only in the event of a documented true allergic reaction (e.g., rash, hives, difficulty breathing).
Confusion, delirium, hallucinations	Reduce dose, use a different opioid, and/or give neuroleptic therapy (e.g., haloperidol) or olanzapine.
Constipation	Consider prophylaxis when opioid therapy is initiated.
	Include a mild stimulant laxative (senna) ± stool softener (docusate salts at night or twice daily) as prophylaxis
	Consider adding lactulose or MiraLax when necessary.
	In patients allowed no oral intake, consider intravenous metoclopramide.
Myoclonic jerking	Reduce dose, use a different opioid, and/or treat with clonazepam or baclofen.
Nausea/vomiting	Tolerance may develop.
	It may be helpful to administer one antiemetic on a fixed schedule for a few days in patients with a prior history of opioid-associated nausea and vomiting. Otherwise, the following treatment can be given on an as-needed basis: metoclopramide, ondansetron, prochlorperazine, promethazine, or a scopolamine patch.
Pruritus	Pruritus in the absence of rash is a central μ-opioid receptor–related phenomenon (not related to histamine). It is best treated with nalbuphine intravenously as needed and not with an antihistamine.
	For refractory pruritus, consider changing opioids.
Respiratory depression	Withhold opioid, use tactile and verbal stimulation, and implement supportive measures.
	Assist ventilation with bag-valve mask and supplemental oxygen if patient cannot be aroused.
	Give dilute naloxone (0.4 mg in 9 mL normal saline, 40 μg/mL) in 1- to 2-mL increments at 2- to 3-minute intervals until a response is observed.
	Naloxone's half-life is shorter than that of most of the opioid agonists, and respiratory depression may recur. Be alert for the need to readminister a bolus dose of naloxone, or consider use of a naloxone infusion.
Sedation	Tolerance typically develops. First withhold sedatives and anxiolytics; then consider withholding the opioid or reduce the dose. If sedation is persistent, consider a central nervous system stimulant such as caffeine, methylphenidate, or dextroamphetamine.

*Nonopioid analgesic options should be considered to limit opioid-related side effects. All adverse events should be carefully evaluated to rule out other potential causes.

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Some women are not candidates for postoperative neuraxial analgesia; for example, they may have a contraindication to a neuraxial procedure and therefore receive general anesthesia for their cesarean delivery. These women require multimodal analgesia that usually includes systemic opioid administration.

Although pain after vaginal delivery is usually less severe than pain after cesarean delivery, its severity is highly variable. A large episiotomy with a third- or fourth-degree perineal laceration may warrant administration of a single dose of a neuraxial opioid for postpartum analgesia.[47]

The analgesic effect of opioids can vary significantly among patients; one study observed a fivefold difference in the maximum blood drug concentration still associated with pain (MCP).[48] The MCP decreases over time after a surgical procedure. The goal of opioid administration is to achieve a minimum effective analgesic concentration (MEAC) with minimal side effects.[49] Because both the MEAC and the MCP vary greatly among patients, an **individualized approach** to pain control is required. There are no maximum allowable doses for specific opioids; the primary limiting factor is the occurrence of side effects (Table 27-1).

Patients with hepatic or renal dysfunction (which may occur with severe preeclampsia), morbid obesity, and/or obstructive sleep apnea are particularly susceptible to the respiratory depressant effects of opioids. Patients who have never received opioids may be especially prone to the occurrence of side effects. It is important to monitor the respiratory rate and sedation level before giving an additional dose or adjusting the bolus dose that the patient can self-administer. After adjusting the dose, the clinician must document the respiratory rate and pattern, sedation level, and analgesic response. The use of a multimodal analgesic approach helps provide adequate analgesia while limiting opioid-related side effects (see later discussion).

Intravenous Patient-Controlled Analgesia

In the past, opioids were commonly administered intramuscularly or subcutaneously; these simple routes of administration do not require the postoperative return of

TABLE 27-2 **Opioid Characteristics**

Agonist	Route	Onset (min)	Peak Effect (min)	Duration of Effect (h)
Morphine	IV	5-10	10-30	3-5
	Oral	15-60	90-120	4
Codeine	IM	10-30	90-120	4-6
	Oral	30-45	60	3-4
Hydromorphone	IV	5-20	15-30	3-4
	Oral	15-30	90-120	4-6
Oxycodone	Oral	15-30	30-60	4-6
Methadone	IV	10-20	60-120	4-6
	Oral	30-60	90-120	4-12
Fentanyl	IV	< 1	5-7	0.75-2+
Oxymorphone	IV	5-10	30-60	3-6
	Oral	60 (meaningful relief)	—	4-6

IM, intramuscular; *IV,* intravenous.
Courtesy of the Dana Farber Cancer Institute Pain and Palliative Care Program and the Brigham and Women's Hospital Pain Committee. Modified with permission from Bridget C. Fowler, PharmD, Clinical Pharmacy Manager, Dana Farber Cancer Institute.

bowel activity or the use of sophisticated equipment. Intramuscular and subcutaneous medications are inexpensive, easy to administer, and associated with a long history of safety. Disadvantages of this approach include the need for repeated painful injections, a delayed (and sometimes erratic) absorption of drug, and an inconsistent analgesic response due to variations in plasma opioid concentrations.

A number of studies have compared intravenous opioid PCA to traditional nurse-administered parenteral analgesia. A 2006 meta-analysis concluded that intravenous PCA provided better postoperative analgesia and greater patient satisfaction than conventional nurse-administered opioid analgesia.[50] Although the use of intravenous PCA was associated with greater opioid use and a higher incidence of pruritus, the incidence of other side effects was not different between groups.[50] The American Society of Anesthesiologists (ASA) Task Force for Acute Pain Management in the Perioperative Setting[51] recommends that "these modalities [epidural or intrathecal opioids, systemic opioid PCA, and peripheral regional techniques] should be used in preference to intramuscular opioids ordered 'as needed.'"

PCA has been used with intravenous and epidural routes of administration after cesarean delivery. In a study of intravenous versus epidural **meperidine** PCA, higher pain scores with rest and movement, greater sedation, and lower patient satisfaction were observed with the intravenous route of administration.[52] Moreover, plasma meperidine and normeperidine concentrations were almost double with the intravenous route.[52] Similarly, another study that compared intravenous versus epidural **fentanyl** PCA after cesarean delivery reported higher pain scores and greater fentanyl consumption with the intravenous route, although patient satisfaction ratings were similar in the two groups.[53] Another study compared intravenous versus epidural **hydromorphone** PCA after cesarean delivery.[54] Hydromorphone requirements were threefold to fourfold higher in the intravenous group. The two groups had similar pain and sedation scores, but patients in the intravenous group reported more frequent drowsiness and less pruritus.[54]

Several studies have compared intravenous morphine PCA to *single-shot* epidural morphine for postcesarean analgesia.[45,55,56] Although the incidence of pruritus was higher with epidural morphine than with intravenous morphine PCA, analgesia and patient satisfaction were better with epidural morphine.[45,55,56] The incidence of nausea was not different between groups[45,55,56]; sedation was greater in the intravenous PCA group.[45]

Choice of Opioid

Overall, factors that affect the choice of opioid are speed of onset, duration of action, overall efficacy, and the type and frequency of side effects (Table 27-2). If side effects prevent adequate analgesia, other opioids or nonopioid adjuvants should be used. Patient preferences based on past experiences and desired analgesia should also be considered.

Historically, **meperidine** has been a popular opioid for postoperative analgesia. It is the least potent of the opioids used clinically, and it has a long-acting active metabolite, normeperidine, that is excitotoxic to the central nervous system. In the past two decades a concerted effort has been made to decrease the use of meperidine for postoperative analgesia.[57] In 1999, the American Pain Society stated that "meperidine should not be used for more than 48 hours for acute pain…[it] should be reserved for brief courses in otherwise healthy patients who have demonstrated an unusual reaction or allergic response to other opioids."[58] The American College of Obstetricians and Gynecologists (ACOG)[59] has discouraged the use of meperidine because of the accumulation of normeperidine in the neonate and its subsequent effect on neurobehavioral scores.

TABLE 27-3 **General PCA Dosing in Opioid-Naive Patients**

Drug	Morphine	Hydromorphone	Fentanyl
Concentration	5 mg/mL	1 mg/mL	10 μg/mL
PCA Bolus Dose	1-1.5 mg	0.2 mg	20 μg
Lockout Interval (min)	7	7	7
4-Hour Dose Limit	Calculated by settings	Calculated by settings	Calculated by settings
Typical PCA Dose Change	0.5 mg	0.1 mg	5 μg
Rescue Doses	2 mg IV q 5 min (up to 3 doses)	0.3 mg IV q 5 min (up to 3 doses)	25 μg IV q 5 min (up to 3 doses)
Remarks	Relatively contraindicated in patients with impaired renal function	More potent than morphine	Shorter clinical effect than morphine

Recorded as: PCA bolus dose/lockout interval/4-hour limit/continuous infusion rate. A continuous background infusion is typically avoided except in selected cases (e.g., opioid tolerance).
IV, intravenous; *PCA,* patient-controlled analgesia.
Courtesy of the Dana Farber Cancer Institute Pain and Palliative Care Program and the Brigham and Women's Hospital Pain Committee. Modified with permission from Bridget C. Fowler, PharmD, Clinical Pharmacy Manager, Dana Farber Cancer Institute.

Safety

Health professionals who use PCA should (1) be able to evaluate candidates for PCA (e.g., mental state, level of consciousness, patient understanding); (2) know drug selection criteria, dosing schedules, lockout periods, and infusion devices; (3) be able to provide patient education on pain management and the use of PCA; (4) understand when to alter PCA settings and when to give or withhold additional (rescue) doses of medications; and (5) be able to respond to side effects and adverse events.

In December 2004, The Joint Commission[60] issued a Sentinel Event Alert on PCA "by proxy" (i.e., when other individuals, including family members, become involved in drug administration). The Joint Commission acknowledged that PCA is a safe and effective method of controlling pain when used as prescribed; however, serious adverse events, including oversedation, respiratory depression, and death, can result when analgesia is delivered "by proxy." The Joint Commission[60] made the following recommendations: (1) develop criteria for selecting appropriate candidates for PCA, (2) carefully monitor patients, (3) teach patients and family members about the proper use of PCA and the dangers of others' pressing the button for the patient, (4) alert staff to the dangers of administering a dose outside a prescribed protocol, and (5) consider placing warning tags on all PCA delivery pendants stating, "Only the patient should press this button."

When intravenous PCA is used for postoperative analgesia, guidelines for safe administration should be employed and documented. At many institutions two registered nurses must verify all pump settings when they are entered or changed and during communications associated with all patient transfers or nurse shift changes. The amount of opioid administered is recorded from the pump every 2 hours and when a drug cartridge is changed. The PCA settings (drug, demand dose, lockout interval, 4-hour limit, and the rate of continuous infusion, if used) are documented on a flow sheet. Any changes in PCA settings are clearly documented. In our institution, the use of a continuous background infusion is discouraged except in patients who were taking opioids preoperatively or in patients in whom nonstandard dosing requirements have already been demonstrated.

Infusion Pump Settings

A number of PCA parameters must be considered, including drug choice, incremental dose, maximum dose, and lockout interval (Table 27-3). Owen et al.[48,61-63] performed a number of investigations of PCA in patients undergoing abdominal surgery. In an assessment of PCA morphine demand bolus doses (0.5, 1, or 2 mg with a 5-minute lockout interval), more patients in the 0.5-mg group had inadequate pain relief, whereas those in the 2-mg group had more side effects, including respiratory depression (i.e., respiratory rate < 10 breaths/min).[62] These results correlated with the total dose of self-administered morphine. Although the role of the lockout interval was not addressed in this study, the investigators suggested that inadequate analgesia could be produced by lockout intervals that were too long or demand doses that were too small. By contrast, larger doses or shorter lockout intervals might lead to more opioid-related side effects. Therefore, longer lockout intervals typically require larger bolus doses, whereas smaller bolus doses typically require shorter lockout intervals.

Although patients who experience inadequate analgesia would be expected to make more PCA demands, this is often not the case.[62] Patients may be afraid to administer too much opioid or anticipate more severe side effects. Additionally, it has been suggested that patients are discouraged by an inadequate analgesic effect or they may expect a delayed response.[62] For this reason, a hydrophilic opioid (e.g., morphine) with a longer latency may be preferred over a lipophilic opioid (e.g., fentanyl).

The amount of opioid delivered in a **continuous basal (background) infusion** may or may not alter the analgesic efficacy of patient-controlled bolus doses. One study compared PCA bolus doses of morphine (0.4, 0.7, or 1.0 mg) combined with a continuous infusion of morphine at 1.5 mg/h after gynecologic surgery.[61] The number of demand bolus doses and the quality of

analgesia did not vary among groups despite the overall higher use of morphine in the group that received the largest bolus dose. In addition, there were no differences among groups in patient satisfaction or side effects. In an earlier study, Owen et al.[63] observed that the *patient-administered* morphine dose did not differ in patients randomized to receive patient-administered bolus morphine compared with patient-administered bolus morphine with a continuous basal infusion (morphine 1.5 mg/h). Moreover, the quality of analgesia was similar in the two groups despite a twofold higher *total dose* of morphine in the group receiving a continuous infusion.

Controversy exists regarding the use of a continuous basal infusion during administration of intravenous opioid PCA. Studies of patients undergoing gynecologic surgery do not support the use of a continuous background infusion to provide better postoperative analgesia. Parker et al.[64] evaluated 230 women who had undergone an abdominal hysterectomy; one group received a demand bolus dose of morphine (1 to 2 mg) without a continuous infusion, and the other three groups received a continuous infusion of morphine (0.5, 1, or 2 mg/h) in addition to the demand bolus dose. No differences in the number of demand or delivered doses per hour, pain scores, or overall morphine consumption were observed, except that an overall higher dose of morphine was administered in the 2 mg/h continuous infusion group than in the demand bolus–only group. A subsequent study by the same investigators in a similar patient population compared a group receiving an intravenous PCA morphine (2 mg demand bolus dose) regimen with a group receiving the same intravenous PCA regimen and a nighttime continuous infusion of morphine (1 mg/h).[65] There were no differences between groups in postoperative pain, sleep patterns, demand or delivered bolus doses per hour, opioid consumption, or recovery from surgery. The investigators reported that the use of a continuous infusion resulted in six errors during the programming of the device and that three patients required discontinuation of the continuous infusion because of significant oxyhemoglobin desaturation.[65]

Thus, a continuous basal infusion is often avoided in opioid-naive patients because of concern about the risks of oversedation and respiratory depression. The ASA Task Force on Acute Pain Management[51] concluded that intravenous PCA with a continuous background infusion of morphine results in use of a larger total dose of analgesic drug than intravenous PCA without a background infusion; the findings were equivocal regarding comparisons of quality of analgesia and the incidence of nausea, vomiting, pruritus, and sedation.[51] The Task Force concluded that special caution should be taken when a continuous infusion is used, owing to the potential for adverse effects from opioid accumulation.[51] The American Pain Society has also urged caution in the use of a continuous basal infusion in opioid-naive patients receiving intravenous opioid PCA.[66]

With the use of PCA, the ratio of patient demands to bolus doses delivered appears to be a good measure of analgesia and is strongly correlated with pain scores.[67] A high ratio is likely to reflect patient misunderstanding or inadequate analgesia, but a ratio close to 1 signifies adequate pain relief. Patients use PCA bolus demands for different reasons, including worsening pain at rest, pain with movement or coughing, and anticipation of an activity that is likely to produce pain.[61] Inadequate analgesia most likely can be improved by an increase in the demand bolus dose, a shorter lockout interval, or a change of opioid. Patients also should be encouraged to use demand bolus doses before movement or activity.

A commonly neglected but important guideline is the achievement of adequate analgesia and the initiation of intravenous PCA *before* the patient is discharged from the postanesthesia care unit (PACU). Although there is significant variation in individual perception of pain and response to analgesia, the assessment of pain scores can facilitate evaluation of the adequacy of analgesia. In a study of postoperative patients after general anesthesia (the surgical procedures were not disclosed), Aubrun et al.[68] demonstrated that the relationship between visual analog pain scores (VAPS, 0 to 100 scale) and morphine requirements was represented by a sigmoid curve; they observed one plateau below a score of 40 and another plateau above a score of 80. Although patients with a VAPS of 70 or higher were considered to have severe pain and required a larger total dose of morphine to obtain a VAPS lower than 50, a smaller total dose of morphine was required to reduce a VAPS of 50 to a score of 30 or less.[68] This study suggests that pain scores are slow to change when severe pain exists but that the scores decline rapidly once pain begins to improve. Other investigators have identified relevant VAPS thresholds associated with changes in intravenous PCA dose requirements after intra-abdominal surgery as 30 or less, 31 to 70, and more than 70.[69] Only 4% of patients with a VAPS of 30 or less requested an increase in analgesic dose, whereas 80% of patients with a VAPS higher than 70 requested a higher dose. Among patients with a VAPS between 31 and 70, those whose scores improved at least 10 points were less likely to request additional analgesia than those with little change or an increase in VAPS.[69] Thus, a patient's perception of pain improvement may depend, in part, on her initial pain score.

Severe pain most likely antagonizes the sedative and respiratory depressant side effects of opioids, a possibility that becomes increasingly important in patients requesting higher doses of opioids. Therefore, a transition from an opioid-only to a multimodal, balanced analgesia approach should be employed to optimize pain control and minimize opioid-related side effects. The morbidity associated with high doses of opioids should invoke the application of algorithms for pain assessment, management, and monitoring. At many institutions, postcesarean patients are assessed every 4 hours for respiratory rate and quality, oxygen saturation, pain score, and sedation level. Patients are asked whether their level of pain relief is acceptable; and if not, an adjustment of analgesic dose is performed and documented. The pain score is reassessed within 15 to 30 minutes before additional interventions are made. High-risk patients, including those with hepatic or renal dysfunction, obstructive sleep apnea, and/or morbid obesity, are assessed every 2 hours for 12 hours after initiation of intravenous PCA therapy and then every 4 hours if the respiratory rate is 8 breaths/

TABLE 27-4 Opioid Equi-analgesic Doses

Drug	Oral (mg)	Subcutaneous/ Intravenous (mg)
Morphine	30	10
Oxycodone	20	NA
Hydrocodone	20	NA
Hydromorphone	7.5	1.5
Fentanyl	NA A 25-μg/h transdermal patch is equi-analgesic to ≈50 mg of oral morphine per day	0.1 (100 μg)
Oxymorphone	10	1

NA, not applicable.

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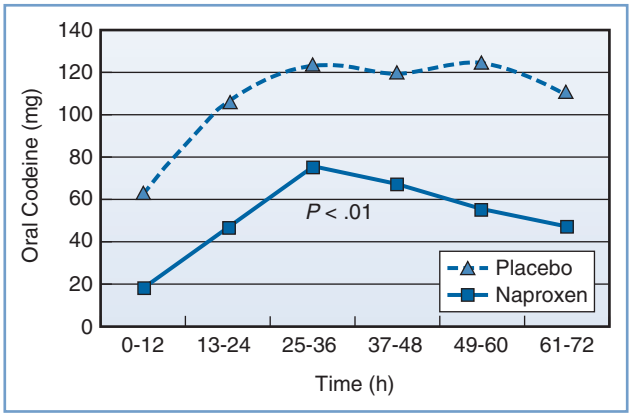

FIGURE 27-2 ■ **Effect of naproxen on requirement for oral codeine after cesarean delivery: oral codeine use in milligram equivalents (expressed as mean) over time by group.** (From Angle PJ, Halpern SH, Leighton BL, et al. A randomized controlled trial examining the effect of naproxen on analgesia during the second day after cesarean delivery. Anesth Analg 2002; 95:741-5.)

minute or higher, oxygenation is stable, and sedation level is minimal. Patients are assessed every 30 minutes for the first hour after the intravenous PCA dose is increased; thereafter, if pain relief is adequate and the clinical condition is unchanged, patients are assessed every 4 hours as previously described.

Acute postoperative pain is limited in duration, so a plan should be devised for the transition from intravenous opioids to oral agents when the patient's pain is controlled and she is able to take medication by mouth. Table 27-4 lists the equi-analgesic doses for commonly used opioids.

Oral Opioid Analgesia

Some investigators have advocated the use of **oral analgesics** rather than intravenous PCA for postcesarean pain.[70-73] Advantages of this approach are cost-effectiveness, facilitation of early mobility by discontinuation of the intravenous catheter and other equipment, and, perhaps, greater patient satisfaction.

In a randomized controlled comparison of oral oxycodone-acetaminophen and intravenous morphine PCA, patients randomized to the oral regimen experienced less pain, nausea, and drowsiness at 6 hours after cesarean delivery.[73]

MULTIMODAL ANALGESIA

Multimodal analgesia, also known as "balanced analgesia," has been used effectively in treatment of cancer and chronic pain for many decades. The rationale behind its use is the optimization of additive and/or synergistic analgesic effects of different modes of analgesia or drug classes, while reducing doses and minimizing the side effects of each drug.[74] A primary goal of multimodal analgesia is to provide adequate analgesia with minimum maternal side effects. Important secondary goals include minimizing transfer of drugs to breast milk and reducing maternal side effects that may interfere with breastfeeding or caring for the neonate. Various combinations of opioids, NSAIDs, acetaminophen, and local anesthetics, among other drugs, have been used with varying degrees of success.[75] Several analgesic regimens have been shown to reduce opioid use and opioid-induced side effects when used to treat postcesarean pain.

Nonsteroidal Anti-inflammatory Drugs

All NSAIDs have opioid-sparing activity. **Ibuprofen** is one of the most widely recognized NSAIDs that is available without prescription. It nonselectively inhibits cyclooxygenase-1 and cyclooxygenase-2 (COX) enzymes. As such, in addition to its anti-inflammatory, analgesic, and antipyretic properties, ibuprofen inhibits platelet adhesion and causes renal artery vasoconstriction and gastrointestinal irritation; therefore, its use in patients at risk for hemorrhage and renal failure warrants caution. Nonetheless, in most parturients without risk factors for hemorrhage or renal failure, its use is safe. There is limited transfer of drug to breast milk, making it particularly beneficial for lactating mothers. In a small study (oral ibuprofen 400 mg every 6 hours for 24 hours), less than 1 mg of ibuprofen was excreted in breast milk in a 36-hour period.[76] Many centers administer 600 to 800 mg every 8 hours as a standard dose. In a study comparing oral **naproxen** 500 mg every 12 hours to placebo after elective cesarean delivery,[77] the authors found a considerable reduction in incision pain with sitting (mean ± SD VAPS of 38 ± 26 and 51 ± 26 in the treatment and placebo groups, respectively) that was accompanied by a decrease in opioid consumption (Figure 27-2). Similar to other analgesics, fixed-interval dosing of NSAIDs provides more effective analgesia and results in better patient satisfaction than on-demand dosing.[78]

Diclofenac has also been extensively studied and found to be effective for postcesarean analgesia. Diclofenac rectal suppositories (100 mg twice a day) decreased morphine consumption (14 mg versus 22 mg in 32 hours) compared with placebo in patients who had undergone cesarean delivery.[79] A single dose of diclofenac rectal suppository 100 mg prolonged the mean time to first analgesic administration by more than 5 hours in patients who received intrathecal morphine for postcesarean analgesia.[80] Patients who received intrathecal morphine doses as small as 25 μg (0.025 mg) required no rescue analgesic when intramuscular diclofenac 75 mg was administered every 8 hours.[81]

Parenteral **ketorolac** is another NSAID that is useful in the treatment of postpartum pain. In a randomized, controlled study, Lowder et al.[82] provided evidence that ketorolac decreased pain scores at 2, 3, 4, 6, 12, and 24 hours after cesarean delivery and also significantly decreased opioid consumption. Unlike other NSAIDs, the U.S. Food and Drug Administration (FDA) has a mandated black box warning that states that ketorolac is "contraindicated in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates."[83] This warning was mandated in spite of a study showing minimal to undetectable ketorolac levels in breast milk.[84] The American Academy of Pediatrics (AAP) considers ketorolac safe for nursing mothers.[85]

Selective Cyclooxygenase-2 Inhibitors

COX-2 specific inhibitors have a potential benefit compared with traditional nonselective NSAIDS in that they have minimal effects on platelet adhesion and thus are less likely to interfere with blood clot formation and contribute to hemorrhage. However, concerns about the potential to increase the risk for cardiovascular and thrombotic events, combined with the baseline elevated risk for these events during pregnancy and postpartum, have prevented COX-2 inhibitors from playing a major role in postpartum analgesia. **Celecoxib** is the only widely available COX-2 selective inhibitor in the United States. The breast milk content of valdecoxib and its pro-drug precursor parecoxib was studied after a single 40-mg intravenous dose of parecoxib following cesarean delivery. The breast milk concentration was very low, and neonatal neurologic and adaptive scores were normal.[86]

Acetaminophen

Despite widespread popularity, few published data support the use of acetaminophen (paracetamol) for postcesarean analgesia. A 2012 meta-analysis identified four randomized controlled trials evaluating acetaminophen and its effect on opioid consumption after major surgery; only one study included obstetric patients.[87] The meta-analysis revealed that acetaminophen was less effective than NSAIDs in decreasing opioid consumption and postoperative nausea and vomiting.[87] A comparison of intravenous acetaminophen with oral ibuprofen in postcesarean patients failed to show an advantage in pain scores, opioid consumption, or patient satisfaction.[88] The combination of NSAIDs and acetaminophen is synergistic in human experimental pain studies.[89]

Intravenous acetaminophen has gained popularity owing to reports of slower absorption of oral acetaminophen in patients treated with morphine[90] and higher peak plasma and CSF levels of acetaminophen after intravenous administration.[91] However, in patients with a functioning gastrointestinal system, there is no documented analgesic advantage in using intravenous rather than oral administration.

α_2-Adrenergic Receptor Agonists

α_2-Adrenergic agonists have been used for the treatment of acute and chronic pain in nonobstetric patients.[92] Intravenous **dexmedetomidine** has been used as an adjunct to opioids for labor analgesia and as a component of general anesthesia for cesarean delivery.[93] Dexmedetomidine may be preferred over **clonidine** for intrapartum intravenous administration because an isolated, perfused human placenta model suggested that less dexmedetomidine is transferred across the placenta to the fetus. The investigators noted that more dexmedetomidine was retained in the placenta, which they attributed to its higher lipophilicity.[94]

Neuraxial clonidine has been used for labor analgesia but is not commonly used for analgesia after cesarean delivery. The epidural formulation of clonidine carries the following "black box" warning from the U.S. FDA[95]:

> *Clonidine hydrochloride injection (epidural clonidine) is not recommended for obstetrical, postpartum or perioperative pain management. The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients. However in a rare obstetrical, postpartum or perioperative patient, potential benefits may outweigh the possible risks.*

The combination of intrathecal clonidine (150 μg) and bupivacaine compared with sufentanil combined with bupivacaine has been shown to reduce peri-incisional hyperalgesia but does not alter pain scores or opioid consumption after elective cesarean delivery.[96] These findings suggest that intrathecal clonidine might be beneficial in a patient who is at risk for the development of chronic pain after cesarean delivery. Another randomized trial compared intrathecal clonidine 75 μg combined with hyperbaric bupivacaine to saline combined with bupivacaine.[97] Clonidine prolonged the duration of analgesia, but there was no difference in the need for rescue analgesia. Epidural clonidine (75 μg and 150 μg) added to a mixture of morphine, bupivacaine, and epinephrine prolonged the duration of analgesia and reduced morphine consumption without a significant increase in the incidence of side effects in patients who had undergone cesarean delivery.[98] However, given the availability of other agents and the lack of overwhelming evidence in favor of α_2-agonists, routine use of these agents in the postpartum period should be restricted to patients in whom other agents are contraindicated or in those with risk factors for chronic pain.

Magnesium Sulfate

Indications for peripartum magnesium sulfate therapy include tocolysis of preterm labor, seizure prophylaxis in preeclamptic women, and fetal neuroprotection in women at risk for preterm delivery.[99] A 2013 meta-analysis of trials of *intravenous* magnesium for the treatment of acute postoperative pain after nonobstetric surgery performed with general anesthesia concluded that magnesium sulfate administration resulted in a trivial reduction in pain scores and a more substantial reduction in opioid use; however, the incidence of nausea and vomiting was not reduced.[100] *Epidural* magnesium sulfate 500 mg (off-label route of administration) added to bupivacaine was more effective than bupivacaine alone in decreasing pain scores and opioid consumption but was not as effective as combining bupivacaine with morphine 1.5 mg.[101] Albrecht et al.[102] reviewed 18 trials of the efficacy and safety of *neuraxial* magnesium sulfate for postoperative analgesia. They observed an overall increase in the interval to first analgesic request (mean difference of 40 minutes [P = .0009] after intrathecal administration and mean difference of 110 minutes [P = .02] after epidural administration). However, the authors concluded that there were not enough patients (n = 140) and trials to evaluate the risk for neurologic complications.

Gabapentin

Gabapentin is an anticonvulsant that has analgesic properties, particularly in the setting of neuropathic pain. Although extensively studied in the management of chronic pain, its mechanism of action is uncertain. As part of a multimodal analgesic regimen in patients undergoing cesarean delivery, a preoperative dose of oral gabapentin 600 mg was associated with significantly lower pain scores with movement and at rest; however, the incidence of sedation was greater in the gabapentin group than in the placebo group (19% versus 0%).[8] In a follow-up study, placebo was compared with two doses of gabapentin (300 mg and 600 mg) in the hope of finding an efficacious dose associated with less sedation. Unfortunately the trial failed to show efficacy in either gabapentin group.[103] Limited evidence of efficacy and concerns about excessive sedation limit enthusiasm for routine use of gabapentin for postcesarean analgesia.

Ketamine and Dextromethorphan

Ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, has analgesic properties and may play a role in the treatment of acute postoperative pain and prevention or reversal of central sensitization.[104] It also is used as an intraoperative adjuvant to neuraxial anesthesia in patients undergoing cesarean delivery; small intravenous doses provide significant analgesia with minimal respiratory depression. An evaluation of low-dose ketamine for postcesarean analgesia compared intravenous ketamine 0.15 mg/kg, intrathecal fentanyl 10 μg, and placebo.[105] The study demonstrated a prolonged duration of analgesia in both the fentanyl and ketamine groups compared with the placebo group (time to first analgesic request: 145 minutes in the placebo group, 165 minutes in the fentanyl group, 199 minutes in the ketamine group). Ketamine was also superior to fentanyl and placebo in reducing pain scores both at 90 and 180 minutes, and reducing analgesic requirements in the first 24 hours, but not in the second 24 hours, after cesarean delivery.[105] In another study,[106] women undergoing cesarean delivery were randomized to receive intravenous ketamine 10 mg or placebo shortly after delivery as part of a multimodal regimen of intrathecal morphine and regular NSAID therapy. Oral acetaminophen/hydrocodone was administered for rescue analgesia. The authors were unable to demonstrate a difference in breakthrough pain, time to first analgesic request, or cumulative rescue analgesic requirements.[106] However, they demonstrated lower pain scores in the ketamine group 2 weeks after the surgery.[106]

Dextromethorphan, which is another NMDA antagonist, has been evaluated for its effect on postoperative analgesia, with mixed results.[107] After cesarean delivery, the addition of oral dextromethorphan 60 mg to various doses of intrathecal morphine failed to produce a significant change in pain scores.[11] Given the current level of evidence, routine use of NMDA antagonists for postcesarean analgesia is not recommended. However, low-dose ketamine may be useful in patients who suffer from superimposed chronic pain.

NON-NEURAXIAL REGIONAL ANALGESIC TECHNIQUES

Transversus Abdominis Plane Block

The transversus abdominis plane (TAP) block is a regional anesthetic technique in which local anesthetic is injected between the internal oblique and the transversus abdominis muscle layers to block the plexus of nerves supplying the anterior abdominal wall (Figure 27-3). In a trial in patients undergoing elective cesarean delivery, women randomized to receive a TAP block with 0.75% ropivacaine required significantly less morphine, had a longer time before first analgesic request, and had lower pain scores than women who received a block procedure with saline.[108] In another trial, bilateral TAP block with ropivacaine 0.5% was compared with saline; the ropivacaine group consumed less morphine (ropivacaine group, 18 mg; saline group, 32 mg; P < .05) and reported greater patient satisfaction.[109]

Several trials have compared intrathecal morphine analgesia to a TAP block after cesarean delivery.[110,111] In one such trial, patients who received intrathecal morphine 0.2 mg had a longer time to first analgesic request (8 hours versus 4 hours; P = 0.005) and decreased analgesic requirements in the first 12 hours compared with those who received a TAP block.[110] However, the incidence of nausea, vomiting, and pruritus was greater in the intrathecal morphine group.[110] Similarly, Loane et al.[111] randomized patients to receive intrathecal morphine 0.1 mg or a TAP block; intrathecal morphine resulted in lower opioid consumption and pain scores but was associated with a greater incidence of nausea, vomiting, and pruritus.[111] Finally, Costello et al.[112] found that

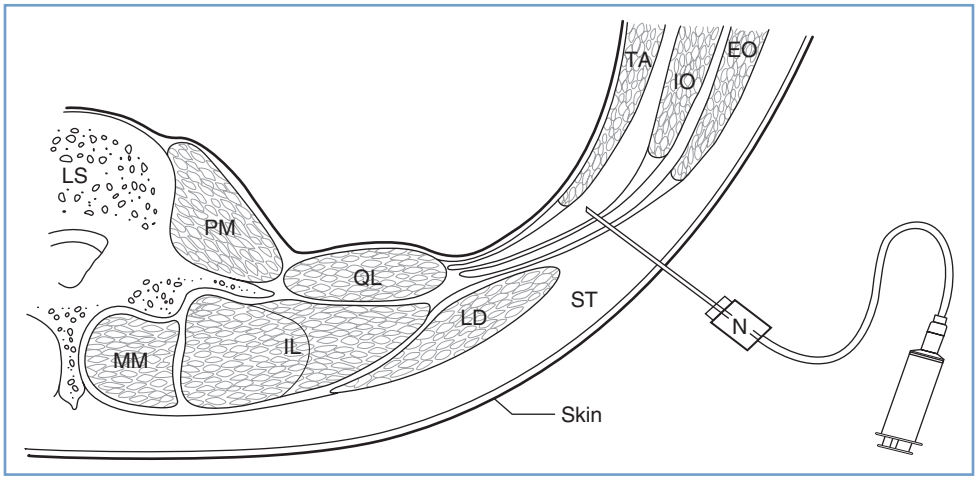

FIGURE 27-3 ■ Line drawing of a transverse section through the abdominal wall at the level of the lumbar triangle of Petit *(TOP)*. The floor of the triangle is composed, from superficial to deep, of the fascial extensions of external oblique, internal oblique, and transversus abdominis, respectively, and the peritoneum. The needle is inserted through the triangle, using the loss-of-resistance technique. The needle is shown in the transversus abdominis plane, and the fascial layers have separated as a result of the injection of local anesthetic. *LS,* lumbar spine; *LD,* latissimus dorsi; *PM,* psoas major; *QL,* quadratus lumborum; *MM,* multifidus muscle; *IL,* longissimus, iliocostalis; *TA,* transversus abdominis; *IO,* internal oblique; *EO,* external oblique; *N,* 50-mm blunt-tipped needle; *ST,* subcutaneous tissue. (From McDonnell JG, Curley G, Carney J, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg 2008; 106:186-91.)

the combination of intrathecal morphine and TAP block did not provide better postcesarean analgesia than intrathecal morphine alone.[112] Thus, TAP block represents a reasonable alternative for patients who are unable to receive neuraxial morphine, but TAP block should not replace neuraxial opioid analgesia as the gold standard for postcesarean analgesia.

Technique

The TAP block can be performed blindly using surface landmarks or with ultrasonographic guidance.[113] Continuous infusion of local anesthetic has been described, but the block is usually performed as a single-shot technique. The originally described landmark/loss-of-resistance technique involves introduction of the needle into the triangle of Petit.[114] Using ultrasonographic guidance, an anterior oblique-subcostal approach, a midaxillary approach, and a posterior approach have been described.[114] The pattern of local anesthetic spread within the transversus abdominis plane may vary depending on the site of injection; thus, the block characteristics, including extent of analgesia, may also vary depending on the specific technique.[114]

The classic, midaxillary, ultrasonography-guided TAP block is performed with the patient in the supine position. An area of skin on the lateral abdominal wall between the subcostal margin and the iliac crest is prepared with antiseptic solution. Using a high-frequency (8 to 12 MHz) linear array ultrasound probe, the abdominal wall is scanned between the anterior and posterior axillary line (Figure 27-4). The muscle layers are identified, and the needle (usually a 21- to 22-gauge, 80- to 100-mm short-bevel needle with extension tubing attached to a syringe with saline solution) is inserted in-plane from medial to lateral. Using ultrasonographic guidance, the needle tip is advanced through the muscle layers until it is positioned in the fascial plane between the internal oblique and transversus abdominis muscles. A small amount of saline is injected to verify hydrodissection of the plane. After correct identification of the plane, 15 to 20 mL of local anesthetic solution is *incrementally* injected into the plane, again with ultrasonographic guidance.

Complications of the block include intravascular injection resulting in local anesthetic systemic toxicity (LAST) and bowel perforation. The local anesthetic dose/volume/concentration–response relationships have not been well studied. Griffiths et al.[115] performed bilateral TAP blocks with a total ropivacaine dose of 2.5 mg/kg (diluted with 0.9% saline to a total volume of 40 mL) in women who had spinal anesthesia for elective cesarean delivery. (This dose corresponds to 20 mL of 0.5% ropivacaine on each side for an 80-kg patient.) The mean (± SD) peak plasma ropivacaine concentration (30 minutes after injection) was 1.82 ± 0.69 μg/mL. Although this concentration is below the reported threshold for systemic toxicity (2.2 μg/mL), 12 of 30 patients had peak concentration measurements above this threshold (maximum, 3.76 μg/mL), and 3 patients had symptoms of LAST (perioral tingling, metallic taste).[115] These findings suggest that ropivacaine doses less than 2.5 mg/kg should be used and that patients should be observed for at least 30 minutes after the block is performed.

Wound Infusion Catheters

Wound infusion catheters have gained popularity for pain relief after general and orthopedic surgery as ambulatory disposable pumps have become widely available. However, data are conflicting regarding the efficacy of these catheters. In a study comparing pain control provided by wound infusion and epidural levobupivacaine, the

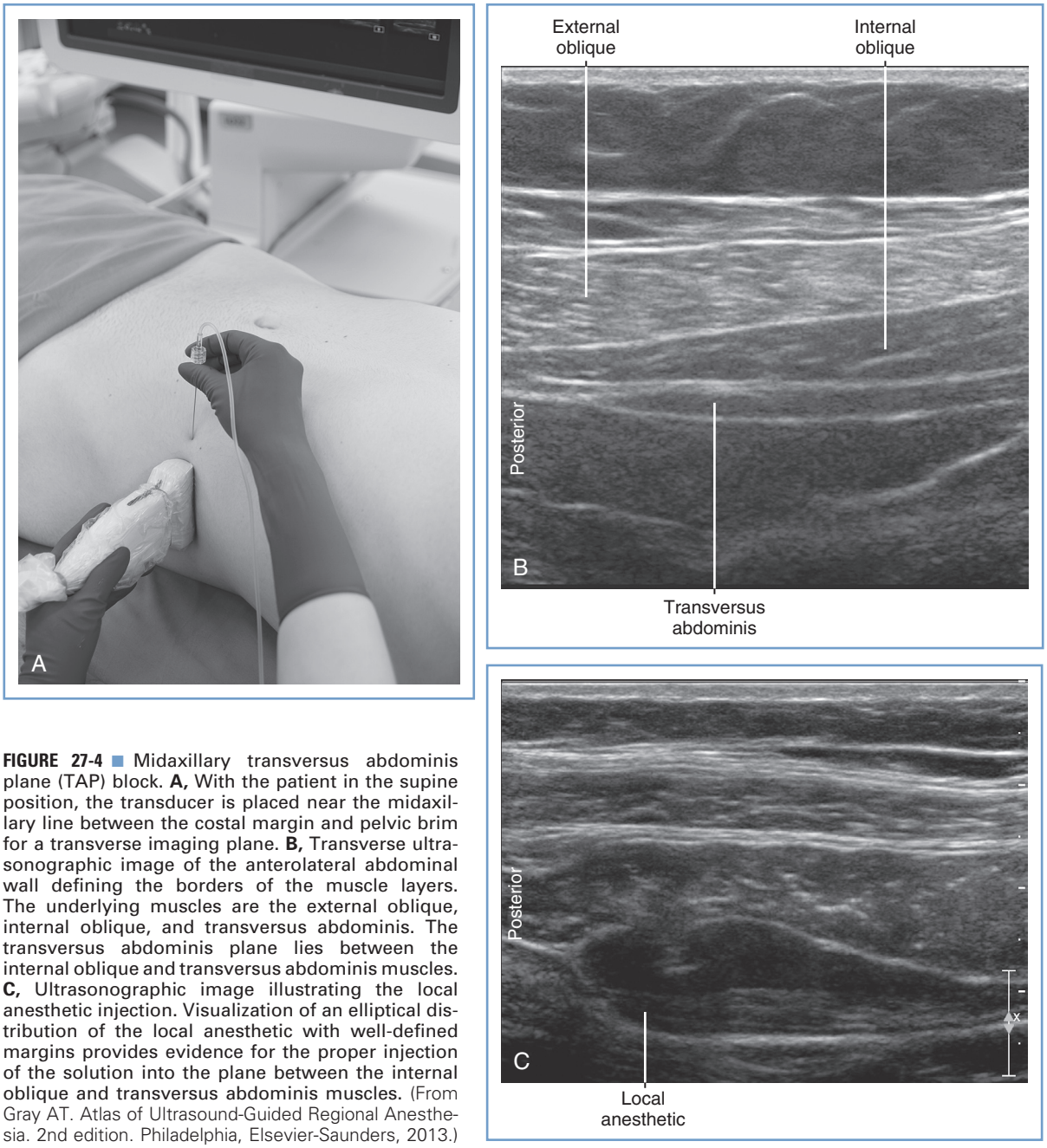

FIGURE 27-4 ■ Midaxillary transversus abdominis plane (TAP) block. **A,** With the patient in the supine position, the transducer is placed near the midaxillary line between the costal margin and pelvic brim for a transverse imaging plane. **B,** Transverse ultrasonographic image of the anterolateral abdominal wall defining the borders of the muscle layers. The underlying muscles are the external oblique, internal oblique, and transversus abdominis. The transversus abdominis plane lies between the internal oblique and transversus abdominis muscles. **C,** Ultrasonographic image illustrating the local anesthetic injection. Visualization of an elliptical distribution of the local anesthetic with well-defined margins provides evidence for the proper injection of the solution into the plane between the internal oblique and transversus abdominis muscles. (From Gray AT. Atlas of Ultrasound-Guided Regional Anesthesia. 2nd edition. Philadelphia, Elsevier-Saunders, 2013.)

epidural group had less pain only at the 4-hour time point. There were no significant differences between groups in opioid consumption.[9] In another study comparing intrathecal morphine and wound infusion with ropivacaine or saline,[116] more oxycodone was required in the ropivacaine wound infusion group than in the intrathecal morphine group during the first 24 hours (48 mg versus 26 mg; $P = .004$); there was no difference in oxycodone use between the ropivacaine wound infusion and saline-control groups.[116] By contrast, another group of investigators found that wound infusion with ropivacaine 0.2% at 5 mL/h provided superior analgesia and a lower incidence of nausea and vomiting compared with epidural morphine 2 mg administered every 12 hours.[117] Carvalho et al.[118] added ketorolac to bupivacaine for wound infusion; compared with infusion of bupivacaine alone, pain scores and opioid consumption were decreased, as were local inflammatory mediators collected from the wound.[118] The addition of hydromorphone to bupivacaine did not alter these outcomes.[118]

Some of the differences in outcomes among these studies may be due to differences in catheter insertion technique, local anesthetic concentration, and rate of infusion; however, current evidence does not support the

superiority of local anesthetic wound infusion over neuraxial opioid administration. Although some centers use wound infusion catheters, the additional cost of the pump and the inconvenience may be prohibitive.

Local Infiltration

Local infiltration of the wound is a relatively simple component of multimodal postoperative analgesia. In a study of patients who did not receive neuraxial morphine for postcesarean analgesia, infiltration of 0.25% bupivacaine with epinephrine (40 mL) before wound closure was associated with decreased opioid requirements in the first 12 hours compared with saline-placebo.[119] However, wound infiltration with 30 mL bupivacaine 0.5% did not provide additional analgesia when combined with neuraxial opioid administration.[120]

Ilioinguinal-Iliohypogastric Block

Ilioinguinal-iliohypogastric block is useful for postoperative analgesia after lower abdominal surgery. Similar to TAP blocks, these blocks can be performed with ultrasonographic guidance. Evidence is inconsistent as to whether ilioinguinal-iliohypogastric blocks improve analgesia provided by neuraxial morphine.[121,122] In a study of women who did not receive neuraxial morphine, bilateral, multilevel ilioinguinal-iliohypogastric blocks were associated with lower systemic opioid use, but a decrease in opioid side effects was not observed.[123]

NONPHARMACOLOGIC INTERVENTIONS

Nonpharmacologic interventions may play a role as adjuvant treatments in the management of postcesarean pain, but these interventions have not been subjected to rigorous investigation. Acupuncture has been used to treat pain after cesarean delivery. In one trial, patients treated with acupuncture used 30% less opioid in 24 hours and reported lower pain scores at 2 hours.[124] Foot and hand massage has been reported to reduce reported pain scores and the need for rescue pain medication.[125]

IMPACT OF PAIN AND ANALGESIC TREATMENT ON BREAST-FEEDING

The AAP strongly supports breast-feeding because of its benefits to the infant, mother, and society. However, patients may discontinue breast-feeding when taking analgesic medications because of incomplete or incorrect information regarding neonatal health. The AAP Committee on Drugs recommends that physicians take the following steps before prescribing medications to breast-feeding women: (1) determination of the reasons for the medication, (2) identification of the safest available medication in a particular category, and (3) measurement of blood concentrations of drug in those neonates for whom the drug presents a significant risk.[85] The AAP has also suggested that the best time for the mother to take a medication is immediately after breast-feeding or just before the infant takes a nap.[85]

The two most important items needed to determine the potential neonatal risks of maternal drug administration are the amount of medication excreted in breast milk and the therapeutic effect of that medication when given to the infant.[126] Some investigators have arbitrarily defined a breast milk concentration lower than 10% of the therapeutic infant plasma concentration (or a breast milk dose less than 10% of the weight-normalized maternal dose) as a safe level of exposure. In breast-feeding infants, the estimated *absolute infant drug dose* is calculated by multiplying the average infant breast milk intake by the average concentration of the drug in the milk (area under the pharmacokinetic curve). The absolute infant drug dose is then expressed as a percentage of the maternal dose, normalized by weight (mg/kg/day), to yield the *relative infant dose*. If the relative infant dose is high and the drug has potential to harm the infant, or if side effects attributed to the drug are detected in the infant, clinicians should consider discontinuing the drug, modifying the dose, or changing to a different drug.

Persistent pain is associated with sympathetic nervous system activation, vasoconstriction, and decreased breast milk production in animal models.[127] Better pain management after cesarean delivery is associated with more episodes of breast feeding.[128] Clearly, pain requires treatment after cesarean delivery, and the optimal method or methods to prevent adverse neonatal effects through breast milk transfer is an important consideration. Because significantly smaller total opioid doses are required in women who receive neuraxial opioids, less opioid is available for transfer to breast milk. In a parturient treated with continual intrathecal morphine for chronic pain, minimal morphine concentrations were detected in the neonate, and neurobehavioral scores were normal.[129] A relatively small amount (1.6%) of the maternal dose of hydrocodone is transferred to the neonate as hydromorphone in breast milk.[130] In general, the small amounts of analgesic drugs that are transferred to breast milk in the postpartum period are not harmful to the neonate.

Standard references, including the AAP list of drugs that are usually compatible with breast-feeding,[85] should be consulted before prescribing drugs to breast-feeding women.[131]

MATERNAL ANESTHESIA AND BREAST-FEEDING

Surgeons and breast-feeding mothers often have questions about whether breast-feeding should be interrupted when the mother undergoes anesthesia for a surgical procedure. Short-term administration of other potent medications commonly used for sedation and analgesia (e.g., midazolam, propofol, fentanyl) has been found to result in breast milk doses less than 1.25% of the weight-normalized maternal dose.[132] Thus, women do not have to "pump and dump" because of concerns of infant exposure to anesthetic agents.

KEY POINTS

- Postcesarean pain is produced by direct trauma to nerve endings and/or subsequent inflammation induced by tissue injury.
- The experience of pain may be associated with genetic variability of the μ-opioid receptor.
- Results from studies of postoperative analgesia in nonobstetric patients may not be directly applicable to pregnant women undergoing cesarean delivery.
- Postpartum pain may be modulated by the unique hormonal and emotional changes of pregnancy. In addition, stress, anxiety, and depression may accompany postpartum sleep disturbances and the responsibilities of providing care for a neonate.
- Opioids are the most common systemic medications administered for postcesarean analgesia. Adverse effects associated with opioids, which often limit their use, include respiratory depression, sedation, constipation, nausea and vomiting, urinary retention, and pruritus.
- Factors that should affect the choice of opioid are the speed of onset, duration of action, and overall efficacy of the agent and the type and frequency of its side effects.
- There are no maximum allowable doses for specific opioids; therefore, the main limiting factor is the side effects associated with their use.
- Optimal postcesarean analgesia consists of a multidisciplinary approach that should involve physicians, nurses, pharmacists, and other health care providers.
- There may be a benefit to giving oral analgesic drugs early in the postoperative period at a fixed interval, rather than on patient request (prn).
- Multimodal techniques provide effective postcesarean analgesia by acting on different pain pathways. In addition, multimodal analgesia achieves better analgesia while limiting side effects. One multimodal strategy might consist of the continuous instillation of local anesthetic at the surgical incision site, the administration of a nonsteroidal anti-inflammatory drug, and intravenous opioid patient-controlled analgesia.
- The two most important items necessary to determine the potential neonatal risks of maternal drug administration to the breast-feeding mother are an estimate of the amount of medication excreted in breast milk and the therapeutic effect of that medication when given to the infant.

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CHAPTER 28

Postoperative Analgesia: Epidural and Spinal Techniques

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CHAPTER OUTLINE

The cesarean delivery rate in the United States has steadily increased as a result of changing patterns in obstetric practice,[1] and recent data indicate that more than 1 million cesarean deliveries are now performed annually in the United States.[2] With cesarean delivery accounting for an ever-increasing proportion of all deliveries in the United States and in many other developed countries,[3] strategies for reducing adverse postcesarean maternal outcomes, including postoperative pain, have important clinical and public health implications.

Postoperative pain after cesarean delivery can be moderate to severe and is equivalent to that reported after abdominal hysterectomy.[4] Management of postoperative pain is frequently substandard, with 30% to 80% of patients experiencing moderate to severe postoperative pain.[5,6] In an effort to improve pain management in the United States, The Joint Commission has stated that postoperative pain should be the "fifth vital sign."[7] The Joint Commission also proposed the goal of having patients experience uniformly low postoperative pain scores of less than 3 (based on a numerical pain scale [0 to 10] at rest and with movement). In the United Kingdom, the Royal College of Anaesthetists[8] has proposed the following standards for adequate postcesarean analgesia:

1. More than 90% of women should have a pain score of less than 3 (as measured by a numerical pain scale [0 to 10]).
2. More than 90% of women should be satisfied with their pain management.[8]

A 2007 study suggested that these goals for postcesarean analgesia and maternal satisfaction are frequently not attained.[9] A sample of expectant mothers attending birthing classes identified pain during and after cesarean delivery as their most important concern (Table 28-1).[10] Effective pain management should be highlighted as an essential element of postoperative care.

TABLE 28-1 Women's Ranking and Relative Value of Potential Anesthesia Outcomes before Cesarean Delivery*

Outcome	Rank†	Relative Value‡
Pain during cesarean delivery	8.4 ± 2.2	27 ± 18
Pain after cesarean delivery	8.3 ± 1.8	18 ± 10
Vomiting	7.8 ± 1.5	12 ± 7
Nausea	6.8 ± 1.7	11 ± 7
Cramping	6.0 ± 1.9	10 ± 8
Itching	5.6 ± 2.1	9 ± 8
Shivering	4.6 ± 1.7	6 ± 6
Anxiety	4.1 ± 1.9	5 ± 4
Somnolence	2.9 ± 1.4	3 ± 3
Normal	1	0

*Data are mean ± standard deviation.
†Rank = 1 to 10 from the most desirable (1) to the least desirable (10) outcome.
‡Relative value = dollar value patients would pay to avoid an outcome (e.g., they would pay $27 of a theoretical $100 to avoid pain during cesarean delivery).
From Carvalho B, Cohen SE, Lipman SS, et al. Patient preferences for anesthesia outcomes associated with cesarean delivery. Anesth Analg 2005; 101:1182-7.

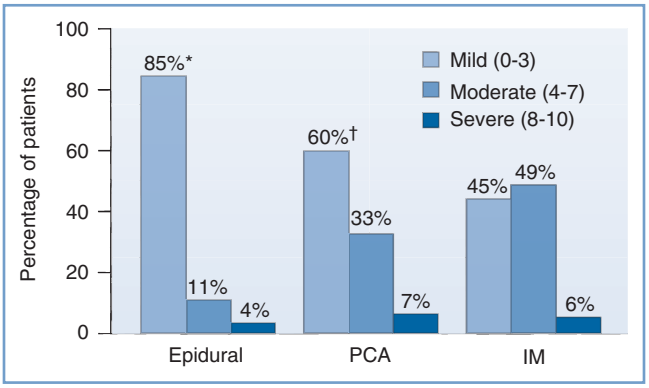

FIGURE 28-1 ■ Randomized trial of postcesarean analgesia with epidural analgesia, intravenous patient-controlled analgesia (*PCA*), or intramuscular (*IM*) administration of morphine. Percentage of patients reporting mild, moderate, or severe discomfort during a 24-hour study period. *$P < .05$, epidural versus PCA and IM; †P = NS, PCA versus IM. (From Harrison DM, Sinatra RS, Morgese L, et al. Epidural narcotic and PCA for postcesarean section pain relief. Anesthesiology 1988; 68:454-7.)

NEURAXIAL TECHNIQUES FOR CESAREAN DELIVERY

In the United States and the United Kingdom, most cesarean deliveries are performed with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural [CSE] techniques).[11-13] A meta-analysis found no differences between spinal and epidural anesthetic techniques with regard to failure rate, additional requests for intraoperative analgesia, need for conversion to general anesthesia, maternal satisfaction, postoperative analgesic requirements, or neonatal outcomes.[14] There may be other nonclinical factors that influence the choice of neuraxial anesthetic technique for cesarean delivery. Spinal anesthesia has been shown to be more cost effective than epidural anesthesia for cesarean delivery, because needle placement is technically less challenging and adequate surgical anesthesia is achieved more rapidly.[15] These advantages, combined with the low incidence of post–dural puncture headache with noncutting spinal needles (see Chapter 12), have increased the popularity of spinal-based anesthetic techniques for patients undergoing cesarean delivery. A 2008 survey of members of the Society for Obstetric Anesthesia and Perinatology found that 85% of elective cesarean deliveries are performed with spinal anesthesia.[13] A workforce survey in the United States demonstrated that the majority of laboring women receive epidural analgesia.[11] If a patient receiving epidural analgesia during labor subsequently requires a cesarean delivery, most anesthesia providers choose to administer medications through the epidural catheter to achieve adequate surgical anesthesia (see Chapter 26).[11-13]

A CSE technique incorporates the rapid onset of spinal anesthesia with placement of an epidural catheter for supplementation of intraoperative anesthesia and/or for provision of postoperative analgesia. The CSE technique is increasingly used when prolonged duration of surgery is anticipated (e.g., obesity, multiple previous surgeries).[16] After surgery, patients with an epidural catheter *in situ* may benefit from intermittent bolus injection or continuous epidural infusion of local anesthetic and/or opioid for postoperative analgesia.

EFFICACY AND BENEFITS OF NEURAXIAL ANALGESIA

Neuraxial opioid administration currently represents the "gold standard" for providing effective postcesarean analgesia. A meta-analysis of studies involving a broad population of patients undergoing a variety of surgical procedures confirmed that opioids delivered by either patient-controlled epidural analgesia (PCEA) or continuous epidural infusion (CEI) provide postoperative pain relief that is superior to that provided by intravenous patient-controlled analgesia (PCA).[17] Similar results have been reported in studies comparing intrathecal and epidural opioid administration with intravenous opioid PCA or intramuscular opioid administration after cesarean delivery (Figure 28-1).[18-21] A 2010 systematic review found that neuraxial morphine provides better analgesia than parenteral opioids after cesarean delivery.[22] Neuraxial opioids also provide postcesarean analgesia that is superior to that provided by local anesthetic techniques (e.g., transversus abdominis plane blocks) and oral analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], opioids) (see Chapter 27).[23-26] Wound infiltration of a local anesthetic has been proposed as an alternative to an epidural technique for postcesarean analgesia[27,28]; however, the efficacy and reliability of this technique are

variable.[29-31] Intrathecal morphine is particularly effective after abdominal surgery.[32] Although neuraxial analgesia offers important benefits in optimizing postoperative analgesia, multimodal analgesic strategies should be used to augment the analgesic effect of neuraxial opioids in this setting.[25]

Persistent and chronic incisional and pelvic pain have been described after cesarean delivery, with an incidence of 1% to 15%.[33-41] Psychosocial and pathophysiologic factors may also increase the likelihood of chronic postoperative pain.[42,43] Severe acute postoperative pain is one of the most prominent associated factors.[34,37,42,44] The development of chronic pain after surgery has been associated with central sensitization, hyperalgesia, and allodynia. Measures to attenuate or prevent pain sensitization may reduce the likelihood of development of chronic postoperative pain. Studies have shown that the use of perioperative neuraxial blockade may prevent central sensitization and chronic pain.[33,45,46] De Kock et al.[45] found that intrathecal clonidine, administered before colonic surgery, had antihyperalgesic effects and resulted in less residual pain 6 months after surgery than did placebo. Lavand'homme et al.[46] reported that the administration of a multimodal antihyperalgesic regimen (intraoperative intravenous ketamine and epidural analgesia with bupivacaine, sufentanil, and clonidine) was associated with a lower incidence of residual pain 1 year after colonic surgery compared with intravenous analgesia administered during and after surgery. A study investigating risk factors for chronic pain after hysterectomy found that spinal anesthesia was associated with a lower frequency of chronic postoperative pain compared with general anesthesia.[47] In another study, persistent postoperative pain was more frequent after cesarean delivery performed with general anesthesia compared with neuraxial anesthesia.[34] Additional mechanistic and clinical research is needed to improve our understanding of persistent pain after cesarean delivery and to improve current treatment regimens for managing patients with postcesarean-related pain syndromes.

Although neuraxial opioids provide postcesarean analgesia that is superior to that provided by systemic opioids, some opioid-related side effects (e.g., pruritus) commonly occur after neuraxial opioid administration.[18,48,49] Both higher[49,50] and lower[21,51] maternal satisfaction scores have been reported with neuraxial opioid administration for postcesarean analgesia. This variability in reported maternal satisfaction scores may be influenced by how patients judge analgesic quality against the presence and severity of opioid-related side effects (e.g., pruritus, nausea and vomiting).

Neuraxial anesthetic and analgesic techniques may also confer important physiologic benefits that decrease perioperative complications and improve postoperative outcomes.[52-54] The potential benefits include a lower incidence of pulmonary infection and pulmonary embolism, an earlier return of gastrointestinal function, fewer cardiovascular and coagulation disturbances, and a reduction in inflammatory and stress-induced responses to surgery.[52-54] In contrast to the wealth of data from clinical studies and meta-analyses that have shown a reduction in postoperative pain with neuraxial analgesia, there is less consistent evidence linking neuraxial anesthesia with a reduction in postoperative morbidity and mortality.[52,55]

Most patients undergoing cesarean delivery are young, healthy, and at low risk for major perioperative morbidity and mortality. For this patient population, the benefits of neuraxial analgesia include better postoperative analgesia, increased functional ability, earlier ambulation, and earlier return of bowel function.[56-59] However, differences in postcesarean complication rates with the use of neuraxial versus systemic opioid analgesia have not been definitively demonstrated.[56,60] Surgical trauma and postoperative immobility are associated with an increased risk for postoperative deep vein thrombosis and pulmonary embolism. The risk for venous thromboembolism is 6-fold higher in pregnant women and 10-fold higher in puerperal women than in nonpregnant women of similar age.[61] In theory, early ambulation and avoidance of prolonged immobility may reduce the risk for postpartum deep vein thrombosis and pulmonary embolism. Effective postoperative analgesia can reduce pain on movement, thereby facilitating deep breathing, coughing, and early ambulation. These beneficial effects may lead to a reduction in the incidence of pulmonary complications (i.e., atelectasis, pneumonia) after cesarean delivery.

Neuraxial analgesic techniques may be more likely to reduce perioperative morbidity in high-risk obstetric patients. Women with severe preeclampsia, cardiovascular disease, and morbid obesity may benefit from the reduction in cardiovascular stress and improved pulmonary function associated with effective postcesarean analgesia.[62,63] Rawal et al.[63] compared the efficacy of intramuscular versus epidural morphine in 30 nonpregnant, morbidly obese patients after abdominal surgery. Patients in the epidural morphine group were more alert, ambulated more quickly, recovered bowel function earlier, and had fewer pulmonary complications.

Investigators have found that CEI of an opioid with a dilute solution of local anesthetic attenuates coagulation abnormalities, hemodynamic fluctuation, and stress hormone responses in nonpregnant patients.[64-66] Some studies have suggested that opioid-based PCEA may improve postoperative outcome.[67-69] Patients treated with PCEA meperidine after cesarean delivery ambulated more quickly and experienced an earlier return of gastrointestinal function compared with similar patients who received intravenous meperidine PCA.[67]

PHARMACOLOGY OF NEURAXIAL OPIOIDS

Prior to 1974, investigators speculated that the analgesic effect of opioids was due to pain modulation at supraspinal centers or increased activation of descending inhibitory pathways, without a direct effect at the spinal cord. The identification of endogenous opioid peptides, specific opioid binding sites, and opioid receptor subtypes has helped to clarify the site and mechanism of action of opioids within the central nervous system

(CNS).[70-73] The discovery that opioid receptors are localized within discrete areas in the CNS (laminae I, II, and V of the dorsal horn) suggested that exogenous opioids could be administered neuraxially to produce antinociception. Opioids administered to superficial layers of the dorsal horn produced selective analgesia of prolonged duration without affecting motor function, sympathetic tone, or proprioception.[74] In addition, the analgesia provided by intraspinal opioids suggested that many of the unwanted side effects of intraspinal local anesthetic administration could be avoided.[75] In 1979, Wang et al.[76] published the first report of intraspinal opioid administration in humans. Intrathecal morphine (0.5 to 1 mg) produced complete pain relief for 12 to 24 hours in six of eight patients suffering from intractable cancer pain, with no evidence of sedation, respiratory depression, or impairment of motor function. Subsequently, researchers and clinicians have validated the analgesic efficacy of neuraxial opioids.

Central Nervous System Penetration

Opioids administered epidurally must penetrate the dura, pia, and arachnoid membranes to reach the dorsal horn and activate the spinal opioid receptors. The arachnoid layer is the primary barrier to drug transfer into the spinal cord.[77] Movement through this layer is passive and depends on the physicochemical properties of the opioid. Drugs penetrating this arachnoid layer must first move into a lipid bilayer membrane, then traverse the hydrophilic cell itself, and finally partition into the other cell membrane before entering the cerebrospinal fluid (CSF). Opioid penetration of spinal tissue is proportional to the drug's lipid solubility. Opioids that are highly lipid soluble (e.g., sufentanil, fentanyl) are unable to cross the hydrophilic cell, whereas those that are hydrophilic have difficulty crossing the lipid membrane.[78] Highly lipid-soluble drugs have poor CSF bioavailability because of (1) poor penetration through the arachnoid layer, (2) rapid absorption and sequestration by epidural fat, and (3) high vascular uptake by epidural veins.

Some investigators have questioned the neuraxial specificity of lipophilic opioids given epidurally and have suggested that the primary analgesic effect occurs via vascular uptake, systemic absorption, and redistribution of the drug to supraspinal sites.[79-84] Earlier studies suggested that parenteral fentanyl provides analgesia equivalent to that provided by epidural fentanyl.[84,85] Investigators postulated that systemic absorption of fentanyl from the epidural space resulted in the subsequent analgesic effect.[84,85] Ionescu et al.[86] reported that plasma levels of sufentanil were comparable throughout a 3-hour sampling interval after epidural or intravenous injection. In contrast, more recent evidence suggests that epidural fentanyl provides analgesia via a spinal mechanism.[87-89] Cohen et al.,[90] comparing a continuous infusion of intravenous fentanyl with epidural fentanyl after cesarean delivery, reported improved analgesia and less supplemental analgesic consumption despite lower plasma fentanyl levels with epidural administration. There is evidence that bolus administration of lipophilic opioids has both spinal and supraspinal effects in obstetric patients.[87-89] After the administration of an epidural bolus of sufentanil 50 μg,* CSF concentrations of sufentanil were 140 times greater than those found in plasma; however, the amount detected in cisternal CSF was only 5% of that measured in lumbar CSF.[91]

Hydrophilic morphine has a higher CSF bioavailability, with better penetration into the CSF and less systemic absorption. A bolus dose of epidural morphine 6 mg results in peak plasma concentration of 34 ng/mL at 15 minutes after administration and a peak CSF concentration of approximately 1000 ng/mL at 1 hour.[92] A poor correlation between the analgesic effect and plasma levels of morphine has been observed after epidural administration, indicating a predominantly spinal location of action.[93,94]

Intrathecal administration allows for injection of the drug directly into the CSF. This is a more efficient method of delivering opioid to spinal cord receptors than epidural or parenteral administration. A bolus dose of intrathecal morphine 0.5 mg results in a CSF concentration higher than 10,000 ng/mL, with barely detectable plasma concentrations.[95]

Distribution and Movement of Opioids within the Central Nervous System

The movement and distribution of opioids within the CNS has been described as follows (Figure 28-2):

1. **Movement in the spinal cord (white and gray matter)**. Lipophilic agents (e.g., fentanyl) are taken up by the white matter with much greater affinity than hydrophilic agents (e.g., morphine), and less drug will reach the dorsal horn in the gray matter.[77,78,96]
2. **Movement within the epidural space (and subsequently epidural fat or veins)**. Lipophilic agents are more likely to be absorbed and transported from the epidural space to the systemic circulation.
3. **Rostral spread in the CSF to the brainstem**. Rostral spread is determined by CSF drug bioavailability and the drug concentration gradient; hydrophilic opioids (e.g., morphine) are associated with more rostral spread.[91,97]

Although opioid dose, volume of injectate, and degree of ionization are important variables, lipid solubility plays the key role in determining the onset of analgesia, the

*The Institute of Safe Medicine Practices (ISMP) has recommended that health care providers never use μg as an abbreviation for micrograms, but rather they should use mcg (http://www.ismp.org/tools/errorproneabbreviations.pdf, Accessed February 2013). The use of the symbol μg is frequently misinterpreted and involved in harmful medication errors. The abbreviation may be mistaken for mg (milligrams), which would result in a 1000-fold overdose. The symbol μg should never be used when communicating medical information, including pharmacy and prescriber computer order entry screens, computer-generated labels, labels for drug storage bins, and medication administration records. However, most scholarly publications have continued to use the abbreviation μg. The editors have chosen to retain the use of the abbreviation μg throughout this text. However, the editors recommend the use of the abbreviation mcg in clinical practice.

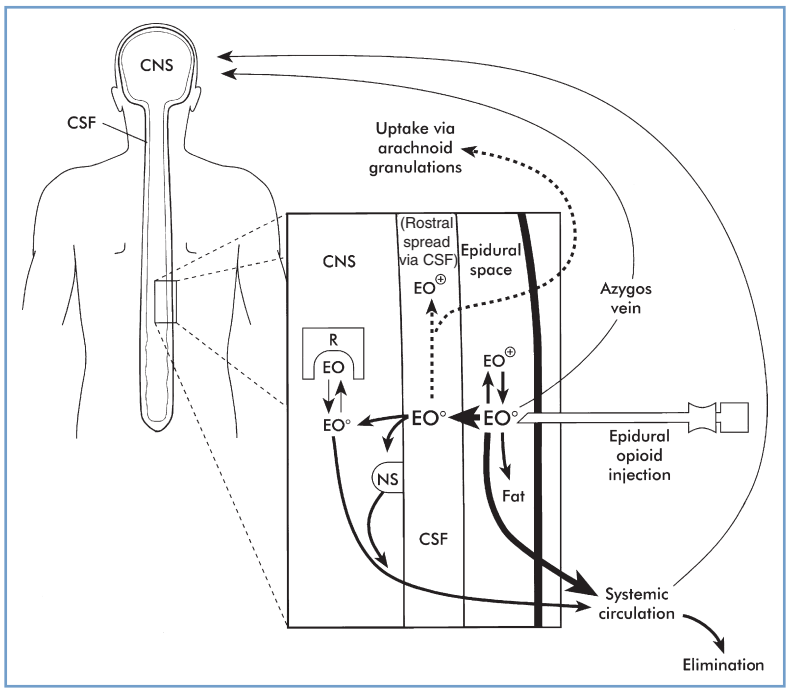

FIGURE 28-2 ■ Factors that influence dural penetration, cerebrospinal fluid (*CSF*) sequestration, and vascular clearance of epidurally administered opioids. The major portion of epidurally administered opioids (*EO*) is absorbed by epidural and spinal blood vessels or dissolved into epidural fat. Molecules taken up by the epidural plexus and azygos system may recirculate to supraspinal centers and mediate central opioid effects. A smaller percentage of uncharged opioid molecules (EO^0) traverse the dura and enter the CSF. Lipophilic opioids rapidly exit the CSF and penetrate into spinal tissue. As with intrathecal dosing, the majority of these molecules either are trapped within lipid membranes (nonspecific binding sites [*NS*]) or are rapidly removed by the spinal vasculature. A small fraction of molecules bind to and activate opioid receptors (*R*). Hydrophilic opioids penetrate pia-arachnoid membranes and spinal tissue slowly. A larger proportion of these molecules remain sequestered in CSF and are slowly transported rostrally. This CSF depot permits gradual spinal uptake, greater dermatomal spread, and a prolonged duration of activity. *CNS,* central nervous system; EO^+*,* charged epidurally administered opioid molecules. (From Sinatra RS. Pharmacokinetics and pharmacodynamics of spinal opioids. In Sinatra RS, Hord AH, Ginsberg B, Preble LM, editors. Acute Pain: Mechanisms and Management. St. Louis, Mosby, 1992:106.)

TABLE 28-2 Spinal Opioid Physiochemistry and Pharmacodynamics

Opioid	Molecular Weight	Lipid Solubility*	Parenteral Potency	pKa	μ-Opioid Receptor Affinity	Dissociation Kinetics	Potency Gain (Epidural versus IV or SC)	Onset of Analgesia	Duration of Analgesia
Morphine	285	1.4	1	7.9	Moderate	Slow	10	Delayed	Prolonged
Meperidine	247	39	0.1	8.5	Moderate	Moderate	2-3	Rapid	Intermediate
Methadone	309	116	2	9.3	High	Slow	2-3	Rapid	Intermediate
Hydromorphone	285	25	10		High	Slow	5	Rapid	Prolonged
Alfentanil	417	129	25	6.5	High	Very rapid	1-2	Very rapid	Short
Fentanyl	336	816	80	8.4	High	Rapid	1-2	Very rapid	Short
Sufentanil	386	1727	800	8.0	Very high	Moderate	1-1.5	Very rapid	Short

IV, Intravenous; *SC,* subcutaneous.
*Octanol-water partition coefficient at pH of 7.4.

dermatomal spread, and the duration of activity (Table 28-2).[80,98] Highly lipid-soluble opioids penetrate the spinal cord more rapidly and have a quicker **onset of action** than more ionized water-soluble agents. The **duration of activity** is affected by the rate of clearance of the drug from the sites of activity. Lipid-soluble opioids are rapidly absorbed from the epidural space, whereas hydrophilic agents remain in the CSF and spinal tissues for a longer time (see Figure 28-2).[80,98] Sufentanil is more lipid soluble than fentanyl; however, sufentanil has a greater μ-opioid receptor affinity, resulting in a comparatively longer duration of analgesia after neuraxial administration.

Intrathecal and epidural opioids often produce analgesia of greater intensity than similar doses administered parenterally. The gain in potency is inversely proportional to the lipid solubility of the agent used. Hydrophilic opioids exhibit the greatest gain in potency; the potency ratio for intrathecal to systemic morphine is approximately 1:100.[98,99]

TABLE 28-3 **Epidural Opioids for Cesarean Delivery**

Drug(s)	Dose	Onset (min)	Peak Effect (min)	Duration (h)	Advantages	Disadvantages
Morphine	2-4 mg	30-60	60-90	12-24	Long duration	Delayed onset Side effect profile Potential for delayed respiratory depression
Fentanyl	50-100 μg	5	20	2-3	Rapid onset	Short duration
Sufentanil	10-25 μg	5	15-20	2-4	Rapid onset	Short duration
Meperidine	25-50 mg	15	30	4-6	Rapid onset	Nausea and vomiting
Hydromorphone	0.4-1 mg	15	45-60	10-20	Intermediate onset and duration	Side effect profile similar to that of morphine
Morphine/fentanyl	3 mg/50 μg	10	15	12-24	Rapid onset Long duration Fewer side effects than morphine 5-mg dose	
Morphine/sufentanil	3 mg/10 μg	5	15	12-24	Rapid onset Long duration Fewer side effects than morphine 5-mg dose	

EPIDURAL OPIOIDS

The provision of cesarean delivery anesthesia using an epidural catheter (placed during labor or as part of a CSE technique) has prompted an extensive evaluation of epidural opioids to facilitate postoperative analgesia (Table 28-3).

Morphine

Preservative-free morphine received U.S. Food and Drug Administration (FDA) approval for neuraxial administration in 1984, and subsequently epidural morphine administration has been widely investigated and extensively used.[100] Epidural administration of morphine provides postcesarean analgesia superior to that provided by intravenous or intramuscular morphine.[18-21] A meta-analysis concluded that epidural morphine administration increases the time to first analgesic request, decreases pain scores, and reduces postoperative analgesic requests during the first 24 hours after cesarean delivery compared with systemic opioid administration.[22] However, epidural morphine administration is associated with an increased risk for pruritus (relative risk [RR], 2.7; 95% confidence interval [CI], 2.1 to 3.6) and nausea (RR, 2.0; 95% CI, 1.2 to 3.3), compared with systemic opioid administration.[22]

Onset and Duration

After epidural administration, plasma morphine concentrations are similar to those observed after intramuscular injection. Epidural morphine has a relatively slow onset of action, as a result of its low lipid solubility and slower penetration into spinal tissue.[80-82,98] The peak analgesic effect is observed 60 to 90 minutes after epidural administration.[92] Nonetheless, we prefer to delay epidural morphine administration until immediately after delivery of the infant, or later if maternal hemodynamic instability warrants further delay.

Morphine has a prolonged duration of analgesia, and analgesic efficacy typically persists long after plasma concentrations have declined to subtherapeutic levels.[80,92,98] Epidural morphine provides pain relief for approximately 24 hours after cesarean delivery[58,101-103]; however, there is wide variation in analgesic duration and efficacy among patients. Within the narrow range of doses studied, investigators have not demonstrated a correlation between the dose of morphine and the duration of analgesia.[101,103,104]

The volume of the diluent does not appear to affect the pharmacokinetics or clinical activity of epidural morphine. The quality and duration of analgesia, the need for supplemental analgesics, and the incidence of side effects were similar when epidural morphine 4 mg was administered with 2, 10, and 20 mL of sterile saline.[105]

The choice of local anesthetic used for epidural anesthesia may affect the subsequent efficacy of epidural morphine.[106] Some parturients who received 2-chloroprocaine as the primary local anesthetic agent for cesarean delivery have experienced unexpectedly poor postoperative analgesia (typically lasting < 4 hours).[106,107] In contrast, Hess et al.[108] observed no difference in pain scores, side effects, or the need for supplemental analgesics when epidural morphine 3 mg was given after epidural administration of preservative-free 3% 2-chloroprocaine or placebo; however, the epidural agents were administered 30 minutes after performance of a CSE technique that included intrathecal hyperbaric bupivacaine 11.25 mg and fentanyl 25 μg in women undergoing elective cesarean delivery. The occurrence of inadequate analgesia may therefore be related to the relatively rapid regression of 2-chloroprocaine anesthesia and the delay to peak effect of epidural morphine, rather than the postulated μ-opioid receptor antagonism of 2-chloroprocaine.[106,108,109]

Single-Dose Regimens to Optimize Postcesarean Analgesia and Minimize Opioid-Related Side Effects

In a prospective dose-response study, Palmer et al.[104] observed that postcesarean analgesia (assessed by need for supplemental intravenous morphine PCA) improved as the dose of epidural morphine increased from 0 to 3.75 mg. A further increase in dose (to 5 mg) did not significantly improve analgesia or reduce the amount of supplemental intravenous morphine used in the first 24 postoperative hours (Figure 28-3).[104] Chumpathong et al.[101] did not observe any difference in pain relief, patient satisfaction, or side effects in women receiving epidural morphine 2.5 mg, 3 mg, or 4 mg for postcesarean analgesia. Rosen et al.[102] found that epidural morphine 5 mg and 7.5 mg provided similar analgesic efficacy, as opposed to a 2-mg dose, which provided ineffective analgesia. Epidural morphine 3 mg was recommended by Fuller et al.[103] after a large retrospective study of epidural morphine in doses ranging from 2 to 5 mg for postcesarean analgesia.

In contemporary clinical practice, doses of epidural morphine 2 to 4 mg are most commonly used. Lower doses may not provide effective analgesia, and women may require additional supplemental analgesia,[102,104] whereas higher doses may increase opioid-related side effects without improving analgesia.

The long duration of epidural morphine analgesia prompts many clinicians to remove the epidural catheter after bolus administration. However, some investigators have proposed that the epidural catheter should be left *in situ* to allow administration of additional doses.[110] Zakowski et al.[110] reported that only 36% of patients who received two doses of epidural morphine 5 mg (at the time of delivery and at 24 hours postoperatively) required supplemental analgesics, compared with 76% of patients who received one dose of 5 mg at the time of delivery.

Epidural versus Intrathecal Administration

A number of studies have compared the postcesarean analgesic efficacy of epidural and intrathecal administration of opioids.[14,111,112] Equipotent doses have been evaluated, with use of a conversion ratio of 20:1 to 30:1 between epidural and intrathecal administration. Sarvela et al.[112] compared epidural morphine 3 mg with intrathecal morphine 0.1 mg and 0.2 mg; they found that the two routes of administration provided postcesarean analgesia with similar efficacy and equal duration (Figure 28-4). Duale et al.[111] observed modest improvements in pain scores and less morphine consumption with epidural morphine 2 mg than with intrathecal morphine 0.075 mg. In both studies, the incidence of side effects (e.g., sedation, pruritus, nausea and vomiting) was not significantly different between the epidural and intrathecal routes of administration.[111,112] No differences in postoperative pain scores, analgesic consumption, or treatment of side effects (e.g., nausea, vomiting, pruritus) were reported in a cohort of women who underwent scheduled cesarean delivery and received intrathecal morphine 0.2 mg, compared with a cohort who underwent intrapartum cesarean delivery and received epidural morphine 4 mg.[113] A meta-analysis concluded that both epidural and intrathecal techniques provide effective postcesarean analgesia, with neither technique being superior in terms of analgesic efficacy.[14] However, intrathecal administration results in less systemic drug exposure and less potential fetal drug

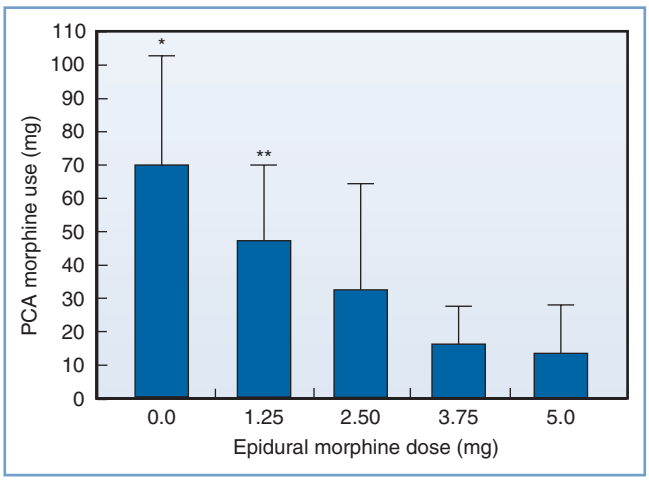

FIGURE 28-3 ■ Random allocation dose-response trial of epidural morphine 0, 1.25, 2.5, 3.75, and 5.0 mg for postcesarean delivery analgesia. Breakthrough pain as assessed by total 24-hour patient-controlled analgesia (*PCA*) morphine use. Data are mean ± 95% confidence interval. Groups were significantly different ($P < .001$). *Group 0.0 mg was significantly different from groups 2.5, 3.75, and 5.0 mg. **Group 1.25 mg was significantly different from groups 3.75 and 5.0 mg. (From Palmer CM, Nogami WM, Van Maren G, Alves DM. Postcesarean epidural morphine: a dose-response study. Anesth Analg 2000; 90:887-91.)

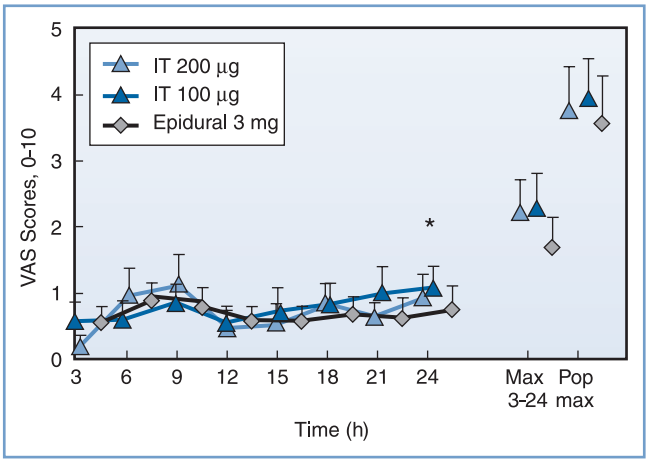

FIGURE 28-4 ■ Randomized trial of epidural morphine 3 mg, intrathecal (*IT*) morphine 100 µg (0.1 mg), and IT morphine 200 µg (0.2 mg). Visual analog scale (*VAS*) scores of postoperative pain during the first 24 hours at 3-hour intervals, as well as the maximal pain score at rest for each patient during the first 24 hours (*Max 3-24*) and the maximal pain score when moving (*Pop max*), expressed as means and 95% error bars in the three groups. *$P < .05$, epidural compared with both IT groups at 24 hours. (From Sarvela J, Halonen P, Soikkeli A, Korttila K. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesth Analg 2002; 95:436-40.)

exposure and may have a faster onset of action than epidural administration of morphine. Additionally, unintentional subdural or intrathecal administration of a dose intended for epidural administration can lead to profound sedation and respiratory depression, requiring opioid reversal and intensive care monitoring with possible ventilatory support.[114] If a CSE anesthetic is planned, intrathecal administration of the opioid may be preferable.

Fentanyl

Fentanyl is not approved by the FDA for neuraxial administration, but it is very commonly administered "off label" for postcesarean analgesia. Commercial preparations of fentanyl contain no preservatives, are suitable for epidural or intrathecal administration, and have an excellent safety record. Grass et al.[115] reported that the 50% and 95% effective doses (ED_{50} and ED_{95}, respectively) of epidural fentanyl to reduce postcesarean pain scores to less than 10 mm (using a 100-mm visual analog scale) were 33 µg and 92 µg, respectively. Epidural fentanyl doses of 1 µg/kg have also been suggested to optimize *intra*operative analgesia.[116] In clinical practice, doses of 50 to 100 µg are given alone or in combination with epidural morphine. Adverse neonatal effects should be considered if fentanyl is administered before delivery. It may be prudent to delay fentanyl administration until the umbilical cord has been clamped if high doses (> 100 µg) are planned. Epidural fentanyl doses less than 50 µg do not provide optimal analgesia.[117]

The slow onset of action of morphine limits its ability to provide optimal intraoperative analgesia, and more lipophilic opioids (e.g., fentanyl) with a faster onset of analgesia are more appropriate for supplementation of intraoperative analgesia (see Table 28-2).[98,118,119] Although single-dose epidural fentanyl improves intraoperative analgesia, no meaningful postoperative pain relief occurs beyond 4 hours.[120] Naulty et al.[121] reported that epidural fentanyl 50 to 100 µg provided 4 to 5 hours of pain relief and significantly reduced 24-hour analgesic requirements after cesarean delivery. However, Sevarino et al.[122] reported an analgesic duration of only 90 minutes and no reduction in 24-hour opioid requirements in patients who received epidural fentanyl 100 µg with epidural lidocaine anesthesia for cesarean delivery. A dose-response study of epidural fentanyl 25, 50, 100, and 200 µg (with lidocaine and epinephrine) found that the duration of analgesia ranged from 1 to 2 hours.[115] These discrepancies in the duration of analgesia can likely be attributed to the use of different local anesthetics in these studies. Bupivacaine has a long duration of action and may potentiate spinal opioid analgesia by altering opioid receptor conformation and facilitating opioid receptor binding.[123,124] Prior epidural administration of 2-chloroprocaine may be associated with a short duration of epidural fentanyl analgesia. This effect does not appear to be a pH-dependent phenomenon; it may reflect µ-opioid receptor antagonism caused by 2-chloroprocaine.[109]

Lipophilic opioids do not spread rostrally in CSF to any great extent and tend to have limited dermatomal spread.[80, 98] Birnbach et al.[125] found that the onset and duration of analgesia provided by epidural fentanyl 50 µg could be improved by increasing the volume of normal saline in the epidural injectate (Figure 28-5); this finding contrasts to observations of epidural morphine (see earlier discussion).

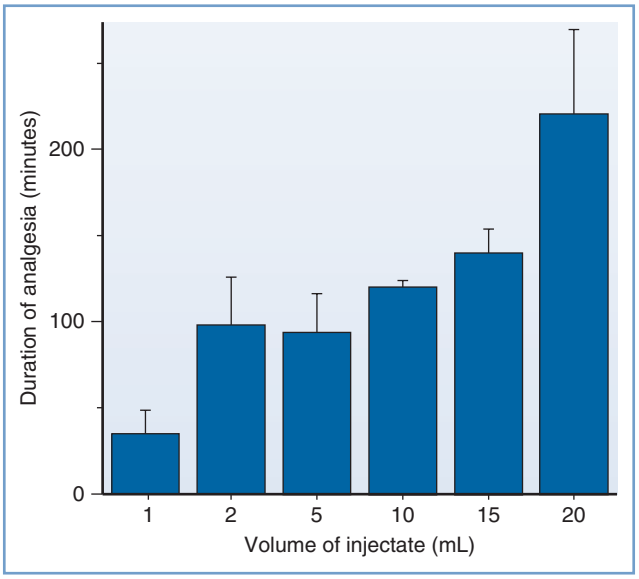

FIGURE 28-5 ■ Duration of postcesarean analgesia provided by epidural fentanyl 50 µg administered in different volumes of normal saline. $P < .001$, each group compared with the control group (1 mL). (Data from Birnbach DJ, Johnson MD, Arcario T, et al. Effect of diluent volume on analgesia produced by epidural fentanyl. Anesth Analg 1989; 68:808-10.)

Local anesthetics may have a synergistic effect with epidurally administered opioids. The concurrent administration of local anesthetic reduces epidural fentanyl dose requirements after cesarean delivery.[126] Epidural fentanyl, administered either as a single dose or as a continuous or patient-controlled infusion, generally has fewer side effects than epidural morphine.[83,121,122] Some investigators have suggested that the administration of epidural fentanyl before incision may provide preemptive analgesia that improves postoperative analgesia.[116]

Sufentanil

Epidural sufentanil is a lipid-soluble opioid that provides a rapid onset of effective postcesarean analgesia. In patients recovering from cesarean delivery, the potency ratio of epidural sufentanil to epidural fentanyl is approximately 5 : 1.[115] No differences in onset, quality, or duration of analgesia were found after epidural administration of equi-analgesic doses of sufentanil and fentanyl.[115] Like fentanyl, epidural sufentanil does not provide postoperative analgesia of significant duration. Rosen et al.[127] compared postcesarean epidural morphine 5 mg with epidural sufentanil 30, 45, or 60 µg. Although most patients who received sufentanil reported pain relief within 15 minutes, the duration of analgesia was 4 to 5 hours, in contrast to the 26 hours of analgesia with epidural morphine.[127] The duration of analgesia is dose dependent; an epidural bolus of sufentanil 25 µg produced less than 2 hours of analgesia, whereas 60 µg provided 5 hours of pain relief.[115,127]

The rapid onset and short duration of action of sufentanil are desirable characteristics for continuous epidural infusion. The vascular uptake of epidural sufentanil is significant, and plasma concentrations increase progressively after epidural administration. However, no data exist to establish dose limits for epidural sufentanil administration in this setting.

Meperidine

Epidural meperidine has been used for postcesarean analgesia and has local anesthetic properties. Two clinical trials compared the safety and efficacy of epidural meperidine 50 mg and intramuscular meperidine 100 mg administered to patients after cesarean delivery.[128,129] Epidural meperidine provided a faster onset of analgesia with a duration (2 to 4 hours) similar to that provided by intramuscular meperidine. Paech[130] evaluated the quality of analgesia and side effects produced by a single epidural bolus of meperidine 50 mg or fentanyl 100 μg. The onset of pain relief was slightly faster with fentanyl; however, the duration of analgesia was longer with meperidine. Ngan Kee et al.[131,132] compared different doses of epidural meperidine (12.5, 25, 50, 75, and 100 mg) as well as varying volumes of diluent. The investigators concluded that meperidine 25 mg diluted in 5 mL of saline was superior to 12.5 mg and that doses greater than 50 mg offered no improvement in the quality or duration of analgesia. Epidural meperidine is not associated with marked hemodynamic effects, which are more commonly observed after intrathecal administration.[133] Studies that have compared a single bolus dose of epidural or intrathecal morphine with PCEA meperidine have reported superior analgesia with morphine, but with a higher incidence of opioid-related side effects such as nausea, pruritus, and sedation.[134,135] The potential for accumulation of the active metabolite normeperidine limits meperidine doses and duration of treatment in this setting.[136]

Other Epidural Opioids

Hydromorphone

Hydromorphone is a hydroxylated derivative of morphine with a lipid solubility intermediate between that of morphine and meperidine.[137] The quality of epidural hydromorphone analgesia after cesarean delivery appears to be similar to that observed with epidural morphine; however, its onset is faster and its duration is slightly shorter.[138-140] Evidence suggests a potency ratio of 3:1 to 5:1 between epidural morphine and epidural hydromorphone.[137]

Chestnut et al.[140] evaluated postcesarean analgesia with epidural hydromorphone 1 mg. Most patients reported good or excellent pain relief, and the mean time to first request for supplemental analgesia was 13 hours. Dougherty et al.[138] reported that epidural hydromorphone 1.5 mg provided 18 hours of postcesarean analgesia and could be prolonged to 24 hours with the addition of epinephrine. Henderson et al.[139] observed 19 hours of postcesarean analgesia with epidural hydromorphone 1 mg. The incidence of pruritus was high in the two latter studies.[138,139] Halpern et al.[141] found no overall differences in quality of postcesarean analgesia or severity of side effects between patients who received either epidural hydromorphone 0.6 mg or epidural morphine 3 mg. Pruritus was more pronounced in the hydromorphone group in the first 6 hours; however, the incidence was higher in the morphine group at 18 hours. A Cochrane review suggests that epidural morphine and hydromorphone provide analgesia with similar efficacy and side effects when given for the treatment of acute or chronic pain.[142]

Diamorphine

Diamorphine is a lipid-soluble derivative of morphine that is commonly administered neuraxially in the United Kingdom.[143] The lipid solubility of diamorphine provides rapid-onset analgesia, and its principal metabolite (morphine) facilitates a prolonged duration of analgesia. Epidural diamorphine 5 mg provides rapid onset and effective postcesarean analgesia.[144,145] Roulson et al.[146] found that epidural diamorphine 2.5 mg provided postcesarean analgesia for 16 hours. Other investigators have found the duration of postcesarean analgesia provided by epidural diamorphine to be 6 to 12 hours.[144,145,147] In the United Kingdom, the National Institute of Clinical Excellence (NICE) suggests a dose of epidural diamorphine of 2.5 to 5 mg for postcesarean analgesia.[148]

Butorphanol

The mixed agonist-antagonist opioid butorphanol offers two theoretical advantages when administered epidurally: (1) modulation of visceral nociception due to selective κ-opioid receptor activity, and (2) a ceiling effect for respiratory depression even if opioid molecules spread rostrally to the brainstem.[71] Unfortunately, significant sedation often occurs as a result of vascular uptake and activation of supraspinal κ-opioid receptors. Although epidural butorphanol 2 to 4 mg provides up to 8 hours of postcesarean analgesia,[149,150] a dose-dependent increase in sedation occurs. Low doses (0.5 and 0.75 mg) of epidural butorphanol are not associated with significant sedation but provide modest analgesia after cesarean delivery compared with epidural bupivacaine alone.[151] Camann et al.[152] found that epidural butorphanol 2 mg offered few advantages over a similar dose given intravenously. In addition to excessive maternal somnolence, there is concern about the neurologic safety of epidural butorphanol, which is based on observations after repeated intrathecal injections in animals.[153,154] Epidural butorphanol is *not* recommended for postcesarean analgesia because of its potential neurotoxicity, and it is not approved by the FDA for neuraxial use.

Nalbuphine

Nalbuphine is a semisynthetic opioid with higher lipid solubility than morphine. *In vitro* studies have shown that moderate agonist activity occurs at κ-opioid receptors, and antagonist activity occurs at μ-opioid receptors. In animal models, neuraxial nalbuphine provides effective

analgesia. The rapid onset and intermediate duration of action of nalbuphine are consistent with its lipid solubility and rapid clearance.[155] However, Camann et al.[156] found that for doses ranging from 10 to 30 mg, epidural nalbuphine provided minimal analgesia and significant somnolence after cesarean delivery. The addition of nalbuphine 0.02 to 0.08 mg/mL to an epidural infusion of hydromorphone 0.075 mg/mL did not improve analgesia after cesarean delivery.[157]

Epidural Opioid Combinations

Theoretically, the epidural administration of a lipophilic opioid combined with morphine should provide analgesia of rapid onset and prolonged duration. The use of lipophilic opioids administered intrathecally (e.g., fentanyl 15 µg) or epidurally (e.g., fentanyl 100 µg in combination with epidural morphine 3.5 mg) improves analgesia and reduces nausea and vomiting *during* cesarean delivery.[158,159] Some investigators have expressed concern that opioid interactions might reduce analgesic efficacy after epidural administration and that neuraxial fentanyl might initiate acute tolerance or affect the pharmacokinetic and receptor-binding characteristics of morphine. However, these concerns have not been confirmed in subsequent studies.[159,160] Epidural fentanyl, administered immediately after delivery of the infant, improved the quality of intraoperative analgesia without worsening epidural morphine analgesia after cesarean delivery.[159]

Dottrens et al.[161] compared a single epidural dose of either morphine 4 mg, sufentanil 50 µg, or morphine 2 mg with sufentanil 25 µg. The addition of sufentanil to epidural morphine provided a more rapid onset and similar duration of postcesarean analgesia than morphine alone.[161] Morphine alone or in combination with sufentanil provided analgesia of significantly longer duration than sufentanil alone (Figure 28-6). Sinatra et al.[162] were unable to show any potentiation when epidural sufentanil 30 µg was added to morphine 3 mg, and the duration of this combination was shorter than that of epidural morphine 5 mg alone. The addition of a lipophilic opioid to epidural morphine is popular clinically and may improve intraoperative analgesia; however, the dose of morphine should not be reduced because postoperative analgesia may be compromised.

Studies that have evaluated the combination of butorphanol and morphine have provided conflicting results.[163-165] Lawhorn et al.[164] found that the combination of epidural morphine 4 mg and butorphanol 3 mg provided a duration of analgesia similar to that provided by epidural morphine alone. Wittels et al.[163] noted that patients who received epidural butorphanol 3 mg with morphine 4 mg reported superior pain control, a lower incidence of pruritus, and greater satisfaction during the first 12 hours after cesarean delivery than patients who received morphine alone. In contrast, Gambling et al.[165] observed no significant differences in pain, satisfaction, nausea, or pruritus when epidural butorphanol (1, 2, or 3 mg) was added to morphine 3 mg, and butorphanol administration resulted in significantly higher somnolence scores.

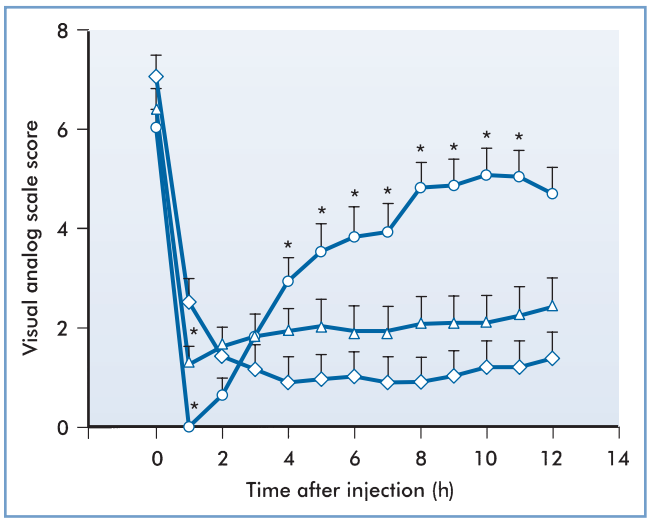

FIGURE 28-6 ■ Randomized trial of epidural morphine 4 mg (◇), sufentanil 50 µg (○), or the combination of morphine 2 mg and sufentanil 25 µg (△). Postcesarean delivery pain as measured by visual analog scale before and after epidural study drug administration. $*P < .05$ in comparison with time-matched data points for epidural morphine administration. (From Dottrens M, Rifat K, Morel DR. Comparison of extradural administration of sufentanil, morphine and sufentanil-morphine combination after caesarean section. Br J Anaesth 1992; 69:9-12.)

A low dose (5 mg) of epidural nalbuphine added to epidural morphine 4 mg has been found to reduce the severity of morphine-induced pruritus without affecting postcesarean analgesia; however, a 10-mg dose increased postoperative pain scores.[166]

Patient-Controlled Epidural Analgesia

The use of continuous epidural analgesia is a popular means of providing postoperative analgesia in patients undergoing thoracic or upper abdominal surgery. Improved analgesic outcomes have been reported in reviews of studies that compared epidural analgesia with intravenous PCA after nonobstetric surgery.[6,17]

Several studies have suggested that PCEA, using fentanyl and bupivacaine, provides better analgesia than CEI.[167,168] Other potential advantages of PCEA over CEI are lower total doses of local anesthetic, fewer nursing and physician interventions, improved patient autonomy, and better patient satisfaction.[169] A systematic review of studies comparing PCEA, CEI, and intravenous PCA suggested that CEI provides significantly better analgesia than PCEA in nonobstetric patients.[17] However, marked heterogeneity among studies prevented definitive conclusions.

Epidural morphine has a prolonged latency; therefore the use of morphine for PCEA is not a viable option owing to the accompanying risk for delayed respiratory depression. Thus, more lipophilic drugs have been more widely evaluated for PCEA after cesarean delivery (Table 28-4).

Previous investigations have compared **meperidine** PCEA with other routes of parenteral administration (PCA, intramuscular). Yarnell et al.[67] reported that PCEA meperidine provided better postcesarean analgesia than intermittent intramuscular meperidine. Patients

TABLE 28-4 **Comparative Studies Investigating Opioid-Containing, Patient-Controlled Epidural Analgesia (PCEA) Regimens for Postcesarean Analgesia**

Comparison(s)*	PCEA Dosing Regimen	Pain Scores	Mean Total 24-h Opioid Usage
PCEA versus Intramuscular Opioids			
Meperidine PCEA versus meperidine IM (100 mg, q3-4 h)[67]	B = 10 mg LO = 20 min BI = 10 mg/h	PCEA group lower VAS score (3-24 h)	625 mg versus 485 mg (PCEA versus IM; $P < .05$)
PCEA versus Epidural Opioid			
Meperidine PCEA versus epidural morphine (B = 4 mg)[171]	B = 15 mg LO = 10 min No BI	VAS score lower at 2 h; higher at 8, 10, 24 h in PCEA group	PCEA = 192 mg (NA for epidural morphine)
Fentanyl PCEA versus epidural morphine (B = 3 mg)[174]	B = 50 μg LO = 5 min (max 100 μg/h)	No differences in pain outcome measurements	PCEA = 680 μg
PCEA versus PCA			
Meperidine PCEA versus meperidine PCA (B = 20 mg; LO = 5 min)[170]	B = 20 mg LO = 5 min No BI	PCEA lower VAS score (2-24 h)	NA
Meperidine PCEA versus PCA; fentanyl PCEA versus PCA (4 groups: cross-over study)[172]	Meperidine PCEA/PCA: B = 20 mg LO = 6 min No BI Fentanyl PCEA/PCA: B = 40 μg LO = 6 min No BI	Meperidine PCEA versus PCA: lower VAS score Meperidine versus fentanyl: no difference in VAS score (PCEA and PCA)	NA
Hydromorphone PCEA versus PCA (B = 0.15 mg, LO = 10 min)[176]	Hydromorphone PCEA: Loading dose = 0.225-0.9 mg B = 0.15 mg LO = 30 min	No differences in pain VAS score	PCEA 1.8-2.1 mg versus PCA 7.6 mg
PCEA versus PCEA			
Meperidine PCEA versus fentanyl PCEA[173]	Meperidine PCEA: B = 25 mg LO = 20 min No BI Fentanyl PCEA: B = 50 μg LO = 20 min	No differences in pain VAS score	NA
Three groups: Bupivacaine 0.1% PCEA Fentanyl PCEA 4 μg/mL Bupivacaine 0.1% + fentanyl PCEA 4 μg/mL[68]	All PCEA regimens: B = 5 mL LO = 10 min	No differences in pain VAS score on coughing	NA
Four groups: Hydromorphone PCEA Hydromorphone PCEA + BI Hydromorphone + 0.08% bupivacaine PCEA Hydromorphone + 0.08% bupivacaine PCEA + combination BI[69]	All PCEA regimens: B = 2 mL LO = 30 min Hydromorphone BI = 0.0375 mg/h Combination BI = hydromorphone 0.0375 mg/h + bupivacaine 0.04 mg/h	No differences in pain VAS score	NA
Sufentanil PCEA 0.8 μg/mL versus fentanyl PCEA 2 μg/mL†[177]	All PCEA regimens: B = 3 mL LO = 15 min BI = 16 mL/h	No differences in pain VAS score	NA

B, bolus; *BI,* background infusion; *IM,* intramuscular injection; *LO,* lockout interval; *NA,* data not available; *PCA,* intravenous patient-controlled analgesia; *PCEA,* patient-controlled epidural analgesia; *VAS,* visual analog scale.
*Superscript numbers indicate chapter references.
†Both groups received 0.01% bupivacaine + epinephrine 0.5 μg/mL.

receiving PCEA were also able to ambulate and nurse their infants earlier. Paech et al.[170] performed a crossover study to compare PCEA with intravenous PCA meperidine for the first 24 hours after cesarean delivery; patients were randomly assigned to either PCEA or intravenous PCA for 12 hours before crossing over to the other route of drug administration for the next 12 hours. The PCEA and PCA meperidine protocols in this study were identical (20-mg bolus, 5-minute lockout). Patients receiving meperidine PCEA had lower pain scores at rest and with coughing than patients receiving intravenous PCA. Other studies have compared PCEA meperidine with other opioids for postcesarean analgesia. Fanshawe[171] compared PCEA meperidine with single-dose epidural morphine. Postoperative pain scores were significantly lower with PCEA meperidine at 2 hours but were higher at 6, 8, and 24 hours. The investigators speculated that the variability in analgesic outcomes could have resulted from a suboptimal PCEA meperidine bolus dose of 15 mg. Studies have suggested that a meperidine bolus dose of 25 mg would be better suited for PCEA use (analgesic onset 12 minutes, median duration 165 minutes).[132,136] Ngan Kee et al.[172] and Goh et al.[173] used different crossover study designs to investigate the analgesic effects of meperidine and fentanyl using intravenous PCA and PCEA modalities. Ngan Kee et al.[172] observed that PCEA (fentanyl or meperidine) regimens were associated with lower pain scores compared with the respective PCA regimens. Goh et al.[173] observed similar analgesic profiles among patients receiving fentanyl and meperidine PCEA, but noted more favorable side-effect profiles and better patient satisfaction among patients receiving meperidine PCEA.

Fentanyl PCEA (50-μg bolus, 5-minute lockout, maximum dose 100 μg/h) has been shown to produce similar analgesia and less pruritus compared with epidural morphine 3 mg.[174] Cooper et al.[68] postulated that the combination of epidural fentanyl with local anesthetic (fentanyl 2 μg/mL with 0.05% bupivacaine) would provide better analgesia than that provided by a single-drug regimen (fentanyl 4 μg/mL or 0.1% bupivacaine PCEA). The combination-drug regimen was associated with lower pain scores at rest and significantly lower total drug requirements. However, no significant differences in pain scores during coughing were reported among the three groups (Figure 28-7). Matsota et al.[175] compared PCEA with 0.15% ropivacaine, 0.15% levobupivacaine, and a 0.15% ropivacaine-fentanyl 2 μg/mL combination regimen for postcesarean analgesia. Administration of the ropivacaine-fentanyl combination resulted in higher patient satisfaction despite a lack of difference among groups in pain scores or local anesthetic consumption.

The efficacy of **hydromorphone** (single drug and combination) PCEA regimens after cesarean delivery has been investigated (see Table 28-4).[69,157,176] Parker and White[176] compared hydromorphone PCEA with intravenous PCA; no significant differences in pain scores were found between the two treatment groups. However, investigators found that patients who received hydromorphone PCEA received less opioid in the first 24 hours, had less pruritus, and reported a more rapid return of bowel function. In a follow-up study, these investigators

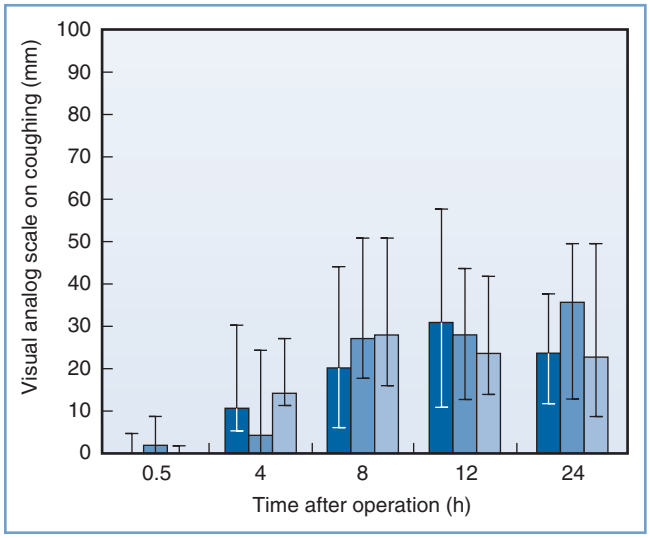

FIGURE 28-7 ■ Randomized trial of postcesarean delivery patient-controlled epidural analgesia (PCEA) with fentanyl 4 μg/mL, 0.1% bupivacaine, or both fentanyl 2 μg/mL and 0.05% bupivacaine. Pain scores during coughing on a visual analog scale. Median score and interquartile range for groups who received epidural bupivacaine (*dark blue bars*), fentanyl (*medium blue bars*), and bupivacaine plus fentanyl (*light blue bars*). There were no differences in scores among the 3 groups. (From Cooper DW, Ryall DM, McHardy FE, et al. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. Br J Anaesth 1996; 76:611-5.)

assessed hydromorphone PCEA, with and without a background infusion, and hydromorphone combined with 0.08% bupivacaine, with and without a background infusion.[69] No differences in pain scores, PCEA usage, or 24-hour PCEA requirements were noted, and the combination of hydromorphone-bupivacaine PCEA with a background infusion was associated with a greater degree of lower extremity numbness and weakness.

Parker et al.[157] assessed how varying concentrations of epidural **nalbuphine** may alter the analgesic efficacy and side-effect profile of hydromorphone PCEA. The investigators found that higher doses of nalbuphine were associated with partial reversal of analgesia, more pruritus, less nausea, and decreased urinary retention.

PCEA with **sufentanil** has been evaluated for postcesarean analgesia.[177,178] Cohen et al.[177] compared fentanyl and sufentanil PCEA after cesarean delivery. The PCEA regimen in each group included 0.01% bupivacaine and epinephrine 0.5 μg/mL. Pain scores and side effects (nausea, pruritus, and sedation) were similar in the two groups; however, vomiting occurred more commonly in the sufentanil group. Vercauteren et al.[178] compared sufentanil PCEA (bolus 5 μg, lockout 10 minutes) with an identical PCEA regimen accompanied by a background infusion of sufentanil 4 μg/h.[178] Pain was significantly lower at 6 hours in the group receiving PCEA with a background infusion, but no other differences in analgesia were reported between 6 and 24 hours. The overall incidence and severity of sedation were higher in the background infusion group.

Integrating different epidural regimens (PCEA with CEI) may be beneficial in optimizing postoperative analgesia. In a study assessing analgesia after intra-abdominal

surgery, patients receiving fentanyl PCEA with bupivacaine CEI reported pain scores similar to those in patients receiving a bupivacaine-fentanyl CEI; however, the total fentanyl requirements were lower in the PCEA group.[179] Further work is necessary to evaluate PCEA regimens that optimize analgesic efficacy while maintaining adequate patient mobility and ambulation after surgery. It remains unclear whether a single drug or a combination PCEA drug regimen is preferable or whether a background infusion optimizes analgesia for patients receiving PCEA.

Although CEI or PCEA can provide satisfactory postoperative analgesia, these techniques diminish maternal mobility, increase costs, and potentially increase the risk for catheter-related complications (e.g., hematoma, infection) in comparison with single-dose administration of neuraxial morphine.[180] In addition, epidural catheter movement commonly occurs with ambulation or patient movement and ultimately can result in ineffective postoperative analgesia.[26] These disadvantages associated with epidural catheter–based techniques (CEI and PCEA) have limited their popularity for provision of postcesarean analgesia compared with the use of single-bolus doses of intrathecal or epidural morphine.[13]

Extended-Release Epidural Morphine

Extended-release epidural morphine (EREM) (DepoDur) is an FDA-approved drug that delivers standard morphine sulfate via DepoFoam (Pacira Pharmaceuticals, Inc., San Diego, CA). DepoFoam is a drug-delivery system composed of multivesicular lipid particles containing nonconcentric aqueous chambers that encapsulate the active drug.[181,182] These naturally occurring lipids are broken down by erosion and reorganization, resulting in a sustained release of morphine for up to 48 hours after epidural administration of a single dose.[182-184]

Two studies have evaluated the analgesic efficacy of EREM for postcesarean analgesia.[57, 58] Both studies concluded that patients receiving EREM report lower pain scores and have lower requirements for supplemental analgesia over 48 hours than patients receiving standard epidural morphine.[57,58] In the first study, overall supplemental opioid use was approximately 50% less in the EREM 10-mg and 15-mg groups than in the standard epidural morphine 5-mg group (Figure 28-8).[57] A follow-up study, which allowed concurrent administration of an NSAID in both groups, compared a single dose of EREM 10 mg with standard epidural morphine 4 mg after cesarean delivery. The investigators found that analgesic consumption was 60% less in women in the EREM group than in women in the standard epidural morphine group.[58] Patients who received EREM also had better and more prolonged pain control both at rest and with movement (Figure 28-9). A retrospective study of patients undergoing knee and hip arthroplasty found that EREM resulted in similar levels of pain control, improved ambulation, but more respiratory depression and nausea, compared with a CEI of 0.1% bupivacaine with morphine 40 µg/mL.[185] In the two postcesarean studies, there was no significant difference in the incidence of nausea, pruritus, or sedation between the EREM and standard epidural morphine groups, and no respiratory depression or hypoxic events were observed.[57,58] However, it is likely that the study groups were too small for accurate evaluation of side-effect profiles. Pooled data from EREM studies for nonobstetric surgery suggest that EREM is associated with more side effects than standard epidural

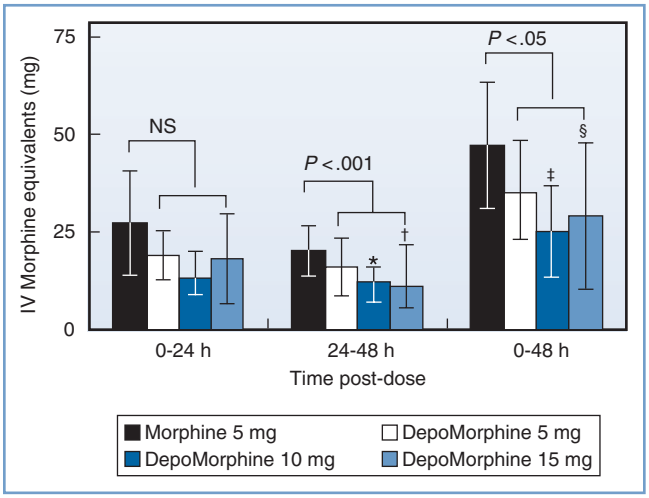

FIGURE 28-8 ■ Randomized trial of single-shot epidural morphine compared with extended-release epidural morphine (EREM). Use of supplemental opioid analgesics (in morphine mg-equivalents) during the 48 hours after the study dose (DepoMorphine is EREM). *IV,* intravenous. **P* = .0134; †*P* = .0001; ‡*P* = .0108; §*P* = .0065. (Modified from Carvalho B, Riley E, Cohen SE, et al. Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. Anesth Analg 2005; 100:1150-8.)

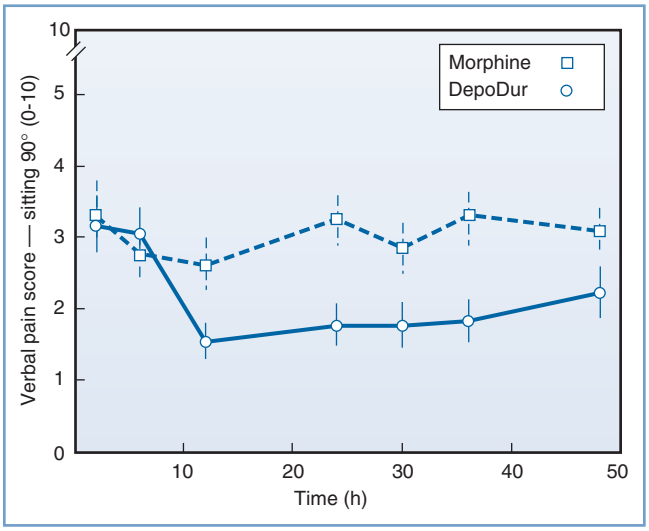

FIGURE 28-9 ■ Randomized trial of single-shot epidural morphine 4 mg and extended-release epidural morphine (EREM) 10 mg for postcesarean analgesia. Pain intensity over time (verbal rating scale for pain [VRSP] 0-10) during activity (sitting up 90 degrees) plotted as means with standard deviations. *P* = .003 for EREM (DepoDur) group versus the conventional morphine group. (From Carvalho B, Roland LM, Chu LF, et al. Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for postcesarean pain. Anesth Analg 2007; 105:176-83.)

morphine, especially with higher doses.[182,186] A meta-analysis found that EREM was associated with a significantly higher risk for respiratory depression compared with intravenous opioid PCA (odds ratio [OR], 5.8; 95% CI, 1.1 to 31.9; $P = .04$).[187] Further research is needed to assess the side-effect and safety profile of EREM in obstetric patients.

When EREM is given correctly in the epidural space, monitoring for respiratory depression should be continued for 48 hours (compared with 24 hours with standard epidural morphine).[188] Unintentional intrathecal EREM administration has the potential to result in profound and prolonged opioid-related side effects; however, a case report of unintentional intrathecal administration of a standard dose of EREM did not result in profound side effects or respiratory depression.[189] Although single-dose EREM may reduce the need for additional doses of opioid, more prolonged monitoring is necessary, which may increase the required level of nursing care in the postoperative period.[190]

Currently, there is insufficient clinical evidence to advocate a change in the planned anesthetic technique (from a spinal to an epidural or CSE technique) *solely* for the purpose of EREM administration in patients undergoing cesarean delivery. However, many clinicians already use CSE techniques for elective cesarean delivery in selected patients (when the duration of the cesarean delivery is expected to extend beyond that provided by spinal anesthesia). In addition, many cesarean deliveries are performed in women in whom an epidural catheter has been placed previously during labor. Therefore, it is possible that EREM may be an attractive option for clinicians who plan to use or insert an epidural catheter for cesarean delivery. However, caution should be exercised when the administration of EREM follows the use of any epidural local anesthetic. Early pharmacokinetic studies suggested a potential physicochemical interaction between EREM and epidural local anesthetics, which could negate the *sustained-release* effect derived from the DepoFoam. A 2011 study found that epidural lidocaine administration (20 to 35 mL) for cesarean delivery, administered 1 hour before EREM administration, increased peak venous blood morphine levels and increased the incidence of vomiting, use of supplemental oxygen, and hypotension, compared with a control group who did not receive epidural lidocaine.[191] However, Gambling et al.[192] demonstrated no differences in the pharmacokinetic and pharmacodynamic profiles of EREM when administered 15, 30, and 60 minutes after epidural bupivacaine 0.25%. The package insert advises: "Local anesthetics other than a 3-mL test dose of lidocaine are not permitted. If the 3-mL test dose is used, wait 15 minutes and then flush the epidural catheter with 1 mL of saline before administration of EREM."[193]

In summary, EREM provides effective postoperative pain relief and reduces the need for supplemental analgesics in comparison with standard epidural morphine for up to 48 hours after cesarean delivery.[57,58] This analgesic advantage must be weighed against potential disadvantages associated with EREM administration. The role of EREM for postcesarean analgesia remains unclear[186]; however, selective use may be beneficial in a subset of patients with significant analgesic needs. In such cases, a single dose of EREM 6 to 10 mg is recommended after the infant is delivered (and the umbilical cord is clamped), as an alternative to standard epidural morphine.

INTRATHECAL OPIOIDS

Spinal anesthesia has become the preferred anesthetic technique for patients undergoing elective cesarean delivery in the United States and the United Kingdom.[11-13] Intrathecal opioids are commonly administered with a local anesthetic to improve intraoperative and postoperative analgesia (Table 28-5).

Morphine

The potency differences between intrathecal and epidural opioids account for the smaller doses of intrathecal opioid used for cesarean delivery. Intrathecal morphine 0.075 to 0.2 mg has been found to be equivalent to epidural morphine 2 to 3 mg.[111,112] Initial reports of increased side effects with intrathecal administration likely resulted from the use of very high doses (2 to 10 mg). The

TABLE 28-5 **Intrathecal Opioids for Cesarean Delivery**

Drug	Dose	Onset (min)	Peak Effect (min)	Duration (h)	Advantages	Disadvantages
Morphine	0.075-0.2 mg (75-200 μg)	30-60	60-90	12-28	Long duration	Side-effect profile Potential for delayed respiratory depression
Fentanyl	10-25 μg	5	10	2-3	Rapid onset	Minimal postoperative analgesia Short duration Pruritus
Sufentanil	2.5-5 μg	5	10	2-4	Rapid onset	Minimal postoperative analgesia Short duration Pruritus
Meperidine	10 mg	10-15	15-20	4-5	Rapid onset	Minimal postoperative analgesia Nausea and vomiting

analgesic efficacy, duration of action, and side-effect profile of intrathecal morphine are similar to that of epidural morphine in patients undergoing cesarean delivery (see earlier discussion).[111,112,194]

Onset and Duration

Intrathecal morphine administration may result in a faster onset of analgesia than epidural morphine, but 45 to 60 minutes are still required for the drug to achieve a peak effect. The duration of analgesia is similar to the duration after epidural administration (14 to 36 hours).* A systematic review and meta-analysis found that the median time to first analgesic request was 27 hours (range, 11 to 29 hours) after intrathecal morphine administration for postcesarean analgesia (Figure 28-10).[51] A meta-analysis of studies of intrathecal opioid administration in adults undergoing orthopedic, urologic, gynecologic, or general surgical procedures reported that intrathecal morphine (0.05 to 2 mg) provided postoperative analgesia with a mean duration of 503 minutes (95% CI, 315 to 641).[198] The duration of analgesia may be dose dependent.[51,195] Abboud et al.[195] observed that postcesarean analgesia increased from 19 hours to 28 hours with intrathecal morphine 0.1 mg and 0.25 mg, respectively.

*References 50, 51, 98, 111, 112, 194-197.

Optimal Dosage

Several studies have attempted to determine the optimal dose of intrathecal morphine for postcesarean analgesia. Palmer et al.[199] compared postcesarean intravenous PCA morphine use after doses of intrathecal morphine ranging from 0.025 to 0.5 mg. The investigators found no significant difference in PCA morphine use with morphine doses greater than 0.075 mg.[199] They concluded that there was little justification for using a dose of intrathecal morphine higher than 0.1 mg for postcesarean analgesia. Milner et al.[200] noted that intrathecal morphine 0.1 mg and 0.2 mg produced comparable analgesia but that the lower dose led to less nausea and vomiting. Yang et al.[201] showed that intrathecal morphine 0.1 mg

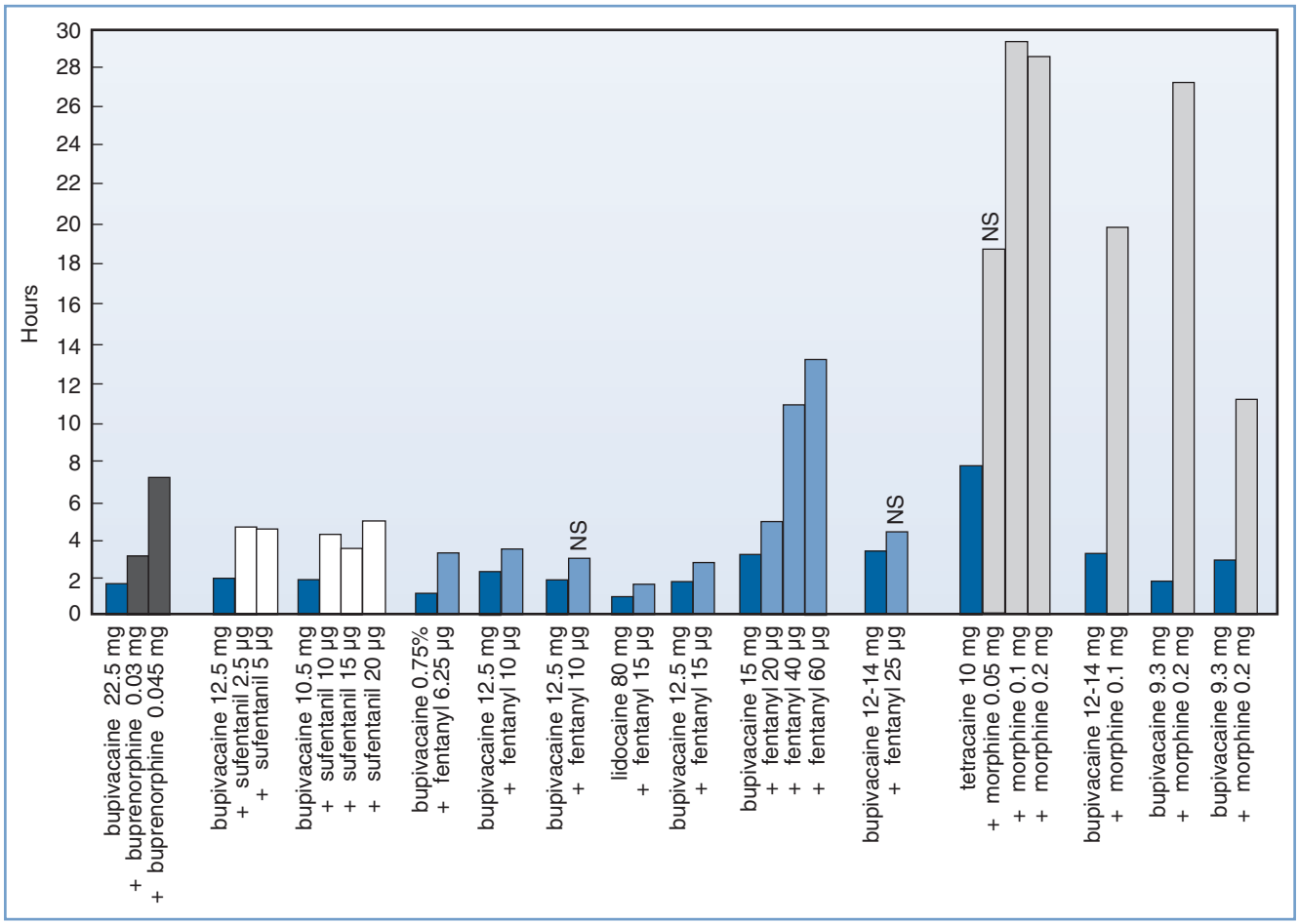

FIGURE 28-10 ■ Systematic review of intrathecal opioid analgesia for post–cesarean delivery analgesia. Time to first administration (in hours) of postoperative supplemental analgesics in patients receiving spinal anesthesia with local anesthetic alone (*dark blue bars*) or local anesthetic combined with buprenorphine, sufentanil, fentanyl, or morphine in varying doses (*various bars*). *NS,* no significant difference from control. (From Dahl JB, Jeppesen IS, Jorgensen H, et al. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia. Anesthesiology 1999; 91:1919-27.)

provided similar postcesarean analgesia with fewer side effects in comparison with 0.25 mg. Uchiyama et al.[202] performed a dose-response study with intrathecal morphine 0, 0.05, 0.1, and 0.2 mg. They observed that 0.1 mg and 0.2 mg provided comparable and effective postcesarean analgesia for 28 hours. The 0.05-mg dose was less effective, and the incidence of side effects was greater with the 0.2-mg dose; therefore, the investigators concluded that intrathecal morphine 0.1 mg is the optimal dose for postcesarean analgesia.[202] A recent retrospective study reported that intrathecal morphine 0.2 mg provided better analgesia than 0.1 mg but with the "trade-off" of increased nausea.[203] Girgin et al.[204] reported no differences in analgesia with intrathecal morphine doses ranging from 0.1 to 0.4 mg; however, pruritus was increased with higher morphine doses. A systematic review recommended 0.1 mg as the intrathecal morphine dose of choice.[51]

Several studies have compared the analgesic efficacy and side-effect profile of intrathecal morphine with those of PCEA after cesarean delivery. A study comparing intrathecal morphine 0.15 mg with PCEA with 0.06% bupivacaine and sufentanil 1 μg/mL found superior analgesia and fewer side effects with the PCEA regimen.[180] Paech et al.[135] compared intrathecal morphine 0.2 mg with PCEA meperidine for postcesarean analgesia. Patients in the morphine group reported lower pain scores but also had a higher incidence of pruritus, nausea, and drowsiness. In a study of intrathecal morphine (0, 0.05 and 0.1 mg) followed by a CEI (0.2% ropivacaine at 6 mL/h), intrathecal morphine improved postcesarean analgesia compared with placebo.[205]

In summary, the intrathecal administration of a small dose of morphine (0.075 to 0.2 mg) provides effective analgesia for 14 to 36 hours after cesarean delivery. Larger doses may increase side effects without conferring additional analgesic benefit. Because of the variability in patient response to intrathecal morphine, some patients may experience inadequate postoperative analgesia and/or opioid-related side effects. Thus, the use of low-dose intrathecal morphine as a component of multimodal analgesia may provide optimal analgesia with a low risk for side effects (see Chapter 27).

Fentanyl

Intrathecal fentanyl improves intraoperative analgesia (especially during uterine exteriorization), reduces intraoperative nausea and vomiting, decreases local anesthetic dose requirement, and provides a better postoperative transition to other pain medications during recovery from spinal anesthesia for cesarean delivery.[206-209] However, intrathecal fentanyl provides a limited duration of postcesarean analgesia, with a median time to first request for additional analgesia of 4 hours (range, 2 to 13 hours) (see Figure 28-10).[51] The aforementioned meta-analysis of studies of intrathecal opioid administration in adults undergoing nonobstetric surgery reported that intrathecal fentanyl (10 to 50 μg) provided postoperative analgesia with a mean duration of 114 minutes (95% CI, 60 to 168).[198] A study that compared intrathecal morphine 0.1 mg with fentanyl 25 μg found that morphine provided better and longer postoperative analgesia after cesarean delivery.[210]

The analgesic effects, duration of analgesia, and side effects after intrathecal fentanyl are dose related.[51,206,207] Belzarena et al.[206] found that intrathecal fentanyl provided analgesia for a duration of 305 to 787 minutes (with 0.25 μg/kg and 0.75 μg/kg, respectively). However, patients who received the higher dose experienced decreased respiratory rates and a high incidence of side effects (e.g., pruritus, nausea). Dahlgren et al.[207] reported that intrathecal fentanyl 10 μg added to bupivacaine increased the mean time of effective analgesia from 121 minutes to 181 minutes. Hunt et al.[211] compared a range of intrathecal fentanyl doses (2.5 to 50 μg) in combination with intrathecal bupivacaine for cesarean delivery. Intrathecal fentanyl doses larger than 6.25 μg were associated with better intraoperative analgesia and a longer time to first request for additional analgesia than administration of bupivacaine alone (72 minutes versus 192 minutes, respectively).[211] Chu et al.[212] found that fentanyl doses of 12.5 to 15 μg were required to increase the duration of effective analgesia.

In summary, intrathecal fentanyl optimizes intraoperative analgesia and provides immediate postoperative analgesia. However, intrathecal fentanyl (10 to 25 μg) provides a limited duration of postcesarean analgesia (2 to 4 hours) and does not decrease subsequent postoperative analgesic requirements.

Sufentanil

Sufentanil has a fast onset of action, which may improve intraoperative analgesia and reduce the dose of local anesthetic required for cesarean anesthesia.[213] However, its pharmacokinetic properties limit the duration of effective postcesarean analgesia after intrathecal administration.[51] Courtney et al.[214] found that intrathecal sufentanil 10, 15, or 20 μg resulted in a mean duration of postcesarean analgesia of approximately 3 hours. More than 90% of patients reported pruritus, but only one patient required treatment. Dahlgren et al.[207] compared the safety and efficacy of the co-administration of sufentanil 2.5 or 5 μg, fentanyl 10 μg, or placebo with hyperbaric bupivacaine 12.5 mg for cesarean delivery. The duration of effective analgesia was longer with the opioids, particularly in the sufentanil groups; sufentanil 5 μg provided the longest duration of analgesia but also had the highest incidence of pruritus. Patients receiving intrathecal sufentanil had lower requirements for intraoperative antiemetics and postoperative intravenous morphine.[207] A study that compared intrathecal sufentanil 2.5, 5.0, and 7.5 μg found that 5.0 and 7.5 μg provided more effective postcesarean analgesia than was observed in a control group (no intrathecal opioids); however, the incidence of pruritus was higher with sufentanil, especially with the 7.5-μg dose.[215] Karaman et al.[216] found that intrathecal sufentanil 5 μg delayed the time to first analgesic request to 6 hours, compared with 20 hours for intrathecal morphine 0.2 mg. A study that compared intrathecal ropivacaine 15 mg to ropivacaine 10 mg with sufentanil 5 μg showed that sufentanil provided effective analgesia with a mean duration of only 260 minutes. However, women

in the sufentanil group had less intraoperative hypotension, shivering, and vomiting, as well as a shorter duration of motor blockade.[217] A study that compared intrathecal fentanyl 20 μg and sufentanil 2.5 μg added to bupivacaine for cesarean delivery found no difference in the quality of intraoperative and postoperative analgesia, as well as no difference in the frequency of nausea and pruritus between the two opioid groups.[218]

Other Intrathecal Opioids

Meperidine

Intrathecal meperidine reduces the intensity of pain associated with the regression of spinal anesthesia and provides postoperative analgesia of intermediate duration (4 to 5 hours).[219,220] Yu et al.[221] found that the addition of meperidine 10 mg to hyperbaric bupivacaine 10 mg prolonged the mean duration of postcesarean analgesia (234 minutes in the meperidine group versus 125 minutes in a placebo group). However, the incidence of intraoperative nausea and vomiting was greater in the meperidine group. A dose of 7.5 mg added to bupivacaine 10 mg provided postoperative analgesia for 257 ± 112 minutes (mean ± SD) compared with a saline group (161 ± 65 min).[222]

Unlike other opioids, meperidine possesses local anesthetic qualities. Some anesthesia providers have administered intrathecal 5% meperidine (1 mg/kg) as the sole anesthetic agent for cesarean delivery under spinal anesthesia. However, surgical anesthesia was unreliable, with a mean anesthetic duration of 41 ± 15 minutes.[219,220]

Diamorphine

Diamorphine has physicochemical properties that are of value in providing intrathecal analgesia. A high lipophilicity (octanol-water coefficient = 280) results in a rapid onset of analgesia, and diamorphine's active metabolite (morphine) provides a prolonged duration of analgesia.

Kelly et al.[223] compared intrathecal diamorphine 0.125, 0.25, and 0.375 mg for cesarean delivery. The 0.25-mg and 0.375-mg doses provided effective postcesarean analgesia; the incidence of both vomiting and pruritus was dose related. Stacey et al.[224] reported that the duration of analgesia was dose dependent and found that intrathecal diamorphine 1 mg provided 10 hours of postcesarean analgesia, compared with 7 hours for 0.5 mg. The rapid onset of diamorphine is a potential advantage in the provision of intraoperative as well as postoperative analgesia.[225,226] Saravanan et al.[227] concluded that the ED_{95} for intrathecal diamorphine to prevent intraoperative discomfort was 0.4 mg. A dose-response study using intrathecal diamorphine 0.1, 0.2, or 0.3 mg reported a dose-dependent enhancement of analgesia and an increase in pruritus.[9]

Husaini et al.[228] observed that intrathecal diamorphine 0.2 mg and intrathecal morphine 0.2 mg provided similar postcesarean analgesia as measured by postoperative intravenous PCA morphine requirements. However, the patients who received intrathecal morphine had a higher incidence of pruritus and drowsiness. Hallworth et al.[229] reported that *intrathecal* diamorphine 0.25 mg produced the same duration and quality of postcesarean analgesia as did *epidural* diamorphine 5 mg, with less nausea and vomiting.

Diamorphine has been commonly used in the United Kingdom, but it is not available for clinical use in the United States. In the United Kingdom, the National Institute of Clinical Excellence suggests an intrathecal diamorphine dose of 0.3 to 0.4 mg for postcesarean analgesia.[148]

Nalbuphine

Culebras et al.[230] compared intrathecal morphine 0.2 mg with intrathecal nalbuphine (0.2, 0.8, or 1.6 mg) for postcesarean analgesia. Intrathecal nalbuphine 0.8 mg provided good intraoperative and early postoperative analgesia without side effects. However, intrathecal morphine provided significantly longer postoperative analgesia. In an accompanying editorial, the study was criticized because the safety and neurotoxicity of nalbuphine had not been adequately assessed.[155]

Intrathecal Opioid Combinations

Intrathecal administration of morphine in combination with a lipophilic opioid (e.g., fentanyl, sufentanil) may offer some advantages. Intrathecal morphine has a delayed onset, and therefore lipophilic opioids with a rapid onset may improve intraoperative analgesia and reduce the intensity of pain associated with the regression of spinal anesthesia in the postanesthesia care unit after surgery. Chung et al.[231] found that the combination of intrathecal meperidine 10 mg and morphine 0.15 mg provided better intraoperative analgesia, less need for supplemental analgesia, and higher satisfaction than intrathecal morphine alone for cesarean delivery. Intrathecal sufentanil 5 μg co-administrated with morphine 0.15 mg provided better and longer pain relief than intrathecal sufentanil plus a single injection of subcutaneous morphine; however, a higher incidence of side effects, such as nausea and vomiting, was observed with intrathecal morphine.[232]

Some investigators have suggested that intrathecal morphine may be less effective when concurrently administered with intrathecal fentanyl.[233] Cooper et al.[233] reported that patients who received intrathecal fentanyl 25 μg with bupivacaine had higher postoperative intravenous morphine PCA requirements than patients who received bupivacaine alone. The investigators postulated that this phenomenon was due to acute spinal opioid tolerance. Carvalho et al.[234] found no difference in postoperative analgesia requirement but small differences in pain scores with the addition of increasing doses of intrathecal fentanyl (5, 10, or 25 μg) to intrathecal morphine 0.2 mg for cesarean delivery. The authors suggested that intrathecal fentanyl may induce subtle acute tolerance to intrathecal morphine. However, the clinical significance of this finding is unclear, especially in light of the intraoperative benefit of using intrathecal fentanyl. Sibilla et al.[197] found that the intrathecal combination of fentanyl 25 μg with morphine 0.1 mg provided similar

postoperative analgesia to that provided by intrathecal morphine alone. Many anesthesia providers currently administer both intrathecal morphine and fentanyl when giving spinal anesthesia for cesarean delivery.[13] The co-administration of intrathecal fentanyl does *not* appear to significantly compromise the postoperative analgesia provided by intrathecal morphine.

Multimodal Analgesia

Despite the appropriate administration of neuraxial techniques, the quality and duration of analgesia after cesarean delivery is often incomplete. Thus, neuraxial opioids are rarely the sole analgesic technique used for postcesarean analgesia. Rather, neuraxial opioids should be considered as part of a multimodal analgesic approach for the treatment of postcesarean pain.[25,26,59] Multimodal strategies (with neuraxial opioid and postoperative NSAID and acetaminophen administration) optimize analgesia and reduce analgesic requirements and side effects (see Chapter 27).

Maternal Safety and Neonatal Effects

Careful evaluation of the potential adverse effects of neuraxial pharmacologic agents is necessary before clinical administration of these agents.[235] In obstetric patients, adverse maternal effects (e.g., neurotoxicity, altered uteroplacental perfusion) as well as potential adverse neonatal effects should be assessed. Although many agents are used routinely and safely in clinical practice, not all are licensed for neuraxial administration in the United States.

Maternal Safety

Neurotoxicity (safety) studies that have been conducted for morphine, fentanyl, sufentanil, meperidine, clonidine, and neostigmine suggest that these agents are safe for neuraxial administration.[236-239] Morphine is approved by the FDA for neuraxial administration. Although unlicensed for neuraxial administration, fentanyl and sufentanil have been used for many years without evidence of neurotoxicity. Studies in sheep have reported potential neurotoxicity with intrathecal butorphanol.[153] Culebras et al.[230] demonstrated potential toxic interactions with the co-administration of nalbuphine and local anesthetic. However, Rawal et al.[153] evaluated the behavioral and histopathologic effects of butorphanol, sufentanil, and nalbuphine after intrathecal administration in sheep and found that nalbuphine caused the least evidence of neural tissue damage.

Clinicians should avoid neuraxial administration of any agent before adequate evaluation for potential neurotoxicity has been completed.[240-242] Drugs and diluents that are proven safe for parenteral use may have adverse effects when administered intrathecally. Despite these valid concerns, a number of opioid analgesics, including fentanyl and sufentanil, have been administered intrathecally to healthy obstetric patients without adequate investigation of their safety profile in animal and clinical volunteer studies.[242]

Preservatives that are added to many commercial preparations may be hazardous if administered neuraxially. Examples are sodium (meta)bisulfite and disodium ethylenediaminetetraacetic acid (EDTA), which are known to incite inflammatory and fibrotic changes in pia-arachnoid and spinal tissue after intrathecal administration. Dezocine has been shown to cause neuropathologic changes in the dog spinal cord.[243] Similarly, glycine, a preservative added to remifentanil preparations, is contraindicated for neuraxial injection.

Neonatal Effects

All opioids have the potential for placental transfer and neonatal effects. Minimal neonatal effects have been found after the administration of epidural morphine 2 to 7.5 mg for cesarean delivery.[244] However, it may be preferable to administer neuraxial opioids after umbilical cord clamping to avoid placental transfer. Lipophilic opioids are associated with greater systemic uptake; if indicated (e.g., intraoperative pain during cesarean delivery), the smallest necessary dose should be administered. Courtney et al.[214] found that intrathecal sufentanil (10, 15, or 20 μg) did not affect neonatal outcome as assessed by umbilical cord blood gas measurements and Apgar and neurobehavioral scores. Intrathecal opioids are associated with less neonatal drug transfer than epidural or intravenous opioid administration, given that smaller doses are used for intrathecal administration.[245]

SIDE EFFECTS OF NEURAXIAL OPIOIDS

Respiratory Depression

Pharmacokinetics and Pharmacodynamics

Neuraxial opioids can depress the respiratory centers in the brainstem via direct and/or indirect mechanisms (Table 28-6).[80,82,97,98,246-248] Respiratory depression after neuraxial morphine administration is biphasic.[249] Early respiratory depression can occur 30 to 90 minutes after epidural morphine administration (owing to systemic vascular absorption),[98] whereas delayed respiratory depression can occur 6 to 18 hours after epidural or intrathecal morphine administration (owing to rostral spread in CSF and slow penetration into the brainstem).[118] In contrast, lipophilic opioids (e.g., fentanyl, sufentanil) do not cause delayed respiratory depression but may cause early-onset respiratory depression, typically within 30 minutes, because of significant vascular uptake and rostral spread in CSF and, potentially, direct transit in epidural veins.[246,247]

Incidence

Although rare, perioperative opioid-induced respiratory depression represents a significant concern that can lead to death or permanent brain damage.[250,251] The reported incidence of respiratory depression after neuraxial opioid administration ranges from 0% to 3.4%.[252] Differences in the observed incidence of respiratory depression may reflect differences in patient population, opioid dose,

TABLE 28-6 Neuraxial Opioids and the Principal Mechanisms of Action Leading to Respiratory Depression

Mechanism	Lipophilic Opioids (e.g., fentanyl)	Hydrophilic Opioids (e.g., morphine)
Vascular uptake (by the epidural or subarachnoid venous plexuses and circulation) to the respiratory center in the brainstem	+++	+
Rostral spread via direct perimedullary vascular channels	++	+
Dural penetration of opioids	+	++
Rostral spread via the aqueous cerebrospinal fluid to the brainstem	+	+++

The + symbols denote the relative importance of the mechanism for the type of opioid.
Data from references 80, 81, and 214-216.

monitoring protocol, and definition of respiratory depression.[253] The incidence is likely lower in healthy obstetric patients receiving low-dose neuraxial opioid analgesia. The incidence of respiratory depression after neuraxial morphine administration in obstetric patients ranges from 0% to 0.9%.[254] The analgesic benefits derived from neuraxial opioids outweigh the risks of respiratory depression in most patients. No studies in the obstetric setting have reported serious morbidity, although some patients have required naloxone administration for treatment of respiratory depression.[103] Early reports suggested that intrathecal morphine was more likely to cause delayed respiratory depression than epidural morphine.[98] However, this likely reflected the higher intrathecal morphine doses (1 to 10 mg) used in early clinical studies.[255] Subsequently, lower doses of intrathecal morphine were found to provide effective analgesia with a very low risk for clinically significant respiratory depression. The incidence of respiratory depression associated with systemic (intravenous or intramuscular) opioids is likely to be higher than that observed with neuraxial opioids.[195,256,257]

Extended-Release Epidural Morphine and Lipophilic Opioids

The incidence of respiratory depression with EREM may be higher than with standard epidural morphine, with a reported range of 2% to 16%.[182,186,187] EREM is also associated with a significantly higher risk for respiratory depression compared with intravenous PCA (see earlier discussion).[187] However, patients in these studies received large EREM doses (15 to 30 mg), were older, had more comorbidities, and often received general anesthesia for surgery. Studies of EREM in patients undergoing cesarean delivery have reported no clinically significant respiratory depression[57,58,191]; however, the small sample sizes in these studies and low incidence of respiratory depression did not allow for an accurate assessment of the incidence of respiratory depression. EREM use should be carefully considered prior to its administration to high-risk obstetric patients (e.g., obesity, obstructive sleep apnea, co-administration of magnesium sulfate). Its use requires more prolonged monitoring and nursing care.[190,254]

There are a few case reports of respiratory depression after neuraxial administration of a lipophilic agent in the obstetric setting. In one report, respiratory depression occurred 25 minutes after spinal anesthesia with intrathecal fentanyl 15 μg and required reversal with naloxone.[258] Respiratory depression has been described after administration of epidural fentanyl 90 to 100 μg for cesarean delivery.[259,260] Cohen et al.[247] reported that epidural sufentanil 30 to 50 μg depressed the ventilatory response to CO_2 after cesarean delivery. Although overt respiratory depression did not occur, the highest sedation scores and depression of CO_2 response occurred 45 minutes after administration. Another group reported that epidural fentanyl 100 μg or sufentanil 10 to 50 μg added to lidocaine for cesarean delivery caused significant changes in respiratory rate and end-tidal CO_2.[261]

Prevention

Identify Patients at Risk. Risk factors for respiratory depression in the surgical setting include advanced age, obesity, cardiopulmonary disease, obstructive sleep apnea, and preoperative opioid tolerance.[196,262] To identify patients at increased risk for respiratory depression, a history and physical examination directed at identifying sleep apnea and other relevant medical comorbidities should be performed prior to neuraxial opioid administration.[262,263] Caution should be exercised when women are receiving magnesium sulfate, parenteral or oral opioids, or sedative drugs (e.g., diphenhydramine), because these agents may increase the risk for respiratory depression.[251] Fortunately, most obstetric patients are relatively young and healthy and rarely have significant pulmonary disease or other risk factors for respiratory depression. However, opioid-induced respiratory depression occasionally occurs in healthy patients who have received standard doses of a neuraxial opioid,[251] and vigilance is needed to prevent this rare but hazardous adverse outcome (Table 28-7).[264]

Limit Opioid Dose. Historically, respiratory depression was more common because patients received doses of a neuraxial opioid greater than those currently used in modern practice. For cesarean delivery, neuraxial morphine appears to have a limit or "ceiling" in terms of analgesic efficacy. More specifically, effective doses of intrathecal and epidural morphine are 0.075 to 0.2 mg and 2 to 4 mg, respectively.[51,104,199,252] Higher doses of neuraxial morphine may increase side effects without significant improving or prolonging postoperative analgesia.[252]

TABLE 28-7 Recommendations to Reduce the Risk for Respiratory Depression after Neuraxial Administration of Opioids

Principle	Recommendation(s)	Clinical Example(s)
Prevention	Identify high-risk patients	Patients with obesity or sleep apnea or who are receiving magnesium or sedatives
	Limit neuraxial morphine dose	Intrathecal morphine 0.075 to 0.2 mg Epidural morphine 2 to 4 mg
Detection	Appropriate monitoring of:	
	Level of consciousness	Clinical signs, sedation scores
	Adequacy of ventilation	Respiratory rate, end-tidal CO_2 level
	Adequacy of oxygenation	Pulse oximetry, arterial blood Po_2
	Monitoring continued for duration of effect	Fentanyl/sufentanil: 4 h Morphine: 24 h Extended-release epidural morphine: 48 h
Treatment	Implementation of clinical protocols for detecting and treating respiratory depression	
	Nursing and physician education	

Monitoring, Detection, and Treatment

Monitor Respiration and Understand the Limitations of Monitoring Techniques. A closed-claims analysis showed that 56% of respiratory events after neuraxial opioids could have been prevented.[251] American Society of Anesthesiologists (ASA) guidelines address the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration.[262] However, these guidelines do not specifically address obstetric patients.[254] Opioid effects on respiration include reduced minute ventilation (decrease in respiratory rate, tidal volume, or both) and decreased response to hypoxemia and changes in Pco_2.[255] All patients receiving neuraxial opioids should be monitored for adequacy of ventilation, oxygenation, and level of consciousness.

Current monitoring technology and clinical observation practices have limitations.[251,265] *Intermittent evaluation of* **clinical signs** (e.g., respiratory rate, level of sedation, pupil size) is often an unreliable predictor of respiratory depression.[251,266] Intermittent respiratory monitoring may miss transient episodes of desaturation and bradypnea, because respiratory depression typically progresses slowly and is often preceded by increasing maternal sedation. The Anesthesia Patient Safety Foundation recommends **continuous electronic monitoring** in all hospitalized patients receiving opioids.[251] Although **pulse oximetry** is considered the most useful electronic monitor currently available, it has poor sensitivity in detecting hypoventilation and hypercarbia, especially when supplemental oxygen is administered.[251,265] Brief episodes of desaturation are common up to 24 hours after cesarean delivery; in one study, 71% of post–cesarean delivery patients had one or more episodes of desaturation (Spo_2 less than 85%) after epidural morphine 5 mg.[267] Continuous pulse oximetry is often inconvenient, owing to motion-artifact alarms that may affect patients' sleep and nursing care. **Apnea monitors** are also frequently associated with false alarms and do not detect hypoventilation. **End-tidal CO_2 monitoring** in patients whose trachea is not intubated has significant limitations and is not universally available.

Despite these limitations, vigilant nursing care and hourly assessments of respiratory effort, respiratory rate, and somnolence are probably adequate for low-risk patients.[103,254,268,269] Continuous pulse oximetry, although appropriate for the obstetric patient with risk factors for respiratory depression such as obesity, may be unnecessary in healthy postcesarean patients receiving small doses of neuraxial opioid (e.g., intrathecal morphine ≤ 0.2 mg, epidural morphine ≤ 4 mg).[254] Greater surveillance and ventilation monitoring (e.g., capnography) may be warranted in patients at high risk for respiratory depression who are receiving supplemental oxygen.[265]

Monitor Respiration for an Appropriate Duration. The duration of respiratory monitoring corresponds to the expected duration of action of the administered opioid. The onset of respiratory depression after neuraxial opioids is variable and has been reported to range from 2 to 12 hours.[256] CO_2 responsiveness is depressed for up to 24 hours after cesarean delivery after administration of epidural morphine 5 mg.[149] The ASA recommends that respiratory monitoring after neuraxial administration of standard morphine should occur at least every hour for the first 12 hours and then every 2 hours for the next 12 hours (and then every 4 hours for *another* 24 hours in patients who have received EREM).[186,262]

Early-onset respiratory depression associated with lipophilic opioids usually occurs within 30 minutes of administration and is likely to occur in a high-visibility, controlled setting (e.g., operating or labor room). The ASA recommends that respiratory monitoring after administration of neuraxial fentanyl should continue for a minimum of 2 hours.[262] However, it is prudent to continue monitoring for at least 3 to 4 hours with larger doses (e.g., intrathecal fentanyl > 20 μg, epidural fentanyl >100 μg), because delayed onset of respiratory depression (up to 180 minutes) has occurred after administration of lipophilic opioids.[246,259] Patients receiving a continuous infusion of neuraxial opioid should be monitored during the infusion and for the expected residual duration of action after cessation of the infusion.[262]

Treating Respiratory Depression. Physicians and nursing staff must be educated to prevent, recognize, and treat respiratory depression. Treatment protocols

and mechanisms to ensure a rapid response to respiratory events are recommended. The patient who displays an altered level of consciousness, bradypnea, or hypoxemia should receive continuous supplemental oxygen until she is alert with no evidence of respiratory depression or hypoxemia. The routine use of supplemental oxygen is not advised because of the associated risk for prolonged apnea as well as limitations in the sensitivity of pulse oximetry to detect hypoventilation.[251] An intravenous bolus dose of naloxone is indicated in patients with profound somnolence and respiratory depression who do not respond to arousal. Continued observation is advised after naloxone administration, because its half-life (43 to 90 minutes) may be shorter than the duration of effect for long-acting opioids. If naloxone fails to reverse severe respiratory depression or arrest, prompt mask ventilation and/or tracheal intubation should be performed. An intravenous infusion of naloxone should be maintained for as long as the patient remains symptomatic. It may be feasible to titrate an intravenous infusion of naloxone to treat respiratory depression without significantly reducing the quality of neuraxial analgesia.[270-272] Although naloxone is a viable therapeutic option for reversing the opioid-induced respiratory depression, the routine administration of prophylactic naloxone is not recommended.[269] Patients who require continuous positive airway pressure devices should be advised to continue using these devices during the postpartum period.

Nausea and Vomiting

Nausea and vomiting are common complaints after cesarean delivery, and the etiology of these symptoms is presumed to be multifactorial. A 2005 review highlighted the anesthetic and nonanesthetic causes of intraoperative nausea and vomiting (IONV) (Table 28-8).[273] It is unclear whether patients are at increased risk for postoperative nausea and vomiting (PONV) if these symptoms occur intraoperatively. Neuraxial opioids may increase the risk for PONV after cesarean delivery. Nausea results either from the rostral spread of opioid in the CSF to the brainstem or from vascular uptake and delivery to the vomiting center and chemoreceptor trigger zone.[118, 274] Palmer et al.[199] found no difference in PONV between intrathecal morphine (0.025 to 0.5 mg) and placebo, nor a relationship between PONV and morphine dose. A similar study by the same group found no difference in the severity of PONV in patients receiving increasing doses of epidural morphine (1.25 to 5 mg).[104] Importantly, neither study was adequately powered to investigate PONV as a primary outcome measure.

Many studies have investigated different regimens to reduce PONV in patients receiving neuraxial opioids for cesarean delivery; however, these studies did not standardize PONV outcome measures and did not stratify patients according to risk for PONV. Information about the use of prophylactic antiemetic agents in actual clinical practice is lacking. A survey in Germany indicated that 82% of anesthesia departments did not provide any antiemetic prophylaxis for patients undergoing cesarean delivery.[275]

TABLE 28-8 **Causes, Preventive Measures, and Treatment Measures for Intraoperative Nausea and Vomiting during Cesarean Delivery**

Causes	Prevention/Treatment
Anesthetic Causes	
Hypotension	Left uterine displacement, adequate preload, vasopressors
Neuraxial opioids	Use optimal doses
Parenteral opioids	Avoid or use minimum effective doses
Increased vagal activity	Use vagolytics
Nonanesthetic Causes	
Surgical manipulation	Avoid excessive manipulation
Motion	Avoid vigorous movements
Uterotonic agents	Titrate to clinical effect with adequate doses

Modified from Balki M, Carvalho JC. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. Int J Obstet Anesth 2005; 14:230-41.

Individual Antiemetic Agents

Older-generation antiemetics, such as metoclopramide and droperidol, have been commonly used to prevent or treat neuraxial opioid-induced emesis in the obstetric setting. **Metoclopramide** 10 mg has been shown to decrease early PONV after intraoperative intravenous fentanyl and epidural morphine administration.[276] In a meta-analysis of studies that assessed efficacy of antiemetic prophylaxis, metoclopramide was associated with a reduced incidence of IONV and early PONV compared with placebo (Figure 28-11).[277] Metoclopramide antagonizes dopamine receptors in the chemoreceptor trigger zone. It is often administered preoperatively owing to its favorable prokinetic properties, and it is associated with a reduction in rates of IONV and PONV in patients receiving spinal anesthesia.[278]

Droperidol is a butyrophenone that antagonizes dopaminergic (D_2) receptors in the chemoreceptor trigger zone. Prophylactic administration of droperidol (0.625 to 2.5 mg) has been shown to decrease PONV after epidural anesthesia with epidural fentanyl[279] and epidural morphine.[280] Sedation and drowsiness may occur with droperidol, although their appearance does not appear to be a dose-related phenomenon. Droperidol has been less widely used by anesthesia providers since the FDA issued a "black box" warning in 2001, which highlighted concern related to conduction abnormalities (QT interval prolongation and an increased risk for development of *torsades de pointes*).

The use of a transdermal **scopolamine** patch may also lower the incidence of PONV after cesarean delivery. Early work by Kotelko et al.[281] indicated that scopolamine is effective at reducing PONV during the first 10 hours after cesarean delivery. A transdermal scopolamine patch (1.5 mg) provided efficacy similar to that provided by ondansetron 4 mg in reducing postcesarean emesis

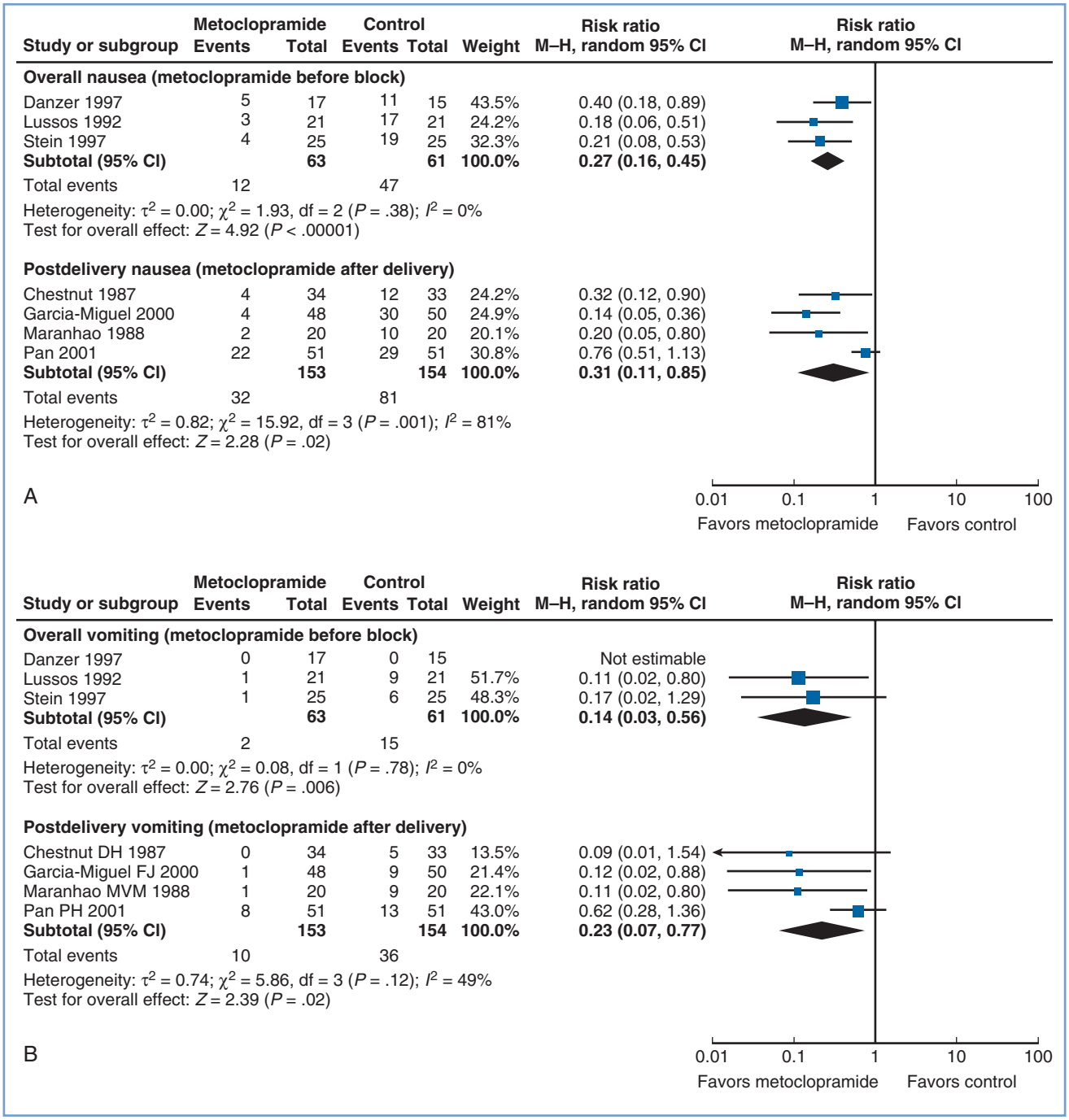

FIGURE 28-11 ■ Meta-analysis of metoclopramide for nausea and vomiting prophylaxis during and after cesarean delivery. **A,** Forest plots for intraoperative nausea in patients undergoing cesarean delivery with neuraxial anesthesia. **B,** Forest plots for intraoperative vomiting in patients undergoing cesarean delivery with neuraxial anesthesia. In each series, separate analyses were performed according to whether metoclopramide was administered before block placement (overall incidence) or after umbilical cord clamping (postdelivery incidence). *CI,* confidence interval. (Forest plots from Ashraf Habib, Duke University, Durham, NC. See Mishriky BM, Habib AS. Impact of data by Fujii and colleagues on the meta-analysis of metoclopramide for antiemetic prophylaxis in women undergoing Caesarean delivery under neuraxial anaesthesia. Br J Anaesth 2012; 109:826.)

among patients receiving spinal anesthesia (incidence of 40% and 42% respectively, versus 59% in a control group).[282] However, transdermal scopolamine has a latency period of 3 to 4 hours, which limits its ability to treat early PONV. It also has a number of commonly reported side effects, including dry mouth, visual disturbances, dizziness, and agitation.

Serotonin (5-HT_3) receptor antagonists have been used for both prophylaxis and treatment of PONV. These drugs specifically bind to 5-HT_3 receptors in the chemoreceptor trigger zone and at vagal afferents in the gastrointestinal tract. Prophylactic administration of **ondansetron** 4 to 8 mg has been shown to have a better antiemetic profile in the first 24 hours after intrathecal

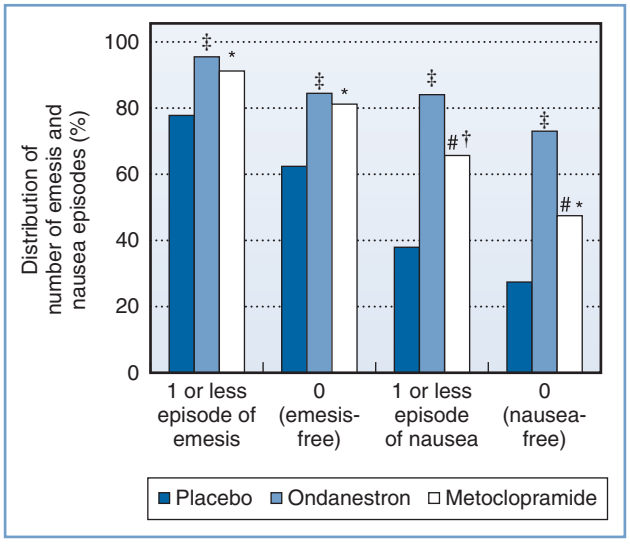

FIGURE 28-12 ■ Randomized trial of postoperative nausea and emesis in patients undergoing cesarean delivery with epidural anesthesia (2% lidocaine with epinephrine and fentanyl) and who received prophylactic ondansetron, metoclopramide, or placebo. Distribution of number of nausea and emesis episodes. Values are given as percentages. #Group metoclopramide versus ondansetron; $P < .05$. *Group metoclopramide versus placebo; $P < .05$. †Group metoclopramide versus placebo; $P < .005$. ‡Group ondansetron versus placebo; $P < .005$. (Data from Pan PH, Moore CM. Comparing the efficacy of prophylactic metoclopramide, ondansetron, and placebo in cesarean section patients given epidural anesthesia. J Clin Anesth 2001; 13:430-5.)

and epidural opioid administration compared with placebo (Figure 28-12).[283,284] Research evaluating the antiemetic profile of **granisetron** in patients receiving spinal anesthesia for cesarean delivery is limited. Balki et al.[285] found no difference in the rate of IONV in patients receiving granisetron 1 mg compared with placebo (20% versus 17%). A recent meta-analysis of six trials found that the use of 5-HT_3 receptor antagonists reduced the incidence of PONV and the need for rescue antiemetic treatment in women who received intrathecal opioids for cesarean delivery.[286]

Administration of the corticosteroid **dexamethasone** has been successful in preventing and treating emesis after chemotherapy, and subsequently the drug has become more popular as an antiemetic agent in anesthesia practice. Corticosteroids have various effects in the CNS, including the regulation of transmitter levels, receptor densities, and neuronal configurations.[287] Corticosteroid receptors have been identified in areas important to the signal processing of nausea and vomiting, including the nucleus of the solitary tract, the nucleus of raphe, and the area postrema. Tzeng et al.[287] reported that intravenous dexamethasone 8 mg and droperidol 1.25 mg provided similar efficacy in the prevention of PONV. Wang et al.[288] suggested that dexamethasone 5 mg is the minimum effective dose for preventing PONV. In both of these studies, patients received epidural morphine 3 mg. In a recent meta-analysis of studies of obstetric and gynecologic patients who received neuraxial morphine, prophylactic dexamethasone (2.5 to 10 mg) was associated with a reduced risk for PONV and need for antiemetic rescue therapy compared with placebo.[289] Administration of **cyclizine** 50 mg has been reported to be associated with significantly fewer episodes of PONV (0 to 12 hours after cesarean delivery) than administration of dexamethasone 8 mg after intrathecal opioid (fentanyl and morphine) administration.[290]

Combination Antiemetic Regimens

Few studies have compared the effects of individual drugs with those of combination antiemetic regimens. Administration of drugs acting at two different receptor sites may improve antiemetic efficacy through synergism.[291] Drug combinations may also facilitate a concomitant reduction in drug doses. Wu et al.[292] reported lower rates of PONV after intrathecal morphine administration with use of a combination of dexamethasone 8 mg and droperidol 0.625 mg than with use of dexamethasone 8 mg or droperidol 1.25 mg alone.

Nonpharmacologic Techniques

A number of studies have investigated the prophylactic use of **acupressure** (using wrist bands with a plastic bead placed bilaterally on the P6 [HG-6] acupoint) in reducing PONV after neuraxial anesthesia for cesarean delivery. Ho et al.[293] reported significantly less PONV with acupressure in cesarean delivery patients who received epidural morphine (3 mg increments, 8 mg average total dose) in the postanesthesia care unit. A similar effect was seen in a study of patients who received intrathecal morphine 0.2 mg.[294] However, other studies investigating prophylactic acupressure before spinal anesthesia reported no reduction in PONV in patients who received intrathecal morphine 0.25 mg and fentanyl 10 μg[295] or in patients who did not receive neuraxial opioids.[296] A meta-analysis of six studies (649 patients) that assessed the effect of P6 stimulation versus placebo to reduce IONV and PONV revealed inconsistent results, thereby limiting any definitive conclusions regarding the efficacy of this intervention.[297]

Pruritus

Pruritus is a common side effect of neuraxial opioid administration in obstetric patients. A retrospective review of 4880 cesarean delivery patients who received epidural morphine 2 to 5 mg observed that 58% of patients reported pruritus.[103] However, a sample of patients who received spinal anesthesia for cesarean delivery ranked pain, nausea, and vomiting as more undesirable than pruritus (see Table 28-1).[10] The incidence and severity of pruritus are likely influenced by the opioid dose, route of administration (more common after intrathecal administration), and method of assessment.[298] Approximately 40% of patients reporting pruritus after receiving epidural morphine request treatment.[103,299,300]

Pruritus may manifest in the dermatomal distribution of neuraxial opioid spread as well as nonspecific areas of the head and neck; specific symptoms and severity vary among patients.[301] These effects typically occur within a few hours of neuraxial opioid administration. Although

opioid-induced histamine release from mast cells is well described, this does not appear to be the causative mechanism for pruritus after *neuraxial* opioid administration. Plasma opioid and histamine levels are clinically insignificant at the time of symptom presentation (3 to 6 hours after intraspinal morphine administration).[98,118,302] In addition, sufentanil and fentanyl can produce pruritus but do not stimulate histamine release. At present, the mechanisms of spinal and epidural opioid–induced pruritus remain unclear. Postulated theories of causation include (1) direct or indirect excitatory effects on central μ-opioid receptors; (2) cephalad migration of the opioid within the CSF to the trigeminal nucleus (which contains the subnucleus caudalis, integrates facial sensory input, and exhibits high opioid receptor density); (3) excitatory effects on dorsal or ventral horn neurons; and (4) other mechanisms (e.g., effects on dopamine-2 [D_2] receptors, prostaglandin system, serotonin 5-HT_3 receptors, and central nervous system gamma-aminobutyric acid [GABA] and glycine receptors).[302] Pregnant patients may be more susceptible as a result of possible estrogenic interactions with opioid receptors.[303] Pharmacogenetics may also play a role. Polymorphisms at the human μ-opioid receptor gene have been implicated as a potential explanatory factor because central-type pruritus induced by neuraxial opioids may be influenced by tonic inhibitory control of pain signaling.[304] The incidence of moderate-to-severe pruritus with epidural morphine given for postcesarean analgesia has been reported to be lower in patients homozygous for the G118G polymorphism in the μ-opioid receptor gene (*OPRM1*) than in patients with the A118G or A118A genotypes (incidence 5%, 42%, and 53%, respectively).[305]

Drug Therapy

There is little consensus regarding treatment of neuraxial opioid-induced pruritus after cesarean delivery.[306] Further, there are currently no validated or consistent methods for assessing pruritus, which limits the analysis of data from studies investigating the efficacy of antipruritic regimens.

Opioid antagonists are commonly employed to treat opioid-related pruritus. The efficacy of opioid antagonists depends, in part, on the drug-opioid receptor interaction (antagonist versus mixed agonist-antagonist). Studies comparing opioid antagonists for the treatment of pruritus have demonstrated mixed results. Cohen et al.[300] compared naloxone (0.2 mg, with a maximum of three doses) with nalbuphine (5 mg, with a maximum of three doses) after administration of epidural morphine 5 mg for postcesarean analgesia. Nalbuphine significantly reduced the severity of pruritus after 30 minutes, and fewer patients in the nalbuphine group required additional doses for treatment of persistent pruritus. Somrat et al.[307] suggested that smaller doses of nalbuphine (2 to 3 mg) could adequately treat moderate-to-severe pruritus after intrathecal morphine administration. Butorphanol has attracted interest as an antipruritic agent. Wu et al.[308] found that butorphanol 1 mg followed by an infusion of 0.2 mg/h was associated with reduced postcesarean pruritus in patients who received intrathecal morphine compared with a saline-control group.

Pretreatment with opioid antagonists has also been investigated as a method of reducing the incidence of opioid-induced pruritus. Morgan et al.[309] reported that pretreatment with intravenous nalbuphine (20 mg, at skin closure) with subsequent postoperative administration (40 mg, in divided doses) was ineffective in reducing pruritus in patients receiving epidural morphine. Similarly, pretreatment with subcutaneous naloxone (0.4 mg) did not significantly reduce the incidence of pruritus in patients receiving intrathecal fentanyl and morphine for elective cesarean delivery.[310] Naloxone may be more efficacious as an infusion, and Luthman et al.[311] reported reductions in the severity and incidence of pruritus using a naloxone infusion (0.1 mg/h) after cesarean delivery. Naloxone and nalbuphine in patient-controlled bolus doses, combined with a background infusion, have also been found to reduce the incidence of pruritus after cesarean delivery in patients who received epidural morphine 5 mg.[299] Abboud et al.[312] observed that the use of the long-acting opioid antagonist naltrexone (9 mg, administered orally) was associated with a lower incidence of pruritus compared with placebo after cesarean delivery in patients who received epidural morphine 4 mg. However, these investigators also noted a significant increase in the incidence of unsatisfactory analgesia. A similar trend was reported with a 6-mg dose of oral naltrexone after administration of intrathecal morphine 0.25 mg.[313] A cautious approach is needed when considering high-dose naloxone therapy for treating pruritus to avoid reversing the analgesic effect of neuraxial opioids.[300]

The effects of neuraxially administered opioid antagonists have also been investigated. Jeon et al.[314] reported less pruritus in patients receiving epidural naloxone (1.2 mg over 48 hours) with epidural 0.1% bupivacaine and morphine (6 mg over 48 hours) than in a control group not receiving naloxone. Similarly, Culebras et al.[230] investigated the effects of three different doses of intrathecal nalbuphine (0.2, 0.8, and 1.6 mg) and found a significantly lower incidence of pruritus in all of the nalbuphine groups compared with a control group that received intrathecal morphine without nalbuphine. However, the duration of analgesia was significantly shorter among patients in the nalbuphine groups.[230] Studies in animals and nonobstetric patients have suggested no adverse neurologic effects after neuraxial administration of opioid antagonists. Of note, the use of experimental drugs and drugs not approved for neuraxial administration continues to raise concerns regarding the potential for adverse neurotoxic effects. These concerns have limited the clinical assessment of neuraxially administered drugs for the prevention and treatment of opioid-induced pruritus and other side effects. To avoid reversal of opioid-induced analgesia, further work is necessary to identify the optimal dose of each opioid antagonist for the prevention and treatment of pruritus.

NSAIDs are often incorporated into multimodal analgesic regimens for patients undergoing cesarean delivery. Some investigators have postulated that prostaglandins are involved in the etiology of pruritus after neuraxial opioid administration, owing to their ability to enhance

C-fiber transmission to the CNS and release histamine. However, there is limited evidence that NSAIDs reduce the occurrence of opioid-induced pruritus. A study evaluating the effect of oral celecoxib 200 mg after intrathecal morphine 0.3 mg reported no significant difference in the severity of pruritus or the need for rescue medications between the treatment and placebo groups.[315]

Propofol has been reported to relieve pruritus caused by neuraxial opioids in nonobstetric patients after a 10-mg bolus dose without an infusion[316] and after a 10-mg bolus dose followed by a 30 mg/24 h infusion.[317] The antipruritic effect of propofol has been proposed to occur as a result of inhibitory effects on posterior horn transmission rather than specific antagonism of the opioid receptors.[316] However, this effect has not been observed in obstetric patients who received subhypnotic doses of propofol (10 to 20 mg) for treatment of intrathecal morphine–induced pruritus.[318,319] A comparative study demonstrated that intravenous nalbuphine 3 mg is superior to propofol 20 mg for treating pruritus after administration of intrathecal morphine.[320]

The use of **5-HT_3 receptor antagonists** for *prophylaxis* of neuraxial opioid–induced pruritus after cesarean delivery has attracted interest. A meta-analysis of studies of surgical patients receiving neuraxial opioids concluded that prophylaxis with a 5-HT_3 antagonist results in a reduced risk for postoperative pruritus, compared with placebo (OR, 0.44; 95% CI, 0.29 to 0.68).[321] Direct stimulation of 5-HT_3 receptors found in the dorsal horn of the spinal cord and in the nucleus of the spinal tract of the trigeminal nerve in the medulla may occur after subarachnoid opioid administration. Intravenous **ondansetron** 4 to 8 mg has been shown to be more effective than placebo in reducing the incidence of postcesarean pruritus after intrathecal administration of morphine 0.15 to 0.2 mg.[322,323] However, other studies that compared ondansetron 8 mg with placebo found no significant reduction in pruritus after intrathecal administration of morphine (0.1 to 0.2 mg) alone[324] or in combination with a lipophilic opioid (sufentanil or fentanyl).[283,325] The lack of antipruritic effect may be due to the peak effect of ondansetron occurring much sooner (at 15 minutes) than that of intrathecal morphine. The antipruritic effects associated with ondansetron may depend on the dose, lipophilicity, and duration of action of the intrathecal opioid.[326] A study of epidurally administered ondansetron (8 mg over 2 days) in patients who received epidural ropivacaine and morphine after cesarean delivery demonstrated a reduction in the incidence of pruritus.[327] The investigators found no histologic evidence of neurotoxic sequelae after intrathecal ondansetron administration in rats.[327] There are conflicting data on the antipruritic effect of **granisetron** in patients receiving intrathecal morphine for postcesarean analgesia. Siddik-Sayyid et al.[324] found no significant differences in the incidence or severity of pruritus among patients who received granisetron 3 mg or ondansetron 8 mg and those in a control group. In contrast, Tan et al.[328] observed that the severity of pruritus was reduced at 8 and 24 hours after cesarean delivery in patients who received granisetron 3 mg compared with those who received ondansetron 8 mg.

A meta-analysis of studies (published up to 2008) in women receiving spinal anesthesia for cesarean delivery indicated that *prophylactic* administration of a 5-HT_3 antagonist did not reduce the risk for pruritus compared with a control group; however, administration of a 5-HT_3 antagonist reduced the severity of pruritus and the need for rescue treatment compared with placebo.[286] Heterogeneity and small sample sizes in the studies included in this systematic review limited detailed analysis of the efficacy of prophylactic administration of a 5-HT_3 antagonist. Large-scale prospective studies are needed to better investigate the prophylactic antipruritic efficacy of neuraxial 5-HT_3 antagonists. Few studies have assessed the *therapeutic* effect of 5-HT_3 antagonists for managing postcesarean pruritus induced by neuraxial opioids. In one study, ondansetron 4 mg had a high rate of success for the treatment of moderate-to-severe pruritus compared with placebo (80% and 36%, respectively).[329]

Pentazocine, a κ-opioid receptor agonist and partial μ-opioid receptor agonist, may be a potentially useful drug for treating opioid-induced pruritus.[330] Tamdee et al.[331] found that pentazocine 15 mg was more effective than ondansetron 4 mg for the treatment of moderate-to-severe pruritus in patients who received intrathecal morphine for postcesarean analgesia.

Historically, **antihistamines** have been a popular first choice for treatment of pruritus. However, the efficacy of these agents has been questioned in patients receiving neuraxial opioids that do not cause histamine release (e.g., fentanyl, sufentanil). Using a tailored treatment algorithm, Alhashemi et al.[332] demonstrated that diphenhydramine was less effective than nalbuphine (higher itching scores and more treatment failures) after administration of intrathecal morphine 0.2 mg. Yeh et al.[323] found that the incidence of pruritus was comparable among patients receiving diphenhydramine 30 mg and a placebo (80% and 85%, respectively); however, both groups had a higher incidence of pruritus than did a group that received ondansetron 0.1 mg/kg (25%). In contrast, Siddik-Sayyid et al.[333] found that the therapeutic success rates for ondansetron 4 mg and diphenhydramine 25 mg were identical (70% for each drug), with similar recurrence rates in successfully treated patients (28% versus 35%, respectively). Differences in study methodology and drug-dosing regimens may explain the inconsistent antipruritic effect of diphenhydramine observed in these studies.

Urinary Retention

The mechanisms by which neuraxial opioids affect specific components of micturition (urge sensation, detrusor and sphincter function) are not fully understood, although spinal and supraspinal sites of action are likely to be involved. Kuipers et al.[334] performed urodynamic studies of healthy male volunteers receiving intrathecal sufentanil and morphine. Both opioids caused dose-dependent decreases in detrusor contractility and the "urgency to void." Patients receiving intrathecal sufentanil had earlier recovery of lower urinary tract function than those receiving intrathecal morphine.[334] Intrathecal local anesthetics (bupivacaine and lidocaine) have been shown to

cause complete absence of detrusor contractility and urge sensation until the dermatomal block regresses to S2 to S3, with no partial recovery until this regression has occurred.[335]

Although neuraxial opioids may increase the risk for postpartum urinary retention after cesarean delivery, there is a lack of consensus on the definition of postpartum urinary retention in this setting. Postpartum urinary retention has been previously described as "no spontaneous voiding within 6 hours of removal of an indwelling catheter (more than 24 hours after cesarean delivery)."[336] Some authorities advocate a diagnosis based on clinical diagnostic features (e.g., "the sudden inability to void") or postvoid residual bladder volume (PVRV). However, there is marked variability in defining "significant" PVRV values (40 to 500 mL) associated with postpartum urinary retention.[337]

Few studies have investigated the incidence of urinary retention in patients who have received a neuraxial opioid for postcesarean analgesia. Evron et al.[338] performed an observational study investigating the effects of epidural morphine and methadone in 120 women undergoing cesarean delivery. Difficulty in micturition and need for bladder catheterization were greater in the morphine group (58%) compared with the methadone group (3%).[338] A similar study by Liang et al.[339] reported a higher incidence of postcesarean urinary retention and urinary catheterization (22%) among patients receiving epidural morphine compared with other analgesia modalities (PCEA with ropivacaine-fentanyl [7%]; intramuscular meperidine [3%]). In a study of male volunteers, naloxone reversed the impact of neuraxial morphine on urodynamic function.[340] To avoid impairment of bladder/detrusor function, urinary catheterization should be considered if voiding has not occurred within 6 hours.[341] Risk factors for postcesarean urinary retention include low body mass index and multiparity.[342]

Hypothermia and Shivering

Perioperative and postoperative hypothermia and shivering are commonly observed in patients who receive neuraxial anesthesia for cesarean delivery and are caused by a number of interrelated processes. The true incidence of core hypothermia and shivering in this setting is unclear; however, results from earlier studies suggest that these complications may occur in up to 66% and 85% of patients, respectively.[343,344] Core-to-periphery heat redistribution is the major cause of core hypothermia after spinal or epidural anesthesia and is due to the effects of sympathetic and motor nerve blockade.[345] A study of healthy volunteers reported that core temperature can decrease by a mean (± SD) of 0.8° ± 0.3°C in the first hour of anesthesia.[346] Neuraxial anesthesia also impairs centrally mediated thermoregulatory control, lowers the vasoconstriction and shivering thresholds, and promotes greater environmental heat loss than metabolic heat production.[347-349]

The onset and the severity of hypothermia and shivering vary according to the anesthetic technique, the anesthetic agents administered, and baseline thermal status of the patient. Saito et al.[350] found that spinal anesthesia reduces initial core temperature more rapidly than epidural anesthesia during cesarean delivery. Interestingly, there was no difference in the incidence of shivering between groups, but the severity of shivering was significantly less in the group receiving spinal anesthesia. The more intense sensory block observed with spinal anesthesia inhibits central thermoregulatory control more than epidural anesthesia, which can affect shivering thresholds and intensity.[351]

The effect of neuraxial opioids on thermoregulation and shivering in patients undergoing cesarean delivery is not fully understood. One study demonstrated that patients who received *intrathecal* morphine 0.15 mg had a greater degree of hypothermia than patients who received no intrathecal opioid.[352] However, intrathecal administration of both fentanyl and morphine is associated with a lower incidence of shivering than single-dose intrathecal morphine alone.[353] Hong and Lee[354] reported that intrathecal meperidine 10 mg produced fewer and less intense shivering episodes than intrathecal morphine (0.1 and 0.2 mg). Core hypothermia occurred to a similar extent in all study groups. In a different study, intrathecal meperidine (12.5 or 25 mg) was independently associated with a lower incidence of shivering compared with a no-meperidine control group; however, rates of PONV were significantly higher in the meperidine groups.[355] The effect of *epidural* opioids on thermoregulation may be more consistent, with a number of studies reporting a reduction in the incidence and severity of shivering after epidural meperidine, butorphanol, fentanyl, and sufentanil.[356-359]

Preoperative patient warming with forced air has been shown to reduce the incidence of perioperative and postoperative core hypothermia and shivering in patients undergoing cesarean delivery with *epidural* anesthesia.[360] However, a subsequent study found that perioperative forced-air warming does *not* prevent maternal hypothermia after cesarean delivery with *spinal* anesthesia that includes fentanyl and morphine.[343] It is likely that forced-air warming cannot compensate for the initial rapid drop in core temperature (from heat redistribution) after administration of spinal anesthesia.

NEURAXIAL NONOPIOID ANALGESIC ADJUVANTS

The addition of neuraxial nonopioid adjuvants to local anesthetic agents may improve the quality of both intraoperative and postcesarean analgesia. Nonopioid neuraxial adjuvants have different sites and mechanisms of actions, and interactions between neuraxial opioids and nonopioid adjuvants may be additive or synergistic. Potential advantages of neuraxial drug combinations include a reduction in dose of individual drugs (with subsequent reductions in dose-dependent side effects), in particular a reduction in postoperative opioid requirements and opioid-related side effects.[361]

Alpha-Adrenergic Agonists

α_2-Adrenergic agonists bind to presynaptic and postsynaptic α_2-adrenergic receptors at peripheral, spinal (dorsal

horn), and brainstem sites. Epidural and intrathecal α_2-adrenergic agonists provide analgesia by mimicking the activity of the descending noradrenergic system.[362,363] This process subsequently leads to norepinephrine release, which in turn modulates pain processing in the dorsal horn by inhibiting the release of substance P and increasing acetylcholine levels to produce analgesia.[364,365] **Clonidine,** an α_2-adrenergic agonist, provides a more potent analgesic response when administered neuraxially than when administered systemically. Clonidine is also associated with more profound sensory and motor block when administered with epidural local anesthetics and acts additively or synergistically with intraspinal opioids.[361,365] In combination with an intrathecal local anesthetic, intrathecal clonidine may also prolong the regression of sensory block, improve postoperative analgesia, and decrease the risk for intraoperative pain.[366] However, a combination of intrathecal clonidine and local anesthetic may increase the risk for hypotension in a non–dose-responsive manner.[366] Pregnancy may further enhance the analgesic effects of α_2-adrenergic agonists.[367]

Initial clinical studies of **epidural clonidine** 700 to 900 μg demonstrated a rapid onset of analgesia (within 20 minutes) lasting approximately 5 hours.[368] Mendez et al.[369] compared the analgesic efficacy of low-dose clonidine (400 μg bolus) with that of high-dose clonidine (800 μg bolus), followed by an epidural clonidine infusion at 10 or 20 μg/h after cesarean delivery. The investigators found a dose-dependent analgesic effect in the first 6 hours and dose-dependent sedation and motor block in the first 3 hours postoperatively. These time-dependent side effects might lead to delays in the discharge of the patient from the postanesthesia care unit. Huntoon et al.[370] reported similar postcesarean analgesia in patients receiving epidural clonidine 400 or 800 μg after epidural bupivacaine anesthesia. Absent or reduced postcesarean analgesia was observed in separate groups that received epidural 2-chloroprocaine anesthesia with epidural clonidine 400 or 800 μg. This finding may have been due to the calcium chelator (disodium EDTA) present in the 2-chloroprocaine solution (Figure 28-13). These investigators also evaluated the effect of a postoperative epidural clonidine infusion (40 μg/h). Postcesarean analgesia was sustained in patients who had received epidural bupivacaine; in the 2-chloroprocaine group, analgesia was prolonged only in patients who received epidural clonidine 800 μg.[370]

Few studies have compared epidural clonidine with systemic or neuraxial opioid analgesia. Narchi et al.[371] found that postcesarean pain scores were lower after individual bolus doses of epidural clonidine 150 to 300 μg than with intramuscular morphine 10 mg in the first 3 hours after cesarean delivery. The investigators reported that epidural clonidine 300 μg was paradoxically associated with higher pain scores and greater episodes of obstructive apnea with desaturation ($Spo_2 \leq 90\%$) than occurred with clonidine 150 μg. Several studies have investigated epidural clonidine in combination with epidural opioids for optimizing postcesarean analgesia. An isobolographic evaluation of epidural clonidine (in doses ranging from 50 to 400 μg) with fentanyl (15 to 135 μg) did not demonstrate synergy between clonidine and

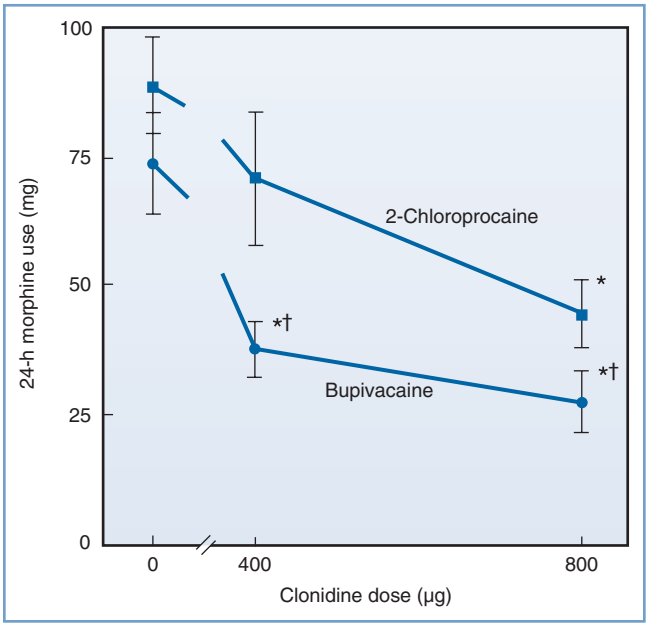

FIGURE 28-13 ■ Randomized trial of epidural 0.5% bupivacaine compared with 3% 2-chloroprocaine with epidural clonidine 400 μg or 800 μg: 24-hour morphine use. 2-chloroprocaine (■) or bupivacaine (•). *$P < .05$ versus saline control (0 μg clonidine). †$P < .05$ versus 2-chloroprocaine group. (From Huntoon M, Eisenach JC, Boese P. Epidural clonidine after cesarean section: appropriate dose and effect of prior local anesthetic. Anesthesiology 1992; 76:187-93.)

fentanyl in patients recovering from cesarean delivery.[372] Results of this study suggest that these two drugs interact in an additive rather than a synergistic manner in humans. However, marked variability in drug response and failure of high doses to produce complete analgesia limited the validity of dose-response and ED_{50} analyses. Capogna et al.[373] observed that the addition of clonidine 75 to 150 μg to epidural morphine 2 mg significantly lengthened the duration of postcesarean analgesia without increasing the incidence of side effects. Vercauteren et al.[374] compared three different PCEA regimens with an epidural background infusion (sufentanil 2 μg/mL; sufentanil 2 μg/mL with epinephrine 2.5 μg/mL; sufentanil 2 μg/mL with clonidine 3 μg/mL) in patients who had undergone cesarean delivery. Although 24-hour sufentanil consumption was lowest in the clonidine admixture group, there were no significant differences among groups with regard to pain scores (at 10 or 24 hours), sedation, or hypotension.

A number of studies have evaluated the potential role of **intrathecal clonidine** for postcesarean analgesia. Filos et al.[375] observed that patients undergoing general anesthesia for cesarean delivery who were randomly assigned to receive intrathecal clonidine 150 μg at 45 minutes after extubation experienced earlier onset of analgesia (within 20 minutes), lower maximal pain scores at 90 minutes, and more prolonged analgesia (> 6 hours) than patients who received intrathecal saline (the control group). However, patients in the clonidine group had higher sedation scores, a greater maximal decrease in mean arterial pressure, and more complaints of dry mouth than the control group. Utilizing a similar study

design to compare different doses of intrathecal clonidine (150, 300, or 450 μg), the same investigators observed that both the onset and duration of analgesia and sedation were dose dependent.[376] Intrathecal clonidine was also associated with a significant reduction in mean arterial pressure. Van Tuijl et al.[377] assessed postcesarean analgesia in patients who received intrathecal clonidine 75 μg combined with bupivacaine *before* surgery versus intrathecal bupivacaine alone. Early postoperative analgesia (1 to 2 hours) was improved with clonidine; however, no difference was found in 24-hour morphine consumption between the groups.

Studies of intrathecal opioids in combination with clonidine have investigated the contribution of each drug to the subsequent analgesia and side-effect profile. Benhamou et al.[378] evaluated postcesarean analgesic outcomes in patients who received hyperbaric bupivacaine alone or bupivacaine and clonidine 75 μg with and without fentanyl 12.5 μg. Patients receiving the clonidine-fentanyl combination reported less intraoperative pain and more prolonged postcesarean analgesia (time to first analgesia request 215 minutes) than those receiving bupivacaine-clonidine and bupivacaine alone (183 and 137 minutes, respectively). However, significantly higher rates of pruritus and sedation were reported for the clonidine-fentanyl group. Paech et al.[379] performed a six-arm study assessing postcesarean analgesia after intrathecal bupivacaine 12.5 mg with fentanyl 15 μg and one of the following regimens: clonidine 150 μg; morphine 0.1 mg; and morphine 0.1 mg with clonidine 30, 60, 90, or 150 μg. The investigators concluded that the morphine-clonidine regimens provided optimal postcesarean analgesia with significantly lower pain scores at rest and with coughing in the first 4 hours. The minimum effective intrathecal dose of clonidine was 30 to 60 μg when combined with bupivacaine, fentanyl 15 μg, and morphine 0.1 mg. However, a significant increase in intraoperative sedation was observed in all groups receiving clonidine. Lavand'homme et al.[380] compared postcesarean antihyperalgesic effects in patients receiving intrathecal clonidine 150 μg with bupivacaine, clonidine 75 μg with bupivacaine-sufentanil, or bupivacaine-sufentanil. The bupivacaine-clonidine group had a significantly reduced area of peri-incisional hyperalgesia and a lower incidence of hyperalgesia compared with the other study groups. However, no between-group differences were observed in postoperative morphine consumption or in pain scores before and after discharge. The relationship between postoperative wound hyperalgesia and chronic wound pain after cesarean delivery remains unclear (see Chapter 27).

In summary, neuraxial clonidine does not appear to offer substantial improvement in analgesia over that provided by neuraxial opioids. Epidural clonidine (150 to 800 μg) may improve postcesarean analgesia when given in combination with epidural opioids. Intrathecal clonidine (75 to 450 μg) has modest efficacy and a relatively short duration of action. Ongoing concern about the adverse side-effect profile of epidural or intrathecal clonidine—notably sedation and hypotension—limit the neuraxial administration of this agent in patients undergoing cesarean delivery. Additionally, in the United States, epidural clonidine has a "black box" warning stating that it is not recommended for obstetric, postpartum, or perioperative pain management due to the risk for hemodynamic instability, especially hypotension and bradycardia. In selected cases the anesthesiologist may conclude that the potential benefits may outweigh the possible risks.

No published studies have assessed the administration of neuraxial **dexmedetomidine** in pregnant patients. A study in patients undergoing bladder surgery who received spinal anesthesia with bupivacaine and clonidine 30 μg or dexmedetomidine 3 μg found similar sensory and motor block duration, with no hemodynamic compromise or sedation.[381] However, when dexmedetomidine was applied to strips of pregnant human myometrium *in vitro*, significant increases in uterine contractility were observed.[382]

Neostigmine

By interfering with the breakdown of acetylcholine, neostigmine indirectly stimulates spinal nicotinic and muscarinic receptors and the release of nitric oxide. The resulting analgesia is most likely due to central and peripheral alterations in pain modulation and transmission. Initial studies of *intrathecal* neostigmine in animals and human volunteers have demonstrated analgesic effects without neurotoxic effects.[235,383-385] However, despite producing dose-dependent analgesia, intrathecal neostigmine at doses greater than 25 μg also results in nausea that is resistant to traditional antiemetic treatment (droperidol, ondansetron) and cholinergic antagonists.[384]

Krukowski et al.[386] reported that escalating doses of intrathecal neostigmine (10 to 100 μg) improved analgesia in a dose-independent manner when given after epidural anesthesia for cesarean delivery. The reduction in morphine requirements lasted up to 10 hours. The incidence of nausea varied from 50% to 100%. Chung et al.[387] showed that the postoperative analgesia provided by intrathecal neostigmine 25 μg was similar to that observed with intrathecal morphine 0.1 mg. The investigators observed that the combination of neostigmine 12.5 μg with morphine 0.05 mg prolonged the analgesia in an additive (rather than a synergistic) manner, was associated with less need for supplemental analgesia, and had fewer side effects than observed with either drug administered alone in higher doses (Figure 28-14). Pan et al.[388] compared analgesic outcomes after intrathecal bupivacaine given either alone or in combination with three different admixtures: intrathecal neostigmine 50 μg, intrathecal clonidine 150 μg, or a neostigmine-clonidine combination (same doses of each). Although patients in the clonidine-neostigmine group had lower pain scores in the first 10 postoperative hours, they experienced more significant side effects, including a prolongation of motor block, a higher incidence of hypotension, and a higher incidence (with greater severity) of nausea and vomiting.

Kaya et al.[389] assessed the analgesic efficacy of *epidural* neostigmine administration after cesarean delivery. In this study, a CSE technique was employed with

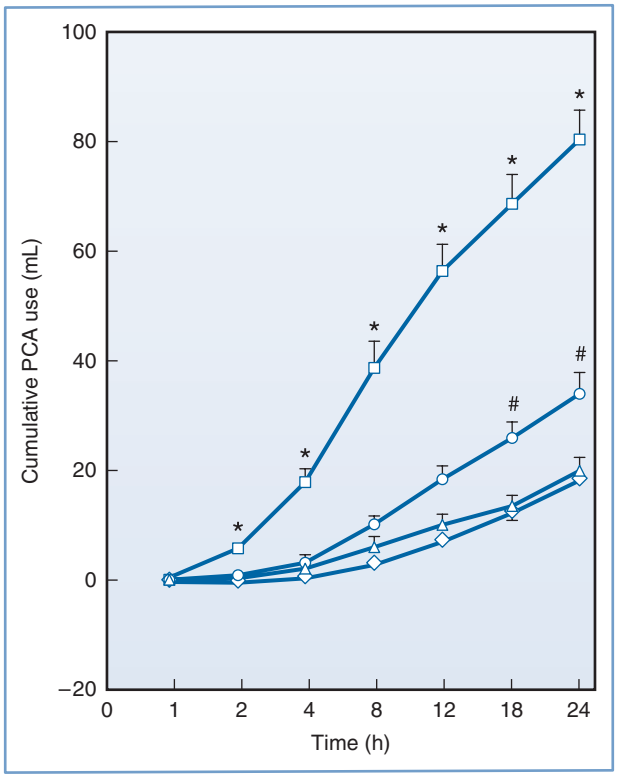

FIGURE 28-14 ■ Randomized trial of postcesarean analgesia with intrathecal saline (□), neostigmine 25 μg (○), morphine 0.1 mg (△), or the combination of neostigmine 12.5 μg and morphine 0.05 mg (◇) with hyperbaric bupivacaine 12 mg. Cumulative patient-controlled analgesia (*PCA*) consumption. Intravenous PCA was started with fentanyl 500 μg and ketorolac 150 mg in a total volume of 100 mL. The PCA device was set to deliver a bolus of 5 mL (i.e., fentanyl 25 μg and ketorolac 7.5 mg), with a lockout interval of 10 minutes and no basal infusion. Each value represents the mean ± SE. $*P < .05$ versus the other three groups; $\#P < .05$ versus the combination group. (From Chung CJ, Kim JS, Park HS, Chin YJ. The efficacy of intrathecal neostigmine, intrathecal morphine, and their combination for post-cesarean section analgesia. Anesth Analg 1998; 87:341-6.)

intrathecal bupivacaine 8 mg and fentanyl 10 μg, and patients subsequently received epidural neostigmine doses of 75, 150, or 300 μg after delivery. The investigators reported modest, short-lived, and dose-independent reductions in postoperative pain in the neostigmine groups.[389] No differences among groups in 24-hour morphine consumption after surgery were observed.

In summary, dose-dependent side effects of intrathecal neostigmine limit its use as a single neuraxial adjunct for postcesarean analgesia. Intrathecal neostigmine 12.5 to 25 μg may be used in combination regimens to improve analgesia and reduce side effects. The use of epidural neostigmine is not currently recommended until additional studies substantiate greater postcesarean analgesic benefits with fewer side effects. Although data regarding the maternal and fetal safety profile of epidural neostigmine are reassuring,[390] additional studies are needed to substantiate whether epidural neostigmine can be considered as a viable alternative or adjunct to opioids for postcesarean analgesia.

N-Methyl-D-Aspartate Antagonists

Ketamine

Anesthetic and subanesthetic doses of ketamine have analgesic properties as a result of noncompetitive antagonism of *N*-methyl-D-aspartate (NMDA) receptors. Animal studies suggest that NMDA receptor blockade can prevent opioid tolerance and reduce the progressive increase in action potential discharge known as the "wind-up phenomenon."[391-393] Research in dogs has indicated that no clinical or histologic disturbance in spinal tissue or the meninges occurs after exposure to a single intrathecal injection of preservative-free S(+)-ketamine at a dose of 1 mg/kg.[394]

Limited data exist for the role of neuraxial ketamine in the provision of postcesarean analgesia. In patients undergoing cesarean delivery randomly assigned to receive intrathecal bupivacaine alone or in combination with S(+) ketamine 0.05 mg/kg or fentanyl 25 μg,[395] significantly prolonged and better quality analgesia was observed in the fentanyl group. No differences in side effects were observed between the ketamine and fentanyl groups.[395] It is unclear whether the S(+) or R(–) isomers of ketamine have analgesic advantages over the racemate. Currently, the use of intrathecal ketamine does not appear to offer an analgesic benefit for postcesarean analgesia; moreover, the potential for neurotoxicity for both preservative-containing and preservative-free ketamine has not been adequately studied.[396]

Two systematic reviews have evaluated postoperative analgesia with perioperative epidural ketamine administration in patients undergoing nonobstetric surgery.[397,398] Subramaniam et al.[397] analyzed results from eight studies that compared a combination of epidural ketamine with opioids to epidural opioids alone. Although marked heterogeneity was observed among studies, the pain scores at rest were moderately lower in the patients who received epidural ketamine. No overall difference between the groups was observed in pain scores with movement. A Cochrane review also reported marked heterogeneity and mixed analgesic outcomes in studies that assessed preoperative and postoperative epidural administration of ketamine.[398] To date, no published studies have evaluated perioperative epidural ketamine administration in patients undergoing cesarean delivery. In a study of patients undergoing gynecologic surgery, Kawana et al.[399] noted that low-dose epidural ketamine (4, 6, or 8 mg) provided inferior analgesia compared with epidural morphine 3 mg.

In summary, epidural ketamine provides limited postcesarean analgesia and cannot be recommended for patients undergoing cesarean delivery. Further research is needed to evaluate the role of epidural and intrathecal ketamine as part of a multimodal regimen for postcesarean analgesia.

Magnesium

Magnesium is an NMDA receptor antagonist that may alter pain signaling by preventing central sensitization after nociceptive stimulation.[400] The antinociceptive

properties of magnesium are due to its noncompetitive NMDA receptor antagonism resulting in ion channel blockage in a voltage-dependent manner. Studies investigating intrathecal or epidural magnesium have shown variable analgesic effects after cesarean delivery. Sun et al.[401] compared the postcesarean analgesic profile of four different *epidural* solutions administered in the perioperative period. All patients received 0.1% bupivacaine 10 mL with one of the following: morphine 1.5 mg, magnesium 500 mg, morphine 1.5 mg *and* magnesium 500 mg, or placebo. Patients who received all three drugs (bupivacaine, magnesium, and morphine) had significantly lower postoperative pain scores at rest and with movement, an increased time to first analgesic request, and increased satisfaction at 24 hours after surgery compared with women who received only two drugs. In women who received a CSE technique with intrathecal bupivacaine 10 mg and epidural bupivacaine 25 mg with fentanyl 100 µg, postoperative analgesic requirements were lower for women who received magnesium sulfate 500 mg compared with a control (no magnesium) group.[402]

Intrathecal magnesium sulfate 50 mg prolongs the duration of spinal anesthesia and improves postoperative analgesia in patients undergoing nonobstetric surgery with bupivacaine and fentanyl spinal anesthesia.[403,404] There are limited data regarding the analgesic effects of intrathecal magnesium sulfate in women undergoing cesarean delivery. No difference in the first request for postcesarean analgesia was found among patients who were randomized to receive intrathecal magnesium sulfate 50 mg compared with placebo (median time, 100 minutes versus 105 minutes, respectively), and patients who received intrathecal fentanyl 25 µg had a longer time to first request for analgesia (132 minutes) compared with the magnesium group.[405]

Intravenous magnesium sulfate, given in either a "low-dose" regimen (25 mg/kg bolus and a 24-hour infusion at 1 g/h) or a "high-dose" regimen (50 mg/kg bolus and a 24-hour infusion at 2 g/h), was evaluated in patients undergoing spinal anesthesia for cesarean delivery.[406] No differences in sequential pain scores or cumulative opioid consumption were found up to 48 hours postoperatively. Some investigators have postulated that the blood-brain barrier may affect the rate of transfer of magnesium into the CSF, a possibility that may explain why CSF magnesium concentrations do not directly reflect plasma concentrations.[404]

In summary, epidural administration of magnesium, co-administered with neuraxial opioids, may have a favorable analgesic effect in patients after cesarean delivery. However, more research, including dose-response studies, are needed to more formally assess the analgesic efficacy of epidural and intrathecal magnesium in the postcesarean period.

Epinephrine

Epinephrine has a direct analgesic effect by binding to alpha-adrenergic receptors and may potentiate local anesthetics by inducing local vasoconstriction and decreased drug clearance. A number of clinical studies have investigated epinephrine as a spinal or epidural adjunct. Robertson et al.[83] reported that *epidural* epinephrine 25 µg prolonged the duration of analgesia with epidural fentanyl 100 µg but increased the incidence of pruritus. Similar improvements in duration of analgesia have been observed when epinephrine (5 to 30 µg/mL) was combined with either epidural diamorphine or sufentanil; however, the incidence of side effects (including vomiting that required treatment) was increased.[145,407] In contrast, McMorland et al.[408] found that epidural epinephrine did not enhance the efficacy of postcesarean analgesia provided by epidural sufentanil.

In a study assessing postoperative outcome measures for PCEA, patients who received 0.01% bupivacaine with epinephrine (0.5 µg/mL) and fentanyl reported better analgesia than those who received either fentanyl or fentanyl-epinephrine.[409] No significant differences in side effects were reported between PCEA regimens with and without epinephrine. In another study, no improvement in analgesia and no reduction in opioid consumption were found with the addition of epinephrine 5 µg/mL to PCEA meperidine 5 mg/mL.[410] Patients in the epinephrine group reported more nausea at 2 and 24 hours as well as higher pruritus scores at 2 hours than patients in the no-epinephrine group. The investigators attributed the epinephrine-associated increase in side effects to enhanced transfer of meperidine into the CSF. Studies of epidural 2% lidocaine or 0.5% bupivacaine with epinephrine (5 µg/mL) have not demonstrated any detrimental effects of epinephrine on umbilical artery blood flow-velocity waveforms, uteroplacental or fetal vascular resistance, fetal myocardial function, or fetal heart rate.[411,412]

The use of *intrathecal* epinephrine as an adjuvant to local anesthetics, with or without opioids, has been evaluated in a number of studies. The addition of epinephrine 200 µg to hyperbaric spinal bupivacaine improved perioperative analgesia but was associated with a longer duration of residual sensory and motor block.[413] In a separate study, a combined intrathecal regimen of epinephrine 200 µg with morphine 0.2 mg did not significantly improve postoperative analgesia compared with intrathecal morphine 0.2 mg alone.[414] Zakowski et al.[415] found earlier and higher peak plasma bupivacaine concentrations with the addition of spinal epinephrine 200 µg to spinal bupivacaine in patients undergoing cesarean delivery. The investigators postulated that epinephrine might have a vasodilatory or biphasic action on certain vascular beds. In contrast, plasma levels of morphine were approximately 66% *lower* in the epinephrine group than in the control group.[415]

In summary, the use of epidural epinephrine (2.5 to 30 µg/mL) seems to prolong the duration of analgesia with epidural opioids but may increase opioid-related side effects. The use of intrathecal epinephrine 200 µg does not seem to enhance neuraxial opioid analgesia and is associated with prolonged sensory and motor block.

Newer Agents

In the future, newer agents and adjuvants may enhance postoperative pain management strategies in patients receiving neuraxial anesthesia for cesarean delivery.

Adenosine (and adenosine analogues) may have antinociceptive effects that involve spinal adenosine A_1 receptors.[416] Intrathecal adenosine may enhance the effect of intrathecal clonidine, ketamine, and morphine. However, studies have not demonstrated improved analgesia with intrathecal adenosine administration in patients undergoing hysterectomy.[417,418] Among pregnant women, no beneficial effects in the quality or duration of analgesia have been observed in patients who received both intrathecal adenosine 500 μg and sufentanil compared with intrathecal sufentanil alone.[419]

A direct relationship may exist between central potassium channels and antinociception. Several animal studies have investigated **potassium channel openers** (nicorandil, sildenafil) administered by the intrathecal[420] or epidural[421] route. These drugs may also enhance the analgesic effects of neuraxial opioids and α_2-adrenergic agonists.

Intrathecal **midazolam** produces analgesia by acting on $GABA_A$ receptors and reducing dorsal (sensory) and motor horn excitability. Midazolam's solubility in water is pH dependent, and the likelihood of drug precipitation is high at physiologic pH and concentrations greater than 1 mg/mL.[422,423] There has been growing interest in the use of midazolam as an intrathecal agent for treating acute postoperative pain. A meta-analysis of studies that assessed the clinical benefit and side effects of intrathecal midazolam in obstetric and nonobstetric patients indicated that it has a favorable pharmacologic profile.[424] Intrathecal midazolam was associated with significantly improved analgesia and a reduced risk for PONV. Important side effects (including respiratory depression, prolonged motor block, and neurotoxicity) were reported as rare and were not significantly increased in patients who received intrathecal midazolam, compared with those who received placebo. Tucker et al.[425] performed a cohort study to investigate potential neurotoxic effects of intrathecal midazolam 2 mg in 1100 patients receiving spinal anesthesia; they reported no increased risk for neurologic or urologic symptoms up to 1 month after neuraxial block. In the obstetric setting, one study demonstrated that the combination of intrathecal midazolam 2 mg and intrathecal fentanyl 10 μg reduced labor pain to a greater degree than was observed with either drug given alone.[426] No adverse maternal or fetal events and no clinical evidence of neurologic impairment were reported among subjects in this study. After cesarean delivery, patients who received intrathecal midazolam 2 mg (without neuraxial opioids) had more prolonged postoperative analgesia and lower pain scores for 6 hours after surgery compared with patients who received either intrathecal midazolam 1 mg or no midazolam.[427] The impact of multimodal regimens that include intrathecal midazolam on postcesarean analgesia remains unclear.

Several neuraxially administered drugs have been shown to produce antinociceptive effects by altering calcium channel conductance at the spinal level. Intrathecal **gabapentin** reduced incision-induced allodynia in rats,[428,429] and epidural **verapamil** lowered postoperative opioid consumption after lower abdominal surgery.[430] **Ziconotide,** a neuronal N-type-selective voltage-sensitive calcium entry–blocking agent, has been shown to have analgesic effects after intrathecal administration.[431]

Before recommendations can be made about the potential use of new adjuncts, neurotoxicity studies are necessary to ensure these agents' safety for neuraxial administration. In addition, studies assessing analgesic efficacy, side effects, and toxicity must demonstrate that these agents result in significant improvement over the neuraxial local anesthetic and opioid regimens currently used in clinical practice.

KEY POINTS

- Epidural or intrathecal administration of opioids provides better postoperative pain relief than systemic administration.
- Effective postoperative analgesia provided by neuraxial techniques confers many physiologic benefits and may improve postoperative maternal and neonatal outcomes after cesarean delivery.
- Neuraxial administration of a hydrophilic opioid (e.g., morphine) has a delayed onset of analgesia owing to slow penetration of drug into the spinal cord but results in a prolonged duration of action (14 to 36 hours) because of high bioavailability in the cerebrospinal fluid and minimal absorption into the systemic circulation.
- Neuraxial administration of a lipophilic opioid (e.g., fentanyl, sufentanil) has a rapid onset of analgesia owing to rapid spinal tissue penetration of drug. Neuraxial administration of lipophilic opioids may improve intraoperative analgesia. However, these agents are also rapidly absorbed systemically and consequently have a limited duration of activity (2 to 4 hours) after cesarean delivery.
- In clinical practice, single-dose epidural (2 to 4 mg) or intrathecal (0.075 to 0.2 mg) morphine administration is most commonly used. Higher doses may increase opioid-related side effects without improving analgesia.
- Epidural and intrathecal administration of morphine provide similar analgesic efficacy and result in comparable incidence and severity of opioid-related side effects.
- Patient-controlled epidural analgesia (PCEA) regimens with lipophilic opioids (e.g., fentanyl, sufentanil) may improve postcesarean analgesia and maternal satisfaction and may be worthwhile for patients with high postoperative analgesic requirements. No consensus currently exists regarding optimal PCEA regimens (e.g., opioid with or without local anesthetic; demand bolus with or without a background infusion). The disadvantages associated with PCEA (reduced maternal mobility, higher cost, additional nursing workload, and potential catheter-related complications) may limit the use of this approach for provision of postcesarean analgesia.

- Delayed respiratory depression is rare after neuraxial morphine administration for cesarean delivery, but when it occurs it may result in maternal morbidity or mortality. "At risk" patients should be identified before cesarean delivery, and adequate monitoring should be in place to assess respiratory function and sedation in the postoperative period.
- Pruritus, nausea, and vomiting are common postoperative side effects of neuraxial opioid administration. Opioid antagonists (e.g., nalbuphine 2 to 5 mg) are suggested as first-choice agents for managing opioid-related pruritus. 5-HT_3 receptor antagonists are useful in treating nausea and vomiting. Combination regimens may be more effective than individual antiemetic agents in treating nausea and vomiting.
- Nonopioid adjuncts (e.g., α_2-adrenergic agonists, anticholinesterases, magnesium) may be considered as alternatives to, or be combined with, neuraxial opioids. However, these adjuncts are associated with modest analgesic benefits and significant side effects. The risks of spinal neurotoxicity in pregnant patients for many of these drugs and other newer agents are also uncertain.

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PART VIII

ANESTHETIC COMPLICATIONS

Donald Caton, MD

James Young Simpson introduced anesthesia to obstetrics when the practice of medicine was in a period of great flux. As late as 1820, most Western medical schools were still practicing a form of medicine derived from the teachings of Galen, a second-century Greek physician. According to Galenic principles, all disease originated from an imbalance among the four elements (earth, air, fire, and water), hydraulic pressures, or electrical forces. Treatment consisted of the time-honored measures of purging, bleeding, cupping, or the administration of stimulants or depressants. Simpson, Meigs, Channing, and all the others involved in the early debate about obstetric anesthesia learned this style of practice as students.

Within a few years of their graduation, Galenic forms of medicine had been discredited and had disappeared. In its place Laennec, Louis, and other French physicians developed principles of medical theory and practice that we use today—physical diagnosis, statistical analysis, physiology, pathology, and chemistry.[1]

Thus the introduction of anesthesia represented a significant challenge. Physicians who had once been taught to treat the pain of childbirth with bloodletting could now use ether or chloroform. They recognized the therapeutic potential of the drugs, but they also recognized their dangers and questioned their safety and effects on labor and the newborn.[2]

Evaluating the risks of anesthesia was quite different from recognizing the problems. In 1850, pharmacology was in its infancy, and medical physiology, pathology, and biochemistry were not very well developed. There was no tradition for drug testing that Simpson and Meigs could model. Their inexperience with medical science was reflected in their response to obstetric anesthesia. For example, seeking a better agent to replace ether, Simpson simply tried a series of compounds on himself and his friends until he stumbled upon one that worked—chloroform. Within a month he had administered chloroform to a patient and had published a paper. He conducted no animal studies or clinical trials, collected no data, and performed no statistical analyses of his results. His claims were reviewed by no clinical board or governmental agency, and he had no reason to fear a malpractice suit. Such an approach led to a rapid dissemination of new ideas, but it took years before anyone identified the problems associated with the new remedy, much less sorted them out. Accordingly, after the introduction of obstetric anesthesia, more than half a century passed before physicians began to develop the tools that they needed to understand the problems associated with the use of ether and chloroform.[3]

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CHAPTER 29

Aspiration: Risk, Prophylaxis, and Treatment

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CHAPTER OUTLINE

HISTORY

In 1848, Sir James Simpson first suggested aspiration as a cause of death during anesthesia. Hannah Greener, a 15-year old given chloroform for a toenail extraction, became cyanotic and "sputtered" during the anesthetic. A "rattling in her throat" then developed, and she soon died. Her physician administered water and brandy by mouth. Simpson[1] contended that it was the aspiration of water and brandy, and not the adverse effects from the chloroform, that caused her death. In 1940, Hall published a report of 15 cases of aspiration, 14 of which occurred in mothers receiving inhalation anesthesia for a vaginal or cesarean delivery.[2] Among the 14 obstetric cases, 5 mothers died.

Subsequently, Curtis Mendelson, in a landmark paper, reported a series of animal experiments that clearly described the clinical course and pathology of pulmonary acid aspiration.[3] In the same paper, Mendelson also audited 44,016 deliveries at the New York Lying-In Hospital between 1932 and 1945. He identified 66 (0.15%) cases of aspiration, of which the aspirated material was recorded in 45 cases; 40 mothers aspirated liquid, and 5 aspirated solid food. Importantly, no mothers died of acid aspiration, but 2 mothers died of asphyxiation caused by the aspiration of solid food. At this time general anesthesia usually involved the inhalation of ether, often as Mendelson observed, by "a new and inexperienced intern." Mendelson therefore advocated (1) the withholding of food during labor, (2) the greater use of regional anesthesia, (3) the administration of antacids, (4) the emptying of the stomach before administration of general anesthesia, and (5) the competent administration of general anesthesia. This advice became the foundation of obstetric anesthesia practice during subsequent decades.

INCIDENCE, MORBIDITY, AND MORTALITY

Maternal mortality from pulmonary aspiration of gastric contents has declined to almost negligible levels in the past 3 decades (Figure 29-1).[4-6] This decline can probably be attributed to the following factors: (1) the greater use of neuraxial anesthesia; (2) the use of antacids, histamine-2 (H_2) receptor antagonists, and/or proton-pump inhibitors; (3) the use of rapid-sequence induction of general anesthesia; (4) an improvement in the training of anesthesia providers; and (5) the establishment and enforcement of *nil per os* (NPO) policies. Arguably, the common

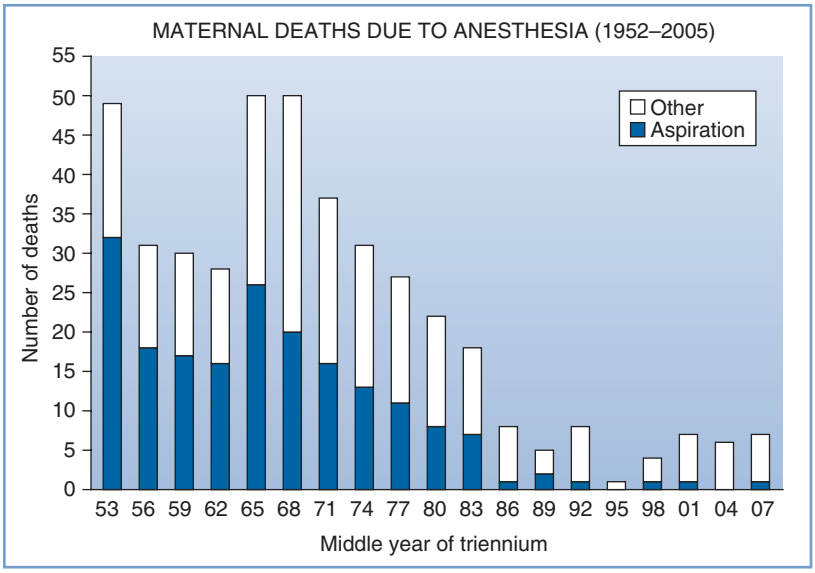

FIGURE 29-1 ■ Maternal mortality from anesthesia and pulmonary aspiration in the United Kingdom, 1952-2008. (Compiled from data from references 4 through 6.)

use of neuraxial analgesic/anesthetic techniques, both during labor and for cesarean delivery, is the single most important factor in this remarkable decline in maternal mortality from pulmonary aspiration.

The reported incidence of aspiration pneumonitis depends on the criteria used for making the diagnosis. The relative risk for aspiration in pregnant versus nonpregnant women can best be estimated from comparisons within single-study populations. Olsson et al.[7] reported an overall incidence of aspiration of 1 in 2131 in the general population undergoing anesthesia and 1 in 661 in women undergoing cesarean delivery (i.e., a threefold higher aspiration risk). In two other surveys related to aspiration (one a retrospective review of 172,334 consecutive patients undergoing general anesthesia and the other a review of 133 cases of aspiration from the Australian Anaesthetic Incident Monitoring Study [AIMS]), there were no cases of pulmonary aspiration in women undergoing either elective or emergency cesarean delivery.[8,9] However, in the latter two studies, emergency surgery was a significant predisposing factor for aspiration; this finding may be relevant for the practice of obstetric anesthesia, given that many obstetric surgical procedures are performed on an urgent or emergency basis. The AIMS study also implicated obesity as a significant risk factor for aspiration; others have noted that obesity is associated with an increased risk for maternal mortality.[4,5]

Morbidity and mortality associated with aspiration vary according to (1) the physical status of the patient, (2) the type and volume of aspirate, (3) the therapy administered, and (4) the criteria used for making the diagnosis. Since 1952, the Department of Health in the United Kingdom has published detailed triennial reports on all maternal deaths. Data from these reports, now administered by the body *Mothers and Babies—Reducing Risk through Audits and Confidential Enquiries across the UK* (MBRRACE-UK), indicate that death from pulmonary aspiration in obstetrics is vanishingly rare (see Figure 29-1).[4-6] In the last five reports, which cover the 15-year period from 1994 to 2008, there were three maternal deaths from aspiration; one was an obese parturient, the second was a mother anesthetized 3 days after delivery, and the third was a women with a placenta previa who required an emergency cesarean delivery after eating a full meal and aspirated on emergence from general anesthesia. Although the number of anesthetics, particularly general anesthetics, administered to parturients during this 15-year period is unknown, there were approximately 10.5 million deliveries, indicating that the mortality rate from aspiration was less than 1 in 3.5 million deliveries.

Data on pulmonary aspiration in obstetrics in the United States are more difficult to evaluate. Despite the establishment of an ongoing National Pregnancy Mortality Surveillance System by the Centers for Disease Control and Prevention (CDC), it is often difficult to obtain adequate and detailed information about every maternal death. Prior to 1990, aspiration was the most common cause of anesthesia-related maternal death in the United States; it has been calculated that at that time there were 17 deaths related to general anesthesia for every one death related to regional anesthesia.[10] By the early 1990s, this ratio had improved to 6 to 1. By 2002, death rates for both general and regional anesthesia were similar.[11] However, mortality statistics are generally a poor predictor of maternal morbidity; several studies have indicated that perioperative aspiration can be associated with important morbidity in obstetric patients,[12,13] and thus all possible measures still must be taken to prevent pulmonary aspiration in obstetric patients.

GASTROESOPHAGEAL ANATOMY AND PHYSIOLOGY

Esophagus

In adults, the esophagus is approximately 25 cm long and the esophagogastric junction is approximately 40 cm from the incisor teeth. In humans, the proximal one third

of the esophagus is composed of striated muscle but the distal end contains only smooth muscle. Muscular sphincters at both ends are normally closed. The cricopharyngeal or upper esophageal sphincter prevents the entry of air into the esophagus during respiration, and the gastroesophageal or lower esophageal sphincter prevents the reflux of gastric contents. The lower esophageal sphincter is characterized anatomically and manometrically as a 3-cm zone of specialized muscle that maintains tonic activity. The end-expiratory pressure in the sphincter is 8 to 20 mm Hg above the end-expiratory gastric pressure. The lower esophageal sphincter is kept in place by the phrenoesophageal ligament, which inserts into the esophagus approximately 3 cm above the diaphragmatic opening (Figure 29-2). The lower esophageal sphincter is not always closed; transient relaxations occur that account for the gastroesophageal reflux that healthy subjects experience.[14]

Gastrointestinal Motility

Differences in fasting and fed patterns of gut motility are now firmly established. During fasting, the main component of peristalsis is the migrating motor complex (MMC).[15] Each MMC cycle lasts 90 to 120 minutes and comprises four phases: phase I has little or no electrical spike activity and thus no measurable contractions, phase II has intermittent spike activity, phase III has spikes of large amplitude and is associated with strong contractile activity, and phase IV is a brief period of intermittent activity leading back to phase I. The MMC first appears in the lower esophageal sphincter and stomach, followed by the duodenum, and finally the terminal ileum, at which time a new cycle begins in the lower esophageal sphincter and stomach. The phase of the MMC at the time of administration of certain drugs can affect absorption and thereby the onset of therapeutic effect.[16] Eating abolishes the MMC and induces a pattern of intermittent spike activity that appears similar to that in phase II. The duration of the fed pattern is determined both by the calorie content and the type of nutrients in the meal.

The stomach, through the processes of receptive relaxation and gastric accommodation, can accept 1.0 to 1.5 L of food before intragastric pressure begins to increase. The contraction waves that propel food into the small intestine begin in the antrum. The pylorus closes midway through the contraction wave, allowing some fluid to exit into the duodenum but causing the remaining fluid to move retrograde toward the body of the stomach.[17] The jet of fluid that exits the pylorus contains primarily liquid and fine particles. Large particles that lag behind are caught in the retrograde flow of fluid, which assists in their disintegration. Therefore, the manner by which individual components of a meal pass through the stomach depends on the particle size and the viscosity of the suspension. Small particles and fluids exit the stomach faster than larger particles.[17] The outlet of the stomach—the pylorus—limits outflow by means of both its chronic tone

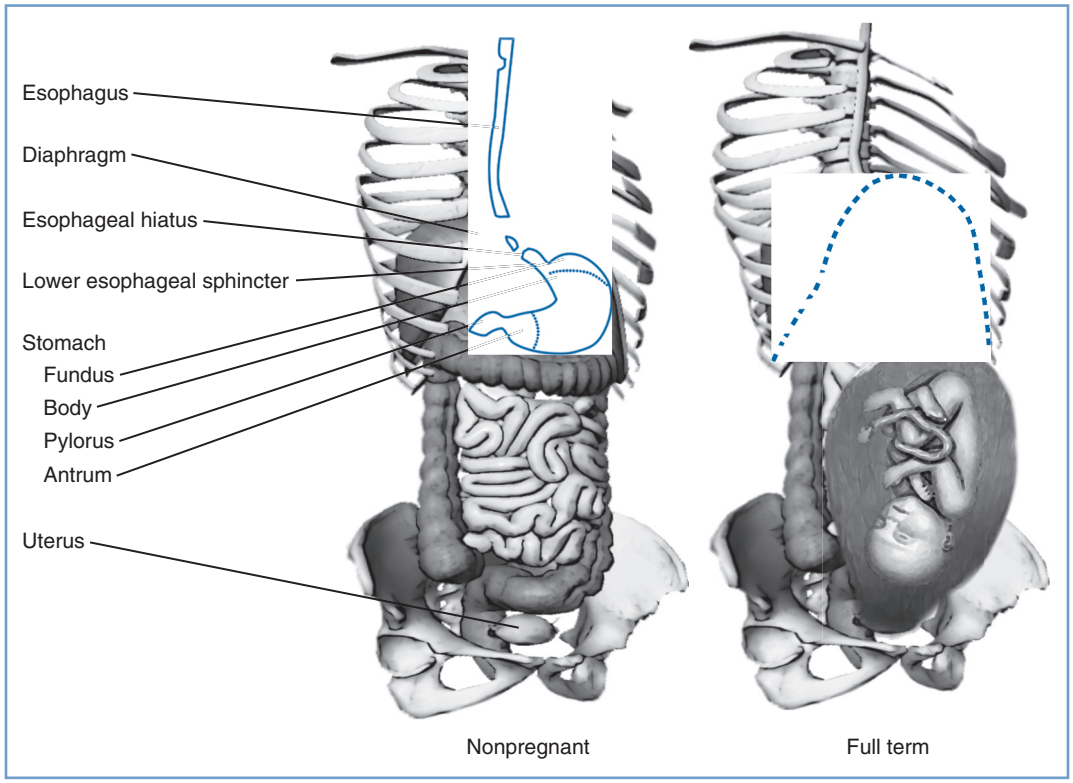

FIGURE 29-2 ■ The stomach and its relationship to the diaphragm in nonpregnancy *(left)* and pregnancy *(right)*. The stomach consists of a fundus, body, antrum, and pylorus. The function of the lower esophageal sphincter depends on the chronic contraction of circular muscle fibers, the wrapping of the esophagus by the crus of the diaphragm at the esophageal hiatus, and the length of the esophagus exposed to intra-abdominal pressure. The gravid uterus may encroach on the stomach and alter the effectiveness of the lower esophageal sphincter. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

and its anatomic position. The pylorus is higher than the most dependent portion of the stomach in both the supine and standing positions.[17]

Gastric Secretion

In one day, the stomach produces as much as 1500 mL of highly acidic fluid containing the proteolytic enzyme pepsin.[18] Normal individuals can produce a peak acid output of 38 mmol/h.[19] Acid is secreted at a low basal rate of approximately 10% of maximal output, even when the stomach is empty.[19,20] There is diurnal variation in this basal rate of gastric acid secretion, with the lowest and highest outputs occurring in the morning and evening, respectively.

The stomach lining has two types of glands: pyloric and oxyntic. The **pyloric glands** contain chief cells, which secrete pepsinogen, the precursor for pepsin. The **oxyntic glands** contain the oxyntic cells, which secrete hydrochloric acid. Water molecules and carbon dioxide in the oxyntic cells combine to form carbonic acid, which dissociates into hydrogen ions and bicarbonate. The bicarbonate leaves the cell for the bloodstream, and the hydrogen ions are actively exchanged for potassium ions in the canaliculi connecting with the lumen of the oxyntic gland. The secretions of the oxyntic cell can contain a hydrochloric acid concentration as great as 160 mmol/L (pH 0.8).[18] **Proton pump inhibitors (PPIs)** block the hydrogen ion pump on the canaliculi to decrease acid production.[21]

The pylorus contains G cells, which secrete **gastrin** into the bloodstream when stimulated by the vagus nerve, stomach distention, tactile stimuli, or chemical stimuli (e.g., amino acids, certain peptides). Gastrin binds to gastrin receptors on the oxyntic cell to stimulate the secretion of hydrochloric acid. **Acetylcholine** binds to muscarinic (M_1) receptors on the oxyntic cell to cause an increase in intracellular calcium ion concentration, which results in hydrochloric acid secretion. **Histamine** potentiates the effects of both acetylcholine and gastrin by combining with H_2 receptors on the oxyntic cell to increase the intracellular cyclic adenosine monophosphate concentration, leading to a dramatic increase in the production of acid.[18] **H_2-receptor antagonists** (e.g., ranitidine, famotidine) prevent histamine's potentiation of acid production (Figure 29-3).

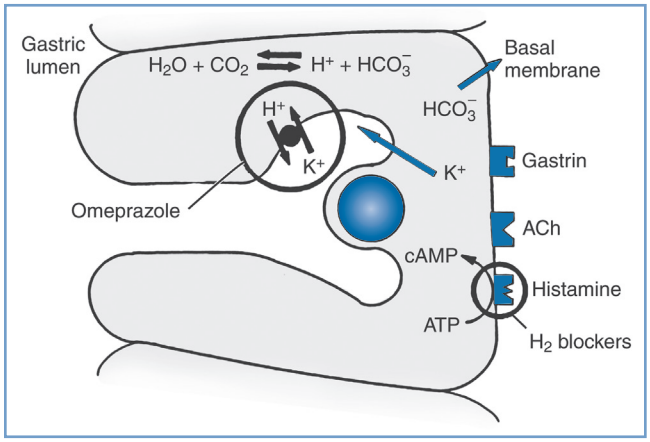

FIGURE 29-3 ■ The oxyntic cell produces hydrogen ions that are secreted into the gastric lumen and bicarbonate ions that are secreted into the bloodstream. H_2-receptor antagonists (e.g., ranitidine, famotidine) and proton-pump inhibitors (e.g., omeprazole) act on the oxyntic cell to reduce gastric acid secretion. H_2-receptor antagonists block the histamine receptor on the basal membrane to decrease hydrogen ion production in the oxyntic cell. Omeprazole blocks the active transport of the hydrogen ions into the gastric lumen. *ACh,* acetylcholine; *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *CO_2,* carbon dioxide; *H^+,* hydrogen ion; *HCO_3^-,* bicarbonate; *H_2O,* water; *K^+,* potassium.

Ingestion of Food

When a meal is eaten, the mechanisms that control the secretion of gastric juice and the motility and emptying of the stomach interact in a complex manner to coordinate the functions of the stomach. The response to eating is divided into three phases: cephalic, gastric, and intestinal. Chewing, tasting, and smelling cause an increase in the vagal stimulation of the stomach, which in turn increases gastric acid production. This represents the **cephalic phase** of digestion.[18] In this phase, gastric acid output increases to approximately 55% of peak output.[22] The **gastric phase** begins with the release of gastrin. Gastric acid secretion depends on antral distention, vagal activity, gastrin concentration, and the composition of the meal.[20,22,23] Gastric acid secretion during a mixed-composition meal increases to approximately 80% of peak acid output.[19] The **intestinal phase** begins with the movement of food into the small intestine and is largely inhibitory. Hormones (e.g., gastrin, cholecystokinin, secretin) and an enterogastric reflex further modulate gastric acid secretion and motility depending on the composition and volume of the food in the duodenum.[18,24] This inhibition of gastric emptying by food in the duodenum enables the duodenal contents to be processed before more material is delivered from the stomach.

After the ingestion of a meal, gastric emptying depends on (1) the pre-meal volume, (2) the volume ingested, (3) the composition of the meal, (4) the size of the solids, (5) the amount of gastric secretion, (6) the physical characteristics of the stomach contents entering the duodenum, and (7) patient position.[20,24-26] A mixture of liquids and solids passes through the stomach much more slowly than liquids alone. Gastric emptying is slowed by high lipid content, high caloric load, and large particle size.[20,27,28] Thus, predicting an exact time for the passage of liquids and solids through the stomach is very difficult. For non-nutrient liquids (e.g., normal saline), the gastric volume decreases exponentially with respect to time.[26] In one study, 90% of a 150-mL saline meal given to fasting adults in the sitting position passed through the stomach in a median time of 14 minutes; however, in adults in the left lateral position, the median time for gastric emptying was 28 minutes.[25] In another study, 100% of a 500-mL saline meal given to fasting adults passed through the stomach within 2 hours, as determined by a polyethylene glycol marker.[20] However, despite complete emptying of the saline test meal, the mean residual gastric volume at the end of 2 hours was 46 mL; this was because of greater secretion of gastric acid. Progressively less complete

gastric emptying and higher mean residual gastric contents were observed with meals containing amino acids, glucose, and glucose with fat.[20] These studies indicate that the volume and composition of the test meal, as well as the resulting gastric secretions, strongly affect gastric emptying and residual gastric content. For example, the subject described in Figure 29-4 responded to the test meal by secreting 800 mL of gastric juice and consequently the volume in the stomach remained high for almost 2 hours despite early, rapid emptying.[29]

Effects of Pregnancy on Gastric Function

Gastroesophageal reflux, resulting in heartburn, is a common complication of late pregnancy. Pregnancy compromises the integrity of the lower esophageal sphincter; it alters the anatomic relationship of the esophagus to the diaphragm and stomach, raises intragastric pressure, and in some women limits the ability of the lower esophageal sphincter to increase its tone.[30-33] Progesterone, which relaxes smooth muscle, probably accounts for the inability of the lower esophageal sphincter to increase its tone.[34] Lower esophageal pH monitoring has shown a higher incidence of reflux in pregnant women at term, even in those who are asymptomatic, than in nonpregnant controls. Therefore, at term gestation the pregnant woman who requires anesthesia should be regarded as having an incompetent lower esophageal sphincter. These physiologic changes return to their prepregnancy levels by 48 hours after delivery.[33]

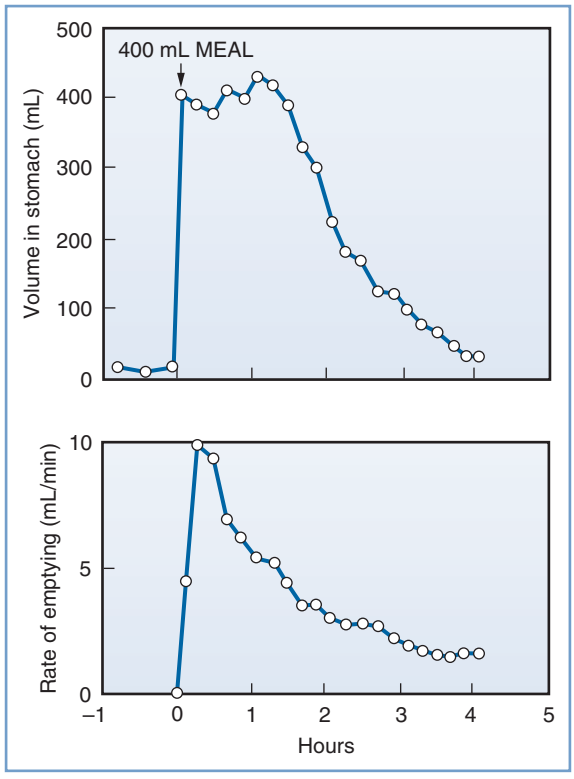

FIGURE 29-4 ■ Volume of gastric contents and rate of gastric emptying in a subject eating a 400-mL meal of steak, bread, and vanilla ice cream. (From Malagelada JR, Longstreth GF, Summerskill WHJ, et al. Measurements of gastric functions during digestion of ordinary solid meals in man. Gastroenterology 1976; 70:203-10.)

Serial studies assessing **gastric acidity** during pregnancy have proved difficult to perform because pregnant women do not usually wish to swallow nasogastric tubes repeatedly for research purposes. However, in the most comprehensive study of gastric acid secretion during pregnancy, basal and histamine-augmented gastric acid secretion was measured in 10 controls and 30 pregnant women equally distributed throughout the three trimesters of pregnancy.[35] No significant differences in basal gastric acid secretion were seen between the pregnant and nonpregnant women. However, when the women were divided into groups according to gestational age, the mean rate of gastric acid secretion was found to be reduced during the second trimester. The maximal response to histamine was significantly lower in women in the first and second trimesters than in women who were either not pregnant or in the third trimester of pregnancy.[35]

Assessment of **gastric emptying** during pregnancy and labor presents technical and ethical challenges, and a variety of techniques have been used (Table 29-1).[36-60] Pregnancy does not significantly alter the rate of gastric emptying.[39] In addition, gastric emptying was not found to be delayed in either obese or nonobese term pregnant women who ingested 300 mL of water after an overnight fast.[56,57] However, management of obese parturients should take into account the possible presence of other associated problems in this group of patients (e.g., hiatal hernia or difficult airway). Gastric emptying appears to be normal in early labor but becomes delayed as labor advances[49]; the cause is uncertain. Pain is known to delay gastric emptying, but even when labor pain is abolished with epidural analgesia using a local anesthetic alone, the delay still occurs.[60] Parenteral opioids cause a significant delay in gastric emptying, as do bolus doses of epidural and intrathecal opioids.[40,45,49,51,58] Continuous epidural infusion of low-dose local anesthetic with fentanyl does not appear to delay gastric emptying until the total dose of fentanyl exceeds 100 μg.[51]

The plasma concentration of the gastrointestinal hormone motilin is decreased during pregnancy.[61] Studies have shown either no change[30,32,62] or an increase[63] in the plasma concentration of gastrin.

RISK FACTORS FOR ASPIRATION PNEUMONITIS

Mendelson[3] divided aspiration pneumonitis into two types: liquid and solid. Whereas the aspiration of solids could result in asphyxiation, Mendelson demonstrated that the sequelae from the aspiration of liquids were more severe clinically and pathologically when the liquid was highly acidic (Figure 29-5). His observations, together with the results from other investigations,[64-72] suggest that the morbidity and mortality of aspiration depend on the following three variables: (1) the chemical nature of the aspirate, (2) the physical nature of the aspirate, and (3) the volume of the aspirate. Aspirates with a pH less

TABLE 29-1 **Studies of Gastric Emptying during Pregnancy and Labor**

Method of Assessment	Study*	Study Period and Subjects	Gastric Emptying
Radiographic	Hirsheimer et al. (1938)[43]	Labor (10 subjects)	Delay in 2 subjects
	La Salvia et al. (1950)[46]	Third trimester and labor	Third trimester: no delay Third trimester + opioids: marked delay Labor: slight delay Labor + opioids: marked delay
	Crawford (1956)[38]	Labor (12 subjects)	Delay in 1 subject
Large-volume test meal	Hunt & Murray (1958)[44]	Serial study Small numbers Second and third trimesters, postpartum	No change
Double-sampling test meal	Davison et al. (1970)[39]	Third trimester and labor	Labor: delay, with altered pattern of emptying
Epigastric impedance	O'Sullivan et al. (1987)[50]	Nonpregnant controls, third trimester, 60 minutes postpartum	No delay
Applied potential tomography	Sandhar et al. (1992)[52]	Sequential study 10 mothers: 37-40 weeks' gestation, 2-3 days postpartum, 6 weeks postpartum	No delay
Acetaminophen absorption	Nimmo et al. (1975)[49]	Labor with intramuscular opioids Postpartum 2-5 days	Labor: No delay Labor + opioids: marked delay Postpartum: no delay
	Nimmo et al. (1977)[60]	Labor	Labor: slight delay Labor + epidural analgesia (no opioid): slight delay
	Simpson et al. (1988)[53]	Nonpregnant controls, 8-11 weeks' gestation, 12-14 weeks' gestation	8-11 weeks: no delay 12-14 weeks: delay
	Macfie et al. (1991)[48]	Nonpregnant controls, first, second, and third trimesters	No delay in any trimester
	Geddes et al. (1991)[41]	Postcesarean delivery Epidural fentanyl 100 μg	Delay
	Gin et al. (1991)[42]	Postpartum: day 1 and day 3, 6 weeks	No delay
	Wright et al. (1992)[58]	Labor with epidural bolus: (1) bupivacaine 0.375%; (2) bupivacaine 0.375% + fentanyl 100 μg	Epidural opioids: delay
	Whitehead et al. (1993)[55]	Nonpregnant controls, first, second, and third trimesters Postpartum: 2, 18-24, and 24-48 hours	Pregnancy: No change Postpartum: 2 hours: delay 18-24 hours: no delay 24-48 hours: no delay
	Ewah et al. (1993)[40]	Labor with epidural infusion: (1) bupivacaine 0.25%; (2) bupivacaine 0.25% + fentanyl 50 or 100 μg, or diamorphine 2.5 or 5 mg	Epidural opioids: delay
	Levy et al. (1994)[47]	Nonpregnant controls, 8-12 weeks' gestation	Delay
	Stanley et al. (1995)[54]	Second and third trimesters and 8 weeks postpartum	No delay
	Zimmermann et al. (1996)[59]	Labor with epidural infusion: (1) bupivacaine 0.125%; (2) bupivacaine 0.125% + fentanyl 2 μg/mL	No delay
	Porter et al. (1997)[51]	Labor with epidural infusion: (1) bupivacaine 0.125%; (2) bupivacaine 0.125% + fentanyl 2.5 μg/mL	Epidural fentanyl total: < 100 μg: no delay > 100 μg: delay
	Kelly et al. (1997)[45]	Labor with neuraxial bolus: (1) epidural bupivacaine 0.375%; (2) epidural bupivacaine 0.25% + fentanyl 50 μg; (3) intrathecal bupivacaine 2.5 mg + fentanyl 25 μg	Epidural fentanyl: no delay Intrathecal fentanyl: delay
Real-time ultrasonography	Carp et al. (1992)[36]	Nonpregnant controls, third trimester	No delay
	Chiloiro et al. (2001)[37]	Serial study in 11 women: first and third trimesters, 4-6 months postpartum	No delay
Real-time ultrasonography and acetaminophen absorption	Wong et al. (2002)[56]	Third trimester Crossover study	50 mL or 300 mL water: no delay Faster gastric emptying with 300 mL
	Wong et al. (2007)[57]	10 obese parturients Third trimester Crossover study	50 mL or 300 mL water: no delay

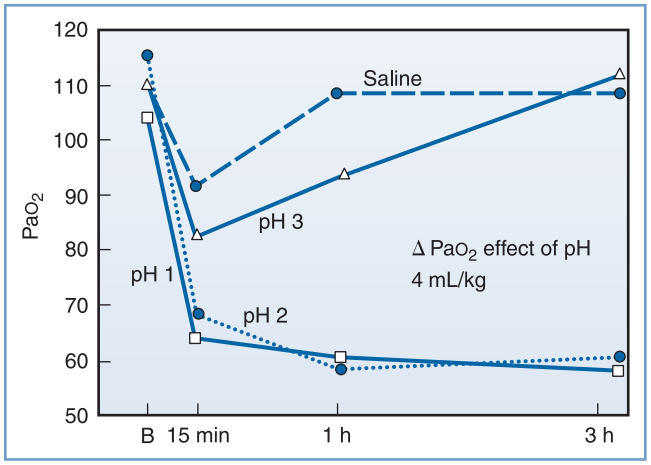

FIGURE 29-5 ■ Relationship between acidity and Pa_{O_2}. In this study, 4 mL/kg of fluid of varying pH was instilled into the tracheas of dogs. The severity of the hypoxemia correlated with the pH of the aspirate. A maximal decrease in Pa_{O_2} occurred with aspirates with a pH of less than 2.5. *B,* baseline. (From Awe WC, Fletcher WS, Jacob SW. The pathophysiology of aspiration pneumonitis. Surgery 1966; 60:232-9.)

than 2.5 cause a granulocytic reaction that continues beyond the acute phase.[72] Aspiration of particulate material can engender a clinical picture with severity equal to or greater than that caused by the aspiration of acidic liquid.[71] Aspiration of small volumes of neutral liquid results in a very low rate of mortality. However, aspiration of large volumes of neutral liquid results in a high mortality rate, presumably as a result of the disruption of surfactant by the large volume of liquid or from a mechanism similar to that seen in "near drowning."[67]

Historically, anesthesia providers have considered a nonparticulate gastric fluid with a pH less than 2.5 and a gastric volume greater than 25 mL (i.e., 0.4 mL/kg) as risk factors for aspiration pneumonitis.[64,69,70] No human study has directly addressed the relationship between preoperative fasting, gastric acidity and volume, and the risk for pulmonary aspiration during anesthesia.[73,74] There appears to be a reasonable scientific basis using a gastric pH cut-off value of less than 2.5 as a risk factor. In animal experiments, the risk for aspiration pneumonitis clearly increased with decreasing pH of the tracheal aspirate.[64,67] Awe et al.[64] illustrated this concept in a graph of Pa_{O_2} versus time for aspirates of varying pH (see Figure 29-5).

Animal studies have also demonstrated that an increase in the volume of tracheal aspirate is associated with a higher risk for aspiration pneumonitis.[67] However, the volume of aspirated material associated with risk has been disputed. The commonly accepted volume of 0.4 mL/kg (approximately 25 mL in a 70-kg adult) originated from an experiment in a single rhesus monkey in which 0.4 mL/kg of an acidic liquid was administered into the right mainstem bronchus and resulted in the animal's death.[70] The investigators made the assumption that this entire volume, if contained in the stomach, could be aspirated. However, Raidoo et al.[75] demonstrated variability in the response of juvenile monkeys to different volumes of an acidic tracheal aspirate. Death was seen with aspirate volumes of 0.8 mL/kg and 1.0 mL/kg but not with volumes of 0.4 mL/kg and 0.6 mL/kg. Similarly, Plourde and Hardy[76] refuted the assumption that all the gastric contents would be aspirated and demonstrated that gastric volumes of 0.4 mL/kg did not increase the risk for aspiration. Hence the gastric volume that puts a patient at risk for aspiration pneumonitis has not been determined. However, a reasonable goal of prophylactic therapy would be a gastric pH greater than 2.5 and a gastric volume as low as possible.

PATHOPHYSIOLOGY

Aspiration pneumonitis (Mendelson's syndrome) describes a chemical injury to the tracheobronchial tree and alveoli caused by the inhalation of sterile acidic gastric contents, whereas **aspiration pneumonia** may be regarded as an infectious process of the respiratory tract caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria. Aspiration of gastric contents could therefore result in acid injury to the lung with or without bacterial and particulate matter–related effects.

Aspiration of acidic liquid injures the alveolar epithelium and results in an alveolar exudate composed of edema, albumin, fibrin, cellular debris, and red blood cells,[3,69,71,72] whereas the aspiration of neutral, nonparticulate liquid leads to an alveolar exudate with minimal damage to the alveoli. The phospholipid and apoprotein composition of surfactant changes, exerting a negative effect on its surface-active properties.[77] This effect leads to an increase in intraalveolar water and protein content and a loss of lung volume, resulting in a decrease in pulmonary compliance and intrapulmonary shunting of blood. The cellular debris and bronchial denuding cause bronchial obstruction. The exudative pulmonary edema, bronchial obstruction, reduced lung compliance, and shunting result in hypoxemia, increased pulmonary vascular resistance, and increased work of breathing. After the direct acid-mediated injury of the respiratory tract, an intense inflammatory response ensues from macrophage activation and secretion of cytokines, interleukins (IL) IL-1, IL-6, IL-8, and IL-10, and tumor necrosis factor-alpha (TNF-α).[78] These inflammatory mediators lead to the chemotaxis, accumulation, and activation of neutrophils in the alveolar exudate, up-regulation of adhesion molecules within the pulmonary vasculature, and activation of the complement pathways. The neutrophils subsequently release oxidants, proteases, leukotrienes, and other proinflammatory molecules.[78] Amplification of these inflammatory processes may result in the development of acute lung injury or acute respiratory distress syndrome (ARDS) (Figure 29-6).[77-79]

The acidic contents of the stomach prevent the growth of bacteria under normal conditions. However, gastric contents may become colonized with pathogenic gram-negative bacteria in patients receiving antacid therapy or with enteral feeding tubes, gastroparesis, or intestinal

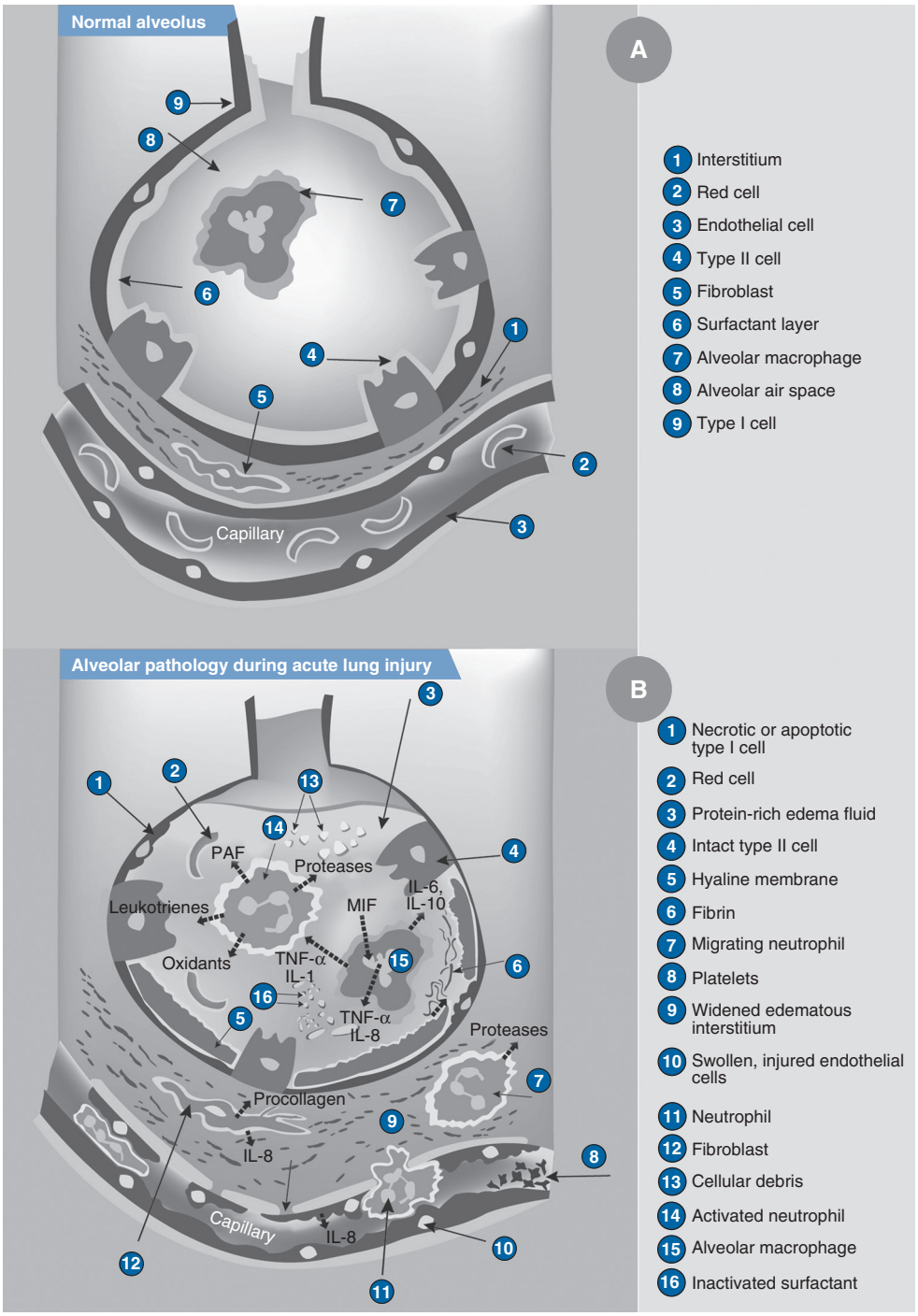

FIGURE 29-6 ■ Illustration showing the normal alveolus (**A**) and the injured alveolus (**B**) during acute lung injury. In the acute phase of acute lung injury there is formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are marginating through the interstitium into the air space. Alveolar macrophages secrete interleukin (*IL*)-1, 6, 8, and 10, as well as tumor necrosis factor-alpha (*TNF-α*), that stimulate and activate neutrophils. Neutrophils release proinflammatory molecules (oxidants, proteases, leukotrienes, platelet-activating factor [*PAF*]). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant and, together with unresolved fibrin depositions, fibrin-rich hyaline membranes are formed. *MIF,* müllerian inhibiting factor. (From Dahlem P, van Aalderen WMC, Bos AP. Pediatric acute lung injury. Paediatr Respir Rev 2007; 8:348-62.)

obstruction. The bacterial content adds to the inflammatory response to acid aspiration.[80]

Aspiration of particulate matter in the supine position most commonly involves injury to the posterior segments of the upper lobes and the apical segments of the lower lobes, whereas aspiration in the semirecumbent or upright position typically leads to injury to the lower lobes. The right lower lobe is the most common site of aspiration injury because the right mainstem bronchus has larger and more vertical architecture compared with

the left mainstem bronchus. Obstruction of the bronchus or bronchioles results in bronchial denudation and collapse of the bronchopulmonary segments. Persistent or unresolved collapse can lead to lung abscesses and cavitation.[80]

After the acute period, the process resolves through the proliferation and differentiation of surviving type II pneumocytes in the alveolar epithelial cells.[78,79] The type II pneumocytes actively transport sodium out of the alveolus, and water follows passively. Soluble proteins are removed by paracellular diffusion and endocytosis, and insoluble proteins are removed by macrophages. Neutrophils are removed by programmed cell death and subsequent phagocytosis by macrophages. Type II pneumocytes gradually restore the normal composition of the surfactant. In a subset of patients with ARDS, the injury progresses to a fibrosing alveolitis—an accumulation of mesenchymal cells, their products, and new blood vessels.

Bronchospasm and disruption of surfactant likely account for the slight decrease in Pao_2 and increase in shunting that are observed.[72] Aspiration of large solid particles may cause atelectasis by obstructing large airways.[3] Aspiration of smaller particulate matter causes an exudative neutrophilic response at the level of the bronchioles and alveolar ducts; the clinical picture is similar after the aspiration of acidic liquid.[66,71,72]

CLINICAL COURSE

In most cases of aspiration during anesthesia, the anesthesia provider witnesses regurgitation of gastric contents into the hypopharynx.[3] Patients who aspirate while breathing spontaneously have a brief period of breath-holding followed by tachypnea, tachycardia, and a slight respiratory acidosis. Significant aspiration always results in some hypoxemia caused by greater shunting and frequent bronchospasm.

An abnormality on a chest radiograph can be seen in 85% to 90% of patients who aspirate gastric contents.[68,81] Because these chest radiographic findings may lag behind clinical signs by as much as 12 to 24 hours, the initial radiograph may appear normal.[81] In mild cases, alveolar infiltrates are seen in the dependent portions of the lungs. Severe aspiration results in diffuse bilateral infiltrates without signs of heart failure (i.e., engorged pulmonary vasculature and/or enlarged cardiac silhouette) (Figure 29-7).

These symptoms and signs may progress to satisfy the Berlin Definition for ARDS; the criteria are as follows[82]:

- *Clinical:* within a week of known clinical insult
- *Chest imaging:* bilateral opacities not explained by effusions
- *Biochemical:* Pao_2/Fio_2 ratio less than 300 with continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) greater than 5 cm H_2O
- *Origin of pulmonary edema:* not explained by cardiac failure or fluid overload

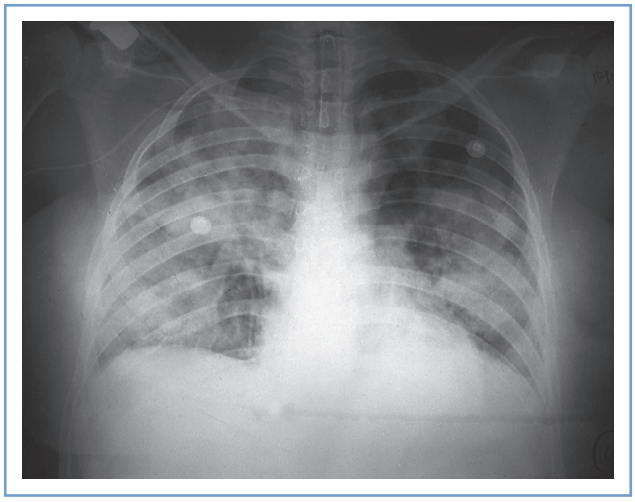

FIGURE 29-7 ■ Radiographic changes after pulmonary aspiration of gastric contents in pregnancy.

TREATMENT

Management of Aspiration

Management principles include rigid bronchoscopy, appropriate use of antibiotics, and management of hypoxemia with CPAP in nonintubated patients. Common treatments that lack evidence to support their use are the administration of corticosteroids and lung lavage with saline and bicarbonate.[80]

Rigid Bronchoscopy and Lavage

Suction of the upper airway followed by tracheal intubation and suction of the primary bronchi commonly precedes rigid bronchoscopy. Rigid bronchoscopy is useful for removing large food particles that cause airway obstruction. Lung lavage with saline or bicarbonate does *not* reduce the parenchymal damage caused by acid aspiration and can worsen preexisting hypoxemia.[80]

Antibiotics

Prophylactic antibiotics are *not* efficacious for aspiration and may lead to the development of infection with resistant organisms. Infection is not a component of acute pulmonary aspiration of sterile gastric contents.[80] Antibiotics should be administered only in the presence of clinical findings that suggest infection (e.g., fever, worsening infiltrates on chest radiographs, leukocytosis, positive result of Gram stain of sputum, clinical deterioration).

In patients who are intubated, a nonbronchoscopic bronchoalveolar lavage sample can be sent for laboratory analysis. Tracheal sputum samples may be insufficient to identify a bacterial pathogen, and some authorities recommend sampling of the lower respiratory tract with a protected specimen brush.[80]

Empirical antibiotic therapy is appropriate in patients with suspected bacterial colonization of gastric contents. The "at risk" group (see earlier discussion) includes patients who have gastroparesis or bowel obstruction and

those who are receiving enteral feeding or antacid therapy. Empirical antibiotic therapy is also appropriate in patients with aspiration pneumonitis that fails to resolve within 48 hours. The choice of antibiotic depends on the observed local patterns of antibiotic resistance. The target pathogens are gram-positive organisms (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*) and some gram-negative organisms (e.g., *Haemophilus influenzae*, *Escherichia coli*, Enterobacteriaceae) when the diagnosis is made less than 48 hours after hospital admission (i.e., community-acquired pneumonia). *Pseudomonas aeruginosa* is a common pathogen in cases of nosocomial (hospital-acquired) aspiration pneumonia. Anaerobes are no longer believed to be present in the majority of cases.[80] Pharmacologic therapy should be altered when specific pathogens and their antibiotic sensitivities are determined.

Treatment of Hypoxemia

Exudation of fluid into the alveoli, decreased surface activity of surfactant, and atelectasis all result in intrapulmonary shunting and hypoxemia. The administration of CPAP in patients breathing spontaneously or the administration of PEEP in patients undergoing mechanical ventilation restores functional residual capacity, reduces pulmonary shunting, and reverses hypoxemia. Supplemental oxygen should be given as required.

Corticosteroids

Despite decades-long use of corticosteroids in the management of aspiration pneumonitis, animal and human studies have failed to demonstrate a beneficial effect on pulmonary function, lung injury, alveolar-capillary permeability, or clinical outcomes after acid aspiration.[80] Thus, the administration of corticosteroids for aspiration pneumonitis cannot be recommended.

Management of Respiratory Failure

Aspiration of gastric contents can result in activation of inflammatory intrapulmonary pathways[80] consistent with the pathophysiology observed in ARDS.[79,82] The basic tenets of management of ARDS include the use of "lung-protective" ventilation strategies, the judicious management of fluids, and the application of basic critical care algorithms. The management of severe ARDS and hypoxemia resistant to conventional management involves the use of rescue therapies (e.g., prone positioning, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation) usually used in the critical care setting[83] and thus will not form part of this overview. The following section outlines the basic principles in immediate management and stabilization. Readers are referred to extensive reviews of management of ARDS for further information.[83-86]

Mechanical Ventilation

The key principles governing mechanical ventilation in ARDS involve limiting the inspiratory plateau pressure to 30 cm H_2O and providing the lowest effective tidal volume to prevent alveolar overdistention and tidal (cyclic) recruitment-derecruitment. Such "lung-protective" strategies correlated with improved outcomes in a prospective multicenter trial of the management of "early" ARDS; the use of initial tidal volumes and plateau pressures of 6 mL/kg and 30 cm H_2O or less was compared with the use of 12 mL/kg and 50 cm H_2O or less.[87]

Positive End-Expiratory Pressure

PEEP is a recommended component of the initial ventilator settings for ventilatory support in the setting of ARDS. A randomized clinical trial of ARDS (n = 549) funded by the National Institutes of Health (NIH) compared the effects of low and intermediate PEEP levels set according to predetermined combinations of PEEP and F_{IO_2} in the setting of a lung-protective mechanical ventilation strategy.[88] There were no significant differences in hospital mortality (24.9% versus 27.5%, respectively) or days to unassisted breathing (14.5 days versus 13.8 days, respectively) between the two groups. However, the role of comparatively higher levels of PEEP in protective ventilation strategies for ARDS is far from clear.[89-91]

Fluid Management

In a 2 × 2 factorial trial design, the ARDS Clinical Trials Network research group evaluated the use of conservative versus liberal fluid strategy and the value of guiding this intervention with central venous pressure or pulmonary artery wedge pressure measurements.[92] The group that received conservative fluid management, whether guided by central venous pressure and/or pulmonary capillary wedge pressure measurements, had much lower net fluid balance, better lung function, and a shorter duration of mechanical ventilation and intensive care unit stay. Further, there appeared to be no increase in the incidence or duration of shock or need for dialysis in the conservative fluid management arm of the trial. Thus, early management of ARDS (after initial resuscitation) focuses on limiting iatrogenic insult with conservative fluid management strategy.

Basic Critical Care Algorithms

To minimize the risk for sepsis, central venous catheters and other invasive hemodynamic monitors should be removed as early as is clinically feasible. Aseptic precautions should be used during care, and infections should be treated with antibiotics specific to the bacterial pathogen for 3 to 7 days. Whether tight and rigorous glycemic control should be employed is controversial. Occasional withdrawal of sedation and the use of prophylaxis for gastrointestinal bleeding and thromboembolic events are currently considered the standard of care in any critically ill patient (see Chapter 55).[93]

Corticosteroids

Recovery from ARDS depends on the functional resolution of the underlying pulmonary disorder, which may

TABLE 29-2 **Prevalence of Fasting Gastric Findings in Various Populations (%)**

Population	pH < 2.5	Volume > 25 mL	pH < 2.5 and Volume > 25 mL
Pregnant[100-102]	57-80	51-54	31-43
Nonpregnant[103, 105]	75-95	45-67	45-60
Postpartum[103, 104, 107]	54-93	61	60
Children[106]	93-100	64-78	64-77
Obese, nonpregnant[108]	88	86	75

follow one of two courses: (1) rapid improvement in lung function with an uncomplicated recovery or (2) slow improvements in lung function, oxygenation, and ventilation with prolonged weaning and recovery.

The corticosteroid controversy in ARDS in the context of aspiration is still unresolved.[80] Although a recent systematic review suggested potential benefit from corticosteroids,[94] their use did *not* appear to improve lung function or recovery in patients with ARDS in two of the well-conducted randomized clinical trials[95,96] and may be associated with longer-term side effects. To further add to the controversy, a 2007 randomized controlled trial reported an improvement in outcomes in patients with ARDS randomized to receive a methylprednisolone infusion versus placebo.[97] In our opinion, there appears to be no benefit from giving corticosteroids with the aim of attenuating lung injury after aspiration. However, if corticosteroids are being used for other reasons (e.g., bronchospasm, steroid replacement), then corticosteroid therapy could be considered.

PROPHYLAXIS

The risk for aspiration is extremely low when gastric emptying is normal and patients, including parturients, are appropriately fasted. Factors predisposing to regurgitation, particularly in obstetrics, include emergency surgery, difficult/failed tracheal intubation, light anesthesia, and gastroesophageal reflux. The risk for failed intubation is 3 to 11 times greater in pregnant patients than in nonpregnant patients[98,99] (see Chapter 30). Airway edema, breast enlargement, obesity, and the high rate of emergency surgery can all contribute to the risk for failed intubation in pregnant women. Aspiration pneumonitis is often associated with difficult or failed intubation during the induction of general anesthesia. In a survey conducted by the Society for Obstetric Anesthesia and Perinatology, intubation was recorded as difficult in 14 of 19 cases of aspiration in which tracheal intubation was used.[100] Moreover, Warner et al.[9] reported that the risk for aspiration during emergence from anesthesia was almost as high as that during induction of anesthesia. Thus, prophylactic regimens must provide protection during both induction of, and emergence from, general anesthesia. Although the risk for aspiration during elective, as opposed to emergency, surgery under general anesthesia is very low, parturients undergoing cesarean delivery or other surgical procedures should receive pharmacologic prophylaxis.

Because the incidence of aspiration pneumonitis is low, the efficacy of prophylactic regimens is measured by their ability to alter gastric pH and volume. In 30% to 43% of pregnant women the fasting gastric volume is greater than 25 mL and the gastric fluid pH is less than 2.5.[101,102] However, the percentage of term parturients at risk may not differ from that of patients undergoing elective abortion, postpartum sterilization, or gynecologic surgery (Table 29-2).[103-105] Gastric volume and acidity at term gestation are similar to gastric volume and acidity during early pregnancy, during the postpartum period, and in nonpregnant patients.[101-108] Decreased lower esophageal sphincter tone and a higher risk for difficult intubation are the primary factors that increase the risk for aspiration during pregnancy and the immediate postpartum period, and these are the factors that mandate the need for pharmacologic prophylaxis.

Preoperative Oral Fluid Administration

Multiple studies have described no increase in gastric volume or acidity after the oral administration of 150 mL of fluid (e.g., coffee, tea, water, other clear liquids, orange juice without pulp) in nonpregnant adults 2 hours before elective surgery.[109,110] The patients in these studies all fasted overnight and should have had a low gastric volume when the test meal was given. Lewis and Crawford[111] noted that in women undergoing elective cesarean delivery, those who had been allowed to consume a meal of both tea and toast 2 to 4 hours preoperatively had an increase in gastric volume and a decrease in gastric pH compared with a control group. Consumption of tea without toast resulted in an increase in gastric volume but it did not alter gastric pH. Particulate material was aspirated from the stomachs of 2 of the 11 patients who consumed both tea and toast. The investigators did not state the volume of tea consumed by these patients.

In addition, when gastric emptying of both 50 mL and 300 mL of water was assessed in nonlaboring term parturients, the gastric emptying half-time for 300 mL was significantly shorter than that for 50 mL.[56] When a similar study was conducted in obese nonlaboring parturients term (mean [±SD] prepregnancy body mass index 41 ± 9 kg/m^2), the gastric emptying time for 300 mL was not longer than that for 50 mL.[57] The latter finding suggests that the American Society of Anesthesiologists (ASA) Guidelines for Obstetric Anesthesia,[73] which state that "the uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia" could

also be applied to healthy, *obese* pregnant women presenting for elective surgery. However, factors other than the rate of gastric emptying can influence the rate of pulmonary aspiration, particularly in obese subjects. Obesity is associated with a higher incidence of gastroesophageal reflux and difficulty with airway management (both intraoperatively and postoperatively) (see Chapter 50). Moreover, the cesarean delivery rate is higher and the success rate of trial of labor after cesarean delivery is lower in obese parturients.[112,113]

Choice of Anesthesia

The Obstetric Anesthesia Work Force Survey demonstrated that the use of neuraxial anesthesia for cesarean delivery rose dramatically from 1981 to 2001, with the use of general anesthesia accounting for less than 5% of elective procedures.[114] A review of procedures performed at a large tertiary care obstetric facility showed that from 1990 to 1995 the use of general anesthesia for cesarean delivery decreased from 7.2% to 3.6%. The yearly incidence of difficult intubation ranged from 1.3% to 16.3%, with one maternal death resulting from a failed intubation.[115] Hawkins et al.[10] reported 67 maternal deaths resulting from complications of general anesthesia and 33 maternal deaths resulting from complications of neuraxial anesthesia in the United States during the years 1979 to 1990. Approximately 73% of general anesthesia–related maternal deaths were due to airway problems, primarily failed intubation and/or aspiration. However, data collected by Hawkins et al. for the more recent period spanning the years 1997 to 2002 indicate that the mortality rates for cesarean delivery are similar for general and regional anesthesia.[11] Studies reviewing failed intubation during the periods 1993 to 1998 and 1999 to 2003 in the United Kingdom showed that whereas the rate of failed intubation during this period had not declined there were no deaths from this potentially fatal complication.[116,117] Although this relative change in maternal mortality from the complications of general anesthesia is very encouraging, other factors such as the worldwide obesity epidemic have increased the challenges presented to anesthesia providers, particularly with respect to emergency operative deliveries. Therefore, techniques for preventing pulmonary aspiration of gastric contents will remain or even become increasingly pertinent to clinical practice.

Antacids

The ASA Practice Guidelines for Obstetric Anesthesia state, "Before surgical procedures (i.e., cesarean delivery, postpartum tubal ligation) practitioners should consider the timely administration of nonparticulate antacids, H_2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis."[73] Particulate antacids should not be used as prophylaxis because when aspirated they cause pulmonary shunting and hypoxemia of magnitude similar to that caused by acid aspiration and greater than that caused by saline, alkalinized saline, or sodium citrate.[118] Therefore, nonparticulate antacids (e.g., 0.3 M sodium citrate, Bicitra, Alka-Seltzer effervescent) should be used; their efficacy depends on the baseline gastric volume and acidity.[119,120] A total of 30 mL of sodium citrate neutralizes 255 mL of hydrochloric acid with a pH of 1.0. The effective duration of action of sodium citrate is variable and depends on the rate of gastric emptying.[121,122] O'Sullivan and Bullingham[121,122] used radiotelemetry pH pills to perform noninvasive assessments of the efficacy of sodium citrate in pregnant women. After the administration of 15 mL of sodium citrate to women in the third trimester of pregnancy, the time that the pH remained greater than 3.0 was less than 30 minutes.[121] When the same study was repeated in laboring women,[122] the mean time that the pH remained greater than 3.0 was 57 minutes in subjects who had received no analgesia and 166 minutes in those who had received meperidine. Nonparticulate antacids should be administered within 20 minutes of the induction of general anesthesia, particularly if the procedure is an emergency and there is insufficient time for a co-administered H_2-receptor antagonist to be effective.

Histamine-2 Receptor Antagonists

The ASA Task Force on Obstetric Anesthesia concluded that H_2-receptor antagonists are efficacious in reducing gastric acidity and volume.[73] H_2-receptor antagonists block histamine receptors on the oxyntic cell and thus diminish gastric acid production, leading to a slight reduction in gastric volume in the fasting patient. When given intravenously, an H_2-receptor antagonist begins to take effect in as little as 30 minutes, but 60 to 90 minutes are required for maximal effect.[102] After oral administration, gastric pH is higher than 2.5 in approximately 60% of patients at 60 minutes and in 90% at 90 minutes.[123] The duration of action is sufficiently long to cover emergence from general anesthesia for a cesarean delivery.

Cimetidine (given in doses of 200 to 400 mg intravenously or orally) reduces gastric acidity within 60 to 90 minutes.[102,123] Therapeutic plasma concentrations are sustained for approximately 4 hours. Cimetidine may decrease the rate of plasma clearance of certain drugs, including some local anesthetics (e.g., lidocaine), by binding to the cytochrome P450 system in the hepatocyte and by reducing hepatic blood flow.[124] Cimetidine crosses the placenta, but this does not appear to have harmful effects.[125] Because arrhythmias and cardiac arrest have been reported with the rapid intravenous administration of cimetidine,[126] a slow rate of intravenous administration or the oral route of administration is recommended. The use of cimetidine in obstetric anesthesia has largely been replaced by the use of other H_2-receptor antagonists.

Ranitidine, a chemically substituted amino-alkyl furan, has been evaluated after the administration of an intravenous or intramuscular dose of 50 to 100 mg or an oral dose of 150 mg.[127-129] These studies have noted that the administration of ranitidine results in a gastric pH greater than 2.5 within 1 hour and sustained therapeutic concentrations for approximately 8 hours.[127-129] Ranitidine does not have any major interaction with the cytochrome P450 system[130] and does not alter plasma concentrations of lidocaine or bupivacaine after their epidural administration.[131]

Nizatidine (given in doses of 150 to 300 mg orally) and **famotidine** (given in doses of 20 to 40 mg orally or intravenously) are alternative H_2-receptor antagonists.[132,133] Both have a duration of action greater than 10 hours and do not interfere with the metabolism of other drugs by the cytochrome P450 system.[132,133]

Tramadol, a synthetic 4-phenyl-piperidine analogue of codeine with a low affinity for μ-opioid receptors, has the additional property of inhibiting type 3 muscarinic receptors that mediate gastric gland secretion and smooth muscle contraction. In one study, 60 healthy parturients undergoing elective cesarean delivery under general anesthesia were randomly assigned to receive either intramuscular tramadol 100 mg or famotidine 20 mg 1 hour before surgery.[134] The median (range) gastric fluid pH after induction of anesthesia was 6.4 (1.7 to 7.2) in the tramadol group and 6.3 (1.9 to 8.1) in the famotidine group. Two patients in each group had a gastric volume greater than 0.4 mL/kg with a pH less than 2.5. Parturients in the tramadol group had better pain scores and used less analgesia during the first 24 hours after delivery. Neonatal well-being was similar in the two groups. Further investigation is required before such a novel method of antacid prophylaxis is adopted into everyday clinical practice.

Proton-Pump Inhibitors

Omeprazole (20 to 40 mg orally) and **lansoprazole** (15 to 30 mg orally) are substituted benzimidazoles that inhibit the hydrogen ion pump on the gastric surface of the oxyntic cell. Purported advantages of proton pump inhibitors (PPIs) are a long duration of action, low toxicity, and the potential for low maternal and fetal blood concentrations at the time of delivery.[21,135,136] For emergency cesarean delivery, studies have suggested that H_2-receptor antagonists and PPIs administered intravenously are equally effective adjuncts to sodium citrate for reducing gastric acidity and volume.[136] However, a meta-analysis has indicated that premedication with ranitidine is more effective than PPIs in reducing the volume of gastric secretion and increasing gastric pH.[137]

Metoclopramide

Metoclopramide is a procainamide derivative that is a peripheral cholinergic agonist and a central dopamine receptor antagonist. An intravenous dose of metoclopramide 10 mg increases lower esophageal sphincter tone and reduces gastric volume by increasing gastric peristalsis. Metoclopramide can have a significant effect on gastric volume in as little as 15 minutes.[101] Unfortunately, prior administration of an opioid or atropine antagonizes the effect of metoclopramide.[138] Extrapyramidal effects are a major potential side effect of metoclopramide. Metoclopramide crosses the placenta, but studies have reported no significant effects on the fetus or neonate.[139]

A Cochrane review of antacid prophylaxis concluded that there was no evidence to support the routine administration of drugs to women in normal labor to reduce the incidence of pulmonary aspiration or Mendelson's syndrome.[140] This conclusion reflects the low incidence of pulmonary aspiration of gastric contents and the absence of high-quality studies of antacid prophylaxis, rather than the presence of studies demonstrating negative results; the Cochrane review cited only three studies, published in 1971, 1980, and 1984. One study assessed the use of metoclopramide and perphenazine in women receiving meperidine in labor, and the other two studies focused on the use of particulate antacids. An audit of acid aspiration prophylaxis during labor in the United Kingdom showed a decreasing number of institutions with policies to administer routine antacid prophylaxis to all laboring women. However, many institutions attempted to identify women at high risk for an emergency cesarean delivery, to whom they gave oral ranitidine 150 mg at 6-hour intervals throughout labor.[141]

Sellick Maneuver and Induction of Anesthesia

Sellick demonstrated that the occlusion of the esophagus by cricoid pressure in cadavers prevented the flow of barium from the stomach to the pharynx.[142] He also reported the successful use of this maneuver in 26 cases to prevent the passive regurgitation of gastric contents into the airway. For proper application of cricoid pressure, the head should be fully extended; it may help to have a trained assistant place a hand behind the patient's neck, so that the cervical vertebrae and esophagus are brought forward, making it easier to occlude the latter. The trained assistant should place the thumb and middle finger on either side of the cricoid cartilage; no more than light pressure should be applied while the patient is awake, to prevent coughing, straining, retching, and esophageal rupture. After denitrogenation (preoxygenation) and administration of induction drugs, an increasingly firm downward pressure is applied to the cricoid cartilage as loss of consciousness occurs. Full application of cricoid pressure requires a force of 30 Newtons (N), 1 N being the force required to accelerate a mass of 1 kg by 1 m/s^2. (As a practical clinical guide to the amount of force to apply, 10 N is approximately equivalent to the downward force exerted by a mass of 1 kg.) Vanner and Pryle[143] demonstrated that 30 N of cricoid force prevented regurgitation of saline in cadavers with esophageal pressures as high as 40 mm Hg. They recommended a modest cricoid force (10 N) before loss of consciousness, increasing to 30 N after loss of consciousness; their data suggested that such pressure should be sufficient to prevent passive regurgitation of esophageal contents during induction of general anesthesia in most patients.[144,145] Cricoid pressure is maintained until the endotracheal tube cuff is inflated and correct endotracheal tube position is confirmed.

The value of cricoid pressure has been questioned. A study employing magnetic resonance imaging of 22 healthy volunteers of mixed sex noted that the resting position of the esophagus was lateral relative to the cricoid cartilage in 53% of the subjects without cricoid pressure and in 91% with cricoid pressure.[146] In addition, cricoid pressure displaced the esophagus relative to its initial resting position to the left and right in 68% and 21% of the subjects, respectively. The authors suggested

that cricoid pressure may lead to airway displacement and an inability to reliably produce midline esophageal compression; these factors could limit the protective effect of the maneuver against passive reflux and make the intubation process more difficult. However, Rice at al.[147] challenged these conclusions in a subsequent magnetic resonance imaging study investigating the efficacy of cricoid pressure. They demonstrated that the hypopharynx, rather than the esophagus, lies behind the cricoid cartilage (Figure 29-8). The relationship of the cricoid and laryngeal cartilages is constant and is maintained by their connecting ligaments and muscles. Because the cricoid cartilage and postcricoid hypopharynx are constantly related, they will behave as a unit when compressed against the cervical spine. They contended that the sealing of the hypopharynx is therefore independent of the position of the esophagus and the actual position of the esophagus is irrelevant to the successful application of cricoid pressure.

When the technique of rapid-sequence induction of anesthesia with tracheal intubation was first described in detail, it was recommended that the trunk be elevated 30 degrees to prevent reflux and aspiration.[148] Over subsequent years, others argued the advantages of both the supine and head-down positions for induction of anesthesia. Hignett et al.[149] demonstrated that the functional residual capacity of healthy term parturients was increased in the 30-degree head-up position compared with the supine position. Moreover, in the 30-degree head-up position, the esophageal pressure is lower and thus the force applied to the cricoid could be reduced to 20 N[143]; this reduction in force may reduce the incidence of airway problems, because these problems are often proportional to the force applied.[150] Further work is required to determine whether the increase in functional residual capacity in the 30-degree head-up position prolongs the time to oxyhemoglobin desaturation during the apnea phase of rapid-sequence induction and whether this position should be routinely adopted for induction of general anesthesia in obstetric patients.

Should the incorrect application of cricoid pressure distort the laryngeal inlet and cause difficulty with laryngoscopy and/or intubation, the cricoid pressure should be promptly released.

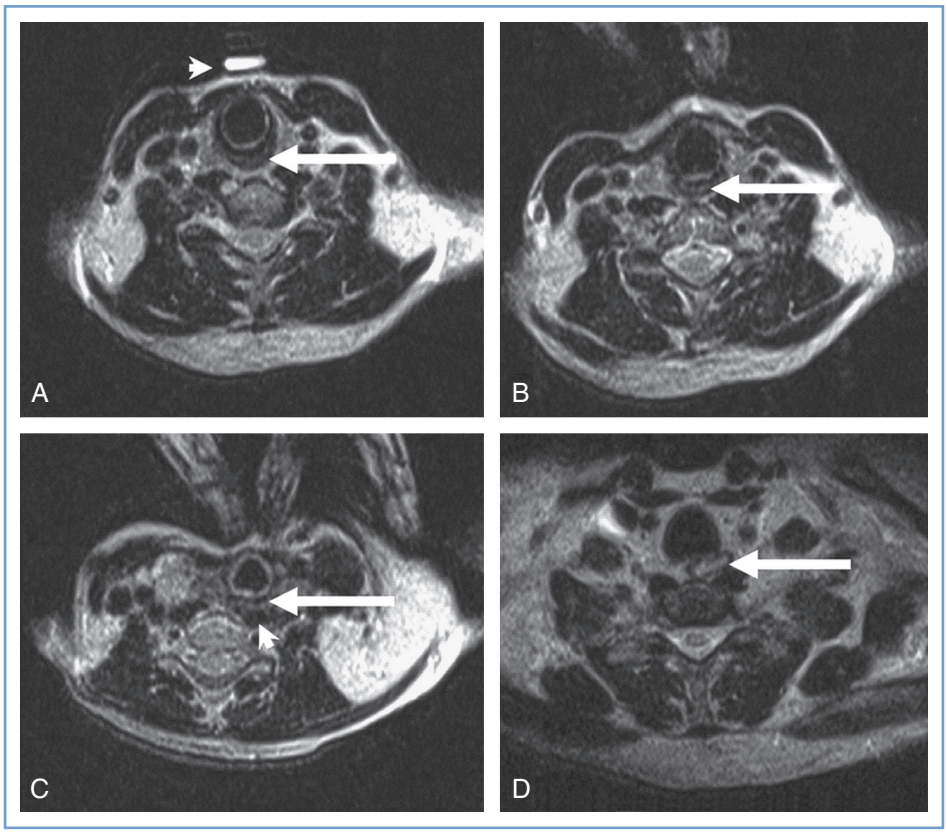

FIGURE 29-8 ■ Axial magnetic resonance images in the sniffing position, without (**A**) and with (**B**) cricoid pressure. **A,** Postcricoid hypopharynx (*arrow*) and the vitamin E marker (*arrowhead*) placed by the anesthesiologist before imaging. **C,** Example of postcricoid hypopharynx compression (*arrow*) lateral to the vertebral body with cricoid pressure. In this image, the postcricoid hypopharynx is compressed against the longus colli muscle group (*arrowhead*). **D,** Image 2 cm inferior to the cricoid ring distinctly shows the cervical esophagus (*arrow*) lateral to the vertebral body. In **B** and **C,** the anesthesiologist's thumb and index finger can be seen pushing on the cricoid cartilage. The axial image chosen for each study (**A-C**) was the image at the most inferior level of the cricoid cartilage. (From Rice MJ, Mancuso AA, Gibbs C, et al. Cricoid pressure results in compression of the postcricoid hypopharynx: the esophageal position is irrelevant. Anesth Analg 2009; 109:1546-52.)

RECOMMENDATIONS FOR CESAREAN DELIVERY

When possible, all mothers should be encouraged to have neuraxial anesthesia for cesarean delivery. Awake fiberoptic intubation should be considered for parturients with a potentially difficult airway who require general anesthesia. For **elective cesarean delivery,** a suitable antacid regimen may include the oral administration of an H_2-receptor antagonist (e.g., ranitidine 150 mg or famotidine 20 mg) or a PPI (e.g., omeprazole 40 mg) at bedtime and again 60 to 120 minutes before the induction of anesthesia. However, given that parturients are now encouraged to drink clear fluids until 2 hours before elective surgery, the morning dose can be taken with the final preoperative drink. Some practitioners also give metoclopramide 10 mg orally at the same time as the H_2-receptor antagonist or intravenously at least 15 minutes before the induction of anesthesia.

For **emergency cesarean delivery under general anesthesia,** 30 mL of sodium citrate should be administered just after transfer of the patient to the operating room. This timing is important because sodium citrate has a relatively short duration of action, except in those mothers in whom gastric emptying has been delayed by the administration of an opioid. In addition, ranitidine 50 mg (or famotidine 20 mg or omeprazole 40 mg) and metoclopramide 10 mg should be given intravenously when time allows. Administration of these drugs may not reduce gastric volume or acidity at the time of intubation but will decrease the risk for aspiration at the time of extubation. Some units administer an H_2-receptor antagonist orally every 6 hours during labor to all mothers considered to be at risk for an operative delivery.

The evidence that H_2-receptor antagonists or PPIs reduce maternal morbidity and mortality has not been conclusively demonstrated; however, increasing the pH and reducing the volume of gastric contents should assist in limiting damage if pulmonary aspiration occurs. The use of cricoid pressure as part of a rapid-sequence induction technique remains standard practice.

ORAL INTAKE DURING LABOR

Women in the third trimester of pregnancy exhibit a state of "accelerated starvation" if denied food and drink.[151] Fasting results in the production of ketones, primarily beta-hydroxybutyrate and acetoacetic acid, and the nonesterified fatty acids from which they are derived. These changes are exacerbated by the metabolic demands of labor and delivery. Consequently, some obstetricians and nurse-midwives have suggested that maternal oral intake policies should be liberalized during labor.[152] It is argued that allowing mothers to eat and drink during labor prevents ketosis and dehydration and subsequently improves obstetric outcome. The widespread use of neuraxial analgesia has resulted in a reduction in the use of systemic opioids for labor analgesia[114]; thus, fewer women may be at risk for opioid-induced delays in gastric emptying (with its inherent potential for aspiration). This trend has increased the demand to liberalize NPO policies during labor.

A randomized study examined the effect of a light diet on the maternal metabolic profile, the residual gastric volume, and the outcome of labor.[153] Women presenting in early uncomplicated labor at term were stratified by parity and randomly assigned to receive either a light diet or water only. The results showed that mothers who consumed a light diet did not have the increase in beta-hydroxybutyrate and nonesterified acid levels seen in the mothers who consumed water only. However, the gastric volumes as measured by ultrasonography were significantly larger in those who had eaten. Thus, mothers who consume a light diet during labor could be at greater risk for aspiration if general anesthesia is required. The same study design was used in another group of mothers, but isotonic "sport drinks" were administered instead of solid food[154]; it was found that these drinks reduced ketosis without increasing intragastric volume.

O'Sullivan et al.[155] evaluated the effect of food intake during labor on obstetric outcome in a randomized controlled study. A total of 2443 low-risk nulliparous women in labor were randomly assigned to either an "eating" or a "water only" group. Intention-to-treat analysis was performed. No significant differences were found in (1) the normal vaginal delivery rate, (2) the instrumental vaginal delivery rate, (3) the cesarean delivery rate, or (4) the incidence of vomiting (Figure 29-9). Similarly, there was no difference between groups in the duration of labor; the geometric mean (GM) labor duration was 597 minutes in the "eating" group and 612 minutes in the "water only" group (ratio of GM, 0.975; 95% confidence interval, 0.927 to 1.025).

Maternal death from Mendelson's syndrome is now extremely rare, and its decline probably owes more to the widespread use of neuraxial anesthesia than to NPO policies. Rigid NPO policies are therefore no longer appropriate on the labor and delivery unit, and women should be allowed to alleviate thirst during labor by consuming ice chips and clear fluids (e.g., isotonic sports drinks, fruit

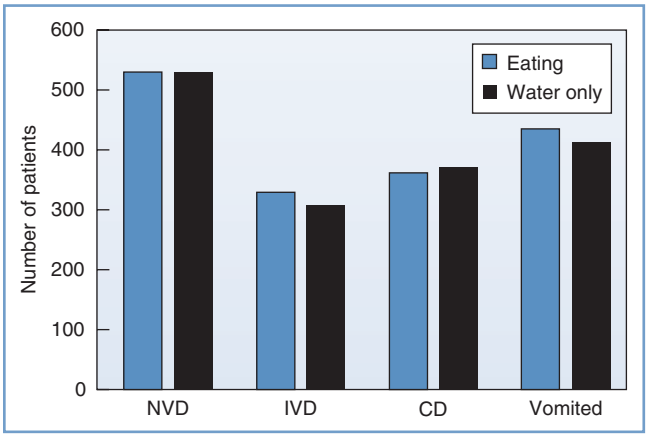

FIGURE 29-9 ■ The effect of eating during labor on maternal obstetric outcome. *CD,* cesarean delivery; *IVD,* instrumental vaginal delivery; *NVD,* normal vaginal delivery. (Based on data from O'Sullivan G, Liu B, Hart D, et al. Effect of food intake during labour on obstetric outcome: randomised controlled trial. BMJ 2009; 338:b784.)

juices without pulp, black tea, and coffee). In some high-risk pregnancies, it will remain appropriate to achieve hydration by the intravenous route, and such cases must be managed individually. The American College of Obstetricians and Gynecologists (ACOG) has stated that adherence to a predetermined fasting period before non-elective surgical procedures (i.e. cesarean delivery) is not possible. They therefore concluded that *solid food should be avoided in laboring patients*.[156] European guidelines also discourage women from eating solid food during labor. However the European guidelines acknowledge the current low incidence of aspiration in obstetrics and therefore state that *low-risk women could consume low residue foods (biscuits, toast, cereals) during labor*.[157] To date, countries with a more liberal attitude to eating during labor (e.g., the Netherlands, the United Kingdom, Australia) have not witnessed a higher incidence of maternal deaths from pulmonary aspiration. Further audit, research, and observation are required to fully inform the guidelines for oral intake during labor.

KEY POINTS

- Airway problems associated with the use of general anesthesia are a common cause of anesthesia-related maternal deaths.
- Reduced lower esophageal sphincter tone and a higher risk for difficult tracheal intubation are the primary factors that increase the risk for aspiration during pregnancy and the immediate postpartum period.
- Although pulmonary aspiration of gastric contents is rare in contemporary obstetric anesthesia practice, fatal aspiration may occur during difficult or failed intubation at cesarean delivery and at extubation.
- The most effective way to decrease the risk for aspiration is to avoid the administration of general anesthesia.
- The mother undergoing elective cesarean delivery should fast from solid food. Preoperative antacid prophylaxis should include an H_2-receptor antagonist.
- Preoperative prophylaxis prior to emergency cesarean delivery under general anesthesia should include a nonparticulate antacid. A clear antacid is preferred because aspiration of a particulate antacid results in pulmonary parenchymal damage similar to the damage that occurs after the aspiration of gastric acid. Strong consideration should also be given to administration of an H_2-receptor antagonist (or a proton pump inhibitor) and metoclopramide. These drugs may be administered after the induction of anesthesia if time does not permit their administration before induction.
- Hypoxemia is the hallmark of aspiration pneumonitis. Mechanical ventilation with positive end-expiratory pressure is the most effective treatment for severe hypoxemia. "Lung-protective" ventilation strategies (i.e., lower tidal volumes and inspiratory pressures) should be employed.
- The oral intake of clear fluids may be allowed during labor.
- Eating during labor results in larger residual gastric volumes. Eating during labor does not improve obstetric outcomes.

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CHAPTER 30

The Difficult Airway: Risk, Assessment, Prophylaxis, and Management

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CHAPTER OUTLINE

RISK

Definitions

A **difficult airway** can be defined in several ways. A practitioner may be said to encounter a difficult airway when he or she experiences difficulty providing adequate maintenance or protection of the airway that leads to hypoxemia or soiling of the tracheobronchial tree.[1] This definition includes difficulty in providing ventilation via a facemask or supraglottic airway (e.g., laryngeal mask airway [LMA]) or tracheal intubation. The American Society of Anesthesiologists (ASA) Task Force on Management of a Difficult Airway defines a difficult airway as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation of the upper airway, difficulty with tracheal intubation, or both.[2]

The prevalence of **difficult facemask ventilation** is dependent on the definition. In one study,[3] 5% of 1502 nonpregnant patients experienced difficulty in facemask ventilation, which was defined as an oxyhemoglobin saturation value less than 92%.[3] A multivariate analysis identified five independent risk factors for difficult facemask ventilation: (1) age older than 55 years, (2) body mass index (BMI) greater than 26 kg/m^2, (3) presence of a beard, (4) lack of teeth, and (5) a history of snoring. **Impossible mask ventilation**, defined as an inability to exchange air during bag-mask ventilation despite multiple providers, airway adjuncts, and neuromuscular blockade, was reported in 77 of 50,000 (0.15%) nonobstetric

anesthetic procedures.[4] Independent predictors of impossible mask ventilation were previous neck irradiation, male gender, diagnosis of sleep apnea, and a Mallampati class III or IV (see later discussion).[4] **Difficult laryngeal mask ventilation** may be defined as the inability within three attempts of device insertion to produce expired tidal volumes more than 7 mL/kg (leak pressure > 15 to 20 cm H_2O).[1] In a study of 11,910 nonobstetric patients,[5] the incidence of difficult laryngeal mask ventilation was 0.19%.

Although failed tracheal intubation is a tangible endpoint, defining **difficult intubation** is more complex. Difficulty may be encountered because of failure to visualize the glottis (difficult laryngoscopy) or due to an anatomic laryngeal or tracheal abnormality. Difficulty has been variously defined by (1) the time taken to intubate, (2) the number of attempts, (3) the view at laryngoscopy, and (4) the requirement for special equipment.

Although a dramatic decrease in the number of anesthesia-related deaths has been reported in the Confidential Enquiries into Maternal Deaths in the United Kingdom over the past 40 years, complications from general anesthesia, primarily complications of airway management, continue to be the leading cause of anesthesia-related maternal mortality.[6] Similarly, data from the United States have demonstrated a higher case-fatality rate with general anesthesia compared with neuraxial anesthesia.[7] Although the development of national guidelines[2,8,9] has resulted in a more systematic approach to the management of the difficult airway, deaths directly resulting from anesthesia still occur owing to failures in ventilation, tracheal intubation, or airway management following extubation. Despite widespread use of neuraxial anesthesia for operative delivery, general anesthesia may still be required in emergency situations, if neuraxial anesthesia is contraindicated or patients refuse it, or if neuraxial anesthesia has failed to provide adequate anesthesia.

Incidence and Epidemiology

The incidence of failed intubation in obstetrics has long been considered to be approximately 1 in 250 to 300,[10-14] which is approximately eight times greater than that in the general population (Table 30-1).[15] A number of reasons have been proposed to explain the increased difficulty with obstetric airway management. There are significant physiologic and anatomic changes of pregnancy (see later discussion) affecting the airway, oxygenation, and metabolism. The majority of obstetric general anesthetics are administered for emergency deliveries, often during off hours[16]; these anesthetic procedures may be conducted by inexperienced anesthesia providers with less proficiency in difficult airway management. Indeed, in one U.K. study,[12] the relative risk of failed intubation at emergency compared with elective cesarean delivery was 1.79 (95% confidence interval [CI], 0.61 to 5.26). Excessive cricoid pressure applied by a poorly trained assistant can worsen the glottic view at laryngoscopy,[17] as can positioning the parturient with left lateral tilt. Marfin et al.[18] proposed that the introduction of disposable airway equipment may adversely affect airway management; single-use, disposable gum elastic bougies are less reliable than reusable devices.

TABLE 30-1 **The Incidence of Failed Intubation in Obstetrics**

Study	Year	Country	No.	Incidence
Lyons[10]	1985	UK	2331	1:291
Rocke[28]	1992	South Africa	1500	1:750
Hawthorne[11]	1996	UK	5802	1:250
Tsen[21]	1998	US	536	1:536
Barnardo[12]	2000	UK	8970	1:249
Rahman[13]	2005	UK	4768	1:238
McDonnell[14]	2008	Australia	1095	1:274
Djabatey[29]	2009	UK	3430	0
McKeen[30]	2011	Canada	2633	1:1300

An increase in the incidence of airway-related complications in obstetric patients has been predicted.[19,20] The change in maternal demographics, most notably an increase in the prevalence of maternal obesity, may increase the risk for complications from general anesthesia, especially when performed for emergency procedures. With a decrease in the number of cesarean deliveries performed under general anesthesia, trainees have fewer opportunities to become familiar with challenges of the obstetric difficult airway.[21-23] Changes in anesthesia training, notably the reduction in trainee working hours and the advent of supraglottic airway (SGA) devices mean that, overall, laryngoscopy and intubation are now less commonly performed than previously. Therefore, the skills required to manage a challenging tracheal intubation are less likely to have been gained before working on the labor and delivery unit without direct supervision. In an editorial, Russell[19] suggested that failure to intubate during emergency cesarean delivery may be a self-fulfilling prophecy as practitioners draw on less experience with intubating the trachea during general anesthesia for an emergency cesarean delivery.

The increasing prevalence of maternal obesity is of significant concern. Obese women are at increased risk for obstetric interventions requiring anesthesia[24] and are more likely to have unsuccessful neuraxial anesthesia, necessitating the use of general anesthesia for emergency delivery (see Chapter 50). Difficulty with intubation has been reported to occur in 15.5% of the nonobstetric obese population.[25] A large Danish cohort study of more than 90,000 nonobstetric patients found that BMI of greater than 35 kg/m^2 was a significant risk factor for difficult intubation (odds ratio, 1.34)[26]; BMI was a more accurate predictor of difficult intubation than weight alone. Data collected from one U.K. region from 1993 to 1998 identified 26 parturients with failed intubation at cesarean delivery; the mean BMI was 33.1 kg/m^2.[12] Poor head and neck positioning at induction of anesthesia, inappropriate cricoid pressure, and operator anxiety may be responsible for a higher incidence of difficult airway management in obese patients.[27]

In contrast to some experts, others have questioned whether the rate of difficult and failed intubation is

increasing in obstetric anesthesia practice.[28-30] A more liberal attitude toward the use of general anesthesia has been suggested to lead to greater familiarity with maternal airway management and subsequent reduced rates of difficulty.[29] The ethics of using a technique potentially associated with greater risk for individual harm to reduce the overall incidence of anesthesia-related mortality associated with the technique presents an interesting dilemma. Certainly the presence of experienced anesthesia staff during induction of general anesthesia is recommended and should reduce the morbidity and mortality, and perhaps the frequency, of difficulty with airway management.[16] It is hoped that the introduction and widespread acceptance of simulation training in obstetrics[31] will lead to improvement in staff performance during critical events such as difficult airway management.

Maternal Morbidity and Mortality

For many years the U.K. Confidential Enquiries into Maternal Deaths have reported thromboembolism, hypertensive disease, and hemorrhage as the leading causes of maternal mortality. In the most recent report, covering the 2006 to 2008 triennium, pregnancy-related mortality from anesthetic causes was the 11th most common cause, accounting for 2.7% of maternal deaths.[6] In the United States between 1991 and 2002, 1.6% of maternal deaths were related to complications of anesthesia care, representing a 59% reduction in anesthesia-related mortality compared with data from 1979 to 1990.[7,32] Experience from both countries demonstrates dramatic improvements in anesthesia-related maternal mortality in the past three decades. This improvement likely reflects the tremendous efforts that been made by national anesthesia organizations in defining standards of care that lead to improved maternal safety.

Compared with neuraxial anesthesia, general anesthesia is associated with a greater risk for maternal mortality (Table 30-2, see Chapter 40).[7] Using data from the Centers for Disease Control and Prevention (CDC), the estimated case-fatality risk ratio for general compared with neuraxial anesthesia was 16.7 between the years 1985 and 1990.[32] However, the estimated risk ratio for the period between 1997 and 2002 was only 1.7 (95% CI, 0.6 to 4.6, $P = .2$).[32] Improvements in monitoring and the publication of algorithms for difficult airway management have been suggested to account for the reduction in mortality from general anesthesia. The case-fatality risk for general anesthesia from the earlier period may have overstated the relative risk because the accuracy of data was questionable and it is likely that general anesthesia was used for more complex cases for which mortality was expected to be greater.[33]

Unfortunately, maternal deaths directly attributable to general anesthesia are still reported.[6] Although protocols for the management of a difficult airway are now ubiquitous, they are not always followed.[12,34]

Hypoventilation and airway obstruction after extubation are now increasingly recognized as causes of maternal mortality.[6,35] In Michigan between 1985 and 2003, eight maternal deaths were believed related to anesthesia care; all deaths occurred during emergence from general anesthesia or the recovery period, and six of the eight patients were obese. System errors in which the care of the patient did not meet recognized standards were identified in five of the eight cases.[35] These errors included inadequate supervision by an anesthesiologist and lapses in postoperative monitoring.

TABLE 30-2 Case-Fatality Rates and Risk Ratios of Anesthesia-Related Mortality during Cesarean Delivery in the United States: 1979 to 2002

	*Case-Fatality Rates**		
Year Range	GENERAL ANESTHESIA	NEURAXIAL ANESTHESIA	**Risk Ratio**
1979-1984	20.0	8.6	2.3 (95% CI, 1.9-2.9)
1985-1990	32.3	1.9	16.7 (95% CI, 12.9-21.8)
1991-1996	16.8	2.5	6.7 (95% CI, 3.0-14.9)
1997-2002	6.5	3.8	1.7 (95% CI, 0.6-4.6)

CI, confidence interval.
*Deaths per million anesthetics.
From Hawkins JL, Chang J, Palmer SK, et al. Anesthesia-related maternal mortality in the United States: 1979-2002. Obstet Gynecol 2011; 117:69-74.

BOX 30-1 Anatomic and Physiologic Risk Factors for Airway Complications during Pregnancy

- Airway edema
- Decreased functional residual capacity
- Increased oxygen consumption
- Weight gain
- Breast enlargement
- Full dentition
- Decreased lower esophageal sphincter tone
- Delayed gastric emptying in labor

Physiologic and Anatomic Changes in Pregnancy

Of the multitude of anatomic and physiologic changes that occur in pregnancy (see Chapter 2), some have a significant effect on the degree of difficulty of laryngoscopy and tracheal intubation (Box 30-1).

Airway Edema

Fluid retention makes the tissues of the head and neck less compliant and may lead to narrowing of the upper airway, especially in the supine position. Consequently, nasal congestion, snoring, and voice changes all occur more frequently in advanced pregnancy.[36] A 34% increase

in Mallampati class IV scores[15,37] from the first to the third trimester of pregnancy has been observed (see later discussion).[38] Difficulty with intubation has been shown to be more than 11 times more common in women with Mallampati class IV than class I scores.[28]

Although changes in the airway develop gradually during pregnancy, more acute changes may be observed during labor. Mallampati class scores deteriorate during labor.[39-41] Decreases in upper airway volume during labor have been demonstrated by acoustic reflectometry.[39] The volume of both the oral component of the airway (from the incisors to the oropharyngeal junction) and the pharyngeal component (from the oropharyngeal junction to the glottis) are decreased, presumably as a result of increasing soft tissue edema. Airway narrowing may be more significant in women with preeclampsia. The airway edema that has been observed during labor may be exacerbated by expulsive efforts during the second stage of labor[42] or after extubation after cesarean delivery.[28] It is therefore prudent to reevaluate the airway before induction of general anesthesia rather than rely solely on a prelabor assessment.[39]

Nasal capillary engorgement during pregnancy increases the risk for epistaxis after nasal instrumentation and has led many practitioners to believe that nasal intubation is relatively contraindicated in pregnancy. In a 2011 review, Arendt et al.[43] challenged this opinion, suggesting that nasal fiberoptic intubation is acceptable after careful and appropriate preparation of the nasal mucosa with topical vasoconstrictors. However, the effects of topical agents on both the prevention of epistaxis and maternal hemodynamic parameters and uteroplacental perfusion must be evaluated and the relative risk of this procedure should be assessed on an individual basis.

Respiratory and Metabolic Changes

As pregnancy progresses, the gravid uterus increasingly encroaches on the diaphragm and lung volumes are reduced. By term, expiratory reserve volume decreases by 25% and residual volume decreases by 15%, resulting in a 20% reduction in functional residual capacity (FRC). This decrease is more marked in the supine than upright position, and in the obese than lean patient. Closing volume is unchanged in pregnancy, but the decrease in FRC results in airway closure in 50% of women if they are supine.[44] Metabolic requirements for oxygen increase by nearly 60% during pregnancy, predominantly because of fetal demands. Oxygen requirement is further increased during labor (see Chapter 2). These changes make pregnant women more likely to become hypoxemic during periods of apnea such as during the induction of general anesthesia.[45] Therefore, adequate denitrogenation (so-called preoxygenation—replacing nitrogen in the FRC with oxygen) is vital to delay the onset of hypoxemia during periods of apnea (see later discussion).

Preoxygenation and the rate of hemoglobin desaturation have been investigated by computer modeling.[46-48] In these models, labor, morbid obesity, and sepsis all hasten preoxygenation; however, desaturation also occurs more rapidly in the moderately ill and the obese (Figure 30-1). Significantly, the time to life-threatening hypoxemia is significantly shorter than that for recovery from paralysis from succinylcholine.[46] Therefore, should ventilation be impossible, it cannot be assumed that the patient will recommence breathing before dangerously low levels of oxygen saturation have been reached.

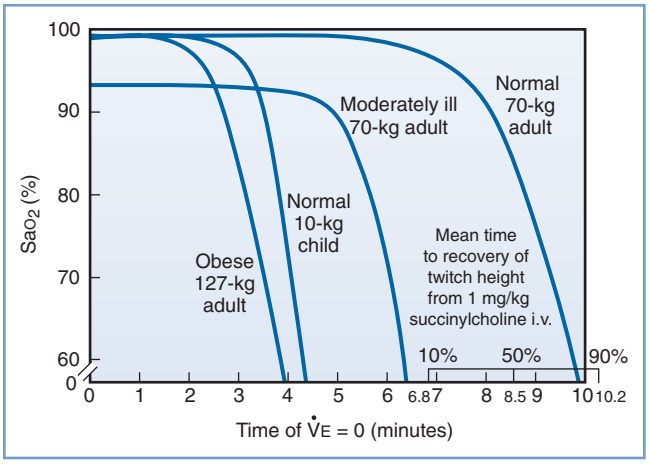

FIGURE 30-1 ■ Time to hemoglobin desaturation (initial Sao_2 = 0.87). Sao_2 versus time of apnea for various types of patients. (From Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 1997; 87:979-82.)

Weight Gain

During pregnancy, most women gain 10 to 15 kg (22 to 33 lb) or more. This weight gain is composed of increases in fat deposition, blood and interstitial fluid volume, and uterine and fetal mass. High BMI is associated with difficulty in mask ventilation and tracheal intubation[4,27] and with a greater risk for requiring emergency cesarean delivery.[24] BMI is directly associated with more rapid oxygen desaturation during apnea during the induction of general anesthesia.

Breast Enlargement

Breast enlargement during pregnancy may impede intubation by interfering with correct placement of the laryngoscope blade and laryngoscopic manipulation to improve visualization of the larynx. Various strategies can minimize this problem, the most important of which is optimizing the patient's position. With both arms abducted, breast tissue falls away from the chest. Ensuring that the patient is in the ideal intubating position (discussed later) further helps with laryngoscope blade insertion; a short-handled laryngoscope is recommended. The handle can be directed toward the shoulder on insertion of the blade and then redirected once the blade is in the oropharynx.

Full Dentition

Full dentition is typically present in young pregnant women and can interfere with direct laryngoscopy,

particularly if the maxillary incisors are protruding or the thyromental distance is small.[28]

Gastroesophageal Changes

Pregnancy-induced changes in the gastroesophageal system do not *per se* make laryngoscopy and intubation more difficult. However, owing to the increased risk for regurgitation and aspiration from the second trimester onward (see Chapters 2 and 29), rapid-sequence induction of anesthesia is advocated for almost all parturients, thus potentially increasing the risk for difficult airway management. Antacid prophylaxis is therefore mandatory when surgical intervention is required.

AIRWAY ASSESSMENT

Preanesthetic assessment of the airway is necessary before both general or neuraxial anesthesia, so that plans for airway management can be made in advance. A variety of bedside tests have been used, either singularly or in combination, to predict the airway difficulty. The validity of many tests has been questioned, and it is useful to consider how these assessments have been investigated.[49] First, *airway difficulty*, the outcome, must be defined. A number of definitions have been used (see earlier discussion), including difficulty or failure with ventilation (with or without a supraglottic airway) or intubation. Second, various predictive factors that are associated with difficult airway management have been tested on different sample populations of patients.

For an assessment to be useful it must be both sensitive (i.e., correctly identify those whose tracheas are difficult to intubate) and specific (i.e., correctly identify those whose tracheas are easy to intubate). Despite having both reasonably high sensitivity and specificity, many predictive tests have limited use in the clinical environment because failed intubation is rare; the number of false-positive tests (those predicted to be difficult that are not) will always be significantly higher than the number of true-positive tests (those predicted to be difficult that are).[49] The positive predictive value (ratio of true-positive tests to the total number of positive tests) for individual difficult airway tests is typically less than 50%, that is, fewer than half of the procedures predicted to be difficult will actually be difficult.[49] However, combining difficult airway tests can raise the index of suspicion for difficulty with airway management. Despite these shortcomings in difficult airway prediction, airway assessment is a vital part of anesthetic management. Preanesthetic assessment allows the consideration of potential airway problems and the creation of a stepwise plan for dealing with difficulties should they arise. Common methods of airway assessment used in clinical practice are discussed next.

Cormack and Lehane Grade

Cormack and Lehane[50] devised a glottic view grading system in 1984. The purpose of the system was to grade the glottic view obtained with direct laryngoscopy as a means of training for general anesthesia in the obstetric patient. Therefore, the Cormack and Lehane grade is not a preoperative assessment tool but rather a classification method to describe the relative difficulty with subsequent tracheal intubation. The original description includes four grades of laryngoscopy (Figure 30-2):

- Grade 1: Full view of glottis
- Grade 2: Partial view of glottis or arytenoids
- Grade 3: Only epiglottis visible
- Grade 4: Neither glottis nor epiglottis visible

Subsequent modifications have been proposed. Grade 2 may be divided into 2A (part of vocal cords visible) and 2B (only arytenoids or very posterior origin of vocal cords visible).[51,52] Further, Grade 3 may be divided into those in which the epiglottis is visible and lifted, such as with a gum elastic bougie (Grade 3A), and those in which the epiglottis is visible but not able to be lifted (Grade 3B).[52,53] Increasing difficulty with intubation is to be expected with each progressive grade of the Cormack and Lehane classification.

Because of the widespread acceptance of the Cormack and Lehane grading system, some useful information can be gained by reviewing the anesthetic records of patients who have a previous history of direct laryngoscopy; the Cormack and Lehane glottic view grade is often documented. However, prior reports should be treated with caution because grades given in the nonpregnant state will likely differ from those determined during pregnancy, and the potential for inter-observer and intra-observer variability exists.

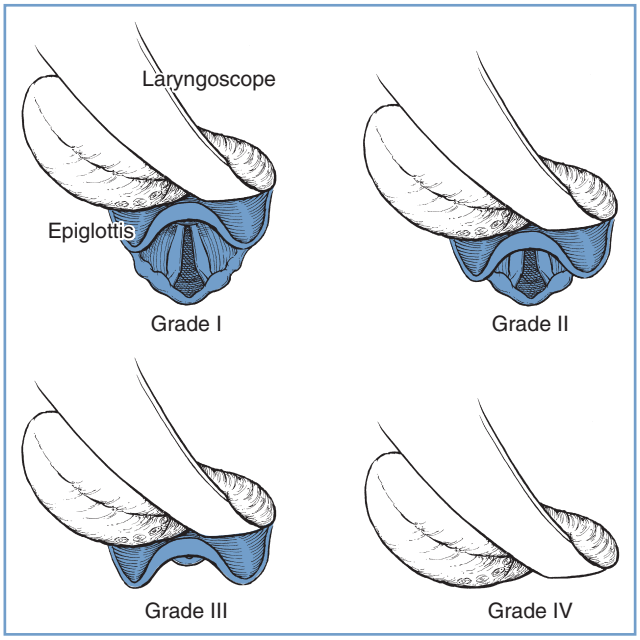

FIGURE 30-2 ■ Cormack and Lehane laryngoscopic view grades. Grade I is visualization of the entire laryngeal aperture. Grade II is visualization of only the posterior portion of the laryngeal aperture. Grade III is visualization of only the epiglottis. Grade IV is visualization of only the soft palate. (From Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia 1984; 39:1105-11.)

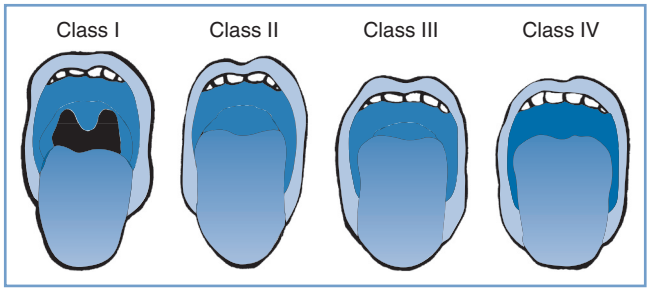

FIGURE 30-3 ■ Modified Mallampati classification of the oropharynx. Classification of the upper airway in terms of the size of the tongue and the pharyngeal structures that are visible with the mouth open. In class I, the soft palate, uvula, and anterior and posterior tonsillar pillars can be seen. In class II, the soft palate and uvula can be seen; the tonsillar pillars are hidden by the tongue. In class III, the soft palate and the base of the uvula can be seen. In class IV, only the hard palate can be seen. (From Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J 1985; 32:429-34.)

Mallampati Class

In 1985 Mallampati et al.[37] described a three-point scale of the oropharyngeal view of the open mouth based on concealment of the faucal pillars, soft palate, and uvula by the base of the tongue; the more the view was obscured, the greater the difficulty with laryngoscopy and intubation. Samsoon and Young[15] later modified the scoring system into a four-point scale (Figure 30-3):

Class I: visualization of soft palate, uvula, and tonsillar pillars
Class II: visualization of soft palate and base of uvula
Class III: visualization of soft palate only
Class IV: visualization of hard palate only

The test should be performed with the patient sitting upright with her head in the neutral position. The patient is instructed to open her mouth as wide as possible and protrude her tongue as far as possible *without* phonation. Increasing difficulty with laryngoscopy and tracheal intubation has been demonstrated with greater Mallampati scores in both obstetric[28] and nonobstetric populations.[37]

Mallampati scores are frequently used as part of an assessment to predict difficult intubation. It is important to remember that scores change during pregnancy[38] and during labor.[39-41] When used as the sole predictor of difficult airway, the incidence of both significant false-positive and false-negative results is high.[54] This poor predictive value may be explained by the use of phonation, poor patient positioning, involuntary arching of the tongue, and interobserver variability in interpretation. A meta-analysis of the Mallampati score concluded that the test had limited accuracy for predicting a difficult airway and was not a useful screening test.[55] Consequently, the Mallampati score is best used in combination with other tests.

Thyromental Distance

During laryngoscopy, the tongue is normally pushed into the mandibular space. The thyromental distance, the distance from the tip of the chin to the notch of the thyroid cartilage, can be used to estimate the size of this space and therefore whether the tongue can easily be displaced to facilitate laryngoscopy.[56] In the absence of other abnormalities, if the thyromental distance is more than 6.5 cm and the horizontal mandibular length more the 9 cm, intubation should proceed without difficulty. A thyromental distance of less than 6 cm suggests an increased risk for difficulty.[54] However, lack of detail in various studies regarding precisely how the thyromental distance was measured (whether it was performed from the inner or outer border of the mandible) make interpretation of this test difficult.

Anatomically, if the mandibular space is small and unable to accommodate the tissues displaced by the laryngoscope blade, few alterations will improve the line of vision during direct laryngoscopy (Figure 30-4).[56] When the mandibular space is small, the larynx lies relatively anterior and the tongue must be pulled forward maximally and compressed to expose the larynx.

Atlanto-occipital Joint Extension

Extension of the atlanto-occipital joint is necessary for the patient to be in the ideal intubating position in which the oral, pharyngeal, and laryngeal axes are aligned (see later discussion). Movement can be assessed with the patient seated with the head and neck in the neutral position facing forward and then with the joint maximally extended (Figure 30-5). Normal extension should be 35 degrees or more; difficulty with intubation can be expected when joint movement is decreased.[56] The accuracy of this assessment is subject to inter-observer variability, making its role in routine airway assessment questionable.

Mandibular Protrusion

The patient's ability to extend the mandibular teeth anteriorly beyond the line of the maxillary teeth may predict adequate visualization of the larynx during direct laryngoscopy. In the mandibular protrusion test, patients are asked to protrude their mandible as far as possible (Figure 30-6); one of three classes is assigned[57,58]:

- Class A: The lower incisors can protrude anterior to the upper incisors.
- Class B: The lower incisors can be brought edge to edge with the upper incisors.
- Class C: The lower incisors cannot be brought edge to edge with the upper incisors.

Class A is a good predictor of a good glottic view with direct laryngoscopy whereas class C is associated with poor glottic view.[57]

The **upper lip bite test** (ULBT) is similar to mandibular protrusion. In class 1 the lower incisors can bite the upper lip above the vermillion border (i.e., the normally sharp demarcation between the lip and the adjacent normal skin); in class 2, the lower incisors can bite the upper lip below the vermillion border; and in class 3, the lower incisors cannot bite the upper lip.[59] The ULBT has been shown to be a better predictor than a Mallampati score for predicting ease with laryngoscopy and

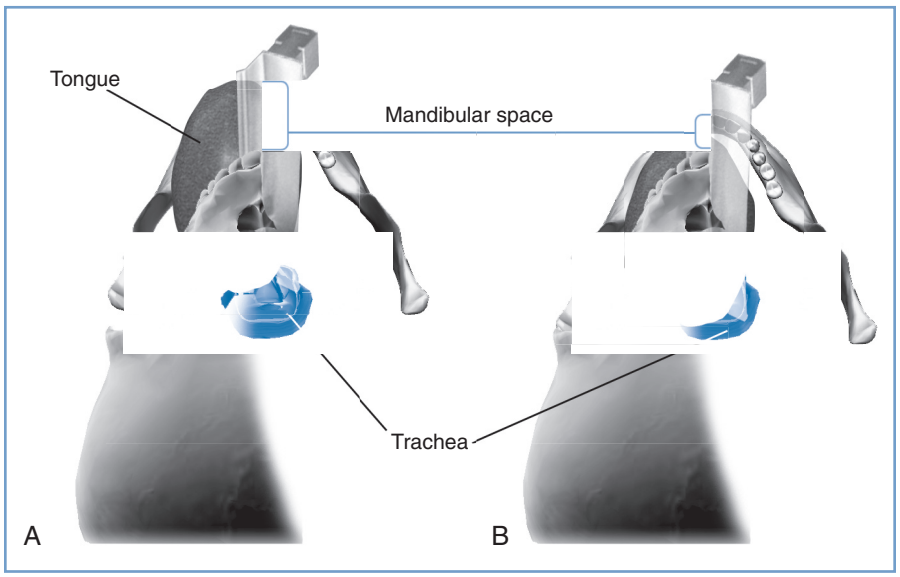

FIGURE 30-4 ■ The mandibular space viewed by the laryngoscopist inserting a curved laryngoscope blade into the airway in a supine patient. The mandibular space is the area bounded by the plane of the line of vision and the part of the mandibular arch in front of this plane (lower and upper extent of brackets, respectively). **A,** Normal-size mandibular space with room for the tongue. The laryngoscopist has an unimpeded view of the glottis. **B,** Small mandibular space—the tongue impedes the view of the glottis. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

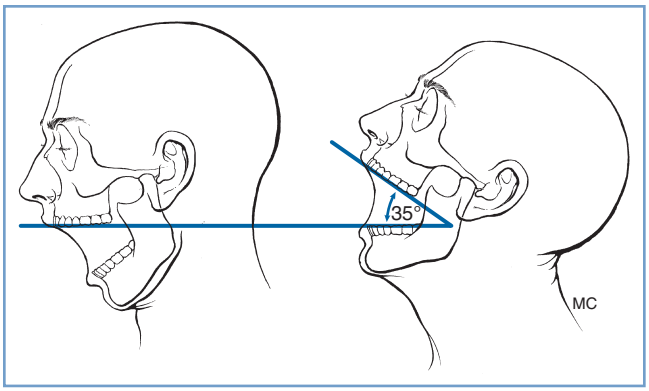

FIGURE 30-5 ■ Clinical method for quantifying atlanto-occipital joint extension. When the head is held erect and faces forward, the plane of the occlusal surface of the upper teeth is horizontal and parallel to the floor. When the atlanto-occipital joint is extended, the occlusal surface of the upper teeth form an angle with the plane parallel to the floor. The angle between the erect and the extended planes of the occlusal surface of the upper teeth quantifies the atlanto-occipital joint extension. A normal person can produce 35 degrees of atlanto-occipital joint extension. (From Bellhouse CP, Dore C. Criteria for estimating likelihood of difficulty of endotracheal intubation with Macintosh laryngoscope. Anaesth Intensive Care 1988; 16:329-37.)

intubation.[59] The ULBT cannot be assessed in edentulous patients.

Other Assessments

Sternomental distance has been suggested to predict difficult laryngoscopy. This distance is measured between the chin and sternum with the head fully extended on the neck and the mouth closed. Unfortunately, the assessment has extremely weak predictive power, and consequently it has largely been abandoned.

Limited mouth opening impedes the introduction of laryngoscope blade as well as other airway devices; an interincisor distance of less than 5 cm may predict difficult intubation. Mouth opening of less than two fingerbreadths has been shown to reduce the prevalence of easy intubation from 95% to 62%.[60] Mouth opening also is influenced by cervical spine movement; if movement is limited, mouth opening may also be restricted.[61] Protruding maxillary incisors, a single maxillary incisor, and missing maxillary incisors have been shown to be predictive of difficult intubation in obstetric patients.[28]

Comorbidities, including those not related to pregnancy, may influence airway management and should be considered before anticipated airway management. Most notably, maternal obesity is associated with an increased incidence of airway problems (see earlier discussion).[24,25,27] Similarly, difficulties in airway management should be anticipated in patients with severe preeclampsia.

Multivariable Assessments

Individual tests are poorly predictive of airway difficulty; therefore, a number of investigators have combined assessments in an effort to improve specificity. Wilson et al.[62] assessed five risk factors (weight, head and neck movement, jaw movement, presence or absence of a receding mandible, prominent teeth). Each variable was scored from 0 to 2, giving a Wilson risk sum. Although 75% of cases of difficult laryngoscopy could be predicted, 12% were falsely predicted to be difficult.[62] Subsequent work using the Wilson risk sum found a positive predictive value of only 9%, and consequently it is now rarely used in clinical practice.[63]

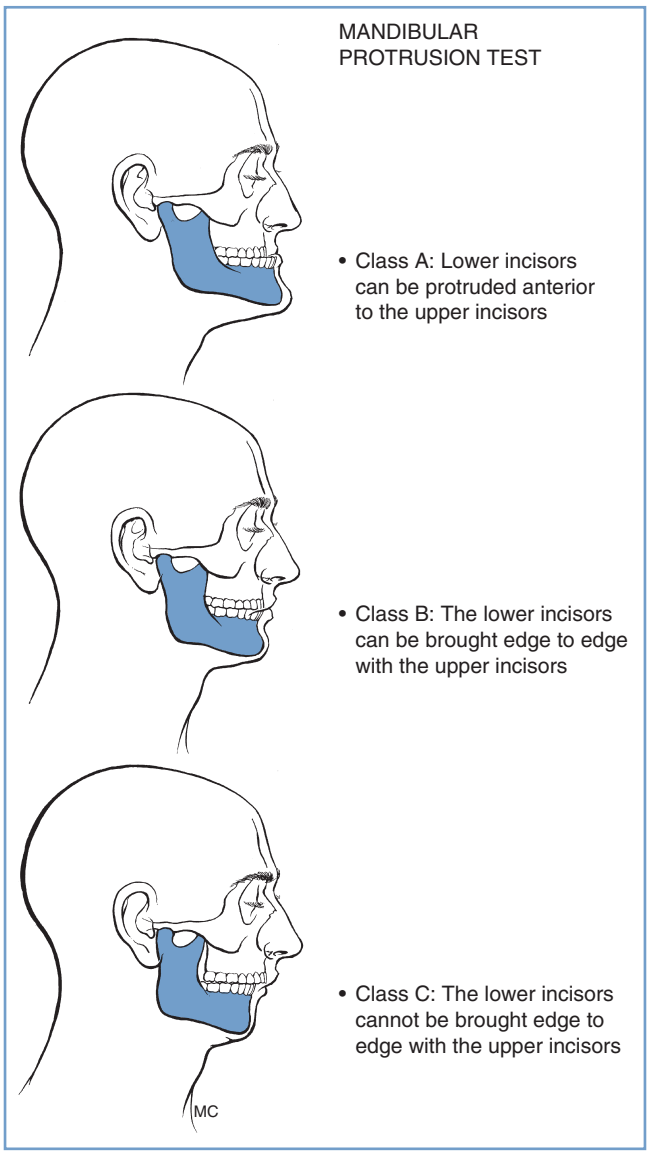

FIGURE 30-6 ■ Mandibular protrusion test. Three classifications are based on the test, which is also referred to as the upper lip bite test. (Redrawn from Munnur U, de Boisblanc B, Suresh MS. Airway problems in pregnancy. Crit Care Med 2005; 33:S259-68.)

Frerk[64] demonstrated that a combination of the Mallampati score and thyromental distance was more predictive than either test alone; the combined assessment had a sensitivity of 81% and a specificity of 98% in predicting a difficult airway. However, owing to the rarity of difficult intubation, the positive predictive value was only 64%.[64] Realizing that there was an absence of a clear description and agreement as to the method of performing individual tests, Lewis et al.[65] assessed different methods of grading the oropharyngeal view and the mandibular space as predictors of difficult laryngoscopy. Twenty-four different oropharyngeal assessments were considered using two body positions, three head positions, and two tongue positions, each with and without phonation. Similarly, the mandibular space was measured in 24 ways using two body positions, three head positions, and two distal and two proximal endpoints. The results were subject to logistic regression analysis. Although most difficult intubations could be predicted, half of those that were anticipated to be difficult were ultimately found to be easy, even with the most predictive combination of tests.[65]

Tse et al.[66] combined the angle at full head extension (in an upright position, the angle made by a line joining the ear tragus [apex] and the corner of the mouth to a line parallel to the floor [horizontal]), thyromental distance, and Mallampati classification in an attempt to predict difficult intubation in a general surgery population. Although these tests were likely to identify easy intubations, they had low sensitivity for predicting those in whom intubation was difficult.[66]

In a study of 400 pregnant women scheduled for elective cesarean delivery, Honarmand and Safavi[67] evaluated Mallampati class score, ratio of height to thyromental distance, and the ULBT, both in isolation and combination. A total of 8.75% patients had a Cormack and Lehane grade 3 or 4 laryngoscopic view; the ratio of height to thyromental distance was the best predictor of this outcome.[67]

Recommendations

The thoroughness of the airway assessment often depends on the urgency with which surgery needs to be performed. For emergency procedures, relatively little time is available; and so it is prudent to assess all women in the labor and delivery suite soon after their arrival, focusing on those with the greatest risk for intervention.[68] However, changes in assessment during the course of labor must be anticipated, and reevaluation before inducing anesthesia is vital to the safe care of these patients.

The assessment should attempt to identify the patients who will be difficult to ventilate and whose tracheas will be difficult to intubate. It should start with a history to detect factors that may indicate the presence of a difficult airway, as well as the potential risk for pulmonary aspiration. Examination of previous anesthetic records, if available, may indicate problems with ventilation or intubation. The presence of comorbidities such as obesity and preeclampsia should be considered. The ASA Practice Guidelines for Management of the Difficult Airway[2] list 11 components that can be assessed (Table 30-3), acknowledging the absence of a single test that can reliably predict who is likely to present difficulty with airway management. Consequently, a combination of assessments is generally considered preferable.

Performing and documenting mouth opening, the Mallampati class, atlanto-occipital mobility, thyromental distance, and mandibular protrusion may be performed relatively quickly and should identify most patients who will present difficulties with airway management. The preanesthesia evaluation should seek to identify risk factors for difficulty with mask ventilation, laryngoscopy, airway device insertion (including intubation), and performance of a surgical airway. When risk factors are identified, appropriate plans for airway management, such as the ready availability of additional equipment and personnel (e.g., individuals experienced with airway management and the creation of a surgical airway) should be

TABLE 30-3 Components of Preoperative Airway Examination

Airway Examination Component	Nonreassuring Findings
1. Length of upper incisors	Relatively long
2. Relation of maxillary and mandibular incisors during normal jaw closure	Prominent overbite (maxillary incisors anterior to mandibular incisors)
3. Relation of maxillary and mandibular incisors during voluntary protrusion	Patient cannot bring mandibular incisors anterior to maxillary incisors
4. Interincisor distance	Less than 3 cm
5. Visibility of uvula	Not visible when tongue protruded with patient sitting (e.g., Mallampati class > II)
6. Shape of palate	Highly arched or very narrow
7. Compliance of mandibular space	Stiff, indurated, occupied by mass or nonresilient
8. Thyromental distance	Less than three ordinary fingerbreadths
9. Length of neck	Short
10. Thickness of neck	Thick
11. Range of motion of head and neck	Patient cannot touch tip of chin to chest or cannot extend neck

Modified from American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway. Anesthesiology 2013; 118:251-70.

made. The proposed plan should consider that the administration of a neuraxial anesthetic technique may be the safest option for both mother and infant, even in the presence of nonreassuring fetal status. The plan must also include alternatives for situations in which the initial plan is not possible. The risks and benefits of various alternatives should be discussed with the patient and the obstetric, neonatal, and nursing teams and documented in the patient's medical record.

PROPHYLAXIS

Neuraxial Labor Analgesia

The widespread acceptance and use of neuraxial analgesic and anesthetic techniques for obstetric patients has significantly reduced the need for general anesthesia and airway manipulation. In obstetric patients in whom difficulty in airway management or neuraxial technique administration is anticipated or when risk factors for an urgent or emergent cesarean delivery are present, early or prophylactic placement of an epidural catheter should be encouraged. A *prophylactic* epidural catheter is one that is placed and tested with a small dose of local anesthetic; analgesia is not established until active labor begins, the patient requests analgesia, and/or an operative delivery is required. Such a catheter provides a readily available conduit for providing neuraxial analgesia or anesthesia, especially if rapid onset (e.g., an emergency cesarean delivery) is desirable. Early epidural catheter placement also allows the procedure to take place in a controlled setting and allows time for catheter manipulation and replacement, if necessary, before further pathophysiologic changes (e.g., decreased platelet count, worsening airway edema) occur. The correct placement of the epidural catheter in the epidural space should be tested with the injection of a local anesthetic test dose and careful bilateral sensory testing to confirm the presence of bilateral neuroblockade.

Unfortunately, labor *analgesia* cannot always be successfully converted to surgical *anesthesia* for an operative delivery; reported failure rates are as high as 8%.[69] A 2012 meta-analysis has demonstrated the need for conversion to general anesthesia in 5% of women who receive epidural analgesia in labor[70]; higher failure rates are observed among women requiring more physician interventions for inadequate epidural labor analgesia, in settings of need for urgent delivery, and when an anesthesiologist without specialty training or experience in obstetric anesthesia is providing care. Consequently, women receiving labor epidural analgesia must be evaluated at regular intervals; if analgesia is inadequate, re-siting the epidural catheter must be considered. A meta-analysis of studies comparing different local anesthetics for conversion of epidural analgesia to anesthesia found that lidocaine with epinephrine has a faster onset than bupivacaine, levobupivacaine, or ropivacaine.[71] The addition of bicarbonate to chloroprocaine or lidocaine with epinephrine further hastens the onset of local anesthetic action (see Chapter 26).

In situations in which conversion of epidural analgesia to anesthesia is not possible, general anesthesia may still be avoided if time permits the initiation of spinal or combined spinal-epidural anesthesia. However, care should be taken when performing a spinal anesthetic after a failed epidural top-up dose of local anesthetic, because cases of high and total spinal anesthesia have been reported in this setting (see Chapter 26). An airway management plan must always be in place, even if the primary plan is for the administration of neuraxial anesthesia.

Fasting and Antacid Prophylaxis

All obstetric patients requiring surgical anesthesia are at risk for pulmonary aspiration of gastric contents, particularly if airway difficulties are encountered (see Chapter 29). Because conversion from neuraxial to general anesthesia may be required either before or during surgery, strategies must be adopted to minimize this risk. The ASA and the American College of Obstetricians and Gynecologists (ACOG) recommendations allow modest amounts of clear liquid with uncomplicated labor, but they recommend the avoidance of solid foods in laboring women.[72,73] Clear liquids and solids are allowed up to 2 hours and 6 to 8 hours, respectively, before an elective operative procedure.[72,73] However, more liberal policies on oral intake in labor have become increasingly widespread as maternal death from

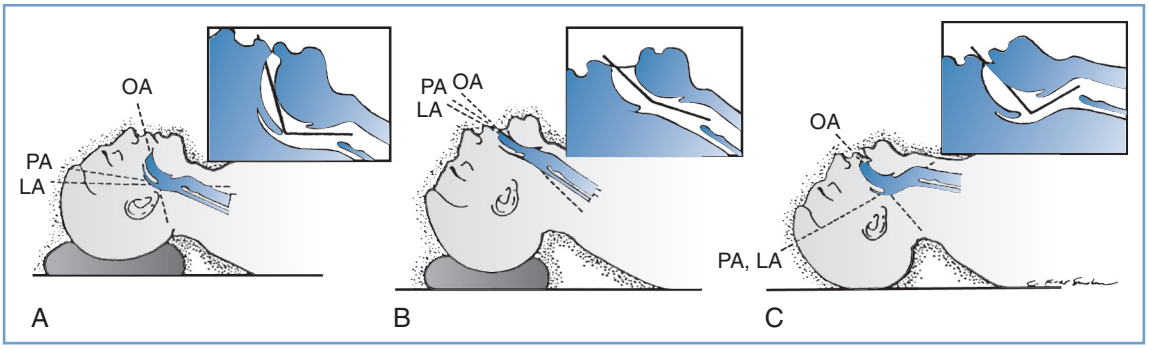

FIGURE 30-7 ■ Head and neck position during laryngoscopy. As the head position changes from neutral, the alignment of the oral axis (OA), pharyngeal axis (PA), and laryngeal axis (LA) changes within the upper airway. **A,** The head is resting on a large pad that flexes the neck on the chest and aligns the LA with the PA (the neutral position). **B,** The head is resting on a pad (which flexes the neck on the chest) and concomitant extension of the head on the neck can be seen, which brings all three axes into alignment (the sniffing position). **C,** Extension of the head on the neck without concomitant elevation of the head on a pad, which results in non-alignment of the PA and LA with the OA. (From Benumof JL. Conventional [laryngoscopic] orotracheal and nasotracheal intubation [single-lumen type]. In Benumof JL, editor. Clinical Procedures in Anesthesia and Intensive Care. Philadelphia, JB Lippincott, 1991:115-48.)

aspiration becomes less common. The U.K. National Institute for Health and Clinical Excellence suggests that women be allowed to drink isotonic fluids in labor and eat a light diet unless they develop risk factors that make general anesthesia more likely.[74] Consequently, all laboring women should be assessed and oral intake restricted if surgical intervention appears likely.

Once surgical intervention is required, antacids such as intravenous histamine-2 (H_2)-receptor antagonists or proton-pump inhibitors should be administered in case general anesthesia is necessary. However, these drugs take up to 30 minutes to become effective. If emergency general anesthesia is required, oral administration of a nonparticulate antacid such as sodium citrate is used to increase the pH of gastric contents. A dose of sodium citrate (0.3 molar) 30 mL is effective for approximately 30 minutes and should be administered shortly before the induction of general anesthesia.[75]

Metoclopramide promotes gastric emptying and increases lower esophageal sphincter tone, although its efficacy is decreased by concurrent use of opioids. It may be given orally in labor or intravenously before general anesthesia.

A number of deaths from presumed aspiration after tracheal extubation were reported in the most recent Confidential Enquiries into Maternal Deaths in the United Kingdom report.[6] The report's authors recommended that when general anesthesia is administered to woman with a potentially full stomach, consideration should be given to passing an "in and out" orogastric tube before extubation.

Patient Positioning

The optimal view during laryngoscopy, which yields the best chance for a successful intubation, requires appropriate patient positioning. The sniffing position, with 35 degrees of neck flexion and 15 degrees of head extension, has been considered the ideal position for facilitating a view of the glottis by aligning the oral, pharyngeal, and laryngeal axes (Figure 30-7).[76] Although use of the sniffing position has recently been questioned, most studies find it superior to other positions. The correct use of the sniffing position requires that the external auditory meatus and sternum are in horizontal alignment. Some video laryngoscopes (see later discussion) do not require the patient's head and neck to be in the sniffing position for successful device use.

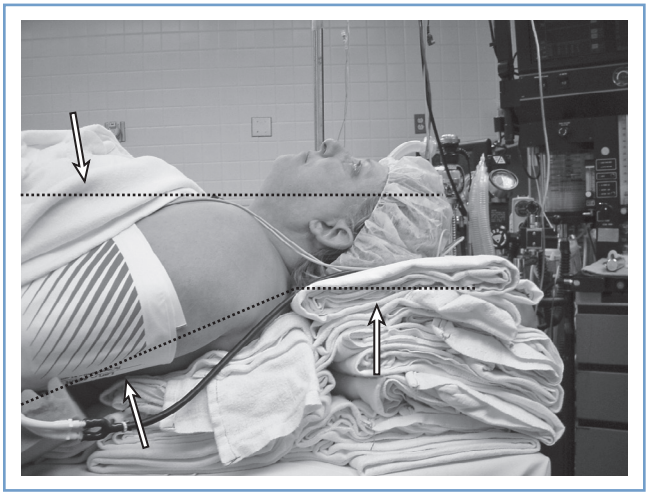

FIGURE 30-8 ■ A morbidly obese patient is in an optimal position for direct laryngoscopy when an imaginary horizontal line can be drawn from the sternal notch through (or slightly anterior to) the external auditory meatus. To achieve this, the upper back and shoulders should be significantly elevated with pads or blankets (or commercial elevation wedge/pillow) to allow the head to be extended at the atlanto-occipital joint. Additional blankets should be used to support the head in this position.

For obese patients, a ramped position is preferable (Figure 30-8). The anteroposterior chest diameter is increased in obese patients, making 35 degrees of neck flexion unachievable in the supine position. Consequently, the shoulders and upper torso need to be raised; this position can be achieved with the use of blankets or pillows or one of the many commercially available, wedge-shaped positioning cushions. Optimal elevation is

verified by checking that the external auditory meatus and sternoclavicular joint are in horizontal alignment. Elevating the back of the operating table by 25 degrees may make laryngoscopy easier and also aids preoxygenation (discussed later). The operating room table should be elevated to a height at which the laryngoscopist is most comfortable, with space at the head of the bed to accommodate access for the anesthesia team and necessary equipment.

Left uterine displacement to minimize aortocaval compression should be maintained during preparation for, and induction of, general anesthesia. This may be achieved by tilting the operating table or by placing a wedge under the right hip.

Denitrogenation (Preoxygenation)

In pregnancy, the decrease in FRC and increase in oxygen requirement result in rapid oxygen desaturation during periods of apnea (e.g., during induction of general anesthesia). The FRC is the primary reservoir for oxygen during apnea. Therefore, effective denitrogenation, or preoxygenation, of the FRC is vital to delay the onset of hypoxemia.

The standard technique for preoxygenation has been to breathe 100% oxygen through a tight-fitting facemask at normal tidal volumes for 3 to 5 minutes. Given the urgent nature of obstetric general anesthesia, attention has focused on whether several maximal deep breaths over a shorter period can be as effective. Chiron et al.[77] compared a traditional 3-minute technique with either eight deep breaths over 1 minute (8 DB/1 min) or four deep breaths over 30 seconds (4 DB/30 sec). By monitoring with end-tidal fractional oxygen concentration ($F_{ET}O_2$), which is probably the best marker of lung denitrogenation, the authors found that 3 minutes of tidal volumes or the 8 DB/1 min technique was more effective than the 4 DB/30 sec technique. They suggested using the 8 DB/1 min technique in the setting of emergency obstetric anesthesia.

The use of maximal deep breaths to achieve denitrogenation may cause maternal hypocarbia and, therefore, should be limited. However, preoxygenation with the 4 DB/30 sec technique leads to more rapid desaturation than standard normal tidal volume breathing or the 8 DB/1 min technique, indicating that a longer period of time is required to maximize oxygen storage in tissue and vascular body compartments. Indeed, during apnea, the time to desaturation depends on (1) the amount of oxygen stored in the lungs, tissue, and blood; (2) the mixed venous oxyhemoglobin saturation; and (3) the presence of intrapulmonary shunting.

A tight-fitting facemask is necessary to prevent air entrainment, which reduces the efficiency of preoxygenation. With normal tidal volume breathing, preoxygenation is best achieved with oxygen flow rates in excess of 10 L/min for 3 minutes,[78] although this may still be inadequate due to air entrainment; some authors suggest $F_{ET}O_2$ should be greater than 0.8 before anesthesia is induced.[79] A 20 degree to 30 degree head-up tilt increases the FRC and delays the time to desaturation, especially in obese patients.[80,81]

Rapid-Sequence Induction and Cricoid Pressure

In an attempt to minimize the risk for aspiration, the rapid-sequence induction has become the standard technique for induction of obstetric general anesthesia. It usually consists of preoxygenation, rapid intravenous injection of a predetermined dose of induction agent followed immediately by succinylcholine administration, application of cricoid pressure, and avoidance of positive-pressure ventilation before tracheal intubation with a cuffed endotracheal tube. The relative urgency of intubation, in a patient in whom ventilation is avoided, may increase the likelihood of failure.

Although in widespread use, the conduct of rapid-sequence induction is not uniform. Induction agents should provide rapid loss of consciousness with minimal hemodynamic instability while improving the quality of intubating conditions.[82] Thiopental has traditionally been the induction agent of choice for obstetric general anesthesia.[83] When used with succinylcholine, it provides intubating conditions that are as good or better than other agents. An additional advantage is that it can be reconstituted and stored for future use. Furthermore, some evidence suggests that, compared with propofol, thiopental leads to less maternal hypotension and fewer detrimental effects on the neonate.[83] Propofol, however, appears to offer better intubating conditions when combined with rocuronium; compared with thiopental in nonobstetric patients, visualization of the vocal cords was significantly more likely with propofol.[84] Its superiority to thiopental is most likely related to its greater ability to suppress pharyngeal and laryngeal reflexes. However, when succinylcholine is used, the choice of induction agent has no significant effect on intubating conditions.[82]

Opioids have traditionally not been part of rapid-sequence induction because of concerns of respiratory depression should intubation fail. Moreover, in the obstetric population, the potential for neonatal depression is greater if opioids are used because of rapid placental transfer of these drugs. In nonobstetric patients, the addition of opioids produces better intubating conditions when combined with rocuronium; this improvement has not been demonstrated with succinylcholine.[82]

Succinylcholine is associated with a number of undesirable side effects, most notably a prolonged duration of action in patients with cholinesterase deficiency and a trigger for malignant hyperthermia and anaphylaxis. However, because of its rapid onset, succinylcholine has traditionally been the muscle relaxant of choice for rapid-sequence induction of anesthesia in obstetric patients. Despite reduced levels of plasma pseudocholinesterase in pregnancy, the duration of action of succinylcholine remains clinically unchanged in the obstetric patient.[85] The ideal dose of succinylcholine, traditionally 1 mg/kg, remains controversial[86]; when combined with opioids in nonobstetric patients, succinylcholine 1 mg/kg fails to produce good intubating conditions at 1 minute in up to 8% of cases.[87] Naguib et al.[87] found that succinylcholine doses as high as 2 mg/kg still do not guarantee excellent intubating condition in all patients; however,

the authors found little extra benefit from using doses above 1.5 mg/kg.

The potential disadvantage of increasing the succinylcholine dose is delayed return of spontaneous respiration; return of spontaneous ventilation is vital should intubation not be achieved. Reducing the succinylcholine dose to 0.5 to 0.6 mg/kg does not appear to compromise intubating conditions, at least when administered in the nonobstetric population with propofol and fentanyl; the lower dose slightly shortens the recovery time.[88] In pregnancy, however, the reduced maternal FRC and greater oxygen demands make significant desaturation likely before the return of spontaneous respiration, no matter the succinylcholine dose. Because thiopental remains a widely used induction agent, and opioids are not commonly administered, continued use of succinylcholine 1 to 1.5 mg/kg is recommended.

The side effect profile of succinylcholine has resulted in consideration of alternative muscle relaxants for the rapid-sequence technique. Rocuronium is often used when succinylcholine is contraindicated; however, its prolonged duration of action is a significant concern when failure to ventilate or intubate occurs. **Sugammadex**, with its ability to rapidly reverse the effects of rocuronium, may help resolve this controversial issue; however, the drug is not available in the United States and there have been no clinical trials in pregnancy. When used with propofol for rapid-sequence induction, a 2008 meta-analysis indicated that succinylcholine (1 mg/kg or greater) produced superior intubating conditions compared with rocuronium (0.6 to 0.7 mg/kg) (relative risk [RR], 0.88; 95% CI, 0.80 to 0.97).[89] No significant difference was observed between the two agents when a larger dose of rocuronium (1.2 mg/kg) was used.[89] Therefore, succinylcholine remains the preferred muscle relaxant for use in rapid-sequence induction.

Cricoid pressure as a method to decrease pulmonary aspiration during induction of anesthesia was first described in 1961.[90] Interest in the technique was promoted by the reports of deaths due to aspiration under general anesthesia.[91] Although the effectiveness of cricoid pressure in preventing pulmonary aspiration of gastric contents has recently been challenged,[92,93] it is frequently used during the induction of obstetric general anesthesia (see Chapters 26 and 29). However, the use of cricoid pressure can adversely affect the ease of ventilation, laryngoscopy, and intubation. In a comparison of cricoid pressure with 20 N, 30 N, and 44 N of force, increasing pressure was more likely to lead to cricoid deformity and esophageal occlusion, particularly in women.[94] Difficulty with ventilation is less likely when 30 N is applied (currently accepted practice) than with 44 N (the previously suggested optimum value).[95] When correctly applied, with an increase in force from 10 N to 30 N with the induction of general anesthesia, there is little evidence of harm. However, when difficulty with intubation or ventilation arises, pressure may need to be reduced or released (see later discussion).

Although the cricoid pressure technique originally described by Sellick[90] was a one-handed technique, the placement of a second hand behind the patient's neck to prevent excessive neck flexion has been observed to provide a superior laryngoscopic view.[96] However, it should also be remembered that the two-handed cricoid pressure technique does not allow the anesthetic assistant to assist with other procedures, such as holding additional equipment necessary for difficult airway management.

MANAGEMENT

Planning

The approach to the difficult airway in the obstetric patient depends on the situation as well as the skill set of the anesthesia provider. In Figure 30-9 a suggested approach is outlined for management of obstetric patients with an anticipated difficult airway. After an initial assessment of the patient, an airway management plan should be created and shared with the patient and other members of the multidisciplinary team. In extreme cases, the anesthesia considerations may influence the mode and timing of delivery. Despite a thorough airway assessment and management plan, unanticipated or unrecognized airway issues and complications may arise; alternative algorithms and equipment should be readily available to ensure oxygenation and ventilation. Emergence and extubation should also be planned in advance. Lack of forethought and planning can lead to poor decision-making in crisis situations.

Neuraxial Anesthesia

The value of establishing and confirming a functional epidural catheter during labor in patients with an anticipated difficult airway has been described (see earlier discussion). A neuraxial anesthetic technique may also be preferable in patients with an anticipated difficult airway undergoing urgent or elective cesarean delivery. The choice of anesthetic technique (e.g., single-shot spinal, combined spinal-epidural, epidural, continuous spinal techniques) depends on the circumstances and preferences of the anesthesia provider. Neuraxial techniques do not obviate the necessity of planning airway management. High spinal anesthesia necessitating urgent airway intervention is a complication of all neuraxial techniques. Epidural anesthesia may be complicated by unintentional intravascular or intrathecal injection. Despite optimal planning and execution, a neuraxial anesthetic technique may fail to provide a surgical blockade of adequate density or duration.[33,58,97] Therefore, plans for securing the airway must always be preformulated, and standard and alternative airway equipment should be readily available.

Awake Intubation before General Anesthesia

Performing an awake intubation may be the safest option for the patient with an anticipated difficult airway, particularly if very difficult or impossible mask ventilation is anticipated or if neuraxial anesthesia is contraindicated or fails. Even patients with an advanced upper airway pathologic process have the ability to breathe when awake. However, the induction of general anesthesia with

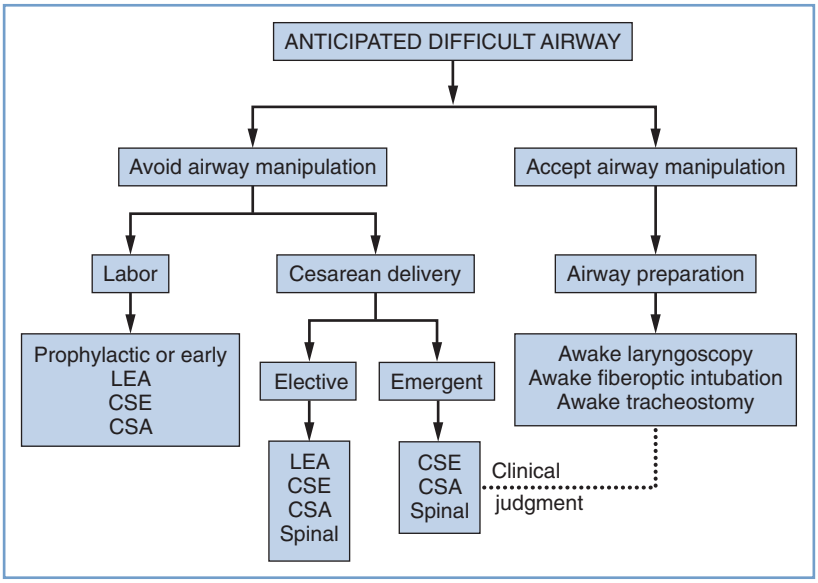

FIGURE 30-9 ■ Algorithm for anticipated difficult airway. This algorithm is not intended to provide comprehensive guidance that addresses every contingency. Rather, it should help anesthesia providers consider the various options that are available. Management should be individualized, and the anesthesia provider's clinical skills and judgment should guide decision-making. For additional information, the reader is referred to the American Society of Anesthesiologists practice guidelines.[2] *CSA,* continuous spinal anesthesia technique; *CSE,* combined spinal-epidural technique; *LEA,* lumbar epidural analgesia or anesthesia technique; *spinal,* spinal anesthesia technique.

paralysis can distort the airway anatomy by allowing soft tissue relaxation and movement of the larynx in an anterior direction; this distortion can make attempts at direct laryngoscopy more difficult. Therefore, an appropriate sequence of events includes securing the airway of these patients while they are awake and spontaneously breathing, before the induction of general anesthesia.[98] There is a perceived notion, particularly among practitioners with limited experience with the technique, that an awake intubation is time consuming, results in patient discomfort and anxiety, and is often difficult. In skilled hands, the technique can be accomplished quickly and comfortably with a high success rate.[99]

Awake intubation can be performed with a number of airway management devices, but the flexible fiberoptic bronchoscope offers unique advantages (Box 30-2). Proper planning and execution, with attention to detail, are keys to patient cooperation and a high success rate. Appropriate equipment must be readily available and experienced assistance is desirable. It is useful to have two anesthesia providers: one to perform the endoscopy and another to monitor the patient.[100] Pulse oximetry, capnography, continuous electrocardiography, and blood pressure monitoring are mandatory. The level of conscious sedation must be constantly monitored to obtain the desired level for the procedure (see later discussion). Supplemental oxygen should be administered.

An unhurried, thorough explanation of the technique to the patient helps to allay anxiety. Pharmacologic premedication should include prophylaxis for pulmonary aspiration and an **antisialagogue** such as intravenous glycopyrrolate 0.2 mg. A dry mouth improves topical oral anesthesia by ensuring better contact between the local anesthetic and the mucosa.[101] Secretions may also cause internal reflection from the light source and distort the fiberoptic view. Performing the procedure with the patient in the upright, rather than supine, position minimizes airway obstruction and aortocaval occlusion, enhances drainage of secretions, and allows better acceptance of topical anesthesia by the patient.

BOX 30-2 Advantages of a Flexible Fiberoptic Bronchoscope for Tracheal Intubation

- Flexibility and continuous visualization allows negotiation of even the most difficult anatomy
- Can be used for oral and nasal intubation
- Can be used with other devices (e.g., LMA/ILMA) to aid intubation
- Ability to instill local anesthetic through working channel is unique
- Immediate definitive endotracheal tube position check
- Excellent patient acceptability
- High success rate

ILMA, intubating laryngeal mask airway; *LMA*, laryngeal mask airway.

Conscious Sedation

The term *awake intubation* is a misnomer because in practice most patients receive some form of sedation to relieve anxiety, produce amnesia, and reduce pain and discomfort during the procedure. Moderate sedation/analgesia, also termed *conscious sedation*, is a drug-induced depression of consciousness during which the patient can respond purposefully to verbal or tactile stimulation. No

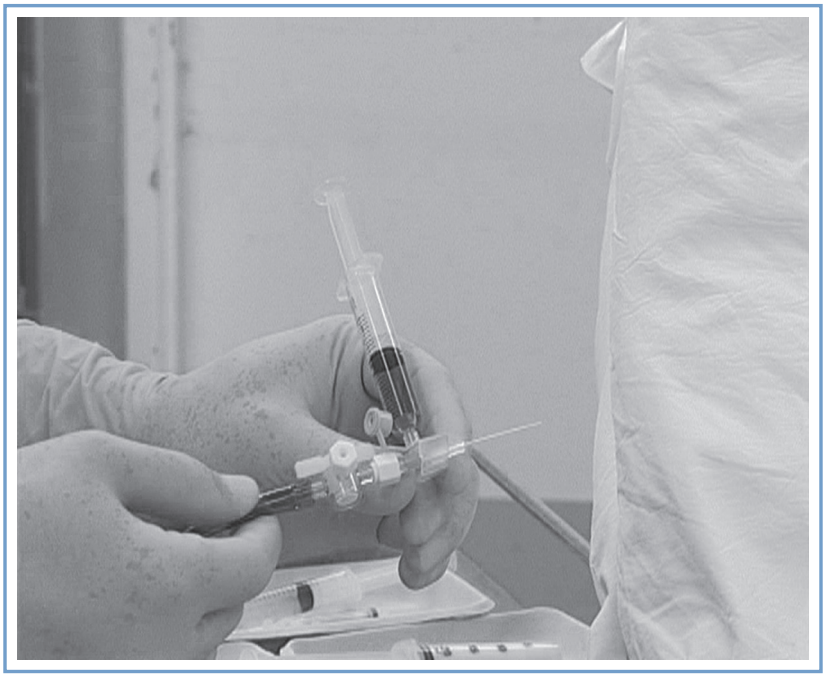

FIGURE 30-10 ■ Topical airway anesthesia. The MacKenzie technique[108] uses a 20-gauge intravenous cannula with an injection port connected to oxygen tubing via a three-way tap to produce a jetlike spray of local anesthetic administered from a syringe connected to the cannula with the oxygen flowing at 2 L/min.

interventions are required to maintain a patent airway, and spontaneous ventilation is adequate.[102] An overdose of the sedative/hypnotic or analgesic drugs can result in airway obstruction, hypoxemia, and cardiorespiratory depression; maintenance of continuous verbal contact is the optimal method for avoiding oversedation.[103]

The choice of drugs to produce conscious sedation depends on the preference and experience of the anesthesia provider. Small boluses of intravenous midazolam (0.5 to 1 mg) and fentanyl (25 to 50 μg) are usually adequate[104]; the use of a propofol infusion has also been described.[105] Remifentanil may confer some advantages over fentanyl in providing rapid onset, more precise titration with the ability to use an infusion, and rapid metabolism and dissipation of effects; decreased respiratory rate or apnea may be quickly reversed by stopping the infusion. Remifentanil infusion rates between 0.05 and 0.175 μg/kg/min have been used for awake fiberoptic intubation in nonobstetric patients[106]; target-controlled infusions of remifentanil, with or without propofol, can also provide ideal conditions.[107] Neonatal effects of the drugs used for sedation are usually minimal; however, the neonatologist should be informed of the drugs administered to the mother before delivery.

Topical Anesthesia

Providing adequate topical anesthesia of the upper respiratory tract is one of the most critical elements of successful awake fiberoptic intubation. Local anesthetic agents can be used in two basic ways to provide topical upper airway anesthesia: direct application to the mucosa or the injection for laryngeal nerve blocks. Topical application of local anesthetic is the most commonly used technique, owing to its ease and effectiveness. There are a number of techniques. For example, the patient can be asked to gargle and slowly swallow viscous lidocaine (2% or 4%), or lidocaine (2%, 4%, or 10%) can be aerosolized and sprayed onto the tongue and oropharynx.

A number of commercially available devices, which are produced in a variety of shapes and sizes, can aerosolize and spray local anesthetic solutions in a jetlike stream. The Mackenzie technique uses an intravenous cannula with an injection port (e.g., 20- or 18-gauge) connected to oxygen tubing via a three-way connector (Figure 30-10). Administration of local anesthetic from a syringe through the connector, with the oxygen flowing at 2 L/min, creates a jetlike spray.[108] An additional method uses a nebulizer mask or mouth piece, with 4% lidocaine (4 to 6 mL) placed in the nebulizer bowl and connected to an oxygen source at a flow rate of 8 L/min. This method is easy to administer, noninvasive, and comfortable for the patient, with minimal or absent coughing. Each of these techniques may be insufficient as a single entity and may be combined with other methods, including instillation of local anesthetic through the working channel of the fiberoptic bronchoscope channel.

The "spray as you go" (SAYGO) technique uses the working channel of the fiberoptic bronchoscope to instill local anesthetic onto the mucous membranes of the airway. The working channel of an intubating fiberoptic bronchoscope, such as the Olympus LF-2 (Olympus America Inc. Centre Valley, PA, USA), is 600 mm long and 1.5 mm in diameter. If a small syringe is directly attached to the working channel port and the solution is merely injected, the local anesthetic is likely to stay in the

channel rather than be sprayed onto the mucosa. This problem can be overcome by placing an epidural catheter through the working channel; using a Luer-Lok connector for the epidural catheter allows a direct and tight connection with the local anesthetic syringe and avoids leakage. The local anesthetic agent is drawn up in a 2-mL syringe and "dripped" on the mucus membranes; this instillation can be better targeted if the distal tip of the epidural catheter is allowed to protrude approximately 1 cm from the tip of the fiberoptic bronchoscope.

Nerve Blocks

The nerve supply to the upper airway is derived from branches of cranial nerves V, VII, IX and X. The lingual branch of the glossopharyngeal nerve (IX), which innervates the submucosal pressure receptors at the base of the tongue, can be blocked with the bilateral administration of 1% lidocaine (2 mL) just under the mucosa at the base of the anterior tonsillar pillars. The value or necessity of this block during performance of awake intubation in obstetric patients is controversial.[109] Laryngeal and tracheal sensation can be minimized with blockade of the internal branch of the superior laryngeal nerve and transtracheal administration of lidocaine, respectively. Blockade of the superior laryngeal nerve may be performed by locating the greater cornu of the hyoid bone, advancing a small-bore needle until the bone is contacted, walking the needle off the edge of the bone into the thyrohyoid membrane, and injecting 1% lidocaine, approximately 3 mL. The injection is then repeated on the other side of the neck.

Historically, nerve blocks were an essential part of preparing the upper airway; today, meticulous topical application is easier to perform, less invasive, and provides effective intubating conditions. The preferred airway anesthesia technique used at our institution for topical anesthesia for oral awake fiberoptic intubation is described in Box 30-3.

Airway Anesthesia and Risk for Aspiration

Some anesthesia providers are concerned that local anesthesia of the larynx might obtund the reflexes for protecting the airway. An early study found that an unprotected glottis might result from translaryngeal block.[110] There is evidence that local anesthetic solutions spread to the superior aspect of the vocal cords after a translaryngeal block.[111] However, in a series of 129 patients, both the translaryngeal injection and SAYGO techniques were effective and safe, with no evidence of regurgitation or aspiration in any patient.[112] It has been suggested that topical anesthesia of the larynx does not impair voluntary motor function of the vocal cords, such as coughing on request,[113] thus allowing the patient to protect her airway. The SAYGO technique may be preferred because the interval between topical anesthesia and endoscopy is minimal and if gastric reflux occurs during endoscopy it can be visualized and the gastric juice aspirated through the fiberoptic bronchoscope. The key to minimizing the risk for aspiration, however, is avoidance of oversedation. Nonetheless, administration of aspiration prophylaxis is advised and the patient should be monitored for possible reflux or emesis.

BOX 30-3 Suggested Airway Anesthesia for Awake Fiberoptic Intubation

Topical Anesthesia

- Tongue and oropharynx: 2% lidocaine gargle (5 to 10 mL) plus 4% lidocaine (3 to 4 mL) sprayed using the Mackenzie technique*
- Supraglottic region: SAYGO through an epidural catheter,† 4% lidocaine (1 to 2 mL)
- Glottic/infraglottic: SAYGO through an epidural catheter,† 4% lidocaine (1 to 2 mL)

Supplemental Anesthesia

- The gag reflex is tested before endoscopy with gentle suction; if it is not obtunded, transtracheal anesthesia is performed (cricothyroid puncture and injection of 4% lidocaine 3 to 4 mL)

SAYGO, spray as you go (see text).
*See Figure 30-10.
†An epidural catheter is inserted through the working channel of the fiberoptic scope. A syringe with local anesthetic is attached to the proximal end (see text).

Fiberoptic Intubation

Fiberoptic laryngoscopy can be performed orally or nasally, but the oral route is more common because of the engorgement of the nasal mucosa and the potential for epistaxis. However, in very specific situations (i.e., when the oral aperture is insufficient to allow fiberoptic bronchoscope passage), the nasal route can be successfully used in the obstetric patient with careful topical preparation of the nasal mucosa with agents that provide anesthesia and vasoconstriction.[43]

A common impediment to successful fiberoptic laryngoscopy is being able to easily advance the endotracheal tube (ETT) into the correct position. Guiding the ETT over the fiberoptic bronchoscope is a "blind" procedure. The ETT most commonly arrests at the right arytenoid cartilage.[114] In a review of the causes, incidence, and solutions to this issue, Asai and Shingu[115] noted that impingement can be minimized by selecting the appropriate size and type of ETT and by using proper advancement technique. Smaller-diameter tracheal tubes (6 to 7 mm internal diameter [ID]) that fit more snugly onto the bronchoscope generally advance more easily. The design and flexibility of the tube and tip may also determine success; for example, the intubating LMA endotracheal tube with its Huber tip is easier to advance than a flexometallic ETT during nasal fiberoptic intubation, probably owing to the acute angle of the Huber tip (Figure 30-11).[116]

The lubricated ETT is loaded over the fiberoptic bronchoscope in its normal position (curve facing anterior, leading edge [tip] on the right, bevel facing left) and the fiberoptic bronchoscope is advanced into the airway. After the tip of the fiberoptic bronchoscope is positioned

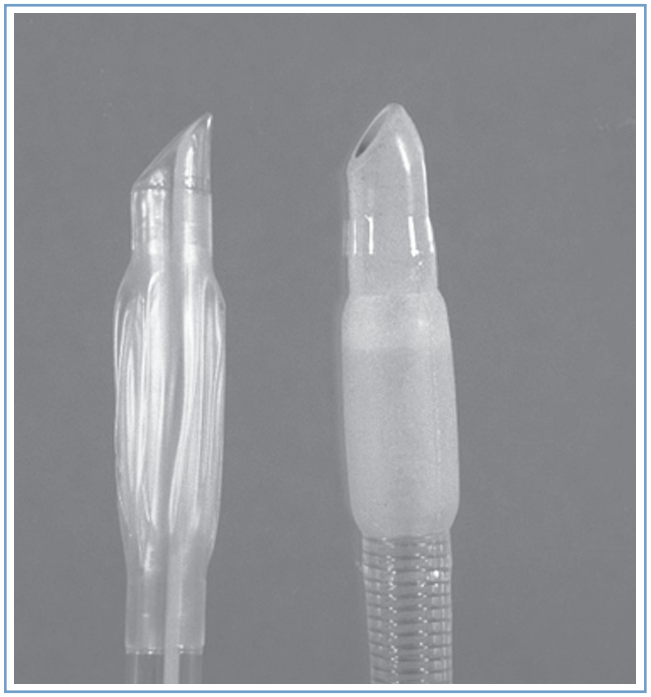

FIGURE 30-11 ■ Endotracheal tube tips. *Left,* The tip of a conventional endotracheal tube. *Right,* The tip of an endotracheal tube used with an intubating laryngeal mask airway (LMA). The Huber tip of the intubating LMA endotracheal tube is less likely to impinge on other structures, thus increasing the success of advancement and correct placement in the trachea.

above the carina, the ETT is advanced over the fiberoptic bronchoscope into the airway. If impingement occurs, the ETT is withdrawn approximately 1 cm and rotated 90 degrees counterclockwise to bring the tip of the ETT anteriorly and the ETT is reinserted. If this does not work, the ETT is rotated a further 90 degrees counterclockwise and advancement is reattempted. Alternatively, the tube can be loaded on the fiberoptic bronchoscope with the tip facing anteriorly or other maneuvers may be employed, such as keeping the airway patent with jaw thrust and application of pressure on the neck to shift the vocal cords posteriorly.

Awake direct laryngoscopy results in more noxious stimulation than fiberoptic laryngoscopy, but a well-prepared and highly motivated patient may tolerate the procedure surprisingly well. Awake intubation also has been described using indirect or video laryngoscopes (see later discussion), but their role in awake intubation in the obstetric setting has yet to be determined. Other techniques for awake intubation, such as blind nasal intubation and retrograde intubation, are performed infrequently in obstetric patients.

Indirect Optical/Video Laryngoscopy

Since the introduction of the Bullard laryngoscope in the late 1980s, a number of rigid indirect-optical laryngoscopes have been developed. Frequently referred to as video laryngoscopes because of a video camera eye positioned near the tip of the blade, these devices can capture an image of the glottis in real time and transmit it to a video screen.[117] Video laryngoscopes offer several advantages over conventional direct laryngoscopy. To obtain a good view of the glottis with a direct laryngoscope, a line of sight from the oral opening to the glottis must be obtained by neck flexion and head extension (see earlier discussion). With video laryngoscopes, a direct line of sight to the glottis is unnecessary. In patients with an anteriorly positioned larynx, an assistant is frequently required to apply pressure on the thyroid cartilage to move the larynx posteriorly and improve the view; with the use of video laryngoscopes, the assistant may watch the screen image to more directly witness the effect of the pressure. Randomized controlled studies have found higher success rates for intubation with several types of video laryngoscopes compared with the Macintosh laryngoscope blade in adult nonobstetric patients with predicted difficult airways.[118-122] Video laryngoscopes are perceived to cause less trauma and stress to patients owing to less need to reposition the head and neck, less pressure on the neck, and less frequent use of ETT introducers[118,123]; however, data are currently insufficient to confirm this perception.[117] Data are conflicting as to whether the elapsed time required to intubate using video laryngoscopy is longer or shorter than that required using conventional laryngoscopy.[117]

The indirect-optical and video laryngoscopes may be classified into three categories[117]:

1. *Macintosh type* (e.g., C–MAC, Karl Storz Endoscopy, Tuttlingen, Germany). These devices have a Macintosh-type blade and an insertion method similar to that used with conventional laryngoscopy. The glottis is visualized either directly or on the video screen. In the setting of anticipated difficult airway, the success rate is generally higher with these devices than with direct laryngoscopy, but external pressure and an ETT introducer are more frequently required.[118]
2. *Anatomically shaped without a tube guide* (e.g., GlideScope video laryngoscope, Verathon Inc., Bothell, WA, USA; McGrath video laryngoscope, LMA North America, San Diego, CA, USA). The curved shape of the blade allows a view of the glottis without flexing or extending the head and neck; however, directing the ETT toward the glottis maybe difficult, resulting in trauma. Several reports have described pharyngeal and palatal injury with use of the GlideScope.[124-128]
3. *Anatomically shaped blade with tube guide* (e.g. Airtraq, King Systems Corporation, Noblesville, IN, USA; The Airway Scope AWS-S100, Hoya-Pentax, Tokyo, Japan). The tip of the tube is captured on the video screen even before the device is inserted, and hence its location can be continuously confirmed during the entire course of intubation.

There are few studies that compare the use of different video laryngoscopes in patients with an anticipated difficult airway.[129,130] Furthermore, it not known whether the preoperative assessments used to predict difficult direct laryngoscopy are valid predictors of difficult video laryngoscopy. Additional investigation is necessary to compare various devices and to ascertain whether specific devices or device types are better for specific airway variations.

Dhonneur et al.[131] reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery under general anesthesia; 2 morbidly obese parturients required the Airtraq device for successful tracheal intubation. The investigators suggested that the device might be an acceptable primary airway management tool in cases of emergency cesarean delivery in parturients with an anticipated difficult airway. Aziz et al.[132] retrospectively analyzed 180 tracheal intubations over a 3-year period in their obstetric unit. Traditional direct laryngoscopy resulted in 157 of 163 successful intubations on first attempt, with one failed intubation (95% CI, 92% to 99%). Video laryngoscopy with a GlideScope resulted in 18 of 18 successful intubations on the first attempt (95% CI, 81% to 100%) and a successful intubation in the patient with the failed direct laryngoscopy. Of note, the patients whose tracheas were intubated with the video laryngoscope were more likely to require urgent or emergency surgery and/or have predictors of difficult direct laryngoscopy than the patients whose tracheas were intubated using direct laryngoscopy.

The GlideScope has also been used for awake intubation or to assist fiberoptic laryngoscopy intubation.[133,134]

Awake Tracheostomy or Surgery Standby

It is possible to perform an awake tracheostomy with local anesthesia, a technique that may be required in some situations in which airway management is anticipated to be extremely difficult and dangerous.[103,135,136] In some cases, particularly if there is a known airway pathologic process, it is prudent to request that a surgical team proficient in emergency surgical airway management be immediately available before the induction of anesthesia for cesarean delivery.

Local Anesthesia for Cesarean Delivery

Rarely, the infiltration of local anesthesia may be used as a *primary* anesthetic technique for emergency cesarean delivery in the patient with an anticipated difficult airway. This technique, which has been well described, is most often used in developing countries, where contemporary anesthetic techniques may not be readily available.[137-139] Few obstetricians today are familiar or proficient with this technique, but some resident training programs still provide instruction on its use.[58] A large volume (i.e., 75 to 100 mL) of a dilute local anesthetic solution, such as 0.5% lidocaine, is often required. Administration of such a large volume entails a risk for systemic local anesthetic toxicity.

Mei et al.[140] described four cases in which cesarean delivery was performed with bilateral transversus abdominis plane (TAP) block and ilioinguinal-iliohypogastric (IIIH) nerve blocks using 0.5% ropivacaine 40 mL.

In some cases it is possible to perform the entire surgical procedure with local infiltration, provided the obstetrician makes a midline abdominal incision, makes minimal use of retractors, and does not exteriorize the uterus. Alternatively, the obstetrician might begin surgery and deliver the infant with the aid of local infiltration. Temporary hemostasis may be achieved until the airway is secured and then surgery completed after the induction of general anesthesia.

Cesarean delivery performed with local infiltration, if successful, has the advantages of preserving maternal hemodynamic stability and a patent airway while allowing emergency delivery of the infant. However, the technique requires a skilled and patient obstetrician. Maternal anesthesia is typically incomplete and often inadequate, a fact that subsequently presents significant management issues, given that the abdomen has been opened, positioning options are limited, and the consequences of the surgical procedure such as hemorrhage may require immediate attention.

THE UNANTICIPATED DIFFICULT AIRWAY

Features of the Obstetric Patient

Despite attempts to adequately assess parturients preoperatively, cases of unanticipated difficulty with airway management do occur (Figure 30-12).[141] Therefore, the anesthesia provider and the entire operating team should have a plan to manage unanticipated difficulties in airway management *before* administering general anesthesia to obstetric patients. Although national guidelines exist for this scenario in the nonobstetric patient,[2,8] none exist specifically for the obstetric patient. The lack of guidelines likely reflects the unique and often difficult conflict posed by the failure to intubate the mother's trachea: the optimal and safe management of the mother may threaten the life of the fetus and vice versa. A classification schema for the degree of urgency of cesarean delivery[142] may help clarify the risks to the mother and fetus, thereby improving communication among providers, particularly between anesthesia providers and team members whose primary focus may be directed toward the fetus (obstetricians, midwives, neonatologists). Communication between anesthesia providers and other members of the multidisciplinary team is vital,[73] especially if the anesthesia provider(s) believes it is in the best interest of the mother to delay delivery of the fetus to manage the difficult airway. The entire operating room team should be familiar with local protocols to manage this infrequent but life-threatening situation. Examples of failed intubation guidelines are available on the website of the Obstetric Anaesthetists' Association (OAA).[143]

The safest method to prevent difficulty in airway management is by making the first attempt at laryngoscopy the best attempt. This is achieved by using optimal head and neck position, applying cricoid pressure correctly, and waiting for an adequate dose of muscle relaxant to act (see earlier discussion). If an adequate view of the larynx is not achieved, a second attempt should be made using a gum elastic bougie and/or a different laryngoscopy blade or device. In experienced hands, laryngoscopy

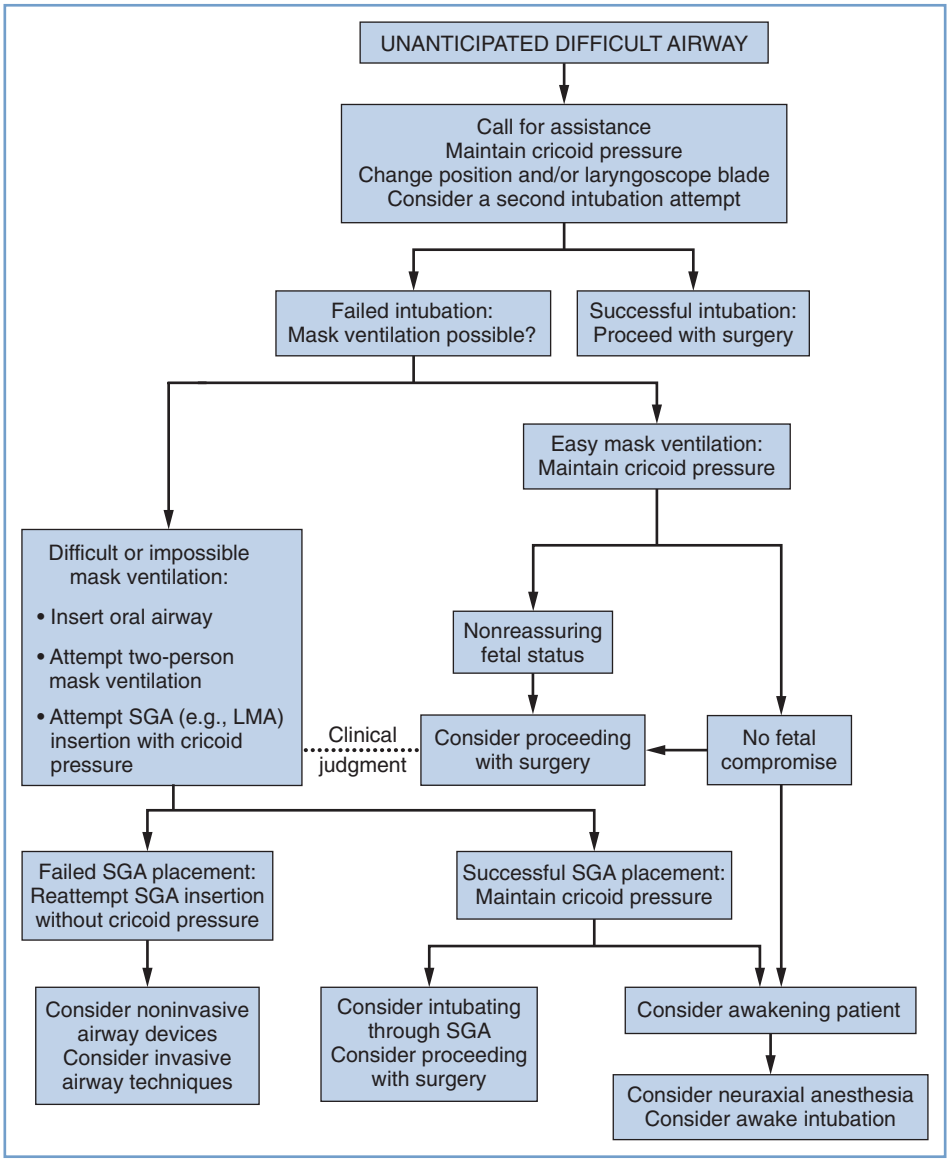

FIGURE 30-12 ■ Algorithm for unanticipated difficult airway. This algorithm is not intended to provide comprehensive guidance that addresses every contingency. Rather, it should help anesthesia providers consider the various options that are available. Management should be individualized, and the anesthesia provider's clinical skills and judgment should guide decision-making. For additional information, the reader is referred to the American Society of Anesthesiologists practice guidelines.[2] *SGA,* supraglottic airway; *LMA,* laryngeal mask airway.

attempts should be limited to no more than three, and the second or third attempt should be performed only in those cases in which a portion of the laryngeal anatomy is visible (Cormack and Lehane grade 3A or better). If a grade 3B or 4 laryngoscopic view is identified with the initial laryngoscopy attempt, the anesthesia provider should immediately focus attention on ensuring adequate oxygenation and ventilation of the mother.[144]

The fact that the trachea cannot be intubated should be conveyed loudly to the entire operating room team and help should be summoned immediately. Maintenance of maternal and fetal oxygenation becomes the anesthesia provider's first priority. Facemask ventilation should be attempted with maintenance of cricoid pressure. Placement of an oropharyngeal airway may be helpful. If difficulty is encountered, a two-person mask technique should be employed, with one person firmly holding the mask in place with two hands while providing a jaw lift as the second person squeezes the reservoir bag.[58,141] Once facemask ventilation is attempted, several scenarios may arise, which are discussed next.

Cannot Intubate but Can Ventilate

In the "cannot intubate but can ventilate" scenario, maternal and fetal status should be rapidly assessed in consultation with the obstetrician. If the mother and fetus are not in immediate jeopardy, then the safest course is to awaken the mother. Once this is accomplished, other anesthetic options, such as an awake intubation or a

neuraxial anesthetic technique, should be considered. The risk for proceeding with surgery in this scenario represents an elective commitment to the possibility of mask airway failure, more airway manipulation, aspiration, and progression to a "cannot ventilate" scenario.

If the situation is immediately life threatening to the mother secondary to hemorrhage (e.g., uterine rupture, placental abruption), it may be necessary to proceed with cesarean delivery to optimize outcome for both the mother and infant. Significant angst and controversy often accompany decision-making in the management of a stable mother with evidence of life-threatening fetal compromise, such as fetal bradycardia as a result of a prolapsed umbilical cord. In such cases, if mask ventilation is easy and adequate, the risk-benefit ratio of proceeding with an unsecured airway and an increased risk for aspiration should be weighed against the benefits of prompt delivery of the infant. In cases in which the maternal risk for aspiration is considered low and mask ventilation is easy, it may be reasonable to continue mask ventilation and avoid further intubation attempts. It is unclear as to whether continued mask ventilation or repeated intubation attempts represent the greater risk to the mother; even insertion of an LMA may further traumatize the airway or precipitate regurgitation.

The anesthesia provider should carefully consider the maternal risks of proceeding with cesarean delivery in a mother with an unsecured and unprotected airway, especially if no urgency exists and/or mask ventilation is difficult. Some obstetric anesthesiologists argue that even a nonreassuring (but non–life-threatening) fetal heart rate tracing does not always justify proceeding with cesarean delivery under general anesthesia in a patient with an unsecured airway. Alternatively, in some of these cases, proceeding with cesarean delivery via mask ventilation or with an SGA may be a better option than awakening the patient, especially in those in whom neuraxial techniques are contraindicated. In these cases, the importance of communication between the obstetric and anesthesia teams cannot be overemphasized (see Chapter 11).

Cannot Intubate and Cannot Ventilate

In the "cannot intubate and cannot ventilate" scenario, the first objective remains the maintenance of maternal and fetal oxygenation. This scenario indicates that facemask ventilation has failed despite optimizing head and neck position, inserting an oropharyngeal airway, and using the two-person mask technique. If partial ventilation exists and succinylcholine has been given, it may be possible to allow the neuromuscular blockade to resolve and spontaneous ventilation to return. If ventilation is not possible, insertion of an SGA (e.g., LMA, laryngeal tube) should be considered (see next section). Initial SGA insertion should be attempted with the application of cricoid pressure[144]; however, pressure may need to be reduced or removed to facilitate insertion. If SGA insertion or ventilation fails, the management team should secure an airway using an anterior neck technique (i.e., jet ventilation via a cannula inserted through the cricothyroid membrane, or surgical cricothyrotomy or tracheostomy). If these methods prove successful, the risks and benefits of proceeding with surgery should be discussed among team members; both maternal and fetal health should be considered. A 14- or 16-gauge cannula placed through the cricothyroid membrane is inherently unstable; thus, ideally, a more definitive airway should be established before surgery is started.[58]

Laryngeal Mask Airway

The LMA is arguably the SGA with which anesthesia providers are most familiar. The introduction of the LMA into anesthetic practice was a significant advance in airway management that resulted in major alterations to the difficult airway algorithms of the ASA and other societies.[2,8] The insertion of an LMA in an obstetric patient who can easily be ventilated by facemask is controversial, because little additional ventilation benefit is obtained and the placement of an LMA can induce vomiting and aspiration in this setting. However, in any situation in which conventional facemask ventilation is difficult or impossible, an SGA is the rescue device of choice.

The LMA has many advantages, most notably its ease of use and a very high initial success rate.[145] Moreover, the LMA need not be perfectly positioned over the larynx to allow adequate ventilation. When assessed by flexible fiberoptic endoscopy, radiography, and magnetic resonance imaging, the placement of the LMA around the larynx is variable[145]; however, 94% to 99% of patients with an LMA have little or no difficulty with ventilation.

In a prospective study, an LMA was inserted by experienced users in 1067 healthy parturients undergoing *elective* cesarean delivery under general anesthesia.[146] The investigators demonstrated that a clinically effective and acceptable airway was obtained on the first attempt in 98% of the patients and on the second or third attempt in an additional 1%. Fewer than 1% of patients required intubation for failure to obtain satisfactory LMA placement within 90 seconds, or for an Spo_2 less than 94%, or an end-tidal CO_2 greater than 45 mm Hg. Moreover, the airway management (which was accomplished with the LMA, maintenance of cricoid pressure until delivery, and mechanical tidal-volume ventilation of 8 to 12 mL/kg) was associated with no episodes of hypoxemia (Spo_2 < 90%), regurgitation, aspiration, laryngospasm, bronchospasm, or gastric insufflation. The investigators concluded that, in experienced hands, an LMA is effective and "probably safe" for ventilation and the administration of a volatile anesthetic agent for general anesthesia in selected healthy patients undergoing elective cesarean delivery.

A number of reports have described the use of an LMA as a rescue device for obstetric patients in whom conventional methods of securing the airway have failed.[147-152] In a national case control study performed in the United Kingdom from 2007 to 2009, 39 of 57 patients with a failed intubation were managed with a classic LMA.[153]

An LMA may also act as a conduit for intubation; however, passage of an ETT without visualization has a low success rate.[154] By contrast, fiberoptic-guided

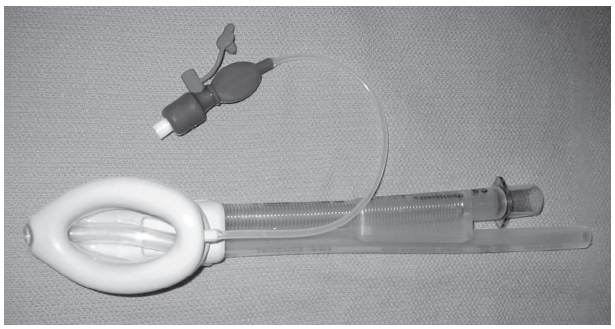

FIGURE 30-13 ■ The ProSeal LMA (laryngeal mask airway). This LMA device has a specialized high-volume/low-pressure cuff, which allows glottis coverage that enables the use of higher ventilation pressures (up to 30-40 cm H_2O) with less air leakage around the cuff and a lower risk for entry of air into the stomach. The ProSeal LMA also contains a specialized drainage tube that bypasses the bowl of the LMA and prevents gastric fluid from entering the glottic area. A gastric tube can be passed down this drainage lumen to assist in emptying the stomach contents.

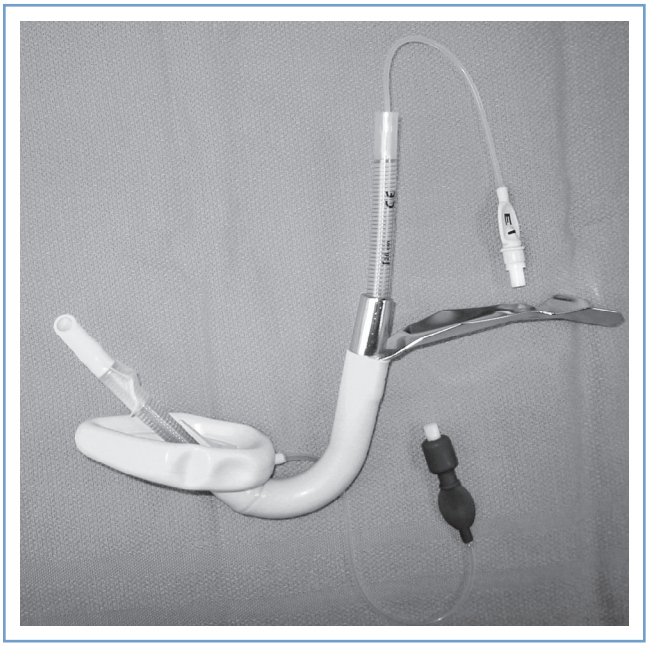

FIGURE 30-14 ■ Intubating laryngeal mask airway (LMA). This device features a more rigid J-shaped design than the conventional LMA to facilitate the alignment of the mask over the glottic opening and better accommodate a special soft-tipped tracheal tube for blind intubation (see Figure 30-11).

intubation through the LMA has a success rate that has approached 100% in some studies.[145]

Despite these benefits, the LMA has been associated with the following disadvantages: (1) placement can induce vomiting; (2) aspiration of gastric contents is not prevented; (3) improper positioning can lead to gastric insufflation; (4) multiple insertion attempts may be required for correct placement, which may result in airway trauma; and (5) use of positive-pressure ventilation may be limited. In 0.4% to 0.6% of patients with normal airway findings, the placement of an LMA leads to inadequate ventilation[145]; reasons for this outcome have been reported to include (1) backfolding of the distal cuff, (2) occlusion of the glottis by the distal cuff, (3) complete downfolding of the epiglottis, and (4) 90- to 180-degree rotation of the mask around its long axis.

Most of the data just cited pertain to the use of the original classic LMA; several variations in LMA design have since become available. Updated designs that have been found to be useful in difficult airway management of parturients are the ProSeal LMA (LMA North America San Diego, CA, USA) and the Fastrach LMA (LMA North America, San Diego, CA, USA). The ProSeal LMA has a specialized high-volume/low-pressure cuff that allows the device to achieve a better fit over the glottis than a classic LMA (Figure 30-13).[155] This design allows the use of higher ventilation pressures (up to 30 to 40 cm H_2O) with less air leakage around the cuff and a lower risk for air entry into the stomach. The ProSeal LMA also contains a specialized drainage conduit that bypasses the bowl of the LMA to minimize the entry of gastric fluid into the glottis. The drainage conduit has been shown to be effective in venting both passive and active regurgitation[156,157] and can accommodate the passage of a gastric tube, which can assist in decompressing or emptying the stomach.

Cook et al.[158] randomly assigned 180 nonparalyzed, nonpregnant anesthetized patients to airway management with a ProSeal or classic LMA. The ProSeal more reliably allowed positive-pressure ventilation than the classic LMA. Halaseh et al.[159] described the use of the ProSeal LMA in 3000 patients undergoing cesarean delivery who had fasted for more than 4 hours and were not thought to have a difficult airway. They established an "effective" airway on the first attempt in 2992 (99.7%) women, with only 8 patients (0.3%) requiring a change to a different LMA size. None of the patients required tracheal intubation, and only one patient experienced regurgitation of gastric contents into the mouth.[159] Minor side effects such as sore throat occurred in 21 patients (0.7%). A number of case reports have described the successful use of the ProSeal LMA after failed intubation in obstetric patients.[160-162]

A disadvantage of use of the ProSeal LMA in an emergency is that it requires practice and experience to use correctly. Further, because the gastric drainage conduit traverses the LMA bowl, the passage of an ETT may be more difficult.[163] A disposable, single-use version of the ProSeal LMA—the LMA Supreme—is now available.

Although designed specifically to facilitate blind tracheal intubation,[164] the Fastrach or intubating LMA can also be combined with fiberoptic bronchoscopy (Figure 30-14).[165,166] Both reusable and disposable versions are available. When properly placed, the intubating LMA allows ventilation similar to that with the original LMA; however, a more rigid J-shaped design improves the alignment of the mask over the glottic opening and better accommodates a special soft-tipped tracheal tube for blind intubation (see Figure 30-11). This special silicone ETT minimizes the risk for airway trauma and is

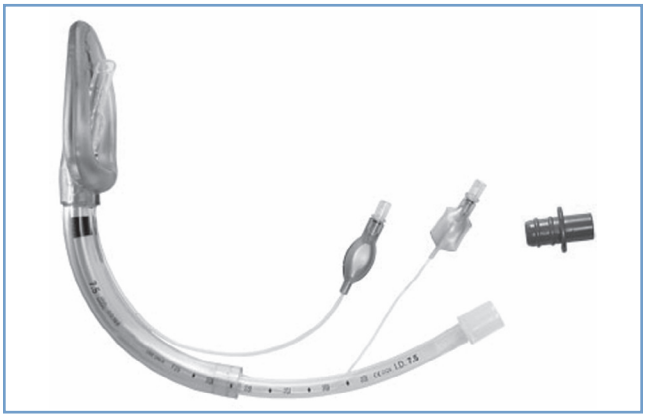

FIGURE 30-15 ■ The Air-Q laryngeal mask airway (LMA). This intubating LMA device features a unique mask tip, a keyhole-shaped airway outlet that elevates the epiglottis, and a removable circuit connector that accommodates an 8.5-mm endotracheal tube (ETT). The LMA depicted has an ETT within its lumen.

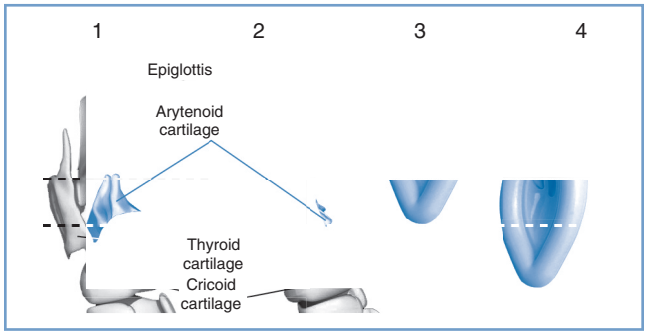

FIGURE 30-16 ■ The position of the laryngeal mask airway (LMA) with and without cricoid pressure. The blue-shaded area indicates the distal part of the LMA that occupies the hypopharynx. The dashed lines indicate anatomic correlation. *1,* Posterior view of the larynx. *2,* Lateral view of the larynx. *3,* Position of the tip of the LMA when cricoid pressure is applied. When cricoid pressure is applied before placement, the LMA, in theory, might be wedged in the hypopharynx but is more likely to occupy the space behind the arytenoid cartilages. The LMA is positioned at least 2 cm more proximal than usual. *4,* Position of the LMA when no cricoid pressure is applied. When the LMA is placed correctly, the distal tip is at the distal end of C5 (fifth cervical vertebra), and the distal part of the LMA should fully occupy the hypopharynx and the pharyngeal space behind both the arytenoid and cricoid cartilages. *A,* arytenoid cartilages; *C,* cricoid cartilage; *E,* epiglottis. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

available in diameter sizes 6.0 to 8.0 mm. In addition, the intubating LMA has an epiglottis elevator bar at its distal end that acts to lift the epiglottis anteriorly as the ETT exits the intubating LMA into the glottis.[164] When a fiberoptic bronchoscope is used with an intubating LMA, the ETT should be advanced far enough to partially elevate the epiglottis elevator bar to assist the passage of the fiberoptic bronchoscope into the trachea. A variation of the intubating LMA, the Air-Q LMA (Mercury Medical, Clearwater, FL, USA), has a different mask tip, a keyhole-shaped airway outlet, and a removable circuit connector that accommodates an 8.5-mm ETT (Figure 30-15). The successful use of the intubating LMA during a failed intubation at emergency cesarean delivery has been reported.[167]

Laryngeal Mask Airway and Cricoid Pressure

With the possible exception of the ProSeal, an LMA does not protect against pulmonary aspiration of gastric contents, and its placement may precipitate regurgitation in a lightly anesthetized patient.[168] Therefore, it is generally recommended that continuous cricoid pressure be maintained after the placement of an LMA in obstetric patients. Although a correctly placed LMA does not appear to compromise the effectiveness of cricoid pressure,[169] the use of cricoid pressure can inhibit proper insertion of the LMA and, in some cases, may make correct insertion impossible (Figure 30-16).[170-175] The application of cricoid pressure can prevent the tip of the LMA from fully occupying the hypopharynx behind the arytenoid and cricoid cartilages. Therefore, if difficulty with insertion of an LMA is encountered during an obstetric airway emergency, consideration should be given to releasing cricoid pressure temporarily while a second attempt is made at insertion.[172] The risk for hypoxemia after failed LMA placement is most likely greater than the small risk for aspiration due to the temporary release of cricoid pressure. Several authors have reported that this maneuver increases the chances of a successful LMA placement.

Once the LMA is in place, cricoid pressure can be reapplied and should not prohibit adequate ventilation.[169] However, in some patients, reapplication of cricoid pressure may decrease tidal volumes during positive-pressure ventilation through an LMA.[176] Difficult ventilation after placement of an LMA should raise suspicion of overzealous administration of cricoid pressure; in such cases, a reduction in cricoid pressure typically allows adequate ventilation.

Laryngeal Mask Airway as a Conduit for Intubation

Intubation through an LMA can be achieved blindly, especially with an intubating LMA, or with the assistance of a fiberoptic bronchoscope. Before starting this maneuver, the risks and benefits of an intubation attempt must be weighed.[177] Intubation attempts should never supersede or compromise active ventilation; however, in certain situations, such as a patient at significant risk for aspiration or if ventilation is marginal, securing the airway with an ETT may take precedence. The use of a fiberoptic bronchoscope through an LMA has been reported to be nearly 100% successful in achieving intubation.[177] A 6-mm ID cuffed ETT may be passed over the fiberoptic bronchoscope and through the shaft of a size 3 or 4 LMA; of note, a nasal RAE tube (Nellcor, Boulder, CO, USA) is a suitable match for this purpose, owing to its adequate length and widespread availability.[8] A 7-mm ID cuffed ETT may be passed in a similar manner through the shaft of a size 5 LMA.

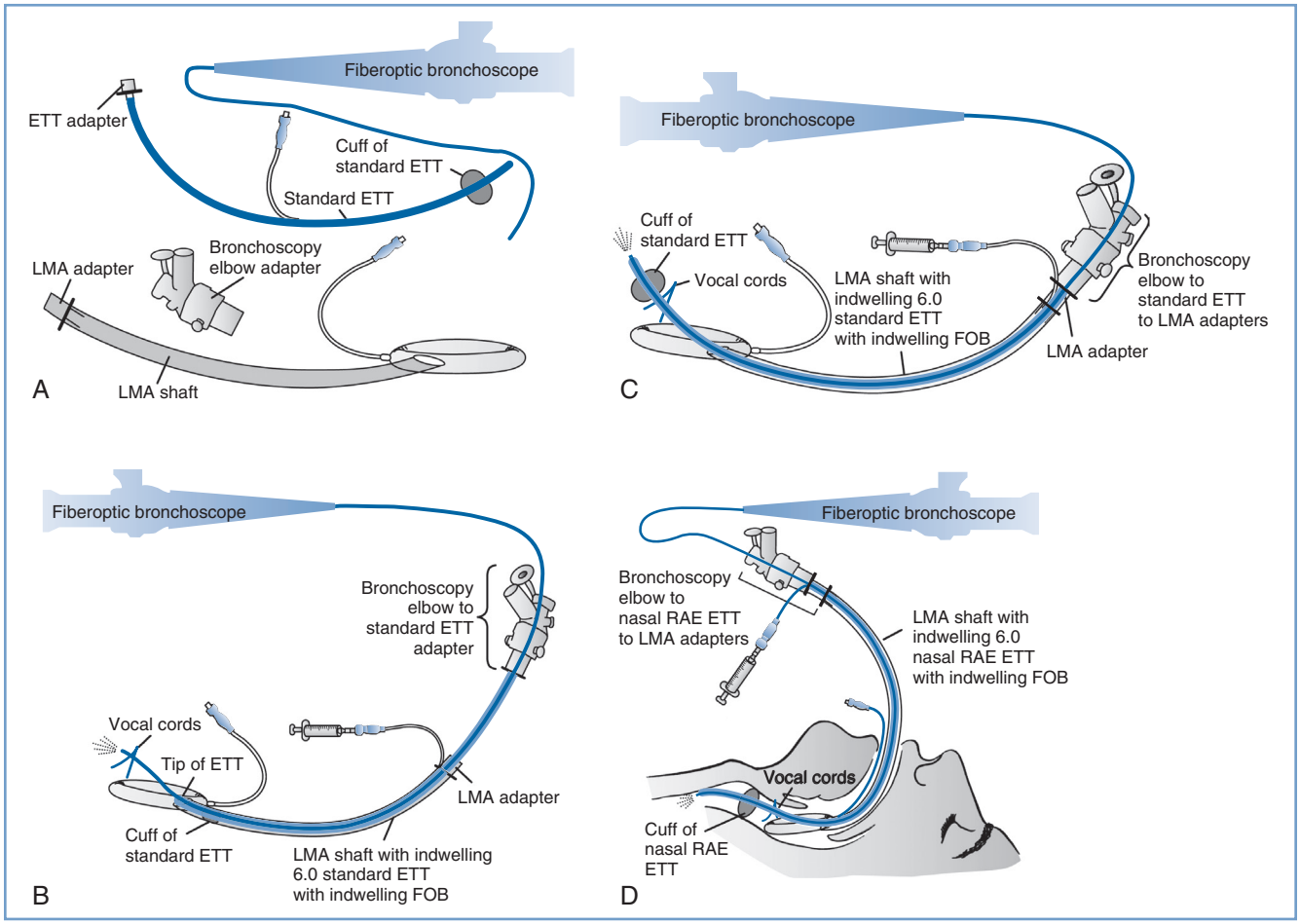

FIGURE 30-17 ■ Schematic diagram of set-up for continuous ventilation during fiberoptic bronchoscopy–guided tracheal intubation using a laryngeal mask airway (LMA) as a conduit for both the endotracheal tube (ETT) and fiberoptic bronchoscope (FOB). In **A** and **B**, a standard 28-cm-long ETT is shown. (A 6-mm inner diameter nasal RAE tube [Nellcor, Boulder, CO] may also be used.) **A,** Components of the continuous ventilation system. **B,** With passage of the tip of a cuffed 6-mm internal diameter tracheal tube to the level of the LMA grille and a 4-mm outer diameter FOB through the self-sealing diaphragm of a bronchoscope elbow adapter, ventilation can occur around the FOB but within the ETT lumen; the deflated cuff inside the shaft of the LMA makes an airtight seal and permits positive-pressure ventilation. **C,** After the fiberoptic bronchoscope is passed into the trachea, the ETT is advanced over the FOB into the trachea until the ETT adapter is near that of the LMA (if using a nasal RAE ETT) or is flush up against the adapter of the LMA (if using a standard ETT). The preformed curvature of the nasal RAE tube presents no problem with insertion if the outside of the tube is adequately lubricated. **D,** Schematic of **C**, with superimposed upper airway anatomy.

When a fiberoptic bronchoscope is passed through an LMA, the bronchoscope should be introduced through the self-sealing diaphragm of an elbow adapter attached to the ETT and the airway circuit to allow continuous ventilation (Figure 30-17). The space available for ventilation around a 4-mm outer diameter (OD) fiberoptic bronchoscope placed within a 6-mm ID ETT is equivalent to that available with a 4.5-mm ID tube. Alternatively, a two-stage method can be employed, in which a fiberoptic bronchoscope is placed through the lumen of an Aintree Intubation Catheter (Cook Critical Care, Bloomington, IN, USA) and the stem of a size 3 or 4 LMA. With the LMA in the oropharynx, the fiberoptic bronchoscope and Aintree Catheter are advanced through the vocal cords, the fiberoptic bronchoscope withdrawn, and then an ETT is guided over the Aintree Catheter.[178] There are no studies assessing the success rate of these advanced techniques that use the LMA as a conduit for tracheal intubation; however, these techniques take time and skill and should be performed by anesthesia providers experienced in their use.

Laryngeal Tube and Esophageal-Tracheal Combitube

The laryngeal tube (VBM Medizintechnik GmbH, Sulz, Germany) is another SGA device.[179,180] Laryngeal tubes are manufactured from either silicone or polyvinylchloride (PVC) and have ventilation apertures between a proximal oropharyngeal cuff and a distal esophageal cuff. The laryngeal tube is inserted into the oropharynx until resistance is met, which should result in positioning of the ventilation apertures directly above the glottic opening. These devices are reported to provide seal pressures similar to those with the ProSeal LMA (40 cm H_2O) and insertion times and success rates comparable

to those of the LMA.[181] The Laryngeal Tube-S (LTS) contains a second lumen that can be used for drainage of the stomach.[182] The LTS has been used successfully after a failed intubation and ventilation in a patient undergoing emergency cesarean delivery.[183]

The esophageal-tracheal Combitube (ETC) (Sheridan Catheter Corporation, Argyle, NY, USA) is a twin-lumen plastic tube with an outer diameter of 13 mm. One lumen has an open distal end and thus resembles a tracheal tube (i.e. the tracheal lumen), and the other (esophageal) lumen has a closed distal end. The ETC has a 100-mL proximal pharyngeal balloon; when the ETC is correctly positioned, the pharyngeal balloon fills the space between the tongue base and soft palate. When inflated, the proximal balloon seals the oral and nasal cavities. Distal to the pharyngeal balloon, but proximal to the level of the larynx, are eight perforations in the esophageal lumen. A smaller 15-mL distal cuff, similar to that on an ETT, seals either the esophagus or trachea when inflated. The ETC is inserted, with or without the aid of a laryngoscope, but its insertion does not require visualization of the larynx. Indeed, in the usual clinical context, the larynx cannot be visualized. The ETC enters the esophagus 96% of the time, allowing ventilation through the esophageal lumen perforations.[184] If the ETC enters the trachea, the patient's lungs can be ventilated directly through the tracheal lumen. Therefore, regardless of whether the distal end of the ETC enters the trachea or esophagus, the anesthesia provider can ventilate the lungs, assuming correct identification of which lumen should be used for ventilation.

The ETC allows adequate ventilation while preventing aspiration of gastric contents. If the distal end of the ETC enters the esophagus, the ETC can assist in removing gastric fluids through suction applied to the "tracheal" lumen. When long-term ventilation is anticipated or required, the ETC should be exchanged for an endotracheal tube.

Use of the ETC in the out-of-hospital setting has been associated with a notable incidence of serious complications, including upper airway bleeding, esophageal laceration and perforation, and mediastinitis.[185] Although a lower incidence of serious complications would be expected in the more controlled operating room environment with an anesthesiologist using a laryngoscope to facilitate placement, the stiffness and the anterior curvature of the ETC, as well as the potential for balloon overinflation, still represent potential sources of airway and esophageal injury.

Cannula and Surgical Cricothyrotomy

The anesthesia provider must diagnose the failure of facemask and alternative devices to oxygenate and ventilate the patient and decide that direct tracheal access is necessary. A delay in performing cricothyrotomy results in greater morbidity and mortality than complications resulting from the attempt.[35,186] Three techniques for cricothyrotomy are available[187]:

1. Narrow-bore cricothyrotomy using a purpose-designed cannula less than 2 mm ID (e.g., Ravussin; VBM Medizintechnik GmbH, Sulz, Germany)
2. Wide-bore cricothyrotomy using a purpose-designed cannula greater than 4 mm ID (e.g., QuickTrach; VBM Medizintechnik GmbH, Sulz, Germany)
3. Surgical cricothyrotomy using a scalpel to enable placement of a small (< 6 mm ID) standard tracheal or tracheostomy tube

Narrow-bore cannula cricothyrotomy requires the use of a high-pressure ventilation source (e.g., Manujet) for transtracheal jet ventilation (TTJV). The other two techniques use standard ventilation circuits. Most TTJV systems have an in-line regulator that allows the delivery pressure to be controlled to between 0 and 50 psi. A minimum pressure of 20 to 30 psi is required in the majority of patients to inflate the chest and provide appropriate tidal volumes and minute ventilation.[188] During TTJV, it is critical that the operator allow time for exhalation of inspired gas to avoid hyperinflation of the lungs, potential air trapping, and barotrauma.[189-191] Exhalation can be facilitated by keeping the airway patent by some means (e.g., nasal/oral airway, jaw thrust, LMA). There are numerous reports of the use of TTJV as a means to prevent hypoxemia during life-threatening airway emergencies[192-194] and as a temporizing measure before a more definitive surgical airway can be established.

Although cannula cricothyrotomy is faster and carries significantly fewer risks, its success rate is much lower than that of surgical cricothyrotomy.[187] Skill fade associated with increased length of time since training is likely to have a more significant impact on outcome than choice of device.[187] The choice of technique can therefore be determined by local protocols. The anesthesia provider should evaluate and practice various airway techniques to maximize success during an emergency.

EXTUBATION OF THE PATIENT WITH A DIFFICULT AIRWAY

General Principles

Tracheal extubation is a critical step during emergence from general anesthesia. Airway condition at time of tracheal extubation may be less favorable than at induction of anesthesia. The patient's disease process (e.g., preeclampsia) may contribute to worsening airway edema, as do the fluid and blood products that have been administered during the procedure. Comorbidities, such as obesity and obstructive sleep apnea, may contribute to an increased risk for airway compromise after extubation of the trachea. Although the majority of extubations occur without incident, a number of serious adverse events, including hypoxic brain injury, occur during emergence from general anesthesia and tracheal extubation or in the postoperative period.[35,195-198]

After publication of the ASA guidelines for management of the difficult airway,[2] there was a statistically significant reduction in airway claims arising from injury at *induction* of anesthesia.[199] However, the number of claims arising from intraoperative events and those at extubation and during recovery has not changed. Death and brain

injury occur more commonly after extubation and during recovery than during induction of anesthesia.[199] Not surprisingly, extubation problems are more common in obese patients and in those with obstructive sleep apnea.[199] In the fourth National Audit Project (NAP4) of the Royal College of Anaesthetists and the Difficult Airway Society (DAS), major airway complications in patients receiving anesthesia occurred during emergence or recovery in approximately one third of the reported cases.[100]

Extubation is an elective procedure that should always have a management strategy.[200-202] The goals of extubation management are to ensure uninterrupted oxygen delivery, avoid airway stimulation, and allow ventilation and possibly reintubation with minimum difficulty and delay should extubation fail. The U.K. Difficult Airway Society Extubation Guidelines[9] describe a four-step approach to the safe management of tracheal extubation:

Step 1: Plan extubation
Step 2: Prepare for extubation
Step 3: Perform extubation
Step 4: Postextubation care: recovery and follow-up

The planning and preparation steps allow the anesthesia provider to stratify risk and categorize the patient as either at *low risk* or *at risk* for extubation complications. A fasted patient with an uncomplicated airway is at *low risk*, whereas a patient at risk for aspiration in whom the ability to oxygenate and reintubate is potentially difficult is *at risk*.[9] By definition, all obstetric patients fall into the "at-risk" group owing to the risk for pulmonary aspiration.[9] A crucial decision is to determine whether it is safe to extubate the trachea or to postpone the extubation. Unfortunately, studies attempting to identify risk factors that can reliably predict difficulty with extubation, performed almost entirely in the critical care population, have been inconclusive.[203] The leak test, in which the ETT cuff is deflated, the proximal end of the tube is occluded, and the patient is evaluated to determine if she can spontaneously ventilate around the tube, has not been uniformly demonstrated to predict success with extubation.[204]

If the surgical procedure was long, or massive bleeding and significant fluid replacement has occurred, consideration should be given to transferring the patient to the intensive care unit and delaying tracheal extubation. The decision to remove the ETT should follow a full assessment of the patient (i.e., ability to follow commands, appropriate level of consciousness, recovery from neuromuscular blockade). The head of the bed can be elevated or the patient positioned on her left side. Patients for whom oxygenation and/or reintubation is predicted to be difficult may benefit from the insertion of an airway exchange catheter before tracheal extubation (see later discussion).

Airway Exchange Catheters

In situations in which the patient appears ready for extubation but concerns exist regarding potential difficulty with—and/or need for—re-intubation (e.g., difficult intubation), establishing continuous airway access may be of benefit; such access can be achieved with an airway-exchange catheter (AEC) inserted through the ETT before extubation.[205,206] There are many commercially available AECs: the Cook AEC (Cook Critical Care, Bloomington, IN, USA) is a long, thin, hollow tube made from semi-rigid thermostable polyurethane. It has a blunt end with distal terminal and side holes; it is radiopaque and has length markings on its outer surface. The catheter is supplied with a removable 15-mm connector that is compatible with anesthetic circuits for oxygenation and Luer-Lok connectors for use with high-pressure source (jet) ventilation. AECs are available in various sizes; the most appropriate sizes for extubation are of sufficient length (e.g., 83 cm) and diameter (e.g., 11- to 14-gauge) to remain between the vocal cords while removing and/or reinserting an ETT. These catheters are compatible with tracheal tubes of internal diameters greater than 4 and 5 mm, respectively. Successful reintubation can be enhanced by the use of a smaller tracheal tube and rotation of the ETT 90 degrees during insertion to facilitate passage of the bevel through the vocal cords.[115]

Mort[207] evaluated 354 patients with potentially difficult airways who were extubated over an AEC; 51 required reintubation. The reintubation success rate was greater than 90%. Complications during airway management, including low oxygen saturation, bradycardia, hypotension, esophageal intubation, and the need for accessory airway adjuncts, were less common when an AEC was used to assist re-intubation. Successful outcomes have been reported in other similar studies.[205,208] Visualization of the larynx, either by direct or video laryngoscopy, during AEC use can also increase the success of reintubation and reduce the incidence of complications.[209]

Morbidity associated with AEC use is predominantly a result of inappropriate positioning and failure of oxygenation. The distal tip of the AEC is ideally positioned in the mid trachea; oxygen insufflation and jet ventilation through an AEC should only be undertaken with extreme caution, because barotrauma and death have been reported.[206,210,211]

KEY POINTS

- The morbidity and mortality associated with airway management are key concerns for obstetric anesthesia providers.
- Difficulties with airway management occur with both intubation and extubation of the trachea.
- Physiologic and anatomic changes of pregnancy, such as airway edema, respiratory and metabolic changes, weight gain, breast enlargement, and the risk for gastroesophageal reflux, contribute to difficult airway management.
- All parturients receiving either general or neuraxial anesthesia must undergo airway assessment; plans should be devised for airway management.
- Airway difficulty is best predicted using a combination of assessments, including Mallampati class, thyromental distance,

atlanto-occipital extension, and protrusion of the mandible.

- Early administration of neuraxial labor analgesia is recommended in those with an anticipated difficult airway.
- Antacid prophylaxis should be given to all parturients who require general or neuraxial anesthesia.
- Correct positioning of the parturient on the operating table is necessary to maximize the chance of successful intubation, especially in the obese parturient.
- Securing the airway before inducing general anesthesia may be the safest option in patients in whom airway management is expected to be difficult.
- Maintenance of maternal and fetal oxygenation is the primary objective in the management of an unanticipated difficult airway.
- If conventional mask ventilation is difficult or impossible, a supraglottic airway (e.g., laryngeal mask airway) is the rescue device of choice.
- Needle cricothyrotomy with transtracheal jet ventilation can be life sustaining when other means to achieve adequate oxygenation have failed.
- In parturients known to be difficult to intubate or with risk factors for a difficult airway, caution must be employed with both intubation and extubation of the trachea.
- Potential or actual airway difficulties should be discussed with obstetricians, and management decisions should incorporate multidisciplinary communication and cooperation.

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CHAPTER 31

Postpartum Headache

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CHAPTER OUTLINE

Postpartum headache is the complaint of cephalic, neck, or shoulder pain occurring during the first 6 weeks after delivery. The incidence of postpartum headache throughout the 6-week postpartum period has not been followed in a prospective manner. However, information is available from an evaluation of women during the first week postpartum,[1] from a database that recorded symptoms during pregnancy and in the first week after delivery,[2] and from a survey of women at 5 months and 1 year postpartum.[3] Goldszmidt et al.[1] evaluated 985 women during the first week postpartum and found a 38.7% incidence of headache. The median time to onset of symptoms was 2 days, and the median duration of headache was 4 hours. Benhamou et al.[2] examined information collected on pregnant women who delivered at their institution during a 2-year period; exclusion criteria included recognized dural punctures, preterm deliveries, multiple gestation, and/or elective cesarean delivery. Headache was reported by 12% of 1058 patients who had epidural anesthesia without dural puncture and by 15% of 140 patients who delivered without epidural anesthesia. Saurel-Cubizolles et al.[3] surveyed 1,286 postpartum women and found the incidence of headache was 22% and 42% at 5 and 12 months, respectively.

Post–dural puncture headache (PDPH) is one of the most common postpartum complications of neuraxial anesthesia. However, physicians and nurses should be aware that a dural puncture is only one of many causes of postpartum headache (Table 31-1). Most headaches are benign or do not require immediate attention; however, the timely diagnosis of some headaches (e.g., cortical vein thrombosis, subdural hematoma) is critical to good outcomes. Knowledge of both benign and nonbenign headaches is important for the anesthesiologist who is frequently the first physician to evaluate the patient with postpartum headache. Difficult diagnostic problems may require the opinion of a neurologist. The purpose of this chapter is to discuss the differential diagnosis of postpartum headache and PDPH in particular.

DIFFERENTIAL DIAGNOSIS OF POSTPARTUM HEADACHE

The classification of headaches follows the International Classification of Headache Disorders (ICHD), created in 1988 by the Headache Classification Subcommittee of the International Headache Society. This classification system, which has been updated (ICHD-II), identifies two broad categories of headaches: primary and secondary (Box 31-1).[4] Primary headaches are classified as migraine, tension-type headache, cluster headache and trigeminal autonomic cephalalgia, or other. Secondary headaches are attributable to a specific underlying pathologic process. Primary headaches are 20 times more common than secondary headaches among women in the first week postpartum.[1]

After delivery, women frequently suffer from headache. Stella et al.[5] retrospectively reviewed 5 years of hospital records to identify women who had postpartum headaches between 24 hours and 6 weeks after delivery. Ninety-five women met these criteria, and although the incidence of postpartum headache could not be calculated, the study did identify some important features of postpartum headache. Most women (82%) were still in the hospital at time of onset of the headache. Additionally, the demographics of the study population largely reflected the general obstetric population; the mean age was 25 years, 87% of the women had received some type of neuraxial analgesia/anesthesia, and 29% had a cesarean delivery.

TABLE 31-1 **Differential Diagnosis of Postpartum Headache**

Headache Etiology	Primary Symptoms/Signs	Diagnostic Modality
Tension headache	Mild to moderate headache, lasting 30 minutes to 7 days Often bilateral, nonpulsating, and not aggravated by physical activity	History and physical examination
Migraine	Recurrent moderate to severe headache, lasting 4 to 72 hours Often unilateral, pulsating, and aggravated by physical activity Associated with nausea, photophobia, and phonophobia	History and physical examination
Musculoskeletal	Mild to moderate headache accompanied by neck and/or shoulder pain	History and physical examination
Preeclampsia/eclampsia	Hypertension and/or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome Headache often bilateral, pulsating, and aggravated by physical activity	History and physical examination Laboratory evaluation (alanine aminotransferase [ALT], aspartate transaminase [AST], uric acid, platelet count, urine protein)
Post–dural puncture headache	Headache within 5 days of dural puncture Worsens within 15 minutes of sitting or standing Associated with neck stiffness, tinnitus, photophobia, and nausea	History and physical examination Possible MRI
Cortical vein thrombosis	Nonspecific headache that may have a postural component. Often accompanied by focal neurologic signs and seizures	History and physical examination CT or MRI Possible angiography
Subarachnoid hemorrhage	Abrupt onset of an intense and incapacitating headache Often unilateral Accompanied by nausea, nuchal rigidity, and altered consciousness	History and physical examination CT without contrast or MRI (FLAIR sequence)
Posterior reversible (leuko) encephalopathy syndrome (PRES)	Severe and diffuse headache with an acute or gradual onset Possible focal neurologic deficits and seizures	History and physical examination, MRI
Brain tumor	Progressive and often localized headache Often worse in the morning Aggravated by coughing/straining	History and physical examination CT or MRI
Subdural hematoma	Headache usually without typical features Often overshadowed by focal neurologic signs and/or altered consciousness	History and physical examination CT or MRI
Carotid artery dissection	Late developing headache that is constant in nature Bilateral or unilateral location	History and physical examination. Carotid ultrasonography or MRA
Cerebral infarction/ischemia	Moderate headache accompanied by focal neurologic signs and/or altered consciousness	History and physical examination CT or MRI (showing angiographic "string of beads" appearance)
Idiopathic intracranial hypertension (pseudotumor cerebri/benign intracranial hypertension)	Progressive nonpulsating headache Aggravated by coughing/straining Associated with increased CSF pressure and normal CSF chemistry	History and physical examination Lumbar puncture
Spontaneous intracranial hypotension	No history of dural trauma Diffuse, dull headache worsening within 15 minutes of sitting or standing Associated with neck stiffness, nausea, tinnitus, and photophobia CSF opening pressure < 60 mm H_2O in the sitting position	History and physical examination Lumbar puncture Radioisotope cisternography CT myelography
Sinusitis	Frontal headache with accompanying facial pain Development of headache coincides with nasal obstruction Purulent nasal discharge, anosmia, and fever	History and physical examination Nasal endoscopy CT or MRI
Meningitis	Headache is most frequent symptom Often diffuse Intensity increases with time Associated with nausea, photophobia, phonophobia, general malaise, and fever	History and physical examination Lumbar puncture

TABLE 31-1 **Differential Diagnosis of Postpartum Headache—cont'd**

Headache Etiology	Primary Symptoms/Signs	Diagnostic Modality
Pneumocephalus	Frontal headache Often an abrupt onset immediately after dural puncture Symptoms can worsen with upright posture	History and physical examination CT or MRI
Caffeine withdrawal	Onset of headache within 24 hours of cessation of regular caffeine consumption* Often bilateral and pulsating Relieved within 1 hour of ingestion of caffeine 100 mg	History and physical examination
Lactation headache	Mild to moderate headache associated temporally with onset of breast-feeding or with breast engorgement	History and physical examination
Ondansetron headache	Mild to moderate headache associated with ondansetron intake	History and physical examination

CSF, cerebrospinal fluid; *CT,* computed tomography; *FLAIR,* fluid-attenuated inversion recovery; *MRA,* magnetic resonance angiogram; *MRI,* magnetic resonance imaging.

*The International Classification of Headache Disorders-II criteria state that caffeine-withdrawal headache occurs on cessation of ≥ 200 mg daily caffeine consumption for more than 2 weeks.[4] However, others have suggested that caffeine-withdrawal headache may occur after as little as 3 days' exposure to 300 mg/day or 7 days' exposure to 100 mg/day.[35]

BOX 31-1 International Classification of Headache Disorders (ICHD-II) Classification

Primary

- Migraine
- Tension-type headache
- Cluster headache and other trigeminal autonomic cephalgias
- Other primary headaches

Secondary

- Headache attributed to:
  - Head and/or neck trauma
  - Cranial or cervical vascular disorder
  - Nonvascular intracranial disorder
  - A substance or its withdrawal
  - Infection
  - Disorder of homeostasis
  - Disorder of the cranial structures (e.g., eyes, ears, nose, sinuses, teeth, mouth)
  - Psychiatric disorder
- Cranial neuralgias and central causes of facial pain
- Other headache, cranial neuralgia, central or primary facial pain

Modified from Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24(Suppl 1):9-160.

Primary Headaches

The postpartum patient can present with a recurrence of her known primary disorder or with the first manifestation of a primary condition. Patients with a history of headache disorders typically are diagnosed with one of the four major types of primary headaches. The most common postpartum headaches are tension-type and migrainous headaches, which account for almost two thirds of headaches during this period.[1,2] **Tension-type headaches** are often circumferential and constricting, can be associated with scalp tenderness, and are usually of mild to moderate severity.

Migraine

Migrainous headaches (or migraines) are defined as recurring cranial pain lasting 4 to 72 hours, often with typical features such as pulsating pain in a unilateral location, nausea, and photophobia.[4] Headache with aura is a subtype of migraine that is characterized by focal neurologic symptoms preceding the headache. The prevalence of migraine is approximately 17% in the female population (three times more common than in men) and is more common in patients between 30 and 50 years or age.[6] Pregnancy has an ameliorating effect on migraine frequency in the majority of sufferers. However, symptoms may recur soon after delivery, with reports of 34% within the first week postpartum and 55% within the first month.[7] Generally, the symptoms are similar to their typical pattern, although often milder and less often unilateral. It is rare for a migraine to manifest for the first time during the postpartum period. There appears to be an association between migraines and preeclampsia, which may reflect an underlying predisposition to cerebral ischemic injury.[8]

Secondary Headaches

A common secondary headache in the postpartum period is the **musculoskeletal headache**, exacerbated by the maternal physical exertion of labor and associated sleep deprivation. This headache has accompanying neck and shoulder pain without a history of dural puncture. Approximately 11% to 14% of postpartum headaches are diagnosed as musculoskeletal.[1] Other causes of secondary headache are discussed in the following paragraphs.

Hypertension

Hypertensive disorders of pregnancy, including preeclampsia, are commonly associated with headaches.

Eclampsia is a form of hypertensive encephalopathy that includes headache, visual disturbances, nausea, vomiting, seizures, stupor, and sometimes coma. Seizures may occur in the absence of severe hypertension. Headache is a serious premonitory sign, being present in over 50% of women in whom eclampsia develops.[9] Other hypertensive disorders, with or without superimposed preeclampsia, are also associated with headaches both antepartum and postpartum and may lead to encephalopathy. The diagnosis can be complex if the parturient's labor and delivery course is complicated by a dural puncture.[10]

Posterior Reversible Leukoencephalopathy Syndrome

Posterior reversible (leuko)encephalopathy syndrome (PRES) was described in 1996 after recognition of consistent symptom presentation and brain magnetic resonance imaging (MRI) findings in a diverse group of patients. Conditions associated with PRES include preeclampsia, uremia, hemolytic-uremic syndrome, and exposure to immunosuppressant drugs.[11] Approximately 25% of cases of PRES occur during pregnancy or in the immediate postpartum period. PRES symptoms include headache, seizures, altered mental status, visual changes, and, occasionally, focal neurologic deficits.[12]

The neuroradiologic features of PRES include symmetric areas of cerebral edema, predominantly involving the white matter regions of the posterior circulation (occipital lobes, posterior parietal and temporal lobes) (Figure 31-1). The pathophysiology of PRES is similar to that of hypertensive encephalopathy in that altered cerebrovascular regulation causes loss of blood-brain barrier integrity. The accompanying vasogenic edema can be reversed by prompt recognition and supportive therapy (e.g., cessation of provocative medications, aggressive treatment of hypertension, seizure prophylaxis). However, irreversible cytotoxic edema with permanent neurologic damage can occur if the initial disorder is not diagnosed early. This syndrome often manifests in the postpartum period, frequently in conjunction with preeclampsia. Distinguishing PRES from preeclampsia or eclampsia is complex because headache, seizures, and focal neurologic deficits, such as temporary loss of vision, are common symptoms of both disorders.[13,14] Typical features that distinguish PRES from other postpartum headaches include seizures and focal neurologic deficits, such as temporary loss of vision. Definitive diagnosis is made with MRI.

Cortical Vein Thrombosis

The incidence of cerebral cortical vein thrombosis is increased during pregnancy and in the puerperium, and is estimated to be 10 to 20 per 100,000 deliveries in developed countries. The incidence appears higher in developing countries (e.g., 450 per 100,000 deliveries in India).[15] Often it is difficult to distinguish cortical vein thrombosis from PDPH, because the headache of cortical vein thrombosis may have a postural component. Preceding dural punctures have been reported, and it has been hypothesized that the reductions in cerebrospinal fluid (CSF) pressure and cerebral vasodilation that accompany dural puncture predispose to thrombosis development.[16] Associated features may include focal neurologic signs, seizures, and coma. Cerebral infarction may ensue if diagnosis is delayed. Diagnosis is best confirmed by MRI, because computed tomography (CT) appears to identify only one third of cases.[17] Treatment of cortical vein thrombosis largely is symptomatic, with the aim of preventing seizures. Anticoagulation therapy is commonly used to treat these patients, with observational and randomized trial studies indicating better outcomes.[18]

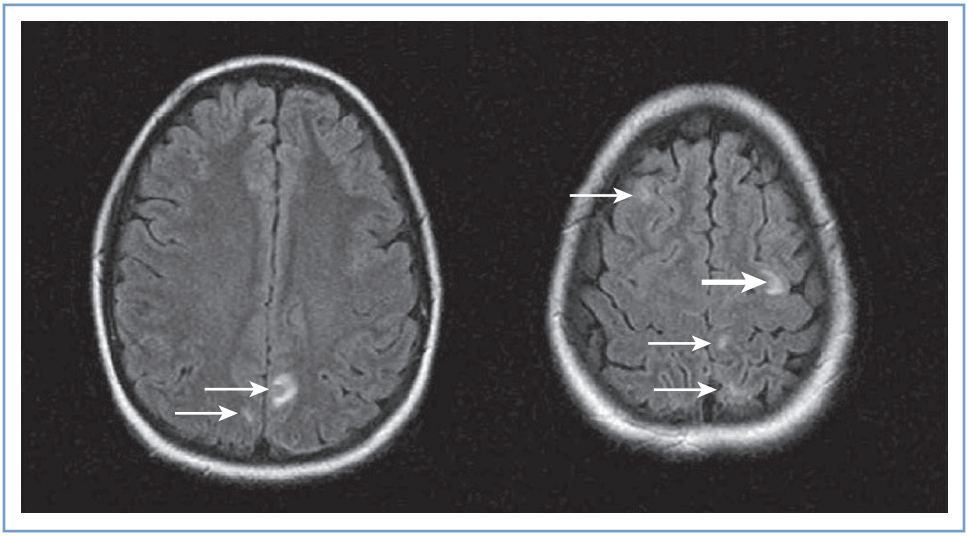

FIGURE 31-1 ■ Posterior reversible (leuko)encephalopathy syndrome (PRES). Axial fluid-attenuated inversion-recovery (FLAIR) images demonstrate foci of abnormally increased T2 signal (*arrows*) in the subcortical white matter and cortex of the frontal and parietal lobes involving both anterior and posterior circulations. (From Long TR, Hein BD, Brown MJ, et al. Posterior reversible encephalopathy syndrome during pregnancy: seizures in a previously healthy parturient. J Clin Anesth 2007; 19:145-8.)

Cerebral Infarction/Ischemia

Cerebral arterial insufficiency is one cause of stroke in pregnancy with an estimated incidence of 4 to 11 per 100,000 deliveries.[19] Approximately half of the events occur in the peripartum period, and the clinical presentation often comprises a sudden onset of a nonpostural thunderclap headache, vomiting, seizures, and focal neurologic deficits. Postpartum cerebral angiopathy has been detected with the aid of cerebral angiography, in which a characteristic "arterial beading" pattern indicative of arterial spasm is evident.[20] Initial CT and MRI findings are often normal, and intracranial Doppler or angiographic investigations may be necessary to diagnose the arterial ischemia or infarct. Treatment is supportive and may include vasodilator therapy.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) occurs secondary to aneurysmal or nonaneurysmal causes. The risk for SAH due to nonaneurysmal causes appears to be increased during pregnancy. A 2012 U.S. population–based study estimated an overall incidence of peripartum SAH at 5.8 per 100,000 deliveries.[21] The classic presentation consists of the sudden onset of a severe headache that is unlike any previous headache. Associated symptoms may be present, such as decreased level of consciousness and focal deficits. Pregnancy may increase the risk for bleeding because of increased blood volume and hormonal changes that affect arterial integrity. Two thirds of all cases in pregnancy occur in the postpartum period, but maternal mortality appears to be less than in nonpregnant patients.[21] Other factors associated with SAH during pregnancy include advanced maternal age, African American race, hypertensive disorders, smoking history, alcohol abuse, and intracranial venous thrombosis. Suspicion of SAH necessitates urgent investigation by CT scan, because nonsurgical therapies (e.g., endovascular ablation) are available and long-term sequelae can be minimized.

Subdural Hematoma

In rare instances, dural puncture is associated with the subsequent development of a subdural hematoma (see later discussion). In several case reports, the identification of the subdural hematoma was preceded by symptoms of a PDPH.[22] Dural puncture results in leakage of CSF and decreased intracranial pressure (ICP). Presumably, the reduction in ICP causes stress on bridging cerebral vessels, which may precipitate bleeding. Neurologic signs of subdural hematoma are variable but include evidence of increased ICP (e.g., headache, somnolence, vomiting, confusion) and focal abnormalities.

Carotid Artery Dissection

A rare, vascular cause of postpartum headache is spontaneous carotid artery dissection. Borelli et al.[23] reviewed the 19 known published cases of postpartum carotid artery dissection. The mean interval from delivery to headache onset was 9.3 days. The headaches were constant in character and both unilateral and bilateral. Stricken woman appeared older (mean age, 35 years) than the average parturient. Diagnosis was made after carotid vessel ultrasonography or magnetic resonance angiography.

Brain Tumor

Intracranial tumors may manifest as postpartum headache. Headache that is dull rather than throbbing may be an early feature of a brain tumor. Nausea, vomiting, seizures, and/or focal neurologic signs may be present. Neurologic examination may reveal evidence of increased ICP. Case reports suggest that atypical presentation of the headache, either with persisting headache symptoms in the supine position or exacerbation after epidural blood patch, should prompt further neuroradiologic investigations.[24,25]

Idiopathic Intracranial Hypertension

Parturients with idiopathic intracranial hypertension (i.e., increased ICP in the absence of a mass lesion, also known as pseudotumor cerebri or benign intracranial hypertension) have headache and visual disturbances, usually in the antepartum period. The features of the postpartum headache of pseudotumor cerebri mimic the usual chronic headache symptoms experienced by the patient. The diagnosis largely is one of exclusion (see Chapter 49). Treatment involves reduction of CSF pressure, either with glucocorticoids, carbonic anhydrase inhibitors, diuretics, or serial lumbar punctures. Case reports describe the use of an intrathecal catheter for labor analgesia[26] and administration of epidural blood patch for PDPH in patients with idiopathic intracranial hypertension.[27]

Spontaneous Intracranial Hypotension

Spontaneous intracranial hypotension develops because of CSF leakage secondary to dural tears. The tears usually occur at the thoracic spinal level and are not associated with prior spinal intervention.[28] Diagnosis requires radioisotope cisternography and CT myelography, which may also identify the level of the leak. Presentation of this disorder is identical to that of PDPH, because the pathophysiology is the same. The only difference is the lack of a prior neuraxial procedure in spontaneous intracranial hypotension. One case report has described the development of a postural headache 4 days after a spontaneous vaginal delivery without neuraxial anesthesia.[29] The patient was found to have a cervicothoracic dural leak.

Pneumocephalus

The subdural or subarachnoid injection of air used for identification of the epidural space may be associated with the sudden onset of severe headache, sometimes accompanied by neck pain, back pain, or changes in mental status.[30] Headache symptoms can mimic PDPH in that they are worse in the sitting position and may be relieved by lying down. Radiologic studies confirm the

presence of intracranial air; the headache typically resolves over the first week. Administration of oxygen by nasal cannula or face mask may hasten resorption of the air and speed recovery, although this has yet to be proven with pneumocephalus after neuraxial anesthesia.[31]

Meningitis

The severe headache of meningitis typically manifests within the first several postpartum days (see Chapter 32). It is accompanied by fever, nuchal rigidity, and the presence of Kernig and Brudzinski signs. Lethargy, confusion, vomiting, seizures, and a rash also may occur. The most common pathogen is *Streptococcus viridans*.[32,33] These organisms are found in the upper airway and vagina; the causative organism has been linked to the oropharyngeal flora of the proceduralist in a number of reports of iatrogenic meningitis after dural puncture procedures. Aseptic technique during the neuraxial procedure, including donning of a mask by the proceduralist, is of paramount importance. The diagnosis is confirmed by examination and CSF culture.

Sinusitis

Headache caused by inflamed paranasal sinuses is associated with purulent nasal discharge and, occasionally, fever. Pain may be unilateral or bilateral, depending on the extent of the disease, and the skin over the affected sinus may be tender. Frontal sinus infection causes headache in the frontal region. Ethmoidal and sphenoidal sinus infections cause periorbital pain, and maxillary sinus infection may cause diffuse facial discomfort. The sinuses fill overnight, and pain typically is worse on awakening. Pain improves in the upright position, which assists drainage.[34]

Caffeine Withdrawal

The withdrawal of caffeine may lead to headache, increased fatigue, and anxiety. Caffeine withdrawal headaches may occur after just 3 days' exposure to 300 mg/day or 7 days' exposure to 100 mg/day of caffeine.[35] Normal-sized caffeinated drinks usually contain 50 to 100 mg of caffeine per serving. Although caffeine withdrawal headache has not been documented as a cause of postpartum headache, if the parturient has been drinking beverages with caffeine during the pregnancy the diagnosis should be considered.

Lactation Headache

Askmark and Lundberg[36] reported episodes of intense headache during periods of breast-feeding in a woman known to suffer from migraine. Onset of headaches occurred within the first few minutes of breast-feeding, and the headaches resolved after cessation of nursing. The headaches were associated with an increase in plasma vasopressin concentration. Headaches have also been described in women with breast engorgement who either have elected not to breast-feed or have reduced the frequency of breast-feeding.[37]

Ondansetron

Sharma and Panda[38] reported a case in which a woman received ondansetron for nausea and vomiting after uneventful spinal anesthesia for cesarean delivery. Several hours later she developed a severe frontal headache that was worse in the upright position and in the morning and evening hours. The symptoms abruptly stopped after the discontinuation of ondansetron.[38] Headache is a common side effect of ondansetron (incidence, 3% to 17%), owing to its antagonism of serotonin 5-HT_3 receptors, and should be considered in the differential diagnosis of postpartum headache.

POST–DURAL PUNCTURE HEADACHE

Incidence

PDPH may occur after intentional dural puncture with a spinal needle or unintentional dural puncture with an epidural or other needle. A meta-analysis of studies of PDPH in obstetric patients (n = 328,769) calculated a pooled risk for unintentional dural puncture with any epidural needle of 1.5% (95% confidence interval [CI], 1.5% to 1.5%).[39] After a dural puncture with an epidural needle, the risk for PDPH was 52.1% (95% CI, 51.4% to 52.8%) (Figure 31-2). The rate of PDPH after dural puncture with spinal needles ranged between 1.5% and 11.2%, depending on the needle size and type of needle (see later discussion) (Table 31-2).[39-43] Although PDPH is often considered a "minor" complication of dural puncture, it was the cause of 14% of obstetric claims in the American Society of Anesthesiologists (ASA) Closed-Claims Project database (see Chapter 33).

Symptoms

Patients typically experience headache pain in the frontal and occipital regions, but location is not diagnostic. Pain often radiates to the neck, which may be stiff. Some women have a mild headache that permits full ambulation. In others, pain is severe and incapacitating. Symptoms are worse in the upright position and are usually relieved in the horizontal position. Abdominal compression may relieve pain in some patients. The ICHD-II defines PDPH as occurring within 15 minutes of moving to an upright position (sitting or standing) and resolving within 15 minutes of moving to the supine position, and requires one of the following symptoms to be present: headache, neck stiffness, tinnitus, hypacusis, photophobia, or nausea.[4]

Lybecker et al.[44] reported the incidence of these symptoms in a prospective study of 75 nonobstetric patients with PDPH (Table 31-3). Cranial nerve palsy, thought to be secondary to nerve traction due to low CSF volume, is occasionally associated with PDPH. The sixth cranial nerve is most susceptible to traction during its long intracranial course. The traction results in failure of the involved eye to abduct, and patients may have diplopia. Hearing loss is usually in the low-frequency range and may be secondary to endolymph and perilymph

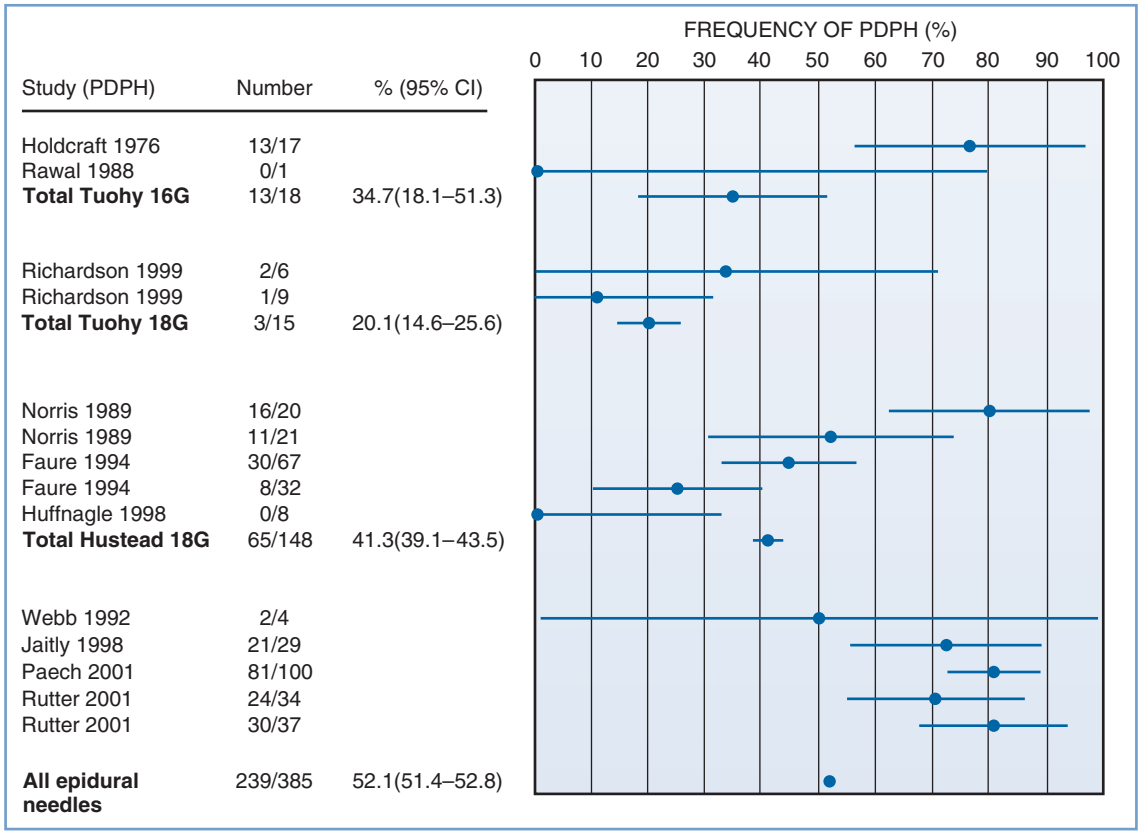

FIGURE 31-2 ■ Meta-analysis of post–dural puncture headache (*PDPH*) frequency for epidural needles in the obstetric population. The *dots* represent the percentages of patients experiencing the event. The *horizontal lines* represent the 95% confidence interval (*CI*). (From Choi PT, Galinski SE, Takeuchi L, et al. PDPH is a common complication of neuraxial blockade in parturients: a meta-analysis of obstetric studies. Can J Anaesth 2003; 50:460-9.)

TABLE 31-2 Frequency of Post–Dural Puncture Headache in Obstetric Patients According to Spinal Needle Design

Needle Design	Gauge	n/N	Frequency of PDPH (%)*	95% Confidence Interval†
Quincke	24	15/238	11.2	10.2-12.2[39,43]
	25	114/1792	6.4	5.3-7.6[39,43]
	26	139/2467	5.6	5.6-5.7[39]
	27	34/1167	2.9	2.0-4.0[39,43]
Atraucan	26	16/350	4.6	2.6-7.3[40-42]
Whitacre	22	1/68	1.5	1.2-2.8[39]
	25	137/6992	2.0	1.6-2.3[39-41,43]
	27	13/820	1.6	0.08-2.7[39,43]
Sprotte	24	57/1767	3.5	3.5-3.5[39]
Polymedic	25	22/292	6.6	5.9-7.4[39]
BD	26	205/2560	5.8	5.6-5.9[39]
Gertie Marx	24	8/201	4.0	1.7-7.7[42]

n, number of headaches; *N*, total number of procedures; *PDPH*, post–dural puncture headache.
*Estimates based on binomial probability estimation.
†Superscript numbers indicate reference citations at the end of the chapter.

TABLE 31-3 Symptoms Associated with Post–Dural Puncture Headache

Symptom	Incidence (%)
Nausea	60
Vomiting	24
Neck stiffness	43
Ocular*	13
Auditory†	12

*Ocular symptoms include photophobia, diplopia, and difficulty in accommodation.
†Auditory symptoms include hearing loss, hypacusis, and tinnitus.
Data from Lybecker H, Djernes M, Schmidt JF. Postdural puncture headache (PDPH): onset, duration, severity, and associated symptoms. An analysis of 75 consecutive patients with PDPH. Acta Anaesthesiol Scand 1995; 39:605-12.

imbalance and alteration of hair cell position in the inner ear.[45] The risk for hearing loss appears to be increased with advanced age (> 40 years) and dural puncture with larger-gauge needles. Other rare symptoms associated with PDPH include seizures,[46,47] vertigo,[48] bilateral forearm pain,[49] abdominal pain, and diarrhea.[50] In all these case reports the headache and associated symptoms cleared after therapy with an epidural blood patch.

Onset and Duration

Headache typically occurs on the first or second day after dural puncture; by ICHD-II criteria, it must appear within 5 days of dural puncture.[4] However, Choi et al.[39] found that PDPH can occur up to 7 days after dural puncture, and one case report identified a woman who developed a PDPH 12 days after labor neuraxial analgesia.[51] Ninety-five percent of PDPH headaches last less than a week. The National Obstetric Anaesthesia Database project of the Obstetric Anaesthetists' Association demonstrated that 75% of 975 women with PDPH had difficulty with performing activities of daily living.[52] Rarely, symptoms may persist for months or even years.[53] Webb et al.[54] found that 18% of women who sustained a dural puncture with a 17-gauge Tuohy needle suffered from chronic headaches compared with 5% of women in a matched cohort who did not sustain dural puncture with an epidural needle. These findings require confirmation, but they suggest that there may be long-term sequelae from dural puncture with a large-gauge needle.

Imaging

Imaging investigations are not routinely recommended for the postpartum patient with a PDPH unless the symptoms suggest other diagnoses or the diagnosis of PDPH is in doubt. Contrast-enhanced MRI is the method of choice to study the meninges and has revealed characteristic findings of PDPH.[55,56] These findings include (1) marked, diffuse pachymeningeal thickening and enhancement; (2) compression of the ventricles; (3) caudal displacement of the brain, brainstem, and optic chiasm; (4) cerebellar ectopia; (5) pituitary enlargement and enhancement; (6) and expansion of the superior sagittal sinus. The enlarged venous sinus may represent compensatory venous expansion in response to low CSF pressure. The presence of intracranial air on CT imaging (after using a loss-of-resistance to air technique to identify the epidural space) may help differentiate headache due to pneumocephalus from a low-CSF pressure headache.[57]

Pathophysiology

Debate continues regarding the precise etiology of PDPH symptoms. The original theory was that pain-sensitive nerve fibers were stimulated by a downward shift of the brain secondary to a loss of CSF volume. German surgeon August Bier[58] is credited with the first description of successful spinal anesthesia and PDPH after his pioneering work on spinal anesthesia with cocaine. Bier and his assistant, Hildebrandt, performed spinal anesthesia on each other; using blows to the shin with an iron hammer and application of a burning cigar to the skin they demonstrated adequate sensory blockade.[58] Both experienced severe PDPH. The assistant forced himself to work the next day, but Bier stayed home for 9 days. Bier suggested the PDPH might be caused by CSF loss. Today there is no doubt that leakage of CSF initiates the syndrome. Kunkle et al.[59] consistently produced PDPH by draining 20 mL of CSF from volunteers. Symptoms were immediately relieved by subarachnoid injection of saline to restore initial CSF pressure.

Total CSF volume is estimated to be 150 mL, and the production rate is approximately 0.35 mL/min or a daily rate of 500 mL. The rate of CSF leakage through a dural hole may exceed the rate of CSF production. If this occurs, low CSF pressure results in a loss of the cushioning effect provided by intracranial fluid.

CSF pressure during labor is normal between contractions but increases significantly during painful contractions and expulsive efforts. Effective epidural analgesia attenuates this increase in CSF pressure.[60] In a study of five women with unintentional dural puncture, epidural pressures were normal preceding the development of headache.[61] However, with development of headache symptoms, the mean epidural pressure measurements were found to decrease significantly.

Not all patients with PDPH symptoms have decreased CSF pressure, and not all patients with a significant CSF leak experience symptoms. The pain of PDPH may be caused, in part, by an increase in cerebral blood flow (and cerebral vasodilation) as a consequence of low CSF pressure or volume. This phenomenon has been observed in animals.[62,63] The inverse relationship between intracranial blood volume and CSF volume reflects the body's effort to maintain a constant intracranial volume.[64] The lumbar CSF compartment is a dynamic structure and acts as a reservoir for intracranial CSF volume adjustment.[65] The occurrence of cerebral vasodilation may explain the relief of headache symptoms with vasoconstrictors such as caffeine, theophylline, and sumatriptan.

Risk Factors

In a classic study of 10,098 spinal anesthetics published in 1956, Vandam and Dripps[66] noted that three patient factors influenced the incidence of PDPH: age, gender, and pregnancy. The analysis did not allow determination as to whether these factors were independent risk factors. Subsequently, other risk factors for development of PDPH have been identified.

Age

Extensive evidence supports the observation that PDPH is uncommon in patients older than 60 years of age and is most common in patients who are younger than 40 years of age.[67] In the elderly, the dura may be inelastic and less likely to gape after puncture. CSF leakage may be impeded by adhesions and calcification. The cerebrovascular system also may be less reactive in older patients. Further, this group is less active physically and older patients may be less likely to complain.

Gender

Vandam and Dripps[66] observed a twofold higher incidence of PDPH after spinal anesthesia in women than in men (14% versus 7%, respectively). This difference may be related to differences in cerebrovascular reactivity, because it is well known that migraine headaches occur predominantly in females and are influenced by

hormonal changes. Women may have enhanced vascular reactivity, or perhaps changes in cerebral blood flow are more likely to produce pain in women than in men. A meta-analysis of randomized clinical trials identified a twofold higher risk for PDPH in nonpregnant females than in males.[68]

Vaginal Delivery

Vandam and Dripps[66] also observed a high incidence of PDPH (22%) in women who received spinal anesthesia for vaginal delivery. This high incidence may be a result of the mechanical consequences of expulsive efforts during the second stage of labor and/or postpartum hormonal changes in cerebrovascular reactivity. Expulsive efforts in the second stage may increase CSF leakage. This possibility has prompted some physicians to restrict maternal pushing after dural puncture and to use forceps to shorten the second stage of labor. In a 20-year retrospective review of 460 parturients who experienced unintentional dural puncture during labor at the Birmingham Maternity Hospital in the United Kingdom, Stride and Cooper[69] did not identify a lower incidence of PDPH in women who underwent prophylactic forceps delivery than in those who had spontaneous vaginal delivery. In contrast, in a retrospective review of the records of 33 laboring women who had experienced unintentional dural puncture, Angle et al.[70] found that women who were allowed to push were much more likely to develop PDPH (relative risk [RR], 7.4; 95% CI, 1.1 to 48.2) and also were more likely to require an epidural blood patch.

Morbid Obesity

In a retrospective study, Faure et al.[71] found that morbidly obese patients are less susceptible to PDPH and are also less likely to receive an epidural blood patch for treatment of PDPH, suggesting either a reduced severity of PDPH or anesthesia provider reticence to perform an epidural blood patch in this patient population. Possible but unproven explanations of a lower incidence and severity of PDPH in obese patients include increased abdominal pressure (which may reduce the extent of CSF leakage) and/or reduced physical activity in these patients. Other confounding factors, such as differences in the mode of delivery (higher rate of cesarean delivery) and neuraxial opioid administration, may also play a role. In contrast to these findings, Webb et al.[54] found that the median body mass index was greater in women who developed PDPH after unintentional dural puncture with a Tuohy needle than in women who did not develop PDPH.

History of Previous Post–Dural Puncture Headache

A history of PDPH after previous spinal anesthesia is associated with the development of PDPH with subsequent spinal anesthesia.[72] A cohort of nonobstetric women with a history of previous spinal anesthesia was monitored prospectively after a second spinal anesthesia procedure. Those with a previous history of PDPH were 2.3 times more likely (95% CI, 1.0 to 5.1) to have a second PDPH than women without a history of headache (24.2% versus 10.6%, respectively). This finding suggests that certain individuals are predisposed to the development of PDPH.

Multiple Dural Punctures

Seeberger et al.[73] found that multiple dural punctures significantly increased the risk for PDPH. Surgical patients who received a second spinal injection owing to failure of the initial spinal puncture had a 4.2% incidence of PDPH compared with a 1.6% incidence among patients who had a single dural puncture.

Neuraxial Anesthetic Technique

Technical factors related to the neuraxial technique influence the incidence of PDPH.

Epidural Needle Size/Design. The high rate of PDPH after unintentional dural puncture with an epidural needle has led investigators to alter the epidural needle design or size in an attempt to reduce headache incidence or severity. Data on the success of this endeavor are conflicting. In an *in vitro* study using cadaver dura, no differences were found in fluid leak rate among punctures made with Hustead, Tuohy, Crawford, and Sprotte epidural needles.[74] In contrast, in an *in vivo* study, Morley-Forster et al.[75] observed a lower incidence of PDPH with the use of an 18-gauge Sprotte needle than with the use of the standard 17-gauge Tuohy needle, despite no difference in the unintentional dural puncture rate. A pilot study has examined the use of a 19-gauge Tuohy needle with 23-gauge epidural catheter.[76]

Spinal Needle Design. Historically, the beveled Quincke needle (Figure 31-3) has been the most widely used needle for dural puncture for both diagnostic and anesthetic purposes (see Chapter 12). A modification of the Quincke needle, the Atraucan needle, has a cutting tip and a double bevel, which is intended to cut a small

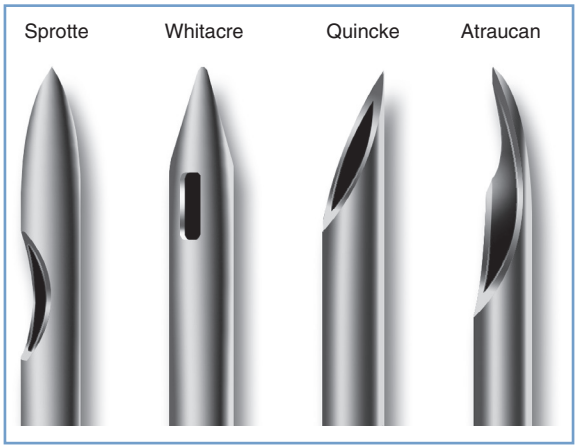

FIGURE 31-3 ■ Designs of spinal needle tips (not to scale). (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

dural hole and then dilate it.[40] Clinical experience with the Atraucan needle has been generally good,[40,41] although studies appear to suggest that the use of this needle is associated with a higher risk for PDPH than the use of a non-cutting, pencil-point needle (see Table 31-2).[42]

In 1951, Hart and Whitacre[77] introduced a solid-tipped, pencil-point spinal needle with a lateral injection port, which is now known as the Whitacre design (see Figure 31-3). They believed that their new needle would stretch and separate rather than cut the dural fibers and result in a lower incidence of PDPH. Currently, both 25- and 27-gauge Whitacre needles are very popular, and studies have confirmed the anticipated low incidence of PDPH.[39] A randomized comparison of 27-gauge Quincke and Whitacre needles in outpatients undergoing spinal anesthesia found a lower incidence of PDPH in the Whitacre needle group.[78] *In vitro* evidence suggests that fluid leak through the dural puncture site is lower after use of a pencil-point needle than after use of a beveled needle.[79] With the recognition that pencil-point spinal needle tips reduce the incidence of PDPH, other tip designs have appeared. In 1987, Sprotte et al.[80] reported experience with the use of a new needle that was designed to reduce the risk for neural and dural trauma (see Figure 31-3). The Sprotte needle has a solid oval tip and a longer orifice than the Whitacre needle. The incidence of PDPH was 0.02% with its use in a heterogeneous patient population of almost 35,000 patients.[80] Subsequent studies have shown the incidence of PDPH with the Sprotte needle is lower than that with Quincke needles of smaller gauge (see Table 31-2).[39] There are currently many other non-cutting spinal needle products available and all are associated with a low PDPH rate.

Spinal Needle Size. With the Quincke needle, the incidence and severity of PDPH are directly related to the size of the needle. The incidence of PDPH appears to be lower with a 27-gauge needle than with 25- and 26-gauge needles (see Table 31-2). A similar relationship may exist with pencil-point needles. When needles smaller than 27-gauge are used, the incidence of PDPH is very low, but technical problems with needle insertion and failure to produce adequate anesthesia are more common.[81] Locating the epidural space before insertion of the spinal needle (e.g., using the epidural needle as an introducer needle) may improve the success rate with these fine-gauge needles.

The current popularity of spinal anesthesia in obstetric patients is largely a result of new needle technology, which has led to a reduction in the incidence of PDPH. Because of the morbidity associated with PDPH, every effort should be made to use a needle associated with a low incidence of PDPH (e.g., a small-gauge, non-cutting needle).[82] There are times when urgency or body habitus will dictate the use of a larger needle, but there is seldom justification for using a Quincke needle larger than 27-gauge.

Direction of Bevel of the Quincke Needle. Studies have confirmed that puncturing the dura mater with a Quincke needle bevel parallel to the long axis of the spine reduces the incidence of PDPH by 70% compared with a perpendicular orientation.[83] An early study by Franksson and Gordh[84] demonstrated that orientation of the bevel of a Quincke spinal needle parallel to the long axis of the spine produced less dural trauma than occurred when the bevel was inserted perpendicularly. These investigators thought that the dural fibers were predominantly longitudinal in direction. Electron microscopy has revealed that the dural structure is far more complex than originally proposed. Fink and Walker[85] noted that the dura consists of multidirectional interlacing collagen fibers with both transverse and longitudinal elastic fibers. They suggested that the insertion of the needle with the bevel parallel to the long axis of the spine most likely results in less tension on the dural hole and, therefore, a smaller aperture with less CSF leak. *In vitro* studies of bevel orientation and fluid leak have provided conflicting results.[86-88] Despite confusing anatomic evidence, clinical experience strongly supports insertion of the Quincke needle with the bevel parallel to the long axis of the spine.[83]

Direction of the Bevel of the Tuohy Needle. Norris et al.[89] examined two groups of women who received epidural anesthesia with a Tuohy needle. In one group the bevel was kept perpendicular to the long axis of the spine. In the other group the needle entered the epidural space with the bevel parallel to the long axis and the needle was then rotated 90 degrees before insertion of the catheter. The authors observed a decreased incidence of PDPH in the latter group. However, some anesthesiologists argue that rotation of the needle within the epidural space may increase the risk for unintentional dural puncture. Richardson and Wissler[90] randomized laboring women to a cephalad or lateral orientation of the Tuohy bevel during epidural needle insertion. The needle was not rotated before insertion of the epidural catheter. There was no difference in dural puncture or PDPH rates, but catheter insertion was easier with a cephalad orientation of the bevel.

Midline or Paramedian Approach. There is conflicting evidence as to whether the spinal needle approach affects the incidence of PDPH. Haftalvi[91] reported no cases of PDPH in a retrospective survey of 4465 spinal anesthesia procedures. This investigator used a paramedian approach with a 20-gauge Quincke needle, and the skin was punctured 3 cm from the midline. He suggested that tangential dural puncture creates a dural flap and prevents PDPH. In contrast, Viitanen et al.,[92] prospectively monitoring obstetric patients after administration of single-shot spinal analgesia for labor (27-gauge Quincke needle), observed PDPH in 3 of 85 (3.5%) patients in whom the midline approach was used, compared with 15 of 127 (11.8%) patients in whom the paramedian approach was used. Using a rigid paper cylinder model of the dura, Kempen and Mocek[93] studied median and paramedian punctures with a 22-gauge Quincke needle in different orientations. With midline punctures, all entry and exit holes were of uniform size regardless of bevel orientation and no dural flaps were seen. After paramedian punctures, flaps formed when the needle bevel faced the cylinder surface with a near-tangential

angle of perforation, suggesting it may be beneficial to insert the needle via the paramedian approach to reduce the incidence of PDPH. Currently, data are insufficient to recommend either the median or paramedian approach in regard to subsequent PDPH.

Skin Preparation. In a nonrandomized, nonblinded study reported in a letter, Gurmarnik[94] found that the removal of dried povidone-iodine solution from the skin before placement of the spinal needle was associated with a lower incidence of PDPH (6% versus 0%). This investigator recommended removal of the povidone-iodine solution before insertion of the spinal needle and suggested that chemical meningismus resulting from povidone-iodine introduced into the intrathecal space by the spinal needle contributed to PDPH. This finding has not been confirmed by other investigators. Simsa[95] suggested that using an introducer needle so the spinal needle does not touch the povidone-iodine solution may be preferable and accomplish the same goal. (*Editors' note:* We do not recommend removal of povidone-iodine [or other solutions used for skin antisepsis] before initiating neuraxial analgesia, because povidone-iodine works by desiccating bacteria, and removing the povidone-iodine reduces its antibacterial effect. Rather, the solution should be allowed to dry on the skin.)

Air versus Saline Method of Locating the Epidural Space. The medium (air or saline) used for the loss-of-resistance technique to identify the epidural space has not clearly been shown to influence the incidence of PDPH. Many anesthesia providers have adopted the loss-of-resistance-to-saline technique in the belief that it is associated with a lower incidence of unintentional dural puncture and PDPH than the use of air.[96] However, the data are inconsistent, and not all studies have found a difference.[97,98] In a meta-analysis of prospective randomized studies comparing air to saline and the incidence of both unintentional dural puncture and PDPH, no difference in either outcome was found.[99] Segal and Arendt[100] suggested that a randomized study of air versus saline may not be the best approach to study headache rate; the study design may lead to overestimation of the difference between air and saline, should one exist, because it is impossible to blind the anesthesia provider to technique and it forces the provider to use a less preferred technique. They performed a retrospective study comparing air with saline; the rate of unintentional dural puncture was not different between groups. However, among anesthesia care providers who had a preference for one technique, use of their preferred technique was associated with fewer unintentional dural punctures. Thus, current data do not support a difference in the incidence of PDPH between air and saline used for the loss-of-resistance technique to identify the epidural space, and one should certainly not change techniques hoping it may decrease headache rates.

Choice of Local Anesthetic Drug for Spinal Anesthesia. Naulty et al.[101] reported that the use of bupivacaine-glucose or lidocaine-glucose for spinal anesthesia was associated with a higher incidence of PDPH than the use of tetracaine-procaine. They postulated that osmotic, cerebral irritant, and/or cerebrovascular effects of the glucose could be responsible for these findings. Whether this finding is applicable to other non–glucose-containing local anesthetic preparations, such as plain bupivacaine, is unknown.

Continuous Spinal Anesthesia. A multicenter trial published in 2008 reexamined the safety and use of 28-gauge microcatheters for spinal labor analgesia.[102] There was no difference in the incidence of PDPH (9% versus 4%, respectively) or epidural blood patch (5% versus 2%, respectively) between women randomly assigned to receive an intrathecal catheter and those who received an epidural catheter; however, the study was insufficiently powered to assess these outcomes. Spinal microcatheters are not currently commercially available in North America.

A 23-gauge spinal catheter inserted using a catheter-over-needle technique is available in North America. Three case series have evaluated this catheter for labor analgesia or cesarean delivery.[103-105] The headache rate ranged from 9% to 29% in these series. This rate is greater than that reported in other studies using traditional epidural or combined spinal-epidural techniques.

Combined Spinal-Epidural Anesthesia. The combined spinal-epidural (CSE) technique is widely used for both labor analgesia and cesarean delivery. Intuitively, it seems that the incidence of PDPH should be identical to, or greater than, that observed after single-shot spinal anesthesia with the same size and type of needle. However, the available evidence, primarily from observational studies, suggests that the risk for PDPH is not increased with the CSE technique.[106-108] PDPH rates with the CSE technique in these three studies were 1.7%, 0.43%, and 1.4%, respectively, compared with 1.6%, 0.45%, and 0.8% for the epidural technique. Initial placement of the epidural needle facilitates precise dural puncture, and the subsequent increase in epidural space pressure after the epidural injection of local anesthetic may reduce CSF leakage. If the anesthesia provider is in doubt about correct epidural needle placement, a needle-through-needle dural puncture might resolve the issue and prevent unintentional dural puncture with a large-gauge epidural needle.

Complications

The immediate problems associated with post–dural puncture headaches include (1) the inability to perform activities of daily living, such as providing care for the newborn; (2) an extended duration (almost one full day) of hospitalization; and (3) a higher number of emergency department visits, with almost 40% of patients returning for more than one visit.[109] Although these complications are very bothersome to the patient, they are short-lived and do not result in long-term morbidity. However, rare but serious complications may occur after dural puncture and PDPH.

Zeidan et al.[110] reviewed the published reports of subdural hematoma after dural puncture. They found that **subdural hematoma** was associated with new neurologic

symptoms in addition to changing headache characteristics. The proposed mechanism of subdural hematoma development is ongoing intracranial hypotension leading to caudal movement of the brain and rupture of fragile, bridging subdural veins. These cases have been managed expectantly, with an epidural blood patch, as well as with neurosurgical decompression.

Dural sinus thrombosis has been documented after unintentional dural puncture and treatment of PDPH with an epidural blood patch.[111] Responsible factors may be cerebral venous dilation (associated with decreased ICP) and the hypercoagulability that occurs during pregnancy. Therapy may include anticoagulation.[18]

Diplopia or **hearing loss** after dural puncture, secondary to cranial nerve dysfunction, may be permanent, even after successful treatment of the PDPH with an epidural blood patch.[112] A review of 95 cases of neurapraxia or axonotmesis of the ocular cranial nerves (oculomotor, trochlear, and abducens nerves) concluded that symptoms may last from 2 weeks to 8 months but that almost 90% of patients recover.[113]

Three studies have focused on the long-term morbidity arising from unintentional dural puncture or spinal anesthesia in obstetric patients.[54,114,115] Women delivering between 1978 and 1985,[114] between 1991 to 1996,[115] and between 2009 to 2010[54] were asked to recall symptoms beginning after their deliveries, including back pain and headache. The responses of women with unintentional dural punctures or spinal anesthesia were compared with women who had uneventful procedures. The first study found that 18% of women with unintentional dural puncture had complaints of frequent headaches or neck ache compared with only 7% of women experiencing uneventful neuraxial procedures.[114] The second study, from the same labor and delivery unit in Birmingham, England, did not confirm an increased risk for headache with prior unintentional dural puncture but instead found a higher rate of backache symptoms.[115] The third and most recent study compared patients with unintentional dural puncture (identified from a database and contacted at 12 to 24 months after delivery) with 40 women who received neuraxial techniques without an unintentional dural puncture.[54] Using validated pain questionnaires, the investigators found that 11 of 40 (28%) women with an unintentional dural puncture had chronic headaches compared with 2 of the 40 (5%) women in the control group.

Prevention

Many practices and maneuvers have been used in an attempt to reduce the incidence of PDPH after unintentional dural puncture, most with limited success. A 2005 survey of British obstetric anesthesiologists quantified the frequency of such practices.[116] These include encouraging postpartum fluid intake (91%), regular analgesia (83%), caffeine administration (30%), and using an intrathecal catheter (15%) at the time of unintentional dural puncture. Older practices, such as avoiding pushing during the second stage, restricting postpartum mobility, abdominal binders, and prophylactic epidural administration of saline or autologous blood, appear to be declining in use. Panadero et al.[117] suggest it may be prudent to restrict air travel after discharge from the hospital. Presumably, the headache can be precipitated by a change in the gradient between the subarachnoid space and the epidural space due to decreased atmospheric pressure. A 2010 systematic review of prevention strategies summarized the evidence from comparative studies and concluded that studies were heterogeneous and that "no clinical recommendation can be made until the superiority of one preventative intervention over another has been unequivocally proven in a definitive multicenter RCT [randomized controlled trial]."[118]

Posture

In a systematic review, Sudlow and Warlow[119] reviewed the evidence for reducing PDPH by use of bed rest rather than early mobilization (usually within 6 hours of dural puncture). The review included eleven trials with 1723 patients, and the results were consistent across all patient types; there was no benefit to bed rest compared with early mobilization (PDPH incidence 31% versus 27%, respectively). It is important to encourage early ambulation during the puerperium. Pregnant women are hypercoagulable and at increased risk for deep vein thrombosis and pulmonary embolism, and immobility increases this risk (see Chapter 39).

Hydration

Despite the widespread practice of encouraging women to increase oral fluid intake after unintentional dural puncture, there is little evidence that greater hydration prevents PDPH. A 2002 systematic review identified only one randomized trial in 100 nonobstetric patients. There was no difference in the incidence of PDPH in patients randomly assigned to receive 3 L or 1.5 L of fluid per day.[119]

Caffeine

Two clinical trials in nonobstetric patients have evaluated the efficacy of oral caffeine to prevent PDPH, but neither study showed a reduction in the incidence of headache.[120,121] Based on these results, prophylactic caffeine is not advocated for prevention of PDPH.

Cosyntropin

Hakim[122] evaluated whether cosyntropin, an adrenocorticotropic hormone (ACTH) analogue, was effective in reducing the incidence of PDPH after unintentional dural puncture in parturients. Patients were randomized to receive intravenous cosyntropin 1 mg or placebo 30 minutes after delivery. The incidence of PDPH was significantly lower in the cosyntropin group (33% versus 69%). The mechanism is unknown but may be related to an aldosterone-stimulating effect on volume expansion, modulation of pain perception via central endorphin-like action, or increased CSF production by enhanced sodium ion transport. Adequate dose-response and safety studies have yet to be performed.

Neuraxial Opioids

Earlier studies suggested that prophylactic neuraxial administration of a hydrophilic or lipophilic opioid does not reduce the incidence of PDPH after spinal anesthesia or unintentional dural puncture.[123,124] However, in a randomized, blinded trial published in 2008, 50 parturients with unintentional dural puncture and subsequent epidural analgesia were randomized to receive epidural morphine 3 mg or saline-placebo after delivery and again 24 hours later, before removal of the epidural catheter.[125] The incidence of PDPH was 48% in the saline-placebo group and 12% in the morphine group. Although no complications were reported, we would caution against routine administration of epidural morphine in these circumstances until this finding is confirmed and further safety studies are undertaken. The movement of morphine across the dura is increased by the presence of a large-gauge needle puncture, possibly increasing the risk for respiratory depression.[126]

Intrathecal Catheters

Placing a 19- or 20-gauge epidural catheter into the intrathecal space after an unintentional dural puncture with an epidural needle has become an increasingly popular technique.[127-129] The immediate benefits of an intrathecal catheter are reliable, low-dose local anesthetic labor analgesia and rapid-onset surgical anesthesia should it be required. Some experts have speculated that the intrathecal catheter might reduce the immediate CSF leak into the epidural space by a mechanical obstruction and induce an inflammatory fibrous reaction in the dura, thus facilitating closure of the puncture after removal of the catheter. Most studies are retrospective and observational and lack rigorous outcome definitions and follow-up. Data from these studies are conflicting but suggest that intrathecal catheters do not significantly reduce the incidence of PDPH unless they are left in place for at least 24 hours after delivery (Table 31-4).[127-133]

Russell[130] conducted a prospective, nonblinded, quasi-randomized multicenter study of parturients who had an unintentional dural puncture during epidural needle placement. Women were randomized in 6-month blocks to a repeat epidural procedure or placement of a spinal catheter through the dural puncture and leaving the catheter *in situ* for 24 to 36 hours. The incidence of PDPH was not significantly different between the epidural (62%) and spinal (72%) catheter groups. Given the current evidence, intrathecal catheters do *not* appear to reduce the incidence of PDPH, but further study is required before a definitive conclusion can be reached.

Prophylactic Epidural/Intrathecal Saline

Trivedi et al.[134] randomly assigned patients with unintentional dural puncture to receive either a prophylactic epidural saline bolus (40 to 60 mL) or blood patch (15 mL) given just before epidural catheter removal or conservative therapy without a saline bolus or blood patch. The incidence of PDPH was not different between the saline and control groups (88% versus 67%, respectively). Shah[61] studied 17 patients who received an epidural saline infusion (at a rate of approximately 40 mL/h) for 24 to 36 hours after unintentional dural puncture. Four patients complained of severe intrascapular pain, which resolved when the infusion rate was reduced. Severe PDPH developed in 47% of patients after the infusion was stopped. In contrast, in a nonrandomized, nonblinded study of patients with unintentional dural puncture, Charsley and Abram[135] reported that *intrathecal* injection of 10 mL of saline immediately before needle or catheter withdrawal resulted in a lower incidence of PDPH (32%) than in a control group who did not receive the saline (62%), as well as a less frequent need for an epidural blood patch. The intrathecal injection of saline after unintentional dural puncture deserves further study. Intrathecal saline should not be administered until residual local anesthetic effects have resolved.

TABLE 31-4 Rate of Post–Dural Puncture Headache after Unintentional Dural Puncture and Prophylactic Intrathecal Catheter Placement

Study*	Study Design	Spinal Catheter, n/N (%)	No Spinal Catheter, n/N (%)
Norris and Leighton[131]	Retrospective cohort; catheter left in place for 2 h	19/35 (54)	11/21 (52)
Cohen et al.[132]	Retrospective cohort:		5/15 (33)
	Catheter discontinued immediately after delivery	8/17 (47)	
	Catheter left in place for 24 h	0/13 (0)†	
Dennehy and Rosaeg[221]	Case series; catheter left in place for 13-19 h	0/3 (0)	
Paech et al.[129]	Prospective cohort; catheter discontinued immediately after delivery	21/24 (87)	60/76 (79)
Rutter et al.[128]	Retrospective cohort; catheter left in place for unknown duration	24/34 (71)	30/37 (81)
Ayad et al.[127]	Retrospective cohort:		34/37 (92)
	Catheter discontinued immediately after delivery	18/35 (51)†	
	Catheter left in place for 24 h	2/31 (6)†	
Russell IF[130]	Prospective, randomized in 6 month blocks, nonblinded intrathecal catheter for 24-36 h	36/50 (72)	29/47 (62)

*Superscript numbers indicate reference citations at the end of the chapter.
†Different than no catheter, $P < .05$.

Prophylactic Blood Patch

Interest in the use of prophylactic epidural blood patch prior to the removal of a labor epidural catheter arose after early observational studies suggested that the incidence of PDPH was lower with such treatment.[136] A 2010 systematic review[137] identified five studies of obstetric patients involving 221 women; four studies found a reduction in the headache rate and one did not.[138] Scavone et al.,[138] in the largest study included in the review, reported a double-blind trial in which 64 parturients with unintentional dural puncture were randomly assigned to receive 20 mL of autologous blood (prophylactic epidural blood patch) or a sham procedure. Both groups had a 56% incidence of PDPH; however, the duration of headache was shorter in the prophylactic blood patch group. The systematic review highlighted the difficulty in estimating the risks and benefits of prophylactic epidural blood patch. Because of the low incidence of unintentional dural puncture, studies are small; therefore, reliable conclusions about the technique cannot be made based on current evidence.[137]

Because unintentional dural puncture with a 16- or 18-gauge epidural needle results in a high incidence of PDPH, some anesthesiologists believe that prophylactic blood patch is always justified. Others argue that with such an approach, a significant number of patients would receive unnecessary treatment and that a blood patch is not devoid of complications. These latter anesthesia providers call attention to the potential for epidural catheters to become contaminated after prolonged use. The injection of blood through a contaminated epidural catheter may be associated with a higher risk for infection than injection through an epidural needle placed *de novo* for a therapeutic blood patch. A case report of a parturient who received a prophylactic epidural blood patch and was subsequently diagnosed with streptococcal septicemia highlights the potential risk for maternal infection during the puerperium.[139]

If performed, a prophylactic blood patch should be delayed until resolution of residual neuroblockade. The occurrence of pain during injection is a signal for the anesthesia provider to stop the injection of blood. If the patient has sensory blockade, she will not perceive pain. Additionally, evidence suggests that lidocaine may inhibit coagulation.[140] Finally, Leivers[141] reported a case of total spinal anesthesia after the epidural injection of 15 mL of blood before epidural anesthesia had regressed. The investigator speculated that residual lidocaine in the lumbar CSF was transferred to the brain as a consequence of an increase in lumbar CSF pressure and reduced volume produced by the patch. (*Editors' note:* One of us [DHC] has observed one case of transient, total blindness after the rapid, bolus injection of 30 mL of epidural saline after vaginal delivery in a patient who had experienced unintentional dural puncture during labor. The blindness resolved after 15 to 20 minutes, and subsequent ophthalmologic and neurologic examinations were normal. The etiology of the transient blindness was unclear. Nonetheless, it seems prudent to delay administration of prophylactic epidural saline or blood until the block has regressed and to avoid rapid epidural administration of blood or saline at any time.)

It is important to avoid the direct intrathecal injection of blood. Aldrete and Brown[142] reported a case of intrathecal hematoma and arachnoiditis with prolonged neurologic sequelae after prophylactic blood patch. Nineteen milliliters of blood were injected through an epidural catheter that, in retrospect, was positioned in the subarachnoid space. There was considerable resistance to injection of the blood, and severe lower back pain with tinnitus accompanied the procedure.

Prophylactic Dextran Patch

Salvador et al.[143] reported the prophylactic epidural injection of 20 mL of dextran-40 in 17 patients who had experienced unintentional dural puncture with a 17- or 18-gauge needle. Three of the patients were parturients, and none of the 17 patients experienced PDPH. This injection was performed before regression of the local anesthetic effect. No additional studies of this technique have been reported; its safety and efficacy remain unclear.

Treatment

Early treatment of PDPH is indicated. Not only does this avert the vicious cycle of immobility, weakness, and depression, but it also may help prevent the rare case of subdural hematoma or cranial nerve palsy in the patient with persistent PDPH.

Psychologic Support

The patient is aware that PDPH is an iatrogenic problem, and she may be angry and resentful as well as depressed and tearful. It is imperative to include disclosure of the risk during the preoperative interview. Headache makes it more difficult to care for the newborn and to interact with other family members. Severe PDPH may delay discharge from the hospital and have economic consequences.[109] Unlike patients who have PDPH after nonobstetric surgery, these patients typically are healthy and do not expect to feel ill. Two patients have eloquently described their own miserable experiences with postpartum PDPH.[144,145] Not surprisingly, a retrospective study of 43 obstetric patients with PDPH showed that this complication leads to a negative attitude toward epidural anesthesia.[146]

It is essential that anesthesia providers visit the patient at least once daily to explain symptoms and prognosis, give support, and offer therapeutic options. If feasible, the patient's partner should attend these discussions. Nurses can help the patient by ensuring adequate analgesics are given on a regular schedule and by teaching alternative breast-feeding techniques, such as the lateral horizontal position.

The anesthesia provider and nurses should write detailed notes in the patient's record. After discharge, follow-up telephone conversations should be documented. Headache associated with neuraxial anesthesia was the third most common reason for litigation among obstetric cases in the American Society of Anesthesiologists

(ASA) Closed-Claims database (see Chapter 33), after maternal death and neonatal brain damage.[147] This fact should dispel any notion that postpartum PDPH is a trivial complaint.

Posture

The diagnosis of PDPH requires demonstration of a postural component. Significant relief should occur when the patient assumes the horizontal position. However, there is no evidence that remaining supine for a prolonged period of time treats or shortens the duration of the headache.[119] The prone position relieves PDPH in some patients, presumably because increased intra-abdominal pressure results in an increase in CSF pressure. Unfortunately, this position is not comfortable for many patients, especially those who had a cesarean delivery.

Hydration

Enhanced oral hydration remains a popular therapy initiated by most anesthesiologists for parturients with PDPH, but there is no evidence that vigorous hydration has any therapeutic benefit in a patient with normal fluid intake. However, no patient with PDPH should be allowed to become dehydrated, because of the increased fluid demands of breast milk formation and CSF production.[119]

Pharmacologic Treatment

In the past, a variety of drugs have been used to treat PDPH, including steroids, vasopressin, alcohol, and ergotamine. A safe and effective oral drug therapy for PDPH would be very useful, even if relief is transient. Blood patch therapy is not appropriate or effective in all patients.

Caffeine. Caffeine has been used to treat PDPH for many years, despite lack of clear evidence of its efficacy. A systematic review of the literature[148] identified a single randomized trial performed by Camann et al.[149] Forty postpartum women with PDPH received a one-time dose of oral caffeine or placebo. Headache pain scores (visual analog scale [VAS], 0 to 100 mm) were lower in the caffeine group at 4 hours than the control group (33 ± 6 versus 49 ± 7 mm, respectively), but there was no difference at 24 hours. It appears that the beneficial effect of caffeine is transient.

The caffeine content of a 150-mL cup of drip coffee is approximately 150 mg. Caffeine is a cerebral vasoconstrictor, and one study has demonstrated a reduction of cerebral blood flow after intravenous administration of caffeine sodium benzoate for the treatment of PDPH.[150] Caffeine is also a potent central nervous system stimulant. There are published case reports of seizures after intravenous[151] and oral administration[152] of caffeine for the treatment of PDPH in postpartum patients.

Caffeine appears in breast milk in very small amounts.[153] To our knowledge, there are no reports of adverse effects on the infant after maternal administration of one or two doses of caffeine for the treatment of PDPH. The risk-to-benefit ratio to mother and newborn of multiple doses of caffeine has not been addressed. Until such studies are available it seems wise to restrict the prescription of oral caffeine to 600 mg in 24 hours, given as 300-mg doses at least 8 hours apart. Long-term caffeine therapy cannot be recommended. Another methylxanthine, theophylline, is also a cerebral vasoconstrictor, and is available in long-acting preparations. Some investigators have found that intravenous theophylline is more effective than placebo in the treatment of PDPH, but it has not become a popular therapy.[154]

Sumatriptan. Sumatriptan is a serotonin receptor agonist that affects predominantly type 1D receptors. Possessing cerebral vasoconstrictor properties, this agent is used in the treatment of migraine headaches. It is given by subcutaneous injection. Side effects include pain at the injection site and, uncommonly, chest tightness. Sumatriptan may cause coronary artery vasospasm and should not be used in those with Prinzmetal's angina or known coronary artery disease. Carp et al.[155] reported that the administration of sumatriptan 6 mg resulted in complete resolution of PDPH in four of six patients, and Paech et al.[129] reported relief of PDPH in one of seven patients treated with sumatriptan. Connelly et al.[156] studied 10 patients with severe PDPH scheduled for epidural blood patch who were randomized to receive either sumatriptan 6 mg or placebo. After 1 hour, only one patient in each group had significant relief, and the authors concluded that sumatriptan was of no value.

Adrenocorticotrophic Hormone. The use of ACTH for the treatment of PDPH was first reported in a 1994 letter to the editor.[157] Subsequently, anecdotal reports have described different regimens of either intramuscular or intravenously administered ACTH or the synthetic drugs cosyntropin or tetracosactrin acetate. Mood elevation, anti-inflammatory effects, increased endorphin levels, and augmented intravascular volume are postulated as possible modes of action in the relief of headache with ACTH. Kshatri and Foster[158] described a curative response to ACTH in two patients with PDPH. The ACTH dose was 1.5 units/kg in 250 mL of normal saline, infused intravenously over 30 minutes. Gupta and Agrawal[159] assessed the effect of ACTH 60 units intramuscularly in 48 patients with PDPH. Complete and permanent relief was obtained in 40 patients, without any side effects. Carter and Pasupuleti[160] reported the management of a patient with intractable PDPH who had already received three epidural blood patches; cosyntropin 0.5 mg in 1 L lactated Ringer's solution was infused over 8 hours, and the headache was completely and permanently relieved.

To date, the only randomized clinical trial of ACTH treatment involved 18 postpartum women who had PDPH after spinal anesthesia or unintentional dural punctures.[161] There was no difference in the severity of headache or the requirement for epidural blood patch between women receiving tetracosactrin acetate 1 mg intramuscularly and those who received saline-placebo.

Oliver and White[162] described three patients who experienced PDPH after administration of epidural

analgesia during labor and who subsequently had seizures. All had received two or three doses of tetracosactrin acetate (1 mg intramuscularly), and one had also received sumatriptan. No epidural blood patch procedures were performed. CT scans showed or suggested infarction in two of these subjects. The investigators stated that before the occurrence of these three cases ACTH had been used regularly to treat PDPH in their institution but that subsequently they had discontinued the administration of ACTH as a therapy for PDPH. No conclusion can be drawn about the possible contribution of ACTH therapy to the observed seizure activity. With the evidence to date, it appears that ACTH therapy cannot be recommended for first-line treatment of PDPH but may be considered for cases that are not amenable to epidural blood patch therapy.

Miscellaneous Medications. Other agents evaluated for their effectiveness in reducing PDPH symptoms include pregabalin, methylergonovine, gabapentin, and hydrocortisone. Randomized clinical trials have been conducted with intravenous hydrocortisone[163] and oral pregabalin.[164] Noyan Ashraf et al.[163] evaluated 60 parturients who developed PDPH after spinal anesthesia and were randomly assigned to receive intravenous hydrocortisone (200 mg loading dose followed by 100 mg three times daily for 2 days) or conventional therapy (bed rest, hydration, and scheduled acetaminophen with meperidine). Patients who received hydrocortisone had a 50% reduction in headache severity as assessed by VAS scores at 6 to 48 hours. A criticism of this study is the lack of blinding on the part of the study participants, which may have influenced their perception of headache pain. Huseyinoglu et al.[164] randomized 40 patients after lumbar puncture and PDPH to receive pregabalin (150 mg daily for 2 days followed by 300 mg for 3 days) or placebo; pain scores and oral analgesic requirements were lower in the treatment group.

Use of gabapentin or methylergonovine has been reported only in case series.[165] Efficacy and side effects (maternal and neonatal) are unclear. All four drugs require further study before they can be recommended for therapy for PDPH.

Epidural Morphine

Eldor et al.[166] reported six nonobstetric patients whose PDPH headaches were successfully treated with epidural morphine 3.5 to 4.5 mg. Further study is required before conclusions can be reached. However, this therapy should be used with caution because epidural morphine injected in the presence of a large dural puncture site may pass readily into the CSF and predispose to respiratory depression.

Epidural/Intrathecal Saline

The use of epidural or intrathecal fluids to treat PDPH preceded the use of epidural blood patches. Intrathecal injection of fluid was first described by Jacobeus et al.[167] in 1923, and epidural injection of saline was reported by Rice and Dabbs in 1950.[168] These first reports were in conjunction with research attempting to understand the pathophysiology of PDPH, and they demonstrated transient elevations of CSF pressure after fluid injection. Subsequently there has been sporadic interest in using injection of fluids (other than blood) into the neuraxial space to treat PDPH.

Usubiaga et al.[169] injected 10 to 30 mL of saline through a lumbar epidural catheter in 11 nonobstetric patients with a PDPH after spinal anesthesia in whom 48 hours of conservative therapy had failed. Immediate relief of headache was observed in 10 patients, and the relief was permanent in 8 patients. However, the investigators did not comment whether other therapies (e.g., supine posture, abdominal binder, analgesics) were continued. In a quasi-randomized trial, 43 parturients with PDPH after unintentional dural puncture during an epidural procedure or after spinal anesthesia with a 25-gauge needle were assigned to receive a 30-mL epidural saline bolus in the lumbar region or a 10-mL lumbar epidural blood patch.[170] Forty-two patients had dramatic relief of their symptoms in the first hour after the intervention; however, 12 of the 21 (57%) patients who had received saline had return of the PDPH in the next 24 hours.

Prolonged epidural saline infusion may provide better therapy for PDPH symptoms than therapy with a single bolus.[171,172] Two case reports described the use of epidural saline infusion for parturients with an unintentional dural puncture, whose PDPH symptoms returned after epidural blood patch therapy. The rate of infusion (15 to 25 mL/h) was limited by the onset of pain in the back, legs, and eyes. A comparative study of epidural saline bolus versus infusion to treat PDPH is needed to determine whether either modality continued over 24 hours would provide better results than conservative therapy. Although both saline techniques seem to only offer temporary relief, these options might be considered for patients who have a contraindication to epidural blood patch therapy.

Epidural Blood Patch

Efficacy. The epidural blood patch is regarded by many as the gold standard therapy for PDPH. Although reported in third person, Gormley, in 1960, is credited with performing the first successful epidural blood patch.[173] He described relief of PDPH symptoms in seven patients after epidural administration of only 2 to 3 mL of blood. However, this report was largely ignored until 1970, when DiGiovanni and Dunbar[174] described the immediate and permanent cure of PDPH in 41 of 45 patients in whom 10 mL of autologous blood was injected into the epidural space. Their success led to the widespread adoption of this technique for the relief of PDPH. An excellent review of the history of PDPH and development of the blood patch was written by Harrington.[175]

In early case series, the reported success rate of epidural blood patch therapy for PDPH series was between 89% and 91%.[174,176] Subsequent studies have not confirmed this high rate of success. Taivainen et al.[177] studied 81 patients with PDPH after spinal needle dural puncture. Initially, symptoms were relieved in 88% to 96% of patients; however, a permanent cure was achieved in only

61%. Safa-Tisseront et al.[178] reviewed their experience with epidural blood patch therapy over a 12-year period (n = 504 patients, including 78 obstetric patients). Complete relief of PDPH was obtained in 75%, partial relief occurred in 18%, and treatment failed in 7% of patients. The investigators noted a significantly higher failure rate of epidural blood patch after large-gauge needle puncture of the dura. The difference in early reports and more modern audits of PDPH and epidural blood patch success may be related to differences in the duration of follow-up or perhaps to other differences in management after blood patch therapy, such as delayed mobilization.

In studies limited to obstetric patients, the published success rates of epidural blood patch have been even less encouraging. Stride and Cooper[69] noted complete and permanent relief of PDPH in 64% of patients after one blood patch procedure. Williams et al.[179] reported only 33% of their patients obtained complete and permanent relief from the first blood patch. The authors suggested that this high failure rate might be related, in part, to their frequent performance of the blood patch procedure within 24 hours of dural puncture. Banks et al.[180] prospectively monitored 100 patients with unintentional dural puncture. Fifty-eight received a therapeutic blood patch; the treatment completely failed in 3 patients, and 17 patients had recurrence of moderate or severe headache requiring further therapy. These observational studies also describe the use of repeat epidural blood patch procedures for parturients with a recurrence of PDPH.

A 2010 systematic review[137] identified three randomized trials comparing epidural blood patch to either a sham procedure or conservative treatment. All three studies found a reduction in headache rate in the treatment group. Seebacher et al.[181] randomized 12 heterogeneous patients with PDPH to receive an epidural blood patch with 10 to 20 mL of blood or a sham patch procedure. Five of six patients receiving a blood patch had complete relief of headache symptoms at 24 hours, and none of the sham procedure patients did. Sandesc et al.[182] described a randomized trial of 32 obstetric and nonobstetric patients with PDPH symptoms for a minimum of 24 hours; subjects were randomly assigned to receive conservative therapy or an epidural blood patch. The primary outcome was headache VAS scores at 2 and 24 hours. At 2 hours the mean VAS score for the conservative therapy group was 8.2 ± 1.4 cm compared with 1.0 ± 0.2 cm for the group receiving a blood patch ($P < .001$). This difference remained at 24 hours. In the largest trial to date, van Kooten et al.[183] randomized 40 subjects with PDPH for 1 to 7 days to receive either conservative therapy or an epidural blood patch using 15 to 20 mL of autologous blood. The primary outcome was headache 24 hours after intervention, but patients were observed for 1 week after therapy. The incidence of headache at 24 hours was 58% in the blood patch group compared with 90% in the conservative therapy group (RR, 0.64; 95% CI, 0.43 to 0.96). At 1 week the difference widened, with 16% incidence of headache in the blood patch group compared with 86% in the conservative group. In summary, administration of an autologous epidural blood patch, although not perfect, often dramatically relieves this debilitating condition and, at present, it is the therapy with the greatest likelihood of success.

Volume. The optimal volume of injected blood remains controversial. Szeinfeld et al.[184] used a gamma camera to observe the epidural spread of technetium-labeled red blood cells during and after epidural blood patch. They injected blood until pain occurred in the back, buttocks, or legs. The mean ± SD volume injected was 14.8 ± 1.7 mL of blood, and the mean ± SD spread was 9.0 ± 2.0 spinal segments. Blood spread more readily in the cephalad than in the caudad direction. The blood patch relieved the headache in all 10 patients. The investigators concluded that 12 to 15 mL of blood should be a sufficient patch volume for most patients.

The best evidence to date is an international, multicenter study by Paech et al.,[185] who randomized 121 women after unintentional dural puncture with a Tuohy needle (16- or 18-gauge) to receive an epidural blood patch with 15, 20, or 30 mL of blood. Partial or complete relief of headache (the primary outcome) occurred in 61%, 73%, and 67% of those who received 15, 20, or 30 mL of blood, respectively. However, complete relief of headache was achieved by only 10%, 32%, and 26% of women in these same groups. The rate of complete headache relief was greater in the 20-mL than the 15-mL group; there was no difference between the 20- and 30-mL groups. Thus, the investigators concluded that 20 mL of autologous blood is the optimal volume for an epidural blood patch. A 2011 survey demonstrated that most North American anesthesiologists inject 20 mL of blood.[186]

Beards et al.[187] performed MRI studies after the performance of an epidural blood patch (18 to 20 mL) in five patients. Similar to Szeinfeld et al.,[184] they noted that the injected blood spread over three to five segments in a predominantly cephalad direction. All patients had an extensive hematoma in subcutaneous fat, and some also had displacement of nerve roots and/or evidence of intrathecal blood. A thick layer of mature clot had formed by 7 hours, which had broken up into smaller clots by 18 hours. These findings may help explain the back pain and occasional nerve root pain that occur after blood patch therapy.

In another MRI study, Vakharia et al.[188] noted compression of the thecal sac and a mean spread over 4.6 segments after the lumbar epidural injection of 20 mL of blood (Figure 31-4). Djurhuus et al.[189] employed CT epidurography in four patients immediately and 24 hours after an 18-mL blood patch. Initial images showed adherence of clot to the dura in three patients as well as dural compression in two patients, but there was no evidence of compression at 24 hours.

Using a goat model, DiGiovanni et al.[190] examined the microscopic appearance of the dura as late as 6 months after dural puncture. Some study animals received a 2-mL blood patch in addition to dural puncture. The investigators concluded that the blood patch acted as a gelatinous tampon that produced no harmful tissue reaction.

Mechanism of Action. The mechanism of action of epidural blood patch for relief of PDPH is unclear. Pain

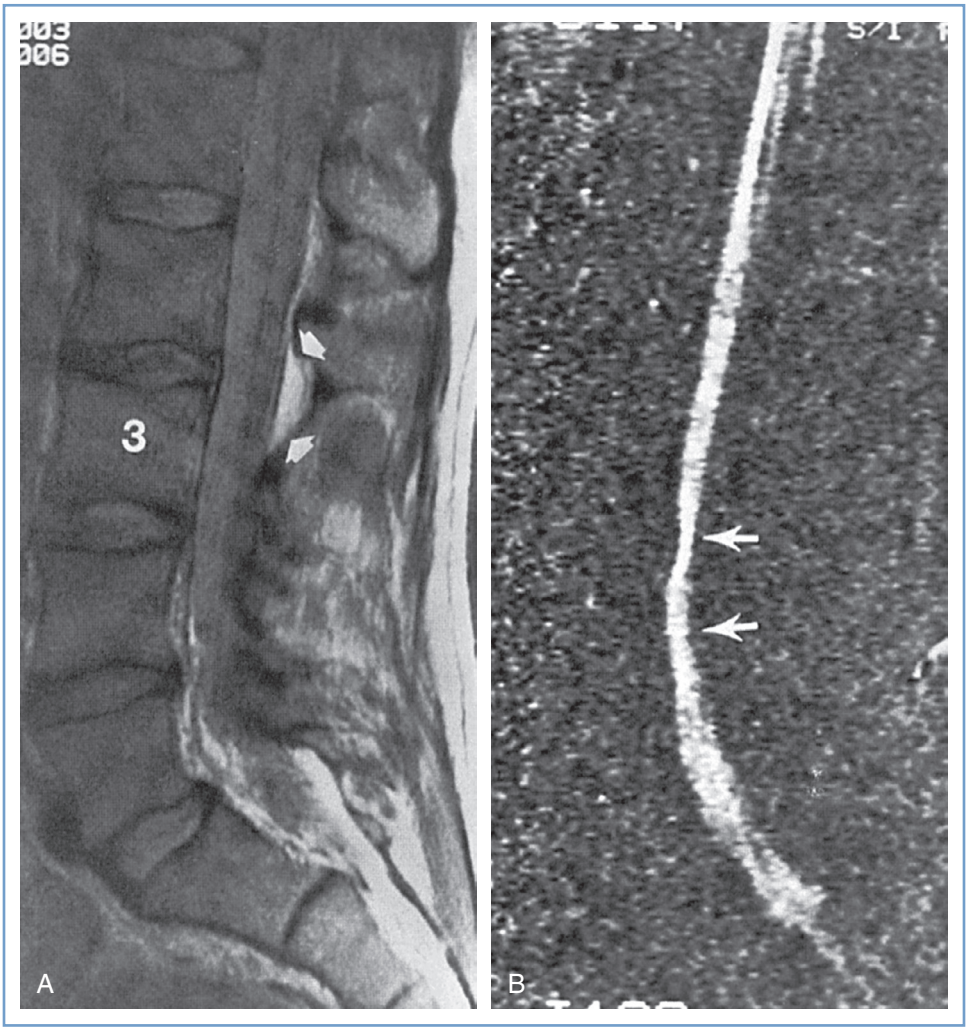

FIGURE 31-4 ■ **A,** Pre–blood patch magnetic resonance imaging using sagittal spin-echo proton density. The dural puncture has been performed at L2 to L3, which local static fluid collection (*arrows*) affirms; *3,* denotes L3 vertebral body. **B,** Post–blood patch magnetic resonance imaging of cerebrospinal fluid flow in systole shows the long length of the compression of the thecal sac posteriorly (*arrows*). (From Vakharia SB, Thomas PS, Rosenbaum AE, et al. Magnetic resonance imaging of cerebrospinal fluid leak and tamponade effect of blood patch in postdural puncture headache. Anesth Analg 1997; 84:585-90.)

relief is often rapid, but CSF volume is not restored immediately. Thus, there must be another explanation for the immediate relief of headache besides "patching" of the dural puncture. Carrie[191] hypothesized that epidural injection of blood increases lumbar CSF pressure, an action that restores intracranial CSF pressure and decreases symptoms. Increased CSF pressure also may result in reflex cerebral vasoconstriction. Coombs and Hooper[192] demonstrated that epidural blood patch resulted in a threefold increase in lumbar CSF pressure. Further, they noted that 15 minutes later, lumbar CSF pressure was sustained at greater than 70% of the peak pressure observed after the injection of blood. Ultrasonographic examination of the optic nerve sheath diameter (a noninvasive measurement that correlates with intracranial pressure) in 10 patients with PDPH demonstrated increased measurements after epidural blood patch.[193] The sheath diameter increased 10 minutes after an epidural blood patch with 17 to 26 mL of blood and was sustained over the 20-hour study period. The only patient whose blood patch failed to successfully relieve the PDPH did not have the same increase in optic nerve sheath diameter.

MRI and CT studies have shown that the epidural blood is largely resorbed or broken up 18 to 24 hours after the procedure.[187,188] It is unlikely that the increase in CSF pressure is sustained or that the blood acts as a mechanical plug to block CSF leak for a prolonged duration. The blood applied to the hole in the dura may initiate an inflammatory reaction that facilitates puncture site repair and closure. It is possible, and even likely, that an epidural blood patch ameliorates PDPH by several mechanisms.

Timing. The optimal timing for administration of a blood patch has not been adequately studied. Observational studies suggest that failure is more likely if the blood patch is performed within 24[178] or 48 hours[185] of the dural puncture. It is unclear, however, whether this finding is a result of selection bias. Early-onset PDPH (often resulting from dural punctures with large-gauge needle) is likely to be more severe and more difficult

to treat. Alternatively, a large CSF leak may displace the clot. Partial healing of the dura may have already occurred if a blood patch is delayed, a possibility that may explain the better outcome of a delayed patch procedure.

Technique. The anesthesia provider should thoroughly explain the risks and benefits of the blood patch procedure to the patient, and the patient should give consent for the procedure. An epidural blood patch can be accomplished on an outpatient basis. Ideally, the environment for the procedure is one conducive to postpartum patients who may have accompanying family and a newborn. Contraindications to the administration of an epidural blood patch are related to complications of placing a needle in the central neuraxis or the injection of blood into the epidural space; they include (1) known coagulopathy, (2) local cutaneous infection or untreated systemic infection, (3) increased ICP due to a space-occupying lesion, and (4) patient refusal. Transient bradycardia has been observed after administration of an epidural blood patch, and some anesthesia providers may choose to establish intravenous access and monitor the electrocardiogram in selected patients.[194]

The blood patch procedure should employ sterile measures equivalent to those used for the administration of any neuraxial procedure. The lateral position is usually more comfortable than the sitting position for patients with severe PDPH. If the anesthesia provider is uncertain about the location of the dural puncture, the more caudad interspace should be chosen. The epidural space is identified in the usual manner. Using meticulous sterile technique (including skin preparation and draping, and donning of a mask and sterile gloves), an assistant withdraws the desired volume of blood (usually 10 to 25 mL) into a syringe. This autologous blood is injected slowly into the epidural space through the Tuohy needle; the injection is terminated if severe back, leg, or neck pain or pressure occurs. Sometimes slowing the injection rate leads to resolution of the back pain. Jehovah's Witness patients may accept a blood patch procedure if a technique is used that keeps blood in continuity with the circulation.[195]

Occasionally a few drops of CSF are encountered on entering the epidural space, leading to doubt about correct needle placement.[196] One can either repeat the epidural needle placement, or a small test dose of a local anesthetic agent can be administered, sufficient to cause a rapid onset of spinal anesthesia. If no block results, the blood patch can be performed. Two case reports have described the use of real-time ultrasound-guided and fluoroscopically guided epidural blood patch.[197,198] The usefulness of these modalities to assist in localizing deposition of epidural blood requires further study.

After the procedure the patient should rest quietly in the supine position for 1 to 2 hours.[199] Subsequently, the patient may resume ambulation, but she should avoid vigorous physical activity for several days. It would be wise for the patient to avoid the Valsalva maneuver and heavy lifting. A stool softener should be considered. Most patients report almost instantaneous relief of headache symptoms, although relief is delayed for 6 to 8 hours in some patients. The patient may continue to have neck and back fullness over the next 24 hours.[185] The back pain can continue up to 5 days after the procedure. Patients should be counseled to immediately report fever, severe back pain, or radiating lower extremity pain. The anesthesia provider should contact the patient after the blood patch procedure.

The blood patch may be repeated if the initial patch fails to relieve pain. Often the second patch is successful. Although not adequately studied, it seems reasonable to wait 24 hours before repeating an epidural blood patch procedure to allow the first procedure adequate time to work. The diagnosis should be reconsidered if headache persists after two failed blood patch procedures. Consultation by a neurologist may be appropriate when a PDPH fails to respond to two blood patches and should definitely be requested if there is any doubt about the diagnosis. Imaging of the head should be considered to exclude other causes of headache.

Complications. Ong et al.[200] reported that the success of neuraxial anesthesia/analgesia was impaired in women with a prior history of unintentional dural puncture with or without epidural blood patch therapy. However, this conclusion has been refuted by follow-up studies in both obstetric[201] and nonobstetric patients.[202] In both of these retrospective studies, a history of blood patch therapy had no apparent effect on the quality of subsequent epidural anesthesia.

Although epidural blood patch therapy is the most reliable method of relieving PDPH symptoms, adverse outcomes are associated with the procedure. These adverse events can be categorized into two broad groups: infectious/hematologic and neurologic.

Infectious/Hematologic Complications. Conventional wisdom holds that the patient should be afebrile at the time of the blood patch procedure. Many anesthesia providers believe that it is wise to avoid the epidural injection of blood in the presence of systemic infection. Meningitis has been reported after a blood patch procedure.[203] After conservative measures have failed, the optimal treatment of a febrile patient with severe, persistent PDPH is controversial. Epidural infusion of saline involves the use of an indwelling epidural catheter for many hours, which also may be undesirable in a febrile patient. A patch using dextran-40 may be an alternative in febrile patients, but further experience is needed in healthy patients before this technique can be recommended. The presence of high fever and/or other evidence of sepsis contraindicate the performance of a blood patch procedure. However, we do not believe that a low-grade fever of known etiology is an absolute contraindication to epidural blood patch, provided the patient is receiving appropriate antibiotic therapy. Management should be individualized, and the known benefits of blood patch should be weighed against the unknown risk for infection.

The risks of epidural blood patch therapy in the presence of human immunodeficiency virus (HIV) infection have been debated (see Chapter 45). However, the central nervous system is infected with HIV at the time of primary infection; therefore, it seems unlikely that the injection of autologous blood into the epidural space would alter progression of the disease. There are

published reports of the successful use of blood patch therapy, without sequelae, in patients with acquired immunodeficiency syndrome (AIDS) or who are HIV positive.[204,205]

The incidence of cancer during pregnancy is increasing, likely secondary to advancing maternal age. The development of PDPH in this population has raised a theoretical concern about seeding the neuraxial space with neoplastic cells if a blood patch procedure is performed. This concern should be discussed with the patient and her oncologist before the procedure. Bucklin et al.[206] reported the conservative management of a woman with acute leukemia and PDPH; the investigators discussed the therapeutic options for this immunocompromised patient. The use of epidural fibrin glue was reported in a nonobstetric patient with metastatic breast cancer and PDPH,[207] whereas a blood patch was performed for PDPH in a young woman with rhabdomyosarcoma.[208]

Neurologic Complications. Serious or permanent problems after epidural blood patch therapy are rare. Diaz and Weed[209] wrote a review of case reports of adverse neurologic complications after epidural blood patch procedures. These authors identified 26 reports published between the years of 1966 and 2004 and stratified the complications into neurologic, neurovascular, or inflammatory events. The events occurring in obstetric patients included lumbovertebral syndrome (defined as low back pain with neurologic impairment of the lower extremities), subdural hematoma, arachnoiditis, radicular back pain, pneumocephalus, seizures, and acute meningeal irritation. Compressive complications (e.g., lumbovertebral syndrome, subdural hematoma, cauda equina syndrome) were associated with a larger blood patch volume (mean of 35 mL) than the noncompressive complications (17 mL). Cranial nerve palsy symptoms that were present before blood patch administration did not uniformly resolve. The delay in performing the blood patch may have been the significant factor. Two patients who were treated within 4 days of the onset of PDPH symptoms recovered within 6 weeks, whereas three patients treated on days 9 to 11 had palsy that persisted for 3 to 4 months. Two obstetric patients experienced new facial nerve palsies, which manifested as facial weakness after administration of an epidural blood patch.

Abouleish et al.[176] reported the results of the long-term evaluation of 118 patients who had received an epidural blood patch. Back pain was the most common complication; it occurred during the first 48 hours in 35% of patients and persisted in 16% of patients, with a mean duration of 27 days. These investigators also noted cases of neck pain, lower extremity radicular pain, and transient temperature elevation.

Epidural space scarring is also a possibility after placement of a blood patch. Although subsequent epidural analgesia is generally successful (see earlier discussion),[201,202] Collier[210] reported two cases of unsuccessful epidural analgesia related to suspected scarring of the epidural space. In both women, the initial epidural catheter placement was complicated by unintentional dural puncture and PDPH treated with epidural blood patch. During a subsequent pregnancy, epidural catheter placement was complicated by inadequate analgesia, and an epidurogram revealed limited spread of the contrast media, suggesting epidural space scarring.

The development of an inflammatory reaction to epidural blood can cause acute arachnoiditis, an entity that can present several days after epidural blood patch.[211] This phenomenon is believed to be secondary to free radical damage to spinal root nerves in the intrathecal space after hemoglobin degradation. There are case reports of obstetric patients with this entity who required analgesic therapy for prolonged periods.[212] The diagnosis is made with a presenting history of severe back pain, often with radicular pain, and characteristic MRI findings such as nerve root clumping in the intrathecal space and adhesions between nerve roots.

The occurrence of new neurologic symptoms appearing after an epidural blood patch should prompt consideration of the presence of other intracranial pathology. Such symptoms may include (1) mental deterioration due to increased ICP from an intracranial tumor[24] and (2) seizures due to late-onset eclampsia.[213]

Diaz[214] described a woman in whom permanent paraparesis and cauda equina syndrome developed after an epidural blood patch with 30 mL of blood injected slowly and without symptoms. Low back pain and leg pain developed after the blood patch procedure, and later the patient also experienced incontinence. Twelve days after the procedure a subdural hematoma at L2-L4 was diagnosed and surgically treated. Six months later the patient still had marked symptoms. Although a larger volume of blood than usual was injected, the technique appears to have been within normal practice standards. Other long-term sequelae reported in obstetric patients include a postpartum cerebral ischemic event after two blood patches that resulted in permanent hemianopsia[215] and a calcified epidural blood patch leading to chronic back pain.[216]

Alternatives to Epidural Blood Patch

Alternatives to an epidural blood patch may be considered if a blood patch is contraindicated or fails. In extreme cases, surgery may be needed to close the dural tear.

Dextran/Gelatin Patch. Dextran-40 and gelatin-based solutions, including Gelfoam and Plasmion, have been substituted for blood in epidural patches.[143,217] These solutions were chosen as alternatives to blood owing to relative contraindications to injection of blood. The use of these agents appears to be more common in countries outside North America. In an observational study of 56 patients, Barrios-Alarcon et al.[218] reported that epidural administration of 20 to 30 mL of dextran-40 was safe and effective for the relief of PDPH; all headaches were relieved permanently. The only side effect was a transient discomfort or burning sensation at the time of injection in 6 patients. Some physicians have treated intractable PDPH successfully by performing a dextran-40 patch followed by epidural infusion of dextran at 3 mL/h for 5 to 12 hours.[219,220]

Information on neurotoxicity of these materials is scant; Chanimov et al.[221] did not observe neurotoxicity after infusion of dextran-40 or polygeline, a gelatin

powder, into the rat intrathecal space. However, further information is needed before these materials can be widely adopted for epidural administration in humans. From MRI studies in patients with an epidural blood patch, we can anticipate that some dextran will enter the subarachnoid space. The small but definite risk for anaphylaxis after the injection of dextran also must be considered, although the risk appears minimal with dextran-40.

Fibrin Sealant Patch. Fibrin sealant is composed of fibrinogen and thrombin. Several commercial products are prepared from human pooled plasma. Products may also contain antifibrinolytics, such as animal aprotinin.[222] When injected, these products form a firm, nonretractable fibrin clot. Epidural injection of fibrin glue in rats produces a sustained rise in CSF pressure comparable to the increase that occurs after injection of blood.[223] Fibrin sealant has been evaluated for its effectiveness in preventing dural leaks after spinal surgery.[224] An epidural fibrin glue patch has been used successfully to treat recurrent PDPH,[225] spontaneous intracranial hypotension,[226] and CSF leak after long-term intrathecal catheterization.[227] In the future, fibrin glue may have a role in patients with intractable PDPH, but further study is required before it can be recommended for routine use.

Surgery. There are rare reports of curative surgical closure of a dural rent for intractable PDPH. In one case, the interval between dural puncture and surgery was 5 years.[228]

Summary of Treatment

The parturient with PDPH should be actively managed with scheduled analgesics and should receive psychological support as she cares for her newborn and manages her symptoms. If the headache is severe, the physician can consider additional agents, such as caffeine or sumatriptan, or proceed directly to an epidural blood patch. Epidural administration of fluids other than blood, such as saline or dextran, typically is not first-line therapy but may be considered when there are contraindications to the epidural injection of autologous blood or if an epidural blood patch procedure fails. The accuracy of PDPH diagnosis must always be considered when atypical symptoms present or when therapy fails.

UNANSWERED QUESTIONS

Important information about PDPH is still lacking. A large, detailed prospective study of PDPH, with and without epidural blood patch, with a long follow-up period (e.g., 1 year) is needed in obstetric patients. What are the long-term effects of both PDPH and blood patch therapy? How common are residual back pain, neurologic symptoms, and auditory/visual symptoms, and do they interfere with everyday life? Answers to these questions are needed to give our patients reliable information, a sound basis for informed consent, and the best possible care. The Obstetric Anaesthetists' Association and the Association of Anaesthetists of Great Britain and Ireland[229] have recommended that each facility providing obstetric anesthesia services should have institution-specific protocols for the management of PDPH to facilitate the identification of parturients with this complication and to provide consistent care.

KEY POINTS

- Dural puncture is only one of many causes of postpartum headache, although many are quick to blame postpartum headaches on dural puncture. A detailed history and physical examination as well as indicated neuroimaging should ensure diagnostic accuracy.
- A patient with post–dural puncture headache experiences an exacerbation of symptoms when she moves from the horizontal to the upright position, possibly owing to decreased intracranial pressure and secondary cerebral vasodilation, which affect pain-sensitive intracranial structures.
- Anesthesia providers should use a small-gauge (24-gauge or smaller), non-cutting (pencil-point) spinal needle whenever possible to decrease the risk for post–dural puncture headache.
- No therapies reliably prevent the development of post–dural puncture headache after unintentional dural puncture with an epidural needle.
- The initial therapy for post–dural puncture headache consists of psychological support, bed rest in the supine position, and scheduled oral analgesics. Although dehydration should be avoided, no evidence supports a role for vigorous hydration for prophylaxis or therapy for post–dural puncture headache.
- The "gold standard" therapy for post–dural puncture headache is an autologous epidural blood patch. A second blood patch may be performed—and typically is successful—if the first one fails. If the second procedure fails, alternative diagnoses should be excluded. Other therapies have not proved as effective and safe as the epidural blood patch for treatment of post–dural puncture headache.

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CHAPTER 32

Neurologic Complications of Pregnancy and Neuraxial Anesthesia

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CHAPTER OUTLINE

Neurologic complications of childbirth may be associated with neuraxial analgesia and anesthesia or may result from childbirth itself. Complications of neuraxial anesthesia may be immediate, such as motor blockade, unexpectedly high or prolonged blockade, and seizures after unintentional intravenous injection of local anesthetic, or they may be prolonged or delayed (sequelae). Immediate complications of neuraxial anesthesia are described in Chapter 23; here the discussion is focused on neurologic sequelae.

Although neurologic disorders after childbirth are more likely to have obstetric than anesthetic causes, neuraxial anesthesia is all too often blamed. For example, Tubridy and Redmond[1] described seven women referred with neurologic symptoms after childbirth, all of which had been attributed to epidural analgesia. The women suffered from brachial neuritis, peroneal neuropathy, femoral neuropathy, neck strain, and leg symptoms for which there was no obvious physical cause. In such circumstances, a careful history and neurologic examination, together with diagnostic aids such as electromyography, nerve conduction studies, and imaging techniques, can localize the lesion and differentiate obstetric from anesthetic causes. For example, it should be possible to distinguish by simple clinical means between a mononeuropathy, which is likely to have an obstetric cause, and a radiculopathy resulting from neuraxial blockade. Accurate and prompt diagnosis is essential.

THE INCIDENCE OF NEUROLOGIC SEQUELAE

Patients frequently ask obstetricians and anesthesia providers about the incidence of complications of neuraxial anesthesia, but even if accurate data were available, the question has no true answer. The incidence of neurologic complications varies widely according to local practice and the skill and training of the practitioners. Some old surveys are based on accurate local records, but the data relate to a time when obstetric and anesthetic practices, equipment, and drugs were less safe than they are today. The incidence of serious complications is now too low to be estimated accurately on a local basis. Nonetheless, anesthesia providers have a duty to inform patients of the complications associated with a proposed procedure and are expected to give some figure for the level of risk, however meaningless such an estimate may be.

Obstetric Surveys

In early surveys, the reported incidence of neurologic deficits in obstetric patients ranged from 1 in 2100 to 1 in 6400.[2,3] During this period, long labor and difficult rotational forceps delivery were commonplace and neuraxial anesthesia was relatively unusual. Many surveys have subsequently attempted to assess the incidence of

BOX 32-1 Limitations of Surveys of Neurologic Sequelae of Neuraxial Anesthesia in Obstetrics

- Poor response rate
- Positive reporting bias
- Absence of controls without neuraxial anesthesia
- Greater attention given to those who received neuraxial anesthesia
- Inadequate investigation and lack of accurate diagnosis
- Variable skill and care of obstetric and anesthetic providers
- Older surveys relate to outdated obstetric and anesthetic practices
- Lack of statistical power to assess incidence of rare disorders
- Inaccurate counting of numerator and denominator
- Likelihood of missing cases that arise after hospital discharge

neurologic complications of neuraxial anesthesia, overlooking obstetric problems and other sources of error (Box 32-1).

Some of the more relevant surveys are listed in Table 32-1, those of the 20th century having been ably reviewed by Loo et al.[4] in 2000. Ong et al.[5] reviewed the medical records of all women who delivered in Winnipeg over a 9-year period and interviewed all those who received anesthesia care. All neurologic deficits in this series were transient, with none lasting more than 72 hours. The incidence of neurologic symptoms was similar after epidural and general anesthesia, but symptoms were more likely to be reported by women who received anesthesia than by those who received none. This is not surprising because only women who received anesthesia were interviewed. Indeed, the survey identified 45 cases of neurologic deficit, but only 10 had been noted in the hospital record, suggesting that many deficits may have been missed in the patients who were not interviewed. Moreover, modern statistical methods such as logistic regression analysis were not used to tease out the influence of prolonged labor and traumatic delivery, which the investigators noted as possible causative factors.

In a large retrospective survey of long-term symptoms, women who delivered in one hospital in Birmingham, United Kingdom, were asked to recall events 2 to 9 years after delivery.[6] The response rate was only 39%, and all those (and only those) who received epidural analgesia had been interviewed intensively about their symptoms immediately postpartum, thereby enhancing subsequent recall in this subset of the population. Logistic regression analysis demonstrated a link between epidural analgesia and many symptoms, including tingling and numbness in the arms, calling into question any causative link with neuraxial anesthesia. No major neurologic sequelae were detected.

Scott and Hibbard[7] conducted a retrospective British survey of more than 500,000 epidural procedures administered between 1982 and 1986, which detected a number of serious sequelae, including one epidural abscess, one hematoma, and one anterior spinal artery syndrome, but many of the diagnoses were presumptive.[7] This survey probably failed to detect many minor lesions, but it was followed by a smaller prospective survey by Scott and Tunstall,[8] which included some spinal anesthetics and involved a self-selected group of respondents. The investigators found no major neurologic disorders but a more believable number of what were termed *mononeuropathies*.

A French survey based on a questionnaire covering the years 1988 to 1993, and sent to all hospitals with maternity units, recorded one cranial subdural hematoma but no cases of epidural abscess or hematoma in 288,351 obstetric epidural procedures.[9] Seven deaths were reported. Complications of spinal anesthesia were not included in this survey.

Both the Scott surveys[7,8] and the French inquiry[9] overlooked the need for a control group of laboring patients who did not receive neuraxial analgesia/anesthesia. The study by Holdcroft et al.[10] avoided this pitfall; the denominator consisted of all 48,066 women who delivered in one region over a year, and every effort was made to detect genuine neurologic symptoms in the community. Because the women themselves were not sent questionnaires, however, the response rate could not be estimated. The investigators judged that only one case of paresthesia, without physical signs, could be attributed to epidural analgesia and none to spinal anesthesia. Peripheral nerve damage was more common. The most serious was one case of foot drop in a woman who had a spontaneous delivery of a large baby with inhalation analgesia only.

With the increase in popularity of spinal anesthesia, concern about the growing numbers of reports of paresthesias and possible root trauma led Holloway et al.[11] to conduct a retrospective U.K. national survey of spinal and combined spinal-epidural (CSE) anesthesia in the 1990s. No difference in frequency of neuropathy was detected between Whitacre and Sprotte needles or between single-shot spinal and CSE techniques. Imprecise diagnoses made it difficult to differentiate anesthetic from coincidental causes, but after eliminating obvious obstetric or peripheral nerve palsies while otherwise erring on the pessimistic side, the investigators estimated that the incidence of neurologic sequelae was approximately 1 in 1000, including two cases of conus damage, one of meningitis, and the rest minor root palsies.

Two thorough local audit reports of immediate postpartum symptoms provided somewhat contrasting findings. One from Perth, Australia,[12] involved prospective recording of complications in 10,995 parturients who received epidural analgesia, but it regrettably did not include a control group. The investigators detected only a single lasting neurologic problem. Although they termed the injury a traumatic mononeuropathy, it was apparently a radiculopathy, because it was attributed to a traumatic epidural procedure.

The second report, from Leeds, United Kingdom, involved 3991 women who delivered in one center in 1 year.[13] Twenty-one women presenting with symptoms after neuraxial blockade were matched with 21 asymptomatic control patients who had also received neuraxial blockade and 21 who had not. Only 1 woman who had not had a neuraxial block presented with symptoms, and

TABLE 32-1 Surveys of Neurologic Complications of Childbirth and of Neuraxial Blocks in Obstetrics

Study	Type of Study	Population	No. of Neurologic Deficits (Risk Ratio)
Ong et al., 1987[5]	Medical record review of all patients, interview of those receiving anesthesia in one center (1975-1983)	23,827 deliveries	45, all transient (1/530)
		12,964 inhalational or no analgesia	5 (1/2,593)
		9,403 epidural procedures	34 (1/277)
		1,460 general anesthetics and other	6 (1/243)
Scott & Hibbard, 1990[7]	Retrospective multicenter review (1982-1986), no control group	505,000 epidural procedures	47 (1/10,745) 1 anterior spinal artery syndrome 1 epidural abscess, 1 epidural hematoma (unconfirmed) 38 mononeuropathies, 5 cranial nerve palsies 1 subdural hematoma
MacArthur et al., 1992[6]	Questionnaire sent in 1987 to mothers delivering in one center (1978-1985)	11,701 women (39%) who responded	Tingling/paresthesias:
		4766 epidural procedures	143 upper limb, 23 lower limb
		6935 no epidural procedures	150 upper limb, 3 lower limb
Palot et al., 1994[9]	Questionnaire listing possible complications sent to hospitals with obstetric beds (1988-1993), no control group	288,351 epidural procedures	92 (1/3134) 1 cranial subdural hematoma 88 temporary radiculopathy (1/3277) 3 meningitis (1/96,117) (also reported negligence cases: 1 sciatic nerve palsy, 1 intracranial hematoma)
Scott & Tunstall, 1995[8]	Prospective multicenter review (1990-1991), no control group	467,491 deliveries	46 neuropathies (details for procedures not given)
		108,133 epidural procedures	38 (1/2846)
		14,856 spinal procedures	8 (1/1857)
Holdcroft et al., 1995[10]	Regional community and hospital-based trawl (1991-1992)	48,066 deliveries	10 new neurologic complications (1/4807)
		34,430 no neuraxial block	1 foot drop, 1 cervical nerve lesion (1/17,215)
		13,007 epidural procedures	1 paresthesia of nerve root distribution (1/13,007) (Disorders unrelated to anesthesia: 2 cranial nerve palsies, 1 hypotensive cord damage; 5 peripheral nerve lesions)
		629 spinal procedures	0
Paech et al., 1998[12]	Prospective local audit (1989-1994), no control group	10,995 epidural procedures	1 traumatic "mononeuropathy" (1/10,995)
Holloway et al., 2000[11]	Retrospective multicenter trawl, elastic time frame, no control group	29,698 spinal procedures	4 unrelated to anesthesia (3 meralgia paresthetica, 1 peroneal neuropathy), 10 ?root damage, 1 conus damage, 22 uncertain (overall incidence ?1/986)
		12,254 CSE procedures	5 unrelated to anesthesia (1 femoral neuropathy, 2 foot drop, 2 paresthesia), 6 root damage, 1 meningitis, 1 conus damage, 6 uncertain (overall incidence ?1/901)
Dar et al., 2002[13]	Prospective local audit of immediate symptoms (1998-1999)	1,376 vaginal deliveries without anesthesia (random sample of 21 examined + 1 complaint)	4 peripheral neuropathy, 1 foot drop, 2 vague (1/3)
		2,615 regional blocks (all followed up)	21 had neurologic symptoms:
		1,782 vaginal deliveries	7 peripheral neuropathies, 1 foot drop, 3 vague (1/162)
		833 cesarean deliveries	8 numb areas, 2 vague (1/83)
Auroy et al., 2002[15]	Prospective multicenter survey, no control group	29,732 epidural procedures	0
		5,640 spinal procedures	2 "peripheral neuropathy"
Moen et al., 2004[16]	National postal survey and search of administrative files (1990-1999), no control group	205,000 epidural procedures	1 epidural hematoma (HELLP), 1 epidural abscess, 2 cord damage, 2 intracranial subdural hematoma, 1 abducent nerve palsy (1/29,286)
		50,000 spinal procedures	1 spinal hematoma (HELLP), 1 cord damage (1/25,000)
Cook et al., 2009[18]	National audit of major complications of neuraxial blockade over 1 year (unstated), obstetric and nonobstetric, no control group	329,425 obstetric procedures	1 epidural abscess, 2 nerve injury, 1 unknown Incidence of possible harm per 100,000 (95% CI)
		161,550 epidural procedures	0.6 (0-3.4)
		133,525 spinal procedures	1.5 (1-5.4)
		25,350 CSE procedures	3.9 (1-22)

CSE, combined spinal-epidural.

she was found to have foot drop after a vacuum extraction. Typical peripheral neuropathies occurred among those who delivered vaginally; sacral numbness was most commonly detected after cesarean delivery. All changes were transient, and none could be attributed to neuraxial anesthesia. Similar neurologic deficits were detected among the randomly selected, asymptomatic 21 control patients who had had no anesthetic intervention. In contrast, negligible deficits could be detected among the 21 asymptomatic control women who *had* had an anesthetic intervention. These results demonstrate that minor neurologic deficits are to be found postpartum quite frequently if sought, but only those who have had anesthetic intervention are likely to complain.

A prospective survey among 6057 women who delivered in 1 year in Chicago[14] does not feature in Table 32-1 because the patients were not grouped by type of analgesia, but the findings of this survey corroborate those of the Leeds study.[13] The incidence of lower limb nerve injuries was approximately 1% (24 lateral femoral cutaneous nerve, 22 femoral nerve, 3 peroneal nerve, 3 lumbosacral plexus, 2 sciatic nerve, 3 obturator nerve, and 5 radicular injuries).[14] Significant risk factors identified by logistic regression analysis included nulliparity and a prolonged second stage of labor but not neuraxial anesthesia.

In a nationwide 10-month prospective French survey, only two so-called peripheral neuropathies and no major sequelae were detected among 5,640 spinal and 29,732 epidural procedures in obstetric patients.[15] In contrast, in a retrospective Swedish national survey covering the years 1990 through 1999, Moen et al.[16] reported nine serious sequelae among an estimated 200,000 epidural and 50,000 spinal procedures in parturients.

Ruppen et al.[17] attempted to conflate the findings of various surveys to derive a consensus incidence of neurologic injury after obstetric epidural block. Unfortunately, this study took no account of the now widespread use of spinal and CSE techniques, denominators were calculated inaccurately, and the findings of surveys were not always interpreted correctly. For example, cranial subdural hematoma was counted as a spinal hematoma. Therefore, reliable information cannot be derived from this publication.

A U.K. national audit of neuraxial blocks, without controls, published in 2009, found that the risk for major complications was 6- to 14-fold higher for perioperative than for obstetric procedures. Among the obstetric patients, the risk was highest for CSE, intermediate for spinal, and lowest for epidural procedures.[18]

Several conclusions can be drawn from these surveys. Despite an increased cesarean delivery rate, obstetric palsies (albeit now more short-lived) still occur, and the reported frequency of neurologic sequelae depends on how hard one seeks them. The risk for transient mild deficits after childbirth may be quite high.[13,14] A true figure for anesthetic complications cannot be calculated even from thorough surveys because (1) the diagnosis is rarely accurate; (2) definitions, severity, and duration are often ill defined; and (3) anesthesia provider skills vary. Table 32-1 demonstrates a variation in the incidence of neurologic sequelae from 1 in 3 for mild symptoms with no neuraxial block[13] to 1 in 30,000 for epidural analgesia.[16] Moreover, bias is created when more attention is paid postpartum to patients who have received neuraxial blockade than to those who have not.

Other Surveys

Modern surveys of neurologic complications of spinal and epidural anesthesia among nonobstetric populations may yield more reliable results but still lack sensitivity to detect all potential problems and are commonly conducted in relatively elderly and sick populations. Moreover, the occurrence of case clusters gives the lie to the existence of a "true" incidence of complications.[16] Auroy et al.,[15] Moen et al.,[16] and Cook et al.[18] surveyed mixed populations and found a lower incidence of serious sequelae in obstetric than in other patients. It is therefore invalid to extrapolate findings from one population to the other. The reported risk for neurologic problems varies greatly with the patient population, local practice and skill, completeness of detection, and inclusion criteria. Hence, it is meaningless to attempt to put any firm figure on the risk for neurologic complications after neuraxial anesthesia.

PERIPHERAL NERVE PALSIES

Postpartum nerve injury is often assumed to be due to neuraxial anesthesia, but peripheral nerve palsies, which generally have obstetric causes, are much more common, with a reported incidence between 0.6 and 92 per 10,000.[19] They may arise from compression in the pelvis by the fetal head, or from more distal compression, the signs of which may be overlooked in the presence of neuraxial anesthesia. In contemporary obstetric practice, cesarean delivery is usually preferred to prolonged labor and difficult or forceps delivery. The incidence of pelvic nerve trauma and compression should therefore be lower than in years past. Surveys have shown that although obstetric palsies still occur,[11,13,14] most are short-lived and less disabling than hitherto.[2,3] Foot drop, however, is still reported,[10,13,14,20] primarily in cases in which the effort to avoid cesarean delivery leads to vaginal delivery of a disproportionately large baby.[10,13] Abnormal presentation, persistent occiput posterior position, fetal macrosomia, breakthrough pain during epidural labor analgesia, a prolonged second stage of labor, difficult instrumental delivery, and prolonged use of the lithotomy position may presage postpartum neuropathy.

Reference to the distribution of spinal dermatomes and peripheral nerve sensory innervation clearly demonstrates the distinction between peripheral and central lesions (Figure 32-1). Spinal nerve root lesions are also manifested by weakness that involves several lower extremity joints and movements (Figure 32-2).

Compression of the Lumbosacral Trunk

Compression of the lumbosacral trunk by the fetal head at the pelvic brim (Figure 32-3) preferentially affects the more medial fibers that make up the peroneal rather than the tibial nerve.[19] In addition to weakness that

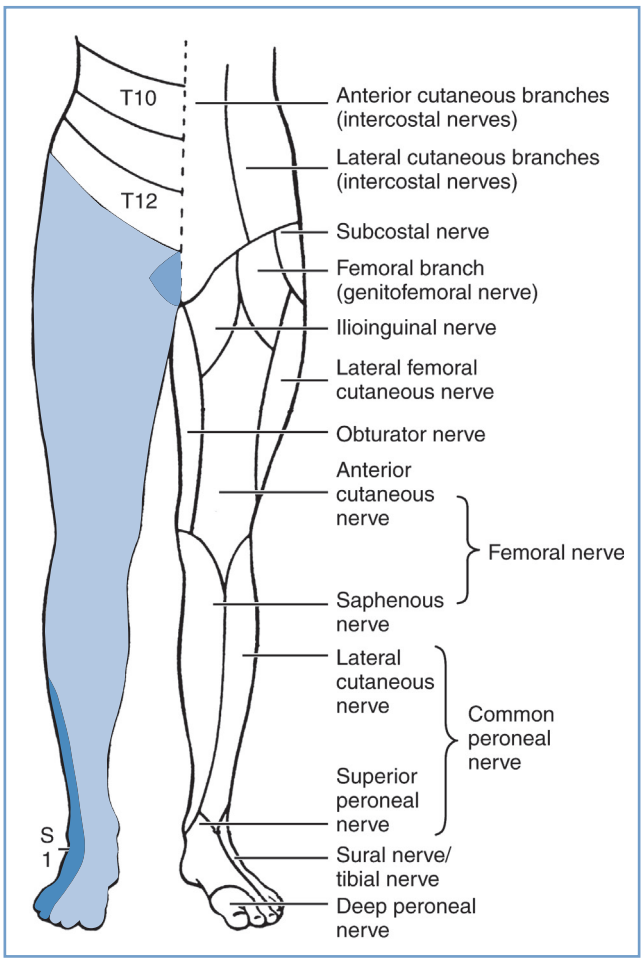

FIGURE 32-1 ■ Segmental (*right leg*) and peripheral (*left leg*) sensory nerve distributions useful in distinguishing central from peripheral nerve lesions. (From Redick LF. Maternal perinatal nerve palsies. Postgrad Obstet Gynecol 1992; 12:1-6.)

		L1	L2	L3	L4	L5	S1	S2	S3	S4
Hip	Flexion	■	■	■	▪					
	Extension				■	■	■	■		
	Abduction					■	■			
	Adduction		■	■	■					
	Medial rotation	■	■	■	■	■	■			
	Lateral rotation					■	■	■		
Knee	Flexion		▪	▪	▪	■	■	■		
	Extension		■	■	■					
Ankle	Dorsiflexion				■	■				
	Plantar flexion						■	■		
Big toe dorsiflexion					■	■	■			
Levator ani								■	■	■
Coccygeus										■

FIGURE 32-2 ■ The spinal segments involved in movements of joints in the leg. Lighter shading denotes a minor contribution. (Data from Russell R. Assessment of motor blockade during epidural analgesia in labour. Int J Obstet Anesth 1992; 4:230-4.)

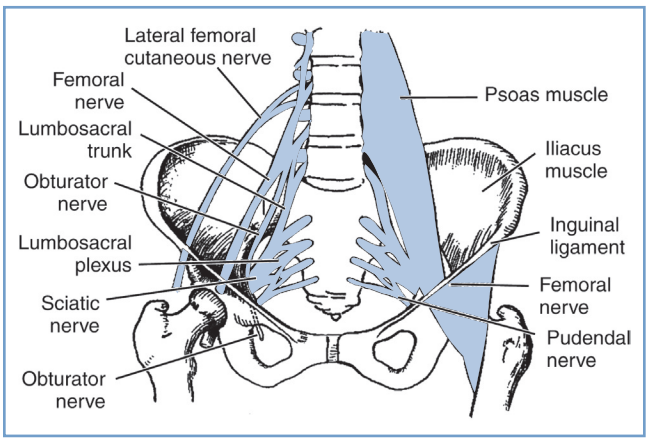

FIGURE 32-3 ■ The principal nerves in the pelvis. The lumbosacral trunk (L4 to L5) and obturator nerve (L2 to L4) are vulnerable to pressure as they cross the pelvic brim, particularly in cases of cephalopelvic disproportion. The femoral (L2 to L4) and lateral femoral cutaneous (L2 to L3) nerves are particularly vulnerable in the lithotomy position, where they pass beneath the inguinal ligament. (Adapted from Cole JT. Maternal obstetric paralysis. Am J Obstet Gynecol 1946; 52:374.)

predominantly affects ankle dorsiflexion (foot drop), compression of the lumbosacral trunk produces sensory disturbance mainly involving the L5 dermatome (see Figure 32-1). This palsy most often results from some cephalopelvic disproportion and is therefore typically seen after prolonged labor and difficult vaginal delivery.[2,3,11-14]

Obturator Nerve Palsy

The obturator nerve is susceptible to compressive injury as it crosses the brim of the pelvis or within the obturator canal (see Figure 32-3). The mother may complain of pain when the damage occurs, followed by weakness of hip adduction and internal rotation, with sensory disturbance over the upper inner thigh (see Figure 32-1). Cases are reported after both labor and cesarean delivery[20-22]; three were detected in a prospective study by Wong et al.[14] Because the nerve would appear to be in a vulnerable position, it may be that injury occurs more often than is reported, but is misdiagnosed.

Femoral Nerve Palsy

Approximately one third of the postpartum palsies detected by Wong et al.[14] were femoral nerve palsies. Dar et al.[13] detected five cases in their small population, although the symptoms were transient. The femoral nerve does not enter the pelvis and is therefore not vulnerable to compression by the fetal head but is vulnerable to stretch injury as it passes beneath the inguinal ligament. Damage may result from prolonged flexion, abduction, and external rotation of the hips during the second stage of labor and also during procedures conducted in an excessive lithotomy position.[23] The hips should therefore never remain continuously flexed during the second stage of labor. In femoral neuropathy, the nerve supply to the iliopsoas muscle is spared, so that

some hip flexion is still possible. The patient with a femoral neuropathy may walk satisfactorily on a level surface but may be unable to climb stairs; the patellar reflex is diminished or absent.

Meralgia Paresthetica

Meralgia paresthetica is a neuropathy of the lateral femoral cutaneous nerve, a purely sensory nerve also known as the lateral cutaneous nerve of the thigh. First described more than 100 years ago, meralgia paresthetica is commonly encountered in pregnancy and childbirth.[13,14] It may arise both during pregnancy, typically at about 30 weeks' gestation, and intrapartum,[14,24] in association with increasing intra-abdominal pressure. It may recur during successive pregnancies. The most likely cause is entrapment of the nerve as it passes around the anterior superior iliac spine beneath or through the inguinal ligament, where its vulnerability is increased by a large intra-abdominal mass or by retractors used during pelvic surgery. The compressive effect of edema may also contribute. Meralgia paresthetica manifests as numbness, tingling, burning, or other paresthesias affecting the anterolateral aspect of the thigh. The distribution is quite unlike that of a nerve root lesion (see Figure 32-1), yet the disturbance is commonly attributed to neuraxial blockade by those ignorant of neuroanatomy. The condition can be expected to resolve after childbirth; transient pain may be relieved by local infiltration analgesia.

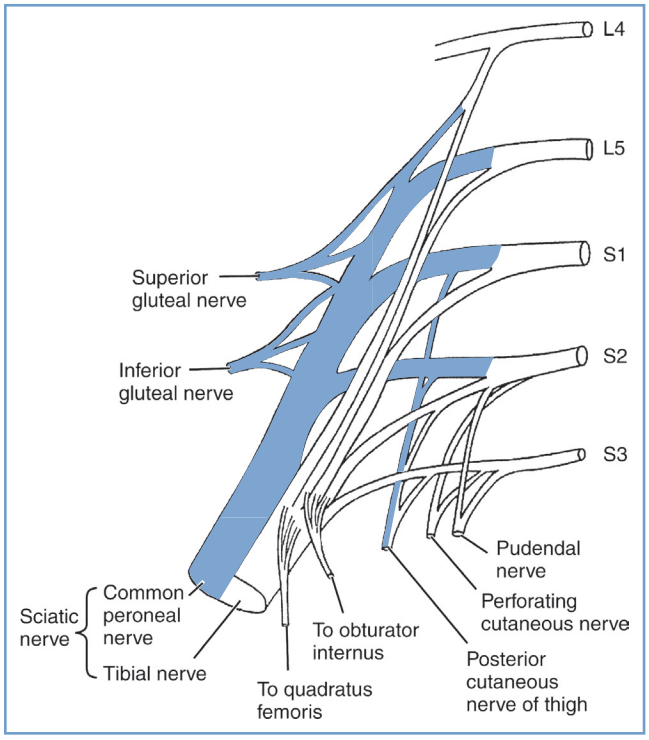

FIGURE 32-4 ■ **The sacral plexus. The dorsal divisions of the anterior primary rami are shaded.** (From Silva M, Mallinson C, Reynolds F. Sciatic nerve palsy following childbirth. Anaesthesia 1996; 51:1144-8.)

Sciatic Nerve Palsy

Sciatic nerve palsy arises from compression of the nerve, usually in the buttock. It is not commonly mentioned in surveys or generally recognized as a complication of childbirth, possibly because it is mistaken for a lesion of the lumbosacral trunk. It gives rise to loss of sensation below the knee with sparing of the medial side and loss of movement below the knee. Posterior cutaneous nerve and gluteal function are preserved, implying damage distal to the lumbosacral plexus, where the gluteal nerves branch off the sciatic nerve (Figure 32-4). It has occurred during childbirth under neuraxial blockade, either from sitting in one position too long[25] or from a hip wedge misplaced during cesarean delivery.[25-27] Hypotension may be contributory. Three cases were detected by Wong et al.[14] Despite the peripheral location of the lesions, neuraxial anesthesia cannot be exonerated, because the symptoms of nerve compression, which otherwise would have prompted a change of position, may be overlooked or wrongly attributed to local anesthetic-induced sensory blockade.

Peroneal Nerve Palsy

The common peroneal nerve is vulnerable to compression as it passes around the head of the fibula below the knee. It is also susceptible to damage while it still forms part of the sciatic nerve as it leaves the pelvis. Peroneal nerve palsy may be caused by prolonged squatting,[28] sometimes popular in "natural childbirth," by excessive knee flexion for any reason, by compression of the lateral side of the knee against any hard object, even the parturient's hand,[29] and by prolonged use of the lithotomy position. These risks are compounded by the presence of neuraxial blockade. When the peroneal nerve is damaged at the knee, there is sensory impairment on the anterolateral calf and the dorsum of the foot; foot drop may be profound, with steppage gait and weak ankle eversion, but plantar flexion and inversion at the ankle are preserved.

Compression as a Risk Factor for Peripheral Neuropathy

During pregnancy, nerve compression due to edema may be a factor in the genesis of several peripheral neuropathies, such as carpal tunnel syndrome, Bell's palsy, and meralgia paresthetica.[24,30,31] Anesthesia providers cannot be wholly absolved from responsibility for peripheral neuropathies, the signs of which may be overlooked or attributed to neuraxial anesthesia.[26,29] Adverse factors can be minimized by attention to simple rules (Box 32-2). One group of patients, those with hereditary neuropathy with liability to pressure palsy, requires particular attention. In these women even relatively brief periods of immobility or pressure on any one site must be avoided.[32,33]

POSTPARTUM BLADDER DYSFUNCTION

There are several mechanisms by which bladder function may be disturbed postpartum (Figure 32-5). In theory,

neuraxial blockade (1) may provoke the need for bladder catheterization with increased risk for infection, (2) may allow bladder distention to go undetected, and (3) on very rare occasions, may be associated with cauda equina syndrome (see later discussion). However, several postpartum studies of bladder function have found no association with neuraxial analgesia[34,35] or only a weak correlation between epidural analgesia and an increased residual volume immediately postpartum.[36] In contrast, a prolonged second stage of labor, instrumental delivery, and perineal damage have been identified as significant factors for postpartum bladder dysfunction.[34-36] In the previously described large survey of long-term symptoms after childbirth conducted in Birmingham, United Kingdom, no association was found between epidural analgesia and stress incontinence or urinary frequency.[8,37] By far the most common cause of bladder dysfunction appears to be non-neurologic. Nevertheless, it must be part of the anesthesia provider's responsibility to ensure that the bladder does not become overdistended either intrapartum or postpartum.

BOX 32-2 Safeguards to Minimize Peripheral Nerve Compression

- Be watchful for patient positioning that contributes to nerve compression, particularly with neuraxial blockade.
- Avoid prolonged use of the lithotomy position; regularly reduce hip flexion and abduction.
- Avoid prolonged positioning that may cause compression of the sciatic or peroneal nerve.
- Place the hip wedge under the bony pelvis rather than the buttock.
- Use low-dose local anesthetic/opioid combinations during labor to minimize numbness and allow maximum mobility.
- Encourage the parturient to change position regularly.
- Ensure that those caring for women receiving low-dose local anesthetic/opioid combinations understand that numbness or weakness may be signs of nerve compression; such symptoms should prompt an immediate change of position.

CENTRAL NERVOUS SYSTEM LESIONS

Lesions of the central nervous system (CNS) after childbirth have complex causes (Figure 32-6), which may be classified as **traumatic** (to nervous tissue, meninges, or blood vessels), **infective, ischemic,** or **chemical** (to nervous tissue or meninges). Anesthesia providers should bear in mind that even central lesions may have causes other than neuraxial block, the most obvious being a prolapsed intervertebral disc. Apart from sequelae of dural puncture, serious iatrogenic complications are remarkably rare.

Neurologic Sequelae of Dural Puncture

The subject of post–dural puncture headache is discussed in detail in Chapter 31. There are several other causes of severe postpartum headache, some of which have serious neurologic implications. Postpartum headache requires diagnosis first and foremost, followed by treatment that is curative rather than palliative.

Postpartum cortical vein and venous sinus thrombosis are more common than expected because of the hypercoagulable state of the blood.[38-40] Cortical vein thrombosis has been associated with dural puncture and post–dural puncture headache. Headaches caused by meningitis, venous sinus thrombosis, preeclampsia, hypertensive encephalopathy, subdural hematoma, internal carotid artery dissection, and posterior reversible encephalopathy syndrome may cause difficulty in diagnosis, particularly if they occur after epidural bolus injection, unintentional dural puncture, or administration of an epidural blood

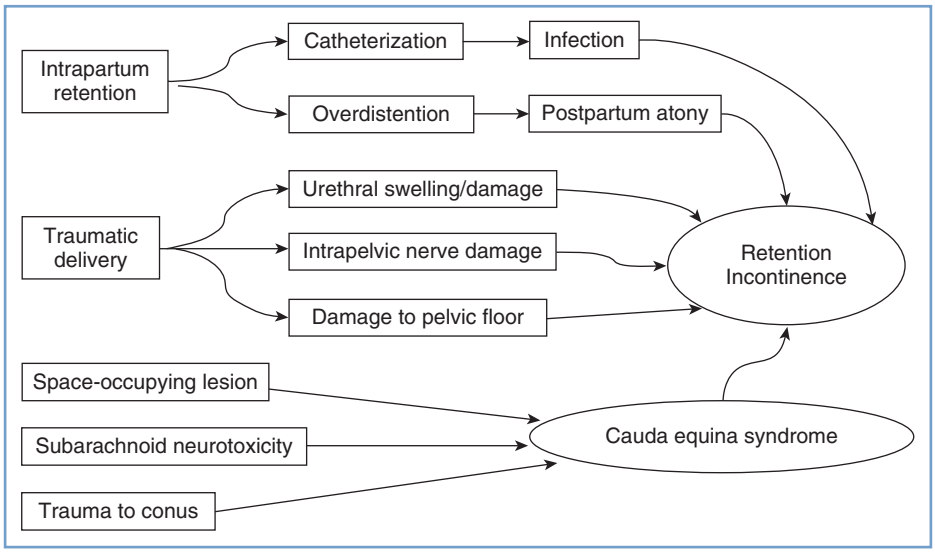

FIGURE 32-5 ■ Mechanisms by which bladder function may be disturbed after parturition.

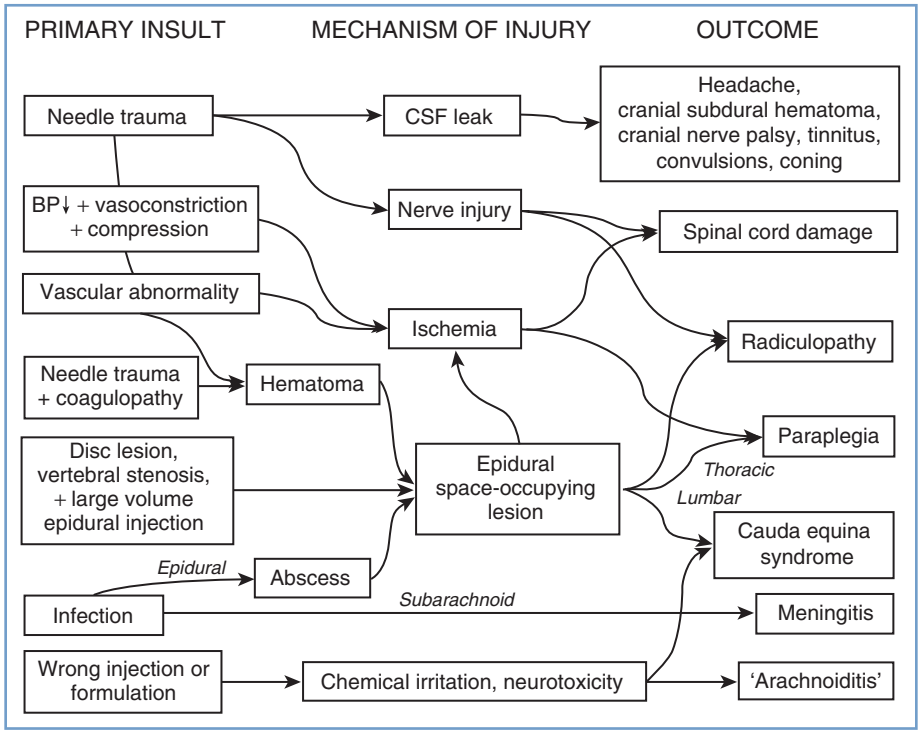

FIGURE 32-6 ■ Mechanisms by which lesions of the central nervous system may arise in parturients.

patch. Seizures may occur in patients with eclampsia, hypertensive encephalopathy, meningitis, or pneumocephalus but may also follow dural puncture or performance of an epidural blood patch.[38-49]

It is commonly assumed that headache after dural puncture will resolve spontaneously over time, but unfortunately a dural leak can persist and may occasionally have more serious consequences, including cranial nerve palsy and subdural hematoma. Neglected cerebrospinal fluid (CSF) leak has also been known to induce medullary and tentorial coning.[50] Although serious problems are more likely to occur from unintentional dural puncture with a large epidural needle and a neglected headache, they may occasionally follow deliberate dural puncture with a small-gauge spinal needle.[50]

Cranial Nerve Palsy

Major loss of CSF, usually following unintentional dural puncture with a large needle, may cause a number of cranial nerve palsies; those affecting cranial nerves VI, VII and VIII are the most frequently reported.[51-57] Because of its long course within the cranium, the **abducens nerve** (VI) is the most vulnerable. All cranial nerve palsies require prompt epidural blood patch, but even after the blood patch, recovery may be delayed. In the case of cranial nerve VIII dysfunction, tinnitus may become permanent.[56,57] Trigeminal nerve dysfunction is usually a transient effect of high spinal blockade.

Cranial Subdural Hematoma

More seriously, reduced CSF pressure may cause rupture of bridge meningeal veins and result in cranial subdural hematoma, a potentially fatal condition that has been reported sporadically over many years.[50] Palot et al.[9] found one case in 288,351 obstetric epidural procedures; in 2000, Loo et al.[4] identified eight obstetric cases, and more have been reported since.[58-62] Although commonly believed to result only from neglect of a dural puncture with a large needle or a cutting spinal needle, subdural hematoma requiring craniotomy has been reported after puncture with a small-gauge, pencil-point spinal needle[60] and after an unintentional dural puncture that had been appropriately treated with an epidural blood patch.[58] Whenever headache persists after treatment with an epidural blood patch (particularly if the headache is accompanied by altered consciousness, seizures, or other focal neurologic findings), magnetic resonance imaging (MRI) is warranted to exclude subdural hematoma, which may be fatal without urgent surgery.

One case of cranial *epidural* hematoma arose after spinal anesthesia for removal of the placenta; the hematoma occurred after a seizure.[63] Nothing was as it seemed, however; the seizure was not eclamptic, but rather epileptic, and the hematoma was not a result of spinal anesthesia.

Trauma to Nerve Roots and the Spinal Cord

Insertion of a spinal needle or epidural catheter is not infrequently accompanied by paresthesia that is sometimes painful. Although a flexible catheter is unlikely to do lasting damage to a nerve root in the epidural space, nerve roots in the subarachnoid space are more vulnerable.

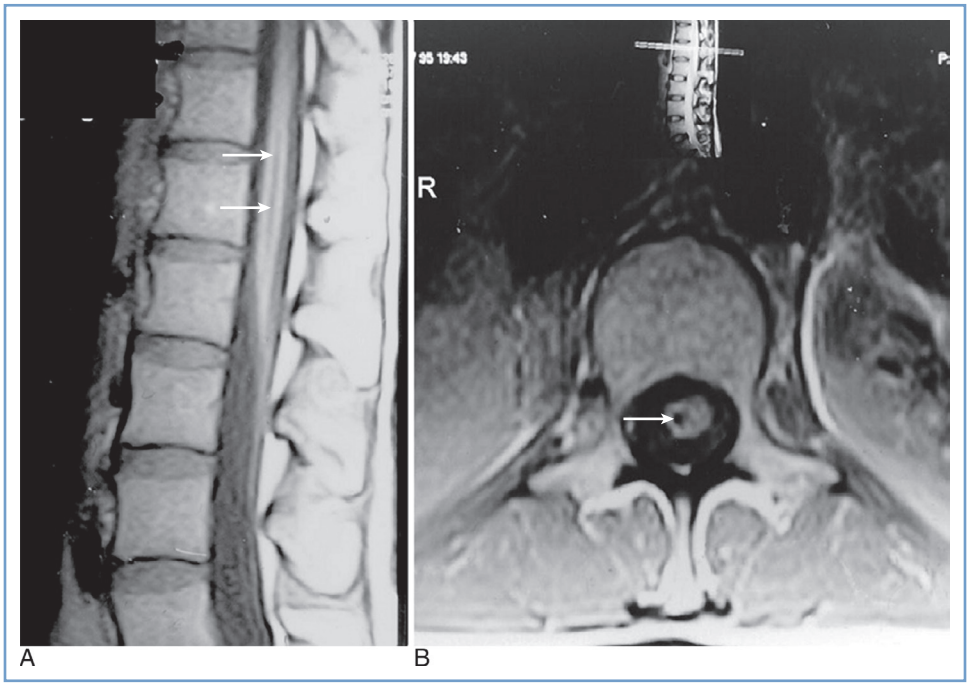

FIGURE 32-7 ■ **A** and **B,** Magnetic resonance images of a conus medullaris lesion (*arrows*). (From Reynolds F. Damage to the conus medullaris following spinal anaesthesia. Anaesthesia 2001; 56:238-47.)

Trauma Associated with Attempted Epidural Catheter Insertion

An epidural catheter may injure nerve roots either because it is inappropriately rigid[64] or because an undue length is threaded and ensnares a root.[65] A catheter seemingly threaded into the epidural space may lodge in an intervertebral foramen or even pass into the paravertebral space. In rare instances the epidural catheter and the artery of Adamkiewicz share the same foramen. If the epidural catheter is stiff enough to compress the artery within the unyielding foramen, the blood supply to the spinal cord may be impaired. This is a possible cause of anterior spinal artery syndrome. Clinical reports indicate that the condition resolves rapidly and completely if the catheter is withdrawn before permanent damage has occurred.[66,67]

Injury to the spinal cord may result from attempted identification of the epidural space in the presence of undetected spina bifida occulta or a tethered cord[68] or as a result of an unsteady grip or uncontrolled advancement of the epidural needle. Insertion of an epidural catheter in an anesthetized patient greatly increases the risk for spinal cord damage, and catastrophic injury may occur with injection of fluid into the substance of the spinal cord.[69]

Trauma Associated with Spinal Anesthesia

Insertion of a spinal needle below the level of the spinal cord sometimes causes brief radiating pain or paresthesia, which may be associated with persistent paresthesia in the same dermatomal distribution. Prolonged symptoms involving more than one spinal segment suggest damage to the spinal cord itself. Damage to the terminal portion of the cord (the conus medullaris) without intracord injection has also been reported in healthy conscious parturients receiving spinal or CSE anesthesia using a pencil-point needle.[11,16,70,71] Typically, the patient complains of pain on needle insertion before any fluid is injected, often followed by the normal appearance of CSF from the needle hub, easy injection of the local anesthetic agent, and a normal onset of neural blockade. On recovery, there is unilateral numbness, which is succeeded by pain and paresthesia in the L5 to S1 distribution and foot drop, and in some cases urinary symptoms; sensory symptoms may last for months or years. The MRI appearance is one of a small syrinx or hematoma within the conus at the level of the body of T12 on the same side as the pain on insertion and subsequent leg symptoms (Figure 32-7).[71] In the majority of cases, the anesthesia provider believed the interspace selected was L2-L3. In one patient who subsequently died of other causes, hematomyelia was confirmed at autopsy.[72] Since a spate of cases of conus damage in the 1990s, the practice of spinal needle insertion may have been modified, but an abnormally long cord may still be damaged with the best of techniques.[73]

These injuries may have occurred for the following reasons:

- Anesthesia providers, accustomed to siting epidural needles and catheters, had forgotten the precautions necessary to avoid contact with the spinal cord during dural puncture. Moreover, the option to use an *upper* lumbar interspace was sanctioned by some reputable textbooks.[74]
- Identification of lumbar interspaces was far from accurate. Studies showed that it was common to select a space that is higher than assumed by one,

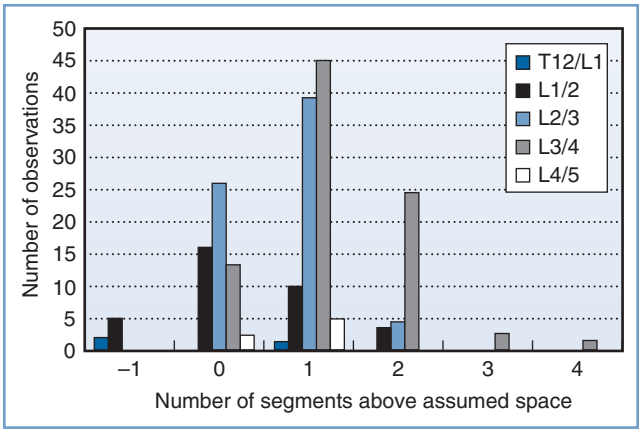

FIGURE 32-8 ■ Identification of lumbar interspaces by Oxford anesthetists. The horizontal axis shows the position of the actual interspace identified on magnetic resonance imaging, relative to the assumed space, in 200 observations. (Data from Broadbent CR, Maxwell WB, Ferrie R, et al. Ability of anaesthetists to identify a marked lumbar interspace. Anaesthesia 2000; 55:1122-6.)

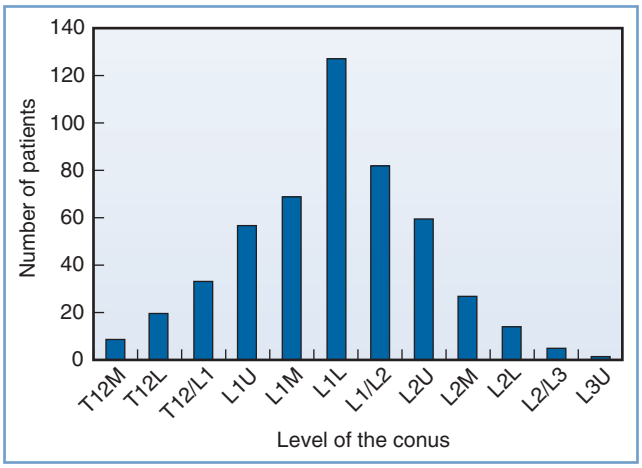

FIGURE 32-9 ■ Variation in the level of the tip of the conus medullaris assessed by magnetic resonance imaging of the lumbar spine among 504 consecutive adults. *L,* lower third of vertebral body listed; *M,* middle third of vertebral body listed; *T12/L1,* interspace between T12 and L1; *U,* upper third of vertebral body listed. (Data derived from Saifuddin A, Burnett SJ, White J. The variation of position of the conus medullaris in an adult population: a magnetic resonance imaging study. Spine 1998; 23:1452-6.)

two, or even more segments (Figure 32-8).[75,76] Anesthesia providers had little opportunity for feedback to improve their skill in interspace identification.

- Although the spinal cord typically ends level with the lower body of L1 or the L1-L2 interspace, the length varies (Figure 32-9).[77] From the L1-L2 interspace, the needle tip can easily reach the conus in 27% of men and 43% of women.[78]
- The standard method of identifying lumbar interspaces involves the use of Tuffier's line, the imaginary line joining the two iliac crests. This method can be inaccurate, however, particularly in obese or pregnant women (Figure 32-10). Moreover, even when accurately assessed, Tuffier's line is an inconstant landmark.[79] Although typically at the level of the L4 spinous process, it may lie anywhere between the L3-L4 and L5-S1 interspaces. Other means of identifying the interspace, such as counting down from C7 or finding the vertebra that is attached to the 12th rib, are tedious and of little help in obese patients.
- Pencil-point spinal needles must be advanced further than cutting needles before the orifice is within the subarachnoid space, at which point the tip may impinge on the spinal cord.

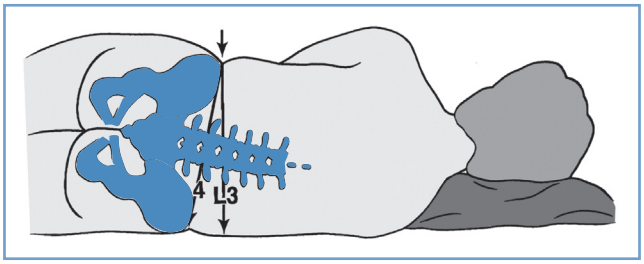

FIGURE 32-10 ■ Error that may arise if Tuffier's line is judged in a pregnant patient in the lateral position, when a line is drawn perpendicularly from the upper iliac crest rather than through both iliac crests. In pregnant patients at term, the hips may have a greater width than the shoulders. The resulting cephalad pelvic tilt may lead to an error in the cephalad direction.

BOX 32-3 Points to Remember to Reduce Risk for Damage to the Conus Medullaris during Spinal Anesthesia

- The conus medullaris reaches L2 in 27% of men but in 43% of women.
- Tuffier's line is not in a constant position relative to the spine.
- The interspace chosen is usually higher than supposed.
- The spinal needle should not knowingly be inserted above the L3 spinous process.
- Pencil-point spinal needles have at least 1 mm of "blind tip" beyond the orifice.
- Spinal needles must be advanced with gentleness and control.
- Advancement of the spinal needle should be halted immediately, and the stylet removed to check for CSF, if entry of the needle tip into the subarachnoid space is suspected.
- The procedure should be abandoned if the patient is unable to cooperate.

Medical students and residents are usually instructed to select the L4-L5 interspace for diagnostic lumbar puncture, but anesthesia providers have been more liberal in their approach. Given the inaccuracy of identification of lumbar interspaces and the variability of the position of the conus, it is both logical and prudent to insert a spinal needle below the spinous process of L3, or at least into a lower lumbar interspace, especially in women. Box 32-3 summarizes the problems and precautions in identifying lumbar interspaces and avoiding damage to the conus medullaris.

Space-Occupying Lesions of the Vertebral Canal

Space-occupying lesions of the vertebral canal include intraspinal hematomas (epidural or subdural), epidural abscess, and intraspinal tumors, any of which, within the rigid confines of the bony spinal canal, can cause dangerous compression of nervous tissue and its blood supply. Urgent laminectomy is required to avoid permanent neurologic damage. Delayed recognition and treatment (> 6 to 12 hours after onset of symptoms) may have a catastrophic outcome and grave medicolegal consequences.

Epidural analgesia in labor does not normally behave like a space-occupying lesion and produces no lasting deformation of the thecal sac on MRI.[80] Nevertheless, in the presence of vertebral stenosis or lumbar disc protrusion, a large volume injected into the epidural space may tip the balance and produce signs of nervous tissue compression that normally resolve in a few hours.[81,82]

The neurologic deficit that may arise from a compressive lesion depends on the vertebral level; lower thoracic lesions are associated with leg weakness or paraplegia, and lumbar lesions with cauda equina syndrome, including urinary retention and incontinence. Back pain (often radiating to the legs) is a common feature.

Spinal Hematoma

Spinal hematomas may be classified as epidural, subdural, or subarachnoid.[83] Keppel et al.[83] found 613 cases of spinal hematoma published in the medical literature between 1826 and 1996, 461 of which were epidural, 25 subdural, and 96 subarachnoid. Spinal hematomas were described at all vertebral levels. Twice as many patients were male as female. Many patients were elderly and only five were pregnant (details unknown). The majority of cases (44%) were spontaneous or followed minor trauma, and 22.5% were related to coagulopathy or anticoagulant treatment; only 63 cases followed lumbar puncture or neuraxial anesthesia. Of these 63 patients, 26 were without coagulopathy.

Similarly, during pregnancy and the puerperium, spontaneous epidural hematoma is reported more frequently than hematoma associated with neuraxial blockade. Loo et al.[4] found three cases (that may have been included in the earlier review[83]) and more have been reported in the 21st century.[84-88] Epidural hematoma in pregnancy associated with coagulopathy but without neuraxial anesthesia is also reported.[89,90] It has been suggested that pregnancy-induced structural changes in vessel walls, together with hemodynamic changes, may predispose to spinal hematoma.[86]

Epidural Hematoma after Neuraxial Blockade.

Incidence. Epidural hematoma after neuraxial blockade typically causes neurologic deficit in elderly patients with arterial disease; it is very rare in obstetric patients, despite the engorgement and possible fragility of epidural veins. Nine surveys, covering 1,331,171 obstetric epidural procedures,* found two cases (see Table 32-1), one without confirmatory details[7] and the other in a patient with HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome.[16] This gives an incidence of 0.150 per 100,000 epidural procedures (95% confidence interval [CI], 0.018 to 0.543). Any estimate of the incidence of epidural hematoma in the surgical population is equally meaningless because, as with obstetric cases, it depends on how assiduously neuraxial blockade is avoided in the presence of coagulopathy and also on the incidence of vessel puncture, which in turn is affected by the skill of the anesthesia provider.

Causation. Risk factors identified from comprehensive reviews of case reports include (1) difficult or traumatic epidural needle/catheter placement, (2) coagulopathy or therapeutic anticoagulation, (3) spinal deformity, and (4) spinal tumor.[4,91,92] Antiplatelet therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) is believed not to increase the incidence of neurologic dysfunction after neuraxial anesthesia,[93] although NSAIDs were involved in three cases in one survey of a mixed population.[91]

Of the five cases of epidural hematoma in obstetric patients found by Loo et al.,[4] four were without details and the other associated with coagulopathy. In the most recent analysis from the American Society of Anesthesiologists' (ASA) Closed-Claims Project database,[94] there were four cases of epidural hematoma, of which only one had coagulopathy; again, details were not provided. Two further case reports are of interest. An eclamptic patient with thrombocytopenia suffered a persistent lower limb deficit after a traumatic epidural catheter insertion using the loss-of-resistance-to-air technique.[95] Laminectomy revealed multiple bubbles and a 4-mL blood clot, the exact site of which was not stated. Such a small volume could have caused neurologic deficit only if it was subdural rather than epidural. An epidural hematoma was reported presenting *nine days* after removal of an epidural catheter that had been sited and used uneventfully for labor analgesia.[96] Apparently the only risk factors were a traumatic insertion and self-medication with ibuprofen postpartum. The coagulation assessment was normal, but the hematoma was extensive and required decompressive surgery. It is of course possible that this was a spontaneous hematoma and neuraxial analgesia was coincidental.

Both vessel damage and coagulopathy (whether inherited, acquired, or due to anticoagulation) are usually necessary to produce a hematoma large enough to cause a neurologic deficit in the parturient. Safe epidural catheter insertion in coagulopathic parturients has often been recorded, but the frequency of vessel trauma is rarely mentioned.[97-100] Vessel trauma can arise not only during insertion but also on removal of the epidural catheter.

Protective Factors. It may be that, in obstetric patients, many epidural hematomas arise but are too small to cause neurologic deficit. One factor may be the hypercoagulable status of blood peripartum. Another is the ease with which a large volume of anticoagulated blood may flow out of the unrestricting intervertebral foramina in young

*References 5,7-10,12,15,16,18

patients. Injected blood is known to disappear from the epidural space rapidly in the parturient.[80,101] During performance of an epidural blood patch, 20 mL of blood is commonly injected with impunity. Although compressive symptoms may be experienced with a volume larger than 20 mL, they do not normally presage any neurologic deficit in obstetric patients.

Subdural and Subarachnoid Hematoma. Spinal subdural hematoma has been reported in obstetric patients, one in association with an ependymoma,[4] one after spinal anesthesia and an epidural blood patch,[102] and another in a woman with preeclampsia, known vessel puncture during epidural catheter insertion, and mild coagulopathy.[103] A subarachnoid hematoma after spinal anesthesia was reported in a patient with HELLP syndrome.[104] More worryingly, one woman suffered a major subarachnoid hematoma after apparently straightforward CSE anesthesia.[105] All four patients developed cauda equina syndrome and laminectomy was required in three.

Dural puncture (with or without arachnoid puncture) is a prerequisite for subdural and subarachnoid hematoma. On the other hand, coagulopathy may *not* be a prerequisite, because the extravasated blood is confined in a small space and may compress adjacent nerve roots more readily than in the capacious epidural space.

Prevention, Diagnosis, and Management. It is clearly important to check coagulation status in an at-risk parturient not only when inserting but also when removing an epidural catheter. If neuraxial blockade is found to have been conducted in the presence of risk factors for spinal hematoma, it is an essential responsibility of the anesthesia provider to examine the lower extremities after delivery, to confirm and document the return of normal motor and sensory function, and to request subsequent checks by the nursing staff. Severe back pain and a significant delay in normal recovery or deterioration of lower extremity or bladder function signal the need for emergency imaging of the spine. If intraspinal compression is confirmed by MRI, a neurosurgical opinion must be urgently sought.

The dangers of neuraxial anesthesia in the presence of coagulopathy and anticoagulant treatment are discussed in Chapters 39 and 44.

Infection

Neuraxial infection (epidural abscess and meningitis) was identified as the most common cause of neuraxial injury in obstetric cases in the ASA Closed-Claims Project database between 1980 and 1999.[106] Infections that have been reported include epidural abscess, paraspinal and other epidural-related infection, and meningitis.

Epidural Abscess

Frequency. Epidural abscess may occur spontaneously in pregnancy and the puerperium as at other times.[4,107] An analysis of 915 reports of spinal epidural abscess published between 1954 and 1997 found that epidural blockade had been performed in only 5.5% of cases.[108] After neuraxial blockade, epidural abscess, like spinal hematoma, appears to be rare in obstetric patients. Three cases were found among 1,331,171 epidural procedures listed in nine surveys summarized in Table 32-1, a frequency of 0.225 per 100,000 (95% CI, 0.047 to 0.659). The incidence among surgical patients has been reported as 10-fold[16] to 100-fold[109] higher, with most cases arising in elderly and immunocompromised patients. A careful 4-year Australian study of 9482 obstetric patients who underwent childbirth in a center where correct sterile procedures were used found 49 epidural catheter–related infections (0.52%): 45 superficial, 2 epidural, and 2 paraspinal, giving an epidural infection rate of 21 per 100,000,[110] which was 100-fold higher than the calculated frequency from larger, but apparently less sensitive, surveys.

Sixteen case reports of well-authenticated epidural abscess after epidural analgesia in obstetric patients[111-126] have been tabulated elsewhere.[127] All cases occurred after epidural catheterization, with three as part of CSE anesthesia. None followed spinal anesthesia alone. One case was reported as meningitis but was actually an epidural abscess.[122]

One additional case report concerned a mother who developed back pain 12 months after uneventful epidural analgesia for labor.[128] After 2 further months she developed leg weakness; diagnostic lumbar puncture provoked further acute neurologic deterioration, and she was found to have an epidural abscess from the cervical to the lumbar region.

Possible risk factors identified from these cases are outlined in Table 32-2. An epidural abscess typically follows prolonged epidural catheterization, usually between 1 and 4 days in obstetric cases. Other possible etiologic factors are traumatic or difficult insertion of the catheter,[112,114,117,120] epidural administration of opioid *without* local anesthetic,[110,112,118,119] and diabetes or immunosuppression from any cause.[109,112,115,121] Inflammation at the epidural catheter entry point may presage epidural space infection.[110,114,119] In light of these reports it may be prudent to avoid prolonged epidural catheterization in the patient with other risk factors for infection.

Some practitioners have suggested that administration of an epidural blood patch necessitates prior blood culture. However, a Medline search carried out in April 2012 for "epidural abscess AND epidural blood patch" did not yield any cases, and the only recorded instance of an infected blood patch is one that appears to have entered the subcutaneous fat (see later discussion).

Clinical Presentation. Symptoms of epidural abscess typically start between 4 and 10 days after removal of the epidural catheter. The interval of 14 months cited earlier is extreme and poses the question whether the epidural catheter was causative. Severe backache (with local tenderness) and fever, with or without radiating or root pain, are the presenting features. The catheter entry point may be inflamed with some fluid leak, and a hematology screen typically reveals leukocytosis and increased C-reactive protein. Fever, neck stiffness, headache, and signs of inflammation serve to differentiate epidural abscess from hematoma. These signs and symptoms should prompt MRI, which may allow early diagnosis

TABLE 32-2 **Possible Etiologic Factors for Epidural Abscess and Meningitis**

	Epidural Abscess	Meningitis
Entry Point	Through the epidural catheter or along its track	Via the dural puncture
Usual Causative Organism	*Staphylococcus aureus*	*Streptococcus salivarius*
Possible Source of Infection	Patient's skin, tracking along the catheter entry point Epidural equipment contaminated by operator's skin Body fluids in the bed Injectate without racemic local anesthetic	Operator's mouth Talking without a mask Blood borne Vagina
Risk Factors	Prolonged catheterization Poor aseptic technique Multiple attempts at insertion, traumatic insertion No bacterial filter Lying in a wet, contaminated bed Polyurethane occlusive dressing Immunocompromise: corticosteroids, diabetes, acquired immunodeficiency syndrome	Dural puncture Labor No face mask Manual removal of the placenta Vaginal infection Bacteremia Immunocompromise?

before the onset of neurologic changes (Figure 32-11).[129] If untreated, symptoms may progress to leg weakness, paresthesias, bladder dysfunction, and other evidence of cauda equina syndrome. Blood culture may identify the organism before or without surgical drainage. Diagnostic lumbar puncture is *contraindicated.*[128]

Etiology. *Staphylococcus aureus* is the most common causative organism in cases of epidural abscess, with the occasional infection with *Streptococcus* and *Pseudomonas* species. The skin appears to be the most likely source of infection.[4]

The skin is commonly colonized by *Staphylococcus epidermidis* and other weakly pathogenic bacteria and occasionally by *S. aureus.* The highest concentration of colonies is found in the hair follicles,[130] where organisms may be protected from briefly applied disinfectants. Infectious organisms from the skin can reach deeper tissue planes via the needle track or an implanted epidural catheter to create a localized abscess in the paraspinal or epidural space. Despite all aseptic precautions, some level of detectable bacterial colonization of the epidural catheter is very common, but robust host defenses normally prevent infection. When defenses are weak and infection containment breaks down, epidural abscess formation begins.

Management. As with spinal hematoma, once neurologic signs are present, early diagnosis with prompt laminectomy is essential to recovery. In the presence of mild symptoms without neurologic changes, successful conservative treatment with antibiotics[116] and successful percutaneous needle drainage[131] of epidural abscesses have also been reported, although only laminectomy can ensure that all loculations are drained under direct vision. Prompt identification of the infectious organism(s) and directed antibiotic therapy are mandatory. Antibiotic treatment should be continued for 2 to 4 weeks.[129]

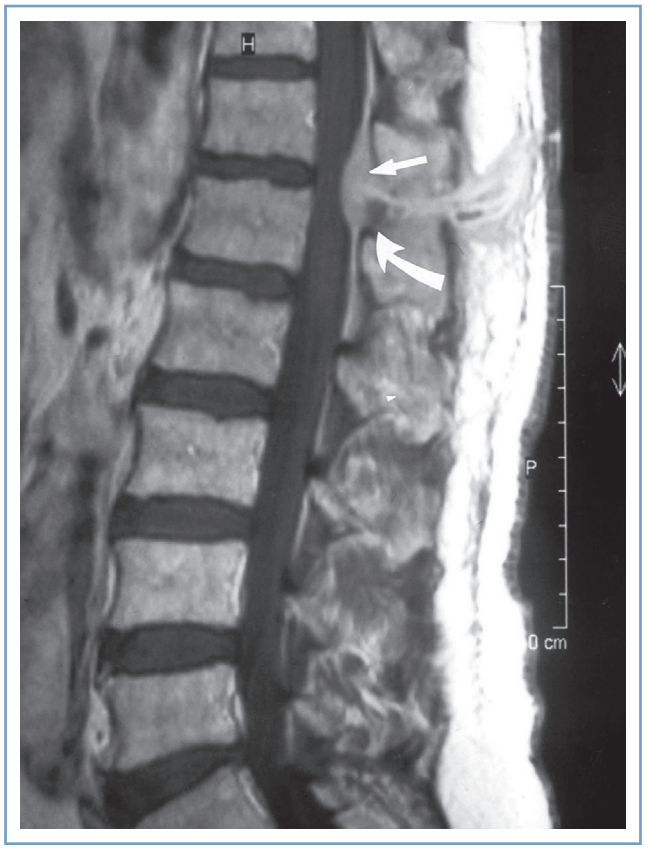

FIGURE 32-11 ■ Epidural abscess. Midsagittal T1-weighted magnetic resonance image of the lumbar and lower thoracic region, after intravenous gadolinium DTPA. Note the dorsal epidural mass located at T12-L1 (*arrows*), convex anteriorly but not compressing the conus. Normal epidural fat is flat anteriorly. (From Royakers AANM, Willigers H, van der Ven AJ, et al. Catheter-related epidural abscesses—don't wait for neurological deficits. Acta Anaesthesiol Scand 2002; 46:611-5.)

Epidural-Related Infection

Paraspinal abscess and osteomyelitis after epidural analgesia[132-137] and discitis after spinal blockade[138] have been reported in obstetric patients. Catheter-site inflammation is relatively common with prolonged postoperative epidural analgesia.[110,139] One report described both a subdural abscess after CSE anesthesia and infection in the subcutaneous tissues after an apparently misplaced epidural blood patch.[140]

TABLE 32-3 **Case Reports of Post–Dural Puncture Meningitis Among Obstetric Patients**

	References: First Author, Year of Publication	No. of Cases	Organism; Comments
Spinal Analgesia for Labor (11 cases)	Gibbons, 1969[142]	3	Case cluster, no growth, "chemical meningitis," CSF findings suggested bacterial etiology
	Phillips, 1970[143]	1	No growth, CSF findings suggested bacterial etiology
	Corbett, 1971[144]	3	Case cluster, single anesthesiologist, unsterile technique, *Pseudomonas aeruginosa*
	Newton, 1994[145]	1	*Streptococcus salivarius*
	Lurie, 1994[146]	1	*Streptococcus viridans*
	CDC, 2010[147]	2	Case cluster, single anesthesiologist, *Streptococcus salivarius,* one death
Spinal Anesthesia for Cesarean Delivery (11 cases)	Bugedo, 1991[148]	1	Signs of bacterial meningitis, labor unknown
	Lee, 1991[149]	1	No growth, CSF findings suggested bacterial etiology, in labor, three attempts at epidural analgesia
	Stallard, 1995[150]	1	No growth, CSF findings suggested bacterial etiology, in labor, three attempts at epidural analgesia, spinal anesthesia at same interspace
	Donnelly, 1998[151]	1	No growth, CSF findings suggested bacterial etiology, membranes ruptured
	Thomas, 2001[152]	1	Preeclampsia, labor unknown, patient died
	Rodrigo, 2007[153]	6	*Aspergillus*, five elective cesarean deliveries, one in labor, three patients died
Spinal Anesthesia for Retained Placenta (1 case)	Roberts, 1990[154]	1	Two attempts at spinal anesthesia, no growth, CSF findings suggested bacterial etiology
CSE Analgesia for Labor (9 cases)	Harding, 1994[155]	2	No growth, CSF findings suggested bacterial etiology
	Cascio, 1996[156]	1	*Streptococcus salivarius* (dismissed as contaminant)
	Bouhemad, 1998[157]	1	*Streptococcus salivarius*
	Duflo, 1998[158]	1	*Streptococcus viridans*
	Vernis, 2004[159]	1	One case in the course of a randomized trial
	CDC, 2010[147]	3	Cluster, single anesthesiologist, *Streptococcus salivarius*
Unintentional Dural Puncture in Labor (3 cases)	Berga, 1989[160]	1	*Streptococcus sanguis*
	Sansome, 1991[45]	1	No growth, CSF findings ambivalent
	Baer, 2006[141]	1	*Staphylococcus simulans* and *Streptococcus salivarius;* patient died
"Uncomplicated" Epidural Analgesia for Labor (6 cases)	Neumark, 1980[161]	1	Coxsackievirus B (?chance event)
	Ready, 1989[162]	2	1 *Streptococcus uberis* 1 *Streptococcus faecalis* (epidural inflammation)
	Davis, 1993[163]	1	Group B streptococcus
	Goldstein, 1996[164]	1	Group B streptococcus
	Choy, 2000[165]	1	Two attempts at epidural analgesia, no growth, CSF findings suggested bacterial etiology, patient died
Total (41 cases)	35 known dural punctures 5 elective cesarean deliveries, all after tsunami 7 deaths		

CSE, combined spinal-epidural anesthesia; *CSF,* cerebrospinal fluid.

A variety of organisms have been associated with epidural-related infections.[127] All such conditions are associated with back pain and signs of inflammation and pose a threat of spread to the epidural space. Moreover, paraspinal abscess may itself cause neurologic deficit.[132,133]

Meningitis

Although not consistently included in surveys, post–spinal meningitis has become a cause for concern[141] and is an important serious neurologic complication of neuraxial labor analgesia. It was suspected in two cases in the prospective survey of 108,133 epidural procedures and 14,865 spinal anesthetic procedures by Scott and Tunstall,[8] although the specific type of anesthesia was not stated. Palot et al.[9] reported three cases of meningitis among 288,351 obstetric epidural procedures but did not state whether they followed dural puncture. One case was identified in a survey of spinal and CSE anesthesia (1/42,000 procedures).[11] A recent review found an incidence derived from surveys of spinal and CSE anesthesia in obstetrics of 1 in 39,000.[127] Table 32-3 summarizes 41 published reports of post–spinal meningitis in obstetric patients.[45,141-165]

Causative Organisms. Community-acquired meningitis may occur in pregnancy as at other times. It is commonly caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*, while occasional cases due to tuberculosis, several β-hemolytic streptococci, and viruses are also reported in pregnancy. Post–spinal meningitis, by contrast, is most commonly caused by streptococci of the viridans type (α-hemolytic streptococci such as *S. salivarius*, *S. sanguis*, and *S. uberis*) (see Table 32-3). These organisms are found in the upper airway and the vagina. *Pseudomonas* meningitis has also

been reported.[144] Neither *Pseudomonas* nor α-hemolytic streptococci are normally virulent; they do not, for example, cause wound infection, but they thrive in a watery medium and flourish if introduced into CSF. In several early cases (before the use of the polymerase chain reaction), no organisms were grown on culture and chemical meningitis was diagnosed. In most cases, however, there were features of bacterial meningitis, including low CSF glucose concentration. Of note, streptococci of the viridans type do not grow readily in conventional culture media and may well have been present but not detected.

Risk Factors. Dural puncture is probably a prerequisite for iatrogenic meningitis. A retrospective review of surgical patients in one hospital in Brazil found three cases among 38,128 patients receiving spinal anesthesia (1/12,709) and none among 12,822 patients receiving other types of anesthesia.[166] Among 73 women with β-hemolytic streptococcal infections in the puerperium identified in a survey from Iowa,[167] the only woman who suffered meningitis had received spinal anesthesia. In normal circumstances, the blood-brain barrier (the endothelial lining of the capillaries, which are continuous with tight junctions and no pinocytotic vesicles) protects the CNS against weakly pathogenic bacteria. The dura mater should not be confused with the blood-brain barrier, but dural puncture is commonly associated with vascular trauma,[168] which allows blood to enter the CSF.

Of the 41 published cases of puerperal post–spinal meningitis for which details are available (see Table 32-3), 35 occurred after known dural puncture. Among the six cases that followed apparently uncomplicated epidural analgesia, one was viral and may have been a chance event,[161] one was probably an epidural abscess,[162] and two were blood borne from vaginal infection due to group B streptococcus.[163,164] One case, sadly fatal, followed multiple attempts at epidural catheter insertion.[165] Uncomplicated epidural catheterization itself is unlikely to increase the risk for puerperal meningitis. Although it is used more commonly than spinal analgesia during labor, case reports of meningitis after spinal analgesia far outnumber those after epidural analgesia. A causative relationship between epidural catheterization and meningitis after vaginal delivery may be attributed to unrecognized dural puncture, which may occur during multiple attempts at epidural catheter insertion or even with apparently uncomplicated catheter insertion.

Labor may also be a risk factor for meningitis. The great majority of parturients with nosocomial meningitis had labored (see Table 32-3). In the latest survey from Sweden, where spinal and CSE anesthesia are rarely used during labor, meningitis was found only among surgical patients.[16] Meningitis appears surprisingly rare after elective cesarean delivery, despite the extensive use of spinal anesthesia in this context. The five exceptions were among six unusual cases in Sri Lanka, which resulted from *Aspergillus* contamination of syringes that had been donated after the 2005 tsunami and stored in an unsuitable warehouse at 41°C and 75% humidity.[153]

The possible reasons why meningitis is reported more commonly in laboring women than among those undergoing elective cesarean delivery are as follows:

1. The vagina may be colonized by streptococci, and vaginal delivery is commonly followed by mild bacteremia. Thus labor, with its potential for vaginal trauma, is clearly an important risk factor. Unlike vaginal delivery, elective cesarean delivery is not normally associated with streptococcal bacteremia.
2. For elective cesarean delivery, spinal anesthesia is administered in the operating room, which is a cleaner environment than the labor and delivery room.
3. The anesthesia provider is more likely to wear a mask in the operating room.
4. The nonlaboring patient is not thrashing about in a (possibly) contaminated bed.
5. An antibiotic is usually administered immediately before or after cesarean delivery.

Infection at a remote site may also be a risk factor for meningitis. Bacteremia has been detected in approximately 8% of women with chorioamnionitis,[169] although two small studies found no evidence of spinal infection among 12 women with bacteremia who received epidural blockade without antibiotic treatment.[170,171] Although such negative findings are reassuring, they are not conclusive and do not apply to spinal anesthesia. Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) should not be regarded as contraindications to neuraxial analgesia, in view of the early presence of the virus within the CNS (see Chapter 45).[172] Performing an epidural blood patch in the presence of bacteremia is also a theoretical risk for both meningitis and abscess, but neither has been reported in this context. Neuraxial analgesia in the presence of maternal fever is discussed in detail in Chapter 37.

Other risk factors for meningitis include faulty technique, in particular failure to wear a mask (see later discussion). Manual removal of the placenta is a postulated risk factor for meningitis, and one such case has been reported,[154] although given the popularity of spinal anesthesia for this indication, one would perhaps expect a higher frequency. It may be postulated that use of the CSE technique, with the presence of a foreign body next to a dural hole, may increase the risk for meningitis.

Clinical Presentation and Management. Fever, headache, photophobia, nausea, vomiting, and neck stiffness are typical symptoms of meningitis; when they are accompanied by confusion, drowsiness, and Kernig's sign (inability to straighten the knee when the hip is flexed), meningitis should be strongly suspected. The onset of nosocomial meningitis may be 12 hours to a few days after delivery. Diagnostic lumbar puncture (best avoided in the presence of raised intracranial pressure or suspicion of epidural abscess) shows increased CSF pressure, increases in protein level and white blood cell count (mainly polymorphonuclear leukocytes in patients with bacterial meningitis), and a CSF glucose concentration that is lower than that in the blood. Because of the nature of the *S. viridans* group, culture on plates rather than in broth may have negative results, particularly if antibiotics have been given, or the growth may be assumed to be a contaminant.[141] Treatment with an appropriate antibiotic should not await the microbiology results and should result in full recovery.[4] Vancomycin and third-generation

BOX 32-4 Procedures to Decrease the Risk for Infection after Neuraxial Anesthesia

- Avoid dural puncture unless indicated:
  - During labor.
  - In the presence of known genital tract infection.
- Wear an effective mask; wear a new mask for each patient.
- Remove hand jewelry and watches, and wash hands with an alcohol-based scrub solution.
- In the United Kingdom, a gown is worn for epidural catheter insertion.
- Don sterile gloves in a sterile manner.
- Paint the patient's skin with chlorhexidine in alcohol solution, following the package instructions, and allow the skin to dry after application.
- Make sure the back is securely draped.
- Avoid contaminating any equipment that is used in the procedure, and minimize touching parts of the equipment that will enter the patient.
- After the procedure, apply a suitable dressing to the catheter entry point.
- Use a bacterial filter with an indwelling epidural or spinal catheter if the catheter will remain in place longer than several days.
- Do not leave an epidural catheter *in situ* after delivery if:
  - The dura has been punctured during labor.
  - Multiple attempts at insertion were made.
  - There is any evidence of sepsis.
  - Immunosuppression is present for any reason.
- If there is concern about sepsis or contamination, administer appropriate antibiotics.

cephalosporins have been recommended as first-line treatment.[166] The treatment regimen should be adjusted according to results of culture and sensitivity testing.

Prevention of Intraspinal Infection after Neuraxial Anesthesia

Measures to prevent intraspinal infection are described in Chapter 12 and summarized in Box 32-4. Means of preventing meningitis and epidural abscess are not identical, because abscess usually follows epidural catheterization and is commonly caused by *S. aureus*, which enters via the skin, whereas meningitis classically follows dural puncture, is caused by vaginal or nasal organisms, may be bloodborne, and is usually caused by streptococcus and never by *S. aureus*.

Because adverse outcomes are rare, the use of sterile precautions can rarely be supported by evidence from randomized trials. The components of good sterile technique should be guided by common sense and the best available indirect evidence. It is notable that in many case reports of neuraxial infection, sterile precautions used in initiating neuraxial blockade receive no mention.

A practice advisory published in 2010 by the ASA Task Force on Infectious Complications Associated with Neuraxial Techniques[173] concerns prevention, diagnosis, and management of infectious complications. Certain key aspects are discussed here.

Mask. Several surveys indicate widespread disregard of surgical masks for infection control during neuraxial block administration.[166,174,175] Among case reports of nosocomial meningitis, a mask was not mentioned[143,154,160-162] or was not worn ("as it is of doubtful value"[149] or because it "contributes little to prevent infection during spinal or epidural anesthesia,"[146] or is not considered part of "full aseptic technique"[163]).

Confusion has arisen because randomized trials have demonstrated that omission of masks in the operating room does not increase the occurrence of *wound* infection.[176] This is not surprising, however, because organisms from the upper airway do not cause wound infection, but they certainly do cause nosocomial meningitis. The effect of wearing a mask in the prevention of such rare complications cannot readily be ascertained by a randomized controlled trial. Nevertheless, the obvious value of masks in reducing the dispersion of bacteria from the mouth and nose has been well demonstrated.[177,178] A mask is an essential part of aseptic precautions that should be taken for neuraxial needle and catheter insertion.[141,173] Masks must be of good quality, preferably fiberglass and not simply woven linen or paper, not allowed to become wet, and changed for each patient.[167]

Sterile Gown. Although undeniably part of "full aseptic precautions" employed by surgeons, a sterile gown is rarely worn for spinal needle placement. For insertion of an epidural catheter, a gown is commonly worn in the United Kingdom, although this is not the typical practice in the United States or France. The value of wearing a gown is not supported by good evidence, but it can only be safer than not doing so. During epidural catheter insertion by a novice who is not wearing a gown, the catheter may inadvertently come into contact with the skin of the provider's upper arm or unsterile clothing. This occurrence may facilitate entry, via the catheter, of skin organisms that may cause epidural abscess.

Sterilizing the Skin. Evidence from laboratory and clinical studies shows that chlorhexidine in 70% alcohol consistently outperforms povidone-iodine for skin disinfection.[130,139,179] The concentration of chlorhexidine used varies from 0.5% to 2%. It is superior in speed of onset and duration of action, it is less likely to provoke a skin reaction, and unlike povidone-iodine it is effective in the presence of blood or pus, it stays sterile in the container, and bacterial resistance to it is unlikely.[127] Alcohol provides the rapid onset, and chlorhexidine provides the longer duration of action.

The one question over its use concerns that of neurotoxicity. Neither chlorhexidine nor iodine is licensed for skin sterilization before neuraxial block administration. The risk for infectious complications, however, far outweighs that for neurotoxicity, and the superiority of chlorhexidine as an antiseptic should be paramount. It is appropriate, nevertheless, to take precautions, such as using the lowest effective concentration and not allowing it to come into contact with solutions or equipment that will enter the patient's neuraxis. Use of a spray can overcome this concern; otherwise the chlorhexidine container must be removed from the cart before equipment for

neuraxial insertion is deployed. The ASA practice advisory states that the aseptic technique for neuraxial procedures should include use of chlorhexidine in alcohol with adequate drying time.[173]

Maintaining Sterility of the Epidural Catheter, Its Contents, and the Entry Point. The entry point of the epidural catheter clearly needs to be protected from contamination by a suitable dressing.[180] For prolonged analgesia, racemic bupivacaine may be safer than an opioid alone or the pure L-isomers of local anesthetics, which may permit bacterial growth in the solution.[127] Although it would seem logical, there is no evidence to support or discourage the use of a bacterial filter during a short-term (1 to 2 days) epidural infusion.[180] Prolonged catheterization is best avoided after dural puncture, whether unintentional or deliberate, and when sepsis or immunocompromise is present or suspected.

Vascular Disorders

Ischemic Injury to the Spinal Cord

Ischemic injury to the spinal cord is typically seen in elderly patients after epidural or spinal anesthesia, often with an epinephrine-containing solution, and indeed after general anesthesia with accompanying hypotension. It is rare in the obstetric population, in whom arterial disease is unusual and hypotension is treated aggressively.

The blood supply to the spinal cord depends on a single anterior spinal artery and bilateral posterior spinal arteries. The arteries arise from the circle of Willis and receive reinforcements during their descent in the spinal canal. The posterior spinal arteries receive regular contributions from radicular arteries, but the single anterior spinal artery, which supplies the anterior two thirds of the spinal cord, receives only sporadic reinforcement. **Anterior spinal artery syndrome**, which may result from arterial compression or hypotension, is characterized by a predominantly motor deficit, with or without loss of pain and temperature sensation, but with sparing of vibration and joint sensations, which are transmitted in the posterior columns. The condition has been reported among obstetric patients with particular risk factors (see later discussion).[4,7,181] One report described a series of accidents.[182] A parous woman received epidural analgesia with lidocaine, then bupivacaine with epinephrine followed by 2-chloroprocaine, when she required urgent cesarean delivery. Hypotension due to blood loss from a placenta previa *and* a ruptured uterus was followed by typical irreversible anterior spinal artery syndrome. Hypotension due to blood loss is likely to cause a greater degree of ischemia than that due to vasodilation, and the use of epinephrine may have contributed to the adverse outcome in this case.

Chemical Injury

The Epidural Space

The epidural space is remarkably tolerant of foreign and potentially neurotoxic substances because of two protective factors. First, vascular uptake and outward flow via the intervertebral foramina remove a large proportion of solutions deposited in the epidural space. Second, nerve roots within the epidural space are protected by a cuff of dura and arachnoid as well as pia mater. Severe neuraxial damage occurs only when these defenses are overwhelmed either by gross overdose or if there is unintentional contamination of the subarachnoid space. There are many case reports of unintentional epidural injection of the wrong substance, including the following:

1. **Vasopressors** (**ephedrine** and **metaraminol**). Epidural administration resulted in severe hypertension.[183]
2. **Potassium chloride**. At least four well-documented cases have been reported.[184,185] All the patients had profound motor and sensory block with pain or depolarizing spasms. Only one, who received the largest epidural dose (15 mL of 11.25% KCl), remained permanently paraplegic.[185]
3. **Other potentially noxious substances**. Administration of an unknown substance, possibly paraldehyde, given in error as an epidural bolus injection during labor, resulted in permanent painful quadriplegia and the largest monetary award for damages in the United Kingdom at that time.[186] Unintentional misconnections of intravenous and epidural infusion systems have led to large-volume epidural infusions of potentially harmful substances, including total parenteral nutrition solutions with a high osmolality[187] and ranitidine in a phenol-containing solution.[188] Fortunately, in most cases of this type of drug error, neurologic sequelae have not been reported.

In summary, with a few exceptions, the epidural space appears to be merely an exotic means of systemic administration of analgesia/anesthesia. Nevertheless, the possibility of occult dural puncture means that unintentional administration of a potentially neurotoxic substance (e.g., traces of alcohol, antioxidant, or preservative) may migrate into the subarachnoid space. Vigilance and systems to avoid these errors are mandatory.

The Subarachnoid Space

The subarachnoid space, with its poorly protected nerve roots and direct communication with intracranial structures, presents a greater risk than the epidural space for adverse outcome after unintentional injection of toxic substances. Intrathecal potassium does not merely maim, it can kill.[189] Irritant solutions may cause neurotoxicity and arachnoiditis (see later discussion). Transient neurologic syndrome (see later discussion) may be a minor and transient form of neurotoxicity. Neurotoxicity may manifest as cauda equina syndrome or, if more extensive, as paraplegia or quadriplegia.

Nerve roots within the subarachnoid space are highly vulnerable to chemical damage, particularly the sacral roots, which are poorly myelinated. Therefore, neurotoxicity associated with a small-volume intrathecal injection classically produces **cauda equina syndrome.** For example, in 1937, 14 cases of severe cauda equina syndrome were reported after spinal anesthesia using a

solution called "heavy duracaine," a mixture (in 15% ethanol) of procaine, glycerin, and gliadin or gum acacia, which presumably was added in an attempt to prolong the action of procaine.[190] In the 1940s and 1950s in the United Kingdom, spinal injection of 10 mL of hypo-osmolar dibucaine was associated with paraplegia, but whether the paraplegia resulted from disturbance of the intrathecal milieu or contamination with phenol is argued.

More recently, there were numerous reports of cauda equina syndrome after intrathecal injection of lidocaine (all types of administration, both intended and unintended, most commonly hyperbaric 5%)[191-193] and occasionally after intrathecal administration of other local anesthetics.[194,195] None of these cases involved obstetric patients. In all cases, other causes of neurologic deficit (trauma, ischemia, infection, compression, contamination, and adverse positioning) were excluded. An upper safe dose limit for intrathecal lidocaine of 60 mg[192,196] has been recommended. Hyperbaric lidocaine is not available in either Australia or the United Kingdom. The various risk factors for neurotoxic damage are summarized in Box 32-5.

Conus damage and **cauda equina syndrome** may appear similar. Although conus damage may involve upper motor neuron signs, these are not always present, and both conditions may have unilateral or bilateral features.[71] However, the causation is different. Whereas conus damage may result from ischemia or trauma, cauda equina syndrome typically results from either compression or chemical damage within the lumbar spinal canal.

Transient Neurologic Syndrome

Transient neurologic syndrome (also called transient radicular irritation) is not associated with any detectable neurologic deficit, but the distribution of pain in the back, buttocks, and thighs mirrors the distribution of nerve damage in cauda equina syndrome sufficiently to support the theory that the nerves are indeed irritated by a noxious intrathecal injection. Like cauda equina syndrome, it follows spinal anesthesia, most commonly with lidocaine. Moreover, other risk factors for cauda equina syndrome and transient neurologic syndrome are similar (see Box 32-5), although transient neurologic syndrome may be less dependent on lidocaine dose or the presence of a vasoconstrictor.[197] Transient neurologic syndrome occurs more than four times more frequently with spinal lidocaine than with other local anesthetics.[198] It is, however, much more common in surgical than obstetric patients, with a median frequency, according to one review, of 22%.[197] Parturients are not exempt from transient neurologic symptoms, with reported frequencies of 0%,[199] 4.2%,[200] 5.3%,[201] and 8.9%.[202]

BOX 32-5 Risk Factors for Chemical Damage to the Cauda Equina

- Poor spread of local anesthetic:
  - Block failure, followed by repeat injection
  - Fine-gauge or pencil-point needle
  - Microspinal catheter
  - Continuous infusion
  - Hyperbaric solution
  - Lithotomy position
- Unintentional intrathecal injection of a large volume intended for the epidural space
- Incorrect formulation, with unsuitable preservative or antioxidant
- Intrathecal injection of lidocaine, particularly 5% (also tetracaine or dibucaine?)

Arachnoiditis

Arachnoiditis is a disastrous condition, usually with a delayed onset of permanent quadriplegia. It is extremely rare, and it has not been detected in any surveys of neurologic sequelae of obstetric neuraxial blockade. Among parturients, chronic adhesive arachnoiditis of chemical origin has arisen after unintentional intrathecal injection of a large dose of 2-chloroprocaine with antioxidant and preservative intended for the epidural space,[203] while seven cases occurred in Miami after epidural analgesia for childbirth with 2% lidocaine, probably with preservative.[204] Six cases were reported among Italian surgical patients after apparently standard epidural anesthesia with bupivacaine and/or mepivacaine, usually with epinephrine.[205] The local anesthetic agents, however, were obtained from multidose vials containing parabens as preservative, and the glass syringes used for loss-of-resistance identification of the epidural space had been washed in detergent. With earlier publications it is not always possible to distinguish the cause of arachnoiditis, but it seemed to appear in clusters, suggesting that there may have been shortcomings in anesthetic technique. In a more recent single case in the United Kingdom, a woman suffered severe arachnoiditis after spinal anesthesia for elective cesarean delivery.[206] Her skin had been cleaned with iodine and then chlorhexidine in alcohol and allowed to dry. It was unclear whether the tray containing antiseptic solutions was removed before the rest of the procedure. Because of pain during attempted insertion of the spinal needle, the skin was infiltrated at least three times with lidocaine before intrathecal bupivacaine was given. Shortly thereafter she became disturbed and experienced a severe headache, so she was given general anesthesia for the operation. Postpartum she developed obstructive hydrocephalus and extensive adhesive arachnoiditis. The judge determined that, on balance of probabilities, there must have been contact in some way between the chlorhexidine and the local anesthetic solution.

Vulnerable Patients

Various conditions may render some women more vulnerable than normal to neurologic injury precipitated by neuraxial anesthesia. The following discussion of conditions is not exhaustive.

Vertebral Abnormality

Skeletal abnormalities involving the spine, including congenital anomaly, trauma, and back surgery, can make

epidural or spinal needle insertion difficult. Patients with spina bifida are at risk for accidental dural puncture and nerve root damage unless the needle is inserted above the defect. Those with tethered cord syndrome are at risk for cord damage if spinal or epidural needle insertion is attempted at a vertebral level that would normally be expected to be below the conus.[68] Occasionally, a low-lying conus may be present without any premonitory signs.[73] Pressure from spinal stenosis or prolapsed intervertebral disc, coupled with a large-volume epidural injection, may result in spinal cord compression and neurologic deficit.[82]

Vascular Abnormalities

Vascular disease and malformation are risk factors for spinal cord ischemia, hematoma, and compression. The major supply to the lumbar enlargement of the spinal cord is the artery of Adamkiewicz, a unilateral structure that typically arises from the lower thoracic or upper lumbar portion of the aorta between T9 and L2. Compression of this single vessel may therefore jeopardize the blood supply to the lower cord in susceptible individuals. In 15% of individuals, a secondary blood supply to the spinal cord that ascends from the internal iliac arteries[207] assumes a major role. These ascending arteries lie close to the lumbosacral trunk and are, in theory, vulnerable to pressure from the fetal head or damage by obstetric instrumentation, thus causing conus ischemia.

An **arteriovenous malformation** is an obvious cause for concern for the obstetric anesthesia provider.[208] Small arterial feeders from a segmental intercostal artery supply dilated serpiginous epidural veins that may extend over many segments of the spinal canal.[209] The resulting hemangioma raises the pressure on epidural veins and reduces spinal cord blood flow. Oxygen delivery to local tissues is reduced, and the risks of spinal hematoma or ischemic damage and compression are increased. Pregnancy and epidural analgesia have been known to precipitate paraplegia in previously asymptomatic patients[210,211]; aortocaval compression, a large blood volume, and a large epidural injection (which may cause severe pain) all increase epidural pressure.

The preanesthesia examination should include inspection of the back for cutaneous angiomas or macular areas of skin discoloration, which may suggest the presence of an underlying spinal angioma at the same segmental level. Because spinal cord capillary flow is compromised in the drainage area of an arteriovenous malformation, systemic arterial pressure should be kept close to normal throughout the peripartum period, regardless of anesthetic technique.

Spinal Tumor

Epidural blockade has been reported to precipitate neurologic symptoms in the presence of previously undiagnosed spinal tumors. Spinal tumors also predispose to spinal hematoma after neuraxial blockade,[4] and epidural analgesia may precipitate extreme pain.[212]

Coagulopathy or Anticoagulation

The risk for neuraxial procedures in patients with a preexisting coagulopathy or anticoagulation therapy is discussed earlier in this chapter and also in Chapters 39 and 44.

Immunocompromise

The majority of cases of epidural infection that have been reported in surveys involve elderly patients with immunocompromise.[16,109] This topic is covered in an excellent review.[213] It is advisable to avoid prolonged epidural catheterization in immunocompromised patients.

Preexisting Neurologic Disorder

Relapse rates in patients with multiple sclerosis are increased after delivery, and the fear is that neuraxial blockade will be blamed.[214] It has been postulated that spinal anesthesia may worsen demyelinating conditions, although surveys are inconclusive.[215] If affected nerve roots are indeed at higher risk for neurotoxicity, epidural anesthesia may be safer than spinal anesthesia. Indeed, some anesthesia providers prefer epidural or even general anesthesia over spinal anesthesia in women with multiple sclerosis. It is clearly important to document neurologic status and to discuss relapse rates with the mother before and after any anesthetic intervention.

Patients with hereditary neuropathy with liability to pressure palsy are particularly sensitive to compression neuropathy during the course of labor and delivery.[32,33,216]

It is postulated that patients with preexisting peripheral neuropathies may be more susceptible to nerve injury when exposed to a second insult, the so-called *double crush phenomenon*.[215] To explore whether neuraxial anesthesia represented such an insult, Hebl et al.[215] reviewed the charts of 567 patients with peripheral neuropathies who had spinal or epidural blockade, including 12 obstetric patients. There were two instances of worsening neurologic status, both in elderly diabetic patients. There were no control patients, but clearly, if there is a risk that neuraxial anesthesia will exacerbate a neuropathy, it is very small.

Diabetes

Diabetic patients are vulnerable to neurologic injury for three reasons. They are susceptible to infection, they may have vascular disease, and they may have a peripheral neuropathy. Diabetic patients are at increased risk for epidural abscess, either catheter-associated or spontaneous.[16,109] Anterior spinal artery syndrome has also been described in diabetic parturients,[181] and worsening neuropathy has been observed in diabetic surgical patients.[215]

RISK MANAGEMENT AND FOLLOW-UP

High-risk women should be referred to the obstetric anesthesia clinic during pregnancy, so that an anesthesia

provider can obtain a thorough history, examine the patient, organize consultations or imaging studies as needed, and plan the anesthetic strategy. The recommended points to explore during the history and physical examination are summarized in Boxes 32-6 and 32-7.

In addition to minimizing risk by adopting good and safe practices, vigilance must be extended postpartum to detect, diagnose, and treat any disorders that may arise. Early hospital discharge presents a problem in the detection of post–dural puncture headache and space-occupying lesions, both of which require urgent assessment and treatment. It is important that those caring for women in the puerperium are taught to look for signs of neurologic pathology and that the women themselves, once home, are taught to recognize postanesthesia symptoms and to contact an anesthesia provider if they experience them.

BOX 32-6 Topics to Explore in the Preanesthesia History

- Allergies or recreational drugs
- Diabetes or cardiovascular disorder
- Previous spinal or epidural anesthetics (What was the outcome?)
- Preexisting neurologic signs or symptoms (e.g., sciatica, leg weakness)
- Skeletal abnormality or back surgery
- History of trauma or automobile accident (Is it under litigation?)
- Anticoagulant medication
- Recent history of bleeding gums after dental hygiene (common in late pregnancy and not relevant as an isolated sign) or bruising
- Recent infection, including vaginal or skin infection involving the back
- Possibility of immunocompromise

BOX 32-7 Preanesthesia Neurologic Examination

- If there is a question of neurologic disorder, examine the lower limbs:
  - Sensation to pinprick or ice, and vibration sense using a tuning fork
  - Knee and ankle tendon reflexes and Babinski reflex
  - Motor power of hips, knees, and ankles
- Examine the back for:
  - Signs of infection (pustules to be avoided)
  - Nevi, suggesting arteriovenous malformation
  - Midline hair tuft or fat pad, suggesting dysraphism (e.g., spina bifida occulta)
  - Scoliosis
  - If the spine looks technically difficult, as in severe scoliosis, is there an easily palpable sacral hiatus as an alternative to the lumbar epidural space?
- Look for signs of bleeding tendency
- Document:
  - The history and physical examination
  - Abnormalities and treatment decisions
  - Differences of opinion
  - The reasons the anesthetic is administered despite a relative contraindication

Diagnosis of Possible Neurologic Injury

Through simple clinical examination coupled with knowledge of basic neuroanatomy outlined in this chapter, it should be possible to distinguish peripheral from central lesions. Preanesthesia history and physical examination may reveal some helpful clues, and any preexisting signs or deficits documented in the record will narrow the search or even provide an immediate answer. The history and physical examination should seek to establish whether the complaint is genuine and to determine its site and cause.

The basic physical examination outlined in Box 32-7 should be repeated, and the results should be compared with the preanesthesia findings. Fever and leukocytosis indicate an infective cause. Severe back pain and localized tenderness suggest epidural abscess, and pain radiating to the legs or buttocks is a late and urgent sign of spinal cord or cauda equina compression. Headache, fever, and neck stiffness suggest meningitis. Viral or other community-acquired types of meningitis may coincide with pregnancy, but the responsible organisms differ from those causing nosocomial infection.

MRI has revolutionized the speed and precision with which intraspinal lesions can be identified, and gadolinium enhancement further improves its sensitivity. MRI cannot distinguish clearly between blood and other fluid, although the distinction can usually be made on other grounds. In the presence of meningitis, MRI with gadolinium enhancement shows swelling of the cord and punctate areas of increased density, reflecting inflammatory cell infiltrates. Arteriovenous malformations of the cord or dura may be visible, and the enlarged veins draining them may be seen as serpiginous signal voids.

KEY POINTS

- Maternal obstetric palsy may arise from (1) the process of childbirth, (2) preexisting maternal disease that predisposes to peripartum palsy, (3) coincidental pathology, or (4) neurologic injury directly attributable to the anesthetic.
- Intrapartum nerve compression may go unnoticed during neuraxial analgesia/anesthesia; therefore, neurologic status should be regularly assessed and the patient should be encouraged to change positions.
- Postpartum neurologic deficit is less likely to have anesthetic than other causes. Transient postpartum peripheral palsy is common. Nevertheless, there is a widespread tendency to attribute neurologic deficits to neuraxial anesthesia.
- Careful examination and knowledge of anatomy can usually suggest whether the lesion is central or peripheral.
- Meticulous technique, vigilance, and frequent observation of the patient are keystones to avoiding complications.

- Proper sterile technique involves wearing a mask, hand washing, donning sterile gloves, and cleaning the skin with chlorhexidine in alcohol and allowing it to dry before initiating neuraxial blockade.
- Good epidural needle insertion technique should minimize the risk for accidental dural puncture. Post–dural puncture headache, should it occur, must never be neglected.
- The CSE technique carries a higher risk for complications than either epidural or spinal anesthesia alone.
- Risk for trauma to the spinal cord may be minimized by choosing a lower lumbar interspace (below L3) for insertion of the spinal needle.
- The risk for meningitis may be decreased by avoiding dural puncture during labor in a patient with systemic or vaginal infection.
- Mistakes in drug administration must be avoided by obsessive and careful reading of drug labels.
- The results of the history and physical examination, the rationale behind the chosen anesthetic procedure, and the details of all procedures should be thoroughly documented.
- Rapid diagnosis and treatment are essential to minimizing permanent neurologic sequelae. Compressive intraspinal lesions with neurologic changes require urgent laminectomy within 6 to 12 hours of the onset of symptoms.
- Early hospital discharge necessitates a safety net to detect neurologic complications arising after return home. Patients should be informed about the presenting symptoms of rare but potentially catastrophic complications of neuraxial anesthesia.

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CHAPTER 33

Medicolegal Issues in Obstetric Anesthesia

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CHAPTER OUTLINE

Childbirth is a natural process in which unexpected and potentially severe adverse events can occur. Responses to such events require timely and collaborative efforts among all caregivers. Obstetric anesthesia providers have a challenging role. Some women have high expectations about the availability and effectiveness of anesthesia services for labor and vaginal or cesarean delivery; these expectations may be influenced by the experiences and biases of family members and friends. By contrast, other women may view anesthesia for labor as an intrusion upon the natural labor process; yet, some of these women may ultimately need or request anesthesia services. The informed consent and decision-making process is fundamental to securing a woman's understanding and support. The effectiveness of this process is subject to cultural and socioeconomic influences as well as the pain of labor.

The degree to which patients and their families possess a realistic understanding of the benefits and risks associated with childbirth and obstetric anesthesia may influence the decision to pursue legal remedies in the event of a real or perceived adverse outcome. Adverse outcomes may profoundly affect families and health care providers. Patients and their families must adjust to the reality of an unanticipated adverse outcome as well as potentially overwhelming and long-term financial costs. Physicians and other caregivers also may be profoundly affected emotionally by an adverse outcome. Medicolegal claims associated with such events (regardless of the merit of the claim) may compound such emotions, raise the costs of liability coverage, and ultimately impact the availability and overall cost of health care services.

Anesthesia providers should possess an understanding of basic medicolegal issues and should proactively embrace risk management strategies that support optimal patient care and minimize both patient dissatisfaction and the legal consequences of an unanticipated adverse outcome. Insights and opportunities for promoting safer and more effective anesthesia and obstetric care are rapidly evolving and are gaining support among payers, governmental agencies, and others.

LAWSUITS INVOLVING CLAIMS AGAINST HEALTH CARE PROVIDERS

Importance of Effective Communication

The ability to effectively communicate information in a manner that is understood by the patient is fundamental to securing patient understanding and cooperation. Lapses in communication may preclude obtaining truly informed consent and may lead to patient dissatisfaction, lapses in patient safety, and inadequate explanation of an unanticipated adverse outcome.

Communication failures are frequent elements in malpractice claims; these failures include lack of informed consent, poor patient rapport, language barriers, and inadequate discharge instructions, among others.[1] There is an increasing recognition that limited **health literacy** interferes with effective communication.[2] Health literacy is defined as the "degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[3] Providers should strive to adopt methods and approaches that encourage patient engagement, reduce risk, and improve treatment compliance.[4]

Theories of Liability

Every physician has a duty to provide professional services that are consistent with a minimum level of competence. This is an objective standard based on the physician's qualifications, level of expertise, and the circumstances of the particular case.[5] The failure to meet this objective standard of care may give rise to a cause of action for medical negligence. The standard of care for medical practice is dynamic and changes as the profession adopts new treatments and approaches for patient care. Therefore, changes in accepted medical practice may create additional professional obligations and, in turn, additional legal responsibilities for physicians.

Although the specific medical malpractice laws vary from state to state, several different causes of action may be brought against a physician. Patients may sue for injuries resulting from the provision of health care by using one or more of three different theories (or causes of action): (1) medical malpractice, (2) breach of contractual promise that injury would not occur, and (3) lack of informed consent.[6] Plaintiffs (patients) commonly file lawsuits that allege improper care on the basis of more than one of these theories (e.g., alleging both a violation of the standard of care and a lack of informed consent for the medical treatment rendered). Medical malpractice may involve failure to make the diagnosis, failure to obtain informed consent, surgical errors, drug prescription and administration errors, and other mistakes. For a plaintiff to prevail with regard to a medical malpractice claim, he or she must prove that the injury resulted from the failure of the health care provider to follow the accepted standard of care. The standard of care may be defined as "that degree of care, skill, and learning expected of a reasonably prudent health care provider at that time in the profession or class to which he belongs…acting in the same or similar circumstances."[7] This objective standard is applied to the particular facts of the plaintiff's situation in a malpractice action.

A mistake or a bad result does not necessarily denote negligence. Similarly, unless a physician contracts otherwise with the patient (i.e., makes a promise of a specific outcome), the provision of medical care alone does not warrant or guarantee that an illness or disease will be cured. A physician is liable for a misjudgment or mistake only when it is proved to have occurred through a failure to act in accordance with the care and skill of a reasonably prudent practitioner.

Claims of medical malpractice must be filed within a certain period after the alleged incident of medical malpractice. Most jurisdictions in the United States have enacted **statutes of limitations** that are specifically applicable to malpractice claims. Recognizing that a significant time may elapse before symptoms or injury manifest, many states have established **discovery rules** that apply to situations in which the patient has no way of knowing that the injury was caused by wrongdoing or negligence. One example of an unknown injury is sterility that is discovered only when the patient attempts to conceive. Another example is the Rh-negative mother who delivers an Rh-positive child and does not receive Rho(D) immune globulin (RhoGAM). Such an injury would be apparent only when the mother has another child with Rh-positive blood. Other exceptions to—or extensions of—the statutes of limitations might involve situations of fraudulent concealment, an undiscovered foreign object, situations involving long-term continuous treatment, and issues involving infants or minors.

Establishing Medical Malpractice

In most malpractice cases, the following four elements are required for proving medical negligence:

1. **Duty**. It must be shown that a duty to provide care existed (i.e., a health care provider–patient relationship existed). This may apply to situations in which the provider renders medical advice over the telephone to a patient never seen in the office or through a "curbside" consult with another physician.
2. **Breach**. It must be shown that the health care provider failed to meet his or her duty to provide reasonable care (i.e., the health care provider was negligent).
3. **Injury**. It must be shown that the patient experienced an injury that resulted in damages.
4. **Proximate cause**. It must be shown that the negligence of the health care provider proximately caused the patient's injury (i.e., there must be a sufficiently direct connection between the negligence of the health care provider and the injury experienced by the patient).[7]

If any one of these elements is missing, the plaintiff cannot establish medical malpractice. The plaintiff has the burden of proof to establish each of these elements by a "preponderance of the evidence." This quantum of proof means that a proposition is more probably true than not true (i.e., > 50% certainty).

If the malpractice claim involves the issue of whether a physician used a proper method of treatment, the

plaintiff must use expert testimony to establish that the defendant physician violated the standard of care and that such violation probably caused the plaintiff's injury.[7] Expert testimony to establish how a reasonably prudent health care practitioner would act under similar circumstances typically must be provided by an expert with the same educational background and training as the defendant physician.

In certain cases, the plaintiff may not be required to present expert testimony to prove negligence, and the burden of proof may shift to the defendant. This represents the doctrine of *res ipsa loquitur* (i.e., the thing speaks for itself). This doctrine has the following three conditions: (1) the injury ordinarily does not occur in the absence of negligence, (2) the injury must be caused by an agency or instrumentality within the exclusive control of the defendant, and (3) the injury must not have been a result of any voluntary action or contribution on the part of the plaintiff.[5] Claims involving injuries sustained during administration of anesthesia have been made under this doctrine. In one case, a patient complained of pain that he described as a "strong electric shock" after a spinal block was administered. The patient subsequently lost all sensation below that spinal level and became incontinent. Because one would not ordinarily expect a permanent sensory loss from a spinal anesthetic, the verdict was upheld at the appellate level.[8]

Establishing Lack of Informed Consent

Lack of informed consent is a common cause of action in medical malpractice claims. Within the context of the physician-patient relationship, the **doctrine of informed consent** is based in English common law, by which doctors could be charged with the tort of *battery* if they had not gained the consent of their patient before the performance of surgery or another procedure. In the United States, the New York Court of Appeals established the legal principle of informed consent in 1914.[9] In this case, the plaintiff, Mary Schloendorff, was admitted to a New York hospital and consented to examination under ether anesthesia to determine whether a fibroid tumor was malignant, but she withheld consent for its removal. The physician examined the tumor, found it to be malignant, and removed it—in disregard of the patient's wishes. The Court found that this operation constituted medical battery. Writing on behalf of the Court, Justice Benjamin Cardozo wrote, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages. This is true except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained."[9]

This principle remains embedded in modern medical ethics and has been adopted by most state legislatures in the form of informed consent statutes. To establish negligence for failure to obtain informed consent, a plaintiff must prove (1) the existence of a material and reasonably foreseeable risk unknown to the patient, (2) a failure of the physician to inform the plaintiff of that risk, (3) that disclosure of the risk would have led a reasonable patient in the plaintiff's position to reject the medical procedure or choose a different course of treatment, and (4) a causal connection between the failure to inform the plaintiff of the risk and the injury resulting from the occurrence of the nondisclosed risk.[10]

Expert testimony is typically required to establish at least some of the elements of an informed consent claim, especially the materiality of the risk. However, expert testimony is not essential if an issue falls within the general knowledge of lay persons or if the doctor failed to give the patient *any* information about the risks involved, because a lay person can conclude that in the absence of any information, informed consent is not possible.

The obligation to obtain informed consent lies with the physician.[11] Ordinarily, the hospital or other organization has no independent duty to obtain a patient's informed consent. Likewise, a consultant physician who advises the treating physician has no such duty. A referring physician is not required to obtain informed consent unless he or she actually participates in or controls the subsequent treatment by the other physician.[12]

There are differences of opinion as to the perspective to be embraced when a physician is disclosing the nature and likelihood of a given risk. Specifically, should it arise from the patient's or the physician's point of view? Theoretically, both would desire the same scope of disclosure. Often, the pivotal issue is the determination of which party's viewpoint should dictate the standard for judging the physician's conduct.[13] Most jurisdictions use a "reasonable person" or "prudent patient" standard. Under this rule, a physician is expected to disclose to the patient in lay terms all material information that a prudent or reasonable patient would consider significant to making his or her decision.[14] This approach concerns itself with the patient's needs, rather than the physician's judgment; this approach follows the rationale that the physician should neither impose his or her values on the patient nor substitute his or her level of risk aversion for that of the patient.[15] Under this standard, the jury determines whether a reasonable person in the plaintiff's position would have considered the risk significant in making his or her decision. The issue is not what a particular patient would want to know but rather what a reasonable person in the patient's condition would want to know, taking into account factors such as the individual's medical condition, age, and risk factors.[16] This objective standard protects physicians from potentially self-serving testimony of plaintiffs, who inevitably assert that they would have refused a given procedure if they had been properly informed of the risk.

The materiality of risk is an issue under this "reasonable" or "prudent" patient standard. It is generally accepted that a physician is not required to present every possible risk of a proposed treatment. If the probability of its occurrence is practically nonexistent, then the risk, no matter how severe, is not material. Conversely, even a small risk for occurrence may be significant to a patient's decision if the potential consequences could be severe.[17] Disputes concerning the proper scope of disclosure tend to center on whether the risk was foreseeable or remote.

Some jurisdictions still adhere to the *professional* standard of disclosure. This approach assumes the perspective of the physician and is concerned with what information a reasonable practitioner would share with a patient under the same or similar circumstances.[18]

Even in circumstances in which the health care providers acknowledge their failure to provide important information to the patient or the patient's legally authorized surrogate decision-maker, the jury is still asked to decide whether the patient or the patient's decision-maker would have consented to such a course of treatment despite the risk. For example, in *Barth v. Rock*, a 5-year-old patient suffered a cardiac arrest (and eventual death) after receiving general anesthesia by mask with sodium thiopental, nitrous oxide, and a succinylcholine infusion for open reduction of an arm fracture. Both the surgeon and the nurse anesthetist admitted that they failed to inform the minor patient's parents about the risks of general anesthesia. The appellate court held that the jury should have been instructed that, as a matter of law, there was no informed consent; the jury then should have decided whether the parents would have consented to the anesthesia had they been adequately informed of the risks.[19]

If a plaintiff establishes the four elements for a cause of action based on lack of informed consent, the burden shifts to the physician to establish a defense that justifies why the material information was not provided (e.g., the insignificant nature of the risk) or why disclosure would not have altered the chosen course of treatment. In addition, the health care providers may claim that the case was a medical emergency. State laws generally supply a defense of "implied consent" for provision of necessary emergency treatment when the patient is unable to provide his or her own consent and no legally authorized surrogate decision-maker is immediately available.[20] If the health care providers' treatment was authorized under a medical emergency, the providers should carefully document their determination of same. The documentation in the patient's medical record should contain a description of the patient's presenting condition, its immediacy, its magnitude, and the nature of the immediate threat of harm to the patient. It is advisable for at least two health care providers to document this information, because the documentation would support their actions if a lack-of-informed-consent lawsuit were filed. The "emergency treatment" rule is limited in two respects. First, the patient must require immediate care to preserve life or health. Second, the physician may provide only the care that is reasonable in light of the patient's condition.

THE LITIGATION PROCESS

It is helpful for health care providers to have a basic understanding of sources of law, how lawsuits are initiated, and typical steps in the litigation process.

Sources of Law

Legal authority has multiple sources, including federal and state constitutions, federal and state statutes, federal and state regulations, and federal and state case law. **Constitutions** are the fundamental laws of a nation or state, which establish the role of government in relation to the governed. Constitutions act as philosophical touchstones for the society, from which other ideas may be drawn. One example is the "right to privacy" established in case law, which flows from the constitutional recognition of individual liberty.[21] **Statutes** are the laws written and enacted by elected officials in legislative bodies. **Regulations** are written by government agencies as permitted by statutory delegation. Although regulations have the force and effect of law, they must be consistent with their enabling legislation. **Case law** refers to written opinions or decisions of judges that arise from individual lawsuits. Case law that may be cited as legal authority (precedent) is limited to cases at the appellate court level (i.e., cases appealed from trial court decisions). The vast majority of lawsuits settle before trial, and only a small percentage of trial court decisions result in appeal; thus, case law reflects a very small portion of actual litigation. Like medicine, the practice of law is dynamic and changes as new legislation and regulations are adopted or new case law is created. In addition, any one or several of these sources of law may be relevant to a particular case.

When creating new laws or applying the law in deciding the proper result for a particular case, a legislative body or a court may also consider other information about standards for health care providers' conduct. For example, the court may give strong weight to The Joint Commission standards and find that a provider acting in accordance with The Joint Commission requirements was adhering to his or her professional obligations.[22] In writing legislation or court decisions, lawmakers also may defer to standards and practice guidelines adopted by professional organizations, such as the American Society of Anesthesiologists (ASA). The adoption of professional standards and practice guidelines strengthens the influence of professional organizations in the lawmaking process because lawmakers often are willing to defer to professional organizations' statements on standards of care and professional ethics.

Some experts have suggested that the value of "evidence-based" guidelines within the venue of medical malpractice has been disappointing, primarily because of a lack of scientific evidence supporting the guidelines.[23] A 2009 analysis of guidelines issued by the American College of Cardiology and the American Heart Association determined that "the significant increase in the quantity of scientific literature concerning cardiovascular disease published in recent years (along with the number of technical and medical advances)—if aimed to address unresolved issues confronting guideline writers—should have resulted in guideline recommendations with more certainty and supporting evidence."[24] Recent federal regulation dictates the funding of some comparative effectiveness studies that may provide additional evidence on which to base clinical guidelines.[25] It will be several years before the merit of these investments can be assessed.

Initiation of a Lawsuit

Medical malpractice lawsuits are typically initiated when a plaintiff files a **complaint** with the court. Some states have

enacted statutes that impose certain conditions (including notification of the defendant physician) before a complaint is filed.[26] The physician receives notice of the legal action when he or she is served with a copy of the **summons** and the complaint. In the complaint, the plaintiff alleges the facts giving rise to the cause(s) of action against the physician. The complaint requires a written **answer** to be filed (by the attorney representing the physician) with the court within a specified period. If a timely answer is not filed, a default judgment may be entered against the physician (i.e., a judgment is allowed because *no response* may be treated as *no defense* against the allegations).

In civil actions against health care providers, plaintiffs are frequently motivated to sue for an award of monetary damages. Medical malpractice lawsuits may involve multiple defendants, such as the treating physician, the hospital, manufacturers of health care equipment, and pharmaceutical companies. Defense counsel evaluates its client's potential liability exposure (i.e., any aspect of care arguably not meeting the standard of care). Both plaintiff counsel and defense counsel weigh the perceived risks if the case proceeds to trial and then determine how much they think the case is worth. The valuation of a case may include more than the estimated dollar value; it may also include considerations such as setting a potential precedent or maintaining a business relationship.

Discovery

Discovery refers to the early phase of litigation after a lawsuit is initiated. During this phase, the litigants on both sides research the strengths and weaknesses of their cases by obtaining and examining medical records, reviewing medical literature, and interviewing and deposing witnesses, including the plaintiff(s), the treating health care provider(s), and potential expert witnesses.

During discovery, certain methods of gathering information are generally used. The methods include interrogatories and depositions. **Interrogatories** are written questions that are served on one party from an opposing party. Interrogatories must be answered in writing, under oath, within a prescribed period. Failure to respond as required may result in the court's issuing sanctions against the nonresponding party. **Depositions** involve testimony given under oath that is recorded by a court reporter. In a deposition taken for the purpose of discovery, the attorneys representing all opposing litigants participate and ask questions of the witness. The purposes of discovery depositions are (1) to obtain facts and other evidence, (2) to encourage the other side to commit to a position "on the record" (i.e., in preserved testimony), (3) to discover the names of other potential witnesses, (4) to assess how strong a witness the deposed individual may make, (5) to limit facts and issues for the lawsuit, (6) to encourage the other side to make admissions against its own interests in the lawsuit, and (7) to evaluate the case for its dollar (or other) value and potential for settlement.

Trial

A trial typically consists of (1) jury selection, (2) opening statements, (3) plaintiff's trial testimony, (4) defendant's trial testimony, (5) closing arguments, (6) jury instructions given by the judge, and (7) delivery of the jury's verdict. There also may be post-verdict proceedings and motions. The lawyers for all parties file briefs with the court in advance of the trial to outline the case for the trial judge. The lawyers also prepare and argue over the content of jury instructions, seeking the best language to support their theories of the case. The judge decides which jury instructions will be given and reads them to the jurors immediately prior to jury deliberation. Attorneys commonly file motions about significant trial proceedings, such as the scope of admissible evidence. The trial judge rules on these motions outside the presence of the jury.

A jury verdict does not necessarily end the case. If a verdict in favor of the plaintiff(s) is reached, defense counsel may file a motion (1) asking the court to set aside the verdict and grant a new trial, (2) asking the court to change the verdict and enter a judgment in the defendant's favor, or (3) asking for a reduction in the amount of damages awarded to the plaintiff(s). Defense counsel also may seek to reopen settlement negotiations or may choose to appeal the case. The plaintiff(s) may take similar post-verdict steps if the jury renders a verdict in favor of the defendant(s).

The vast majority of medical malpractice cases never go to trial. A 1991 study showed that only 2% of persons injured by physicians' negligence ever file a lawsuit.[27] Subsequently, only 10% of all medical malpractice claims go to trial. Settlement negotiations result in the disposal of many cases. Other cases are withdrawn by plaintiffs or are dismissed by the court on legal grounds such as **summary judgment,** whereby a judge may rule that a plaintiff's case is legally insufficient. Defendants win approximately 71% of medical malpractice claims.[28]

In seeking alternatives that might speed the litigation process and reduce the overall costs, a number of states have created medical pretrial screening panels. As an alternative to a full trial, a medical screening panel is typically comprised of several physicians and an attorney, who determine whether the defendant met the appropriate standard of care and if the injury was proximately caused by a failure to meet that standard. The findings of the group are then submitted to the court for further adjudication.[29] The effectiveness of this model is subject to considerable debate. Other alternatives include arbitration, mediation, and other types of alternative dispute resolution.

INFORMED CONSENT

Process and Documentation

A patient's right of self-determination lies at the root of informed consent. A patient can make an informed decision only after (1) a discussion of the diagnosis and the indications for the procedure or therapy; (2) disclosure of material risks, benefits, and alternatives; and (3) provision of an opportunity for questions and answers. This process is neither accomplished nor affirmed solely by having the patient's or the patient surrogate's signature

on a document asserting informed consent. Evidence of this process and the physician's involvement in the process may be found among office notes, informational aids shared with patients, hospital notes, and signed forms acknowledging informed consent.

The necessity of having a specific process is not only an ethical obligation but also a requirement of various state and federal agencies. For example, the U.S. Centers for Medicare and Medicaid Services (CMS) have *Conditions of Participation* that define the requirements that facilities must satisfy to participate in the Medicare and Medicaid programs. Specifically, the *Patients' Rights Conditions of Participation* contain the following interpretive guidelines: "Hospitals must utilize an informed consent process that assures patients or their representatives are given the information and disclosure needed to make an informed decision about whether to consent to a procedure, intervention, or type of care that requires consent."[30] Further, the interpretive guidelines for the CMS *Surgical Services Conditions of Participation* specifically state the following[31]:

> *The primary purpose of the informed consent process is to ensure that the patient, or the patient's representative, is provided information necessary to enable him/her to evaluate a proposed surgery before agreeing to the surgery. Typically, this information would include potential short and longer term risks and benefits to the patient of the proposed intervention, including the likelihood of each, based on the available clinical evidence, as informed by the responsible practitioner's professional judgment. Informed consent must be obtained, and the informed consent form must be placed in the patient's medical record, prior to surgery, except in the case of emergency surgery.*

The interpretive guidelines note that there is no specific requirement for informed consent governing anesthesia services but also state that "given that surgical procedures generally entail the use of anesthesia, hospitals may wish to consider specifically extending their informed consent policies to include obtaining informed consent for the anesthesia component of the surgical procedure."[31]

As patients have become more engaged in their health care and are reaching out to nontraditional sources of information, other approaches to ensuring informed consent have been proposed. Studies have demonstrated that standard counseling often results in inadequate decision quality.[32] Some patients may have an incomplete understanding of the risk and benefits of a treatment, and clinicians are often poor judges of patients' values; consequently, there may be overuse of treatments that informed patients would not choose or value.[33] Thus, decision-making aids are used to improve the quality of informed consent and to reduce unnecessary practice variations by (1) providing facts about the condition, options, outcomes, and risks; (2) clarifying patients' evaluations of the outcomes that are most meaningful to them; and (3) guiding patients in the steps of deliberation and communication so that a choice can be made that reflects their informed values. These decision-making aids may be used by practitioners and/or patients in either individual or group settings, and they may be presented in a variety of formats, such as print, video, the Internet, and interactive devices.[33] In essence, this approach attempts to address the weaknesses in both the "reasonable patient" and the "professional standard" approaches to disclosure, and it becomes even more valuable as the diversity of practitioners and patients increases.

Formal documentation of informed consent has other advantages. Adequate documentation helps health care providers defend their actions if patients subsequently challenge their consent for health care. In some jurisdictions, a valid consent form signed by the patient may provide a direct means of defense and actually shift the burden of proof to the plaintiff who wishes to make a claim of lack of informed consent.[34] Some large medical liability insurance providers have strongly recommended that the clinician responsible for providing anesthesia care should obtain a separate written consent.[35] Further, some anesthesia organizations have recommended not only that an anesthesia-specific form should be used but also that practitioners should highlight specific risks that may be present.[36] A separate anesthesia consent form that highlights specific risks demonstrates a meaningful effort to engage patients in a full discussion of relevant issues and may help establish the basis of a potential defense against a medical malpractice claim. It may also reinforce the importance and significance of anesthesia services and choices in the obstetric setting.

In discussing anesthetic options for a given procedure, anesthesia providers should consider several aspects, including the best options given the skill set of the provider, the comorbidities of the patient, and the preferences of the surgeon. In a review of anesthesia consent procedures, O'Leary and McGraw[37] recommended that an explanation of the relevant risks and benefits of alternative techniques as well as the likelihood and details of a backup plan should be included in informed consent. The investigators recommended that anesthesia providers adopt a separate, written consent form for the administration of anesthesia services. A form that clearly delineates common risks but allows documentation of patient-specific risks should be used. Ideally, the anesthesia provider should obtain the patient's consent for anesthesia and should not rely on other professionals who are not competent to explain the risks and benefits of anesthesia options.

Capacity to Consent/Mental Competence

Physicians are bound by ethics and required by law to obtain a patient's informed consent before initiating treatment. This premise assumes that a patient is competent and/or has the capacity to successfully participate in this process. **Competence** generally refers to the patients' legal authority to make decisions about their health care. Adult patients, typically 18 years of age or older, are presumed to be legally competent to make such decisions unless otherwise determined by a court of law. **Capacity** typically focuses on the clinical situation surrounding the informed consent process. For example, an otherwise normal patient who has been given sedation may be legally competent but temporarily incapacitated and

therefore unable to give informed consent.[38] The determination as to whether a patient has the capacity to provide informed consent generally is a professional judgment made by the treating health care provider. However, if a court has made a judgment regarding a patient's capacity to make such decisions, the health care provider(s) should obtain a copy of the court order, because it may delineate whether the patient is considered able to make his or her own health care decisions. For example, a guardianship is a type of court proceeding that may have an impact on the informed consent process. If a patient has a legal guardian with the authority to make health care decisions on behalf of the patient, that guardian should be consulted about the patient's care and is the person legally authorized to provide consent. A failure to recognize a lack of capacity may expose a physician to liability for treating a patient without valid informed consent.

The legal standards for decision-making capacity vary among jurisdictions but generally encompass the following criteria: The patient must be able to (1) understand the relevant information, (2) appreciate the situation and its consequences, (3) reason about treatment options, and (4) communicate a choice.[39] When the patient is unable to do so, surrogate decision-makers may be sought. In emergency situations, physicians can provide necessary care under the presumption that a reasonable person would have consented to the anticipated treatment.[40] Most states have laws that delineate who is legally authorized to provide consent for health care decisions on behalf of an incapacitated individual. State laws vary, but they typically provide a list of persons (in order of priority) who may give consent. These laws assume that legal relatives are the most appropriate surrogate decision-makers. However, the competent patient is free to select any competent adult to act as his or her health care decision-maker by executing a **durable power of attorney for health care,** which appoints that person as his or her agent.

Health care providers are required to make reasonable efforts to locate a person in the highest possible category to provide consent. If there are two or more persons in the same category (e.g., adult children), then the medical treatment decision must be unanimous among those persons. These surrogate decision-makers generally are required to make "substituted judgment" decisions on behalf of the patient (i.e., they are obligated to decide as they believe the patient would, not as they may prefer). If what the patient would want under the circumstances is unknown, then the surrogate must make a decision consistent with the patient's "best interests."[41] The surrogate decision-maker has the authority to provide consent for medical treatment, including nontreatment.

Minor Patients

Existing laws regarding the ability of minors to provide their own consent for medical care may be viewed as a patchwork quilt. Statutes and case law differ from state to state. There are three ways in which a minor may be deemed able to give his or her own consent for medical care: (1) by state law that permits the minor to consent for the specific type of care, (2) by a clinical determination made by the health care providers that the minor is mature and emancipated for consent purposes, and (3) by a judicial determination of emancipation.

Parental involvement in a minor's health care decisions is usually desirable. For most health care decisions, a parent is required to provide consent for medical treatment of a minor patient.[42] However, many minors will not take advantage of some available medical services if they are required to involve their parents.[43] The list of services for which minors can legally give consent has recently expanded to include (1) sexual and reproductive health care, (2) mental health services, and (3) alcohol and drug abuse treatment. The majority of states also permit minor parents to make important health care decisions regarding their own children.

In most states, consent laws apply to minors 12 years of age and older. For example, 26 states and the District of Columbia allow minors (12 years of age and older) to consent to contraceptive services. All states and the District of Columbia allow minors to consent to treatment for sexually transmitted infections. Thirty states and the District of Columbia allow minor parents to consent to medical care for their children. For some medical treatment, including contraception and obstetric care, case law has generally held that minors have rights of privacy and autonomy that are fundamental and equivalent to the rights of adults.[44]

In addition to statutes and case law regarding a minor's ability to provide consent, there also exists a broader legal concept—the **emancipated or mature minor doctrine**.[45] This doctrine allows health care providers to determine whether a minor is emancipated for providing medical consent. Case law may not give a precise definition of an emancipated minor, but it may list criteria that health care providers should consider. Such criteria may include the minor's age, maturity, intelligence, training, experience, economic independence, and freedom from parental control. When a minor is deemed emancipated for medical consent, the health care provider should document the objective facts that support the emancipation decision, consistent with institutional policies and/or other legal guidance.

Some states have adopted emancipation statutes that permit minors to file for emancipation status in court.[46] Typically, a minor is required to be a minimum age to file for emancipation. Once the court grants emancipation status, a minor generally has the right to give informed consent for health care. A signed copy of the court's emancipation order should be placed in the patient's medical record.

Emancipation *per se* does not alter the requirement that a patient provide informed consent for medical treatment, including nontreatment. Emancipation status affords the minor patient rights (for providing consent) that are equal to those of an adult patient. The emancipated minor (like any adult patient) must have the ability to weigh the risks and the benefits of the proposed treatment or nontreatment.

In summary, health care providers typically should obtain consent from the minor's parents before providing nonemergency treatment unless the minor is emancipated (by either a clinical or judicial determination) or

the minor is permitted by statute to give consent to the type of health care sought.

Consent for Labor Analgesia

It is common practice for surgical patients to sign a preoperative consent form, which often includes a statement giving consent for anesthesia. The situation in obstetrics is somewhat different in that not all laboring women require operative delivery. Several years ago, an unpublished survey of obstetric centers in the greater Seattle, Washington, area revealed that approximately half of the institutions did not require a signed consent form for obstetric procedures other than cesarean delivery. At many of these institutions, a separate written consent signed by the patient is not obtained before administration of anesthesia. A 1995 survey of obstetric anesthesiologists in the United States and the United Kingdom indicated that 52% of U.S. anesthesiologists (but only 15% of U.K. anaesthetists) obtained a separate written consent for epidural analgesia during labor.[47] In a survey performed in the United Kingdom in 2007,[48] only 7% of obstetric units routinely obtained written informed consent for epidural analgesia during labor. In a 2004 survey from Australia and New Zealand,[49] less than 20% of anesthesia providers obtained written consent before initiating neuraxial labor analgesia.

Some health care facilities and organizations have begun using a consent form for obstetric and anesthetic procedures that may be desired or necessary during labor and delivery. The process of reviewing and signing the consent form provides a specific opportunity for the patient to ask questions. It also provides additional documentation that consent was obtained. The combined form has the additional advantage of not requiring the patient to sign multiple medicolegal documents. Although a signed consent form is not necessary, it should be standard practice for anesthesia providers to document that verbal informed consent was obtained before administration of anesthesia.

Ideally, the anesthesia provider will discuss anesthetic options before the patient is in severe pain and distress. Unfortunately, the anesthesia provider often first encounters the patient when she is in severe pain. Although the provider may tailor the consent process to the circumstances, the presence of maternal pain and distress does not obviate the need for a frank discussion of the risks of anesthesia as well as the alternatives. A survey of Canadian women revealed their strong preference to be informed of all possible complications of epidural anesthesia, especially serious ones, even when the risk was quite low.[50] This study and others have emphasized that parturients desire to have these discussions as early in labor as possible.

Gerancher et al.[51] performed a study to evaluate the ability of laboring women to recall the details of a preanesthesia discussion and to determine whether verbal consent alone or a combination of verbal and written consent provided better recall. The investigators randomly assigned 113 laboring women to one of two groups, those from whom verbal consent alone was obtained and those from whom verbal consent plus written consent was obtained. The verbal-plus-written consent group had significantly higher median (range) recall scores (90 [80-100]) than the verbal-only group (80 [70-90]). Only two women (both in the verbal group) believed that they were unable (because of either inadequate information or situational stress) to give valid consent. The investigators concluded that "the high recall scores achieved by the women in both groups suggest that the majority of laboring women are at least as mentally and physically competent to give consent as preoperative cardiac patients."

Clark et al.[52] randomly assigned hospital inpatients to receive either an oral anesthesia discussion alone or both an oral anesthesia discussion and a preprinted anesthesia consent form. In contrast to the results of Gerancher et al.,[51] these investigators found that "patients remembered less of the information concerning anesthetic risks discussed during the preoperative interview if they received a preprinted, risk-specific anesthesia consent form at the beginning of the interview." They speculated that "patients who see an anesthesia consent form for the first time during the preoperative interview may try to read and listen simultaneously, and with their attention divided, may remember less of the preoperative discussion."

Anesthesia providers have expressed concern about the adequacy of the informed consent process when women are experiencing the severe pain of active labor. A 2005 study evaluated whether labor pain and neuraxial fentanyl administration affect the intellectual function of laboring women.[53] The Mini-Mental Status Examination (MMSE) was used to evaluate orientation, registration, attention, calculation, recall, and language both before and after initiation of analgesia in 41 laboring women. There was no difference in MMSE scores before and after administration of neuraxial analgesia.

In summary, it seems reasonable for the patient to provide her signature as evidence of her consent, if her condition permits. This consent can be furnished on a separate anesthesia consent form or as part of a consent form for all obstetric care, including anesthesia. A signed consent form is preferable, but it should be standard practice for the anesthesia provider to explain the intended procedure, risks, and alternatives and to document this discussion in the medical record.

REFUSAL OF CARE

Documentation

Competent adult patients may refuse medical treatment, including life-saving care.[42] Health care providers generally determine whether a patient is capable of making medical treatment choices (see earlier discussion). In theory, the health care providers' clinical judgment about a patient's capacity to provide informed consent is the same regardless of whether the patient approves or disapproves the treatment plan. In practice, however, these situations are often handled differently. When a patient consents to the recommended medical treatment, minimal scrutiny of his or her decision-making capacity

is typically made. However, when a patient refuses potentially life-saving treatment, a higher level of scrutiny is applied to the patient's ability to understand and make a choice for nontreatment. Determination of a patient's capacity to give informed consent is typically a clinical judgment. State law may provide some definitions as to when a person may not be competent.

If a patient refuses potentially life-saving treatment, the health care providers should carefully assess the patient's capacity to provide informed consent. It may be advisable to obtain a psychiatric consultation as part of this clinical determination. It is important to document the determination of capacity and the objective facts supporting the decision. If a patient is deemed able to provide consent, he or she is able to either choose or reject the recommended treatment plan. Institutional policies may require the patient (or health care provider if the patient refuses) to sign an "Against Medical Advice" form for a non–medically approved discharge. If a patient is deemed unable to consent, the health care providers should obtain consent from a legally authorized surrogate decision-maker on the patient's behalf. If an incompetent patient needs emergency medical care, it may be provided consistent with an "emergency exception" (see earlier discussion).

Conflicts Arising out of the Maternal-Fetal Relationship

Almost all pregnant women consider the welfare of their unborn child to be of utmost importance. However, there may be situations in which maternal and fetal interests appear divergent or, potentially, in conflict. One example is when a pregnant woman refuses a diagnostic procedure, a medical treatment, or a surgical procedure that is intended to enhance or preserve fetal well-being. Another may arise when the pregnant woman's behavior is considered harmful to the fetus.[54] Physicians who care for pregnant women may confront challenging dilemmas when their patients reject medical recommendations, use illegal drugs, or engage in other behaviors that may adversely affect fetal well-being.

Appellate court decisions typically have held that a pregnant woman's decisions regarding medical treatment take precedence over the presumed fetal consequences of the maternal decisions.[55] One case illustrates the evolution of this judicial approach. Angela Carder was a 26-year-old married woman who had had cancer since age 13 years. At 25 weeks' gestation she was admitted to George Washington University Hospital, where a massive tumor was found in her lung. Her physicians determined that she would die within a short time. Her husband, her mother, and her physician agreed with her expressed wishes to be kept comfortable during her dying process. Ultimately, the hospital sought judicial review of this course of action. The hospital asked whether a surgical delivery should be authorized to save the potentially viable fetus. The situation was presented to a judge, who authorized an emergency cesarean delivery without first ascertaining (using the principle of substituted judgment) the patient's wishes. A cesarean delivery was performed without full consideration of the patient's wishes, the infant died approximately 2 hours after delivery, and the mother died 2 days later.

This case spawned extensive debate as to whether coercive intervention to protect the fetus is ever morally and legally justifiable.[56] With the assistance of the American Civil Liberties Union, Angela's parents sued the hospital, 2 administrators, and 33 physicians for claims including battery, false imprisonment, discrimination, and medical malpractice. These civil lawsuits were settled after several years of litigation, and as part of this process, the hospital adopted a written policy concerning decision-making for pregnant patients.[57] The court later reversed its initial decision authorizing the surgical delivery and ultimately issued an opinion setting forth the legal principles that should govern the doctor–pregnant patient relationship.[58] The court stated, "In virtually all cases the question of what is to be done is to be decided by the patient—the pregnant woman—on behalf of herself and the fetus. If the patient is incompetent…her decision must be ascertained through substituted judgment." In affirming that the patient's wishes, once ascertained, must be followed in "virtually all cases" unless there are "truly extraordinary or compelling reasons to override them," the court did not foreclose the possibility of exceptions to this rule.

Many contemporary medical ethicists agree that a pregnant woman's informed refusal of medical intervention should prevail as long as she has the capacity to make medical decisions.[59] Newer legislation and some high-profile legal cases (some involving criminal prosecution) have challenged this notion and have raised the question of whether there are circumstances in which a pregnant woman's rights to informed consent and bodily integrity may be subordinated to protect her unborn child. In 2004, Amber Rowland, a woman who had given birth vaginally to six children (with birth weights up to 12 pounds), was told by her treating physicians at a Pennsylvania hospital that she should undergo a cesarean delivery on the basis of an ultrasonographic examination that suggested an estimated birth weight of 13 pounds. When she refused, the hospital obtained a court order for a "medically necessary" cesarean delivery. She and her husband left the hospital against medical advice and went to another facility, where she uneventfully delivered a healthy 11-pound daughter.[60]

Other cases have focused on the pregnant woman's potentially harmful behavior. In 1991, Regina McKnight, who was pregnant at the time, began using cocaine after her mother's death. She had a stillbirth, and the state of South Carolina charged her with homicide by child abuse, claiming that her drug use caused the stillbirth. She became the first South Carolina woman to be convicted of this crime, for what both the defense and prosecution agreed was an unintentional stillbirth, and she spent nearly 8 years in jail. In 2008, the South Carolina Supreme Court unanimously reversed her conviction on the grounds that she did not receive a fair trial, primarily on the basis that her attorney failed to challenge the science that was used to convict her.[61]

Also in 2008, the Southern Poverty Law Center, along with 25 medical, public health, and health advocacy groups, filed an *amicus curiae* brief against the prosecution

of pregnant women in Covington County, Alabama, subsequent to the following event. Shekelia Ward delivered an infant on January 8, 2008. Both she and her newborn tested positive for cocaine during their hospital stay, and the facility reported it to authorities for possible child abuse.[62] The following day she was arrested, imprisoned, and charged with a felony—chemical endangerment of a child. The state statute at issue was passed by the Alabama legislature in 2006, for the purpose of prosecuting parents who exposed children to the toxins associated with methamphetamine production; the statute did not mention pregnant women or their fetuses.[63]

These statutes reflect the concept that a fetus can and should be treated as separable and legally, philosophically, and essentially independent from the mother.[55] The refinement of techniques of intrauterine fetal imaging, testing, and treatment prompted the view that fetuses are independent patients who can be treated directly while *in utero*.[64] The prominence of some ethical models that have asserted that physicians have moral obligations to fetal patients separate from their obligations to pregnant women also contributed to these developments.[65] Finally, a number of laws (primarily passed at the state level) were enacted with the aim of defining fetal rights separate from a pregnant woman's rights. In 2011, the American College of Obstetricians and Gynecologists (ACOG) Committee on Health Care for Underserved Women issued a statement addressing the issue of substance abuse reporting and the role of the obstetrician.[66] This document described a "disturbing trend" in legal actions and policies that criminalized drug abuse during pregnancy when such abuse is thought to be associated with fetal harm or adverse outcomes. Noting that women seeking obstetric care should not be exposed to criminal or civil penalties and that few treatment facilities are available to effectively treat drug abuse in pregnancy, the ACOG concluded that the use of the legal system to address alcohol and substance abuse issues is inappropriate and urged that policy makers and legislators instead focus on strategies to address the needs of pregnant women with addictions.

The American Medical Association (AMA) has taken a similar position, stating that (1) drug addiction is a disease amenable to treatment, rather than a criminal activity, and (2) there is a pressing need for maternal drug treatment and supportive child protective services.[67] Any legislation that criminalizes maternal drug addiction or requires physicians to function as agents of law enforcement will be opposed by the AMA.[67]

During the past two decades, practitioners have only infrequently resorted to court-ordered interventions against the wishes of the pregnant woman. In overturning the previous court's decision in the Angela Carder case (mentioned earlier), the Washington, DC, Court of Appeals noted that if a pregnant woman makes an informed decision, "her wishes will control in virtually all cases."[58] The court added, "We do not foreclose the possibility that a conflicting state interest may be so compelling that the patient's wishes must yield, but we anticipate that such cases will be extremely rare and truly exceptional."[58]

Medical ethicists and practitioners agree that clear communication and patient education represent the best means to address maternal-fetal conflict. Failing resolution, a 1999 ACOG opinion offered the following three options: (1) respect the patient's autonomy and not proceed with the recommended intervention regardless of the consequences, (2) offer the patient the option of obtaining medical care from another individual before conditions become emergent, and (3) request that the court issue an order to permit the recommended treatment.[68] In 2004, the ACOG addressed the situation in which health care providers may consider this last option (i.e., legal intervention against a pregnant woman).[54] Specifically, the ACOG stated that the following criteria should be satisfied: (1) "there is a high probability of serious harm to the fetus in respecting the patient's decision"; (2) "there is a high probability that the recommended treatment will prevent or substantially reduce harm to the fetus"; (3) "there are no comparably effective, less intrusive options to prevent harm to the fetus"; and (4) "there is a high probability that the recommended treatment [will] also benefit the pregnant woman or that the risks to the pregnant woman are relatively small."

The ACOG opinions assume the presence of competency and informed consent. Thus, if a pregnant patient is believed to be incompetent and incapable of providing informed consent, the health care providers may not be required to respect the patient's refusal of care. Moreover, if the patient is deemed incompetent and/or a medical emergency exists, care may be provided with consent from a legally authorized surrogate decision-maker or as an "emergency exception."

In summary, two approaches are available to the practitioner dealing with maternal-fetal conflict. One approach is to honor a competent pregnant patient's refusal of care. The other approach (which appears least favored by many medical ethicists and the ACOG) is to seek judicial authorization of treatment, which overrides a competent pregnant woman's refusal of care.[69]

In honoring a competent patient's desires to refuse treatment, the health care providers should carefully document the woman's competency and ability to provide informed consent. Every attempt should be made to counsel her to follow the treatment recommendations. Documentation should include how, when, and what information was provided to the patient and family regarding the significant risks to both the patient and the unborn child if the recommended care were not provided. If time permits, the treatment options should be reevaluated with the patient at frequent intervals, with detailed documentation in the patient's medical record. Additionally, legal counsel for the health care providers and medical facility may wish to prepare an "assumption of risk" form for the patient (and, if possible, her husband) to sign. This form represents another level of documentation (beyond the detailed notes in the patient's medical record) demonstrating that the patient was fully informed about the risks associated with her refusal of treatment and that she voluntarily elected to accept those risks. However, such a release signed by the parents may not protect the physician and medical facility from a claim brought on behalf of the child who suffers an injury as a result of nonintervention. In some cases the court has found that physicians have a duty to provide care to the unborn child.[70]

Patient "assumption of risk" does not release a health care provider from his or her obligations to provide other treatment within the accepted standard of care. For example, in *Shorter v. Drury*,[71] a case that involved a patient's refusal of blood transfusion because of religious preferences, the court upheld the validity of an "assumption of risk" (i.e., release) that relieved the physician from liability for compliance with the patient's refusal of blood transfusion before and after surgery but nonetheless held him partially responsible for her death because of his negligent performance of the surgery.[71]

Before deciding whether to seek court review, health care providers should identify what issue they want the court to resolve. Is it whether the pregnant woman is competent? Is it whether there is a superior state interest in preserving the life of the viable fetus and/or the pregnant woman despite the (competent) patient's desire to refuse recommended care? Health care providers also should consider whether a court is the proper forum for resolving those issues or whether another forum (e.g., an institutional ethics committee) may be a better choice. If a patient care dilemma is put before a judge, the health care providers give up a large amount of control over the disposition of the case. Nonetheless, if a patient's competency is at issue and there is adequate time, court review to settle the patient's competency may be beneficial and is supported by both the ACOG guidelines[54] and the *In re: A.C.* decision.[58] It is beneficial to obtain authorization for the provision of medically recommended care without waiting until the situation becomes an emergency. If the patient is deemed incompetent, the court may either appoint a surrogate decision-maker or directly authorize (by court order) the provision of medically indicated care.

It is not unusual for physicians to disagree with their patients' health care decisions, and such differences are expected. In some cases, physicians conclude that providing the requested care would present a personal moral problem—a conflict of conscience, which prompts them to refuse to provide the requested care. Conscientious refusals have become especially prevalent in the practice of reproductive medicine, an area characterized by deep societal divisions regarding the morality of contraception and pregnancy termination. The ACOG Committee on Ethics[72] has acknowledged that "respect for conscience is one of many values important to the ethical practice of reproductive medicine." The ACOG stated that when conscience implores physicians to refuse to perform abortion, sterilization, and/or provision of contraceptives, "they must provide potential patients with accurate and prior notice of their personal moral commitments." The ACOG committee opinion also emphasized that providers have an obligation to provide medically indicated care in an emergency that threatens the patient's health, in which referral is not possible.[72]

DISCLOSURE OF UNANTICIPATED OUTCOMES AND MEDICAL ERRORS

In 1999, the Institute of Medicine (IOM) estimated that preventable medical errors in the hospital setting kill 44,000 to 98,000 patients each year.[73] In December 2006, the Institute for Healthcare Improvement (IHI) initiated the 5 Million Lives Campaign.[74] At that time, the IHI estimated that 15 million incidents of harm occurred in U.S. hospitals each year (40,000 per day). Since that time, the prevalence of medical errors remains unacceptably high and continues to draw the focus of the public, regulators, and health care providers.[75] Large-scale efforts are underway to improve the safety in health care, and many organizations have achieved remarkable improvements.[76]

Most practitioners strive to provide the highest quality of care, but even with the growing focus on patient safety, unintended consequences—including patient injury and death—do occur. Unfortunately, most physicians remain largely unprepared to engage patients and their families in a timely, truthful, and candid manner in the aftermath of such events. In 1984, David Hilfiker wrote candidly of a life-altering mistake that he had made as a family physician treating a young woman in a small town in Minnesota.[77] Hilfiker was caring for a young woman named Barb Daily whom they both believed to be pregnant. He had delivered Barb and Russ Daily's first child, Heather, 2 years earlier, and he had been a friend of the couple for some years. After several months of care, her serial urine pregnancy test results remained negative and her uterus was only slightly enlarged. Concluding that she may have experienced a missed abortion, Hilfiker scheduled her for a dilation and curettage. The procedure was performed, but it became apparent that the diagnosis was incorrect and the procedure had been carried out with a live fetus. In his reflections on the event, Hilfiker wrote of a physician's expectations of perfection, the lack of training in dealing with unexpected outcomes and mistakes, and the damaging effects of these conditions on physicians.[77]

Disclosure of errors and unanticipated outcomes is a key component in the national patient safety movement. It is also an ethical mandate and a regulatory requirement. The ethical imperative is captured in the following passage from the *Charter on Medical Professionalism*, published by the American Board of Internal Medicine (ABIM) Foundation[78]:

> *Physicians should also acknowledge that in health care, medical errors that injure patients do sometimes occur. Whenever patients are injured as a consequence of medical care, patients should be informed promptly because failure to do so seriously compromises patient and societal trust. Reporting and analyzing medical mistakes provide the basis for appropriate prevention and improvement strategies and for appropriate compensation for injured parties.*

The AMA's *Code of Medical Ethics* contains the following statement: "It is a fundamental ethical requirement that a physician should at all times deal honestly and openly with patients…. Concern regarding legal liability, which might result following truthful disclosure, should not affect the physician's honesty with a patient."[79] The Joint Commission standard RI.2.90 requires that "patients and, when appropriate, their families, are

informed about the outcomes of care, treatment, and services that have been provided, including unanticipated outcomes."[80] Many states require reporting of medical errors, and some have legislated "apology" laws that encourage practitioners to be empathetic and honest with patients by allowing certain statements of sympathy to be made without fear of admitting medical liability.[81]

Physicians and other health care providers should undergo disclosure training to help them provide prompt and honest communication with patients and families and to help manage the risks of legal liability. Many untoward outcomes do not represent malpractice; they may simply reflect risks or complications of procedures that may or may not have been adequately discussed with patients and their families before the procedure or treatment. Adequate informed consent is an essential element of an effective disclosure program. Iatrogenic injuries, obvious mistakes, wrong-site surgeries, medication errors, and similar events that harm the patient should clearly be disclosed. A failure to disclose such an error may lead the patient (or the attorney) to conclude that health care providers made a deliberate effort to "cover up" the error. Furthermore, nondisclosure after such an event can lead to a charge of fraud. In most situations in which a provider conceals an error, the law provides that the statute of limitations "clock" for filing a malpractice claim does not begin to run until the fraudulent concealment is discovered.

In 2006, the Harvard teaching hospitals and their associated Risk Management Foundation developed a document entitled, "When Things Go Wrong: Responding to Adverse Events."[82] This white paper acknowledged the presence of many barriers to disclosure, including the fear of being sued, but the authors insisted that communication with patients and their families must be timely, open, and ongoing. In addition to stressing the imperative of providing support for the patient and/or family involved in the unexpected outcome, the paper emphasized the need to provide support to the health care providers involved. This concern is reflected in a 2008 survey that indicated that as many as 75% of obstetricians felt that caring for a patient with a stillbirth exacted a large toll on them, with almost 10% of those affected considering giving up their obstetric practice.[83]

Organizations that have adopted robust disclosure policies often have early settlement or "offer" programs, with the goals of reducing the overall costs of claims and speeding the resolution process. Recognizing the longstanding gridlock over tort reform, this and other approaches may provide a better balance between the interests of health care providers and their patients. Not only is it an opportunity to reform the process of compensating those who may have been injured, but it can also be linked to improvements in patient safety. A distinguishing feature of "disclosure and offer" models is that information and insights generated from the investigative process can be shared and analyzed for the purposes of implementing interventions that improve patient safety.[84] Physicians have a unique opportunity to lead such efforts, and their participation promotes the buy-in of other staff members.

CONTEMPORARY RISK MANAGEMENT STRATEGIES

Prevention of medical errors and adverse outcomes frequently focuses on the safety culture of the organization, communication and teamwork, and the intelligent use of protocols and checklists (see Chapter 11). The concept of a safety culture originated in organizations outside of health care sometimes referred to as high reliability organizations (e.g., nuclear industry, aircraft carrier operations).[85] A culture of safety is characterized by an institution-wide commitment to minimize adverse events despite the performance of intrinsically complex and hazardous work.[86] The key features of a "culture of safety" are:

- An acknowledgment of the high-risk nature of an organization's activities and the pursuit of consistently safe operations.
- A "blame-free" environment that encourages individuals to report errors or near misses without fear of reprimand or punishment.
- Encouragement of collaboration across levels and disciplines of the organization to seek solutions to the prevention of errors.
- Organizational commitment of resources to address the safety concerns.

Safety culture has been defined and can be measured; poor safety culture has been linked to increased error rates and adverse outcomes. Achieving a culture of safety in health care is daunting, because a culture of individual blame remains dominant and traditional. An issue that often arises is balancing the twin concepts of "no blame" and appropriate accountability. This is a particular struggle with physicians, given that few organizations have implemented meaningful systems of accountability that apply to the physicians.[87]

Communication and teamwork lapses are one of the primary causes of sentinel events identified by The Joint Commission from 2009 to 2011.[88] A 2010 review of obstetric malpractice risks by a major insurer found that 65% of the malpractice cases involved high-severity injuries, including maternal and infant deaths.[89] The most frequent contributing factors were substandard clinical judgment (77% of claims) and miscommunication (36% of claims). The report specifically noted that "at the intersection of individual decision making and team communication, teamwork training fosters development of a culture and structure for effective communication and decisive action. Its hallmarks—development of shared mental models, broad situational awareness, and clear communication among team members—facilitate clinicians' ability to timely identify signs of distress and take appropriate action."[89]

There is also increasing recognition of the value of smart checklists and protocols. Checklists may simplify complex procedures and make them less prone to error. Checklists may reduce the mental flaws inherent in human behavior.[90] The ACOG has issued an opinion noting that "protocols and checklists have been shown to improve patient safety through standardization and communication. Standardization of practice to improve quality

outcomes is an important tool in achieving the shared vision of patients and their health care providers."[91]

Some health care organizations and liability insurers are now adopting strategies to specifically promote these goals (e.g., offering financial incentives to providers for completing disclosure training, participating in multidisciplinary didactic training programs to support accurate interpretation of electronic fetal heart rate tracings, the adoption of other safe practices). Federal agencies, working with health care organizations and liability providers, are also supporting similar initiatives.[92]

LIABILITY PROFILES IN OBSTETRIC ANESTHESIA: THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS CLOSED-CLAIMS PROJECT

In 1985 the ASA Committee on Professional Liability began an ongoing study of insurance company liability claims involving anesthesiologists. Cases that are closed (i.e., no longer active) are reviewed by practicing anesthesiologists, abstracted, double-checked by the ASA Closed-Claims Committee, and entered into a computer database. In 1991 and 1996 comprehensive analyses of obstetric anesthesia claims were published, based on a total database of 1541 and 3533 claims, respectively.[93,94] In 2009, another publication compared obstetric claims from 1990 to 2003 with those before 1990.[95] As of December 2010, some 9536 claims (excluding those for dental injuries) from more than 35 insurance companies across the country have been reviewed and entered into the ASA Closed-Claims Project database. The analysis reported in this chapter focuses specifically on the 640 obstetric claims in the ASA Closed-Claims Project database between 1990 and 2010.

It is important to recognize the limitations of this kind of study. A closed-claims study cannot determine the incidence of a complication, for a number of reasons. First, the denominator is unknown. Neither the total number of anesthetics given each year in each category nor the actual number of injuries per year is known. Second, not all injuries result in a claim of malpractice, and the anesthesiologist may not be named in a claim resulting from an anesthesia-related injury. This latter category may comprise a significant population of patients, which may make the relationship between cause and injury impossible to construct.[96] Conversely, anesthesiologists may be named in claims in which there was no anesthesia-related adverse event.

The claims that have been reviewed are not a random sample of such data. However, given the large number of participating insurance carriers, they are likely to be broadly representative of liability claims involving obstetric anesthesia care in the United States.

Despite the significant limitations of closed-claims studies, such efforts do provide information that cannot be obtained in other ways. For example, claims involving obstetric anesthesia care can be compared with those from other types of anesthesia practice to determine whether different patterns of injury and outcome emerge.

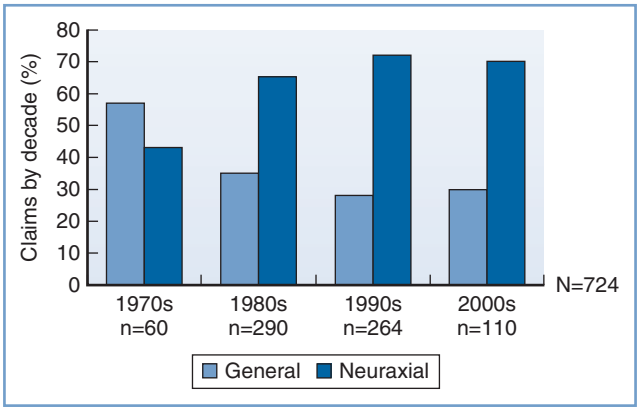

FIGURE 33-1 ■ The percentage of claims in which the anesthetic technique for cesarean delivery was either neuraxial or general. Data are shown as the percentage of the total number of claims for the indicated decade. (Data from the ASA Closed-Claims Project database, N = 9536, December 2010.)

We can ask such questions as: What injuries are most common in obstetric anesthesia claims? What is the relationship between the type of anesthesia and the presumed injury? What are the precipitating events that lead to the injuries? How do payment rates compare between obstetric and nonobstetric claims?

Approximately 12% of the 9536 claims in the ASA Closed-Claims Project database involve anesthesia care for patients undergoing vaginal or cesarean delivery. Of these obstetric claims, 66% involve cesarean delivery. The anesthesia workforce surveys conducted in 1981, 1992, and 2001 revealed a significant increase in the proportion of cesarean deliveries performed under neuraxial anesthesia and a corresponding decrease in those performed with general anesthesia.[97] An analysis of the ASA Closed-Claims Project database illustrates a similar trend in the claims for cases involving neuraxial and general anesthesia for cesarean delivery (Figure 33-1).

Anesthesia-Related Injuries

Table 33-1 lists all injuries or complications that had a frequency of 3% or greater in the obstetric claims that occurred in 1990 or later, as well as the type of anesthesia that resulted in the injury. **Maternal nerve damage** and **neonatal brain damage** were the most common injuries. In contrast to previous analyses, the proportion of nerve damage claims is now greater than maternal death claims. This finding likely reflects the increased use of neuraxial anesthesia (with a corresponding decrease in the use of general anesthesia) in obstetric anesthesia practice over the past two decades. A significantly greater proportion of nerve damage claims were associated with vaginal delivery compared with cesarean delivery. Although nerve damage in obstetric patients is more likely secondary to obstetric causes (e.g., vaginal delivery, fetal position during pelvic descent, maternal position during the second stage of labor [see Chapter 32]) than directly attributable to neuraxial anesthesia, the obstetric claims analysis published in 2009 found that nearly two thirds of the nerve damage claims may be directly linked to a neuraxial procedure.[95] Unfortunately, in many cases it is

TABLE 33-1 Most Common Injuries in Obstetric Anesthesia Claims*

Injury	Obstetric Claims (n = 640)	Type of Anesthesia		Type of Delivery	
		NEURAXIAL ANESTHESIA (n = 489)	GENERAL ANESTHESIA (n = 123)	CESAREAN (n = 387)	VAGINAL (n = 286)
Maternal nerve damage	19% (119)	24% (117)‡	2% (2)	13% (49)‡	29% (69)
Neonatal brain damage	16% (102)	13% (58)‡	29% (33)	21% (74)‡	13% (28)
Maternal death	15% (94)	10% (49)‡	36% (44)	18% (69)‡	7% (17)
Headache	11% (72)	15% (72)‡	0% (0)	7% (27)‡	19% (45)
Back pain	10% (62)	13% (62)‡	0% (0)	5% (20)‡	17% (42)
Neonatal death	9% (60)	6% (26)‡	24% (27)	13% (46)‡	4% (9)
Emotional distress	8% (54)	9% (46)	6% (7)	11% (41)†	5% (13)
Maternal brain damage	7% (44)	7% (34)	7% (8)	9% (36)†	3% (8)
Pain during anesthesia	6% (38)	7% (32)	3% (4)	9% (34)‡	2% (4)
Aspiration pneumonitis	1% (5)	< 1% (2)	2% (3)	1% (4)	< 1% (1)

*The most common injuries in the obstetric group of claims that occurred in 1990 or later are shown as % (n). Percentages are based on the total claims in each group. Some claims indicated more than one injury and are represented more than once. Claims involving brain damage include only patients who were alive when the claim was closed. Claims for which type of anesthesia or form of delivery were unknown are excluded.

†$P \leq .01$; ‡$P < .001$ compared with general anesthesia or vaginal delivery.

Data from the American Society of Anesthesiologists Closed-Claims Project database, N = 9536, December 2010.

almost impossible to differentiate between an anesthetic or obstetric cause for the nerve injury; appropriate neurologic consultation and investigation improves the likelihood of a correct diagnosis in these patients.

Some obstetric patients are reluctant to accept neuraxial anesthesia because of the fear of nerve injury. Because such injuries are uncommon, anesthesia providers often minimize the risks of neurologic injury in their discussions with patients. An ASA Closed-Claims analysis of injuries associated with neuraxial anesthesia in the 1980s and 1990s found that a significantly greater proportion of obstetric neuraxial claims were associated with temporary and low-severity injuries than nonobstetric claims.[98] Epidural abscess accounted for a greater proportion, and epidural hematoma a significantly smaller proportion, of obstetric neuraxial claims than nonobstetric neuraxial claims. Combining both epidural abscess and meningitis claims, infection was the leading cause of obstetric neuraxial complications (46%).[98]

A nonreassuring fetal heart rate tracing and urgent or emergency cesarean delivery were found to be factors in nearly three fourths of neonatal death/brain damage claims in 1990 or later.[95] Determining whether a causal link exists between the anesthetic care (negligent or otherwise) and the injury to the neonate is often difficult. A closer analysis of neonatal brain damage cases in the 1990s found that anesthesia care may have contributed to adverse fetal outcome in less than a fourth of cases; in half of these cases, some delay in anesthesia care was alleged.[95] The payment rate on behalf of the anesthesiologist was 21% in the claims involving neonatal death/brain damage, which was significantly lower than the payment rate of 60% for maternal death/brain damage claims.[95]

Some injuries (e.g., headache, pain during anesthesia, back pain) were almost exclusively associated with neuraxial anesthetic techniques. Most claims involving pain during anesthesia were associated with cesarean delivery (see Table 33-1). This finding suggests that inadequate analgesia for labor and vaginal delivery is rarely a source of liability risk. However, women expect to have satisfactory anesthesia during cesarean delivery, as do patients undergoing other types of surgery. It is also interesting that headache and back pain are relatively more common in the claims involving vaginal delivery. This may result, in part, from factors unique to labor and vaginal delivery (e.g., back strain from assuming unnatural positions during childbirth, increased risk for postdural puncture headache after bearing down during the second stage of labor).[99,100]

TABLE 33-2 Maternal Injuries Compared with Similar Injuries in Nonobstetric Claims*

Type of Injury	Maternal Injury Claims (n = 640)	Nonobstetric Injury Claims (n = 4410)
Maternal/patient nerve damage	19% (119)	20% (868)
Maternal/patient death	15% (94)‡	30% (1325)
Headache	11% (72)‡	1% (44)
Back pain	10% (62)‡	1% (62)
Emotional distress	8% (54)‡	5% (201)
Maternal/patient brain damage	7% (44)†	10% (442)
Pain during anesthesia	6% (38)‡	1% (45)
Aspiration pneumonitis	1% (5)‡	4% (164)

*The most common maternal injuries in the obstetric anesthesia claims occurring 1990 or later are shown as % (n). Percentages are based on the total claims in each group. Some claims had more than one injury and are represented more than once. Claims involving brain damage include only patients who were alive when the claim was closed.

†$P \leq .01$; ‡$P < .001$ compared with nonobstetric claims.

Data from the American Society of Anesthesiologists Closed-Claims Project database, N = 9536, December 2010.

Table 33-2 lists the most common injuries identified after eliminating those involving only the neonate. This allows comparison of the profiles of maternal injury with those among the nonobstetric population. The most

TABLE 33-3 **Most Common Precipitating Events in Obstetric Anesthesia Claims***

Event	Nonobstetric Claims (n = 4410)	Obstetric Claims (n = 640)	Type of Obstetric Anesthesia	
			NEURAXIAL (n = 489)	GENERAL (n = 123)
Respiratory system events	22% (959)§	5% (29)	1% (7)§	16% (20)
Difficult intubation	6% (250)§	2% (15)	< 1% (1)§	11% (14)
Aspiration	3% (149)§	1% (5)	< 1% (1)†	2% (3)
Inadequate ventilation/oxygenation	5% (202)§	1% (7)	1% (5)	1% (1)
Premature extubation	2% (109)§	< 1% (1)	0% (0)	1% (1)
Airway obstruction	2% (72)§	< 1% (1)	0% (0)	1% (1)
Block-related events	11% (473)§	41% (265)	54% (265)§	0% (0)
High spinal/epidural	1% (30)§	6% (41)	8% (41)§	0% (0)
Dural puncture headache	< 1% (20)§	6% (40)	8% (40)§	0% (0)
Inadequate analgesia	< 1% (11)§	5% (35)	7% (35)§	0% (0)
Retained catheter	< 1% (6)§	4% (25)	5% (25)‡	0% (0)
Neuraxial cardiac arrest	1% (43)†	2% (13)	3% (13)	0% (0)
Other block-related**	5% (240)§	16% (101)	21% (101)§	0% (0)
Surgical events/patient condition	9% (416)§	25% (158)	19% (95)§	38% (47)
Cardiovascular system events	15% (682)‡	11% (69)	7% (35)§	26% (32)
Hemorrhage	3% (126)§	6% (38)	3% (15)§	18% (22)
Pulmonary embolism	1% (49)§	4% (23)	3% (15)	7% (8)
Medication events	8% (351)§	4% (27)	4% (18)	6% (7)

*The most common damaging events occurring 1990 or later are shown as % (n). Chronic pain claims are excluded. Percentages are based on the total claims in each group. Specific precipitating events were not identified in all claims. Some claims indicated more than one damaging event, but only the most significant event is listed. Columns do not sum to 100% as minor events are not listed. Statistical comparisons are made between obstetric and equivalent nonobstetric claims as well as between obstetric neuraxial and obstetric general anesthetics.

†$P < .05$; ‡$P < .01$; §$P < .001$ compared with obstetric claims or general anesthesia.

**Of the 101 other block-related claims, 2% (12) were epidural abscess, 1% (5) were epidural hematoma, 2% (13) were other permanent disabling nerve injuries, 7% (43) were temporary or minor nerve injuries, 1% (5) were meningitis, and 4% (23) were other miscellaneous block-related events.

Data from the American Society of Anesthesiologists Closed-Claims Project database, N = 9536, December 2010.

striking finding is that the maternal claims contain a much higher proportion of relatively minor injuries such as headache, pain during anesthesia, back pain, and emotional distress (35%) than do the nonobstetric claims (8%). Obstetric patients may be at greater risk for some of these complications.[98] For example, the popularity of neuraxial anesthetic techniques in obstetric anesthesia combined with the greater risk for post–dural puncture headache in young females may account for the greater number of headache claims in the obstetric group. Pain during anesthesia is almost always associated with cesarean delivery conducted with neuraxial anesthesia. These claims may have resulted from a reluctance by the anesthesiologist to convert to general anesthesia because of the risk for aspiration or anticipated difficult airway management. In some cases claims may have resulted from other factors, such as unrealistic expectations or general dissatisfaction with the care provided.

Precipitating Events Leading to Injuries

Perhaps even more important than the injuries and complications that may result in claims are the precipitating events that lead to the injuries (Table 33-3). Critical events involving the respiratory system were the most common anesthesia-related events in both the obstetric and nonobstetric claims involving general anesthesia. The proportion of difficult intubation and aspiration claims in the obstetric claims was found to be significantly less than that in the nonobstetric claims. Difficult intubation was the precipitating event in 15 (2%) of the obstetric claims, and pulmonary aspiration was the precipitating event in 5 (1%) of the obstetric claims. Among the five aspiration claims, three were related to general anesthesia but only one was associated with a difficult intubation; the other two occurred during the preinduction period. In a fourth case, the patient was sedated with an unprotected airway and aspirated after vomiting. The final case was unrelated to anesthesia.

Several reports have suggested that difficult intubation and pulmonary aspiration are the leading causes of anesthesia-related maternal mortality.[101-103] Interestingly, a study of anesthesia-related maternal deaths in the state of Michigan between 1985 and 2003 found that no deaths occurred during induction of anesthesia; all cases related to airway obstruction or hypoventilation (> 50% of anesthesia-related deaths) occurred postoperatively, often when monitoring and supervision were inadequate.[104]

Despite the reduction in the proportion of claims for respiratory events in the past two decades,[95] these data reemphasize that (1) all obstetric patients are at risk for airway complications (e.g., difficult intubation, aspiration); (2) anesthesia providers should be familiar with protocols such as the ASA difficult airway algorithm; (3) equipment should be immediately available for the management of patients in whom tracheal intubation proves difficult; and (4) obstetric patients require the same standard of postanesthesia care as nonobstetric patients (see ASA "Guidelines for Neuraxial Anesthesia in Obstetrics" [Appendix A]).

Obesity increases the risk for both obstetric[105] and anesthetic[106,107] complications in pregnant women (see

Chapter 50). In the ASA Closed-Claims Project database, damaging events related to the respiratory system were significantly more common among claims involving obese parturients (18%) than in the claims involving nonobese parturients (8%) ($P < .05$). However, the rates of other injuries were not significantly different in obese and nonobese parturients.[93]

With the increasing use of neuraxial anesthesia for both vaginal and cesarean deliveries, it is not surprising that neuraxial blockade–related events are the most common precipitating events in the obstetric population, accounting for a significantly greater proportion of cases than found among the nonobstetric claims. The use of an effective epidural test dose, the incremental injection of the therapeutic dose of local anesthetic, the availability of ropivacaine and levobupivacaine, and the use of pencil-point spinal needles (leading to a greater rate of spinal anesthesia) have undoubtedly contributed to a reduction in the incidence of serious adverse outcomes associated with epidural anesthesia in obstetric patients.[102] However, the database includes several claims for neuraxial anesthesia–associated cardiac arrest (predominantly secondary to unintentional intrathecal injection of drug) and for high spinal or epidural neuroblockade. Ironically, the number of claims for inadequate analgesia during neuroblockade, usually during cesarean delivery, has also increased.

The proportion of cardiovascular events in the obstetric claims has increased over time; maternal hemorrhage was the most common precipitating event (6%). More than half of the cases were associated with abnormal placentation (placenta accreta or percreta); in several cases the abnormal placentation was not diagnosed before delivery. Inability or failure of the anesthesia provider to adequately resuscitate the patient was a factor in the majority of cases. Delayed diagnosis of hemorrhage, poor communication among providers, unavailability of blood products, and inappropriate blood product replacement were other contributing factors. Death secondary to maternal hemorrhage is believed to be the most common preventable cause of maternal mortality.[108] Early diagnosis and intervention (by both surgical and anesthesia providers), and the use of major obstetric hemorrhage protocols to streamline response systems and improve availability of blood products, have been shown to reduce major hemorrhage rates and improve outcomes (see Chapter 38).[109]

An embolic disorder was the second most common cardiovascular event related to maternal death in the ASA Closed-Claims Project database. Of the 23 embolic disorder claims, 20 cases were due to amniotic fluid embolism; only 3 cases were due to venous thromboembolism. This finding may reflect the effectiveness of peripartum thromboprophylaxis measures that have been widely introduced over the past decade.

Payments

The practice of obstetrics is associated with high medicolegal risk. The obstetric anesthesia provider may also be named in a malpractice suit, in an attempt to increase payments beyond policy limits. This belief is reinforced by well-publicized cases involving huge monetary awards. However, the ASA Closed-Claims Project database provides a somewhat different perspective. For the purposes of this discussion, a payment is considered to be any expenditure by the insurance carrier in the form of a settlement or award. Obstetric claims constitute 12% of the ASA Closed-Claims database. Similarly, the obstetric claims account for 11% of the total number of payments made and 14% of the total dollars expended in payments. Clearly, the payments for obstetric claims were not disproportionately frequent or large. Table 33-4 provides additional payment information. For claims in which payments were made, the median payment was greater in the obstetric group. This is not surprising, considering that there are two patients at risk in obstetric anesthesia cases, and both the mother and her infant are younger than the average age of patients in the nonobstetric files. Although the obstetric claims contained a lower proportion of deaths (either maternal or newborn), there was a greater proportion of brain injuries (either maternal or

TABLE 33-4 **Payment Data for Obstetric Anesthesia Claims Compared with Nonobstetric Anesthesia Claims***

	Type of Practice		*Type of Obstetric Anesthesia*		*Type of Delivery*	
	NONOBSTETRIC CLAIMS (n = 4410)	OBSTETRIC CLAIMS (n = 640)	NEURAXIAL (n = 489)	GENERAL (n = 123)	CESAREAN (n = 387)	VAGINAL (n = 241)
Payment Made	53% (2227)	45% (274)‡	43% (198)†	55% (65)	49% (180)	39% (87)†
Median Payment ($)	254,000	398,250‡	284,375‡	1,237,500	557,500	172,000‡
Range ($)	129 to 33.96M	1293 to 19.65M	1293 to 19.65M	8000 to 11.55M	6223 to 19.65M	1293 to 8.33M

M, million.

*Payment frequency, shown as % (n), and dollar amounts (adjusted to 2011 values). Percentages are based on the total number of claims occurring 1990 or later in each group with payment data. Statistical comparisons are made between obstetric and nonobstetric claims, between obstetric neuraxial and general anesthetics, and between vaginal and cesarean deliveries. Claims with missing payment data were excluded from the analysis.

†$P \leq .01$

‡$P \leq .001$.

Data from the American Society of Anesthesiologists Closed-Claims Project database, N = 9536, December 2010.

newborn) than in the nonobstetric claims. Such injuries typically result in higher payments for projected lifelong care requirements.

Lessons Learned

The obstetric anesthesia claims reveal a risk profile that differs from that of the nonobstetric anesthesia claims. Surprisingly, since 1990, problems involving airway management, especially difficult intubation and pulmonary aspiration, are disproportionately represented in the nonobstetric claims. The continuing decrease in the use of general anesthesia in obstetric cases, and the widespread use of difficult airway algorithms, may be factors that have contributed to improvements in obstetric patient safety. The incidence of systemic local anesthetic toxicity has diminished. However, the ASA Closed-Claims Project database continues to receive information on claims for severe adverse outcome resulting from neuraxial anesthesia–associated cardiac arrest (primarily owing to unintentional and unrecognized intrathecal injection of drug). The data suggest that we need to continue our efforts to reduce the risks of major complications of both general and neuraxial anesthesia. The large number of claims for pain during neuraxial anesthesia for cesarean delivery, however, suggests that general anesthesia should not be delayed or avoided if a patient has inadequate anesthesia from neuraxial blockade.

Unfortunately, anesthesiologists frequently are inappropriately named in lawsuits involving "bad baby" outcomes, despite increasing evidence that cerebral palsy is associated with birth asphyxia in only 6% to 8% of cases, and even in these children, prevention may not be possible.[110] In 2003, an ACOG task force published criteria to help define the causal relationship between acute intrapartum events and cerebral palsy (see Chapter 10).[111] Among cases in the ASA Closed-Claims Project database from 1990 and later, anesthesia-related events contributing to newborn death and brain damage were uncommon; a payment was made on behalf of the anesthesiologist in only 21% of claims for newborn death/brain damage.[95] Potentially preventable anesthetic causes of newborn injury included delays in anesthetic care (primarily due to the anesthesiologist being away from the hospital or poor choice of anesthesia technique), substandard anesthesia care, and poor communication between the obstetrician and the anesthesiologist (often related to the urgency of cesarean delivery).[95]

Perhaps the most surprising finding of the analysis of the obstetric cases in the ASA Closed-Claims database is the large proportion of relatively minor injuries in the obstetric claims. This proportion markedly contrasts to that in the nonobstetric claims, suggesting that efforts to reduce the incidence of major injuries will not solve the medical malpractice problem in obstetric anesthesia. Clearly, factors other than major injury must motivate patients to bring a claim. It is overly simplistic to equate lawsuits with injury. A 1991 study found that the proportion of patients harmed by negligent care who actually file a claim is only 2%.[94] However, a lawsuit does not occur unless someone perceives that he or she or a loved one has been wronged. One of the unique advantages of closed-claims studies is that they reflect the consumer perspective.

To some extent the large proportion of relatively minor injuries in the obstetric claims may reflect a higher incidence of such problems among obstetric patients. However, it is clear that many of these patients were unhappy with the care provided and believed that they had been ignored or mistreated. It has been suggested that malpractice litigation serves the purposes not only of reparation of injury and deterrence of substandard care but also of emotional vindication.[112,113] Anesthesia care providers should give attention to conducting themselves in such a manner that patients will not be motivated to bring suit for an unexpected outcome.[114] The importance of establishing good rapport with patients cannot be overemphasized. Whenever possible, anesthesiologists should involve themselves in the prenatal education process. A careful preanesthetic evaluation is very important and should occur as early in labor as possible. Special care should be taken to provide patients with realistic expectations and knowledge of potential major and minor risks associated with anesthetic procedures.

PROFESSIONAL PRACTICE STANDARDS

One beneficial effect of closed-claims analyses has been the greater attention to steps to minimize the occurrence of severe adverse outcomes. On the basis of an analysis of malpractice claims in 1985, the Harvard University–affiliated medical institutions adopted a set of minimal monitoring standards within their system. Since that time the malpractice losses (normalized for the number of anesthetics given) have declined by more than 50%.[115] In 1986, the ASA became the first professional medical society to promulgate professional standards of care. The introduction of the ASA "Standards for Basic Intra-Operative Monitoring" was accompanied by a decrease in the number of anesthesia-related liability claims. Although it is difficult to prove a cause-and-effect relationship between the introduction of these standards and fewer claims and payments, the arguments seem compelling.[115] Better monitoring, especially the greater use of pulse oximetry and capnography, has undoubtedly contributed to the decrease in severe complications and associated large awards.[116]

The ASA also has directed its efforts at improving obstetric anesthesia care in this country through a variety of position statements. In 1986, the ASA House of Delegates and the ACOG approved a joint statement entitled "Optimal Goals for Anesthesia Care in Obstetrics" (see Appendix C). This policy-oriented document recognized the need for (1) appropriately trained physicians to provide anesthesia care, (2) a qualified obstetrician to be readily available during the administration of anesthesia, and (3) equipment, facilities, and support personnel for labor and delivery units equal to that provided in the surgical suite. The document served as the basis for the ASA "Standards for Conduction Anesthesia in Obstetrics," which was approved by the ASA House of Delegates in 1988. Unfortunately, unlike the widely acclaimed "Standards for Basic Intra-Operative

Monitoring," these obstetric anesthesia practice standards generated immediate and widespread controversy. In part, this was because they had implications with regard to nursing, obstetric, and pediatric practices and were considered too restrictive and too difficult to meet, especially for smaller or rural obstetric facilities. Consequently, in 1991, the document was revised and renamed "Guidelines for Regional Anesthesia in Obstetrics." The current document was revised in 2010 and renamed "Guidelines for Neuraxial Anesthesia in Obstetrics" (see Appendix A).

In October 1998, the ASA House of Delegates approved a document developed by the ASA Task Force on Obstetrical Anesthesia. This evidence-based document, titled "Practice Guidelines for Obstetrical Anesthesia," is more clinically oriented than the aforementioned guidelines and was last amended in 2007 (see Appendix B). It synthesizes a large body of published studies "to enhance the quality of anesthesia care for obstetric patients, reduce the incidence and severity of anesthesia-related complications, and increase patient satisfaction." The document provides systematic analyses and meta-analyses of specific anesthetic techniques and practices, along with general recommendations.

It is hoped that these practice guidelines will positively affect the quality of care and the liability profiles in obstetric anesthesia practice. Practice guidelines suggest a standard of care and are based on both evidence and expert opinion. As such they often are used as evidence in cases of medical malpractice. Such documents can be used for exculpatory purposes (i.e., to exonerate a defendant physician) or as inculpatory evidence (i.e., to implicate a defendant physician). A two-part study surveyed 960 randomly selected malpractice attorneys and 259 open and closed claims from two malpractice insurance companies.[117] The claims were opened during a 2-year period (1990 to 1992) and included all claims involving obstetric and anesthetic cases. Practice guidelines played a pivotal role in 17 cases. In 12 cases they were used as inculpatory evidence and in 4 as exculpatory evidence (in 1 case the use of practice guidelines could not be classified). Similarly, the surveyed attorneys responded that guidelines were used to implicate malpractice more than twice as often as they were used to defend against a claim of malpractice (54% versus 23%). The ACOG guidelines were used most frequently in these claims, but the ASA guidelines were used rarely. The authors speculated that the simplicity and clarity of the ASA guidelines may make compliance easier. Clearly, practice guidelines may act as a double-edged sword in medical litigation. Nonetheless, guidelines may reduce litigation expenses by dissuading plaintiffs' attorneys from pursuing cases in which guidelines have been met or by encouraging early settlement by the defense in cases in which guidelines were not followed without good reason.

POTENTIAL RISK MANAGEMENT PROBLEM AREAS

Obstetric anesthesia often is an unpredictable, difficult, and high-stress environment for the anesthesia provider. Compared with the operating room environment, the typical obstetric service is less familiar and more chaotic. The role and responsibility of the anesthesia provider is less clearly defined. Anesthesia services may be urgently requested in a situation in which there is little information available about the patient and the patient is unable or unwilling to answer questions. Laboring women typically are not sedated and calm when they request neuraxial anesthesia. Rather, women in active labor may be uncooperative and even combative during the administration of neuraxial anesthesia. The anesthesia provider may need to provide care for multiple patients simultaneously and may need to entrust some monitoring responsibilities to nurses. In some situations the choice of anesthesia may be dictated by others, and anesthesia providers may feel that they are little more than technicians. Perhaps it is not surprising that many anesthesia providers are uncomfortable in this environment and prefer to minimize their liability and discomfort by limiting their time practicing obstetric anesthesia.

Support Persons during Labor

Unique to obstetric anesthesia care is the presence of the patient's partner or other support persons during anesthesia care. In the past it was considered a privilege for a husband or relative to be present during a cesarean delivery, and often there were preconditions such as documentation of attendance at prenatal classes. Today, in many obstetric centers, it is taken for granted that one or more support persons will be present for virtually any type of delivery. Undoubtedly, this trend has resulted in part from a sincere desire to facilitate a more family-centered experience. A second motivation may be to attract patients in a competitive, market-oriented environment.

We are not aware of specific case law regarding issues involving support persons. However, the topic does raise a number of risk management questions. What are the parturient's rights with regard to having support personnel present during labor and delivery? What are the rights of the institution and health care providers? The presence of a support person often helps reassure and calm the parturient, but this is not always true. In some cases the presence of a support person can adversely affect patient care. Melzack[118] found that women have higher pain scores during labor when the husband is present. Similarly, Orbach-Zinger et al.[119] found that parturient anxiety and pain during the epidural procedure were higher in parturients randomized to the partner's presence during the neuraxial procedure compared with the partner's absence from the labor room.

Many anesthesia providers are not accustomed to having lay observers present during anesthesia procedures. Their presence can distract the provider's attention and adversely affect judgment and performance. It is helpful, especially in obstetrics, for the anesthesiologist to develop a close physician-patient relationship. The presence of a support person often distracts the patient's attention away from the conversation and activities of the anesthesiologist. In some cases this is helpful, but in others that distraction interferes with the provision of anesthesia care.

The support person also may be at risk for unanticipated injury.[120] We are aware of a number of instances in which a father suffered an injury as a consequence of a vasovagal episode. In one case the father dropped the newborn on the floor as he lost consciousness. Although there was no legal action in any of these cases, the potential liability issues are self-evident.

In some cases, support persons may request that they be present during the delivery even when the patient receives general anesthesia. At the University of Washington we do not allow support persons in the operating room during administration of general anesthesia; the patient undergoing general anesthesia does not require "support" in the traditional sense, and the possibility for complications is ever present. Even under the best of circumstances, the presence of such a person makes it more difficult for the anesthesia provider to give full attention to the patient. Routine anesthesia practices and procedures during general anesthesia may be frightening and misunderstood by laypersons. No matter how well intentioned and well prepared, the sight of a loved one who is unresponsive, intubated, and mechanically ventilated can be traumatic emotionally.

Videotaping

Physicians and hospitals also should consider policies regarding the use of audio/video equipment in the delivery room. Clearly all patients have a right to refuse to be photographed, filmed, or videotaped. However, a woman often wants a photographic record or videotape of events surrounding her delivery. Such a record can provide dramatic documentation of unfortunate interactions or suboptimal medical care. Courts typically allow videotapes to be entered into evidence and permit videotapes to be edited reasonably.[121] The visual impact of delivery room events can have a profound impact on a jury, regardless of whether the videotape has been edited to the advantage of the plaintiff. After the presentation of such evidence, it may be difficult to convince a jury of the appropriateness of treatment.

A survey of 35 members of the American College of Legal Medicine identified nine cases in which an obstetric videotape was used as evidence.[121] In response to such cases, some hospitals have instituted policies to limit the use of video equipment in their labor and delivery suites. Such policies may antagonize patients and prompt them to seek care elsewhere. A balanced approach may be the best solution (i.e., it may be reasonable to allow use of video equipment but to establish clear, fair, and unambiguous policies regarding its use). The policies must be understood by all members of the staff and should be made known to patients and their families, preferably before the patient is admitted to the hospital. Prenatal classes can serve as a means to disseminate such information. One approach is to have informational material and/or specific consent forms for patients and their families. Another option is to combine such policy statements with a "hold harmless" waiver for the support person. Although none of these measures can eliminate the potential liability risks associated with these issues, they may serve to educate patients and their families about their rights and about hospital policies and procedures.

KEY POINTS

- Effective communication with the parturient and her family is an important component of obstetric anesthesia practice.
- Honest, caring, and comprehensive discussion with the patient before the administration of anesthesia meets legal and ethical standards, improves the image of the anesthesiologist, and reduces the likelihood of dissatisfaction and possible litigation after unanticipated complications.
- Informed consent may be either verbal or both verbal and written. Written consent provides documentation that the consent process has occurred. If possible, it is best to obtain consent early in labor, before the onset of severe pain.
- Refusal of care by pregnant patients may raise unique legal and ethical concerns. In such situations, the woman's competency or ability to make an informed medical decision may be an issue. When the patient is competent, the health care providers should attempt to resolve treatment conflicts through additional patient education and discussion. Rarely, it may be advisable to seek a court order to resolve competency and/or medical treatment issues.
- Maternal nerve injury was the most common damaging event in obstetric anesthesia claims in the American Society of Anesthesiologists (ASA) Closed-Claims Project database from 1990 onwards. Detailed neurologic examination, involvement of neurologic specialists, and appropriate investigations can assist in making an accurate diagnosis.
- Critical events involving the respiratory system were the most common anesthesia-related events leading to adverse outcome in both obstetric claims and nonobstetric claims involving general anesthesia in the ASA Closed-Claims Project database. Use of a difficult airway algorithm, availability of specialized equipment (e.g., a video laryngoscope), and high-quality postoperative care after general anesthesia may help reduce the incidence of these events.
- Obstetric claims include a much higher proportion of relatively minor injuries (e.g., headache, pain during anesthesia, back pain, emotional distress) than nonobstetric claims.
- Guidelines for obstetric anesthesia practice have been published by the ASA, and a joint statement has been published by the ASA and the American College of Obstetricians and Gynecologists.

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PART IX

OBSTETRIC COMPLICATIONS

Donald Caton, MD

The philosophy of obstetric management changed in the early decades of the twentieth century, and this change had a profound effect on the use of obstetric anesthesia. Until 1900, obstetricians considered childbirth a physiologic process best left to proceed without interference by physician or midwife. They criticized "meddlesome practices" for normal deliveries. Then a new generation of obstetricians, concerned about the high rate of complications associated with routine deliveries, began to advocate more active management of childbirth. They envisioned the practice of obstetrics as a form of preventive medicine. Leaders of this movement, such as Joseph DeLee of Chicago, became strong advocates for the routine use of episiotomy, forceps delivery, and manual removal of the placenta. Of course, these measures also necessitated greater use of anesthesia.[1]

DeLee acknowledged that his method "interferes much with Nature's process," but he felt justified. With conservative management, he said, a dismal outcome was so common that he "often wondered whether Nature did not deliberately intend women should be used up in the process of reproduction, in a manner analogous to that of the salmon, which dies after spawning. Perhaps laceration, prolapse and all the evils are, in fact, natural to labor and therefore normal.…If you adopt this view, I have no ground to stand on, but, if you believe that a woman after delivery should be as healthy, as well as anatomically perfect as she was before, and that the child should be undamaged, then you will have to agree with me that labor is pathogenic, because experience has proved such ideal results exceedingly rare."[2] Other physicians agreed with DeLee. Austin Flint asked how a "process that kills thousands of women each year, leaves a quarter of all cases more or less invalidate, is attended by severe pain and tearing of tissues, and kills three to seven percent of all babies, can be called a normal or physiologic function?"[3]

The change in the philosophy of obstetric management was further stimulated by early feminists. In the United States, but especially in Great Britain, feminists formed a coalition with obstetricians to improve teaching, build new facilities, and fund better care for women in hospitals. They also demanded better anesthesia coverage and even funded research to develop new anesthetic techniques. In response to this movement, physicians developed many new techniques for laboring patients. Many of the anesthetic methods now favored for normal deliveries are a direct outgrowth of public support for innovation and improvement that began during this time.

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CHAPTER 34

Preterm Labor and Delivery

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CHAPTER OUTLINE

Preterm delivery is defined as delivery before 37 weeks' gestation. It occurs in 12% to 13% of all pregnancies in the United States and in 5% to 9% of pregnancies in other developed countries.[1] Preterm delivery is responsible for 75% to 80% of all neonatal deaths and significant neonatal morbidity.[1,2] Birth statistics in the United States reveal a 20% increase in the preterm delivery rate between 1990 and 2006 (from 10.6% to 12.8%) and a 30% increase since 1981.[3] Subsequently, the preterm delivery rate declined to 11.72% of all births in 2011 (Figures 34-1 and 34-2).[4] Preterm births not only account for a significant degree of neonatal morbidity and mortality but also are responsible for a large economic burden to society. For example, in 2005, the costs associated with preterm birth were at least $26.2 billion.[3]

In 2010, late preterm deliveries comprised 71% of all preterm births (see Figure 34-2). There is a notable racial/ethnic disparity in the frequency of preterm birth. In 2010, 10.8% of non-Hispanic whites, 17.1% of non-Hispanic blacks, and 11.8% of Hispanics delivered preterm. Women age 25 to 34 years were least likely to deliver preterm (11.4%), whereas women 40 years or older were most likely to deliver preterm (25.9%).[5]

The concern about preterm birth is not confined to the United States; the World Health Organization (WHO) and other nongovernmental organizations have identified the frequency of preterm birth as a critical health issue. The WHO uses low birth weight as an indicator of early delivery because true gestational age at delivery is often not available (see Figure 34-1). Worldwide, the incidence of low birth weight, defined as a birth weight less than 2500 g, is 15.5 per 1000 births.[6] Africa and Asia have the highest incidence of low birth weight, at 14.3 and 18.3 per 1000, respectively. In contrast, in Europe and North America the incidence of low birth weight is 6.4 and 7.7 per 1000, respectively.[6] Likewise, infant mortality rates are significantly higher in developing nations, particularly the sub-Saharan African countries. The United States has a higher infant mortality rate than Europe (6 versus 3 per 1000 births, respectively), which reflects the higher preterm birth rate in the United States.[7]

In 2006, the Institute of Medicine recommended that investigators focus on (1) better defining the problem; (2) developing treatments to prevent both preterm delivery and morbidity for children born preterm; (3) identifying the causes of preterm birth, including modifiable risk factors and the reasons for disparity among different ethnic, racial, and socioeconomic groups; and (4) developing policies and public programs that can be used to reduce the rate of preterm birth.[3]

DEFINITIONS

A preterm infant is defined as one who is born between 20 0/7 weeks and 36 6/7 weeks, inclusive, after the first day of the last menstrual period. If a good basis does not exist for establishing the gestational age from maternal history, the exact gestational age is difficult to determine. A low birth weight does not necessarily signify that a neonate has been born preterm, because some newborns have a low birth weight because they are small for gestational age (SGA) rather than preterm. A neonate who weighs less than 2500 g at birth is considered to have a low birth weight (LBW), regardless of gestational age. Likewise, an infant who weighs less than 1500 g at birth is considered to have a very low birth weight (VLBW), and an infant who weighs less than 1000 g at birth is considered to have an extremely low birth weight (ELBW).

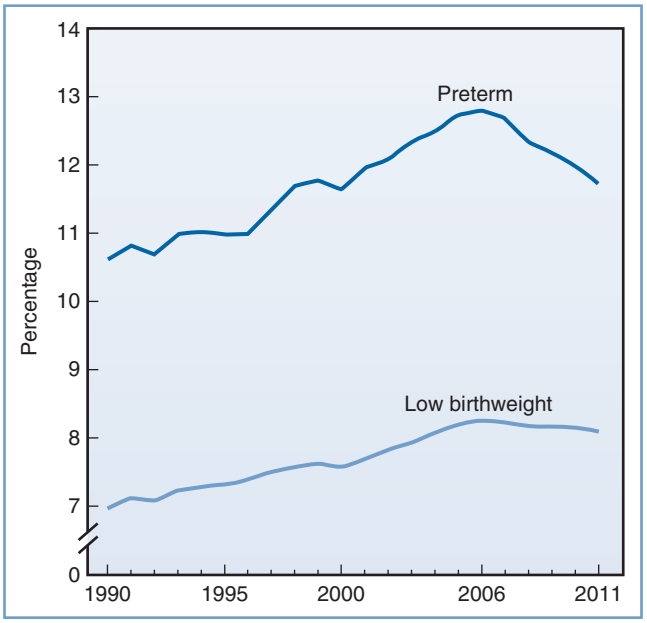

FIGURE 34-1 ■ Preterm and low birth weight rates: United States, final data from 1990 to 2010, preliminary data from 2011. (From Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2011. Natl Vital Stat Rep 2012; 61[5].)

NEONATAL MORTALITY

The survival rate among neonates increases as the birth weight and/or gestational age increases (Figure 34-3; Table 34-1).[8] After data are controlled for gestational age and weight, male infants have a higher mortality than female infants.[9] During the past three decades, there has been a significant improvement in the survival rate for preterm infants, with the greatest improvement occurring in the subgroup with a birth weight between 501 and 1250 g.[10] The rate of neonatal survival now exceeds 90% for infants born after 30 weeks' gestation, and a neonatal survival rate close to that of a term infant can be expected for those born after 32 weeks' gestation.

However, despite this improvement, infants with a birth weight between 501 and 750 g continue to have high mortality rates (Table 34-2). For example, in a cohort of neonates delivered between 2000 and 2009, the mortality rate for infants weighing between 501 and 1500 g decreased from 14.3% to 12.4%.[10] When stratified by birth weight, mortality ranged from 36.6% for infants who weighed between 501 and 750 g to 3.5% for infants who weighed between 1251 and 1500 g.[10] A retrospective cohort study assessed survival rates for infants delivered between 24 and 26 weeks' gestation.[11] Neonatal survival was 43%, 74%, and 83% at 24, 25, and 26 weeks' gestation, respectively. The majority of women received antenatal corticosteroids, and the majority of neonates received exogenous surfactant. A delay in delivery of even 1 week at this time in gestation leads to significantly better outcome and reduced cost. A similar study that examined a cohort of infants born between 1998 and 2002 showed a survival rate of 0% for infants born at 21 completed weeks' gestation; the survival rate rose steadily to 75% at 25 completed weeks' gestation (see Table 34-1).[12]

Infants born at the threshold of viability (22 to 24 weeks' gestation) continue to have the greatest risk for

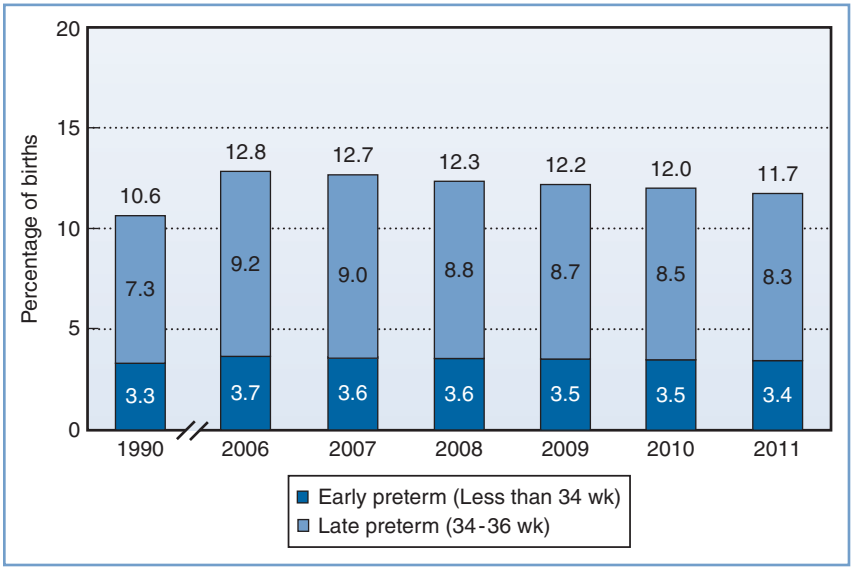

FIGURE 34-2 ■ Total, early, and late preterm birth rates: United States 1990 and 2006 to 2010 (final) and 2011 (preliminary). Preterm birth is defined as less than 37 weeks' completed gestation. Early preterm is defined as less than 34 weeks' completed gestation. Late preterm is defined as 34 to 36 completed weeks' gestation. (*Source:* Centers for Disease Control and Prevention/NCHS, National Vital Statistics System; natality.)

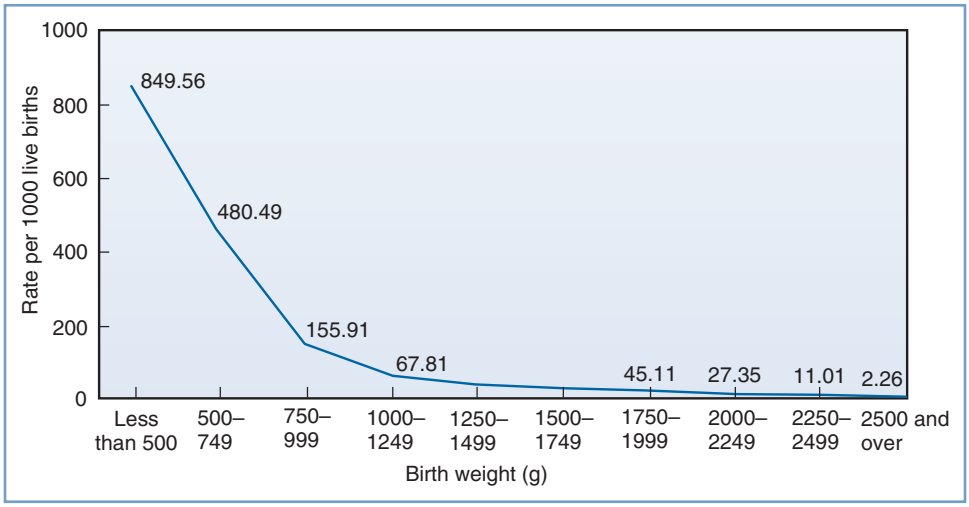

FIGURE 34-3 ■ **Infant mortality rates by birth weight: United States, 2004.** (From Mathews TJ, MacDorman MF. Infant mortality statistics from the 2004 period linked birth/infant death data set. Natl Vital Stat Rep 2007; 55:1-32.)

TABLE 34-1 Neonatal Deaths by Gestational Age

Completed Weeks' Gestation	Percentage of Deaths*
22	94
23	74
24	45
25	28
26	16
27	12
28	8

*Death rate before discharge by gestational age among infants born in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Centers between 2003 and 2007.

Data from Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010; 126:443-56.

TABLE 34-2 Selected Outcomes for Extremely Preterm Infants*

Outcome	Percent (Range†)
Use of antenatal therapy	
Maternal corticosteroid administration	80 (45-97)
Maternal antibiotic administration	67 (55-85)
ROM > 24 h before delivery	25 (18-32)
Cesarean delivery	59 (47-81)
Male gender	53 (47-58)
Multiple birth	25 (18-34)
Delivery room resuscitation	
Delivery room infant tracheal intubation	67 (41-85)
5-min Apgar score ≤ 3	16 (3-25)
Surfactant therapy	76 (58-88)
Survival	72 (55-95)
Survived without morbidity‡	37 (7-50)

ROM, rupture of membranes.

*Birth weight < 1000 g. Data are from the Eunice Kennedy Shriver National Institute of Child Health Development Neonatal Research Network for 9575 infants, gestational ages 22 to 28 weeks, birth weight 401 to 1500 g, between 2003 and 2007.

†Ranges are across 19 Neonatal Research Network centers.

‡Morbidities included severe intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis, infections, and retinopathy of prematurity (ROP) stage ≥ 3.

Data from Stoll BJ, Nansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010; 126:443-56.

poor outcome. A recent study examined outcome for infants born between 22 and 27 weeks' gestation between the years 2002 and 2008. The mortality rate for those born between 22 and 24 weeks' gestation was 61% compared with 19% for those born between 25 and 27 weeks' gestation.[13] Compared with infants born at 22 to 24 weeks' gestation, infants born at 25 to 27 weeks' gestation were more likely to have been exposed to antenatal maternal corticosteroid administration (87% versus 62%), to be delivered by cesarean (70% versus 39%), and to be resuscitated at birth (99% versus 75%). It is estimated that 2% to 5% of VLBW infants who survive to hospital discharge die within 2 years because of medical complications of prematurity.[13]

NEONATAL MORBIDITY

Approximately 90% of preterm births occur between 32 and 36 6/7 weeks' gestation. Compared with earlier gestational ages, mortality is less common, but morbidity is a relatively greater concern in this gestational age range. As with mortality, most morbidity decreases in frequency as the gestational age increases. For example, the incidence of high-grade (III or IV) intraventricular hemorrhage (IVH) diminishes rapidly after 27 weeks' gestation and grade III or IV intraventricular hemorrhages are very rare after 32 weeks' gestation. Likewise, neonatal morbidity from patent ductus arteriosus and

necrotizing enterocolitis diminishes significantly after 32 weeks' gestation.[12] Data from the National Institute of Child Health and Development (NICHD) Neonatal Research Network sites from 1997 through 2002 indicate that survival without complications (e.g., bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis, or a combination of these disorders) ranged from 20% for infants with a birth weight between 501 and 750 g to 89% for those with a birth weight between 1251 and 1500 g.[2]

Piecuch et al.[14] reported data for a cohort of 138 nonanomalous infants delivered between 24 and 26 weeks' gestation between 1990 and 1994. The incidence of cerebral palsy did not differ significantly among the three groups born at 24, 25, and 26 weeks' gestation (11%, 20%, and 11%, respectively). However, the incidence of normal cognitive outcome rose with increasing gestational age at birth (28%, 47%, and 71% at 24, 25, and 26 weeks' gestation, respectively).

The EPICure study group assessed the association between extreme preterm delivery and long-term physical and mental disability in a cohort of infants delivered between 22 and 25 weeks' gestation during a 10-month period in 1995.[15] These investigators noted rates of severe disability of 54%, 52%, and 45% among infants delivered at 23, 24, and 25 weeks' gestation, respectively. In a later cohort of infants, born between 1997 and 2002, the rates of severe disability were 33%, 21%, and 12% for infants delivered at 23, 24, and 25 weeks' gestation, respectively.[16] A 6-year follow-up to the EPICure study cohort showed persistent severe disability in 25%, 29%, and 18% of infants born at 23, 24, and 25 weeks' gestation, respectively.[17]

Hack et al.[18] monitored a cohort of ELBW infants born between 1992 and 1995 until they were 8 years old. The mean birth weight was 810 g, and the mean gestational age at delivery was 26 weeks. Compared with a cohort of age-matched children of normal birth weight, the ELBW group had a higher incidence of significant neurosensory impairment (16% versus 0%, respectively) and asthma (21% versus 9%). The ELBW children differed significantly from the cohort with normal birth weight in rates of suboptimal intelligence, academic achievement, motor skills, and adaptive functioning. These data illustrate the long-term medical, educational, and social services required by these children.

Correspondingly, the economic costs for the care of surviving preterm infants (especially VLBW infants) can be enormous. The Institute of Medicine estimated that the societal economic burden associated with preterm birth in the United States was at least $26.2 billion in 2005, or $51,600 per infant born preterm.[3] These figures likely will continue to rise with the escalating cost of health care.

PRETERM LABOR

Risk Factors

Box 34-1 lists factors associated with preterm labor.[1,19,20] These associations do not necessarily indicate cause-and-effect relationships. Significant risk factors include a history of preterm delivery, non-Hispanic black race (irrespective of socioeconomic status), and multiple gestation.

BOX 34-1 Factors Associated with Preterm Labor

Demographic Characteristics

- Non-Caucasian race
- Extremes of age (<17 or >35 years)
- Low socioeconomic status
- Low prepregnancy body mass index
- History of preterm delivery
- Interpregnancy interval < 6 months
- Abnormal uterine anatomy (e.g., myomas)
- Trauma
- Abdominal surgery during pregnancy

Behavioral Factors

- Tobacco use
- Substance abuse

Obstetric Factors

- Vaginal bleeding
- Infection (systemic, genital tract, periodontal)
- Short cervical length
- Multiple gestation
- Assisted reproductive technologies
- Preterm premature rupture of membranes
- Polyhydramnios

Data from references 1, 19, and 20. Modified from Muir HA, Wong CA. Preterm labor and delivery. In Chestnut DH, Tsen LC, Polley LS, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

The process of normal parturition involves anatomic, physiologic, and biochemical changes that lead to (1) greater uterine contractility, (2) cervical ripening, and (3) membrane/decidual activation.[19,20] The fetus also appears to play a role in parturition. It is hypothesized that the mature fetal hypothalamus secretes more corticotropin-releasing hormone (CRH), which in turn stimulates fetal adrenal production of adrenocorticotropic hormone (ACTH) and cortisol.[19] Preterm labor results from the pathologic activation of one or more of these components (Figure 34-4).[21] Preterm delivery results from (1) preterm premature rupture of membranes (preterm PROM) in approximately 30% of cases, (2) spontaneous preterm labor in approximately 45% of cases, and (3) maternal or fetal indications for early delivery in approximately 25% of cases.[22] However, the "spontaneous" causes do not have a uniform underlying pathophysiology, and it appears that preterm labor is a syndrome with multiple causes influenced by a number of genetic, biologic, biophysical, psychosocial, and environmental factors.

Two emerging factors of interest are the influences of **infection** and **uterine distention** on initiation of myometrial contractility. Infection is thought to be present in up to 40% of preterm deliveries.[1] Commonly identified organisms include *Ureaplasma urealyticum*, *Bacteroides* species, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, group B streptococci, *Staphylococcus aureus*,

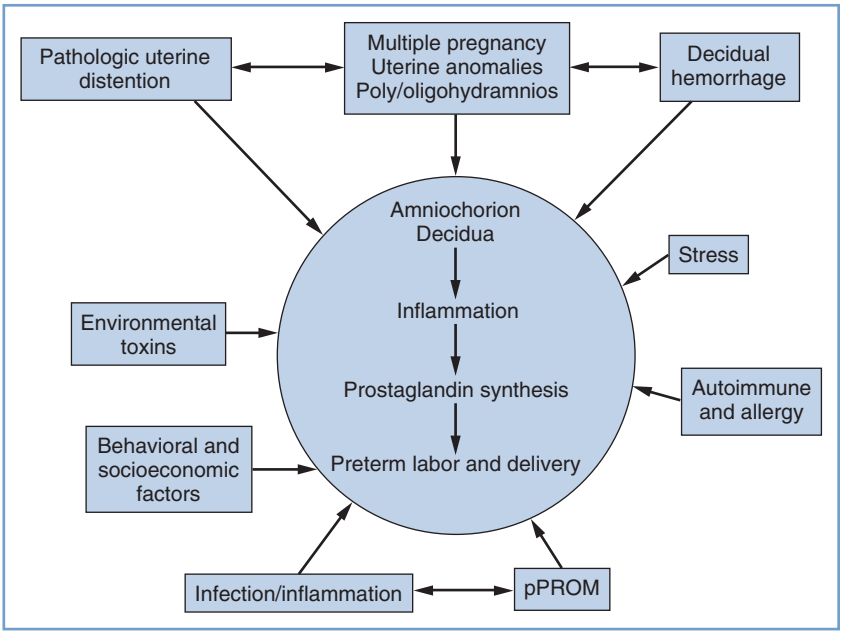

FIGURE 34-4 ■ Major etiologic factors in preterm birth, including activation of the maternal or fetal hypothalamic-pituitary axis (stress), inflammation, decidual hemorrhage, and pathologic distention of the myometrium. The pathways are not mutually exclusive and may overlap, and they share a common biochemical pathway. *pPROM,* preterm premature rupture of membranes. (From Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand 2008; 87:590-600.)

Treponema pallidum, and enteropharyngeal bacteria.[23-25] Although approximately 50% of preterm deliveries occur in women with no apparent risk factors, subclinical infection may precipitate preterm labor in some of these cases.[24]

In the past three decades there has been a significant rise in the incidence of **multiple gestation** (see Chapter 35). The twin birth rate increased by 76% from 1980 to 2009.[5] The triplet and higher-order multiple birth rate rose by over 400% during the 1980s and 1990s but has declined 29% since the 1998 peak.[4] The increased incidence of multiple gestation is due, in part, to the significant increase in the use of **assisted reproductive technologies** (ARTs).[26] Over 50% of all twins and 90% of all triplets are born preterm.[5] Consequently, multiple gestations account for 17% of all preterm births.[27] ART pregnancies are also associated with an increase in risk for preterm delivery, even for singleton pregnancies.[28] A 2004 meta-analysis of 15 studies, which compared outcomes for 12,283 ART singleton pregnancies with outcomes for 1.9 million spontaneously conceived singleton pregnancies, demonstrated a higher risk for preterm and SGA deliveries in the ART group.[28] Placenta previa, gestational diabetes, preeclampsia, and neonatal intensive care unit admission were also more prevalent in the ART group.[28]

Approximately 25% of all preterm deliveries do not result from spontaneous preterm labor or preterm PROM. The obstetrician may choose to perform indicated delivery for maternal or fetal indications, such as severe preeclampsia or a nonreassuring fetal status.

Prediction of Preterm Labor

The ability to prevent spontaneous preterm birth would be facilitated if it were possible to intervene prophylactically to prevent preterm labor or to effectively treat preterm labor once it occurs. Both prophylaxis and treatment would be facilitated if it were possible to accurately predict which asymptomatic or symptomatic patients would have spontaneous preterm delivery. Several methods of predicting preterm delivery have been proposed, including home uterine activity monitoring, salivary estriol measurement, fetal fibronectin screening, and transvaginal cervical ultrasonography.[29]

The use of **home uterine activity monitoring** to identify women at risk for preterm labor has been investigated in a number of randomized controlled trials.[29] Likewise, **salivary estriol** levels have been assessed as a marker of risk for preterm delivery. Neither has been shown to be clinically useful in the prevention of preterm birth.

Fetal fibronectin (fFN) is a basement membrane glycoprotein produced by the fetal membranes. It functions as an adhesive protein of the placental membranes to the decidua.[30] fFN is normally absent from vaginal secretions from 20 weeks' gestation until near term. Detection of elevated levels of fFN is associated with an increased risk for preterm delivery. It is hypothesized that the presence of fFN is a marker of choriodecidual disruption. A study from the Maternal-Fetal Medicine Units Network documented that a positive fFN test result at 22 to 24 weeks' gestation had a sensitivity of 63% in predicting preterm labor before 28 weeks' gestation.[31] If fFN is absent (i.e., a negative result), the risk for preterm delivery within 1 or 2 weeks is less than 1%.[32] The high negative predictive value of this test may make it a useful tool to help triage symptomatic patients more efficiently, although this remains to be demonstrated in randomized trials[33]; currently, there is no role for this test in screening low-risk asymptomatic women.[29]

Short cervical length, as assessed by transvaginal ultrasonography, also is associated with a greater risk for preterm delivery.[34] In a 2006 systematic analysis, Kagan et al.[35] concluded that cervical length is associated with preterm delivery (i.e., the shorter the cervix the greater the risk for preterm delivery) in *symptomatic* women.

Further, multiple studies have shown an increased risk for preterm delivery in asymptomatic women with a shortened cervix.[29] A Maternal-Fetal Medicine Units Network study of nearly 3000 women found that the risk for spontaneous preterm delivery is increased in women with evidence of a short cervix detected by transvaginal ultrasonography between 24 and 28 weeks' gestation. A cervical length below the 10th percentile had a sensitivity of 37% and a specificity of 92% in predicting preterm birth before 35 weeks' gestation, with a corresponding positive predictive value of 18% and a negative predictive value of 97%.[34]

A history of cervical surgery, including conization and loop electrosurgical excision procedure, traditionally has been thought to be a risk factor for preterm birth because of associated cervical injury. However, this relationship may be related to environmental factors and/or behavioral factors that underlie the progression of cervical dysplasia. Uterine instrumentation, such as dilation and curettage, also has been associated with an increased risk for preterm birth in some, but not all, studies; the mechanism is unclear, but it may be a result of intrauterine microbial colonization, injury to the endometrium, or both, together with host and environmental factors.[29]

Prevention of Preterm Labor

Antenatal screening for risk factors for preterm labor and delivery is of value only if interventions are available that can decrease the frequency of preterm delivery and improve neonatal outcome.[29] Unfortunately, few if any interventions have been shown to definitively reduce these outcomes. Interventions that have been studied include detection and suppression of uterine contractions, antimicrobial therapy, prophylactic cervical cerclage, maternal nutritional supplements, and reduction of maternal stress.[20] It is not surprising that most of these simple interventions have not been shown to alter outcome, given that preterm labor is increasingly understood to be a complex syndrome with multiple, overlapping causes.[20]

Prophylactic **cervical cerclage** in the early second trimester has been performed to prevent preterm birth, typically in women with a history of mid-trimester pregnancy loss. Evidence that supports the efficacy of this practice is weak.[36] There remains controversy with regard to whether cerclage should be placed in response to transvaginal ultrasonographic evidence of a short cervix in the second half of the mid trimester. Data do not support such a practice in a general population,[37] but there is some evidence that such a practice may be beneficial among high-risk women, such as those with a prior preterm birth.[38]

Evidence does *not* support the administration of **prophylactic antibiotics** in asymptomatic women at risk for preterm labor.[39] Likewise, evidence does not support the prophylactic use of **beta-adrenergic receptor agonists** to prevent preterm labor in high-risk women.[40]

In contrast, evidence suggests that **progesterone** therapy may be effective in reducing the rate of preterm birth in some patient populations. The Maternal-Fetal Medicine Units Network performed a randomized controlled trial that compared prophylactic intramuscular 17α-hydroxyprogesterone caproate (17P) (250 mg weekly beginning at 16 to 20 weeks' gestation, and continued until delivery or 36 weeks' gestation) with placebo in women with a history of spontaneous preterm delivery.[41] The risk for delivery before 37 weeks' gestation was reduced in the 17P group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.54 to 0.81). Similarly, da Fonseca et al.[42] demonstrated a decreased risk for preterm delivery (< 34 weeks' gestation) in high-risk women randomly assigned to receive either vaginal progesterone (100 mg daily) or placebo. A systematic review of 11 randomized controlled trials (n = 2425) also concluded that progesterone administration was associated with a significant reduction in recurrent preterm birth in women with a history of spontaneous preterm delivery.[43]

Progesterone therapy also has been shown to be efficacious in preventing preterm delivery among women with a short cervix identified by transvaginal ultrasonography. In two double-blind, placebo-controlled trials, women with a mid-trimester diagnosis of a short cervix (< 15 mm in one trial[44] and 10 to 20 mm in the other[45]) were randomized to receive either vaginal progesterone or placebo. Women who received vaginal progesterone experienced a significant reduction in the frequency of preterm delivery before 33 weeks' gestation.[44,45] In contrast, in a trial that enrolled nulliparous women with a cervical length less than 30 mm, women randomized to receive 17P did not experience a reduction in preterm delivery compared with women who received placebo.[46]

A number of studies have examined whether progesterone is efficacious in reducing preterm birth among women with multiple gestation. Uniformly, progesterone therapy has *not* been shown to be beneficial in this population.[47-49]

Even among women for whom progesterone is thought to be indicated, the optimal type, timing, and dosing of progesterone is unclear. Based on existing evidence, the American College of Obstetricians and Gynecologists (ACOG)[29] has concluded that vaginal progesterone should be offered to asymptomatic women with a singleton gestation without a previous preterm delivery, who have a very short cervical length (i.e., ≤ 20 mm at or before 24 weeks' gestation).

Diagnosis

Determining whether a woman is in early preterm labor or in false labor is often difficult. Criteria for the diagnosis of preterm labor include gestational age between 20 0/7 and 36 6/7 weeks' gestation and regular uterine contractions accompanied by a change in cervical dilation, effacement, or both (or initial presentation with regular contractions and cervical dilation of 2 cm or more).[19] Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation.[19]

Assessment and Therapy

Initial assessment of the patient with possible preterm labor includes physical examination and external monitoring of contractions with a tocodynometer (and fetal heart

rate if indicated by the gestational age). Acute conditions associated with preterm labor should be considered, including infection and placental abruption. Maternal physical examination may include a sterile speculum examination to exclude preterm PROM if symptoms or signs indicate this possibility. In many women who have preterm uterine contractions, these contractions will cease spontaneously. In the past, clinicians assumed that intravenous hydration was a useful component of therapy. However, there is no evidence that intravenous hydration reduces the chance of preterm delivery.[50]

Once the diagnosis of preterm labor is established, the obstetric care provider must decide whether intervention is warranted. The therapeutic agents currently thought to be associated with improved neonatal outcomes include antenatal maternal corticosteroid administration to accelerate maturation of fetal lungs and other developing organ systems, and the targeted use of magnesium sulfate for fetal neuroprotection (see later discussion).[51,52] Although widely used before 34 weeks' gestation, acute tocolytic therapy remains a source of controversy. There is no consistent evidence that the use of acute tocolysis reduces the chance of preterm birth or improves neonatal outcome. However, because acute tocolysis has been associated with a short (approximately 48 hour) prolongation of pregnancy, it may be used to facilitate transfer of the patient from a community hospital to a tertiary care facility that can provide optimal care for the preterm neonate. Moreover, a short course of tocolytic therapy may delay delivery for 24 to 48 hours, allowing maternal administration of (1) a corticosteroid to accelerate fetal lung maturity and (2) antibiotic therapy to prevent neonatal group B streptococcal infection. Thus, the ACOG has supported the use of acute tocolysis to allow administration of a complete course of antenatal corticosteroids, but the ACOG discourages the continued use of tocolysis after corticosteroid administration is complete.[19]

Criteria for the use of tocolytic therapy include (1) gestational age after viability and before 34 weeks' gestation, (2) reassuring fetal status, and (3) no overt clinical signs of infection. The potential benefits of delaying delivery of the preterm infant (i.e., decreased neonatal morbidity and mortality) must be weighed against the maternal and fetal risks (e.g., maternal side effects of tocolytic drugs, deterioration of a compromised fetus). Box 34-2 lists contraindications to the inhibition of labor.

In the setting of preterm PROM, obstetricians have worried that tocolytic therapy might increase the risk for maternal and/or fetal infection. It also seems logical that tocolytic therapy is less effective in patients with preterm PROM. Prospective, randomized studies have shown that tocolytic therapy does not improve neonatal outcome compared with conservative expectant management in patients with preterm PROM.[53]

Antenatal Administration of Corticosteroids

The neonatal benefits of corticosteroid administration (Table 34-3) before preterm delivery have been clearly demonstrated in large clinical trials. The NICHD Neonatal Research Network evaluated outcomes for 11,718 preterm infants delivered after antenatal maternal corticosteroid administration between 1988 and 1992. Antenatal corticosteroid treatment significantly reduced the incidence of neonatal respiratory distress syndrome, intraventricular hemorrhage, and neonatal death in all subgroups of the population studied (including male and female infants, African and Caucasian race infants, and infants delivered before 30 weeks' gestation).[54] The reduction in neonatal morbidity and mortality from antenatal corticosteroid administration is additive to the reduction observed with the use of neonatal surfactant alone.[55]

Although there is little controversy about the efficacy of a single course of antenatal corticosteroids, there remains debate over the use of multiple courses of corticosteroids for women who remain undelivered 7 days after the initial dose of corticosteroids. A 2001 review[56] and a National Institutes of Health (NIH) consensus panel statement[57] did not recommend multiple courses of corticosteroids; however, both documents cited some evidence of their possible benefit. These documents also identified possible risks, including a higher incidence of neonatal infection and potentially deleterious effects on neuronal and organ growth.[56,57] A large study performed by the Maternal-Fetal Medicine Units Network randomly assigned women at risk for preterm delivery between 23 and 32 weeks' gestation to receive either a single course or repeated (weekly) courses of antenatal corticosteroids.[58] Weekly corticosteroid administration did not significantly reduce the composite primary morbidity outcome, but it significantly reduced the need for neonatal surfactant, mechanical ventilation, and continuous positive airway pressure (CPAP), as well as the incidence of pneumothorax. In contrast, weekly corticosteroid administration was associated with an increase in the delivery of SGA infants, and there was a significant reduction in the birth weight of the infants whose mothers received four or more courses of corticosteroids.

BOX 34-2 Contraindications to Tocolytic Therapy for Preterm Labor

- Fetal death
- Fetal anomalies incompatible with life
- Nonreassuring fetal status
- Chorioamnionitis
- Severe hemorrhage

Modified from Muir HA, Wong CA. Preterm labor and delivery. In Chestnut DH, Tsen LC, Polley LS, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

TABLE 34-3 Antenatal Corticosteroid Therapy

Drug	Dose and Route	Frequency/Duration
Betamethasone	12 mg IM	Every 24 h × 2
Dexamethasone	6 mg IM	Every 12 h × 4

IM, intramuscular.

From National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: Repeat courses—National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. Obstet Gynecol 2001; 98:144-50.

To balance the potential beneficial effects and risks of additional courses of corticosteroids, some have advocated for a *single* "rescue" course (i.e., a second course of corticosteroids), which is administered at the time of a second episode of preterm labor with a high probability of preterm delivery. One randomized trial demonstrated that additional neonatal benefit could be derived from a single "rescue" course of corticosteroids.[59] The investigators reserved this intervention for patients with intact membranes, whose antecedent corticosteroid treatment had been given at least 2 weeks before the "rescue" course, whose gestational age was less than 33 weeks, and who were judged by the clinician as likely to give birth within the next week. A meta-analysis[60] concluded that a single "rescue" course of antenatal corticosteroids should be considered in women whose prior course of antenatal corticosteroids was administered at least 7 days previously and who were at acute risk for preterm delivery before 34 weeks' gestation. The ACOG[51] has stated that one "rescue" course of corticosteroids may be considered in these specific populations. However, regularly scheduled repeat courses or multiple courses (more than two) of corticosteroids are not currently recommended.[51]

Antibiotic Therapy

The results of a large multicenter randomized controlled trial[61] and a meta-analysis[62] do *not* support the use of prophylactic antibiotic therapy in the management of preterm labor in patients with intact membranes as a method to reduce the likelihood of preterm birth. In fact, in one study that assessed long-term outcome for offspring born to women who participated in a randomized placebo-controlled trial of antibiotic administration in the setting of preterm labor, children born to women who received antibiotic treatment had more functional health impairment.[63] Accordingly, the ACOG[19] does not recommend empirical antibiotic therapy in this population. It should be noted, however, that prophylactic antibiotic administration remains appropriate in women who are positive for group B streptococcus (GBS) and who are thought to be in preterm labor.[64]

In contrast, in patients with preterm PROM, randomized controlled trials and a meta-analysis have concluded that antimicrobial therapy prolongs pregnancy and reduces both maternal and neonatal morbidity.[65,66] Thus, when preterm PROM is diagnosed, the ACOG[67] recommends a 7-day course of antimicrobial therapy; the best antibiotic regimen is not known with certainty, although intravenous ampicillin and erythromycin (48 hours), followed by oral amoxicillin and erythromycin (5 days), is a commonly used regimen for women with preterm PROM who are receiving expectant management.[67]

Neuroprotection

Several clinical trials have provided evidence that maternal administration of magnesium sulfate provides fetal neuroprotection when given to women at risk for preterm delivery. In 2003, Crowther et al.[68] reported the results of a multicenter randomized, placebo-controlled study of 1062 women (1255 infants) at less than 30 weeks' gestation, in whom delivery was planned or expected within 24 hours. The investigators observed no significant difference between groups in the primary outcomes, which included total pediatric mortality, cerebral palsy, or both, at a corrected age of 2 years. However, they observed a significantly reduced rate of substantial gross motor dysfunction, as well as a reduced combined rate of death or substantial gross motor dysfunction, in the children exposed to magnesium sulfate *in utero*.[68] Similarly, a randomized controlled trial of magnesium sulfate administration in 573 pregnant women at less than 33 weeks' gestation, and in whom delivery was planned or expected within 24 hours, found that infants exposed to magnesium sulfate had a reduced rate of total neonatal mortality, severe cerebral white matter injury (which is associated with cerebral palsy), and the combination of severe white matter injury and/or death, but the differences were not statistically significant.[69] In the largest randomized trial,[70] 2241 women at imminent risk for delivery before 32 weeks' gestation were randomized to receive magnesium sulfate or placebo. The offspring who had been exposed to magnesium sulfate *in utero* were significantly less likely to develop moderate/severe cerebral palsy (1.9% versus 3.5%; RR, 0.55; 95% CI, 0.32 to 0.95).[70]

A recent meta-analysis has synthesized the data from the clinical trials and suggests that prenatal administration of magnesium sulfate reduces the occurrence of cerebral palsy when given with neuroprotective intent (RR, 0.71; 95% CI, 0.55 to 0.91).[71] The ACOG[52] recently stated that, based on available evidence, magnesium sulfate—given before anticipated early preterm birth—reduces the risk for cerebral palsy in surviving infants. Because the best regimen of magnesium sulfate administration remains unclear, physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring based on the protocols of the larger published trials.[52]

Selection of Tocolytic Agents

Once the obstetrician has decided to begin tocolytic therapy, an appropriate agent must be selected (Table 34-4). (Each specific class of tocolytic agent is discussed in detail later in this chapter.) A 2003 analysis of studies that compared the four classes of tocolytic agents currently in use (i.e., beta-adrenergic receptor agonists, calcium entry–blocking agents, magnesium sulfate, and nonsteroidal anti-inflammatory drugs [NSAIDs]) concluded that all are more effective than placebo in prolonging pregnancy, but the investigators found no evidence of a beneficial effect on neonatal morbidity or mortality.[72] A more recent analysis suggested that magnesium sulfate specifically is not efficacious and should not be used for tocolysis.[73]

Physiology of Uterine Contractions

The contractile elements in myometrial smooth muscle consist of thick (myosin) and thin (actin) filaments that interact and slide past one another, generating the contractile force for uterine contractions. The myometrium

TABLE 34-4 **Tocolytic Drugs for Preterm Labor**

Drug	Contraindications	Maternal Side Effects	Fetal/Neonatal Side Effects
Calcium entry–blocking agents	Cardiac disease Renal disease (use with caution) Maternal hypotension	Transient hypotension, flushing, headache, dizziness, nausea	None identified
Cyclooxygenase inhibitors (NSAIDs)	Significant renal or hepatic impairment Active peptic ulcer disease Coagulation disorders or thrombocytopenia NSAID-sensitive asthma Other NSAID sensitivities	Nausea, heartburn	Constriction of the ductus arteriosus, pulmonary hypertension, reversible renal dysfunction (leading to oligohydramnios), IVH,* hyperbilirubinemia, necrotizing enterocolitis*
Beta-adrenergic receptor agonists	Cardiac dysrhythmias Poorly controlled thyroid disease Poorly controlled diabetes mellitus	*Cardiopulmonary:* dysrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia *Metabolic:* hyperglycemia, hyperinsulinemia, hypokalemia, antidiuresis, altered thyroid function *Other:* tremor, palpitations, nervousness, nausea/vomiting, fever, hallucinations	*Fetal:* tachycardia, hyperinsulinemia, hyperglycemia, myocardial and septal hypertrophy, myocardial ischemia *Neonatal:* tachycardia, hypoglycemia, hypocalcemia, hyperbilirubinemia, hypotension, IVH
Magnesium sulfate	Myasthenia gravis Myotonic dystrophy	Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest	Lethargy, hypotonia, respiratory depression, demineralization (prolonged use)

IVH, intraventricular hemorrhage; *NSAIDs,* nonsteroidal anti-inflammatory drugs.
*Data are conflicting as to whether cyclooxygenase inhibitors increase risk.
From Muir HA, Wong CA. Preterm labor and delivery. In Chestnut DH, Tsen LC, Polley LS, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009. Modified from Hearne AE, Nagey DA. Therapeutic agents in preterm labor: tocolytic agents. Clin Obstet Gynecol 2000; 43:787-801.

has pacemaker cells with spontaneous contractile ability, which spread activity throughout the rest of the uterus by means of gap junctions between myometrial cells. Myometrial contractions are preceded by a rise in intracellular calcium concentration through the influx of calcium across the sarcolemma and/or release from internal stores such as the sarcoplasmic reticulum. Hormones and neurotransmitters may play a role in the regulation of uterine activity by causing agonist-induced entry of calcium or other ions by means of receptor-controlled channels and the release of calcium from internal stores.[74]

The rise in intracellular calcium results in the formation of a complex between calcium and calmodulin (a regulatory enzyme), which activates myosin light-chain kinase (MLCK). Activated MLCK then phosphorylates the light-chain subunit of myosin, allowing actin to bind to myosin and activate myosin adenosine triphosphatase. Adenosine triphosphate (ATP) is then hydrolyzed, and muscle shortening or contraction results. Relaxation of smooth muscle results from a reduction in the intracellular calcium concentration and/or dephosphorylation of the myosin light chain by myosin light-chain phosphatase. Increases in intracellular cyclic adenosine monophosphate (cAMP) also can result in muscle relaxation by two mechanisms: (1) activation of a cAMP-dependent protein kinase, which decreases the activity of MLCK; and (2) a reduction of the intracellular calcium concentration.

The control of labor and the processes for signaling its onset are complex and incompletely understood. During pregnancy, the uterus remains in a state of functional quiescence as a result of the activity of various inhibitors, including progesterone, prostacyclin, relaxin, nitric oxide, parathyroid hormone–related peptide, corticotropin-releasing hormone, human placental lactogen, calcitonin gene–related peptide, adrenomedullin, and vasoactive intestinal peptide (Figure 34-5).[25] Before term the uterus goes through an activation phase in response to uterotropins, including estrogen. This activation phase is characterized by (1) greater expression of a series of contraction-associated proteins (including myometrial receptors for prostaglandins and oxytocin), (2) activation of certain ion channels, and (3) an increase in connexin-43 concentration. Once activated, the uterus can be stimulated to contract by the action of uterotonics such as oxytocin and prostaglandins E_2 and $F_{2\alpha}$. A parturition cascade likely removes the mechanisms that have maintained uterine quiescence and recruits factors that promote uterine activity.

Once the uterus has been "activated," endocrine, paracrine, and autocrine factors from the fetoplacental unit initiate a change in the pattern of uterine activity from irregular to regular contractions. Evidence from animal models suggests that the fetus may coordinate this change in activity through (1) its influence on the production of placental steroid hormones, (2) mechanical distention of the uterus, and (3) secretion of neurohypophyseal hormones and other stimulators of prostaglandin synthesis. The final common pathway for labor in all species is thought to be the activation of the fetal hypothalamic-pituitary-adrenal axis. Of interest, however, is the observation that spontaneous labor occurs in women with an

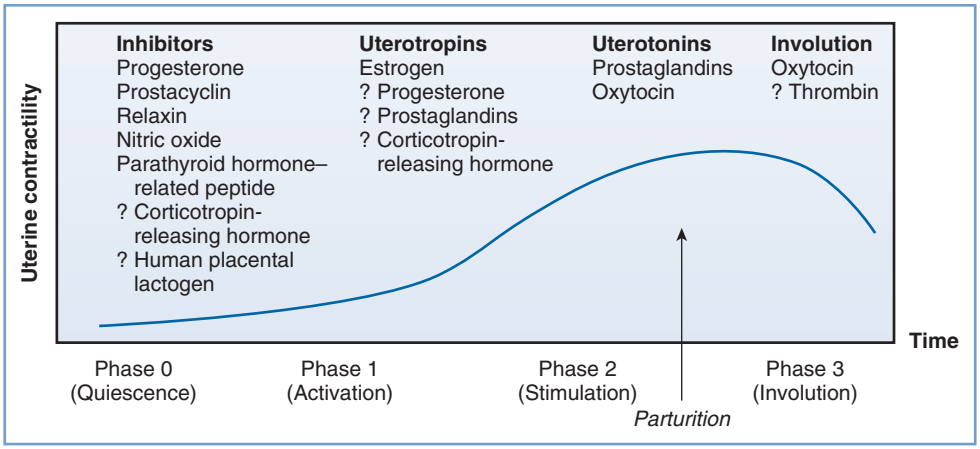

FIGURE 34-5 ■ The regulation of uterine activity during pregnancy and labor can be divided into four distinct physiologic phases—quiescence, activation, stimulation, and involution—that are, or may be, influenced by a number of stimulatory and inhibitory factors. (From Liao JB, et al. Normal labor: mechanism and duration. Obstet Gynecol Clin North AM 2005; 32:146; adapted from Challis JRG, Gibb W. Control of parturition. Prenat Neonat Med 1996; 1:283.)

anencephalic fetus (with no residual pituitary/adrenal function), suggesting that intact neurohypophyseal function is not a prerequisite for the onset of human labor.[75]

Preterm labor may result from a loss of inhibitory factors on uterine quiescence or may represent a short-circuiting of the normal parturition cascade through the overproduction of a critical factor. As the understanding of the physiology of uterine activity increases, the approach to both predicting and treating preterm labor will become more focused. Multimodal therapy may become a standard, given that evidence now suggests that labor is initiated by the interaction of multiple factors.

Significant attention has focused on the role of progesterone in parturition. In nonhuman mammals, the onset of labor is associated with progesterone withdrawal.[75] Although the understanding of its role in human labor remains incomplete, a number of isoforms of the progesterone receptor (PGR) have been identified. One isoform, PGR-B, may play a role in quiescence, whereas another, PGR-A, may act to initiate functional progesterone withdrawal. PGR-A receptors are increasingly expressed with the onset of labor. In concert with the increase in PGR-A relative to PGR-B, an increase in estrogen receptor transcripts is observed. This change may lead to an increase in estrogen responsiveness. A third isoform, PGR-C, may also contribute to antagonism of uterine quiescence. Through a complex interplay of co-regulators such as cAMP, progesterone receptors seem to be responsible for both uterine quiescence and the stimulation of the onset of labor.[75]

Gap junctions facilitate the propagation of electrical impulses and movement of small molecules between cells. Gap junction protein alpha-1 (GJA1, or connexin-43) is one of the main protein components of myometrial gap junctions. The appearance of gap junctions in myometrium is thought to herald the onset of labor.[75] GJA1 expression is stimulated by estradiol and is inhibited by progesterone. Microarray studies of human myometrium (i.e., preterm myometrium, term myometrium not in labor, term myometrium in labor) have added to the knowledge of the genetic modulation that occurs during pregnancy and labor.[76] Differential expression of 118 genes has been identified. A process of remodeling and maturation of the uterus, and the differential expression of the genes that regulate this process, are evident throughout gestation. Further work is needed to fully elucidate the signaling pathways that contribute to human labor.[76]

Efficacy of Tocolytic Therapy

There is general consensus that acute tocolytic therapy for the treatment of preterm labor offers only limited benefit and does not reduce the rate of preterm birth.[77] A meta-analysis suggested that **calcium entry–blocking agents** such as nifedipine are as efficacious as beta-adrenergic receptor agonists, with fewer maternal and fetal side effects.[78] The mechanism of action is thought to be inhibition of voltage-dependent calcium channels, which results in decreased calcium influx into smooth muscle cells, as well as decreased release of intracellular calcium stores into the myoplasm.

The **beta-adrenergic receptor agonists** (e.g., ritodrine, terbutaline) have been widely used as tocolytic agents for many years but have fallen out of favor because other tocolytic agents (e.g., nifedipine, oxytocin antagonists) are equally efficacious with fewer side effects.[78,79] Intravenous ritodrine, for example, is no longer marketed in the United States. Beta-adrenergic receptor agonists relax smooth muscle via β_2-adrenergic receptor stimulation. A 2004 meta-analysis included 17 studies, 11 of which compared beta-adrenergic agonists with placebo.[80] Use of beta-adrenergic agonists reduced the number of women who delivered within 48 hours, but there was no decrease in the number of births within 7 days or in perinatal death or neonatal morbidity. Tocolysis was significantly associated with adverse maternal side effects (see Table 34-4). In 2011, the United States Food and Drug Administration (FDA) issued a warning regarding terbutaline use. Specifically, it stated that *injectable* terbutaline should not be used in pregnant women for prolonged treatment (beyond 48 to 72 hours) of preterm labor in either the hospital or outpatient setting because

of the potential for serious maternal heart problems and death. It also warned that oral terbutaline should not be used for prevention or treatment of preterm labor because it had not been shown to be effective and was associated with similar safety concerns.[81]

Prostaglandins are mediators in the final pathways of uterine contraction. They increase intracellular calcium concentrations, increase activation of MLCK, and promote gap junction formation.[19] The nonselective **cyclooxygenase inhibitor** indomethacin is the agent in this class most often studied as a tocolytic agent. Serious maternal side effects are uncommon. Fetal concerns, in particular in the setting of prolonged use (> 48 hours), include a risk for constriction of the ductus arteriosus and oligohydramnios (due to fetal renal dysfunction).

The **oxytocin receptor antagonist** atosiban has received attention as a tocolytic agent. Although available in Europe, the drug was not approved by the FDA because of a higher rate of fetal deaths in the atosiban arm of a randomized controlled trial.[82] However, this finding may have been due to an imbalance in the number of women less than 26 weeks' gestation who were randomly assigned to receive atosiban. A 2005 meta-analysis concluded that atosiban did not achieve a lower rate of preterm birth than placebo or beta-adrenergic agonists. Several small, randomized controlled trials comparing atosiban with nifedipine have suggested that the drugs are equally efficacious for acute tocolysis.[83,84]

Magnesium sulfate also has been used as a tocolytic agent. A 2002 meta-analysis of nine high-quality randomized controlled trials that compared magnesium with placebo concluded that magnesium is ineffective in delaying or preventing preterm birth.[73]

The **nitric oxide donor** nitroglycerin has also been studied. A meta-analysis suggested that nitroglycerin does not delay delivery or improve neonatal outcome in comparison with placebo or other tocolytic agents.[85]

The ACOG[77] has stated that evidence supports the use of tocolytic treatment with beta-adrenergic agonist therapy, calcium entry–blocking agents, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for antenatal maternal corticosteroid administration. Multiple clinical trials have demonstrated that prolonged use of tocolytic agents (as prophylactic therapy or after completion of acute treatment) does not alter outcome. No matter which tocolytic agent is chosen, the risk for side effects increases when more than one tocolytic agent is administered simultaneously. Thus, combining tocolytic agents is not routinely recommended.

THE PRETERM INFANT

Physiology

Several, but not all, studies have suggested that the incidence of intrapartum acidosis is greater in the preterm fetus than in the term fetus.[86,87] The preterm fetus has lower hemoglobin concentration and oxygen-carrying capacity than a term fetus.[86] Nonetheless, these characteristics do not translate into a higher risk for intrapartum fetal neurologic injury.

Preterm infants are at risk for a number of complications, including respiratory distress syndrome, hyperbilirubinemia, necrotizing enterocolitis, intraventricular hemorrhage, perinatal infection, retinopathy of prematurity, patent ductus arteriosus, pulmonary hypertension, water and electrolyte imbalances, acid-base disturbances, anemia, and hypoglycemia.[2] In the long term, preterm infants also are more likely to experience adverse outcomes such as bronchopulmonary dysplasia, reactive airway disease, failure to thrive, cerebral palsy, neurodevelopmental delay, hearing loss, blindness, pulmonary hypertension, adult hypertension, and impaired glucose regulation.[2]

Method of Delivery

Evidence does not support a conclusion that routine cesarean delivery of preterm infants improves outcome. Malloy et al.[88] analyzed birth and death certificate information from Missouri for the years 1980 to 1984. The cesarean delivery rate for VLBW infants (500 to 1499 g) rose from 24% to 44%. During the same period, the cesarean delivery rate increased from 21% to 26% for infants weighing 1500 to 2499 g and from 14% to 18% for infants weighing 2500 g or more. The first-day death rates were significantly higher among the smallest infants (weighing 500 to 749 g) that were delivered vaginally than among those delivered by cesarean (59% and 33%, respectively), although this finding may very well be related to confounding by indication (i.e., cesarean delivery was more likely to be deferred for those judged to have the least chance of survival). In contrast, the mortality rates for the two methods of delivery for these infants did not differ after the first 6 days of life. There was no association between the method of delivery and first-day death rates for infants weighing between 750 and 1500 g. The investigators concluded that the use of cesarean delivery did *not* improve overall survival for VLBW infants.

Malloy et al.[89] later reviewed the incidence of intraventricular hemorrhage and neonatal mortality in 1765 VLBW infants admitted to seven neonatal intensive care units between 1987 and 1988. After adjusting the data for gestational age at birth and other maternal and fetal factors, these investigators concluded that cesarean delivery did not lower the risk for either mortality or intraventricular hemorrhage for infants who weighed less than 1500 g at birth.

A systematic review of six randomized controlled trials comparing elective with selective cesarean delivery for preterm infants (n = 122) found no difference in outcomes between groups, although the confidence intervals were wide because of the small number of patients included in the analysis.[90] A retrospective analysis of 2466 VLBW preterm infants in the state of Washington between 1994 and 2003 did not demonstrate any benefit of cesarean delivery for improving survival.[91] In a study published in 2012, Reddy et al.[92] examined neonatal outcomes by attempted route of delivery for singleton births that occurred between 24 0/7 and 31 6/7 weeks' gestation. Among women who delivered between 24 0/7 and 27 6/7 weeks' gestation with a vertex presentation, 77.2%

attempted vaginal delivery (85% success rate) with the remainder undergoing scheduled cesarean delivery. No difference was observed in neonatal mortality or other adverse neonatal outcomes between the two groups. Similarly, when examining outcomes in women with a vertex presentation between 28 0/7 and 31 6/7 weeks' gestation, no difference in neonatal mortality was found in women who attempted vaginal delivery compared with those who underwent planned cesarean delivery.[92]

Aside from operative risks in the index pregnancy, preterm cesarean delivery may increase maternal risk in subsequent pregnancies. In an observational study that involved 26,454 women with previous cesarean delivery, the Maternal-Fetal Medicine Units Network noted that women with a prior *preterm* cesarean delivery were at higher risk for uterine rupture than women with a prior *term* cesarean delivery (odds ratio [OR], 1.6; 95% CI, 1.01 to 2.50; $P = .043$).[93]

Most obstetricians perform cesarean delivery for the delivery of VLBW singleton fetus in a breech presentation.[88,89] Head entrapment behind an incompletely dilated cervix is more common in preterm singleton fetuses with a breech presentation because the head is larger than the wedge formed by the buttocks and thighs. Similarly, cesarean delivery has been recommended for preterm twins in whom the presenting fetus has a nonvertex presentation, although there are no prospective, controlled studies to support this practice.[94] The management of preterm twins when twin A is vertex and twin B is nonvertex is more controversial; there are no good data from clinical trials, and the results from observational studies suffer from potential selection bias.[95] Thus, a definitive recommendation regarding whether a breech second twin should be delivered by cesarean remains elusive; it seems reasonable that practitioners with experience can individualize care, taking into account the clinical circumstances, and offer certain patients the option of delivering preterm twins vaginally if the first twin has a vertex presentation.

The survival rate remains low for infants with a birth weight between 500 and 750 g. In these cases, obstetricians must decide whether to recommend cesarean delivery for fetal indications, such as in cases of nonreassuring fetal status or breech presentation. The neonatologist is frequently asked to speak with the patient about the risk for neonatal morbidity and mortality so that the patient can make an informed decision about the method of delivery. Regardless of the mode of delivery, if resuscitation is planned, additional support personnel (ideally a neonatologist and a neonatal resuscitation team) should be prepared and present for the delivery.

Ethical Issues

The antenatal maternal administration of corticosteroids, the application of advanced neonatal ventilation techniques, the use of neonatal surfactant therapy, and the use of extracorporeal membrane oxygenation (ECMO) have reduced mortality and morbidity for preterm neonates. However, below a certain gestational age (i.e., < 23 0/7 weeks), survival is not typically possible and the relationship between new treatments and reduced mortality is not relevant. Around the time when survival becomes at least possible, the chance of survival, and particularly survival without long-term major adverse outcomes, remains low and difficult to predict for any individual neonate. These uncertainties often lead to controversy about the decision to resuscitate (or not resuscitate) a preterm infant. Parents, obstetricians, and neonatologists should all be involved in the decision-making process.

Anesthesia providers may find themselves in the middle of these ethical dilemmas if they are practicing in a location at which the anesthesia provider is responsible for neonatal resuscitation. Although no firm rules exist, some basic principles can be applied. First, the parents should have a critical role in the decision-making process. Second, as much data as possible should be obtained to provide a prognostic assessment. Third, discussion of these issues ideally should be held before delivery, not in the moment of crisis. The ACOG[95] has published general recommendations about the care of infants on the threshold of viability but has not made specific recommendations for neonatal resuscitation on the basis of gestational age. In contrast, the Canadian Paediatric Society and the Society of Obstetricians and Gynaecologists of Canada have issued relatively specific recommendations.[96] For an infant born at 22 to 23 weeks' gestation, they suggest that resuscitation efforts be initiated only if uncertainty about gestational age exists or fully informed parents request that resuscitation be performed. For an infant born at 23 to 24 weeks' gestation, resuscitation can be offered as long as parents are informed of the need to reassess this decision at critical intervals and possibly withdraw therapy. For an infant born at 25 weeks' gestation, full resuscitation in the absence of lethal anomalies is recommended.[96] The American Heart Association and the American Academy of Pediatrics have stated that, with few exceptions, resuscitation is not indicated if the infant is delivered at less than 23 completed weeks' gestation or with a birth weight less than 400 g.[97] Revised neonatal resuscitation guidelines have addressed the ethical issues of non-initiation or discontinuation of resuscitation in the delivery room.[16,97] In some cases, a trial of therapy may be appropriate, but such a trial does not always mandate continued support.

Fetal Heart Rate Monitoring

Most obstetricians use continuous electronic fetal heart rate (FHR) monitoring once preterm labor becomes established and the gestational age and circumstances are consistent with the possibility of neonatal survival. Preterm gestation may complicate the interpretation of FHR patterns, given that the FHR pattern of preterm fetuses may have relatively decreased variability and magnitude of accelerations compared with the FHR pattern of term fetuses.[98]

The value of continuous electronic FHR monitoring over intermittent auscultation of the FHR remains controversial. Luthy et al.[99] performed a randomized trial comparing continuous electronic FHR monitoring (with selective fetal blood gas assessment) with periodic auscultation of the FHR during preterm labor in women with fetuses weighing between 700 and 1750 g. There was no

significant difference between groups in the incidence of cesarean delivery, low 5-minute Apgar scores, intrapartum acidosis, intracranial hemorrhage, or perinatal death. At 18 months of age, the incidence of cerebral palsy was significantly higher in the electronic FHR group than in the intermittent auscultation group (20% versus 8%, respectively).[100]

ANESTHETIC MANAGEMENT

Anesthesia providers often participate in the care of preterm parturients. Many women who deliver preterm request neuraxial analgesia for labor and vaginal delivery. These patients may also require cesarean delivery, for example, in situations of nonreassuring fetal status, and may require urgent administration of anesthesia.

Conventional wisdom holds that the preterm fetus is more vulnerable than the term fetus to the depressant effects of analgesic and anesthetic drugs, for the following reasons: (1) less protein available for drug binding, leading to a reduction in protein-drug affinity; (2) higher levels of bilirubin, which may compete with the drug for protein binding; (3) greater drug access to the central nervous system (CNS) because of the presence of an incomplete blood-brain barrier; (4) decreased ability to metabolize and excrete drugs; and (5) a higher incidence of acidosis during labor and delivery.[87,101] However, few controlled studies have documented the maternal and fetal pharmacokinetics and pharmacodynamics of anesthetic agents throughout gestation. The preterm fetus may be less vulnerable to the depressant effects of local anesthetics than originally thought. The human fetal liver cytochrome P450 system is present as early as 14 weeks' gestation and has the capability to oxidize several drugs.[102,103]

Teramo et al.[104] noted that the amount of lidocaine necessary to produce seizure activity in preterm fetal lambs was greater than that required in older fetal lambs. These investigators also observed that the cardiovascular response to lidocaine (i.e., increases in blood pressure and heart rate) was less severe in fetuses with a younger gestational age. Pedersen et al.[105] evaluated the effects of gestational age on the pharmacokinetics and pharmacodynamics of lidocaine in gravid ewes and fetal lambs. They studied two groups of animals, preterm (119 ± 1 days' gestation or 0.8 of term pregnancy) and near-term (138 ± 1 days' gestation or 0.95 of term pregnancy). They administered an intravenous infusion of lidocaine to obtain a maternal steady-state plasma concentration of 2 μg/mL. Transplacental transfer of lidocaine did not adversely affect fetal cardiac output, organ blood flow, or blood gas and acid-base measurements in either group. Tissue uptake of lidocaine was similar in the two groups of fetal lambs, except that it was greater in the lungs and liver of the term fetuses. The investigators concluded that there was no significant difference in the pharmacokinetics and pharmacodynamics of lidocaine between the two gestational ages studied.[105]

Smedstad et al.[106] also concluded that there was no difference in fetal blood pressure, heart rate, or blood gas measurements in response to maternal intravenous infusion of lidocaine or bupivacaine between early preterm (119 days' gestation) and late preterm (132 days' gestation) fetal lambs. In addition, the plasma concentrations of bupivacaine and lidocaine and the fetal-to-maternal ratios of both drugs were similar in the two groups of fetuses.

None of these studies evaluated the effects of anesthetic agents on the acidotic preterm fetus. Asphyxia may increase the risk for adverse effects by causing the following changes in the fetal environment: (1) reduced plasma protein-binding capacity (which increases the proportion of free drug available)[107]; (2) greater maternal-fetal hydrogen ion difference, which causes "ion trapping" of weak bases (e.g., amide local anesthetics, opioids) on the fetal side of the circulation[108]; (3) greater blood-brain barrier permeability[109]; and (4) enhanced susceptibility to the myocardial depressant effects of local anesthetics.[110,111]

Morishima et al.[110] subjected a group of preterm fetal lambs (0.8 of term gestation) to asphyxia by causing partial occlusion of the umbilical cord. They subsequently administered either lidocaine or saline-control intravenously to the gravid ewes for 180 minutes. The mean (± SD) maternal and fetal steady-state plasma lidocaine concentrations were 2.32 ± 0.12 and 1.23 ± 0.17 μg/mL, respectively. (These concentrations are similar to those that occur during administration of epidural anesthesia in humans.) Umbilical cord occlusion resulted in the typical fetal compensatory response to hypoxia (i.e., decreased FHR and increased blood flow to the fetal brain, heart, and adrenal glands). Maternal administration of saline-control did not result in additional deterioration of the fetus. However, maternal administration of lidocaine resulted in a significant increase in $Paco_2$, and decreases in pH, mean arterial pressure (MAP), and blood flow to the brain, myocardium, and adrenal glands. Thus, lidocaine attenuated the normal fetal compensatory response to asphyxia.

In an earlier study, the same investigators observed that lidocaine did not affect the fetal compensatory response to asphyxia in term fetuses.[111] They concluded that "the immature fetus loses its cardiovascular adaptation to asphyxia when exposed to clinically acceptable plasma concentrations of lidocaine obtained transplacentally from the mother."[110] Limitations of this study include (1) a failure to compare the fetal response to lidocaine with the response to other anesthetic, analgesic, or sedative drugs and (2) consideration of only the effects of a steady-state concentration of lidocaine in the presence of asphyxia. That is, the investigators did not evaluate the potential benefits derived from epidural anesthesia, such as reduced maternal concentrations of catecholamines and the ability of epidural anesthesia to facilitate a controlled, atraumatic delivery of the preterm infant.

Bupivacaine has a low fetal-to-maternal plasma concentration ratio because of its relatively high (96%) maternal protein binding; therefore, the potential for fetal toxicity seems minimal.[101] Studies of the effects of bupivacaine on the compensatory response to asphyxia in preterm fetal lambs have demonstrated results similar to those seen with lidocaine. Santos et al.[112] observed that bupivacaine abolished the compensatory increase in blood flow to vital organs in asphyxiated preterm fetal lambs. However, bupivacaine did not affect fetal heart rate, blood pressure, or acid-base measurements. The investigators

suggested that these changes were less severe than those seen with lidocaine in their earlier study.[110,112]

Ropivacaine and bupivacaine have almost identical dissociation constants (pK_B of 8.0 and 8.2, respectively), but ropivacaine's protein binding is slightly less than that for bupivacaine (92% versus 96%, respectively), and it is substantially less lipid soluble than bupivacaine.[113] These differences may affect maternal and fetal free plasma concentrations of drug. Investigators have documented higher maternal and fetal plasma concentrations with ropivacaine than with bupivacaine.[114,115] Studies suggest that ropivacaine is less cardiotoxic than bupivacaine. However, no study has evaluated the effect of ropivacaine on the fetal compensatory response to hypoxia.

2-Chloroprocaine also is a good choice of local anesthetic in preterm patients because it is rapidly metabolized in both the maternal plasma and fetal plasma.[116] Further, placental transfer of 2-chloroprocaine is not increased by fetal acidosis.[117]

Vaginal Delivery

Neither pudendal nerve block nor local infiltration of the perineum provides profound relaxation of the levator ani and bulbocavernosus muscles. Thus, for women in whom more profound analgesia is desired, either for elective or medical indications, neuraxial analgesia is the technique of choice during labor and vaginal delivery.

Neuraxial analgesia decreases maternal concentrations of catecholamines, and in some patients, it may improve uteroplacental perfusion as long as hypotension is avoided.[118] No prospective, controlled studies have evaluated the effect of neuraxial analgesia on preterm infant outcome. The timing of the intrapartum administration of neuraxial analgesia in preterm parturients may be problematic for several reasons. First, there may be uncertainty as to whether women who have contractions are in labor. Second, even women with a clear diagnosis of preterm labor often have a prolonged latent phase of labor, with or without the use of tocolytic agents. Third, once active labor begins, patients often progress though labor very quickly. Thus, in some cases, it may be appropriate to establish neuraxial analgesia even before it is clear that a preterm delivery will soon occur. An advantage of early initiation of neuraxial analgesia is the ability to rapidly convert labor analgesia to surgical anesthesia if emergency cesarean delivery should be necessary.

Cesarean Delivery

Administration of general anesthesia for preterm cesarean delivery is similar to that for parturients at term (see Chapter 26). Most anesthetic agents that are used for induction and maintenance of general anesthesia cross the placenta. If cesarean delivery is necessary, conventional wisdom holds that it is preferable to give either epidural or spinal anesthesia to avoid the depressant effects of agents given for general anesthesia. Rolbin et al.[119] observed that preterm infants exposed to epidural anesthesia for cesarean delivery had higher 1- and 5-minute Apgar scores than similar infants exposed to general anesthesia. Laudenbach et al.[120] performed a secondary analysis of prospectively gathered data from a population-based cohort study of all deliveries before 33 weeks' gestation in nine regions in France in 1997 (n = 1338). Of concern, after controlling for known confounders, infants born by cesarean delivery to mothers who received spinal anesthesia had a higher mortality rate than those born to mothers who received general or epidural anesthesia (adjusted OR, 1.7; 95% CI, 1.1 to 2.6).[120] However, the authors noted that the secondary analysis of a preexisting database did not allow them to adjust for confounders known to affect anesthetic outcome (e.g., intraoperative hypotension, choice of vasopressor, fluid management). Nonetheless, for these high-risk births, it seems reasonable that anesthesia providers should pay meticulous attention to maternal hemodynamic variables regardless of the type of anesthesia that is administered.

Many anesthesiologists have considered the maternal administration of supplemental oxygen during cesarean delivery essential, regardless of the choice of anesthetic technique. Recent studies, however, have questioned this practice. Fetal or neonatal hyperoxia may lead to production of oxygen free radicals that ultimately may result in neuronal damage.[121] Investigators have not demonstrated any clear improvement in neonatal outcome with maternal supplemental oxygen administration, even after a prolonged uterine incision-to-delivery interval.[122,123] Currently, it is not clear whether the maternal administration of supplemental oxygen affects neonatal outcome.

Some data from animal studies have suggested that exposure of the immature brain to anesthetic agents such as propofol, thiopental, ketamine, and inhalation agents can trigger significant brain cell apoptosis in the developing fetal/neonatal brain and cause functional learning deficits later in life.[124,125] However, in these animal studies, the duration of exposure to anesthetic agents was much longer than is typical for cesarean delivery in humans. Whether clinical exposure to anesthetic agents during general anesthesia for cesarean delivery results in clinically significant brain cell apoptosis in humans remains to be determined (see Chapters 10 and 17).

In summary, at the current time there is no evidence to support altering the anesthetic technique for cesarean delivery merely because the infant is preterm. Further study is necessary to determine whether one technique (e.g., spinal or epidural) or specific drug(s) (e.g., ephedrine or phenylephrine) have specific risks or benefits relative to the preterm infant.

INTERACTIONS BETWEEN TOCOLYTIC THERAPY AND ANESTHESIA

Indications for Anesthesia during and after Tocolytic Therapy

There are several situations in which obstetric patients require analgesia or anesthesia during or after tocolytic therapy. First, preterm labor may progress and delivery may occur despite tocolysis. In this case, the patient may desire pain relief during labor and vaginal delivery or may require anesthesia for cesarean delivery. Second, some

obstetricians give a tocolytic agent before and during the performance of cervical cerclage. Third, some obstetricians advocate the bolus injection of a tocolytic agent when there is a tetanic uterine contraction or tachysystole in the setting of an FHR abnormality. Fourth, many obstetricians administer tocolysis when attempting external cephalic version, a procedure that may also involve the request for neuraxial analgesia.

Calcium Entry–Blocking Agents

Among this class of drugs, **nifedipine** has undergone the most extensive evaluation as a tocolytic agent. Many obstetricians have suggested that calcium entry–blocking drugs should become first-line therapy in the treatment of preterm labor because of their low incidence of significant maternal and fetal side effects. Typical nifedipine dose regimens for preterm labor are listed in Table 34-5.

Mechanism of Action

Calcium entry–blocking drugs act by blocking the aqueous voltage-dependent cell membrane channels that are selective for calcium. They also act by preventing calcium release from the sarcoplasmic reticulum. The net result is a decrease in available intracellular calcium, which inhibits MLCK activity. This inhibition leads to decreased actin-myosin interaction, which results in relaxation of smooth muscle (including myometrial smooth muscle).[126,127]

Side Effects

Nifedipine has fewer side effects than beta-adrenergic receptor agonists. Hypotension is the most common side effect. Other side effects include headache, flushing, dizziness, and nausea.[128] Most effects are mild, but pulmonary edema[129] and myocardial infarction[130] have been reported after calcium entry–blocking agent therapy for preterm labor.

Although early animal studies noted that nifedipine and nicardipine decreased uterine blood flow and resulted in fetal hypoxemia and acidosis,[131,132] clinical studies have suggested that short-term administration of nifedipine does not adversely affect the uteroplacental or fetal circulation.[133,134]

Anesthetic Management

Although nifedipine has fewer effects on cardiac conduction than some of the other calcium entry–blocking agents, it has the potential to cause vasodilation, hypotension, myocardial depression, and conduction defects when used in combination with one of the volatile halogenated anesthetic agents.[135] One report noted that administration of both nifedipine and magnesium sulfate was associated with neuromuscular blockade in a preeclamptic patient at 28 weeks' gestation.[136]

Cyclooxygenase Inhibitors

Indomethacin is the prototype cyclooxygenase inhibitor used for tocolysis. Both **sulindac** and **ketorolac** also have been evaluated and found to be effective. Typical doses of this class of medication used for tocolysis are listed in Table 34-5.

Mechanism of Action

Cyclooxygenase inhibitors inhibit cyclooxygenase and thus prevent the synthesis of prostaglandins from the precursor, arachidonic acid. Prostaglandins E_2 and $F_{2\alpha}$ play an important role in the stimulation of uterine contractions by increasing intracellular calcium and activation of MLCK and promoting gap junction formation.[19]

Side Effects

Maternal side effects from indomethacin are minimal when it is used for tocolytic therapy. Indomethacin does not alter maternal heart rate or blood pressure. The most common complaints are nausea and heartburn.[137] Inhibition of cyclooxygenase results in decreased production of thromboxane A_2 and abnormal platelet aggregation. In contrast to aspirin, which permanently inhibits cyclooxygenase and therefore inhibits platelet aggregation for the lifetime of the platelet (7 to 10 days), indomethacin and other cyclooxygenase inhibitors reversibly inhibit cyclooxygenase; thus, their effect on platelet function is only transient.[138]

Maternal administration of a cyclooxygenase inhibitor may cause premature closure of the ductus arteriosus *in utero*. Indomethacin is often used to promote closure of the ductus arteriosus in the preterm neonate.[137] Moise et al.[139] used fetal echocardiography to evaluate the fetal response to short-term (< 72 hours) indomethacin therapy. They observed evidence of transient ductal

TABLE 34-5 Tocolytic Dose Regimens for Preterm Labor

Drug	Initiation Dose	Maintenance Dose
Nifedipine	20-30 mg PO	10-20 mg every 4-6 h
Cyclooxygenase inhibitors (NSAIDs)*:		
Indomethacin	50-100 mg PO or per rectum	25-50 mg every 4 h
Ketorolac	60 mg IM	30 mg every 6 h
Sulindac	200 mg PO	200 mg every 12 h
Terbutaline†	0.25 mg SQ	0.25 mg every 20 min to 3 h
Magnesium sulfate	4-6 g IV bolus over 20 min	2-4 g/h continuous IV infusion

IM, intramuscularly; *IV,* intravenously; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PO,* per os (orally); *SQ,* subcutaneously.
*NSAID administration should be limited to 48 to 72 hours and restricted to gestations < 32 weeks.
†Terbutaline is given until uterine quiescence occurs or maternal heart rate reaches 120 bpm.
Data from references 19 and 143. Modified from Muir HA, Wong CA. Preterm labor and delivery. In Chestnut DH, Tsen LC, Polley LS, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.

constriction in 7 of 14 fetuses between 26 and 31 weeks' gestation. Tricuspid regurgitation was also noted in three fetuses. These changes were reversed within 24 hours of discontinuation of indomethacin. Clinical studies suggest that indomethacin is less likely to cause intrauterine closure of the ductus arteriosus at earlier gestational ages.[137,140-142] Also, studies suggest that adverse neonatal effects (including closure of the ductus arteriosus) are unlikely if indomethacin is used in short courses (e.g., 24 to 48 hours).[137,141,142] For example, investigators[142] retrospectively analyzed fetal echocardiograms performed in 44 patients with preterm labor or polyhydramnios who were treated with indomethacin. The frequency of ductal constriction was relatively low (5% to 10%) until 32 weeks' gestation, when it rose to approximately 50%. Vermillion et al.[142] concluded that ductal constriction can occur at any gestational age but that it is reversible with early identification followed by timely discontinuation of indomethacin therapy.

Indomethacin administration may result in fetal oligohydramnios secondary to decreased fetal urine output.[143] Kirshon et al.[144] noted reduced fetal urine output after short-term[145] and long-term (15 to 28 days) maternal administration of indomethacin for tocolytic therapy. Amniotic fluid volume reaccumulated within 1 week after the discontinuation of indomethacin. Indomethacin may be used to treat polyhydramnios in selected cases. One proposed mechanism for the decrease in fetal urine output is an enhanced antidiuretic hormone effect after inhibition of cyclooxygenase.[146] Wurtzel[147] evaluated renal function during the first 10 postnatal days in 14 preterm infants exposed to indomethacin *in utero* and in 10 control infants. This investigator found that maternal administration of indomethacin did not significantly alter neonatal renal function.

Data are conflicting as to whether maternal cyclooxygenase inhibitor administration increases the risk for adverse neonatal outcomes, including intraventricular hemorrhage and necrotizing enterocolitis. A 2005 meta-analysis concluded that maternal administration of indomethacin at less than 34 weeks' gestation did not lead to an increased risk for adverse events.[148] However, the investigators cautioned that the significant heterogeneity in study design makes it difficult to draw definitive conclusions.

The current recommendation for use of cyclooxygenase inhibitors is to limit the course of therapy to less than 72 hours. This approach may delay delivery and allow maternal administration of corticosteroids to accelerate fetal lung maturity.

Anesthetic Management

The effects of indomethacin on platelet function are transient. Several large studies have demonstrated the safety of epidural and spinal anesthesia in patients receiving low-dose aspirin or one of a variety of cyclooxygenase inhibitors.[149-151] The Consensus Conference on Neuraxial Anesthesia and Anticoagulation (sponsored by the American Society of Regional Anesthesia and Pain Medicine) concluded that such therapy is not a contraindication to administration of neuraxial anesthesia.[152]

Beta-Adrenergic Receptors Agonists

In the past, **ritodrine** and **terbutaline,** among other agents, were commonly used beta-adrenergic tocolytic agents; however, their use has declined substantially. Maternal side effects continue to be a limiting factor in their use.[80]

Mechanism of Action

All beta-adrenergic tocolytic drugs have both β_1-receptor and β_2-receptor effects, but in different proportions. β_2-Receptors are found in smooth muscle (uterus, blood vessels, bronchi, intestine, detrusor, and spleen capsule), adipose tissue, liver, skeletal muscle, pancreas, and salivary glands. Ritodrine and terbutaline are relatively selective for β_2-receptors; stimulation of these receptors in the myometrium results in relaxation of uterine smooth muscle. Unfortunately, other undesired β_2-adrenergic agonist effects (e.g., vasodilation) and β_1-effects still occur. β_1-Receptors are located predominantly in the heart and adipose tissue. β_1-Receptor stimulation has clinically significant cardiovascular side effects, such as increased maternal heart rate and cardiac output.[153]

Beta-adrenergic agonists interact with β_2-receptor sites on the outer membrane of uterine myometrial cells, activating the enzyme adenyl cyclase. This enzyme catalyzes the conversion of ATP to cAMP, causing a rise in the intracellular concentration of cAMP. The higher cAMP concentration decreases the available intracellular concentration of calcium and inhibits MLCK activity. This inhibition, in turn, decreases the interaction between actin and myosin, resulting in myometrial relaxation.[143]

Treatment Regimen

Before beginning tocolytic therapy with a beta-adrenergic agonist, the obstetrician should determine baseline maternal vital signs and weight and exclude significant cardiovascular or pulmonary disease. Prolonged administration results in down-regulation (or desensitization) of the myometrial β_2-receptors.[154] There is no evidence that a continuous long-term infusion of terbutaline alters outcome.[155]

Side Effects

The administration of beta-adrenergic tocolytic therapy may result in the following maternal side effects: (1) hypotension; (2) tachycardia, with or without cardiac arrhythmias and myocardial ischemia; (3) pulmonary edema; (4) hyperglycemia; and (5) hypokalemia.[143] The reported frequency of these side effects has varied. Earlier studies reported an incidence of 2% to 9%.[156,157] However, Perry et al.[158] performed a retrospective review of outcomes for 8709 patients who had received a low-dose, continuous infusion of terbutaline. These investigators noted adverse cardiopulmonary effects in only 47 of 8709 patients, an incidence of 0.54%.

Other uncommon maternal side effects reported with the use of beta-adrenergic agents are elevations in serum transaminase levels,[159] paralytic ileus,[160] cerebral

vasospasm in patients with a previous history of migraine,[161] and respiratory arrest due to increased muscle weakness in a patient with myasthenia gravis.[162]

Anesthetic Management

It would seem ideal to delay administration of anesthesia until maternal tachycardia subsides. A delay of 15 minutes often results in slowing of the maternal heart rate. However, advanced labor, an abnormal presentation, and/or nonreassuring fetal status often require emergency administration of anesthesia. Published reports of anesthetic management after administration of a beta-adrenergic agent are scarce.[163-167] Ravindran et al.[165] reported one case each of intraoperative pulmonary edema, sinus tachycardia, and ventricular arrhythmia during general anesthesia in patients who had received terbutaline therapy immediately before or 15 minutes after the induction of anesthesia. These investigators recommended that induction of general anesthesia be delayed at least 10 minutes after discontinuation of the beta-adrenergic agent.

Chestnut et al.[168] performed a controlled study to determine whether administration of ritodrine worsens maternal hypotension during epidural anesthesia in gravid ewes. Prior administration of ritodrine did not worsen maternal hypotension during epidural lidocaine anesthesia in gravid ewes.

Theoretically, induction of epidural analgesia or anesthesia after beta-adrenergic agonist therapy may cause less hemodynamic compromise than spinal anesthesia because of the slower onset of sympathetic blockade. However, this theory remains unproven. Patients receiving beta-adrenergic agonist therapy are at risk for development of pulmonary edema (as discussed earlier). Therefore, aggressive hydration should be avoided before and during the induction of anesthesia in these patients.

If general anesthesia is required in a patient who has recently received beta-adrenergic tocolysis, agents that might exacerbate maternal tachycardia (e.g., atropine, glycopyrrolate, pancuronium) should be avoided. Residual maternal tachycardia may make it more difficult to assess volume status and depth of anesthesia. Halothane, which sensitizes the myocardium to catecholamine-induced arrhythmias, should not be used. Hyperventilation should be avoided, because it may exacerbate hypokalemia and potentiate the hyperpolarization of the cell membrane. In nonpregnant patients, Slater et al.[169] found that terbutaline pretreatment shortened the onset time and recovery of succinylcholine-induced neuromuscular blockade. It seems prudent to monitor neuromuscular function with a peripheral nerve stimulator during general anesthesia.

Oxytocin Antagonists

Atosiban (1-deamino-2-D-Tyr-[OEt]-4-Thr-8-Orn-vasotocin/oxytocin) is an oxytocin antagonist. It is a competitive inhibitor of oxytocin that binds to both myometrial and decidual receptors. It does not alter the subsequent sensitivity of the myometrium to oxytocin.[170] Clinically, this feature represents a major advantage; it should reduce the risk for postpartum uterine atony and hemorrhage.

Phase II and III studies have shown that atosiban is an effective tocolytic agent.[82,171-175] It has few maternal side effects, undergoes minimal placental transfer, and does not increase maternal blood loss at delivery.[82,171] Studies have suggested that atosiban has efficacy similar to that of beta-adrenergic agonists[174,175] and nifedipine[176] in obtaining and maintaining uterine quiescence. However, a meta-analysis of studies comparing atosiban with either placebo or beta-adrenergic agonists did not demonstrate that atosiban resulted in a reduction in preterm birth or improved neonatal outcome,[177] although side effects were fewer with atosiban. The FDA has not approved atosiban for use in the United States because of a higher rate of perinatal deaths in the atosiban arm of the study that it reviewed.[82]

There are no data on the interaction between atosiban and anesthetic agents. However, given the hemodynamic profile of this agent, one would not expect significant interactions. Atosiban is widely used in Europe.

Magnesium Sulfate

Mechanism of Action

Extracellular magnesium functions as a competitive antagonist of calcium either at the motor end plate or cell membrane, thus reducing calcium influx into the myocyte.[19,143] It also competes with calcium for low-affinity calcium-binding sites on the outside of the sarcoplasmic reticulum membrane and prevents the rise in free intracellular calcium concentration. Hypermagnesemia results in abnormal neuromuscular function. Magnesium also decreases the release of acetylcholine at the neuromuscular junction and the sensitivity of the end plate to acetylcholine.

Side Effects

Most studies have reported that magnesium sulfate results in less frequent and less severe cardiovascular side effects than the beta-adrenergic tocolytic agents.[178-180] Nonetheless, magnesium sulfate may have side effects similar to those that occur during beta-adrenergic tocolytic therapy. Chest pain and tightness, palpitations, nausea, transient hypotension, blurred vision, sedation, and pulmonary edema have been reported.[179,180] Hypermagnesemia may attenuate the normal compensatory responses to hemorrhage in the mother and fetus.[181,182]

Magnesium is eliminated almost entirely by renal excretion. Therefore, patients with abnormal renal function should be monitored carefully if they receive magnesium sulfate.

Anesthetic Management

It has been suggested that magnesium sulfate should be discontinued before the administration of epidural anesthesia because magnesium may increase the likelihood of hypotension through its generalized vasodilating properties. Vincent et al.[183] observed that magnesium sulfate

reduced maternal mean arterial pressure but not uterine blood flow or fetal oxygenation during epidural lidocaine anesthesia in gravid ewes. This study suggests that hypermagnesemia may increase the likelihood of modest hypotension during neuraxial anesthesia in normotensive parturients.

Magnesium attenuates the release of acetylcholine at the neuromuscular junction, reduces the sensitivity of the end plate to acetylcholine, and decreases the excitability of the muscle membrane. The drug potentiates the action of both depolarizing and nondepolarizing muscle relaxants.[184] A defasciculating dose of a nondepolarizing muscle relaxant should not be given before administration of succinylcholine in hypermagnesemic women. A standard intubating dose of muscle relaxant (e.g., succinylcholine 1 mg/kg) should be used because the extent of potentiation by magnesium sulfate is variable.[185] However, a lower dose of a nondepolarizing muscle relaxant should be administered during the maintenance of anesthesia.

Parturients receiving magnesium sulfate often appear sedated. Thompson et al.[186] evaluated the anesthetic effects of magnesium sulfate and ritodrine on the minimum alveolar concentration of halothane in pregnant and nonpregnant rats and reported a 20% decrease with serum magnesium levels of 7 to 11 mg/dL. A more detailed discussion of magnesium sulfate and its interactions with anesthetic agents is found in Chapter 36.

KEY POINTS

- Despite improved antenatal care, the incidence of preterm delivery in the United States remains approximately 12%.
- Preterm birth is a leading cause of neonatal mortality. Survivors have an increased chance of disability.
- Spontaneous preterm labor or preterm premature rupture of membrane (preterm PROM) account for the majority of preterm births.
- Treatment with tocolytic therapy may prolong labor by up to 48 hours, facilitate transfer of the patient from a small community hospital to a tertiary care facility, and delay delivery to allow maternal administration of a corticosteroid to accelerate fetal lung maturity. Long-term tocolytic therapy does not improve neonatal outcome.
- Nifedipine and indomethacin are still used commonly to treat preterm labor in the United States. The oxytocin antagonist atosiban is widely used in Europe. Magnesium sulfate has been widely used as a tocolytic agent in the United States, but it may be falling out of favor because of failure to demonstrate efficacy. Magnesium sulfate is now considered beneficial when it is used specifically for neuroprotection in reducing rates of cerebral palsy in preterm infants. Terbutaline is associated with a relatively high incidence of maternal and fetal side effects.
- Side effects of beta-adrenergic tocolytic therapy include (1) hypotension; (2) tachycardia, with or without cardiac arrhythmias and myocardial ischemia; (3) pulmonary edema; (4) hyperglycemia; and (5) hypokalemia. Pulmonary edema is the most serious complication, and it may be life threatening.
- Prior administration of a beta-adrenergic tocolytic agent does not contraindicate the administration of neuraxial anesthesia.
- Cyclooxygenase inhibitors reversibly inhibit cyclooxygenase, resulting in a transient effect on platelet function. However, their use does not necessitate the assessment of platelet or coagulation function before administration of neuraxial analgesia/anesthesia in a patient whose only risk factor for bleeding is recent ingestion of a cyclooxygenase inhibitor.

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CHAPTER 35

Abnormal Presentation and Multiple Gestation

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CHAPTER OUTLINE

The labor and delivery of a parturient with a multiple gestation and/or fetal breech presentation represents a major challenge for the obstetrician and the anesthesia provider. Anesthetic requirements may change from moment to moment, and an obstetric emergency may necessitate immediate intervention. All members of the perinatal care team must communicate directly and clearly with each other as well as with the parturient and her family to ensure the best possible outcome for both the mother and the neonate(s).

The **presentation** denotes that portion of the fetus that overlies the pelvic inlet. In most cases, the fetal presenting part can be palpated through the cervix during a vaginal examination. The presentation may be **cephalic**, **breech**, or **shoulder**. Breech and shoulder presentations occur with increased frequency in patients with multiple gestation. Cephalic presentations are further subdivided into **vertex**, **brow**, and **face** presentations according to the degree of flexion of the neck. With an **asynclitic** presentation, the fetal head is tilted toward one shoulder and the opposite parietal eminence enters the pelvic inlet first.

The **lie** refers to the alignment of the fetal spine with the maternal spine. The fetal lie can be either longitudinal or transverse. A fetus with a vertex or breech presentation has a longitudinal lie. A persistent oblique or transverse lie typically requires cesarean delivery.

The **position** of the fetus denotes the relationship of a specific fetal bony point to the maternal pelvis. The position of the **occiput** defines the position for vertex presentations. Other markers for position are the **sacrum** for breech presentations, the **mentum** for face presentations, and the **acromion** for shoulder presentations. The **attitude** of the fetus describes the relationship of the fetal parts with one another; the term is typically used to refer to the position of the head with regard to the trunk, as in flexed, military, or hyperextended.

ABNORMAL POSITION

During normal labor, the fetal occiput rotates from a transverse or oblique position to a direct **occiput anterior** position. In a minority of patients with an oblique posterior position, the occiput rotates directly posteriorly and results in a **persistent occiput posterior** position. The occiput posterior position may lead to a prolonged labor that is associated with increased maternal discomfort. Less often, the vertex remains in the **occiput transverse** position; this condition is known as **deep transverse arrest**.

In the past, obstetricians performed manual or forceps rotation to hasten delivery and lessen perineal trauma in women with an abnormal position of the vertex. Today, many obstetricians are reluctant to perform rotational forceps delivery for fear of causing excessive maternal and/or fetal trauma. In cases of persistent occiput posterior position, the contemporary obstetrician is more likely to allow the head to remain in the occiput posterior position at vaginal delivery. Only 29% of nulliparous women and 55% of parous women with a persistent occiput posterior position will achieve spontaneous vaginal delivery.[1] Some cases of persistent occiput

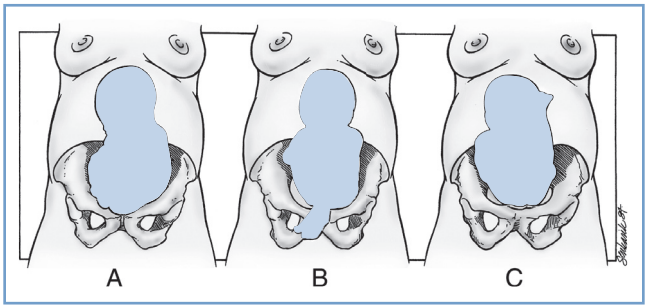

FIGURE 35-1 ■ Three possible breech presentations. **A,** The *complete breech* demonstrates flexion of the hips and flexion of the knees. **B,** The *incomplete breech* demonstrates intermediate deflexion of one or both hips and knees. **C,** The *frank breech* shows flexion of the hips and extension of both knees. (From Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:396.)

posterior position, and many cases of deep transverse arrest, require cesarean delivery because of dystocia.

During administration of epidural analgesia to a patient with an abnormal position, the addition of a lipid-soluble opioid to a dilute solution of local anesthetic is particularly useful. This combination provides analgesia while preserving pelvic muscle tone. Relaxation of the pelvic floor and perineum may prevent the spontaneous rotation of the vertex during labor.[2] In contrast, profound pelvic floor relaxation is needed to facilitate instrumental vaginal delivery with forceps.

BREECH PRESENTATION

Breech presentation describes a longitudinal lie in which the fetal buttocks and/or lower extremities overlie the pelvic inlet. Figure 35-1 shows the three varieties of breech presentation:

- **Frank breech**—lower extremities flexed at the hips and extended at the knees
- **Complete breech**—lower extremities flexed at both the hips and the knees
- **Incomplete breech**—one or both of the lower extremities extended at the hips

Ultrasonographic or radiographic examination typically allows the obstetrician to confirm the type of breech presentation and to exclude the presence of associated severe congenital anomalies (e.g., anencephaly). The type of breech presentation may influence the obstetrician's decision regarding the mode of delivery. The fetus with a frank breech presentation tends to remain in that presentation throughout labor. In contrast, a complete breech presentation may change to an incomplete breech presentation at any time before or during labor.

Epidemiology

The breech presentation is the most common of the abnormal presentations. Both the incidence and the type of breech presentation vary with gestational age (Table 35-1). Before 28 weeks' gestation, approximately 25% of fetuses are in a breech presentation.[3] Most change to a vertex presentation by 34 weeks' gestation, but 3% to 4% of fetuses remain in a breech presentation at term.[3]

Many factors predispose to breech presentation (Box 35-1).[4] Abnormalities of the fetus or the maternal pelvis or uterus may play a role. Among patients with pelvic or uterine abnormalities, a breech presentation may allow more room for fetal growth and movement. Likewise, hydrocephalic fetuses are more likely to assume a breech presentation. Multiparity, multiple gestation, polyhydramnios, and anencephaly also predispose to breech presentation. These conditions may interfere with the normal process of accommodation between the fetal head and the uterine cavity and maternal pelvis. Other factors may also play a role. In a prospective cohort study, low

TABLE 35-1 Types of Breech Presentation

Type of Breech	Percentage of All Breech Presentations	Percentage of Preterm Gestation Breech Presentations
Frank	48-73	38
Complete	5-12	12
Incomplete	12-38	50

Modified from Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012: 396.

BOX 35-1 Factors Associated with Breech Presentation

Uterine Distention or Relaxation
- Multiparity
- Multiple gestation
- Hydramnios
- Macrosomia

Abnormalities of the Uterus or Pelvis
- Pelvic tumors
- Uterine anomalies
- Pelvic contracture

Abnormalities of the Fetus
- Hydrocephalus
- Anencephaly

Obstetric Conditions
- Previous breech delivery
- Preterm gestation
- Oligohydramnios
- Cornual-fundal placenta
- Placenta previa

Modified from Cunningham FG, Leveno KJ, Bloom SL, et al. In Williams Obstetrics. 22nd edition. New York, McGraw-Hill, 2005:565-86; and Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:396-407.

TABLE 35-2 Incidence of Complications Associated with Breech Presentation

Complication	Incidence
Intrapartum fetal death	Increased 16-fold*
Intrapartum asphyxia	Increased 3.8-fold*
Umbilical cord prolapse	Increased 5- to 20-fold*
Birth trauma	Increased 13-fold*
Arrest of aftercoming head	4.6%-8.8%
Spinal cord injuries with deflexion	21%
Major congenital anomalies	6%-18%
Preterm delivery	16%-33%
Hyperextension of head	5%

*Compared with cephalic presentation.
Modified from Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:401.

TABLE 35-3 Risk for Umbilical Cord Prolapse

Type of Breech	Risk for Cord Prolapse (%)
Frank	0.5
Complete	4-6
Incomplete	15-18

Modified from Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:396.

free thyroid hormone (T_4) levels at 12 weeks' gestation were associated with breech presentation at term.[5]

Obstetric Complications

Obstetric complications are more likely with a breech presentation (Table 35-2). Cesarean delivery decreases the risk for some of these complications. Vaginal breech delivery entails a higher risk for neonatal trauma than delivery of an infant with a vertex presentation, but cesarean delivery does not eliminate the risk for trauma to the infant.[6] Rather, cesarean delivery of a breech presentation can be difficult and traumatic, especially if the skin and uterine incisions are insufficient or maternal muscle relaxation is inadequate.

The risk for umbilical cord prolapse varies with the type of breech presentation (Table 35-3). In the parturient with an incomplete breech presentation, the presenting part does not fill the cervix as well as the vertex or buttocks, allowing the umbilical cord to prolapse into the vagina before delivery. Umbilical cord prolapse typically necessitates emergency cesarean delivery.

Morbidity and Mortality

There is a higher risk for **perinatal morbidity and mortality** with a breech presentation, even when the risk is adjusted for preterm gestation. The factors that cause breech presentation are often more important than the presentation itself. For example, the severe congenital anomalies that predispose to breech presentation (e.g., hydrocephalus, anencephaly) significantly contribute to neonatal morbidity and mortality. Relative perinatal mortality rates (calculated from data for linked siblings from the Medical Birth Registry of Norway) confirm that breech presentation is a marker of perinatal risk, regardless of the mode of delivery.[7] Both nonreassuring fetal heart rate (FHR) tracings and dystocia occur more commonly in patients with a term breech presentation, even those who have undergone successful external cephalic version.[8]

Vaginal breech delivery entails a higher risk for **maternal morbidity** (e.g., infection, perineal trauma, hemorrhage) than vertex delivery.[4] However, among women with a fetal breech presentation, maternal outcomes are similar between women who had a planned cesarean delivery and those who had a trial of labor. At 2 years postpartum, maternal morbidity assessed by questionnaire (917 responses for a 79% return) was not different for urinary incontinence, breast-feeding, pain, depression, menstrual problems, fatigue, and distressing memories of the birth experience.[9] In a single-center study of 846 singleton breech deliveries, Schiff et al.[10] also did not find a higher risk for maternal morbidity in women who underwent cesarean delivery during labor than in women who underwent planned cesarean delivery.

Obstetric Management

External Cephalic Version

The process of external cephalic version converts a breech or shoulder presentation to a vertex presentation. The average success rate for this procedure is 58%, with a wide range reported in published studies.[11,12] External cephalic version is most likely to be successful if (1) the presenting part has not entered the pelvis, (2) amniotic fluid volume is normal, (3) the fetal back is not positioned posteriorly, (4) the patient is not obese, (5) the patient is parous, and (6) the presentation is either frank breech or transverse.[13] Early labor does not preclude successful external cephalic version, but external cephalic version is rarely successful when the cervix is fully dilated or when the membranes have ruptured. No scoring system has been developed that reliably predicts which candidates will have a successful version attempt, although the variables just listed can be used when obtaining informed consent.

The optimal timing of external cephalic version is after 36 or 37 weeks' gestation, for the following reasons.[11,14] First, if spontaneous version to a vertex presentation is going to occur, it will likely happen by 36 or 37 weeks' gestation, and successful performance of external cephalic version after 37 weeks' gestation decreases the likelihood of reversion from a vertex to a breech presentation. Second, if complications occur during external cephalic version performed after 37 weeks'

gestation, emergency delivery will not result in delivery of a preterm infant.

Successful external cephalic version helps reduce the risk for perinatal morbidity and mortality associated with breech delivery. The American College of Obstetricians and Gynecologists (ACOG)[11] has suggested that "because the risk of an adverse event occurring as a result of external cephalic version is small and the cesarean delivery rate is significantly lower among women who have undergone successful version, all women near term with breech presentations should be offered a version attempt." Labor and vaginal delivery occur in the majority of patients who have undergone successful external cephalic version, albeit with an increased risk for intrapartum cesarean delivery because of dystocia or a nonreassuring FHR tracing.[15] A meta-analysis found that the intrapartum cesarean delivery rate was 27.6% after successful external cephalic version versus 12.5% in women with a spontaneous cephalic presentation.[15]

External cephalic version is associated with a low rate of morbidity in contemporary obstetric practice, although placental abruption and preterm labor have been reported.[11] Safe external cephalic version requires FHR monitoring and access to cesarean delivery services. In a systematic review of 84 studies that involved 12,955 women, complications included transient (6.1%) and persistent (0.22%) FHR abnormalities, vaginal bleeding (0.30%), placental abruption (0.08%), emergency cesarean delivery (0.35%), and stillbirth (0.19%).[12] Fetal-maternal hemorrhage is another potential complication of external cephalic version.[12] In one study, 16 of 89 (18%) patients undergoing external cephalic version had Kleihauer-Betke stains that signaled the occurrence of fetal-maternal hemorrhage.[16]

Obstetricians usually administer a tocolytic agent (e.g., terbutaline) before performing external cephalic version. A randomized placebo-controlled trial found that the success rate of version was doubled when terbutaline was given rather than placebo.[16] Several studies have shown a benefit to tocolysis only in nulliparous women.[11] A randomized controlled trial of intravenous nitroglycerin for tocolysis (100- to 300-μg bolus doses, up to a maximum total dose of 1000 μg) found that the success rate was 24% in nulliparous women who received nitroglycerin versus 8% in the placebo group.[17] The success rate was higher in parous women (43%), but it did not differ between the nitroglycerin and placebo groups.[17] Interestingly, the rates of hypotension were similar between groups. A Cochrane Review[18] found that tocolytic therapy for external cephalic version increases the number of women with a cephalic presentation at the onset of labor (relative risk [RR], 1.38; 95% confidence interval [CI], 1.03 to 1.85) and reduces the number of cesarean deliveries (RR, 0.82; 95% CI, 0.71 to 0.94).

Several studies have described the use of epidural or spinal analgesia or anesthesia for external cephalic version.[19] Maternal discomfort may be significant during external cephalic version; greater pain during the procedure is associated with a lower chance of success.[20] Some obstetricians argue that the absence of anesthesia limits the force that the obstetrician can apply during the procedure. They contend that administration of anesthesia may encourage the obstetrician to use excessive force, possibly increasing the risk for perinatal morbidity and mortality, but that concern is not supported by published evidence. In fact, spinal anesthesia reduces the force required for successful version.[21]

Weiniger et al.[22] randomly assigned 70 nulliparous women to receive either spinal anesthesia with bupivacaine 7.5 mg or no anesthesia for external cephalic version. The success rate was 67% in those receiving spinal anesthesia, 32% in those without analgesia, and 42% in those who did not consent to enroll in the study. A randomized controlled trial in parous women using similar methodology also found an increased success rate with spinal anesthesia (87% versus 58%).[23] In contrast, Sullivan et al.[24] randomized 96 parturients to receive either intrathecal bupivacaine 2.5 mg with fentanyl 15 μg as part of a combined spinal-epidural (CSE) technique or intravenous fentanyl 50 μg before attempted external cephalic version. There was no difference between groups in the rate of successful external cephalic version (47% with CSE analgesia and 31% with intravenous fentanyl) or vaginal delivery (36% versus 25%), although pain scores were lower and satisfaction scores were higher with CSE analgesia.

A meta-analysis of seven studies using neuraxial blockade to facilitate external cephalic version concluded that administration of an *anesthetic* dose of local anesthetic doubles the success rate of external cephalic version (RR, 1.95; 95% CI, 1.46 to 2.60), whereas an *analgesic* dose does not have any effect (RR, 1.18; 95% CI, 0.94 to 1.49).[25] A subsequent meta-analysis confirmed that neuraxial blockade increases the rate of successful version (60%) compared with no neuraxial block (38%); when the authors calculated the number needed to treat, they determined that five women must receive a neuraxial block to achieve one additional successful version.[19] There was no difference between groups in the rate of cesarean delivery; however, this second meta-analysis failed to distinguish between neuraxial anesthesia and analgesia, and it included at least one trial that allowed both vaginal breech delivery and spinal anesthesia for a subsequent version attempt among control patients who had a failed version.[19] Several investigators have reported successful outcomes with neuraxial analgesia or anesthesia in women in whom the first attempt at external cephalic version without neuraxial analgesia had been unsuccessful.[22,26] These patients elected to undergo another version attempt with neuraxial analgesia. Weiniger et al.[22] found that failure of external cephalic version was attributed to pain in 15 women in their control group. Eleven of those 15 (73%) women subsequently had successful external cephalic version with spinal analgesia. Cherayil et al.[26] reported successful version in 13 of 15 (87%) repeat procedures performed with neuraxial blockade.

In our practices, we do not routinely provide spinal or epidural analgesia during external cephalic version. However, emerging evidence suggests that it may help facilitate successful version and vaginal delivery. If a neuraxial technique is used, administration of an *anesthetic* dose of local anesthetic appears to result in higher success rates than use of an *analgesic* dose.

Mode of Delivery

A substantial number of obstetricians recommend the routine performance of cesarean delivery in patients with a breech presentation. The publication of the Term Breech Trial in 2000 changed clinical practice around the world.[6] In contemporary obstetric practice in the United States, most parturients with a breech presentation are delivered abdominally.

The Term Breech Trial Collaborative Group[6] enrolled 2088 women from 26 countries with a singleton fetus in a frank or complete breech presentation. These women were randomly assigned to undergo planned cesarean delivery or planned vaginal delivery. Using an intent-to-treat analysis, the investigators noted that perinatal and neonatal mortality rates, and serious neonatal morbidity, were significantly lower in the planned cesarean delivery group (1.6% versus 5%). This difference was greatest in those countries with a low perinatal mortality rate (e.g., Canada, United Kingdom, United States).[6] Secondary analysis of perinatal outcomes demonstrated that the lowest risk for adverse outcome occurred when a prelabor cesarean delivery was performed at term gestation. The risk for adverse outcome progressively increased with cesarean delivery performed during early labor and active labor and was highest with a vaginal birth. Labor augmentation and a longer time between the start of pushing and delivery were associated with an increased risk for adverse perinatal outcome, whereas the presence of an experienced clinician at delivery was associated with a reduced risk for adverse perinatal outcome.[27] Interestingly, in a 2-year follow-up study in some centers that participated in the Term Breech Trial there was no difference in the risk for death or neurodevelopmental delay between children delivered by planned cesarean and those delivered by planned vaginal delivery.[28] The following two factors may have contributed to the lack of significant differences in outcome at 2 years of age: (1) the sample size may have been inadequate, and (2) measures of early neonatal morbidity have a low predictive value for long-term outcomes (i.e., most children with early neonatal morbidity survive and develop normally).[28]

In the Term Breech Trial,[6] maternal morbidity and mortality did not differ between the two groups for the first 6 postpartum weeks. Women who underwent planned cesarean delivery were less likely to report urinary incontinence at 3 months[29]; however, there was no difference at 2 years.[9] As assessed by questionnaire, maternal outcomes at 2 years after delivery were similar after planned abdominal delivery and after planned vaginal delivery for singleton breech infants born at term.[9]

As a result of the Term Breech Trial, the number of planned vaginal breech deliveries has decreased in many regions of the world. For example, in Denmark, the proportion of singleton term breech infants delivered vaginally decreased abruptly from 20% before 1999 to 6% after 2001.[30] At the same time, intrapartum or early neonatal mortality among all term breech infants decreased from 0.13% to 0.05% (RR, 0.38; 95% CI, 0.15 to 0.98).[30] These kinds of trends are self-reinforcing. As the number of practitioners with experience in performing vaginal breech delivery has decreased, the number of vaginal breech deliveries available to teach obstetric residents may no longer be adequate.[31] Results from an Australian survey suggest that "few of the next generation of … obstetricians plan to offer vaginal breech delivery to their patients."[32]

Nevertheless, obstetricians in selected regions of the world retain a strong tradition of offering vaginal breech delivery for selected patients. Published in 2006, the PREsentation et MODe d 'Accouchement (PREMODA; presentation and mode of delivery) study[33] described birth outcomes for all term breech deliveries in 2001 through 2002 in 174 centers in France and Belgium. The study included 5579 women who planned cesarean breech delivery and 2526 women who planned vaginal breech delivery, of whom 1796 actually delivered vaginally.[33] The primary outcome captured a composite of fetal and neonatal mortality and serious morbidity and was not different between women who planned to undergo vaginal delivery (1.60%; 95% CI, 1.14 to 2.17) and women who planned to undergo cesarean delivery (1.45%; 95% CI, 1.16 to 1.81), with an overall odds ratio of 1.10 (95% CI, 0.75 to 1.61).[33] The authors suggested that rigorous adherence to protocols for patient selection, intrapartum fetal surveillance, and second-stage management contributed to improved outcomes for women attempting vaginal breech delivery.

In 2006, in recognition of results from the PREMODA study and other single-center descriptions of excellent outcomes for vaginal breech delivery, the American College of Obstetricians and Gynecologists (ACOG) made the following recommendations about mode of singleton breech delivery at term[31]:

- "The decision regarding the mode of delivery should depend on the experience of the health care provider. Cesarean delivery will be the preferred mode of delivery for most physicians because of the diminishing expertise in vaginal breech delivery."
- "Obstetricians should offer and perform external cephalic version whenever possible."
- "Planned vaginal delivery of a term singleton breech fetus may be reasonable under hospital-specific protocol guidelines for both eligibility and labor management."
- "In those instances in which breech vaginal deliveries are pursued, great caution should be exercised, and detailed patient informed consent should be documented."
- "Before embarking on a plan for a vaginal breech delivery, women should be informed that the risk of perinatal or neonatal mortality or short-term serious neonatal morbidity may be higher than if a cesarean delivery is planned."

Although a planned trial of labor and vaginal breech delivery occurs uncommonly in most hospitals in North America and the United Kingdom, vaginal breech delivery still occurs because some patients present in advanced labor. Selection criteria such as those listed in Box 35-2 are used by advocates of a trial of labor and vaginal delivery.[4] The availability of personnel experienced in obstetric anesthesia and neonatal resuscitation are prerequisites for a trial of labor. Hyperextension of the fetal head

BOX 35-2 Criteria for a Trial of Labor and Vaginal Delivery for Patients with Fetal Breech Presentation

- Frank breech presentation
- Adequate pelvis by imaging pelvimetry
- Estimated fetal weight between 2000 and 3500 g by ultrasonography or by two experienced examiners
- Flexion of the fetal head (the neutral position—the so-called military position—is also acceptable)
- Continuous electronic fetal heart rate monitoring
- Spontaneous progression of labor, with timely effacement and dilation of the cervix and timely descent of the breech
- Availability of an individual skilled in vaginal breech delivery and an assistant
- Availability of an individual skilled in the administration of obstetric anesthesia
- Spontaneous delivery to the level of the umbilicus
- Ability to perform an abdominal delivery promptly
- Availability of an individual with skills in neonatal resuscitation

remains an absolute contraindication to a trial of labor in the patient with a breech presentation.[4]

Vaginal Breech Delivery

Several aspects of the conduct of breech labor differ from those for a vertex presentation. The cervix must be fully dilated before the patient begins to push. Indeed, some obstetricians delay maternal expulsive efforts until 30 minutes after the diagnosis of full cervical dilation. Others delay expulsive efforts until the breech is at the perineum.

There are three varieties of vaginal breech delivery. **Spontaneous breech delivery** is delivery without any traction or manipulation other than support of the infant's body. With **assisted breech delivery** (also known as partial breech extraction), the infant is delivered spontaneously as far as the umbilicus; at that time, the obstetrician assists delivery of the chest and the aftercoming head. With **total breech extraction,** the obstetrician applies traction on the feet and ankles to deliver the entire body of the infant. Except for vaginal delivery of a second twin, obstetricians almost never perform total breech extraction. Total breech extraction increases the likelihood of difficult, traumatic delivery, including entrapment of the fetal head.

During assisted breech delivery or total breech extraction, the obstetrician attempts to maintain flexion of the cervical spine during delivery of the aftercoming head. This may be accomplished manually or by the application of Piper forceps (Figures 35-2 through 35-4). In most cases the obstetrician performs a generous episiotomy to prevent perineal obstruction of the aftercoming head.

Cesarean Delivery

Cesarean delivery does not guarantee an atraumatic delivery, especially if the skin and uterine incisions are inadequate. Before 32 weeks' gestation, the lower uterine

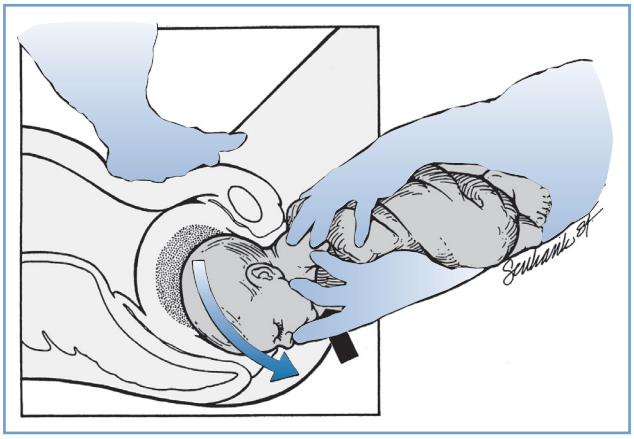

FIGURE 35-2 ■ Vaginal breech delivery. The *black arrow* indicates the direction of pressure from two fingers of the operator's right hand on the fetal maxilla (not the mandible). This maneuver assists in maintaining appropriate flexion of the fetal vertex (*direction of blue arrow*), as does moderate suprapubic pressure from an assistant. Delivery of the head may be accomplished with continued maternal expulsive forces and gentle downward traction. (From Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:400.)

FIGURE 35-3 ■ Vaginal breech delivery. Demonstration of ***incorrect assistance*** during the application of Piper forceps; the assistant hyperextends the fetal neck. Such positioning increases the risk for neurologic injury. (From Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:400.)

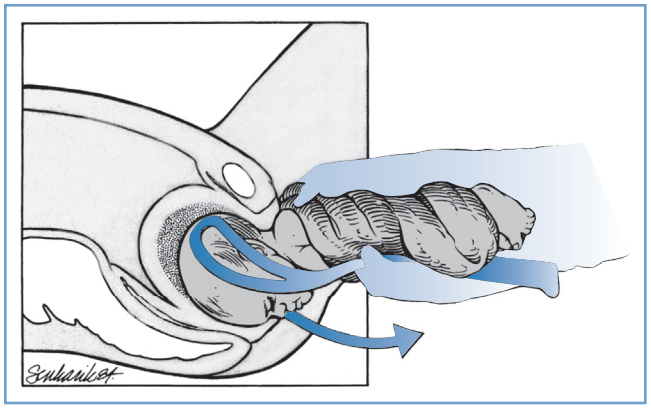

FIGURE 35-4 ■ Vaginal breech delivery. Once the Piper forceps are applied, the fetal trunk is supported by one hand, and gentle traction on the forceps (*arrow*) in the direction of the pelvic axis results in a controlled delivery. (From Lanni SM, Seeds JW. Malpresentations and shoulder dystocia. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:401.)

segment may be inadequate to allow an atraumatic delivery through a low transverse uterine incision. In such cases, the obstetrician should perform a low vertical uterine incision, which can be extended to facilitate an atraumatic delivery. Unfortunately, such incisions often extend to the body of the uterus, which does not heal as well as the lower uterine segment. It is unclear whether this situation increases the risk for uterine rupture during a trial of labor in a subsequent pregnancy (see Chapter 19).

Anesthetic Management

Benefits of neuraxial analgesia during labor include (1) pain relief, (2) inhibition of early pushing by blocking the perineal reflex, (3) ability of the parturient to push during the second stage and spontaneously deliver the infant to the level of the umbilicus, (4) a relaxed pelvic floor and perineum at delivery, and (5) the option to extend analgesia to surgical anesthesia for emergency cesarean delivery if needed.

Analgesia for Labor

Emergency cesarean delivery may be required at any time during a trial of labor. Epidural analgesia and CSE analgesia are excellent choices during a trial of labor in patients with a breech presentation. The anesthesia provider should tailor the analgesic technique to the needs of the individual patient. Patients with a breech presentation often have earlier complaints of rectal pressure than patients with a vertex presentation. It is important to provide sufficient sacral analgesia to inhibit pushing during the first stage of labor. The patient must not push before the cervix is fully dilated; otherwise, the patient might push a fetal lower extremity through her partially dilated cervix, which may result in fetal head entrapment. Early pushing may also increase the risk for a prolapsed umbilical cord. A bolus dose of local anesthetic solution that includes a lipid-soluble opioid (e.g., fentanyl, sufentanil) may be required to block the sacral segments and the reflex urge to push during the late first stage of labor. Use of a local anesthetic alone to eliminate low back and perineal discomfort results in extensive motor blockade, which may decrease the effectiveness of maternal expulsive efforts during the second stage. The advantages of the epidural administration of both a local anesthetic and a lipid-soluble opioid were confirmed by Benhamou et al.,[34] who observed that a continuous epidural infusion of bupivacaine 0.0625% with sufentanil 0.25 μg/mL produced better maternal analgesia and less motor block than administration of bupivacaine 0.125% in parturients with a breech presentation.

Anesthesia for Vaginal Breech Delivery

The patient with a breech presentation should deliver in an operating room where an emergency abdominal delivery can be performed immediately. The anesthesia provider should consider administration of a nonparticulate antacid at the time of transfer to the delivery/operating room. The anesthesia provider should be prepared for emergency administration of general anesthesia at any time. Umbilical cord compression is common during the second stage of labor in a patient with a breech presentation. For these reasons, the mother may receive supplemental oxygen during vaginal breech delivery.

Provision of effective analgesia/anesthesia for vaginal breech delivery represents a true challenge for the anesthesia provider. During the second stage of labor, the anesthesia provider is asked to provide adequate analgesia (which should include neuroblockade of the sacral segments) while maintaining adequate maternal expulsive efforts. If a patient is unable to achieve spontaneous delivery of a *vertex* presentation, the obstetrician may perform instrumental vaginal delivery. In contrast, total breech extraction of a singleton fetus is unacceptable in modern obstetric practice. Most obstetricians insist on spontaneous delivery of the infant to the level of the umbilicus.

At any time, the anesthesia provider may be asked to quickly provide dense anesthesia for vaginal or cesarean delivery. Many obstetricians routinely apply Piper forceps to the aftercoming head. This maneuver requires adequate anesthesia and perineal muscle relaxation. Because a dilute solution of local anesthetic has been administered during the first stage of labor, it is often necessary to administer a more concentrated solution of local anesthetic at the time of delivery. Either 3% 2-chloroprocaine or 2% lidocaine with epinephrine and bicarbonate may be used to rapidly extend the epidural analgesia to anesthesia for operative delivery. To ensure adequate anesthesia for operative delivery, we begin to inject a more concentrated solution of local anesthetic at the first evidence of difficulty.

Perhaps the obstetrician's greatest fear is the risk for **fetal head entrapment**. Most cases of this complication involve entrapment of the fetal head behind a partially dilated cervix. The head may also be entrapped by the perineum. Fetal head entrapment is more likely to occur in patients at less than 32 weeks' gestation. Before 32

weeks' gestation, the fetal head is larger than the wedge formed by the fetal buttocks and thighs. The lower extremities, buttocks, and abdomen may deliver before the cervix is fully dilated, and the cervix may then entrap the head. If this complication occurs, the obstetrician may choose one of the following three options: (1) performance of Dührssen incisions in the cervix, (2) relaxation of skeletal and cervical smooth muscle, or (3) cesarean delivery.

The performance of **Dührssen incisions** may be technically difficult. The obstetrician makes two or three radial incisions in the cervix at the 2-, 6-, and 10-o'clock positions.[4] This procedure is associated with a high risk for maternal morbidity (e.g., genitourinary trauma, hemorrhage). The blood loss may be substantial and concealed. Bleeding within the peritoneal cavity may not be visible externally.

More often, the obstetrician requests that the anesthesia provider establish **relaxation of skeletal and cervical smooth muscle**. Smooth muscle represents less than 15% of total cervical tissue,[35] and some physicians argue that it is not possible to provide profound relaxation of the cervix through smooth muscle relaxation. Nonetheless, the provision of both skeletal and smooth muscle relaxation often facilitates vaginal delivery of the aftercoming head. In the past, the technique of choice was rapid-sequence induction of general anesthesia, followed by administration of a high concentration (2 to 3 minimum alveolar concentration [MAC]) of a volatile halogenated agent. This technique results in uterine and cervical relaxation in 2 to 3 minutes. If fetal head entrapment results from perineal obstruction, delivery may soon follow the administration of succinylcholine.

Immediately after delivery, the anesthesia provider should discontinue administration of the volatile halogenated agent and substitute nitrous oxide, with or without an opioid. Administration of a high concentration of a volatile halogenated agent increases the risk for uterine atony and hemorrhage after delivery. Prompt discontinuation of the volatile halogenated agent, along with intravenous administration of oxytocin, should facilitate adequate uterine tone in most patients. Anesthesia should be maintained until the placenta is delivered, the episiotomy and lacerations are repaired, and hemostasis is secured.

In modern practice, intravenous or sublingual administration of nitroglycerin has nearly replaced the use of volatile halogenated agents as agents for uterine relaxation. Administration of nitroglycerin results in the release of nitric oxide, which helps mediate the relaxation of smooth muscle. Transient hypotension is common. Use of nitroglycerin for this purpose is based on case reports and small series of cases. Well-designed clinical trials of the use of nitroglycerin to provide uterine relaxation in obstetric emergencies are lacking, although the administration of nitroglycerin for this purpose appears safe for both the mother and the infant.[36]

Buhimschi et al.[37] attempted to provide an objective assessment of the effect of nitroglycerin on uterine tone and contractility in laboring women. In a double-blind fashion, 12 parturients were randomly assigned to receive either placebo or sublingual nitroglycerin (three doses, 800 μg each) 10 minutes apart. Intrauterine pressure was measured with a sensor-tip catheter. Sublingual nitroglycerin did not reduce either uterine activity or tone, despite a significant (20%) reduction in maternal mean arterial pressure. The authors suggested that higher doses may be required but may increase the risk for maternal hypotension.

Published case reports have described clinically apparent uterine relaxation achieved with intravenous nitroglycerin doses ranging from 50 to 1500 μg. Sublingual sprays of metered-dose nitroglycerin (400 to 800 μg) may provide a more convenient means of administration, whereas intravenous administration may allow for more rigorous titration. Either sublingual or intravenous routes of administration appear to provide a rapid onset of uterine relaxation, and the effect typically is very brief. The patient should be warned about the acute onset of headache, and she should be treated with a vasopressor such as phenylephrine if hypotension occurs. The anesthesia provider should simultaneously prepare for the induction of general anesthesia should nitroglycerin not provide enough relaxation.

The use of epidural analgesia has likely lowered the incidence of fetal head entrapment during vaginal breech delivery for at least two reasons. First, epidural analgesia inhibits early pushing during the first stage of labor. Second, although epidural analgesia does not relax the cervix at delivery, it provides effective pain relief and skeletal muscle relaxation. A relaxed pelvic floor and perineum facilitates placement of Piper forceps and delivery of the aftercoming head. Moreover, effective analgesia and skeletal muscle relaxation allow an assistant to provide maternal suprapubic pressure, which helps maintain flexion of the fetal cervical spine during delivery.

Anesthesia for Cesarean Delivery

Spinal, epidural, or general anesthesia can be administered for cesarean delivery. At cesarean delivery, the obstetrician should perform a uterine incision that allows an atraumatic delivery of the infant. Rarely, the obstetrician may request provision of uterine relaxation even when a vertical uterine incision has been performed. Uterine relaxation may be necessary in cases of fetal malformations (e.g., sacral teratoma, hydrocephalus). When general anesthesia is used, the anesthesia provider may increase the concentration of the volatile halogenated agent. When neuraxial anesthesia is used, intravenous or sublingual administration of nitroglycerin, or intravenous administration of a beta-adrenergic tocolytic agent such as terbutaline, typically provides adequate relaxation. Rarely, it is necessary to perform intraoperative induction of general anesthesia followed by administration of a high concentration of a volatile halogenated agent.

Regardless of the route of delivery, all members of the obstetric care team should remember that newborn infants with a breech presentation tend to be more depressed than infants with a vertex presentation. An individual skilled in neonatal resuscitation should be immediately available.

OTHER ABNORMAL PRESENTATIONS

Face Presentation

Face presentation occurs in 1 in 500 live births. Vaginal delivery can be achieved in 70% to 80% of infants with a face presentation if the mentum rotates to an anterior position.[4] Manual efforts to flex the fetal cervical spine or convert an unfavorable mentum posterior position to a more favorable mentum anterior position are rarely successful.[4]

Brow Presentation

In patients with a brow presentation, the cervical spine position is intermediate between the full flexion of a normal vertex presentation and the full extension of a face presentation. Brow presentation occurs in approximately 1 in 1500 deliveries. Persistent brow presentation typically requires cesarean delivery due to dystocia. Spontaneous flexion or extension of the neck may occur during labor, which may allow vaginal delivery.[4]

Compound Presentation

Compound presentation (an extremity is prolapsed alongside the main presenting fetal part) occurs in 1 in 400 to 1 in 1200 deliveries. Most often, an upper extremity presents with the vertex. Umbilical cord prolapse is more common (10% to 20%), as is neurologic or musculoskeletal damage to the involved extremity.[4] Labor and delivery may occur safely, but abdominal delivery is needed in patients with cord prolapse or arrest of labor. Manipulation of the prolapsed extremity should be avoided.[4]

Shoulder Presentation

A shoulder presentation (also known as a transverse lie) mandates performance of cesarean delivery except in two circumstances. First, successful external cephalic version may allow vaginal delivery. Second, the obstetrician may perform internal podalic version and total breech extraction of a second twin with a shoulder presentation.

Cesarean delivery of a fetus with a back-down transverse lie can be especially difficult with no presenting part to grasp. This presentation represents one of the few indications in contemporary obstetric practice for a classical uterine incision.

MULTIPLE GESTATION

Epidemiology

Monozygotic twins (which occur when a single fertilized ovum divides into two distinct individuals after a variable number of divisions) exhibit a constant incidence of approximately 4 per 1000 births. The incidence of **dizygotic twins** (which occur when two separate ova are fertilized) varies among races and by maternal age. In the United States, dizygotic twins occur most frequently among non-Hispanic black and white Americans, with an intermediate frequency among Asian Americans and Puerto Ricans, and least frequently among Native Americans and other Hispanic groups.[38] The incidence increases from 15 per 1000 among women younger than 20 years of age to 53 per 1000 among women 35 to 39 years of age, 63 per 1000 among women 40 to 44 years of age, and 227 per 1000 among those 45 years of age and older.[38] The incidence also increases with parity, independent of maternal age.[39] In the United States the rate of multiple gestation increased by 75% between 1980 and 2010.[38] Twin births represented 3.3% of all births in 2010.[38] Higher-order multiples (e.g., triplets) have declined in frequency from 0.2% of all live births in 1998 to 0.14% in 2010. Delayed childbearing and spontaneous twinning among women older than age 30 appears to explain one third of the increase in the rate of multiple gestation between 1980 and 2010, with the remainder attributed to greater use of assisted reproductive technologies.[40]

Placentation

Placentas in multiple gestation may be (1) **dichorionic diamniotic,** (2) **monochorionic diamniotic,** or (3) **monochorionic monoamniotic** (Figure 35-5). In all occurrences of dizygotic twins, the placenta is dichorionic diamniotic. A dichorionic diamniotic placenta is also present if monozygotic twinning occurs during the first 2 to 3 days after fertilization. Twinning between 3 and 8 days commonly results in a monochorionic diamniotic

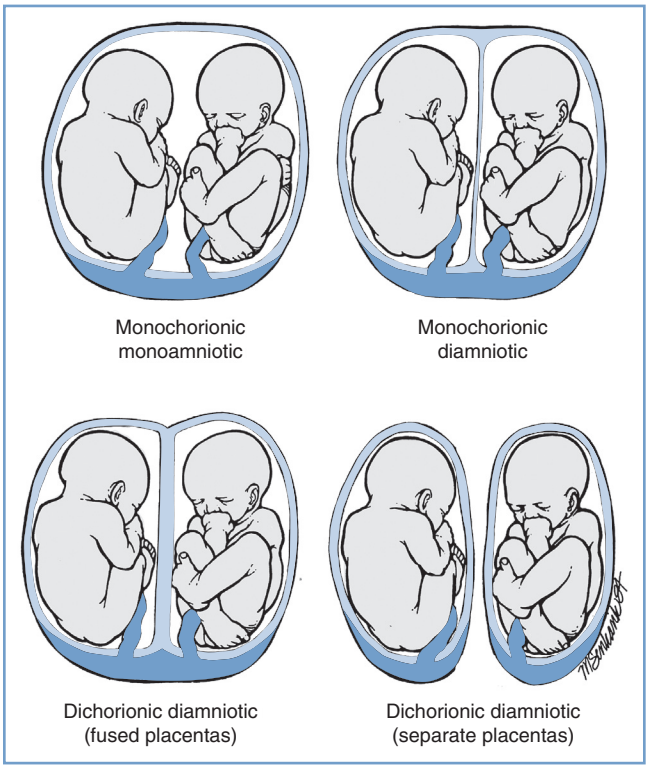

FIGURE 35-5 ■ **Placentation in twin pregnancies.** (Newman R, Unal ER. Multiple gestations. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:674.)

placenta. Monochorionic monoamniotic placentas are found when twinning occurs at 8 to 13 days. Embryonic cleavage between 13 and 15 days results in conjoined twins with a monochorionic monoamniotic placenta. Chorionicity is best determined by ultrasonography in the first or early second trimester.[41]

The type of placentation determines the likelihood of vascular communications. Vascular communications occur in nearly all monochorionic placentas and are rare in dichorionic placentas.[42] Vascular communications may result in twin-to-twin transfusion syndrome and intrauterine fetal death. Monochorionic placentation also increases the risk for intrauterine fetal death from other causes (e.g., cord accident).[42]

Physiologic Changes

Multiple gestation accelerates and may exaggerate the physiologic and anatomic changes of pregnancy. Of interest to the anesthesia provider, multiple gestation intensifies the cardiovascular and pulmonary changes of pregnancy. In contrast, the renal, hepatic, and central nervous system changes resemble those that occur in women with a singleton fetus.

Increased uterine size, especially near term, results in a reduction in both total lung capacity and functional residual capacity. During periods of hypoventilation or apnea, hypoxemia develops more rapidly because of the decreased functional residual capacity and an increased maternal metabolic rate. However, a cross-sectional study demonstrated no significant difference in respiratory function between 68 women with a twin pregnancy and 140 women with a singleton pregnancy.[43] Maternal weight increases at a greater rate after 30 weeks' gestation in women with multiple gestation,[44] a process that may increase the risk for difficult tracheal intubation and ventilation. Greater uterine size displaces the stomach cephalad, decreasing the competence of the lower esophageal sphincter and increasing the risk for pulmonary aspiration of gastric contents.

Maternal plasma volume increases by an additional 750 mL with twin gestation.[45] Relative or actual anemia often occurs. Likewise, multiple gestation results in a 20% greater increase in cardiac output than occurs in women with a singleton fetus, owing to a greater stroke volume (15%) and a higher heart rate (3.5%).[46] The greater fetal weight and larger volume of amniotic fluid predispose the mother with multiple gestation to aortocaval compression and the supine hypotension syndrome.

Obstetric Complications

Fetal Complications

Fetal complications include those related solely to multiple gestation (e.g., twin-to-twin transfusion syndrome) and those related to abnormal presentation (e.g., prolapsed cord) (Box 35-3).

BOX 35-3 Fetal Complications Associated with Multiple Gestation

- Preterm delivery
- Congenital anomalies
- Polyhydramnios
- Cord entanglement
- Umbilical cord prolapse
- Fetal growth restriction
- Twin-to-twin transfusion
- Malpresentation

Twin-to-Twin Transfusion. Nearly all monochorionic twin placentas have vascular anastomoses. Deep arteriovenous anastomoses create a common villous compartment in about half of monochorionic twin placentas. Most of these anastomoses have little fetal consequence. Those with deep arteriovenous vascular communications may result in twin-to-twin transfusion,[47] in which one twin becomes the donor and the other twin becomes the recipient. The donor twin is smaller and is at risk for fetal growth restriction (also known as intrauterine growth restriction) and anemia. The recipient twin is plethoric and is at risk for volume overload and cardiac failure. Alternative explanations for the syndrome include unequal blood volumes secondary to compression of a velamentous umbilical cord insertion and higher arterial blood pressure in the donor than in the recipient. Twin-to-twin transfusion increases both the perinatal mortality rate and the risk for adverse neurodevelopmental outcome in survivors.[48]

The therapeutic options most often considered are decompression amniocentesis, interruption of the placental vessel communications, amniotic septostomy, and selective feticide.[49] Selective fetoscopic laser photocoagulation may be sufficient to address the vascular anastomoses. Decompression amniocentesis or serial amnioreduction may improve circulation to a "stuck" donor twin, allowing restoration of normal amniotic fluid volume and "catch-up" fetal growth. Compared with serial amnioreduction, septostomy has the advantage of requiring only a single procedure.[50] Increasing evidence supports the use of endoscopic laser coagulation to improve perinatal outcome.[51-53]

Fetal Growth Restriction. Twin-to-twin transfusion represents only one of the potential causes of fetal growth restriction in multiple gestation. The polyhydramnios within one fetal sac may limit the growth of the other fetus. In patients with three or more fetuses, limited intrauterine size may restrict fetal growth. Of course, factors that cause fetal growth restriction in singleton pregnancies also may cause fetal growth restriction in multiple gestation (e.g., uteroplacental insufficiency, chromosomal abnormalities).

Preterm Labor. Patients with multiple gestation are at high risk for preterm labor and delivery. Preterm labor occurs in 52% of women with twins resulting from *in vitro* fertilization compared with 22% of women with spontaneous twins.[54] Sixty percent of women with twins deliver before 37 weeks' gestation, and only 6.4% of

triplet pregnancies reach term.[55] Routine use of bed rest, prophylactic cerclage, vaginal progesterone, and/or tocolytic therapy has not been shown to improve perinatal outcome in multiple gestation pregnancies.[56] When preterm labor occurs, the patient may receive parenteral tocolytic therapy to facilitate administration of betamethasone to accelerate fetal lung maturation, or magnesium sulfate for fetal neuroprotection, or both. The side effects of magnesium and other tocolytic agents may affect the response to anesthesia (see Chapter 34) and may increase the risk for postpartum hemorrhage. Multiple gestation most likely increases the risk for pulmonary edema associated with tocolytic therapy.[57]

Abnormal Presentation. Multiple gestation is associated with a higher incidence of abnormal presentation, which results in part from the need to accommodate two or more fetuses within the uterine cavity. Malpresentation increases the risk for umbilical cord prolapse, which may occur either before or after delivery of the first infant.

Morbidity and Mortality. Approximately 9% of all cases of perinatal mortality result from multiple gestation.[58] The perinatal mortality rate in twin pregnancies is almost three times greater than that associated with singleton pregnancies (16 deaths per 1000 births versus 6 per 1000 births, respectively).[58] Preterm delivery accounts for most of this increase, although twins and triplets also have a higher weight-specific mortality, which may be related to twin-to-twin transfusion, congenital malformations, preeclampsia, malpresentation, and/or prolapsed umbilical cord. Some maternal-fetal medicine specialists advocate selective multifetal reduction to reduce the risk for maternal morbidity and the perinatal morbidity and mortality associated with three or more fetuses; this issue is a matter of great controversy. The ACOG[59] has stated:

> *High-order multiple gestation creates a medical and ethical dilemma. If a pregnancy with 4 or more fetuses is continued, the probability is high that not all fetuses will survive intact and that the woman will experience serious morbidity. However, fetal reduction to triplet or twin gestations is associated with a significant risk of losing either another fetus or the whole pregnancy.*

Intensive inpatient monitoring may improve perinatal survival of *monoamniotic* twins. In a retrospective analysis of 87 women who had living twins at 24 weeks' gestation, there were no intrauterine fetal deaths among 43 women who were admitted electively for inpatient surveillance (at a median gestational age of 26.5 weeks).[60] In comparison, among women who were monitored as outpatients and admitted only for routine obstetric indications (at a median gestational age of 30.1 weeks), the rate of intrauterine fetal death was 14.8%.[60] Intensive surveillance may also benefit *monochorionic diamniotic* pregnancies.[61] The long-term outcome of the complications of monochorionicity remains an area of limited knowledge.[62]

Johnson and Zhang[63] evaluated outcome for 150,386 sets of twins and 5240 sets of triplets born between 1995 and 1997; fetal death at 20 weeks' gestation or later occurred in 2.6% of twin gestations and 4.3% of triplet gestations. The investigators noted that "survival of the remaining fetuses was inversely related to the time of the first fetal demise."[63] Opposite-gender twins were more likely to survive, possibly reflecting the absence of monochorionic placentation. In monochorionic twin gestations complicated by twin-to-twin transfusion and fetal death, approximately 40% of the surviving twins experience mortality or serious neurodevelopmental morbidity.[64] Death of one fetus may occur well before term. Obstetric management decisions are based on the cause of death and the status of both the surviving fetus and the mother. If the cause of death was an abnormality of the fetus rather than maternal or uteroplacental pathology, expectant management of the pregnancy may be warranted.[42,59] Development of maternal disseminated intravascular coagulation from dead fetal tissue is a theoretical complication that appears to occur rarely.[59]

Multiple gestation is also associated with an increased risk for neonatal morbidity and mortality. Despite a 95% neonatal survival rate, triplets may have a significantly greater risk for intraventricular hemorrhage and retinopathy of prematurity.[65]

Order of Delivery. Birth order does not seem to influence perinatal outcome in contemporary obstetric practice.[59,66] Administration of neuraxial anesthesia may improve the outcome for the second twin. In 1987, Crawford[67] observed that among women who received epidural analgesia, the two twins had similar umbilical cord blood pH measurements. In contrast, among women who received general anesthesia, the second twin tended to be more acidotic than the first. Likewise, Jarvis and Whitfield[68] reported no difference in outcome for first and second twins when the mother received epidural analgesia. Administration of general anesthesia is increasingly rare for cesarean delivery in women with multiple gestation.[69]

Maternal Complications

Multiple gestation increases the incidence of maternal morbidity and mortality (Box 35-4), even with adjustment of data for confounding factors.[70] The ACOG[59] has

BOX 35-4 Maternal Complications Associated with Multiple Gestation

- Preterm premature rupture of membranes
- Preterm labor
- Prolonged labor
- Preeclampsia/eclampsia
- Placental abruption
- Disseminated intravascular coagulation
- Operative delivery (forceps and cesarean)
- Uterine atony
- Obstetric trauma
- Antepartum and/or postpartum hemorrhage

stated: "Women with multiple gestations are nearly 6 times more likely to be hospitalized with complications, including preeclampsia, preterm labor, preterm premature rupture of membranes, placental abruption, pyelonephritis, and postpartum hemorrhage."[59] The incidence of maternal complications increases in proportion to the number of fetuses. Nearly all triplet gestations are associated with antenatal and/or postnatal maternal complications.[71] Abdominal distention and diaphragmatic elevation can cause respiratory distress and may necessitate early delivery in some patients with three or more fetuses. The increased incidence of cesarean delivery contributes to the higher risk for maternal morbidity and mortality associated with multiple gestation.

Multiple gestation (and the use of assisted reproductive technologies[72]) increases both the incidence and severity of preeclampsia.[42] Preeclampsia prompts delivery by 34 weeks' gestation in as many as 70% of patients with quadruplet pregnancies.[73]

Blood loss with delivery is approximately 500 mL greater in multiple gestation pregnancies than in singleton pregnancies.[42] Uterine distention increases the risk for uterine atony and postpartum hemorrhage. Most cases of atony respond to standard pharmacologic therapy (e.g., oxytocin, methylergonovine, 15-methyl prostaglandin $F_{2\alpha}$ [carboprost]). Persistent uterine atony may require the performance of a uterine brace suture or emergency hysterectomy.

Obstetric Management

Delivery at 38 weeks' gestation for twins and 35 weeks' gestation for triplets may be associated with the lowest risk for perinatal mortality.[59] Twin gestation itself does not contraindicate labor and vaginal delivery. However, multiple gestation is associated with a higher incidence of cesarean delivery. Most obstetricians favor cesarean delivery for all patients with three or more fetuses.[42]

A meta-analysis of four studies involving 1932 infants found no difference in perinatal or neonatal mortality, neonatal morbidity, or maternal morbidity between twins born through planned cesarean delivery and those born through vaginal delivery unless the first twin (twin A) was in a breech presentation.[74] Other studies have shown no maternal benefit to a prophylactic cesarean delivery, whereas maternal febrile morbidity is higher and the mother's risks for future pregnancies are increased.[75,76] Recent studies have found that neonatal morbidity is lower after vaginal delivery compared with scheduled cesarean delivery, even if only the second twin is considered.[77,78] A cohort study of 2597 twin deliveries at or after 34 weeks' gestation, with the first twin in a cephalic presentation, found that intrapartum and postpartum neonatal complications occurred in 26.5% of vaginal deliveries and 31.7% of scheduled cesarean deliveries ($P = 0.005$).[77] The authors concluded that their findings do not support a policy of planned cesarean delivery for twin pregnancies at or after 34 weeks' gestation.[77] A meta-analysis of 39,571 twin pregnancies found that neonatal morbidity was lower after vaginal delivery than after cesarean delivery for twin A, but there was no significant difference in neonatal morbidity between the two modes of delivery for twin B.[78] When outcomes were stratified for both presentation and mode of delivery, the mortality rate was lower after vaginal delivery than after cesarean delivery for both vertex and non-vertex twin B.[78]

Both fetuses have a vertex presentation in 30% to 50% of cases of twin gestation, and in 25% to 40% of cases the presentation is a vertex/breech combination. The remaining patients have various combinations of vertex, breech, and transverse lie. Most obstetricians allow a trial of labor if both twins have vertex presentation. Similarly, a majority of obstetricians opt for cesarean delivery if the first twin has a breech or shoulder presentation. Notwithstanding the results of recent studies,[74,77,78] controversy remains regarding the ideal management in cases in which twin A has a vertex presentation and twin B has a nonvertex presentation.[59,75]

Twin A

Decisions regarding the method of delivery typically revolve around the gestational age and presentation of twin A. An obstetrician who is unwilling to allow a trial of labor in a patient with a singleton breech presentation is unlikely to allow a trial of labor in a patient with a breech presentation for twin A. Moreover, if twin A has a breech presentation and twin B has a vertex presentation, the chins may become interlocked during labor and delivery. This complication occurs infrequently, but the consequences can be devastating.[42] Other indications for cesarean delivery of twin A include (1) evidence of discordant growth (especially if twin B is larger than twin A), (2) twin-to-twin transfusion syndrome, (3) selected congenital anomalies, and (4) evidence of uteroplacental insufficiency.[42] A trial of labor mandates continuous FHR monitoring of both fetuses. After amniotomy, an electrocardiography lead may be placed on the scalp of twin A and Doppler ultrasonography may be used to monitor twin B.

The unanticipated case of head entrapment, deflexed head, or locked twins may necessitate emergency abdominal delivery of both twins. The obstetrician proceeds with cesarean delivery while an assistant supports the exteriorized body of twin A. The obstetrician applies gentle traction on the head while the infant's body is guided back into the vagina. This can be accomplished without major injury to the infant or the mother.[79]

Twin B

If twin A is delivered vaginally, the obstetrician must make a decision about the method of delivery of twin B. If twin B has a vertex presentation and the head is well applied to the cervix, the obstetrician may allow the patient to resume labor and await spontaneous vaginal delivery. Rarely, if twin B has a vertex presentation but the head is not well applied to the cervix, the obstetrician may perform internal podalic version and total breech extraction.

For the twin B with nonvertex presentation, options include (1) external cephalic version followed by a resumption of labor, (2) internal podalic version and total breech extraction, and (3) performance of cesarean

delivery. Real-time ultrasonography facilitates the performance of external cephalic version. This procedure is successful in approximately 70% of cases. The likelihood of success is not associated with parity, gestational age, or birth weight.[80] One study noted that mothers who received epidural anesthesia were more relaxed and tolerated the procedure better than those who did not receive epidural anesthesia.[80]

Delivery of twin B is the one situation in contemporary obstetric practice in which internal podalic version and total breech extraction are considered appropriate. Indeed, breech extraction may be preferable to external cephalic version at the time of delivery. After vaginal delivery of twin A, the second twin requires cesarean delivery in approximately 10% of cases.[81] Predictors of emergency cesarean delivery of twin B include malpresentation, nonreassuring FHR tracing, cephalopelvic disproportion, and cord prolapse.[81] In a cohort study of twin pregnancies that used active management of the second stage of labor, which included breech extraction of the second twin and internal version of a nonengaged second twin, no patients required a cesarean delivery for the second twin after vaginal delivery of the first twin.[82] The investigators stated that an epidural catheter was placed and tested before delivery in all patients that had a trial of labor, and all twin deliveries occurred in the operating room with an anesthesiologist present.[82] The obstetrician will opt for total breech extraction of twin B only if there is evidence that twin B is not larger than twin A. Antepartum ultrasonographic examination allows the obstetrician to assess the head size and weight of both fetuses. If twin B is not larger than twin A, the pelvis and cervical dilation are probably adequate for vaginal delivery of twin B, provided that the cervix has not begun to contract.

In the past, obstetricians favored the delivery of twin B within 15 to 30 minutes of delivery of twin A. However, most data supporting this practice were obtained before the use of intrapartum FHR monitoring. In a review of 118 twin deliveries, Leung et al.[83] demonstrated an association between the twin-twin delivery interval and the umbilical cord blood gas and pH measurements for twin B. The investigators noted that continuous FHR monitoring is essential; 73% of the second twins not delivered by 30 minutes required operative delivery because of a nonreassuring FHR tracing. A German retrospective analysis of 4110 twin pregnancies suggested that the interval between delivery of twins is an independent risk factor for adverse short-term outcomes for twin B.[84] Continuous FHR monitoring of twin B is essential.

Anesthetic Management

Labor and Vaginal Delivery

Epidural analgesia provides optimal analgesia and flexibility for subsequent anesthetic needs. The anesthesia provider must be vigilant, because obstetric conditions and anesthetic requirements may change rapidly. Given the greater risk for cesarean delivery in patients with multiple gestation, the anesthesia provider should aim for optimal epidural anesthesia. If there is any question regarding the location of the catheter or the efficacy of the block, the catheter should be removed and replaced.

Patients with multiple gestation may be at increased risk for aortocaval compression and hypotension during the administration of neuraxial anesthesia. Use of the full lateral position, both during and after induction of epidural anesthesia, reduces the risk for aortocaval compression. Because these patients are at increased risk for uterine atony and postpartum hemorrhage, establishment of large-bore intravenous access is recommended before delivery.

Patients with multiple gestation should deliver in a room where an emergency abdominal delivery can be performed immediately. As the time for delivery of twin A nears, we augment the intensity of epidural blockade to optimize analgesia. We typically extend the sensory level to approximately T8 to T6 using a solution of local anesthetic that is more concentrated than that used earlier during labor. Effective anesthesia facilitates the performance of internal podalic version and total breech extraction of twin B, and it also enables the extension of anesthesia for cesarean delivery if necessary. We prepare a syringe of 3% 2-chloroprocaine to be used if emergency extension of epidural anesthesia is required.

We prefer to administer CSE anesthesia for vaginal delivery in patients with multiple gestation who do not have preexisting epidural analgesia. We prefer *not* to administer single-shot spinal anesthesia for vaginal delivery in those patients because of its lack of flexibility in cases of rapidly changing conditions. However, spinal anesthesia may be appropriate when delivery appears imminent in a patient without preexisting epidural labor analgesia.

Vaginal Delivery of Twin A/Operative Delivery of Twin B

The flexibility associated with epidural analgesia is especially advantageous if the obstetrician delivers twin A vaginally and twin B abdominally. We administer a nonparticulate antacid at the first sign of obstetrician concern, or even before proceeding to the operating room. We inject additional local anesthetic to extend the surgical sensory level to approximately T4. In cases of prolonged fetal bradycardia, it may be necessary to administer general anesthesia if adequate neuraxial anesthesia cannot be achieved rapidly. Typically this problem can be avoided if (1) both the level and intensity of anesthesia are optimized at the time of delivery of twin A and (2) the anesthesia provider is present in the room and gives attention to both the FHR tracing and the obstetrician.

If the obstetrician opts for internal podalic version and total breech extraction of twin B, it is better to perform the procedure shortly after the delivery of twin A, before the uterus and the cervix begin to contract. Pain relief and skeletal muscle relaxation (both provided by epidural anesthesia) facilitate internal version and total breech extraction of twin B. In some cases, pharmacologic uterine relaxation may be required to facilitate internal version and breech extraction of twin B. Sublingual (400 to 800 μg) or intravenous (100 to 250 μg) administration of nitroglycerin should provide adequate relaxation for

internal podalic version.[85,86] Intravenous or subcutaneous terbutaline 250 µg may also be used for uterine relaxation. If this maneuver is unsuccessful, rapid-sequence induction of general anesthesia, followed by administration of a high concentration of a volatile halogenated agent (as discussed earlier) may be needed.

Cesarean Delivery

Epidural, spinal, or general anesthesia can be safely administered for elective abdominal delivery. Spinal anesthesia is increasingly preferred by many anesthesia providers. A historical preference for epidural anesthesia was based on the gradual onset of sympathetic blockade, which was thought to reduce the incidence of severe hypotension. It has been long believed that women with multiple gestation are at higher risk for hemodynamic instability during administration of neuraxial anesthesia than women with a singleton gestation. Ngan Kee et al.[87] compared the incidence of hypotension and vasopressor requirements in women with multiple and singleton gestations undergoing cesarean delivery with spinal anesthesia. There were no differences between groups in maternal and neonatal outcomes.

Comparison of brachial artery and popliteal artery blood pressures allows the detection of occult supine hypotension, which results in reduced uteroplacental perfusion in the presence of a normal brachial artery pressure. If either hypotension or occult supine hypotension is detected, additional left uterine displacement or displacement to the other side may resolve the problem. A nonreassuring FHR tracing for either infant should also prompt the administration of additional efforts to optimize uteroplacental perfusion.

Jawan et al.[88] found that women with multiple gestation had a greater cephalad spread of neuroblockade with spinal anesthesia than women with a singleton gestation, whereas Ngan Kee et al.[87] did not. Similarly, Behforouz et al.[89] found no difference in the extent of sensory blockade after administration of epidural anesthesia between women with higher-order multiple gestation pregnancies and women with a singleton gestation. In any case, any difference that may exist is likely to be of little clinical significance.

Vallejo and Ramanathan[90] demonstrated that mean umbilical venous and umbilical arterial lidocaine concentrations were 35% to 53% higher in twin newborns than in singleton newborns exposed to epidural anesthesia for cesarean delivery. Mean fetal-to-maternal lidocaine ratios were at least 18% higher in the twin newborns than in the singleton newborns. The investigators speculated that this difference may be a result of the greater maternal cardiac output and plasma volume associated with twin gestation as well as the decreased total plasma protein concentration, which leads to an increase in the free lidocaine concentration.[90] The clinical relevance of these findings is unclear.

When general anesthesia is used, the greater oxygen consumption and decreased functional residual capacity associated with multiple gestation increase the risk for maternal hypoxemia during periods of apnea. Adequate denitrogenation (preoxygenation) is essential.

The presence of two or more fetuses results in a prolonged uterine incision-to-delivery interval because of the longer time required to deliver multiple infants. A prolonged interval increases the risk for umbilical cord blood acidemia and neonatal depression. Neonatal depression is less likely with neuraxial anesthesia than with general anesthesia.[68] In any case, an individual skilled in neonatal resuscitation should be immediately available.

KEY POINTS

- A higher incidence of breech presentation occurs among patients with preterm labor.
- External cephalic version is associated with a low rate of morbidity in contemporary obstetric practice and is recommended by the ACOG for all women with a breech presentation near term. Successful external cephalic version helps reduce the risk for perinatal morbidity and mortality associated with breech delivery and lowers the cesarean delivery rate. Neuraxial anesthesia may improve the success rate of external cephalic version, especially after an initial failed attempt.
- Both breech presentation and multiple gestation are associated with an increased incidence of perinatal morbidity and mortality, regardless of the method of delivery.
- Epidural analgesia offers several advantages during a trial of labor in the patient with a breech presentation. Specifically, it (1) provides effective pain relief; (2) inhibits early pushing; (3) relaxes the pelvic floor and perineum, facilitating atraumatic delivery of the aftercoming head; and (4) enables provision of anesthesia for emergency cesarean delivery.
- Multiple gestation exaggerates the physiologic and anatomic changes of pregnancy.
- Epidural analgesia is the analgesic technique of choice during labor in the patient with multiple gestation. Provision of pain relief and skeletal muscle relaxation facilitates the vaginal delivery of twin B. Provision of epidural analgesia also facilitates the administration of anesthesia for emergency cesarean delivery if it is needed.
- The obstetrician may request pharmacologic provision of uterine and/or cervical relaxation to facilitate vaginal delivery of twin B or, in cases of breech presentation, to facilitate the delivery of the aftercoming fetal head. Intravenous or sublingual nitroglycerin may provide rapid-onset uterine relaxation of short duration. Rapid-sequence induction of general anesthesia followed by administration of a high concentration of a volatile halogenated agent is another reliable method of providing uterine and cervical relaxation.

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CHAPTER 36

Hypertensive Disorders

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CHAPTER OUTLINE

Hypertension is the most common medical disorder of pregnancy, affecting 6% to 10% of pregnancies.[1-4] It is a leading cause of maternal mortality, accounting for approximately 26% of maternal deaths in Latin America and the Caribbean, 9% of deaths in Africa and Asia, and 16% of deaths in the developed world.[5] Hypertensive disorders are an important risk factor for fetal complications, including preterm birth, fetal growth restriction (also known as intrauterine growth restriction), and fetal/neonatal death.[4,6-7]

CLASSIFICATION OF HYPERTENSIVE DISORDERS

Hypertensive disorders of pregnancy encompass a range of conditions—chronic hypertension, gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and eclampsia—that can be difficult to diagnose because the clinical presentation is often similar despite complex differences in their underlying pathophysiologies and prognoses. Adding to the challenges for clinicians and researchers alike was a long-standing absence of consensus guidelines for categorizing hypertensive disorders. This lack resulted in the use of conflicting definitions that confounded attempts to compare and interpret data from many older clinical studies. This problem was resolved in 2000, when the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy[3] published a classification scheme establishing definitions that subsequently gained wide international acceptance (Box 36-1). This classification was updated in 2013 when the American College of Obstetricians and Gynecologists (ACOG) Taskforce on Hypertension in Pregnancy reviewed available literature and published a summary of current knowledge and recommendations.[4]

Gestational hypertension is the most frequent cause of hypertension during pregnancy, affecting approximately 5% of parturients.[2,8,9] When mild, it results in outcomes that are generally similar to those of normotensive pregnancies,[10,11] but when severe, it can result in rates of adverse pregnancy outcome that approximate those observed in preeclamptic women.[12] Gestational hypertension presents as elevated blood pressure after 20 weeks' gestation without proteinuria (in the absence of chronic hypertension) that resolves by 12 weeks postpartum.[13,14] Most cases of gestational hypertension develop after 37 weeks' gestation. Approximately one fourth of patients diagnosed with gestational hypertension will develop preeclampsia. A definitive diagnosis of gestational hypertension can be made only in retrospect after delivery when the diagnosis of chronic hypertension can be excluded based on a return to a normotensive state.

Preeclampsia is defined as the new onset of hypertension and proteinuria after 20 weeks' gestation (Box 36-2). The NHBPEP recommends that clinicians also consider the diagnosis of preeclampsia in the absence of proteinuria when any of the following signs or symptoms of end-organ involvement are present: (1) persistent epigastric or right upper quadrant pain, (2) persistent cerebral symptoms, (3) fetal growth restriction, (4) thrombocytopenia, or (5) elevated serum liver enzymes.[3] The term **eclampsia** is used when central nervous system (CNS) involvement results in the new onset of seizures in a

BOX 36-1 Classification of Hypertensive Disorders in Pregnancy

- Gestational hypertension
- Preeclampsia
  - Preeclampsia without severe features*
  - Severe
- Chronic hypertension
- Chronic hypertension with superimposed preeclampsia

*Previously referred to as *mild* preeclampsia.

From the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1-S22; and American College of Obstetricians and Gynecologists Taskforce on Hypertension in Pregnancy. Hypertension in pregnancy. ACOG. Washington, DC, 2013.

BOX 36-2 Diagnostic Criteria for Preeclampsia

Preeclampsia without Severe Features

- BP ≥ 140/90 mm Hg after 20 weeks' gestation
- Proteinuria (≥ 300 mg/24 h, protein-creatinine ratio ≥ 0.3, or 1+ on urine dipstick specimen)

Severe Preeclampsia*

- BP ≥ 160/110 mm Hg†
- Thrombocytopenia (platelet count < 100,000/mm^3)
- Serum creatinine concentration > 1.1 mg/dL or > 2 times the baseline serum creatinine concentration
- Pulmonary edema
- New-onset cerebral or visual disturbances
- Impaired liver function‡

*Fetal growth restriction and severe proteinuria (> 5 g in 24 hours) are no longer considered features of severe preeclampsia.

†Blood pressures should be measured on two occasions at least 4 hours apart while the patient is on bed rest.

‡Indicated by elevated blood concentrations of liver enzymes (more than twice normal) and severe persistent right upper quadrant, or epigastric pain.

BP, blood pressure; *HELLP*, hemolysis, elevated liver enzymes, and low platelets.

Modified from American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. ACOG. Washington, DC, 2013.

woman with preeclampsia. **HELLP syndrome** refers to the development of hemolysis, elevated liver enzymes, and a low platelet count in a woman with preeclampsia. This condition may be a variant of severe preeclampsia, but this classification is controversial because the disease may represent a pathophysiologically distinct entity.

Chronic hypertension involves either (1) prepregnancy systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher or (2) elevated blood pressure that fails to resolve after delivery. Chronic hypertension develops into preeclampsia in approximately one fifth to one fourth of affected patients. However, even in the absence of preeclampsia, chronic hypertension is an important risk factor for adverse maternal and fetal pregnancy outcomes.[6,15]

Chronic hypertension with superimposed preeclampsia occurs when preeclampsia develops in a woman with chronic hypertension before pregnancy. The diagnosis is made in the presence of a new onset of proteinuria or a sudden increase in proteinuria or hypertension or both, or when other manifestations of severe preeclampsia appear. Morbidity is increased for both mother and fetus compared with preeclampsia alone.[16]

The clinical findings in chronic hypertension, gestational hypertension, and preeclampsia are compared in Table 36-1.

PREECLAMPSIA

Preeclampsia is a multisystem disease unique to human pregnancy. It is characterized by diffuse endothelial dysfunction with maternal complications including placental abruption, pulmonary edema, acute renal failure, liver failure, stroke, and neonatal complications, including indicated preterm delivery, fetal growth restriction, hypoxic-neurologic injury, and perinatal death.[17] Although significant advances have been made in the understanding of the pathophysiology of the disease, the specific proximal cause remains unknown. Management is supportive; delivery of the infant and placenta remains the only definitive cure.

The clinical syndrome of preeclampsia is defined as the new onset of hypertension and proteinuria after 20 weeks' gestation. Previous definitions included edema,

TABLE 36-1 **Hypertensive Disorders of Pregnancy**

Clinical Feature	Chronic Hypertension	Gestational Hypertension	Preeclampsia
Time of onset of hypertension	< 20 weeks' gestation	Typically in third trimester	≥ 20 weeks' gestation
Severity of hypertension	Mild or severe	Mild	Mild or severe
Proteinuria*	Absent	Absent	Typically present
Serum uric acid > 5.5 mg/dL (0.33 mmol/L)	Rare	Absent	Present in almost all cases
Hemoconcentration	Absent	Absent	Present in severe disease
Thrombocytopenia	Absent	Absent	Present in severe disease
Hepatic dysfunction	Absent	Absent	Present in severe disease

*Defined as ≥ 300 mg in a 24-h urine collection, urine protein-creatinine ratio ≥ 0.3, or ≥ 1+ result on urine dipstick testing.

From Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med 1996; 335:257-65; and American College of Obstetricians and Gynecologists Taskforce on Hypertension in Pregnancy. Hypertension in pregnancy. ACOG. Washington, DC, 2013.

TABLE 36-2 **Differences between Early- and Late-Onset Preeclampsia**

	Early Onset	Late Onset
Onset of clinical symptoms	< 34 weeks' gestation	> 34 weeks' gestation
Relative frequency	20% of cases	80% of cases
Risk for adverse outcome	High	Negligible
Association with fetal growth restriction	Yes	No
Clear familial component*	Yes	No
Placental morphology	Abnormal†	Normal†
Etiology	Primarily placental‡	Primarily maternal§
Risk factor (relative risk)	Family history (2.9)	Diabetes (3.56) Multiple pregnancy (2.93) Increased blood pressure at registration (1.38) Increased body mass index (2.47) Maternal age ≥ 40 years (1.96) Cardiovascular disorders (3.84)

*Defined as recurrence across generations and occurrence within families.
†From Egbor M, Ansari T, Morris N, et al. Morphometric placental villous and vascular abnormalities in early- and late-onset preeclampsia with and without fetal growth restriction. BJOG 2006; 113:580-9.
‡Reduced extravillous trophoblast invasion.
§Predisposed maternal constitution reflecting microvascular disease or predisposed genetic constitution with *cis*- or *trans*-acting genomic variations subject to interaction.
From Oudejans CB, van Dijk M, Oosterkamp M, et al. Genetics of preeclampsia: paradigm shifts. Hum Genet 2007; 120:607-12.

but edema is no longer part of the diagnostic criteria because it lacks specificity and occurs in many healthy pregnant women. Preeclampsia is classified as **preeclampsia without severe features** or **severe** (see Box 36-2). The ACOG now discourages use of the term "mild" for preeclampsia without severe features because preeclampsia is progressive, and appropriate management involves frequent reevaluation for severe features.[4]

Some authors suggest classifying preeclampsia into the **early form (type I)**, with symptom onset before 34 weeks' gestation, or the **late form (type II)**, with symptom onset after 34 weeks' gestation (Table 36-2).[18] Early-onset preeclampsia begins with abnormal placentation, has a high rate of recurrence, and has a strong genetic component.[19-21] In contrast, late-onset preeclampsia generally occurs in women metabolically predisposed to the disease, and abnormal placentation may feature less prominently in the pathogenesis. These women, who often have long-standing hypertension, obesity, diabetes, or other forms of microvascular disease, are challenged to meet the demands of the growing fetoplacental unit and decompensate near term. Decompensation manifests as late-onset or, less frequently, postpartum preeclampsia.[18]

Epidemiology

Preeclampsia occurs in 3% to 4% of pregnancies in the United States.[2,9] Delivery of the infant and placenta is the only definitive treatment; thus, preeclampsia is a leading cause of indicated preterm delivery in developed countries.[22] Low-birth-weight and preterm infants born to preeclamptic mothers present major medical, social, and economic burdens to families and societies.[23] Preterm delivery is the most common indication for admission to the neonatal intensive care unit.[24] Preeclampsia is also a leading indication for maternal peripartum admission to an intensive care unit.[25,26]

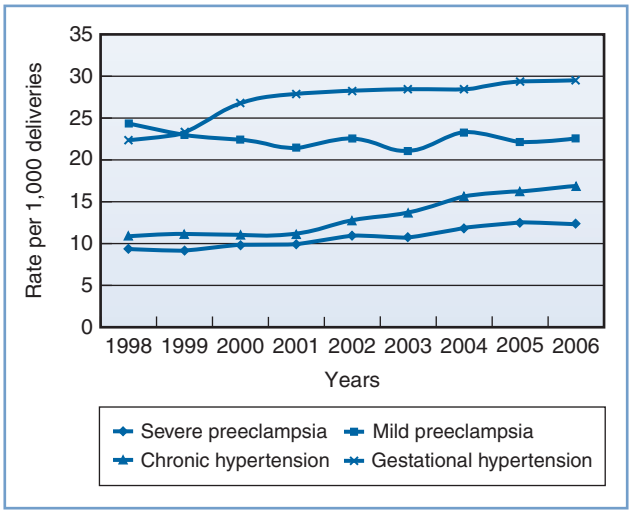

FIGURE 36-1 ■ Age-adjusted prevalence of hypertensive disorders during delivery hospitalization in the United States. (From Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obstet Gynecol 2009; 113:1299-306.)

The clinical findings of preeclampsia can manifest as a **maternal syndrome** (e.g., hypertension and proteinuria with or without other systemic abnormalities) with or without an accompanying **fetal syndrome** (e.g., fetal growth restriction, oligohydramnios, abnormal oxygen exchange).[3,17] In approximately 75% of cases, preeclampsia occurs without severe features near term or during the intrapartum period.[17] In contrast, disease onset prior to 34 weeks' gestation correlates with increased disease severity and worse outcomes for both mother and fetus.

A significant increase in the incidence of hypertensive disorders of pregnancy has occurred over the past decade (Figure 36-1), including an alarming 30% increase in

BOX 36-3 Risk Factors for Preeclampsia

Demographic Factors
- Advanced maternal age > 35 years
- Black race
- Hispanic ethnicity

Genetic Factors
- History of preeclampsia in previous pregnancy
- Family history of preeclampsia
- History of placental abruption, fetal growth restriction, or fetal death
- Partner who fathered a preeclamptic pregnancy in another woman (through fetal genes)

Medical Conditions
- Obesity
- Chronic hypertension
- Diabetes mellitus
- Chronic renal disease
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus

Obstetric Conditions
- Multiple gestation
- Hydatidiform mole

Behavioral Factor
- Cigarette smoking (risk reduction)

Partner-Related Factors
- Nulliparity
- Limited preconceptional exposure to paternal sperm*

*Teenage mother, primipaternity, assisted reproductive technique.

severe preeclampsia/eclampsia.[2] These increases are at least partially explained by major shifts in the demographics and clinical conditions of pregnant women in the United States and other developed countries. Average maternal age is increasing; advanced maternal age is a recognized risk factor for preeclampsia. Both the growing epidemic of obesity and the increased prevalence of diabetes and chronic hypertension in the developed world may also contribute to this trend. An increase in the use of assisted reproductive techniques and the use of donated gametes is contributory; these techniques increase risk for the disease by altering the maternal-fetal immune reaction[27] and by increasing the incidence of multiple gestation. Last, improvements in record-keeping and the use of consistent disease definitions since 2000 may have contributed to the increased number of reported cases.[3]

Numerous preconception and pregnancy-related risk factors associated with the development of preeclampsia have been identified (Box 36-3). Risk factors for preeclampsia can be divided into maternal demographic factors, genetic factors, medical conditions, obstetric conditions, behavioral factors, and partner-related factors.

Risk Factors

Demographic Factors. Advanced maternal age has consistently been shown to be a risk factor for preeclampsia, with women who are 40 years or older having an approximately twofold increase in risk compared with women between 20 and 29 years of age.[28,29] This risk may be independent of the increased prevalence of medical conditions and obesity that accompany advancing age.[28] Teenage pregnancy may also be a risk factor for preeclampsia,[30-32] but data are mixed.[33]

Black women constitute a high-risk group, with increased rates of chronic hypertension,[34,35] obesity,[35,36] and preeclampsia.[37-40] Black women with severe preeclampsia demonstrate more extreme hypertension, require more antihypertensive therapy,[41] and are more likely to die of the condition, compared with women of other racial backgrounds.[42] Hispanic ethnicity may also confer increased risk for developing preeclampsia.[43,44]

Genetic Factors. Maternal genetic factors are known to be important risk factors for the development of preeclampsia. Pregnant women with a family history of preeclampsia are approximately twice as likely to develop the disorder.[45,46] It is estimated that about one third of the variance in liability to preeclampsia is caused by maternal genetic factors.[47]

In a study of 1.7 million births in the Medical Birth Registry of Norway, men who fathered one preeclamptic pregnancy were found to be nearly twice as likely to father a preeclamptic pregnancy in a different woman, irrespective of her previous obstetric history.[48] Therefore, **paternal genes** (in the fetus) contribute significantly to a pregnant woman's risk for preeclampsia. It is estimated that approximately one fifth of the variance in liability for preeclampsia is conferred through the fetal genes.[47]

Women with a history of preeclampsia in a previous pregnancy are at increased risk for preeclampsia in a subsequent pregnancy,[29,49] particularly if the preeclampsia was of early-onset in the previous pregnancy.[50] Risk for recurrence increases with multiple affected pregnancies.[50] In addition, women with a history of previous placental abruption and fetal growth restriction are at increased risk for preeclampsia in a subsequent pregnancy,[51] and women with a history of preeclampsia are at risk for these outcomes even in the absence of recurrent preeclampsia.[52] These associations suggest that some women harbor a susceptibility (potentially genetically mediated) to obstetric conditions caused by placental dysfunction, which manifests differently in different pregnancies.

Medical and Obstetric Conditions. Obesity is an important risk factor for preeclampsia, and risk escalates with increasing body mass index (BMI).[53,54] A systematic review found that an increase in BMI of 5 to 7 kg/m^2 was associated with a twofold increased risk for preeclampsia.[53] Obesity is strongly associated with insulin resistance, another risk factor for preeclampsia. As the prevalence of obesity continues to increase worldwide, it is likely that the incidence of preeclamptic pregnancies will increase as well.

Women with **chronic hypertension** are also at increased risk for preeclampsia. A 2012 population-based study found that primary hypertension increased the odds of developing preeclampsia 10-fold and that secondary hypertension increased the odds nearly 12-fold.[6] Chronic hypertension in association with other risk

factors, including diabetes, renal disease, and collagen vascular disease, confers particularly elevated risk.[6] As women in developed countries delay childbirth, the impact of chronic hypertension will increase because of the increased prevalence of hypertension with advancing age.[55] Indeed, recent data from the United States show a substantial increase in the prevalence of chronic hypertension during pregnancy.[2,6]

Diabetes mellitus is associated with the development of preeclampsia.[6,29] In a study of 334 diabetic pregnancies, the incidence of preeclampsia was 9.9%, compared with 4.3% in nondiabetic control pregnancies. The incidence of preeclampsia also increased with the severity of diabetes as determined by the White classification.[56]

The **metabolic syndrome**, which occurs in 7% of women of childbearing age in the United States, is characterized by the presence of obesity, hyperglycemia, insulin resistance, and hypertension.[57] The metabolic syndrome increases risk for preeclampsia.[58] The insulin resistance and microvascular dysfunction observed in this condition have been implicated as a common factor in both preeclampsia and cardiovascular disease; these conditions may partially mediate the association of preeclampsia and increased risk for cardiovascular disease later in life.[59-61]

Additional maternal medical conditions that are well recognized risk factors for preeclampsia include **chronic renal disease**,[62,63] **antiphospholipid antibody syndrome**,[29] and **systemic lupus erythematosus**.[6,64] Pregnancy-related conditions that increase placental mass, including **multifetal gestation**[29,65] and **hydatidiform mole**,[66] are associated with higher rates of preeclampsia as well.

Behavioral Factors. Paradoxically, **cigarette smoking** during pregnancy has been associated with a decreased risk for preeclampsia,[67,68] an effect consistently observed across studies in various countries. Women who smoke during pregnancy have a 30% to 40% lower risk for developing preeclampsia compared with women who do not smoke. The protective effect is dose related[67]; heavier smokers have a lower incidence of preeclampsia than those who smoke fewer cigarettes.

The duration of this protective effect after smoking cessation has been studied with conflicting results. Its biologic mechanism remains unknown, but it is believed that the mechanism may include nicotine inhibition of thromboxane A_2 synthesis,[69] simulation of nitric oxide release,[70] or a combination of these factors. Further research of this protective mechanism may help elucidate the pathogenesis of preeclampsia.

Recreational Physical Activity. Recreational physical activity during pregnancy has been associated with a decrease in the risk for preeclampsia,[71,72] particularly in nonobese women.[73] Mechanistically, this may occur through exercise promoting placenta growth, decreasing oxidative stress, enhancing endothelial function, and modulating the immune and inflammatory response.[72]

Partner-Related Risk Factors. The unifying theme among partner-related risk factors is limited maternal exposure to paternal sperm antigens before conception, which suggests an immunologic role in the pathophysiology of preeclampsia. A leading risk factor for preeclampsia is nulliparity; the incidence is approximately threefold higher compared with parous women.[29] Long considered a disease of primigravid women, preeclampsia is also more common in (1) parous women who have conceived with a new partner, (2) women who have used barrier methods of contraception prior to conception, and (3) women who have conceived with donated sperm.[74,75] Long-term sperm exposure with the same partner appears to be protective; this protective effect is lost in a pregnancy conceived with a new partner.

Pathogenesis

The exact pathogenic mechanisms responsible for the initiation and progression of preeclampsia are not known. The placenta is the focus of hypotheses regarding disease pathogenesis; delivery of the placenta results in the resolution of disease, and the disease can occur in the absence of a fetus (e.g., a molar pregnancy).[76]

Preeclampsia as a Two-Stage Disorder

Contemporary hypotheses generally conceptualize preeclampsia as a two-stage disorder.[77] The **asymptomatic first stage** occurs early in pregnancy with impaired remodeling of the spiral arteries (the end branches of the uterine artery that supply the placenta).[76] In normal pregnancy, embryo-derived cytotrophoblasts invade the decidual and myometrial segments of the spiral arteries, replacing endothelium and causing remodeling of vascular smooth muscle and the inner elastic lamina (Figure 36-2).[78,79] The luminal diameter of the spiral arteries increases fourfold, resulting in the creation of flaccid tubes that provide a low-resistance vascular pathway to the intervillous space. Furthermore, the remodeled arteries are unresponsive to vasoactive stimuli. These alterations in maternal vasculature ensure adequate blood flow to nourish the growing fetus and placenta.

In contrast, in preeclamptic pregnancies, cytotrophoblast invasion is incomplete and only the decidual segments undergo change; the myometrial spiral arteries are not invaded and remodeled and thus remain small, constricted, and hyperresponsive to vasomotor stimuli.[76] This failure of normal angiogenesis results in superficial placentation. Abnormal placentation results in decreased placental perfusion and placental infarcts, predisposing the fetus to growth restriction (Figure 36-3). Placental ischemia worsens throughout pregnancy as narrowed vessels are increasingly unable to meet the needs of the growing fetoplacental unit.

In some women, the reduced perfusion of the intervillous space in the first stage leads to the **symptomatic second stage**, which is characterized by the release of antiangiogenic factors from the intervillous space into the maternal circulation; these factors cause widespread maternal endothelial dysfunction and an accentuated systemic inflammatory response. In the absence of preeclampsia, healthy endothelium prevents platelet activation, activates circulating anticoagulants, buffers the

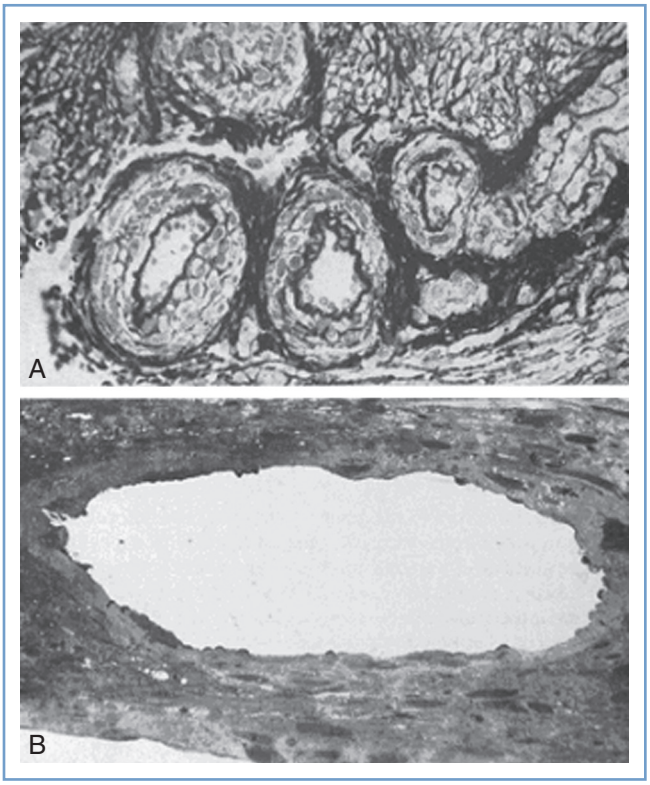

FIGURE 36-2 ■ Sections through spiral arteries (**A**) at the myometrial-endometrial junction of the nonpregnant uterus and (**B**) at the myometrial-decidual junction in late normal pregnancy (×150). (From Sheppard BL, Bonnar J. Uteroplacental arteries and hypertensive pregnancy. In Bonnar J, MacGillivray I, Symonds G, eds. Pregnancy Hypertension. Baltimore, University Park Press, 1980:205.)

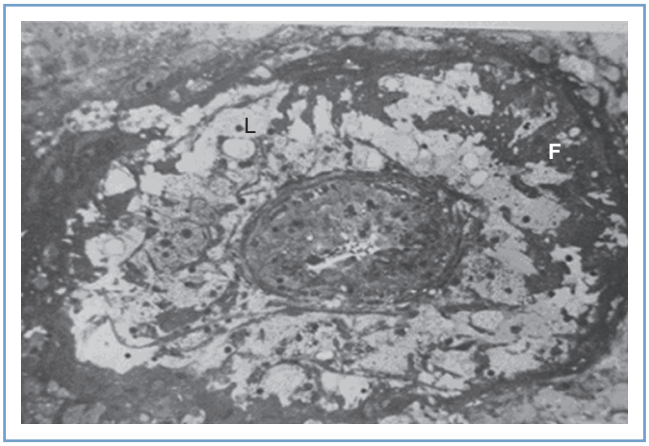

FIGURE 36-3 ■ This figure shows lipid-laden cells (L) and fibrin deposition (F) in this occluded decidual vessel characteristic of both severe preeclampsia and severe fetal growth restriction (×150). (From Sheppard BL, Bonnar J. Uteroplacental arteries and hypertensive pregnancy. In Bonnar J, MacGillivray I, Symonds G, eds. Pregnancy Hypertension. Baltimore, University Park Press, 1980:205.)

response to pressors, and maintains fluid in the intravascular compartment. These normal functions are disrupted in preeclampsia. As a result, the pregnant woman develops hypertension and proteinuria, and is at risk for other manifestations of severe systemic disease (e.g., HELLP syndrome, eclampsia, end-organ damage). These clinical manifestations usually occur after 20 weeks' gestation.

Not all women with impaired placental perfusion develop preeclampsia. The same failure of uterine vascular remodeling occurs in women with isolated fetal growth restriction[80] and in approximately one third of cases of spontaneous preterm birth without maternal clinical manifestations of preeclampsia.[81]

Abnormal Placentation

The basis for abnormal uteroplacental development has not been fully elucidated and is likely due to a complex interaction of immunologic, vascular, environmental, and genetic factors. The hypothesis that immune maladaptation may play a central role in predisposing to abnormal placentation and subsequent preeclampsia is supported by evidence showing that long-term exposure to paternal antigens in sperm is protective. Furthermore, the importance of an intact immune system in the development of preeclampsia is demonstrated by the lower incidence of preeclampsia in women with untreated human immunodeficiency virus; the incidence returns to baseline after treatment with antiretroviral therapy.[82,83]

The immune cells present in the decidua—the endometrium in the nonpregnant state becomes the decidua in pregnancy—include macrophages, dendritic cells, and natural killer (NK) cells. Macrophages and dendritic cells are found in greater density in preeclamptic placentas than in control placentas.[82,84] Similarly, levels of chemokines that attract these immune cells are also elevated.[82,84] Excess macrophages in the decidua are associated with impaired trophoblast invasion, suggesting that excess inflammation may be one of the causal components of impaired placentation.[84] NK cells may also be important in regulating vascular development during placentation. NK cells interact with fetal trophoblast cell markers via killer immunoglobulin receptors (KIR) to influence trophoblastic invasion. Specific genotypic combinations of maternal KIR and trophoblastic human leukocyte antigen C (HLA-C) may increase the risk for preeclampsia.[85] A systematic review of 22 studies examining the association between HLA type and the risk for preeclampsia suggested that HLA-DR correlates with preeclampsia, but it is unclear if this, or any other HLA genotype, is causally related to preeclampsia risk; the authors called for additional studies with larger sample sizes to examine maternal-fetal HLA combinations and the risk for preeclampsia.[86]

Agonistic autoantibodies to the angiotensin receptor-1 (AT_1) are present in many preeclamptic women in association with defective remodeling of the uteroplacental vasculature.[87,88] These autoantibodies activate AT_1 receptors on trophoblast cells, endothelial cells, and vascular smooth muscle cells.[89-91] They appear to block trophoblastic invasion[90] and may induce the production of reactive oxygen species[91] and thus play a significant role in the pathophysiology of preeclampsia (Figure 36-4). Furthermore, introduction of these autoantibodies into pregnant mice increases production of **soluble fms-like tyrosine kinase-1 (sFlt-1)** and results in hypertension

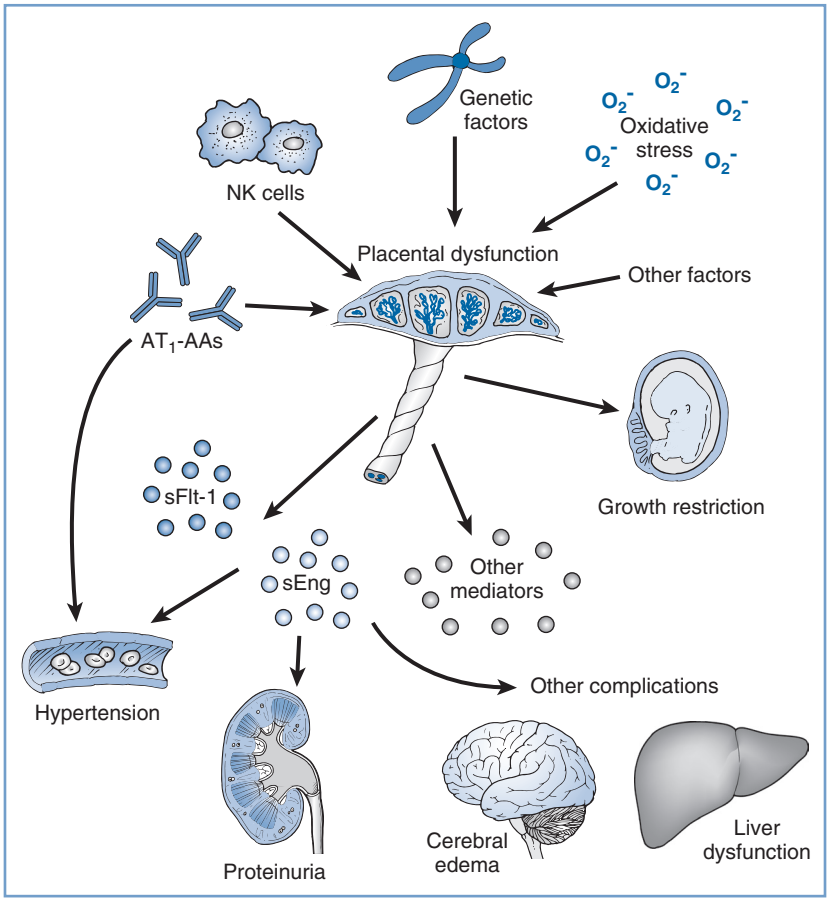

FIGURE 36-4 ■ Angiotensin receptor autoantibodies (AT_1-AAs) in preeclampsia. AT_1-AAs and other factors (e.g., oxidative stress and genetic factors) may cause placental dysfunction, which, in turn, leads to the release of antiangiogenic factors (e.g., sFlt-1 and sEng) and other inflammatory mediators to induce preeclampsia. AT_1-AAs may also act directly on the maternal vasculature to enhance angiotensin II sensitivity and hypertension. (From Parikh SM, Karumanchi SA. Putting pressure on preeclampsia. Nat Med 2008; 14:810-2.)

and proteinuria.[92] Thus, these autoantibodies may play an important role in the pathogenesis of preeclampsia at several different stages.

Oxidative stress is another mechanism that has been postulated as an important component of impaired placentation.[82] Oxidative stress and the resultant free radicals are known to contribute to atherosclerosis and thus may contribute to placental atherosis.[82] Volatile organic compounds measured in a breath test, a marker for oxidative stress, are found in greater quantity in preeclamptic women compared with healthy pregnant controls.[93] Enthusiasm for this theory is tempered by the failure of antioxidant supplementation to decrease the risk for preeclampsia in clinical trials.[82]

Maternal Systemic Disease

The symptomatic second stage of preeclampsia is marked by widespread endothelial activation/dysfunction, and the signs and symptoms of preeclampsia are attributable to the manifestations of endothelial dysfunction specific to each organ system.[76] This notion is supported by studies showing increased levels of biomarkers indicating endothelial activation or injury, or both, in preeclamptic women, including endothelin-1, fibronectin, von Willebrand factor, and thrombomodulin.[76] The central role of endothelial dysfunction is further evidenced by the fact that chronic conditions that cause prepregnancy endothelial injury, including chronic hypertension, preexisting diabetes, and renal disease, are risk factors for preeclampsia. A predilection for endothelial dysfunction may similarly explain the association of preeclampsia and future cardiovascular disease.[76,94]

The mechanistic link between abnormal placentation and subsequent widespread endothelial dysfunction is an area of great interest and ongoing investigation. The prevailing hypothesis is that as the pregnancy progresses, the placenta becomes relatively hypoxic and this change results in an overexpression and release into the maternal circulation of placentally derived antiangiogenic factors, including sFlt-1 and **soluble endoglin (sEng)**.[76,77]

The vascular endothelium requires proangiogenic factors for normal function. sFlt-1 antagonizes the angiogenic growth factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).[95,96] Evidence for a central role for sFlt-1 in the pathogenesis of preeclampsia comes from both animal and human studies. Maynard et al.[95] demonstrated that sFlt-1 levels increase during gestation and fall after delivery and that increased circulating sFlt-1 levels reduce circulating levels of free

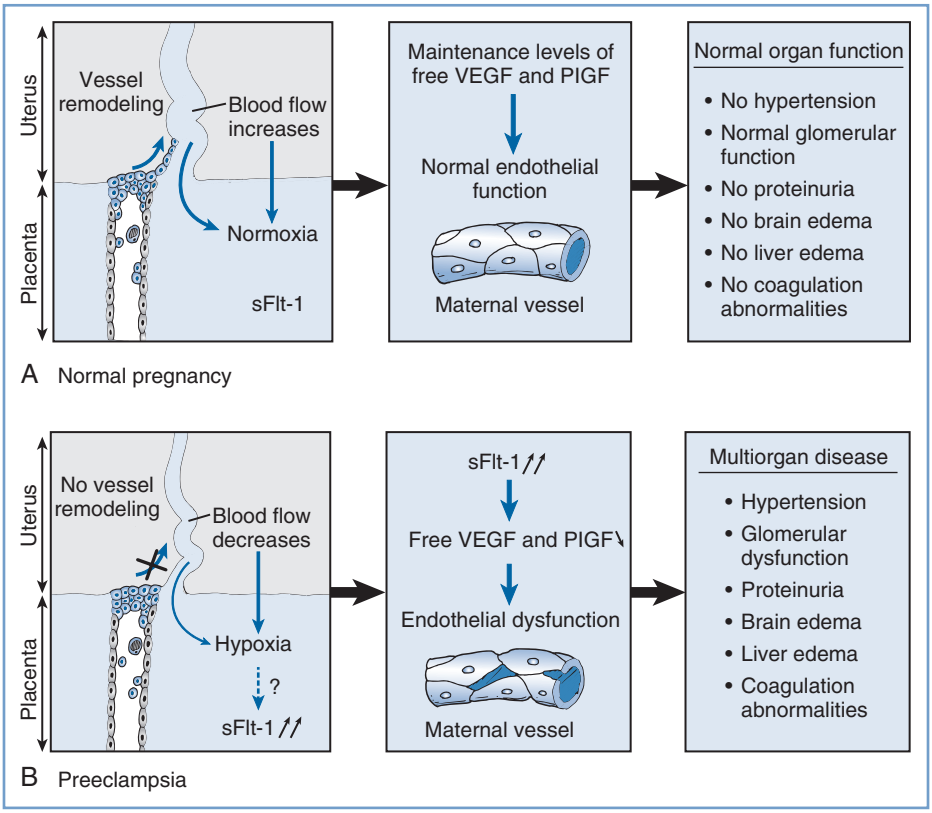

FIGURE 36-5 ■ Hypothesis on the role of soluble fms-like tyrosine kinase (sFlt-1) in preeclampsia. **A,** During normal pregnancy, the uterine spiral arteries are infiltrated and remodeled by endovascular invasive trophoblasts, thereby increasing blood flow significantly to meet the oxygen and nutrient demands of the fetus. **B,** In the placenta of preeclamptic women, trophoblast invasion does not occur and blood flow is reduced, resulting in placental hypoxia. In addition, increased amounts of soluble sFlt-1 are produced by the placenta and scavenge vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), thereby lowering circulating levels of unbound VEGF and PlGF. This altered balance causes generalized endothelial dysfunction, resulting in multiorgan disease. (From Luttun A, Carmeliet P. Soluble VEGF receptor Flt1: the elusive preeclampsia factor discovered? J Clin Invest 2003; 111:600-2.)

VEGF and PlGF, causing endothelial dysfunction that can be rescued by exogenous VEGF and PlGF. Furthermore, these investigators found that the administration of sFlt-1 to pregnant rats induced hypertension, proteinuria, and glomerular endotheliosis, which is the classic renal lesion of preeclampsia. When administered *in vitro*, VEGF and PlGF cause rat renal arteriolar relaxation, which is blocked by sFlt-1. In response to increased circulating levels of sFlt-1, VEGF and PlGF levels are reduced, resulting in endothelial dysfunction in maternal vessels (Figure 36-5). In a study in humans, elevated sFlt-1 levels and reduced levels of PlGF predicted the subsequent development of preeclampsia before the development of any maternal symptoms.[97] Subsequent studies have confirmed the importance of the sFlt-1-to-PlGF ratio as a marker of preeclampsia.[98] Of interest, cigarette smoking, which is known to be protective against preeclampsia, is associated with lower maternal sFlt-1 concentrations during pregnancy compared with nonsmokers.[99]

sEng is another placentally derived antiangiogenic protein that appears to be important in the pathogenesis of preeclampsia.[96] Circulating levels of sEng are markedly increased in women who subsequently develop preeclampsia. Furthermore, if women have both elevated sEng and increased sFlt-1/PlGF ratios, their risk for preeclampsia is elevated approximately 30-fold compared with women with normal levels of both factors/ratios.[100]

The study of antiangiogenic proteins is an active area of current research, and rapid progress is being made in understanding the role of these proteins in the pathogenesis of preeclampsia. However, the importance of recent findings is tempered by the knowledge that preeclampsia does not develop in all women with high sFlt-1 and low PlGF levels, and the syndrome occurs in some women with low sFlt-1 and high PlGF levels.[97,101] These observations are consistent with those from a large, longitudinal study involving 2246 singleton pregnancies that found that PlGF and sFlt-1 levels had limited sensitivity, specificity, and positive predictive value for predicting the development of preeclampsia.[102]

Kanasaki et al.[103] hypothesized that a molecular defect upstream from the soluble factors contributes to preeclampsia. The investigators demonstrated that pregnant mice deficient in **catechol-*O*-methyltransferase (COMT)** demonstrate a preeclampsia-like phenotype in response to the absence of **2-methoxyestradiol (2-ME)**, a natural metabolite of estradiol that is elevated during the third trimester of normal pregnancy. Administration of 2-ME to COMT-deficient mice suppresses placental hypoxia and sFlt-1 elevation. In addition, women with severe preeclampsia have significantly lower

levels of COMT and 2-ME than women with healthy pregnancies. However, a subsequent study in humans failed to find a significant difference in placental COMT expression in women with early-onset, severe preeclampsia compared with normotensive women[104]; therefore, further research is needed to determine what, if any, role COMT plays in the pathogenesis of preeclampsia.

Genetic Factors

There is a strong genetic basis underlying the risk for preeclampsia that is attributable to both maternal and fetal genetic factors. It is estimated that approximately one fifth of the variance in disease risk is attributable to fetal genetic effects, and one third is attributable to maternal genetic factors.[47] Despite this, with the possible exception of thrombophilia genes, no genetic variants have been robustly associated with preeclampsia. Because preeclampsia is extremely likely to be polygenic, genome-wide association studies may provide a useful approach to identify preeclampsia genes. A large, international collaborative is currently undertaking a genome-wide association study of this disease and results are expected soon. In addition to increasing the understanding of the genetic architecture of preeclampsia, the identification of genetic variants associated with the disease may provide new avenues to understanding the basic pathophysiology of this disorder.

Prophylaxis

Administration of **low-dose aspirin** has been proposed for the prevention of preeclampsia based on the observation that thromboxane is increased relative to prostacyclin in preeclamptic pregnancies. Aspirin inhibits the synthesis of prostaglandins by the irreversible acetylation and inactivation of cyclooxygenase. Thromboxane and prostacyclin are arachidonic acid metabolites and physiologic antagonists important in vasoregulation. Thromboxane is a potent vasoconstrictor, and prostacyclin is a strong vasodilator. Aspirin inhibits the biosynthesis of platelet thromboxane A_2, and it has been hypothesized that preeclampsia could be prevented by preventing the imbalance in the thromboxane-to-prostacyclin ratio. Meta-analysis of available data points to a 10% to 20% reduction in the risk for developing preeclampsia in women treated with aspirin or other antiplatelet agents.[105,106] The reduction in risk is most evident in women at moderate or high risk for preeclampsia who initiate aspirin prophylaxis at 16 weeks' gestation or earlier.[107,108] The ACOG suggests daily low-dose aspirin, beginning in the late first trimester, specifically for women with a history of preeclampsia leading to prior preterm delivery before 34 weeks' gestation, or preeclampsia in more than one prior pregnancy.[4]

Calcium supplementation has been studied for preeclampsia prophylaxis based on observations that dietary calcium intake is inversely related to the incidence of preeclampsia.[109] A 2010 meta-analysis of available randomized controlled clinical trial data showed that calcium supplementation decreased the risk for preeclampsia by approximately 50%.[110] The reduction in risk was most pronounced in high-risk women and those with low baseline calcium intake.[110] However, in a large multicenter, randomized, placebo-controlled trial involving 2589 healthy, nulliparous women conducted in the United States, ingestion of 2 g of elemental calcium daily did not reduce the occurrence of preeclampsia or gestational hypertension overall or in a subset of women with low baseline calcium intake.[111] The ACOG does not recommend calcium supplementation to prevent preeclampsia for women with normal dietary calcium intake.[4]

Antioxidant supplementation has also been investigated as prophylaxis because of the important role oxidative stress is thought to play in the pathogenesis of preeclampsia. Numerous studies have been conducted to investigate a possible prophylactic or therapeutic role for antioxidant supplementation in the hypertensive disorders of pregnancy. Although some early, small studies suggested that this may be a promising approach, subsequent larger, high-quality studies have not shown a benefit.[112] In randomized, controlled clinical trials, supplementation with 1000 mg of vitamin C and 400 IU of vitamin E did not reduce the incidence of preeclampsia in healthy nulliparous women[113] or in women at increased risk for preeclampsia.[114,115] One of these trials even showed evidence of harm, with a greater incidence of (1) low birth weight, (2) unexplained fetal death after 24 weeks' gestation, and (3) umbilical cord blood acidemia in patients randomized to the antioxidant group.[115] The ACOG does not recommend the administration of vitamin C or vitamin E to prevent preeclampsia.[4]

Clinical Presentation

Preeclampsia occurs more frequently in nulliparous women and most commonly presents during the third trimester, often near term. Women with early-onset disease (before 34 weeks' gestation) have worse outcomes than women with late-onset disease. The disease typically regresses rapidly after delivery, with resolution of symptoms within 48 hours. However, preeclampsia can also manifest postpartum with hypertension, proteinuria, or the occurrence of seizures (eclampsia). Postpartum preeclampsia usually presents within 7 days of delivery.[116]

Disease manifestations of severe preeclampsia occur in all body systems as the result of widespread endothelial dysfunction.

Central Nervous System

Although the term *preeclampsia* suggests that eclampsia is the end stage of preeclampsia, it is more accurate to consider eclampsia as the outward manifestation of disease progression in the brain, similar to other organ involvement. Central nervous system manifestations include severe headache, hyperexcitability, hyperreflexia, and coma.[3,117] Visual disturbances can include scotoma, amaurosis, and blurred vision.[118]

Noninvasive measurements of cerebral blood flow and resistance, along with other neuroimaging approaches, suggest that the loss of cerebral vascular autoregulation and vascular barotrauma occur with preeclampsia and eclampsia.[118,119] Hyperperfusion of the

brain, particularly in the setting of the endothelial dysfunction present in preeclampsia, causes vasogenic edema. Failure of autoregulation occurs most commonly in the posterior circulation, such that the changes in the brain with severe preeclampsia/eclampsia result in the posterior reversible leukoencephalopathy syndrome (PRES).[118,120-122]

Airway

In pregnant women, the internal diameter of the trachea is reduced because of mucosal capillary engorgement. In women with preeclampsia, these changes can be exaggerated with upper airway narrowing as a result of **pharyngolaryngeal edema**; these changes may compromise visualization of airway landmarks during direct laryngoscopy.[123] **Subglottic edema** can cause airway obstruction. Signs of airway obstruction include dysphonia, hoarseness, snoring, stridor, and hypoxemia.[124,125]

Pulmonary

Pulmonary edema is a severe complication that occurs in approximately 3% of women with preeclampsia.[126] It is relatively infrequent in healthy, younger women; the risk increases in older multigravid women, in women with preeclampsia superimposed on chronic hypertension or renal disease, and among those whose preeclampsia leads to oliguria.

Plasma colloid osmotic pressure is reduced in normal pregnancy because of decreased plasma albumin concentration, and it is decreased even further in preeclamptic women.[127] Women with normal pregnancies have a mean osmotic pressure of approximately 22 mm Hg in the third trimester and approximately 17 mm Hg during the early postpartum period. In contrast, a study of women with preeclampsia demonstrated a mean colloid osmotic pressure of approximately 18 mm Hg before delivery and 14 mm Hg after delivery.[128] Decreased colloid osmotic pressure, in combination with increased vascular permeability and the loss of intravascular fluid and protein into the interstitium, increases the risk for pulmonary edema.[129] Excess intravenous fluid is an important risk factor for pulmonary edema in preeclamptic patients.[130]

Cardiovascular

Women with preeclampsia have increased vascular tone and increased sensitivity to vasoconstrictor influences, which result in the clinical manifestations of hypertension, vasospasm, and end-organ ischemia.[131] Preeclampsia is characterized by severe vasospasm as well as exaggerated hemodynamic responses to circulating catecholamines.[132,133] Characteristically, blood pressure and systemic vascular resistance are elevated. In preeclampsia without severe features, plasma volume may be normal; however, it may be reduced as much as 40% in women with severe disease.[134]

Severe preeclampsia is usually a **hyperdynamic state**. Many studies have attempted to characterize the hemodynamic characteristics of preeclampsia using invasive monitoring techniques or echocardiography.[135-138] Interpretation and comparison of the results of these studies have been difficult because of variation in patient populations, definitions of preeclampsia, disease severity, prior treatment, and the presence or absence of concomitant comorbid disease. Hemodynamic characteristics in preeclamptic women are more complex than originally thought, in part, because hemodynamic measurements change with treatment and disease progression. Overall, studies have found that the majority of affected women exhibit increased cardiac output,[138] hyperdynamic left ventricular function,[135] and mild to moderately increased systemic vascular resistance.[135,138] A smaller group of women comprise a high-risk group who present with decreased left ventricular function, markedly decreased systemic vascular resistance, and severely decreased intravascular volume.[135,139]

Hematologic

Thrombocytopenia is the most common hematologic abnormality in women with preeclampsia. Platelet counts less than 100,000/mm^3 occur most commonly in women with severe disease or HELLP syndrome[17] and correlate with the severity of the disease process.

Studies using thromboelastography have found that women with preeclampsia without severe features are *hyper*coagulable relative to women without preeclampsia and that those with severe disease are relatively *hypo*coagulable.[140] In contrast to normal pregnancies and other hypertensive disorders, platelets are activated in preeclampsia[141]; subsequent platelet degranulation is believed to account for the decreases in platelet function, and aggregation appears to account for the decrease in platelet count.[142]

The syndrome of **disseminated intravascular coagulation** (DIC) occurs in some women with preeclampsia, generally in the setting of severe liver involvement, intrauterine fetal demise, placental abruption, or postpartum hemorrhage.[143] Activation of the coagulation system is marked by consumption of procoagulants, increased levels of fibrin degradation products, and end-organ damage secondary to microthrombi formation. In advanced DIC, procoagulants (e.g., fibrinogen, platelets) decrease to a level that may lead to spontaneous hemorrhage.

Hepatic

Hepatic manifestations include periportal hemorrhage and fibrin deposition in hepatic sinusoids. Hepatic involvement frequently presents as right upper quadrant or epigastric pain. Damage ranges from mild hepatocellular necrosis to the more ominous HELLP syndrome and can be associated with subcapsular bleeding and risk for hepatic rupture. Spontaneous hepatic rupture is rare but is associated with a 32% maternal mortality rate.[144]

Renal

Renal manifestations of preeclampsia include persistent proteinuria, changes in the glomerular filtration rate, and hyperuricemia. The presence of **proteinuria** is a defining

element of preeclampsia. The characteristic renal histologic lesion of preeclampsia is glomerular capillary endotheliosis and manifests as glomerular enlargement and endothelial and mesangial cell swelling. Increasing urinary excretion of protein likely results from changes in the pore size or charge selectivity of the glomerular filter and impaired proximal tubular reabsorption.[145]

During normal pregnancy, the **glomerular filtration rate** (GFR) *increases* by 40% to 60% during the first trimester,[146,147] with a resulting decrease in the serum markers of renal clearance, including blood urea nitrogen (BUN), creatinine, and uric acid. In preeclampsia, this increase in GFR is blunted compared with normal pregnancy.[145] Notably, women with preeclampsia may have BUN and creatinine measurements in the normal range for nonpregnant women despite significantly decreased GFR relative to healthy pregnant women.

The association between preeclampsia and **hyperuricemia** was recognized as early as 1917.[148] Most evidence suggests that decreased renal clearance is the primary mechanism for elevated uric acid levels.[149] Because levels of serum uric acid begin to increase as early as 25 weeks' gestation,[150] it has been investigated as a possible early predictor of preeclampsia.

Oliguria is a possible late manifestation of severe preeclampsia and parallels the severity of disease. Persistent oliguria (< 500 mL urine output in 24 hours) requires immediate assessment of intravascular volume status. Progression to renal failure is rare and is typically preceded by hypovolemia, placental abruption, or DIC.

Uteroplacental Perfusion

Uteroplacental perfusion can be impaired in pregnancies complicated by preeclampsia. In contrast to normal pregnancy, downstream resistance in the uteroplacental bed increases, diastolic flow velocity decreases, and the systolic-to-diastolic flow velocity ratio increases.[151] The systolic-to-diastolic ratio, calculated from Doppler ultrasonographic determination of blood flow velocities, reflects intrinsic arterial resistance. Pathophysiologic changes can result in fetal growth restriction (the fetal syndrome) in some pregnancies complicated by severe preeclampsia.

Obstetric Management

Optimal management of the woman with preeclampsia requires a team approach. There is considerable overlap in areas of concern to the obstetrician and the anesthesia provider.

Obstetric management of preeclampsia centers on the following: (1) fetal and maternal surveillance, (2) treatment of hypertension, (3) seizure prophylaxis, and (4) decisions regarding the timing and route of delivery. Delivery remains the only cure for preeclampsia. Obstetric care of women with preeclampsia without severe features differs little from routine management of healthy pregnant women, with the exception of careful monitoring to detect the progression of disease to severe preeclampsia. Data suggest induction of labor for pregnancies beyond 37 weeks' gestation in women with gestational hypertension or preeclampsia without severe features is associated with improved maternal outcomes compared with expectant management.[4,152] Outcomes in these pregnancies are similar to those in uncomplicated pregnancies.[4,13,77]

In general, induction of labor is recommended for women presenting with severe preeclampsia at 34 weeks' gestation or later.[4,17] For women at less than 34 weeks' gestation, expectant management may improve fetal outcomes without substantially endangering the mother,[77,153] but data are few.[154] Delay of delivery for 24 to 48 hours allows for the administration of corticosteroids to facilitate fetal lung maturity and transfer to a facility with maternal and neonatal intensive care resources. Expedited delivery, regardless of corticosteroid administration, is indicated for patients with eclampsia, pulmonary edema, DIC, placental abruption, abnormal fetal surveillance, a previable or nonviable fetus, or intrauterine fetal demise (Figure 36-6).[4,155] If a woman develops refractory severe hypertension despite maximum doses of antihypertensive agents *or* persistent cerebral symptoms while receiving magnesium sulfate, delivery should occur within 24 to 48 hours, regardless of gestational age or corticosteroid administration.[4,155] Expectant management before 34 weeks' gestation should be undertaken at facilities with neonatal and maternal intensive care resources.[4]

Maternal and Fetal Surveillance

Maternal surveillance is indicated for all preeclamptic women. In women with preeclampsia without severe features, the goal is early detection of severe disease. In women with severe disease, the goal is detection of worsening organ dysfunction. All women should be evaluated for signs or symptoms indicating end-organ involvement, including (1) severe headache, (2) visual disturbances, (3) altered mentation, (4) dyspnea, (5) right upper quadrant or epigastric pain, (6) nausea and vomiting, (7) decreased urine output, and (8) CNS hyperexcitability.[3]

Initial laboratory investigations for the pregnant woman who develops hypertension after 20 weeks' gestation are listed in Table 36-3. The admission platelet count is an excellent predictor of subsequent thrombocytopenia.[156] For preeclamptic women with a platelet count exceeding 100,000/mm^3, further coagulation testing is not required because coagulopathy is rarely present in severely preeclamptic women who have a normal platelet count.[156] If the platelet count is less than 100,000/mm^3, other hemostatic abnormalities (e.g., prolonged prothrombin time [PT] and activated partial thromboplastin time [aPTT], reduced fibrinogen concentration) may be present.[156] Further coagulation studies may be useful, particularly if risk factors for DIC are present (e.g., placental abruption, liver dysfunction, HELLP syndrome). Liver function tests are obtained in all women with preeclampsia because abnormal levels indicate more severe disease and may prompt delivery. Approximately 20% of preeclamptic women have elevated serum aminotransferase levels.[157] The value of uric acid testing is controversial, with conflicting evidence regarding its association with increased fetal or maternal risk for complications.[158-160]

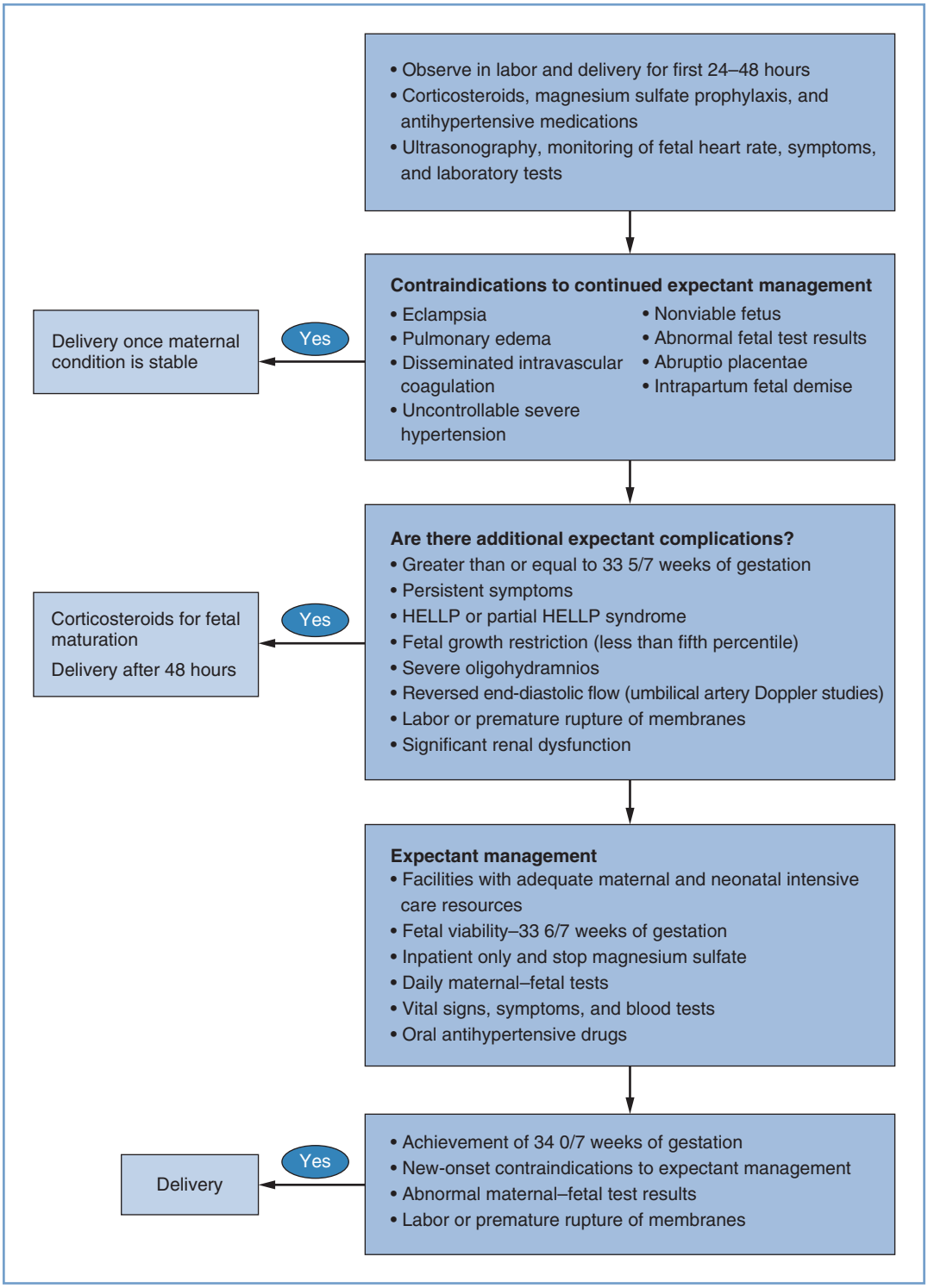

FIGURE 36-6 ■ Suggested algorithm for the management of severe preeclampsia at less than 34 weeks' gestation. *HELLP,* hemolysis, elevated liver enzymes, and low platelet count. (From American College of Obstetricians and Gynecologists Taskforce on Hypertension in Pregnancy. Hypertension in pregnancy. ACOG. Washington, DC, 2013.)

TABLE 36-3 Initial Laboratory Investigations for Women in Whom Hypertension Develops after 20 Weeks' Gestation

Test	Rationale
Hemoglobin and hematocrit	Hemoconcentration supports diagnosis of preeclampsia and is an indicator of severity. Values are decreased if hemolysis is present.
Platelet count	Thrombocytopenia suggests severe preeclampsia.
Urine protein-creatinine ratio or 24-h urine protein excretion	Presence of proteinuria distinguishes preeclampsia from gestational hypertension.
Serum creatinine level	Abnormal or rising creatinine level suggests severe preeclampsia, especially in presence of oliguria.
Serum aminotransferase levels	Elevated serum aminotransferase levels suggest severe preeclampsia with hepatic involvement.

Modified from Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1-S22; and American College of Obstetricians and Gynecologists Taskforce on Hypertension in Pregnancy. Hypertension in pregnancy. ACOG. Washington, DC, 2013.

In general, the frequency of subsequent laboratory evaluation will be guided by the initial findings and the severity of illness and disease progression.[155] A diagnosis of preeclampsia without severe features should prompt at least weekly laboratory investigations, with the frequency modified based on subsequent clinical findings.[4] In the expectant management of severe preeclampsia, hemoglobin, platelet count, liver function tests, creatinine, and coagulation parameters should be assessed daily or every other day.[4,161] For women undergoing induction of labor for whom initial laboratory measurement or daily platelet counts demonstrate thrombocytopenia, serial platelet counts at least every 6 hours may be useful to detect declining platelet counts and to guide decision-making about the timing of delivery and analgesic or anesthetic technique. Finally, for women with indicated delivery, an active type and screen is indicated, with consideration of type and crossmatch of 2 units of packed red blood cells or more, because these women are at increased risk for postpartum hemorrhage.[162]

Preeclampsia is a known risk factor for perinatal death. The ACOG Taskforce on Hypertension in Pregnancy recommends daily fetal movement counts with either nonstress testing or biophysical profile testing at the time of diagnosis and at regular intervals thereafter.[4,163] Ultrasonography is used to estimate fetal weight and amniotic fluid volume. Doppler ultrasonography is used to measure fetal blood flow velocimetry when fetal growth restriction is suspected.[4,164,165]

Treatment of Acute Hypertension

Antihypertensive medications are used to treat severe hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mm Hg) with the goal of preventing adverse maternal sequelae such as hypertensive encephalopathy, cerebrovascular hemorrhage, myocardial ischemia, and congestive heart failure.[163,166]

Although acute control of maternal blood pressure is critical, rapid changes in maternal perfusion pressure may adversely affect uteroplacental perfusion and oxygen delivery to the fetus. Antihypertensive medications should be carefully titrated to avoid abrupt changes in maternal blood pressure. The aim of therapy is to lower the mean arterial blood pressure by no more than 15% to 25%, with a target systolic blood pressure between 120 and 160 mm Hg and a diastolic blood pressure between 80 and 105 mm Hg.[4,167,168] Commonly used drugs include labetalol, hydralazine, and nifedipine. Nicardipine, sodium nitroprusside, and esmolol may be considered second-line agents (Table 36-4). In usual clinical doses, all are considered safe for the fetus.

Systematic review and meta-analysis of available studies show insufficient data regarding the relative efficacy of these commonly used agents and recommend selection based on clinician familiarity and what is known about adverse effects.[169] The systematic review does, however, suggest that some agents are inferior and recommends avoiding diazoxide, katanserin, nimodipine, and magnesium sulfate for the treatment of severe hypertension in pregnancy (although magnesium is recommended for seizure prophylaxis).[169] A 2011 ACOG Committee Opinion recommends labetalol or hydralazine as first-line treatment for acute-onset, severe hypertension in pregnant or postpartum patients.[166]

Labetalol. Labetalol is a combined alpha- and beta-adrenergic receptor antagonist with a 1-to-7 ratio of alpha- to beta-adrenergic receptor antagonism when administered intravenously. Labetalol should be avoided in women with severe asthma or congestive heart failure.[170]

A systematic review[169] and a meta-analysis[171] of small, randomized controlled trials concluded that intravenous labetalol has efficacy similar to intravenous hydralazine but with fewer maternal side effects.

Hydralazine. Hydralazine has been used safely in pregnant women for decades and is also considered a first-line drug for treating severe hypertension in pregnancy.[166] Hydralazine exerts a potent direct vasodilating effect. Plasma volume expansion before administration decreases the risk for maternal hypotension. Other side effects include tachycardia, palpitations, headache, and neonatal thrombocytopenia.[172,173] In a randomized clinical trial, hydralazine was associated with more maternal tachycardia and palpitations and less neonatal bradycardia and hypotension than labetalol,[174] but both antihypertensive drugs are considered safe and effective for the treatment of severe hypertension in pregnant women.

TABLE 36-4 Treatment of Acute Severe Hypertension* In Preeclampsia/Eclampsia

Medication	Onset of Action†	Dose
Labetalol	5-10 min	20 mg IV, then 40-80 mg every 10 min up to maximum dose of 220 mg IV
Hydralazine	10-20 min	5 mg IV every 20 min up to maximum dose of 20 mg IV
Nifedipine	10-20 min	10 mg PO every 20 min up to a maximum dose of 50 mg
Nicardipine	10-15 min	Initial infusion 5 mg/h, increase by 2.5 mg/h every 5 min to a maximum of 15 mg/h
Sodium nitroprusside‡	0.5-1 min	0.25-5.0 μg/kg/min IV infusion

IV, intravenously; *PO,* per os.
*Systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 110 mm Hg, or both, if sustained.
†From Stoelting R, Hillier S. Pharmacology & Physiology in Anesthetic Practice. Philadelphia, Lippincott Williams & Wilkins, 2006.
‡Risk for fetal cyanide poisoning with treatment > 4 hours.
Modified from Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1-S22; Marik PE, Rivera R. Hypertensive emergencies: an update. Curr Opin Crit Care 2011; 17:569-80; and Shekhar S, Sharma C, Thakur S, Verma S. Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol 2013; 122:1057-63.

Nifedipine. Nifedipine is a calcium entry–blocking agent that lowers blood pressure by relaxing arterial and arteriolar smooth muscle. It can be administered as a long-acting oral medication once the severe hypertension has stabilized. Nifedipine immediate-release capsules should never be administered to women with known coronary artery disease, long-standing diabetes mellitus or aortic stenosis, or to women older than 45 years of age because of an increased risk for sudden cardiac death.[77] Although earlier reports suggested that the coadministration of nifedipine with magnesium sulfate causes adverse effects in both mother and fetus, including severe maternal hypotension,[175,176] neuromuscular blockade,[177,178] and nonreassuring FHR patterns,[175,176] subsequent data suggest that these drugs can be used together safely.[179,180]

Other Agents. If labetalol, hydralazine, or nifedipine are not effective in controlling blood pressure, consideration may be given to using a nicardipine or labetalol infusion or other antihypertensive agents.[166]

Nicardipine is a calcium entry–blocking agent that can be administered by intravenous infusion and has been shown to achieve rapid decreases in systolic and diastolic blood pressures in pregnant women.[181] It is an excellent option for treating severe hypertension that is not responsive to labetalol or hydralazine.[166]

Sodium nitroprusside is a potent smooth muscle vasodilator that interacts with sulfhydryl groups on endothelial cells and results in the release of nitric oxide.[182,183] It relaxes arterial vessels and reduces both afterload and venous return, with an almost instantaneous onset. The drug is used in pregnant women with severe hypertension who do not respond to hydralazine or labetalol therapy. It should be used only in emergency situations and then for the shortest time period possible because sodium nitroprusside metabolism produces cyanide, which undergoes placental transfer, thus exposing the fetus to potential cyanide toxicity. However, fetal harm is unlikely to result from short-term use of sodium nitroprusside in doses of 2 μg/kg/min or less. Use of the drug requires careful titration; continuous intra-arterial blood pressure monitoring is mandatory.

Esmolol is a short-acting beta-adrenergic receptor antagonist that can be used to treat acute hypertension. Concerns regarding the use of esmolol during pregnancy arose in 1989 after a report of dose-dependent prolonged fetal bradycardia in a study of gravid ewes receiving esmolol by stepped infusion.[184] Subsequent human case reports have reported variable responses,[185-187] but in most cases fetal bradycardia was transient and FHR returned to baseline after discontinuation of the drug. Placental transfer is rapid and the anesthesia provider should expect to observe the clinical effects of beta-adrenergic receptor blockade in the fetus. Maternal administration of esmolol produces a greater degree of beta-adrenergic receptor blockade in the fetal lamb than that observed after maternal administration of an equipotent dose of labetalol.[184,188]

Seizure Prophylaxis

The routine use of magnesium sulfate for seizure prophylaxis in women with *severe* preeclampsia is an established obstetric practice in the United States and has gained popularity throughout the world. There is clear evidence that magnesium sulfate is the best available agent for prevention of recurrent seizures in women with eclampsia[189,190]; thus, its use has been extended to seizure prophylaxis in women with severe preeclampsia.[4]

A 2010 meta-analysis of the available data identified six trials involving 11,444 women that compared magnesium sulfate for the treatment of preeclampsia with either placebo or no anticonvulsant.[191] Magnesium decreased the risk for developing eclampsia (relative risk [RR], 0.41; 95% confidence interval [CI], 0.29 to 0.58); there was also a trend toward lower risk for maternal death (RR, 0.54; 95% CI, 0.26 to 1.10) but no effect on serious maternal morbidity.[191] Additionally, magnesium therapy reduced the risk for placental abruption but did not adversely affect fetal and/or neonatal outcomes, including stillbirth, perinatal death, or neurosensory disability.[191] Treatment with magnesium increased the risk for maternal respiratory depression (RR, 1.98; 95% CI, 1.24 to 3.15) and cesarean delivery (RR, 1.05; 95% CI, 1.01 to 1.10).[191] Other side effects that were significantly more common in those treated with magnesium included feeling warm or flushed, nausea/vomiting, muscle weakness, hypotension, dizziness, drowsiness/confusion, and headache.[191]

There are insufficient data to justify the use of magnesium sulfate for seizure prevention in preeclampsia without severe features.[4] Studies have failed to show a difference in the number of women who progressed to severe preeclampsia.[192-195]

The mechanism of the anticonvulsant effect of magnesium is not well understood. It was previously believed that eclamptic seizures were the result of cerebral vasospasm, and it was also believed that the cerebral vasodilating properties of magnesium reduced the rate of eclamptic seizures by relieving vasospasm.[196] However, more recent evidence suggests that abrupt, sustained blood pressure elevation overwhelms myogenic vasoconstriction and causes forced dilation of the cerebral vessels, hyperperfusion, and cerebral edema.[119,196-198] This evidence raises the question of how magnesium sulfate—a vasodilator—could be effective in seizure prophylaxis; magnesium would be expected to worsen cerebral hyperperfusion and edema. Using a rat model, Euser and Cipolla[196] demonstrated that the mesenteric vessels are more sensitive to magnesium-induced vasodilation than are cerebral vessels, suggesting that part of the effect may be mediated through decreasing peripheral vascular resistance.[199] Magnesium may also protect the blood-brain barrier,[199] decrease cerebral edema,[199] or act centrally at *N*-methyl-D-aspartate (NMDA) receptors to raise the seizure threshold.[200]

No consensus exists regarding the following: (1) the ideal time to initiate treatment with magnesium sulfate, (2) the best loading and maintenance doses, and (3) the optimal duration of therapy. Many obstetricians administer a loading dose of 4 to 6 g over 20 to 30 minutes, followed by a maintenance infusion of 1 to 2 g/h. The infusion is commonly initiated once the decision is made to deliver and is continued for 24 hours postpartum. Expert opinion recommends that severely preeclamptic women undergoing cesarean delivery should receive magnesium sulfate at least 2 hours before the procedure, during surgery, and for 12 hours postpartum.[4,194]

Magnesium sulfate is eliminated almost entirely by renal excretion,[201] and serum levels may become dangerously high in the presence of renal insufficiency. Side effects include chest pain and tightness, palpitations, nausea, blurred vision, sedation, transient hypotension, and, rarely, pulmonary edema.[202,203] In untreated patients, the normal range for serum magnesium concentrations is 1.7 to 2.4 mg/dL. The therapeutic range lies between 5 and 9 mg/dL.[193] Reflex testing is used as a clinical screen for hypermagnesemia; when deep tendon reflexes are preserved, the more serious side effects are usually avoided. Patellar reflexes are lost at serum magnesium levels of approximately 12 mg/dL. Respiratory arrest occurs at levels of 15 to 20 mg/dL, and asystole occurs when the level exceeds 25 mg/dL.[204] Preeclamptic women with renal impairment should be monitored closely because magnesium toxicity can occur with usual dosing regimens. Serial measurement of serum magnesium levels may be helpful in the management of women with renal dysfunction.

Treatment of suspected magnesium toxicity includes immediate discontinuation of the infusion and the intravenous administration of **calcium gluconate** (1 g) over 10 minutes.[205] In the rare event of respiratory compromise, the patient may require tracheal intubation and mechanical ventilation until spontaneous ventilation returns.

Route of Delivery

Vaginal delivery should be attempted in all women with preeclampsia without severe features, assuming no other indications for cesarean delivery exist. Vaginal delivery should also be attempted in most women with severe disease, especially those beyond 34 weeks' gestation. The report of the NHBPEP Working Group on High Blood Pressure in Pregnancy states[3]:

> *Vaginal delivery is preferable to cesarean delivery for women with preeclampsia, because it avoids addition of the stress of surgery to the multiple physiologic aberrations [of the disease]. Acute palliation for several hours does not increase maternal risk if performed appropriately. Labor induction should be carried out aggressively once the decision for delivery has been made. In gestation remote from term in which delivery is indicated, and with fetal and maternal conditions stable enough to permit pregnancy to be prolonged 48 hours, glucocorticoids can be safely administered to accelerate fetal pulmonary maturity.*

Cesarean delivery is appropriate when the maternal or fetal condition mandates immediate delivery or when other indications for cesarean delivery exist.

Corticosteroid Administration for Severe Preeclampsia or HELLP Syndrome

To accelerate fetal lung maturity, all women who develop severe preeclampsia or HELLP syndrome between 24 and 34 weeks' gestation should receive a course of corticosteroid therapy. A randomized double-blind trial of 218 women with severe preeclampsia at 26 to 34 weeks' gestation found that the infants of those receiving betamethasone, compared with the infants of those receiving placebo, exhibited a significant reduction in the rate of the neonatal respiratory distress syndrome and reduced rates of neonatal intraventricular hemorrhage, infection, and death.[206] The available data also suggest that treatment with corticosteroids results in improvement in the maternal platelet count in women with HELLP, with dexamethasone being more efficacious than betamethasone.[207] However, these studies do not show clear benefit of corticosteroid treatment on the endpoints of severe maternal morbidity or mortality.[207]

Complications

Severe preeclampsia is associated with an increased risk for maternal morbidity and mortality, including HELLP syndrome, cerebrovascular accident, pulmonary edema, renal failure, placental abruption, and eclampsia. In general, these complications are more common in women with early-onset preeclampsia and in women with prepregnancy medical conditions, including diabetes mellitus, chronic renal disease, and thrombophilia.[38]

Cerebrovascular Accident

Although the absolute risk for cerebrovascular accident is low, preeclampsia confers markedly increased risk for intracerebral and subarachnoid hemorrhage[208,209] and ischemic stroke.[210,211] Stroke remains the leading cause of death in women with preeclampsia.[212] In the 2006-2008 Confidential Enquiry into Maternal and Child Health (CEMACH) report, 19 deaths were attributed to eclampsia and preeclampsia; 9 resulted from intracranial hemorrhage. Failure to adequately control hypertension was noted in most of these cases. The CEMACH report emphasized the importance of urgent treatment of preeclamptic women with a systolic blood pressure in excess of 150 to 160 mm Hg or at lower pressures if the clinical condition suggests rapid deterioration.[212]

The endothelial dysfunction of preeclampsia can promote edema, vascular tone instability, platelet activation, and local thrombosis. Reversible cerebral edema is the most common CNS feature of preeclampsia or eclampsia. The loss of cerebral autoregulation causes hyperperfusion that, compounded by endothelial disruption, leads to interstitial or vasogenic edema.[76,213,214] The presence of HELLP syndrome or DIC increases the risk for a hemorrhagic event.

As noted in the CEMACH recommendations,[212] there is growing recognition that mean arterial blood pressure and diastolic blood pressure may not reflect the true risk for stroke. A review of 28 case histories of severely preeclamptic women who suffered a stroke revealed that (1) systolic blood pressure in excess of 160 mm Hg was a far superior predictor of stroke than diastolic hypertension or mean arterial pressure, (2) the majority of strokes were hemorrhagic (93%) as opposed to thrombotic (7%), and (3) the majority of strokes (57%) occurred in the postpartum period.[168] Close attention to blood pressure control throughout the peripartum period is the mainstay of stroke prevention.[166] In keeping with this goal, ergot alkaloids should be avoided in hypertensive patients because their administration can result in severe hypertension.[212]

Pulmonary Edema

Pulmonary edema is a severe complication of preeclampsia that occurs in approximately 3% of affected women.[126] It is relatively infrequent in younger (previously healthy) women; risk increases in older, multigravid women and in women with preeclampsia superimposed on chronic hypertension or renal disease. The clinical presentation is characterized by worsening dyspnea and orthopnea with concomitant signs of respiratory compromise, including tachypnea, rales, and hypoxemia. Causes of pulmonary edema include low colloid osmotic pressure, increased intravascular hydrostatic pressure, and increased pulmonary capillary permeability.[215] All of these factors may coexist in a single patient.

A large proportion of cases of pulmonary edema occur postpartum, usually within 2 to 3 days after delivery, and management is directed toward the underlying cause (e.g., fluid overload, sepsis, cardiac failure).[216] Echocardiography can be helpful in the diagnosis of cardiogenic causes of pulmonary edema.[217,218] Initial treatment includes administration of supplemental oxygen, fluid restriction, and diuretic therapy (e.g., furosemide). A retrospective study of 86 women with peripartum pulmonary edema found that even in the presence of extensive radiographic infiltrates and severe hypoxemia, resolution was typically rapid, with a limited need for intensive care unit admission.[219] Placement of a pulmonary artery catheter can facilitate management of patients with severe refractory pulmonary edema, but a high rate of complications of these catheters in hypertensive patients is reported, and their use should only follow careful assessment of the risks and benefits.[220] Notably, in the last two CEMACH reports,[212,221] there were no deaths attributed solely to pulmonary causes. Presumably, this trend reflects improvements in the fluid management of women with severe preeclampsia.

Renal Failure

Acute renal failure is a rare but serious complication of severe preeclampsia and HELLP syndrome.[222] The true incidence remains unknown. Acute renal failure is divided into three categories: (1) **prerenal**, which refers to renal hypoperfusion; (2) **intrarenal**, which suggests intrinsic renal parenchymal damage; and (3) **postrenal**, which implies obstructive uropathy.[223] The majority of cases (83% to 90%) of acute renal failure in preeclampsia result from prerenal and intrarenal pathologic processes (most commonly acute tubular necrosis) and resolve completely after delivery.[224,225] In contrast, bilateral renal cortical necrosis is a rare and serious condition associated with considerable maternal and perinatal morbidity and mortality. It occurs most commonly in association with known renal parenchymal disease, chronic hypertension with superimposed preeclampsia, placental abruption, DIC, HELLP syndrome, sepsis, or fetal death.[226,227]

Placental Abruption

Placental abruption occurs in approximately 2% of women with preeclampsia and results in increased perinatal morbidity and mortality. A 2006 retrospective case-control study of 161 women with placental abruption and 2000 women without abruption found a threefold increased risk for placental abruption in women with preeclampsia.[228] The incidence is also increased in women with underlying chronic hypertension.[216] Management depends on the extent of abruption and associated hypotension, coagulopathy, or fetal compromise (see Chapter 38). Placental abruption is also associated with the development of DIC.

Prediction of Adverse Maternal Outcome

Identification of women at greatest risk for adverse maternal outcomes is potentially useful in guiding triage to high-risk centers and weighing the risks and benefits of expectant management. A 2011 multicenter, prospective study involving 2023 women with preeclampsia admitted to tertiary care centers described a model for predicting which women would develop fatal or life-threatening complications.[229] Adverse outcomes occurred

in 261 patients. Predictors of adverse maternal outcome included early gestational age, chest pain or dyspnea, oxygen saturation, platelet count, and creatinine and aspartate aminotransferase concentrations. The model showed excellent discrimination with an area under the receiver operating characteristics (ROC) curve of 0.88 for adverse events within 48 hours of admission. It continued to perform well in predicting adverse events up to 7 days after admission.[229]

HELLP Syndrome

The HELLP syndrome is characterized by hemolysis, elevated levels of liver enzymes, and a low platelet count. It may be a variant of severe preeclampsia, but this is controversial because a substantial fraction of HELLP syndrome patients do not have hypertension or proteinuria. It is associated with increased rates of maternal morbidities, including DIC, placental abruption, pulmonary edema, acute renal failure, liver hemorrhage or failure, acute respiratory distress syndrome, sepsis, stroke, and death (Table 36-5).[230] Additionally, 70% of HELLP syndrome patients deliver preterm[230]; prematurity-related neonatal complications increase the risk for perinatal morbidity and mortality. The onset of HELLP syndrome occurs antepartum in 70% of cases and postpartum in 30%.

Because of a lack of universally accepted diagnostic criteria for HELLP syndrome, its incidence cannot be determined accurately. The existence of a subset of preeclampsia complicated by abnormal peripheral blood smear, abnormal liver function tests, and thrombocytopenia has been recognized for decades; in 1982, Weinstein[231] described a series of 29 cases and coined the acronym HELLP. Women who do not demonstrate one or more of these clinical features are said to have "partial" HELLP syndrome.

Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the classic hallmark of HELLP syndrome; peripheral blood smear demonstrates schistocytes, burr cells, and echinocytes.[232] Common histopathologic findings are periportal hepatic necrosis and hemorrhage.[233] Sibai[232] has proposed standardized laboratory diagnostic criteria, as outlined in Table 36-6. Maternal signs and symptoms include right upper quadrant or epigastric pain, nausea and vomiting, headache, hypertension, and proteinuria. Notably, clinical presentation varies; 12% to 18% of women may be normotensive, and proteinuria is absent in approximately 13% of affected women. Diagnosis can be especially challenging because numerous medical and surgical disorders, including acute fatty liver of pregnancy, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, and lupus, can mimic HELLP syndrome (Box 36-4). Pregnant women likely to have preeclampsia, but who demonstrate atypical symptoms, should be screened with a complete blood cell count, platelet count, and liver enzyme assessment.

In general, patients with HELLP syndrome are not considered candidates for expectant management[155]; however, deferred delivery for 24 to 48 hours to allow for corticosteroid administration to accelerate fetal lung maturity may be appropriate for women less than 34 weeks' gestation if the maternal and fetal condition remain stable.[4] Women with HELLP syndrome who have not yet reached 34 weeks' gestation should be managed in a tertiary care facility with a neonatal intensive care unit capable of caring for a compromised preterm neonate.[4] Clinical management is similar to that for severe preeclampsia and includes intravenous magnesium sulfate for seizure prophylaxis and antihypertensive medications to maintain a systolic blood pressure below 160 mm Hg and a diastolic blood pressure below 110 mm Hg.[232] The first priority is to assess and stabilize the maternal condition, with particular attention given to hypertension and coagulation abnormalities. Next, the fetal condition should be assessed with FHR monitoring, Doppler ultrasonography of fetal vessels, a biophysical profile, or several of these options.

TABLE 36-5 Serious Maternal Complications in a Series of 442 Patients with Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) Syndrome

Complication*	No. Patients	Percent
Disseminated intravascular coagulopathy	92	21
Placental abruption	69	16
Acute renal failure	33	8
Severe ascites	32	8
Pulmonary edema	26	6
Pleural effusions	26	6
Cerebral edema	4	1
Retinal detachment	4	1
Laryngeal edema	4	1
Subcapsular liver hematoma	4	1
Acute respiratory distress syndrome	3	1
Maternal death	4	1

*Some women had multiple complications.

Modified from Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993; 169:1000-6.

TABLE 36-6 Diagnostic Criteria for Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) Syndrome

Criteria	Laboratory Tests
Hemolysis	Abnormal peripheral blood smear Increased bilirubin > 1.2 mg/dL Increased LDH > 600 IU/L
Elevated liver enzyme levels	Increased AST ≥ 70 IU/L Increased LDH > 600 IU/L
Thrombocytopenia	Platelet count < 100,000/mm^3

LDH, lactic dehydrogenase; *AST*, aspartate aminotransferase.

Modified from Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol 1990; 162:311-6.

BOX 36-4 Differential Diagnosis of Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) Syndrome

- Acute fatty liver of pregnancy
- Appendicitis
- Cholestasis of pregnancy
- Diabetes insipidus
- Gallbladder disease
- Gastroenteritis
- Glomerulonephritis
- Hemolytic-uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Nephrolithiasis
- Peptic ulcer
- Systemic lupus erythematosus
- Thrombotic thrombocytopenic purpura
- Viral hepatitis

From O'Brien JM, Barton JR. Controversies with the diagnosis and management of HELLP syndrome. Clin Obstet Gynecol 2005; 48:460-77

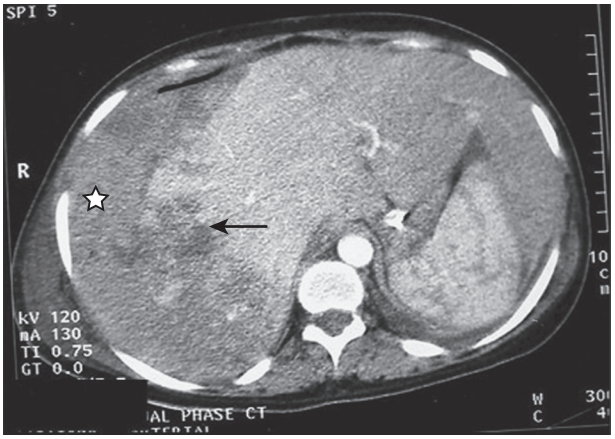

FIGURE 36-7 ■ Contrast-enhanced computed tomography scan showing a large area of parenchymal hemorrhage with hepatic rupture (*arrow*) and subcapsular hematoma (*star*) in the right lobe of the liver. (From Das CJ, Srivastava DN, Debnath J, et al. Endovascular management of hepatic hemorrhage and subcapsular hematoma in HELLP syndrome. Indian J Gastroenterol 2007; 26:244-5.)

The platelet count can fall precipitously in the presence of HELLP syndrome, and it should be evaluated before the administration of neuraxial anesthesia. Women with a platelet count less than 50,000/mm^3 are at significantly increased risk for bleeding,[234] and general anesthesia is the method of choice for cesarean delivery. Data suggest treatment with dexamethasone may improve the platelet count in women with HELLP.[207] If treatment with dexamethasone improves the patient's platelet count, the decision as to whether to use neuraxial anesthesia must weigh the risk of recurrent thrombocytopenia against the risk for a difficult airway and hypertension during induction of general anesthesia.

Platelet transfusions are indicated in the presence of significant bleeding and in all parturients with a platelet count less than 20,000/mm^3. For women with a platelet count less than 40,000/mm^3 who are scheduled for cesarean delivery, the preincision administration of 6 to 10 units of pooled random-donor platelets (or 1 to 2 units of apheresis platelets) has been recommended.[235] The risk for postpartum hemorrhage is significantly increased in patients with HELLP syndrome; at least 2 red blood cell units should be type and crossmatched and large-bore intravenous access obtained.

Rupture of a subcapsular hematoma of the liver is a life-threatening complication of HELLP syndrome and severe preeclampsia[236] that can manifest as abdominal pain, nausea and vomiting, and headaches; the pain worsens over time and becomes localized to the epigastric area or right upper quadrant. Hypotension and shock typically develop, and the liver is enlarged and tender.[237] Diagnosis is confirmed with ultrasonography, computed tomography (CT), or magnetic resonance imaging of the liver (Figure 36-7). Subcapsular hematoma rupture *with shock* is a surgical emergency that requires immediate multidisciplinary treatment that includes intravascular volume resuscitation and blood and plasma transfusions.[237] In some circumstances, selective arterial embolization by an interventional radiologist might be useful.[236,238,239] Patients with fulminant hepatic failure may require liver transplantation.[236] Prompt surgical intervention and refinements in surgical technique have substantially reduced the maternal mortality rate associated with spontaneous hepatic rupture to less than 20% in the past decade.[236] The most common causes of death are coagulopathy and exsanguination.[230,240]

Conservative management is recommended for subcapsular hematoma or intraparenchymal hemorrhage without capsular rupture in *stable* women.[235] Careful monitoring with ultrasonography or CT scan or both is required. An important component of conservative management is to avoid all potential trauma to the liver, including seizures, vomiting, and manual palpation of the abdomen. Patient transport and transfers should be conducted with care to avoid maneuvers that might result in rupture of a hematoma.

Anesthetic Management

The anesthetic management of the woman with preeclampsia without severe features differs little from the management of a healthy pregnant woman. However, the potential for rapid progression to the severe form of the disease mandates careful observation of the patient. The anesthesia provider must recognize the unpredictability of the development and progression of severe preeclampsia and should be prepared at all times for immediate cesarean delivery.

Preanesthetic Evaluation

The preanesthetic assessment of women with confirmed or suspected preeclampsia should focus on the airway examination, maternal hemodynamic and coagulation status, and fluid balance.

Airway. Generalized edema can involve the airway and obscure visualization of anatomic landmarks at laryngoscopy.[123] The anesthesia provider should anticipate the possibility of difficult airway management (see Chapter 30).

Hemodynamic Monitoring. Systemic arterial blood pressure can change rapidly in women with severe preeclampsia, both as a result of disease progression and in response to the administration of intravenous fluids and antihypertensive drugs. In addition, preeclampsia is associated with variable degrees of intravascular volume depletion and the clinical assessment of intravascular volume status can be difficult. Therefore, the use of invasive vascular monitoring may be useful in the management of some women with severe preeclampsia.

The most frequent indications for radial artery catheter insertion are (1) poorly controlled maternal blood pressure; (2) need for frequent arterial blood gas measurements, especially in the context of pulmonary edema; (3) planned use of a rapid-acting vasodilator (e.g., sodium nitroprusside, nitroglycerin, nicardipine infusion); (4) use of calculated systolic pressure variation (SPV)[241] to estimate intravascular volume status; and (5) need for continuous blood pressure monitoring during the induction of and emergence from general anesthesia in hypertensive women with severe preeclampsia.

Invasive central monitoring has been advocated in the assessment of oliguria and to monitor patient responses to fluid administration, but in practice it is rarely used. When invasive central monitoring is desired, a central venous pressure (CVP) catheter is adequate in the majority of cases; a pulmonary artery catheter is generally only used in patients with severe cardiac disease. The placement of an invasive CVP or pulmonary artery catheter is not a benign procedure. Well-recognized risks include arterial trauma, pneumothorax, venous air embolism, neuropathy, and cardiac arrhythmias. Additional risks for an indwelling pulmonary artery catheter include potentially fatal pulmonary artery hemorrhage, thromboembolism, sepsis, and endocardial damage.[242]

The 1991 to 1993 Report on Confidential Enquiries into Maternal Deaths in the United Kingdom described the postpartum death of a woman after several unsuccessful attempts at internal jugular line placement and a likely carotid artery puncture.[243] Despite digital pressure and application of a pressure dressing after vessel puncture, she developed neck tightness and dyspnea 4 hours later. Attempts at reintubation and resuscitation were unsuccessful, and she died. In the 2003 to 2005 CEMACH report, an anesthesia-related maternal death occurred in a woman with fulminant preeclampsia and HELLP syndrome who developed a large right hemothorax after a subclavian line insertion.[221] Because both immediate and delayed[244] maternal deaths have been attributed to the use of invasive central catheters, insertion of these catheters should be done only after careful consideration of risks and benefits.

Further, the timing of the use of invasive central monitoring is important and requires clinical judgment. Many patients are better served by immediate transfer to the operating room for delivery rather than delaying delivery for central line placement. In one study of a critical care unit in an academic hospital, the time from the decision to proceed with placement of a pulmonary artery catheter until the first pressure measurement was obtained was always more than 45 minutes.[245] Insertion time would likely exceed 45 minutes in most labor and delivery settings where the procedure is rarely performed and qualified assistance may not be available. In the majority of cases, the preoperative placement of an invasive central line will not change the intraoperative anesthetic management. Many obstetric care providers prefer to proceed immediately to delivery in women with persistent oliguria and to optimize fluid status after delivery.

Transthoracic echocardiography (TTE) can be used in place of invasive monitoring to quantify cardiac function and volume status.[138] In the hands of experienced practitioners, TTE may be useful in guiding fluid management for women with severe preeclampsia at risk for pulmonary edema and with oliguria.[246] Lung ultrasonography may also be useful in severe preeclampsia to diagnosis the presence of pulmonary edema.[247] Pulse waveform analysis has been suggested as a minimally invasive method to measure cardiac output in patients with severe preeclampsia; cardiac output measurements using this approach closely match those obtained from thermodilution in preeclamptic patients.[248]

In summary, the presence of severe preeclampsia *per se* is not an indication for CVP or pulmonary artery pressure monitoring. There is no indication for central hemodynamic monitoring that is unique to preeclampsia. Preeclampsia is a disorder of the peripheral circulation, not the central circulation. Indications for invasive central monitoring are similar to those in other multisystem disorders such as severe sepsis, multisystem organ dysfunction, pulmonary edema, congenital heart disease, and cardiomyopathy. TTE and arterial waveform monitoring may provide less invasive means of assessing hemodynamic parameters in these patients. Some women will require transfer to an intensive care unit for specialized nursing care and management directed by a critical care medicine specialist.

Neuraxial Analgesia for Labor and Delivery

During labor, early administration of neuraxial analgesia is recommended for several reasons: (1) to avoid general anesthesia and the possibility of airway catastrophe and marked hypertension with laryngoscopy in the event of emergency cesarean delivery, (2) to optimize the timing of epidural catheter placement in the setting of a declining platelet count, and (3) to obtain the beneficial effects of neuraxial analgesia on uteroplacental perfusion.

Continuous lumbar epidural analgesia or combined-spinal epidural (CSE) analgesia are the preferred methods of pain management during labor in women with preeclampsia. Advantages include (1) provision of high quality analgesia, which attenuates the hypertensive response to pain[249]; (2) a reduction in levels of circulating catecholamines and stress-related hormones[250]; (3) possible improvement in intervillous blood flow[251]; and (4) provision of a means for administration of local anesthetic for emergency cesarean delivery, thus

obviating the need for general anesthesia with its attendant risks.

One disadvantage of the CSE technique is that epidural catheter function cannot be fully evaluated until after resolution of the intrathecal analgesia. For this reason, some anesthesia providers avoid the CSE technique in favor of a standard epidural technique in women with severe preeclampsia who have an increased risk for emergency cesarean delivery. Use of a standard epidural technique allows for verification of catheter function within 15 to 20 minutes.

Continuous epidural infusion of local anesthetic has been used in the antepartum period to optimize uteroplacental blood flow in the hope of prolonging pregnancy and avoiding preterm delivery in preeclamptic women remote from term. Kanayama et al.[252] studied 20 severely preeclamptic women at 28 to 32 weeks' gestation who were assigned by physician choice to receive either long-term epidural bupivacaine combined with routine supportive management or routine supportive management alone. Gestational age at delivery and birth weight were greater in the treatment group, and maternal blood pressure and platelet count were also improved, compared with the routine management group. Although promising, this technique remains unproven, and randomized controlled trials are needed to verify that antepartum epidural local anesthetic infusion may facilitate expectant management of women with preeclampsia remote from term.

For the most part, the clinical administration of epidural analgesia to women with preeclampsia does not differ from that in healthy pregnant women without preeclampsia (see Chapter 23). The choice of local anesthetic, method of epidural space identification, and maintenance of analgesia are not affected by the presence of preeclampsia. However, four special considerations exist in preeclamptic women: (1) assessment of coagulation status, (2) intravenous hydration before the epidural administration of a local anesthetic, (3) treatment of hypotension, and (4) use of epinephrine-containing local anesthetic solutions.

Coagulation Status. Platelets contribute to coagulation and hemostasis in two important ways. First, their adhesive and cohesive functions lead to the formation of the hemostatic plug. Second, they activate the coagulation process by exposing a phospholipid surface and acting as a catalytic site for subsequent coagulation and consolidation of the initial platelet plug. Activated platelets release adenosine diphosphate, serotonin, thromboxane A_2, and other adhesive proteins, coagulation factors, and growth factors.[253]

Women with preeclampsia without severe features are usually hypercoagulable relative to women with an uncomplicated pregnancy and should not be denied neuraxial labor analgesia.[140] Women with *severe* preeclampsia (particularly those with HELLP syndrome) may develop thrombocytopenia, which increases the risk for bleeding into the epidural or spinal space with a neuraxial procedure (see Chapter 32). Neuraxial hematoma formation can result in permanent neurologic sequelae. Therefore, documentation of the platelet count is necessary before provision of epidural analgesia in women with severe preeclampsia. The incidence of neuraxial hematoma cannot be precisely determined because not all cases are reported and because there is no accurate method to determine the denominator of all preeclamptic women who have received neuraxial anesthesia. That said, the incidence of epidural hematoma in contemporary obstetric anesthesia practice is exceptionally low.[254]

In the past, a platelet count greater than or equal to 100,000/mm^3 was considered necessary for the safe administration of neuraxial anesthesia. This threshold probably originated from the results of a 1972 study that correlated platelet counts with bleeding times.[255] Critical appraisal of 1,083 human studies concluded that the bleeding time is not a reliable method of assessing the risk for bleeding for a single individual.[256] Coagulopathy is rare in preeclamptic women with a platelet count exceeding 100,000/mm^3, and in the absence of other risk factors for coagulopathy, neuraxial block placement is considered safe without further coagulation testing.[156]

Currently, many anesthesiologists agree that neuraxial procedures may be initiated in pregnant women without other risk factors if the platelet count is higher than 80,000/mm^3.[234] There is general consensus among anesthesia providers that a platelet count less than 50,000/mm^3 precludes the administration of neuraxial anesthesia. For women with a platelet count between 50,000 and 80,000/mm^3, the risks and benefits of neuraxial anesthesia must be weighed against the risks of general anesthesia for the individual patient if emergency cesarean delivery is required, including whether anatomic features of the patient's airway are favorable. Two additional considerations include the trend in the platelet count and any coexisting coagulopathy.

In certain cases, the platelet count decreases rapidly and the nadir in the platelet count cannot be identified prospectively. If serial platelet counts are stable and remain in the normal range, platelet count measurement every 24 to 48 hours is adequate to monitor women undergoing expectant management of severe preeclampsia remote from term.[4,161] Once a decision is made to induce labor, platelet count determination at least every 6 hours will ensure a timely measurement has been obtained at the time of request for neuraxial analgesia. If the platelet count is low (80,000 to 100,000/mm^3), early epidural catheter insertion is recommended in anticipation of worsening thrombocytopenia. If an epidural catheter is inserted before labor pain becomes significant, dilute solutions of local anesthetic may be infused at a low rate.

If the platelet count is less than 100,000/mm^3, other hemostatic abnormalities, including prolonged PT and aPTT and hypofibrinogenemia, may be present.[156] Further coagulation studies may be useful, particularly if risk factors for DIC are present (e.g., placental abruption, HELLP syndrome).[156] Thus, in the presence of thrombocytopenia or abnormal results of liver function tests, the PT and aPTT should be assessed before the initiation of neuraxial anesthesia.[257]

Viscoelastic monitors of coagulation may expedite decision-making about neuraxial block administration for women with preeclampsia-related hemostatic dysfunction. Although thromboelastography (TEG) has shown

some promise in the assessment of coagulation status in pregnant patients with thrombocytopenia,[140] it has been criticized for its inability to diagnose specific coagulation defects, particularly for impairments in primary hemostasis.[258] Platelet function analysis (PFA-100) appears to be more sensitive to coagulation dysfunction in severe preeclampsia.[142] However, with both TEG and PFA, the ability to predict the risk for epidural hematoma after the administration of neuraxial anesthesia is unproven and requires further study.[259]

The risk for **epidural hematoma** formation exists not only at the time of epidural catheter placement but also at the time of its removal. In patients with thrombocytopenia, the catheter should not be withdrawn from the epidural space until there is evidence of an acceptable (and increasing) platelet count. A platelet count of 75,000 to 80,000/mm^3 seems reasonable for epidural catheter removal. The platelet count in women with HELLP syndrome usually reaches a nadir on the second or third postpartum day and then gradually returns to the patient's normal baseline.

If the decision is made to proceed with a neuraxial technique when the platelet count is less than 100,000/mm^3, the following suggestions may help reduce the risk for epidural hematoma and its sequelae:

1. The **most skilled anesthesia provider** available should perform the neuraxial procedure to minimize the number of needle passes and subsequent bleeding.
2. **A spinal technique may be preferable to an epidural technique** (when appropriate) because of the smaller needle size, although supporting data are lacking.
3. **Use of a flexible wire-embedded epidural catheter** may reduce epidural vein trauma.
4. The patient should be carefully monitored after delivery for **neurologic signs that may signal bleeding into the epidural space**.
5. **The platelet count should be checked for evidence of a return toward normal measurements (at least 75,000 to 80,000/mm^3) before removal of the epidural catheter.** Epidural vein trauma at the time of catheter discontinuation can result in epidural bleeding and perhaps epidural hematoma.
6. **Imaging studies and neurologic or neurosurgical consultation should be obtained immediately if there is any question of an epidural hematoma.** Prompt surgical intervention may be required to avoid permanent neurologic injury.

Intravenous Hydration. In the past, when high concentrations of local anesthetic solution (e.g., 0.25% to 0.5% bupivacaine) were administered during labor, intravenous crystalloid hydration preceded epidural local anesthetic administration to prevent or ameliorate hypotension. In contemporary practice, lower concentrations of local anesthetic are used (e.g., 0.0625% to 0.125% bupivacaine in combination with an opioid), hypotension is less common, and fluid administration at the time of analgesia initiation is of less clinical importance. Furthermore, the rapid administration of a large bolus of intravenous fluid (preload) results in only a transient increase in CVP and has little impact on the risk for hypotension.[260] Although the use of a fluid bolus has decreased with current techniques for labor analgesia, careful attention to intravenous fluid infusion rates is necessary in women with severe preeclampsia because of the increased risk for pulmonary edema in these patients.

Treatment of Hypotension. A retrospective study found that parturients with severe preeclampsia were more susceptible to hypotension after initiation of epidural labor analgesia than healthy parturients.[261] The hypotension was associated with an increase in FHR abnormalities,[261] suggesting the need for close attention to maternal blood pressure at the time of initiation of analgesia. Women with preeclampsia may be treated with phenylephrine or ephedrine (although the latter is no longer the agent of choice in healthy women—see Chapter 26). There is an often-expressed concern that severely preeclamptic women may have an exaggerated response to vasopressors that might result in a sharp increase in blood pressure.[262,263] However, supportive data are lacking. The anesthesia provider should initiate treatment with low doses of phenylephrine (25 to 50 μg) or ephedrine (5 to 10 mg) to assess maternal blood pressure response before administration of a larger dose. With careful dosing, increased sensitivity to vasopressors is rarely a clinical problem.

Epinephrine. It has been suggested that local anesthetic solutions containing epinephrine (including the standard epinephrine-containing test dose) should be avoided during the administration of epidural analgesia in preeclamptic women. This concern arises from observations that preeclamptic women exhibit an increased sensitivity to vasopressors, including angiotensin II,[264,265] norepinephrine and epinephrine,[133,266] and a thromboxane A_2-mimetic agent.[267] In addition, clinical studies have demonstrated that smaller doses of ephedrine and phenylephrine are required to restore maternal blood pressure during spinal anesthesia in preeclamptic women compared with healthy women.[262,263,268,269] One case report described a hypertensive crisis in a preeclamptic woman after the incremental administration of 30 mL of freshly mixed 2% lidocaine with epinephrine 5 μg/mL for planned cesarean delivery.[270] However, the onset and duration of hypertension were atypical and a drug error could not be excluded.[270] In contrast, several other case series have used the same solution without adverse effects in women with preeclampsia.[271,272]

No randomized controlled trials have assessed the effects of epidural epinephrine in women with severe preeclampsia. In the absence of malignant hypertension, epinephrine is unlikely to pose a significant risk for hypertensive crisis, given the absence of confirmed reports after decades of its use in obstetric anesthesia practice. Although not necessarily harmful for women with preeclampsia, the use of epinephrine in epidural test doses or analgesic solutions may not be particularly helpful. Patients who have received beta-adrenergic receptor antagonists (e.g., labetalol) do not demonstrate the typical tachycardic response to intravascular

administration of epinephrine.[273] This lack of response will decrease the sensitivity of the epinephrine test dose to detect intravascular administration of local anesthetic solution, and alternative testing strategies to detect intravascular catheter location may be preferred.[274] The addition of epinephrine to local anesthetic solutions results in a modest local anesthetic-sparing effect, at best,[275] and increases the density of motor blockade.[276] Finally, consideration should be given to the consequences of an unintentional intravascular injection of an epinephrine-containing test dose in a patient with baseline hypertension.

Anesthesia for Cesarean Delivery

The administration of neuraxial anesthesia for cesarean delivery in women with preeclampsia does not differ greatly from administration in healthy pregnant women (see Chapter 26). Hepatic dysfunction can result in reduced drug clearance but has little clinical impact on choice of anesthetic or analgesic agents.

The choice of local anesthetic, method of epidural space identification, and maintenance of anesthesia are not affected by the presence of preeclampsia. However, there are three special considerations in preeclamptic women undergoing cesarean delivery: (1) choice of anesthetic technique, (2) technique for induction of general anesthesia, and (3) the interaction between magnesium sulfate and nondepolarizing muscle relaxants.

Neuraxial Anesthesia. In the Seventh and Eighth Reports of the Confidential Enquiries into Maternal Deaths from the United Kingdom,[212,221] the leading cause of death in women with preeclampsia was **intracranial hemorrhage**. Disadvantages of general anesthesia in the presence of preeclampsia include the risk for intracranial hemorrhage from the hypertensive response to both tracheal intubation and extubation. In a study involving more than 300,000 women in Taiwan, general anesthesia for cesarean delivery was associated with a greater than twofold increase in the risk for stroke after adjusting for confounders compared with neuraxial anesthesia.[277] Neuraxial anesthesia also avoids the possibility of difficult tracheal intubation secondary to airway edema. Therefore, neuraxial anesthesia is preferred whenever clinical circumstances permit its use.

The traditional view was that spinal anesthesia is relatively contraindicated in severe preeclampsia because of the possibility of marked hypotension as a result of the rapid onset of spinal anesthesia–induced sympathetic blockade. However, data that have emerged over the past decade suggest that this concern is not supported by evidence, and that both spinal and epidural anesthesia are reasonable anesthetic modalities for women with severe preeclampsia. Wallace et al.[278] randomized 80 women with severe preeclampsia who required cesarean delivery to receive general, epidural, or CSE anesthesia. Notably, the initial spinal dose in the CSE group (hyperbaric bupivacaine 11.25 mg) is a dose comparable to that often used for a single-shot spinal technique. There was no significant difference between the CSE and epidural anesthesia groups in maternal mean arterial pressure over time. Another small prospective study randomized women with severe preeclampsia to receive either spinal or epidural anesthesia, with similar results.[279] Hood and Curry[280] retrospectively reviewed cesarean delivery records for 138 women with severe preeclampsia who received either spinal or epidural anesthesia and found that the lowest mean blood pressure measurements did not differ between groups. Because of the retrospective study design, the possibility that the groups were dissimilar cannot be excluded (i.e., the anesthesia providers may have chosen to administer epidural anesthesia to the more severely ill women). Nonetheless, the expected marked hypotension after spinal anesthesia did not occur. These studies lend support to the safety of spinal anesthesia in women with severe preeclampsia.

In two prospective cohort studies of women undergoing cesarean delivery, Aya et al.[262,268] compared women with severe preeclampsia to healthy pregnant women (both preterm and at term) and found that the risk for significant spinal anesthesia–induced hypotension (defined as requiring the administration of ephedrine) was significantly lower in the preeclampsia group than in the control groups. The authors speculated that the known increased vascular sensitivity to vasoconstrictors may explain the infrequent incidence of hypotension after spinal anesthesia and the ease with which mean arterial blood pressure can be restored to baseline with small doses of vasopressor.

A randomized multicenter study[281] comparing the hemodynamic effects of spinal anesthesia with epidural anesthesia for cesarean delivery in women with severe preeclampsia found that significantly *more* women in the spinal anesthesia group experienced hypotension. However, the duration of hypotension was less than 1 minute in both groups and, although there was more ephedrine use in the spinal group than the epidural group, hypotension was easily treated in both groups. In addition, there was no significant difference in neonatal outcome between infants whose mothers received spinal anesthesia compared with those whose mothers received epidural anesthesia.[282] Another study suggested that spinal anesthesia has little effect on cardiac output in severely preeclamptic women.[263] These data, taken together, suggest that the use of spinal anesthesia for cesarean delivery in women with severe preeclampsia is appropriate.

General Anesthesia. General anesthesia is less desirable than neuraxial anesthesia because of (1) the possibility of difficult tracheal intubation secondary to airway edema and (2) the transient but severe hypertension that accompanies tracheal intubation and extubation. Nonetheless, there are situations in which general anesthesia is the best anesthetic option. Clinical indications include severe ongoing maternal hemorrhage, sustained fetal bradycardia with a reassuring maternal airway examination, and severe thrombocytopenia or other coagulopathy, or a combination of these indications. The platelet count can fall dramatically with rapidly progressing severe preeclampsia or HELLP syndrome and may mandate administration of general anesthesia. Major placental abruption, intrauterine fetal demise, and preeclampsia all increase the risk for DIC. The safe

administration of general anesthesia in women with preeclampsia requires an advanced state of readiness and careful preparation.

Once the decision has been made to proceed with general anesthesia, the anesthesia provider faces three specific challenges: (1) the potential difficulty of securing the airway, (2) the hypertensive response to direct laryngoscopy and tracheal intubation, and (3) the effects of magnesium sulfate on neuromuscular transmission and uterine tone. A suggested technique for the administration of general anesthesia is outlined in Box 36-5.

Airway Considerations. Before proceeding with general anesthesia, careful airway examination is mandatory. Airway edema may be present even with a relatively reassuring airway examination; thus, many anesthesia providers try to avoid emergency administration of general anesthesia if there is any suspicion of a difficult airway. Endotracheal tubes in various sizes and difficult airway equipment should be immediately available (see Chapter 30). In unusually difficult situations, it may be prudent to have a surgeon immediately available to establish a surgical airway, if needed. One of the dangers of repeated tracheal intubation attempts is the risk for traumatic bleeding in the airway, which may make ventilation difficult or even impossible. It is wise to avoid repeated attempts and proceed with insertion of a supraglottic airway device (e.g., laryngeal mask airway) before the airway is irretrievably lost. Because the supraglottic airway devices do not protect the patient from pulmonary aspiration of gastric contents, the obstetrician should be encouraged to complete the procedure as quickly as possible.

If indicated, an awake fiberoptic tracheal intubation should be used to secure the airway. Ideally, invasive blood pressure monitoring should be initiated before tracheal intubation and the induction of general anesthesia in patients with severe preeclampsia so that hypertension can be promptly recognized and treated. Effective topical anesthesia of the airway with nebulized or atomized lidocaine can enhance patients' comfort and decrease the hypertensive response to airway manipulation. Airway injections (including glossopharyngeal nerve blocks and transtracheal injections) are usually best avoided because of coagulopathy in this population.

Hypertensive Response to Laryngoscopy. The hemodynamic instability associated with rapid-sequence induction and tracheal intubation presents a serious problem. The transient but severe hypertension that may accompany tracheal intubation can result in cerebral hemorrhage or pulmonary edema, both potentially fatal complications. Continuous arterial blood pressure monitoring is required for severely hypertensive women to monitor the effects of antihypertensive drugs administered before and after tracheal intubation and to allow rapid detection of adverse hemodynamic responses to laryngoscopy.

Medications that have been used to blunt the hemodynamic response to laryngoscopy include labetalol, esmolol, nitroglycerin, sodium nitroprusside, and remifentanil.[283-287] The goal of treatment is to reduce the arterial blood pressure to approximately 140/90 mm Hg before the induction of general anesthesia and to maintain the systolic blood pressure between 140 to 160 mm Hg and the diastolic blood pressure between 90 to 100 mm Hg throughout laryngoscopy and tracheal intubation.[166] If possible, the FHR should be monitored during intravenous antihypertensive therapy.

BOX 36-5 A Suggested Technique for Administration of General Anesthesia in Women with Severe Preeclampsia

1. Place a radial arterial cannula for continuous blood pressure monitoring in women with severe hypertension.
2. Place an additional large-bore intravenous catheter given the increased risk for postpartum hemorrhage.
3. Verify that smaller-sized endotracheal tubes and supraglottic airway devices are immediately available. Equipment needed for difficult airway management should also be immediately available.
4. Consider the administration of an H_2-receptor antagonist and metoclopramide IV between 30 and 60 minutes before induction of anesthesia.
5. Administer 0.3 M sodium citrate 30 mL by mouth less than 30 minutes before induction of anesthesia.
6. Denitrogenate (3 minutes of tidal-volume breathing or 8 vital capacity breaths with an F_{IO_2} of 1.0 and a tight-fitting facemask).
7. Give labetalol (10-mg bolus doses) IV to titrate systolic blood pressure to 140/90 mm Hg before the induction of anesthesia.
8. Continue to monitor the FHR during labetalol administration.
9. Consider alternative antihypertensive agents for patients who do not respond to labetalol (or those with a contraindication to labetalol). Alternatives include hydralazine or nicardipine, sodium nitroprusside, or nitroglycerin infusion. Consider remifentanil infusion at 0.05 μg/kg/min. (See Table 36-4.)
10. Perform rapid-sequence induction with propofol 2.0 to 2.8 mg/kg and succinylcholine 1.0 to 1.5 mg/kg (avoid ketamine as an induction agent given its sympathomimetic properties). Consider the administration of a bolus dose of labetalol, esmolol, nitroglycerin, sodium nitroprusside, or remifentanil to blunt the hemodynamic response to laryngoscopy.
11. Maintain anesthesia with a volatile halogenated agent and 100% oxygen before delivery. After delivery, decrease the concentration of the volatile halogenated agent to prevent uterine atony and consider using nitrous oxide or a propofol infusion and administering an opioid with or without a benzodiazepine. Avoid giving additional muscle relaxants; if absolutely required, administer a *low dose* of a short-acting nondepolarizing muscle relaxant because of the exaggerated effect of these medications when coadministered with magnesium.
12. At the end of surgery, reverse neuromuscular blockade and give labetalol 5 to 10 mg IV bolus, titrated to effect, to prevent hypertension during emergence and tracheal extubation.

FHR, fetal heart rate; *IV*, intravenously.
Modified from Ramanathan J, Bennett K. Pre-eclampsia: fluids, drugs, and anesthetic management. Anesthesiol Clin North Am 2003; 21:145-63.

Most anesthesia providers consider **labetalol** to be the drug of choice for attenuating the hypertensive response to laryngoscopy in women with severe preeclampsia. Ramanathan et al.[285] compared intravenously administered labetalol with no treatment in a randomized study of preeclamptic women who received general anesthesia for cesarean delivery. Mean arterial blood pressure increased after tracheal intubation in both study groups, but the hypertensive response was significantly less pronounced in the labetalol group. Women in the control group also developed tachycardia (in response to laryngoscopy and tracheal intubation), which did not occur in the labetalol group. Labetalol can be administered using either a bolus technique or a continuous intravenous infusion, or both.

There is also evidence of safe short-term administration of **esmolol** in this setting. A randomized double-blind study of 80 hypertensive women presenting for cesarean delivery demonstrated that intravenous esmolol—in doses as high as 2 mg/kg—can be safely used to dampen the hemodynamic response to laryngoscopy and tracheal intubation.[288]

Nitroglycerin has many desirable properties for blunting the hypertensive response to tracheal intubation. It is a direct vasodilator with a rapid onset, is rapidly metabolized, and has no apparent maternal or fetal toxicity. In a randomized controlled trial, Hood et al.[284] administered intravenous nitroglycerin (200 μg/mL), which decreased mean arterial blood pressure by approximately 20%, before the induction of general anesthesia. Compared with women who did not receive nitroglycerin, the maximal blood pressure with tracheal intubation was significantly lower in the nitroglycerin group. Both Apgar scores and umbilical cord blood gas and acid-base measurements were similar in the two groups.

Sodium nitroprusside infusions have also been used to attenuate hemodynamic responses to tracheal intubation in women with severe preeclampsia. An intravenous infusion can be initiated at 0.5 μg/kg/min and titrated to blood pressure response. Short-term infusions are considered safe for the fetus.

The short-acting opioid **remifentanil** is rapidly metabolized by both mother and neonate by nonspecific blood and tissue esterases and has been administered to preeclamptic women. A clear advantage of remifentanil compared with other opioids is the rapid onset and short duration of the drug; the limited duration of action should not interfere with the resumption of spontaneous ventilation if tracheal intubation is unsuccessful. Ngan Kee et al.[287] randomly allocated 40 pregnant women without preeclampsia who required general anesthesia for cesarean delivery to receive either a one-time intravenous dose of remifentanil 1 μg/kg or saline immediately before induction of anesthesia. The primary outcome was the maximum increase in systolic blood pressure (compared with a baseline measurement). Administration of remifentanil significantly decreased the maximum increase in systolic blood pressure. However, remifentanil crosses the placenta, and two neonates in the remifentanil group required naloxone administration for poor respiratory effort. Park et al.[289] randomized 48 patients with severe preeclampsia to receive remifentanil 0.5 μg/kg or 1 μg/kg before tracheal intubation. Both doses prevented a hypertensive response, but three patients treated with the higher dose required ephedrine to treat hypotension. Apgar scores and umbilical cord blood gas measurements were comparable in both groups. The lower remifentanil dose, 0.5 μg/kg, is therefore likely preferable.

Effects of Magnesium Sulfate. Most severely preeclamptic women will present to the operating room after receiving magnesium sulfate for seizure prophylaxis. The magnesium infusion should continue throughout surgery to minimize the risk of eclampsia.[4] The primary anesthetic considerations for women receiving magnesium sulfate are (1) interaction with nondepolarizing muscle relaxants, (2) effects on uterine tone, and (3) interaction with calcium entry–blocking agents.

Magnesium inhibits the release of acetylcholine at the neuromuscular junction, decreases the sensitivity of the neuromuscular junction to acetylcholine, and depresses the excitability of the muscle fiber membrane. Magnesium sulfate increases the potency and duration of vecuronium, rocuronium, and mivacurium.[290-292] Several case reports have described a requirement for overnight mechanical ventilation after administration of routine doses of vecuronium in women receiving magnesium sulfate.[290,293] Thus, if nondepolarizing muscle relaxants are used, they should be administered in very small doses and the response should be monitored carefully with a peripheral nerve stimulator. Many practitioners avoid the use of depolarizing neuromuscular blocking agents in this setting because of the concern for residual postoperative neuromuscular blockade, which can lead to respiratory complications. Because of abdominal wall distention in the term parturient, neuromuscular blockade is rarely required to facilitate surgical closure after cesarean delivery.

Even though succinylcholine mimics acetylcholine at the nerve terminal, the onset and duration of a single intubating dose is not prolonged when administered concurrently with a magnesium sulfate infusion[294]; a routine intubating dose of 1 to 1.5 mg/kg should be used during rapid-sequence induction of anesthesia.

Used for many years as a tocolytic agent, magnesium depresses smooth muscle contractions and inhibits CNS catecholamine release.[295-297] Therefore, it seems intuitive that the risk for uterine atony and excessive blood loss might be increased in women receiving magnesium sulfate.[193] However, studies[193,203] have not found an increased risk for blood loss in women receiving magnesium sulfate. A blood sample for a type and screen should be sent to the blood bank before cesarean delivery, and uterotonic agents should be immediately available. Although some reports have suggested that coadministration of a calcium entry–blocking agent and magnesium may cause hypotension and/or neuromuscular blockade,[176-179] more recent information suggests that these medications can be used safely together.[180]

Postoperative Analgesia. Options for postoperative analgesia are the same as for healthy pregnancies and include patient-controlled intravenous opioids, neuraxial opioids (single injection), and continuous epidural

infusion of analgesic agents. Many anesthesia providers prefer neuraxial opioid administration for postcesarean analgesia (see Chapter 28). For women whose postpartum hypertension persists longer than one day, the ACOG has suggested that nonsteroidal anti-inflammatory medications be replaced by alternative analgesics, as nonsteroidal anti-inflammatory drugs may contribute to hypertension.[4] In the rare case of a woman with continuing severe refractory hypertension, continuous epidural analgesia is attractive for its blood pressure–modulating properties.

Regardless of the postoperative analgesic technique, all women should be carefully monitored with pulse oximetry for signs of respiratory depression or airway obstruction.

Postpartum Management

The risks of severe preeclampsia do not end with delivery. Postpartum women are at significant risk for pulmonary edema, sustained hypertension, stroke, venous thromboembolism, airway obstruction, and seizures and should receive close monitoring of blood pressure, fluid intake, and urinary output. In addition, severe preeclampsia, the HELLP syndrome, and eclampsia can present for the first time in the postpartum period, with delayed presentation as late as 4 weeks after delivery.[4] A study of almost 4000 women diagnosed with preeclampsia found that the incidence of postpartum onset of disease was 5.7%,[116] and hypertension is the leading indication for postpartum hospital readmission.[298]

The risk for **pulmonary edema** is also highest in the postpartum period. The resolution of preeclampsia usually occurs within 5 days of delivery and is heralded by a marked diuresis that follows mobilization of extracellular fluid and an increase in the intravascular volume. As a consequence, women with severe preeclampsia, particularly those with early-onset disease, renal insufficiency, or pulmonary capillary leak, are at increased risk for the development of postpartum pulmonary edema.[163]

In contrast to women with gestational hypertension, who typically become normotensive within a week of delivery, women with severe preeclampsia may have a longer duration of hypertension; the risk for **cerebrovascular accident** is highest during this time.[168,208,209,299,300] Given the increased risk of postpartum cerebrovascular accident, the ACOG recommends antihypertensive therapy in the postpartum period when systolic blood pressure persistently exceeds 150 mm Hg or diastolic blood pressure exceeds 100 mm Hg.[4] Antihypertensive therapy should be continued, started, or resumed for these women, and blood pressure should be closely monitored. For women in the postpartum period who develop new-onset hypertension associated with headaches or other neurologic symptoms, or new-onset severe hypertension, a 24-hour course of magnesium sulfate administration may help prevent eclampsia or a cerebrovascular accident.[4]

Postpartum venous thromboembolism (VTE) has an estimated incidence of 1 to 18 per 1000 cesarean deliveries[301,302] and is a leading cause of maternal mortality in pregnancy.[303] The risk factors for antepartum and postpartum events differ, suggesting a different pathophysiology for each.[304] Both cesarean delivery[304-307] and preeclampsia[304,305] are independent risk factors for postpartum VTE. An emergency cesarean delivery doubles the risk for VTE compared with a nonemergent cesarean delivery.[308]

The 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend that women with a risk for postcesarean VTE greater than 3% receive either pharmacologic thromboprophylaxis or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) during hospitalization after cesarean delivery.[301] Preeclampsia in the absence of fetal growth restriction is considered a minor risk factor for VTE. VTE prophylaxis is indicated in patients with two or more minor risk factors (e.g., BMI > 30 kg/m^2, use of > 10 cigarettes per day, multiple pregnancy, emergency cesarean delivery, postpartum hemorrhage > 1 L) (see Box 39-4).[301] Preeclampsia with fetal growth restriction is considered a major risk factor (with risk for VTE > 3%), such that all patients with this condition merit VTE prophylaxis after cesarean delivery.[301] The ACOG recommends pneumatic compression devices for all patients undergoing cesarean delivery.[309]

Preeclampsia has been associated with increased upper airway resistance and an increased risk of obstructive sleep apnea.[310,311] A review of anesthesia-related maternal deaths in Michigan[312] described a series of postoperative and postpartum deaths attributed to **airway obstruction** or **hypoventilation**, including the death of one women with severe preeclampsia and sleep-disordered breathing who likely experienced opioid-related respiratory depression while receiving patient-controlled intravenous analgesia after cesarean delivery. Such findings highlight the need for close monitoring and consistent vigilance in the postoperative care of women with severe preeclampsia—particularly those with generalized edema, known airway swelling, snoring, and obesity.

Long-Term Outcomes

Women with a history of preeclampsia are at increased risk for chronic hypertension and cardiovascular disease, including ischemic heart disease and stroke, later in life,[59,61,313-316] and an earlier onset of cardiovascular disease than women with healthy pregnancies.[60,317,318] Risks for ischemic heart disease and stroke are elevated approximately twofold.[61]

In addition, there is evidence of a dose-response relationship between preeclampsia and cardiovascular disease. Women with severe and/or early-onset preeclampsia, and whose pregnancies are complicated by both preeclampsia (the maternal syndrome) and fetal growth restriction (the fetal syndrome) are at higher risk than women with preeclampsia without severe features or gestational hypertension.[59] Women with preeclampsia in both their first and second pregnancies are at even greater risk for future ischemic heart disease.[318]

The mechanism of increased risk for cardiovascular disease in preeclampsia is unclear. It is possible that

preeclampsia causes permanent damage to the endothelium and hastens the onset of cardiovascular disease. Women with a history of preeclampsia have persistent impairment of brachial artery endothelium-dependent vascular relaxation at 1 to 3 years after delivery compared with healthy control women.[319,320] A more likely explanation is that preeclampsia and cardiovascular disease have a common pathogenesis because of shared risk factors. Common risk factors for preeclampsia and atherosclerosis include hypertension, obesity, insulin resistance, advanced age, hypercholesterolemia, and dyslipidemia.[317,321,322] Cigarette smoking is the notable exception in that it is an established risk factor for cardiovascular disease but is protective against preeclampsia.[67,68] Preeclampsia may be a cardiovascular risk marker in women with an underlying predisposition to vascular disease; the hemodynamic and metabolic stress of pregnancy causes the predisposition to manifest as preeclampsia. After pregnancy, women return to a normal state until the threshold for disease development is exceeded in later life.

Regardless of the mechanism of increased risk, these observations represent a potential opportunity for primary disease prevention and risk factor modification. In a 2004 multinational study, 90% of the risk for a first myocardial infarction was attributed to potentially modifiable risk factors.[323] Possible interventions include earlier cardiovascular disease screening and individual counseling regarding the importance of smoking cessation, regular exercise, and a diet low in saturated fat and high in antioxidants.

In contrast to the increased risk for cardiovascular disease, a history of preeclampsia has been associated with a *decreased* risk for cancer. Several earlier studies have suggested that women who have been diagnosed with preeclampsia have a slightly lower risk for breast cancer in later life compared with other parous women.[324,325] However, a 2007 systematic review and meta-analysis of almost 200,000 women with a history of preeclampsia found no association between preeclampsia and future cancer risk.[61]

Evidence indicates that preeclampsia may also result in psychological sequelae. A woman with a history of severe preeclampsia (particularly with early-onset disease and preterm delivery) has experienced a serious complication that threatened her life and the life of her child. In one study, approximately one fourth of women developed post-traumatic stress disorder (PTSD) after early-onset preeclampsia.[326] This association may be mediated by the condition of the offspring after preterm delivery.[327-329] Further research is required to characterize women at risk for PTSD and to investigate strategies for PTSD prevention and intervention.

ECLAMPSIA

Eclampsia is defined as the new onset of seizures or unexplained coma during pregnancy or the postpartum period in a woman with signs and symptoms of preeclampsia and without a preexisting neurologic disorder.[330-333]

Epidemiology

Findings from population-based studies in the past 10 years suggest that the incidence of eclampsia varies from 0.1 to 5.9 per 10,000 pregnancies in developed countries.[9,38,334-338] The variation in rates of eclampsia among studies likely reflects reporting differences among countries or differences in treatment for severe preeclampsia.[335,339] On average, studies have shown a decrease in the incidence of eclampsia in developed countries over time; this decrease is likely attributable to an increase in the use of magnesium for seizure prophylaxis.[335,337,338]

Eclampsia can occur suddenly at any point in the puerperium; however, most seizures occur intrapartum or within the first 48 hours after delivery. Late eclampsia is defined as seizure onset from 48 hours after delivery to 4 weeks postpartum.[331,340] The majority of eclamptic women have evidence of severe preeclampsia, but in 10% to 15% of cases, hypertension is absent or modest and/or proteinuria is not detected.[340] Reported risks include young maternal age, nulliparity, multiple gestation, molar pregnancy, triploidy, preexisting hypertension, renal or cardiac disease, previous severe preeclampsia or eclampsia, nonimmune hydrops fetalis, and systemic lupus erythematosus.[338,341] Major maternal complications of eclampsia include pulmonary aspiration, pulmonary edema, cerebrovascular accident, cardiopulmonary arrest, venous thromboembolism, acute renal failure, and death.[333-335,338] Eclampsia is associated with a high perinatal death rate and has also been associated with placental abruption, severe fetal growth restriction, and extreme prematurity.[330,334,335,338]

Clinical Presentation and Diagnosis

Any of the pathophysiologic changes of preeclampsia can be present in eclampsia. About 80% of patients will have premonitory neurologic symptoms, the most common of which are headache and visual disturbances.[342] Other premonitory signs and symptoms can include photophobia, epigastric or right upper quadrant pain, hyperreflexia, and altered mental status[330,340]; these symptoms can occur before or after the onset of seizures.[330]

Seizures have an abrupt onset, typically beginning as facial twitching that is followed by a tonic phase that persists for 15 to 20 seconds. This phase progresses to a generalized clonic phase characterized by apnea, which lasts approximately 1 minute. Breathing generally resumes with a long stertorous inspiration, and the patient enters a postictal state with a variable period of coma. Cardiorespiratory arrest and pulmonary aspiration of gastric contents can complicate a seizure. Although the definitive diagnosis for eclampsia is a sudden seizure in a pregnant woman who has signs and symptoms of preeclampsia, a woman who lapses into coma without witnessed convulsions can also be classified as eclamptic.[330]

The mechanism of eclamptic seizures remains poorly understood.[332] It may involve a loss of the normal cerebral autoregulatory mechanism, resulting in hyperperfusion and leading to interstitial or vasogenic cerebral

edema and decreased cerebral blood flow.[213,214,332] Neuroradiologic studies suggest that eclampsia might be a form of PRES.[121,122]

Until proven otherwise, the occurrence of seizures during pregnancy should be considered eclampsia. Conditions simulating eclampsia include seizure disorder, stroke, hypertensive encephalopathy, ischemia or hypoxia, cerebral space-occupying lesion, systemic disease (e.g., systemic lupus erythematosus, sickle cell anemia), infection (e.g., meningitis, encephalitis), electrolyte and endocrine disturbances, PRES, vasculitis or angiopathy, amniotic fluid embolism, medications (withdrawal, illicit drug use), and organ failure.[330,331]

Obstetric Management

Immediate goals are to stop convulsions, establish a patent airway, and prevent major complications (e.g., hypoxemia, aspiration). Further obstetric management includes antihypertensive therapy, induction or augmentation of labor, and expeditious (preferably vaginal) delivery. Fetal bradycardia typically begins during or immediately after a seizure but does not mandate immediate delivery unless it is persistent.

Resuscitation and Seizure Control

During the seizure, oxygenation may prove impossible but supplemental oxygen should be delivered by means of a facemask (Box 36-6). Attempts to insert an oral airway should be withheld until the seizure abates. As soon as breathing resumes, ventilation may be gently augmented with a bag-mask device. Pulse oximetry should be used to assess maternal oxygenation. Blood pressure and the electrocardiogram should be monitored to identify hypertension, arrhythmia, or cardiac arrest. While initial resuscitation is underway, an assistant should establish intravenous access, which may be difficult in a combative postictal woman. Judicious sedation might be required to allow further treatment in some patients.

Magnesium sulfate is the preferred drug for the prevention of further seizures in eclampsia.[189,190] The administration of magnesium sulfate in eclamptic women is associated with significantly lower maternal death rates. An initial intravenous bolus of 4 to 6 g is administered, followed by an infusion at 1 to 2 g/h, assuming the patient has adequate renal function.[343] Recurrent convulsions should prompt administration of an additional bolus of 2 to 4 g, infused over 5 to 10 minutes.[343] The patient should be carefully monitored for signs of magnesium toxicity.

BOX 36-6 Eclampsia: The ABCs of Eclamptic Seizure Control

Airway

- Turn patient to left side; apply jaw thrust.
- Attempt bag and mask ventilation (F_{IO_2} = 1.0).
- Insert soft nasopharyngeal airway if necessary.

Breathing

- Continue bag and mask ventilation (F_{IO_2} = 1.0).
- Apply pulse oximeter and monitor S_{PO_2}.

Circulation

- Secure intravenous access.
- Check blood pressure at frequent intervals.
- Monitor electrocardiogram.

Drugs

- Magnesium sulfate
  - 4 to 6 g IV over 20 min
  - 1 to 2 g/h IV for maintenance therapy
  - 2 g IV over 10 min for recurrent seizures
- Antihypertensive agents
  - Labetalol or hydralazine as needed to treat hypertension (see Table 36-4)

IV, intravenously.

Anesthetic Management

The preanesthetic management of an eclamptic woman parallels that of a patient with severe preeclampsia. Considerations[330,344] specific to the woman with eclampsia are as follows:

1. **Assessment of seizure control and neurologic function.** The possibility of increased intracranial pressure is not a cause for concern if the patient remains conscious, alert, and free of seizures. Persistent coma and localizing signs may indicate a major intracranial pathologic process that could affect anesthetic management.
2. **Maintenance of fluid balance.** Intake should be restricted to 75 to 100 mL/h to minimize the risk for exacerbating cerebral edema.
3. **Blood pressure control.** Antihypertensive therapy should be instituted if the systolic pressure is 160 mm Hg or higher, or if the diastolic pressure is 110 mm Hg or higher.
4. **Continuous pulse oximetry monitoring of maternal oxygenation.**
5. **Continuous FHR monitoring.**
6. **Laboratory investigations mimic those for preeclampsia.** Additionally, coagulation studies should be obtained regardless of the platelet count.

The anesthetic plan is tailored to each individual case. In conscious, eclamptic women with no evidence of increased intracranial pressure and whose seizures are well controlled, neuraxial analgesia/anesthesia can be considered. In a retrospective review of 66 stable eclamptic South African women, Moodley et al.[345] found no difference in maternal and neonatal outcomes in women who received epidural anesthesia compared with general anesthesia for cesarean delivery.

Eclamptic seizures are likely associated with an increase in intracranial pressure. In the rare instance of requirement for immediate delivery in a woman with ongoing seizures, a technique similar to that used for neuroanesthesia in patients with increased intracranial pressure should be considered. Intravenous induction agents such as propofol[346] or thiopental[347] will reduce the cerebral metabolic rate and cerebral blood flow, with a consequent decrease in cerebral blood volume and

intracranial pressure. These agents are also effective in terminating seizures.[348,349] Because hyperventilation reduces cerebral blood flow without a reduction in cerebral metabolic rate, it should be employed with caution. On the other hand, hypoventilation is associated with hypercarbia, which can lower the seizure threshold. To prevent further neurologic injury, it is important not to be overly aggressive in the reduction of systemic pressure because cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure.[350] Avoidance of hypoxia, hyperthermia, and hyperglycemia is also important in avoiding an exacerbation of neurologic injury.[351] The tracheas of patients who have not recovered neurologically should remain intubated, and these patients should be monitored in an intensive care unit. If unconsciousness persists, further neurologic evaluation with electroencephalography and brain imaging to rule out persistent seizures and/or other underlying neurologic problems should be performed.

Long-Term Outcomes

Neurologic abnormalities occurring in patients with eclampsia (e.g., cortical blindness, focal motor deficits, coma) do not usually result in permanent neurologic deficits.[330] However, recent studies suggest that formerly eclamptic women had significantly poorer neurocognitive function as well as an increase in visual impairment years after the index pregnancy, both of which may be attributable to permanent white matter changes caused by eclampsia.[352-354]

KEY POINTS

- Preeclampsia is a multisystem disorder of pregnancy characterized by a maternal syndrome with or without a fetal syndrome.
- Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries.
- Disease pathophysiology involves superficial placentation related to abnormal angiogenesis leading to placental hypoxia and the release of soluble substances toxic to vascular endothelium.
- Management of preeclampsia is supportive, and delivery of the fetus and placenta is the only definitive cure.
- Antihypertensive drugs should be used when systolic blood pressure is 160 mm Hg or higher, or the diastolic blood pressure is 110 mm Hg or higher.
- Preeclampsia likely consists of more than one disease; early-onset disease (earlier than 34 weeks' gestation) carries a worse prognosis than late-onset disease.
- Systemic disease manifestations result from widespread maternal vascular endothelial dysfunction.
- Complications of severe preeclampsia include severe refractory hypertension, cerebrovascular accident, pulmonary edema, placental abruption, renal failure, and the HELLP syndrome.
- Important hematologic changes in severe preeclampsia include the potential for thrombocytopenia and disseminated intravascular coagulation.
- There are no indications for invasive central monitoring unique to preeclampsia; indications are similar to those in other multisystem disorders such as severe sepsis or multisystem organ dysfunction.
- Preeclamptic women are at risk for airway edema. The anesthesia provider should anticipate the possibility of difficult airway management.
- The hypertensive response to direct laryngoscopy and tracheal intubation can cause intracranial hemorrhage in women with severe preeclampsia.
- Spinal anesthesia is acceptable for women with severe preeclampsia, especially as an alternative to general anesthesia for emergency cesarean delivery.
- The risks for pulmonary edema, cerebrovascular accident, and venous thromboembolism are increased in the postpartum period.

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CHAPTER 37

Fever and Infection

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CHAPTER OUTLINE

FEVER

Definition and Pathophysiology

In 1868, Carl Wunderlich analyzed more than 1 million axillary temperature measurements from 25,000 patients.[1] He concluded that the average normal temperature of healthy adults was 37°C (98.6°F). However, he found a range of temperatures, with a nadir of 36.2°C between 2:00 and 8:00 AM and a zenith of 37.5°C between 4:00 and 9:00 PM. He also observed that women had slightly higher mean temperatures than men. A 1992 study using modern oral thermometers largely confirmed Wunderlich's original data.[2]

Well-regulated temperature results from hypothalamic integration of afferent thermal information from the skin, spinal cord, and other sites within the central nervous system (CNS). When this integrated temperature deviates from normal, thermoregulatory responses are triggered.[3] In humans, the first (and least metabolically "expensive") response to temperature perturbations is behavioral (e.g., moving to a different environment, putting on appropriate clothing, adjusting room temperature). Such responses obviously are unavailable to an anesthetized patient, although some may be implemented by those caring for the patient. Further responses to temperature perturbations are mediated by the autonomic nervous system. Hypothermia prompts vasoconstriction in peripheral tissues to decrease skin blood flow, decrease heat loss, and retain heat in the core compartment. If vasoconstriction is not adequate to prevent hypothermia, thermoregulatory shivering is triggered to increase heat production. The CNS controls the metabolic activity of skeletal muscle, which converts chemical energy into heat by shivering.

Increased body temperature initially prompts vasodilation. This vasodilation is passive. It results from the release of sympathetic tone, and it is observed in unanesthetized adults exposed to a hot environment before any significant change in central temperature occurs. If vasodilation is not adequate to prevent hyperthermia, thermoregulatory sweating occurs, which increases evaporative heat loss.

An abnormal body temperature can result from drugs or diseases that either change thermoregulatory thresholds or impair thermoregulatory responses. Hypothalamic activity and fever may be triggered by endogenous pyrogens released from immune effector cells in response to invasion by microorganisms (Figure 37-1). Although no single endogenous pyrogen has been conclusively identified as the mediator of the febrile response, tumor necrosis factor seems capable of reproducing many components of the febrile response.[4] Endogenous pyrogen activity appears to depend largely on increased endothelial cell production of prostaglandins. Of interest, many of these substances help mediate uterine activity and parturition.[5] The central neural pathways leading to changes in thermoregulatory physiology are increasingly well understood and involve pathways coordinated in the preoptic area and projecting to the dorsomedial hypothalamus or to the rostral medullary raphe region.[3]

Clinically, temperature measurements greater than 38°C represent fever. During episodes of fever, the thermoregulatory set point is elevated and the normal thermoregulatory mechanisms are used to maintain the elevated temperature. However, there are circumstances in which an abnormally high temperature is measured in the absence of a change in thermoregulatory set point, such as when thermoregulatory responses to

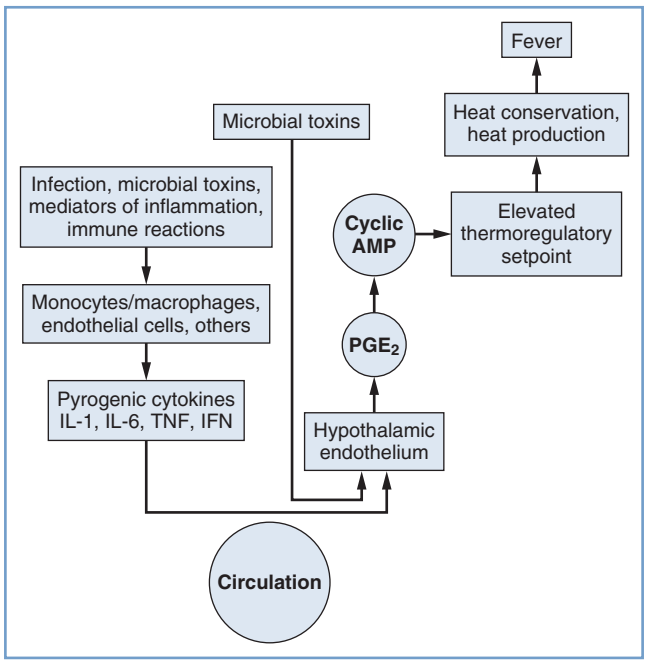

FIGURE 37-1 ■ Chronology of events in the pathophysiology of fever. *AMP,* adenosine-5′-monophosphate; *IFN,* interferon; *IL,* interleukin; *TNF,* tumor necrosis factor; *PGE_2,* prostaglandin E_2. (From Longo DL, Fauci AS, Kasper DL, et al. Harrison's Principles of Internal Medicine. 18th edition. New York, McGraw-Hill, 2012. Available at http://www.accessmedicine.com/. Accessed July 2013.)

hyperthermia are prevented (e.g., block of sympathetically mediated sweating) or overwhelmed (e.g., immersion in hot water, malignant hyperthermia).

The fetus, by virtue of its intra-abdominal location, has a unique problem with heat elimination. The only anatomic routes for egress of heat are the fetal skin surface (through the amniotic fluid) or the uteroplacental circulation. Evidence suggests that the fetus relies on heat exchange across the uteroplacental circulation to dissipate most of its metabolic heat. The normal fetus maintains a temperature that is approximately 0.5° C to 0.75° C higher than maternal temperature.[6-8]

Consequences of Maternal Fever and Infection

Maternal-fetal infection is associated with increased perinatal morbidity.[9,10] The increased morbidity is the result of many factors, including preterm delivery (perhaps related to an increased release of prostaglandins) and direct effects of the infection. Fever, irrespective of its etiology, may be harmful to the fetus, although the mechanisms of injury may differ with various causes. Conversely, some infections may be harmful without producing fever. Infection is the most common cause of fever and involves liberation of inflammatory cytokines, which are implicated in the pathogenesis of many fetal and neonatal injuries (see Chapter 10).[11,12] Noninfectious inflammatory fever, also leading to elevated cytokines, may complicate neuraxial analgesia in the absence of clinical infection (see later discussion).

Experimental evidence suggests that extreme levels of hyperthermia, independent of infection or inflammation, may have a deleterious effect on the fetus. Morishima et al.[13] reported increased uterine activity and fetal deterioration during maternal hyperthermia produced by radiant heat in anesthetized baboons. However, the extreme degree of hyperthermia (approximately 41.7° C) employed in this study produced maternal as well as fetal deaths. Such extreme hyperthermia exceeds the modest fever that often occurs clinically; thus the clinical relevance of this study is unclear. Similarly, Cefalo and Hellegers[14] demonstrated fetal deterioration at levels of hyperthermia that produced maternal cardiovascular collapse in anesthetized gravid ewes. However, the investigators also observed increased umbilical blood flow with clinically relevant, mild to moderate hyperthermia (0.5° C to 1.5° C above baseline). They suggested that increased umbilical blood flow in response to moderate degrees of hyperthermia might be beneficial to the fetus by increasing oxygen delivery and heat removal. Harris et al.[15] demonstrated the preservation of fetal oxygenation and acid-base status during moderate degrees of fever (approximately 1° C above baseline) produced by the injection of bacterial pyrogen in awake pregnant ewes. However, they also observed an increase in fetal heart rate (FHR) and a greater incidence of fetal arrhythmias during fever.

Nonetheless, in humans, hot tub and sauna use in pregnancy has been linked epidemiologically to neural tube defects in the fetus with attributable risk comparable to that observed with febrile illness.[16] Spontaneous abortion[17] and major structural birth defects[18] have similarly been associated with the frequency of use of hot tubs and saunas. Neonatal hypoxic encephalopathy has been observed after prolonged immersion in 39.7° C water during otherwise uncomplicated labor.[19]

Epidemiologic evidence suggests that mild maternal intrapartum fever may not be as benign as has been assumed on the basis of animal studies. Macauley et al.[8] measured fetal scalp temperature *in utero* using a modified intrauterine pressure catheter. They concluded that fetal core temperature may exceed 40° C in some febrile women (Figure 37-2). Lieberman et al.[20] retrospectively reviewed the records of 1218 nulliparous women with singleton, term pregnancies in spontaneous labor who were afebrile on admission. They found fever (> 38° C) in 10% of the patients, nearly all of whom had received epidural analgesia. One-minute Apgar scores less than 7 and hypotonia were more common in the newborns of febrile mothers. Fever higher than 38.3° C was associated with more frequent requirement for bag-and-mask ventilation in the delivery room and need for supplemental oxygen in the nursery. There was also a nonsignificant increase in the incidence of neonatal seizures.[20] The same group performed a case-control study of unexplained neonatal seizures in term infants and found a strong association with intrapartum fever and seizures (odds ratio [OR], 3.4).[21] A similar finding was reported by Perlman,[22] who found a high incidence of maternal fever among a cohort of infants with a 5-minute Apgar score of 5 or less and those requiring resuscitation with chest compressions in the delivery room. The same group found a

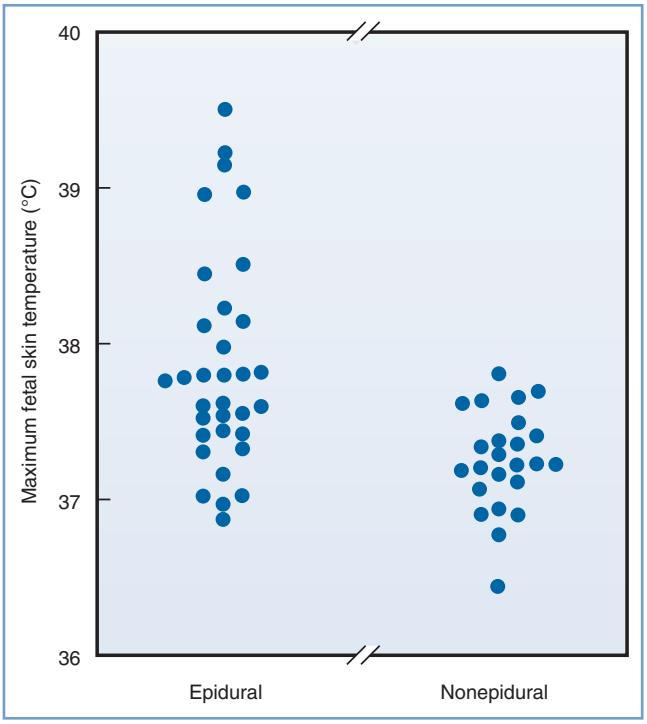

FIGURE 37-2 ■ Maximum fetal scalp temperatures measured *in utero* in women who selected epidural analgesia and those in women selecting other forms of analgesia. $P = .004$ epidural compared with nonepidural group. (From Macaulay JH, Bond K, Steer PJ. Epidural analgesia in labor and fetal hyperthermia. Obstet Gynecol 1992; 80:665-9.)

higher incidence of prolonged positive-pressure ventilation in the delivery room, tracheal intubation, admission to a neonatal intensive care unit, and 5-minute Apgar score less than 6 in febrile newborns born to women with chorioamnionitis compared with afebrile newborns born to women with chorioamnionitis.[23] Similarly, Greenwell et al.[24] found an association between low-grade fever (37.5°C) and adverse neonatal outcomes, including hypotonia and low 1-minute Apgar scores. More extreme fever (> 38.3°C) was also associated with low 5-minutes Apgar scores, assisted ventilation, and seizures.[24]

Even more ominous is the suggestion that maternal fever may correlate with neonatal brain injury, particularly when the fever is associated with clinical or pathologically diagnosed chorioamnionitis (see Chapter 10). In several large epidemiologic studies, otherwise unexplained cerebral palsy was two to nine times more common in infants born to mothers with intrapartum fever (> 38°C) than in those born to afebrile mothers.[25-29] An equally strong association has been observed between maternal fever and neonatal encephalopathy.[30] Even if not apparent at birth or in early infancy, neurologic injury related to maternal fever may appear later in childhood. Dammann et al.[31] reported an increased risk for cognitive deficits (> 2 standard deviations below the mean on a nonverbal intelligence scale) at age 9 among children whose mothers were febrile in labor. Fever during pregnancy, not specifically in the intrapartum period, has also been linked to subsequent development of autism[32,33] and schizophrenia.[34]

The mechanism linking neurologic injuries to maternal fever likely involves the liberation of inflammatory cytokines.[11,12,29,34] Animal models of chorioamnionitis suggest that fetal brain lesions can be induced by infection and blocked by anti-inflammatory cytokines.[35] Infants developing neonatal encephalopathy in the setting of maternal fever do not generally exhibit positive blood cultures, implying that it is neuroinflammation, rather than infection, that causes damage.[30,36] It remains unclear whether intrapartum temperature elevation itself can cause neurologic injury, as distinct from underlying infection or other inflammatory processes that cause both elevated inflammatory cytokines and fever.

Fever also produces significant maternal effects. Elevated temperature is associated with increased maternal heart rate, cardiac output, oxygen consumption, and catecholamine production. Evidence has linked fever after cesarean delivery to risk for uterine rupture during subsequent trial of labor after cesarean delivery.[37] Women who develop fever are more likely to shiver and experience uncomfortable rigors.[38-40] Not surprisingly, obstetricians fearing infection are more likely to treat febrile women with antibiotics.[41,42] Even low-grade fever may prompt obstetricians to choose instrumental vaginal or cesarean delivery over expectant labor management. Lieberman et al.[43] found a twofold higher incidence of operative vaginal as well as cesarean delivery in a retrospective analysis of nulliparous women who were afebrile at admission but developed fever greater than 37.5°C during labor compared with those who remained afebrile, even after controlling for birth weight, duration of labor, and analgesic choice.

Together, these studies suggest that the fetus acutely tolerates modest degrees of maternal fever. Transient neonatal depression, neonatal seizures, and other neurologic disorders may be associated with inflammatory processes that produce maternal fever, although not clearly with fever *per se*. Inflammatory processes resulting in fever, and perhaps severe hyperthermia itself, may be risk factors for neonatal brain injury and other abnormalities.

Infections in Pregnant Women

Fever is most often the result of an infectious process. The most common sites for infection in pregnant women are the fetal membranes, urinary tract, respiratory tract, and postpartum uterine cavity.

Chorioamnionitis

Chorioamnionitis is one of the most common infections in pregnant women. It occurs with variable frequency; reported event rates range from 0.5% to 10%, depending on the means of ascertainment and the demographic and obstetric characteristics of the population. In one review, the incidence was 41% for deliveries occurring at less than 27 weeks' gestation, 15% from 28 to 36 weeks' gestation, and 2% at term.[44] Independent risk factors include low parity, a history of chorioamnionitis in a prior delivery,[45] the number of vaginal examinations, duration of total labor, duration of ruptured membranes, and use

of internal monitors.[45,46] The diagnosis of chorioamnionitis is based on clinical signs, which include temperature greater than 38°C, maternal and/or fetal tachycardia, uterine tenderness, and/or foul-smelling amniotic fluid.[9] Unfortunately, the laboratory diagnosis of chorioamnionitis is neither sensitive nor specific and may not correlate with the clinical presentation.[9,47-51] Moreover, the classic clinical signs of chorioamnionitis often are absent. Goodman et al.[51] reviewed the records of 531 women with pathologically proven chorioamnionitis. They found that only 10% of the patients had abdominal tenderness and only 1% had foul-smelling amniotic fluid. Moreover, histologic evidence of chorioamnionitis can develop without producing clinical signs or symptoms.[52,53]

In most cases, bacteria gain access to the amniotic cavity and the fetus by ascending through the cervix after rupture of the membranes. Chorioamnionitis develops in a significant number of parturients with premature rupture of the membranes. Alternatively, infectious agents present in the maternal circulation may undergo transplacental transport and gain access to the amniotic cavity.[9] Similar to other pelvic infections, chorioamnionitis often is polymicrobial in origin and bacteria normally present in the genital tract most likely are responsible for infections. *Bacteroides* species, group B streptococci, *Mycoplasma* and *Ureaplasma* species, and *Escherichia coli* are organisms commonly isolated from the amniotic fluid of parturients with chorioamnionitis.[9,54] Maternal bacteremia occurs in 7.5% to 12% of women with the clinical diagnosis of chorioamnionitis.[9,47-51,55] *Candida* species occasionally cause chorioamnionitis, especially in preterm labors, and have been associated with severe sequelae, including maternal sepsis and fetal demise.[56] *Ureaplasma urealyticum* has been implicated in intra-amniotic infections even with intact membranes, and infection with this organism is associated with preterm labor.[57]

Maternal complications of chorioamnionitis include preterm labor,[58] placental abruption,[59] postpartum infection,[60] uterine atony,[61] postpartum hemorrhage,[62] peripartum hysterectomy,[63] sepsis, and death. A large prospective observational study found uterine atony, maternal blood transfusion, septic pelvic thrombophlebitis, pelvic abscess, and maternal admission to the intensive care unit to be independently associated with chorioamnionitis.[64] In addition, several studies have noted an increased incidence of cesarean delivery for dystocia in women with chorioamnionitis.* Some investigators have suggested that infection adversely affects uterine contractility and contributes to an increased risk for cesarean delivery.[48] However, in some cases, chorioamnionitis may represent an ascending infection developing late in a labor that is already prolonged and dysfunctional.[55] Satin et al.[55] observed no increase in the incidence of cesarean delivery when chorioamnionitis was diagnosed before the administration of oxytocin. However, they observed a 44% incidence of cesarean delivery when the diagnosis was made after the administration of oxytocin. Thus, the presence of chorioamnionitis may be seen as influencing the clinical decision making of the obstetrician, rather than a direct physiologic cause of dystocia.

Neonatal complications of chorioamnionitis include pneumonia, meningitis, sepsis, and death.[9,47] A strong association between chorioamnionitis and cerebral palsy has been identified.[25,29,65,66] Meta-analyses of more than 20 studies have demonstrated relative risks of cerebral palsy ranging from 1.9 to 4.7 in preterm and term infants born to mothers with clinical chorioamnionitis.[26,66,67] Neonatal stroke has also been linked to chorioamnionitis.[68] Chorioamnionitis has been linked epidemiologically to cystic periventricular leukomalacia, which often produces devastating neurologic impairment in the child.[66,69] The link between maternal infection and neurologic injury in the neonate appears related to intra-amniotic infection or inflammation, particularly when there is evidence of fetal systemic inflammation (funisitis).[29,65]

The effect of intra-amniotic inflammation on the fetal lung is complex. Elevated amniotic cytokines may reduce the incidence of acute respiratory distress syndrome in preterm neonates by stimulating surfactant production.[70] However, chronic lung disease is increased in infants exposed to chorioamnionitis,[71] apparently also related to inflammatory mediators.[9,72] Studies in African women suggest chorioamnionitis is associated with an increased risk for peripartum vertical human immunodeficiency virus (HIV) transmission from infected mothers.[73]

Historically, prompt delivery has been the cornerstone of obstetric management of patients with chorioamnionitis. However, Gibbs et al.[47] did not identify a correlation between poor maternal or neonatal outcome and the time interval from diagnosis of chorioamnionitis to delivery. They performed cesarean delivery only for standard obstetric indications and not for the diagnosis of chorioamnionitis alone.[47] Similarly, a large prospective observational study found no relationship between the duration of infection and most measures of adverse neonatal outcome among 1965 gestations complicated by chorioamnionitis, although low 5-minute Apgar scores and neonatal mechanical ventilation were correlated with duration of chorioamnionitis.[64] No recent studies have reinvestigated this practice as it relates to neonatal neurologic injuries. Monitoring of the FHR pattern is indicated in women with the diagnosis of chorioamnionitis. Many fetuses will exhibit mild tachycardia during maternal fever and infection, but this pattern is not highly predictive of neonatal acidemia and, therefore, by itself, is not an indication for immediate delivery.[74]

For many years, pediatricians requested that obstetricians delay antibiotic therapy until after delivery. They cited the theoretical concern that intrapartum therapy might "obscure the results of neonatal blood cultures."[75] However, studies suggest that early, antepartum treatment results in decreased maternal and neonatal morbidity compared with delayed, postpartum treatment.[76,77] Gibbs et al.[76] randomized 45 women with intra-amniotic infection to receive intrapartum or postpartum antibiotic therapy with ampicillin and gentamicin. Intrapartum antibiotic therapy resulted in a decreased incidence of

*References 9, 47-49, 55, 62, 64.

neonatal sepsis and a shorter neonatal hospital stay. Mothers who received intrapartum antibiotics also had a shorter hospitalization, fewer days with fever, and a lower peak postpartum temperature than mothers whose antibiotic therapy was delayed until after delivery. Currently, most obstetricians give antibiotics before delivery in women with chorioamnionitis. The early use of antibiotics also may affect the anesthesiologist's decision regarding the administration of neuraxial labor analgesia or anesthesia (see later discussion).

Urologic Infections

Urinary tract infections are common during pregnancy, although the incidence of asymptomatic bacteriuria may not be higher than in nonpregnant women. Increased concentrations of progesterone cause the relaxation of ureteral smooth muscle. In addition, the gravid uterus causes partial ureteral obstruction. Both factors cause urinary stasis, which increases the risk for urinary tract infection.[9,78,79] Furthermore, these physiologic changes increase the likelihood that asymptomatic bladder infection will ascend into the kidneys and produce pyelonephritis. Approximately 1.3% of pregnant women will develop symptomatic cystitis,[80] and up to 25% of women with untreated bacteriuria in pregnancy may develop pyelonephritis.[81]

Acute pyelonephritis is a serious threat to maternal and fetal well-being and complicates approximately 1.4% of pregnancies. Symptoms of acute pyelonephritis include fever, chills, flank pain, and other symptoms of lower urinary tract infection. Laboratory tests reveal pyuria and leukocytosis with a left shift. Pregnant women with pyelonephritis may appear severely ill. Approximately 14% to 17% of pregnant women with pyelonephritis will develop bacteremia during the course of this infection.[82,83] Complications may also include anemia, renal insufficiency, and respiratory insufficiency.[83] The most common causative organisms are *E. coli*, gram-positive organisms, *Klebsiella*, *Enterobacter*, and *Proteus* species.[83]

Hospitalization is generally required to initiate aggressive parenteral antibiotic treatment of this serious maternal infection, although limited data support outpatient treatment for carefully selected patients in the first and second trimester.[84] Nevertheless, treatment failures and septic complications have been reported in patients randomized to outpatient therapy in clinical trials.[85]

Pyelonephritis is associated with an increased risk for preterm labor and delivery in animal models.[86] Thus, obstetricians should observe for evidence of preterm labor, although epidemiologic studies have found the incidence to be less than 5%, approximately the same as in the general pregnant population.[83,87]

Pyelonephritis may be associated with organ dysfunction. Nearly 20% of affected women have transient renal dysfunction[88] and the disease may also be complicated by pulmonary injury. Cunningham et al.[89] suggested that "this syndrome was probably caused by permeability pulmonary edema, likely mediated by endotoxin-induced alveolar-capillary membrane injury."[89] Towers et al.[90] compared 11 pregnant women who had pyelonephritis and pulmonary injury with 119 women who had pyelonephritis only. They observed that fluid overload and the use of tocolytic therapy were the most significant predictive factors associated with pulmonary injury. The authors suggested that "strict management of fluids should occur so that patients do not have fluid overload."[90] Contemporary authors, however, have questioned fluid restriction in pyelonephritis and instead suggest fluid administration sufficient to generate urine output of 30 to 50 mL/h, while observing respiratory rate, oxygen saturation, and symptoms of dyspnea to identify impending respiratory compromise. Respiratory failure should be investigated with chest radiography and arterial blood gas analysis and managed with appropriate respiratory support.[9]

Hemodynamic alterations may be present even in infected women who do not demonstrate overt signs of sepsis. Twickler et al.[91] used ultrasonographic techniques to evaluate the central hemodynamic measurements in 27 pregnant women with uncomplicated pyelonephritis. They found decreased mean arterial pressure (MAP) and systemic vascular resistance (SVR) and increased heart rate and cardiac output compared with measurements obtained from the same patients after they had recovered from their infection.[91]

Recent reviews from the Cochrane Database and the United States Preventative Services Task Force strongly support the practice of screening and treating pregnant women for asymptomatic bacteriuria, up to 30% of whom will eventually develop pyelonephritis if left untreated.[92,93] Treatment is associated with a reduced incidence of pyelonephritis (OR, 0.23) and low-birthweight infants (OR, 0.66), although not, as had been previously suggested, in the incidence of preterm delivery.[93] Definitive choice of antibiotics could not be determined in a recent systematic review,[94] but traditional 7-day regimens are likely more effective than single-dose or other abbreviated antibiotic courses.[95] Because pyelonephritis in pregnancy is thought to be preventable, its occurrence may be a marker for poor prenatal care; thus it should alert physicians to other potential pregnancy problems.[96]

Respiratory Tract Infection

Most respiratory tract infections during pregnancy are upper respiratory tract viral infections that do not pose a serious threat to the mother or fetus. Most lower respiratory tract infections are also viral and self-limiting; pneumonia occurs during pregnancy with an incidence approximating that of the nonpregnant population.[97] Pregnancy results in a number of changes that may predispose the pregnant woman to the development of serious respiratory tract infection. Hyperemia and hypersecretion are characteristic of the respiratory tract mucosa during pregnancy, and these changes may intensify the effect of the initial infection.[98] In the case of a viral infection, the excess secretions may predispose the patient to bacterial superinfection. Immunologic modulation during pregnancy may also predispose to pulmonary infection.[99] Furthermore, the increased oxygen consumption, elevation of the diaphragm, and decreased

functional residual capacity characteristic of pregnancy may increase the likelihood that infection will result in maternal hypoxemia.

Benedetti et al.[100] emphasized the importance of early diagnosis and treatment as well as the direct measurement of maternal oxygenation in cases of pneumonia during pregnancy. Most community-acquired pneumonias in healthy young women are bacterial in origin. *Streptococcus pneumoniae* is the most common pathogen.[100,101] *Mycoplasma pneumoniae* and influenza are other common pathogens. *Legionella pneumophila*, *Chlamydia*, and varicella are less common pathogens in this population. Varicella pneumonia has been associated with maternal and fetal morbidity and up to 40% maternal mortality. **Acyclovir** has been used successfully to treat varicella pneumonia during pregnancy.[102] *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia represents the most common cause of death related to acquired immunodeficiency syndrome (AIDS) in pregnancy; mortality is as high as 50%.[103]

Because morbidity and mortality from influenza are increased in pregnancy, influenza vaccination is strongly recommended for all pregnant patients, irrespective of gestational age.[104] The risk for fetal death is increased by maternal influenza infection and is reduced by vaccination.[105] The infant is also passively protected for up to 20 weeks after birth.[106] Aggressive treatment with antiviral drugs (oseltamivir, zanamivir) reduces the severity of the ensuing illness; in the 2009-2010 H1N1 influenza pandemic, initiation of therapy in the first 2 days of the infection reduced hospitalization and intensive care unit admission.[107,108]

Postpartum Infection

The most common source of postpartum infection is the **genital tract**. The urinary tract and less often the breasts or the lungs may also be infected.[9] Postpartum uterine infection typically results in fever, malaise, abdominal pain, and purulent lochia. Bacteremia may occur in as many as 5% to 10% of patients with uterine infection after delivery.[49,50,109,110] Although obstetricians typically refer to postpartum uterine infection as *endometritis*, this infection involves the decidua, myometrium, and parametrial tissues. Bacteria that colonize the cervix and vagina gain access to the amniotic fluid during labor, and they may invade devitalized uterine tissue postpartum.

Patients who undergo cesarean delivery are at increased risk for postpartum endometritis compared with similar patients who deliver vaginally.[9] Prolonged rupture of membranes and/or prolonged duration of labor increase the incidence of postpartum uterine infection. Prophylactic administration of antibiotics decreases the incidence of postpartum uterine infection and wound infection after cesarean delivery in all women, whether performed electively or emergently.[111] No important differences have been identified among various skin preparation solutions used before cesarean delivery.[112] Vaginal preparation before cesarean delivery, however, may reduce endometritis.[113] Systematic reviews have found insufficient evidence to recommend prophylactic antibiotics for operative vaginal delivery or for manual removal of the placenta after vaginal delivery; however, consideration may be given to prophylactic antibiotics in the setting of complex perineal repairs.[114-116] Endometritis typically responds to appropriate antibiotic therapy, and outcomes are generally excellent. However, serious complications (e.g., peritonitis, abscess, septic thrombophlebitis) may rarely occur.[9,49] In future pregnancies, women who have experienced endometritis are at increased risk for uterine rupture, and anesthesiologists and obstetricians should demonstrate extra vigilance for this serious complication.[37]

Sepsis and Septic Shock

Sepsis is a rare, life-threatening complication of maternal infection that complicates approximately 1 in 8000 deliveries.[117] Sepsis is defined by the American College of Chest Physicians and Society of Critical Care Medicine as infection that precipitates the **systemic inflammatory response syndrome** (SIRS), characterized by two or more of the following criteria: hyperthermia, hypothermia, tachycardia, tachypnea, or leukocytosis (see Chapter 55).[118] Pregnancy may complicate the diagnosis, because many healthy pregnant women exhibit some of these signs.[119] Noninfectious inflammation may also lead to SIRS; in all cases the syndrome appears to be triggered by mediators released from immune effector cells, including tumor necrosis factor, interleukins, and cyclooxygenase metabolites of arachidonic acid.[120]

Severe sepsis is defined as sepsis with acute organ dysfunction, hypotension, or sepsis-induced hypoperfusion,[118] and **septic shock** is defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction.[118] The incidence of sepsis and sepsis-related maternal mortality appears to be rising; it was the most common cause of death (1.13 per 100,000 maternities) in the most recent (2006-2008) Confidential Enquiries into Maternal Death in the United Kingdom report.[121]

In pregnant women, sepsis typically is associated with gram-negative bacteremia, although it can occur in association with gram-positive aerobic and anaerobic infections.[122] Polymicrobial etiology is common,[117,123] particularly when the source of sepsis is a pelvic infection.[122] Group A β-hemolytic streptococcal infection appears to predominate in fatal cases or those associated with major morbidity, although *Clostridium* species have been implicated in deaths of several otherwise healthy women undergoing gynecologic or obstetric procedures.[124,125] Untreated pneumonia, chorioamnionitis, pyelonephritis, endometritis, wound infection, incomplete abortion, and self-induced abortion may result in maternal sepsis, severe sepsis, and septic shock; case reports have attributed iatrogenic maternal sepsis to amniocentesis,[126-129] medical abortion,[125] dental procedures, and assisted reproductive procedures.[130] Approximately 45% of cases occur postpartum.[131] The clinical course is often fulminant. In a series of nearly 100 cases from The Netherlands, more than half of the patients demonstrated signs of severe sepsis within 48

hours of the first sign of infection and 39% did so within 24 hours.[131]

Studies have suggested that pregnancy makes laboratory animals more susceptible to infection by a number of mechanisms.[132] For example, Beller et al.[133] infused *E. coli* B6 lipopolysaccharide (endotoxin) into both nonpregnant and pregnant minipigs. The average duration of survival for the nonpregnant animals was 16 hours, whereas the average duration of survival for the pregnant animals was only 3.5 hours. The pregnant animals suffered more pronounced cardiovascular abnormalities and metabolic acidosis than the nonpregnant animals.

It is unclear whether pregnant women are more susceptible to sepsis than age-matched nonpregnant women. Case series of maternal sepsis have reported overall case-fatality rates of 6% and 7.7%.[122,131] This survival rate may reflect the relative youth of pregnant women and the effectiveness of surgical source control for most pelvic infections. Nonetheless, clinical studies have noted that once septic shock develops in pregnant patients, maternal mortality is as high as 30%.[134-136]

The mainstay of therapy is elimination and/or aggressive treatment of the source of infection with antibiotics and, if indicated, surgical extirpation. Initial antibiotic therapy should include broad-spectrum coverage for bacteria such as *E. coli*, enterococcus, and anaerobic organisms. A combination of ampicillin, gentamicin, and clindamycin represents an effective regimen, as does a combination of imipenem, cilastatin, and vancomycin.[137] A 2012 review of cases from the United Kingdom Center for Maternal and Child Enquiries (CMACE) project suggested initial broad-spectrum antibiotic coverage (e.g., gentamicin with either piperacillin-tazobactam or ciprofloxacin), consultation with an infectious disease specialist as soon as possible, and appropriate adjustment of antibiotic therapy once the causative organism and antibiotic susceptibilities have been identified.[138] Local patterns of microbial resistance should be considered when selecting broad-spectrum empirical therapy. In all cases, aggressive antibiotic initiation without delay (within 1 hour of diagnosis) appears important for a favorable outcome.[121,139]

Only a few reports have described the management of these seriously ill patients. Timezguid et al.[122] summarized 66 intensive care unit admissions for sepsis between 1977 and 2008. Seventeen of 22 women with a pelvic source of infection required surgical source control, including termination of pregnancy (n = 5), uterine exploration for removal of placental fragments (n = 6), drainage of a pelvic abscess (n = 5), or hysterectomy (n = 3). Premature termination of pregnancy was more frequent in 12 cases of chorioamnionitis (83%) than in the 32 cases of extrapelvic infections (31%). Vasopressors, mechanical ventilation, and renal replacement therapy were used in 16 (25%), 19 (28%), and 4 (6%) cases, respectively.

Lee et al.[135] reviewed 10 cases of septic shock in obstetric patients between 1984 and 1986, which were caused by pelvic infections in 9 cases and mastitis in 1. Eight of the 10 women required inotropic or vasopressor infusions, or both, guided by pulmonary arterial catheterization. Two women died. The primary hemodynamic abnormalities were decreased systemic vascular resistance and depressed myocardial function.

Mabie et al.[136] reported 18 cases of pregnancy-associated septic shock that occurred during 11 years in a single institution, an incidence of 1 per 8338 deliveries. The most common causes were pyelonephritis (n = 6), chorioamnionitis (n = 3), endometritis (n = 2), and toxic shock syndrome (n = 2). Five patients (28%) died. The hemodynamic profiles of the patients in this series were similar to those described by Lee et al.[135]: four of the five patients who died had mildly or severely depressed myocardial function.[136] Eight patients underwent at least one surgical procedure to control the source of infection.

In most cases, concomitant supportive therapy is required to decrease maternal and fetal morbidity. Physicians must give attention to the maintenance of maternal oxygenation, circulation, and coagulation. Most authorities suggest following the Surviving Sepsis guidelines for treatment of sepsis.[121,138,139] The guidelines recommend goal-directed therapy aiming to achieve a central venous pressure (CVP) between 8 and 12 mm Hg and a MAP of 65 mm Hg, urine output of 0.5 mL/kg/h, and mixed venous oxygen saturation 65% or higher (see Chapter 55).[139] Pregnant women were excluded from trials that evaluated this goal-directed therapy,[140,141] and unfortunately no evidence is available to confirm that this approach offers survival benefit for pregnant or recently delivered women. In nonpregnant patients with septic shock, norepinephrine is considered the first choice vasopressor and may be supplemented with epinephrine or vasopressin to maintain adequate blood pressure.[139]

Evidence from nonobstetric patients receiving intensive care indicates that aggressive glycemic control may not confer a survival advantage in all critically ill patients, although some evidence suggests that avoiding hyperglycemia improves outcomes in surgical patients.[142] Overly tight glycemic targets increase the risk for hypoglycemia; current guidelines recommend treatment to avoid hyperglycemia (> 180 mg/dL), hypoglycemia, and wide swings in glucose levels.[139] More intensive glucose control may be indicated in the intrapartum period to achieve optimal neonatal outcomes. Corticosteroid supplementation is indicated only when fluid resuscitation and vasopressor therapy fail to restore hemodynamic stability.[139,143]

Although the effects of maternal therapy on the fetus should be considered, treatment of the mother has first priority. Often what is best for the mother will be best for the fetus. However, in some cases, maternal sepsis may require preterm delivery, or even delivery before the age of viability, particularly if chorioamnionitis is present. Although the American College of Obstetricians and Gynecologists (ACOG) has stated that "delivery usually is not indicated in the septic pregnant patient in whom the pregnancy is not the source of infection,"[137] a multidisciplinary team should consider the mother's response to initial therapeutic interventions, her vasopressor, oxygen and ventilatory requirements, and the gestational age and fetal well-being when considering the optimal timing and route of delivery.

EPIDURAL ANALGESIA AND MATERNAL FEVER

Incidence

Epidural anesthesia administered for surgery—including cesarean delivery—typically results in hypothermia. This effect occurs because vasodilation produced by the sympathetic neuroblockade causes a redistribution of body heat from the core to the periphery, where it is lost to the environment.[144]

In 1989, Fusi et al.[145] first observed that epidural labor analgesia was associated with progressive intrapartum maternal pyrexia. They reported that the vaginal temperatures of 18 parturients who received epidural analgesia increased approximately 1° C over 7 hours, whereas the temperatures of 15 women who received intramuscular meperidine and metoclopramide remained constant. There was no evidence of infection in any of the women. The authors suggested that epidural analgesia may cause an "imbalance between the heat-producing and heat-dissipating mechanisms."

Fusi et al.[145] measured *vaginal* temperature; this measurement may be affected by the sympathectomy and vaginal mucosal vasodilation associated with epidural analgesia. Tympanic membrane temperature should not be affected by the local vasodilation associated with epidural analgesia, and it may provide a more accurate assessment of core temperature. Camann et al.[146] studied the effect of epidural analgesia on maternal oral and tympanic membrane temperature measurements in 53 laboring women. They studied three groups of patients; one group received intravenous nalbuphine, one group received epidural bupivacaine only, and one group received epidural bupivacaine with fentanyl. The patients were not randomized to receive either nalbuphine or epidural analgesia; however, the women who requested epidural analgesia were randomized to receive epidural bupivacaine only or epidural bupivacaine with fentanyl. The authors maintained ambient room temperature between 20° C to 22° C. Epidural analgesia did not affect maternal temperature during the first 4 hours of the study. At 5 hours and thereafter, the mean tympanic membrane temperatures were significantly higher in both of the epidural groups than the intravenous nalbuphine group (Figure 37-3). Among women in the bupivacaine-only group, mean tympanic temperature increased from approximately 36.6° C at 1 hour to 37.1° C at 9 hours, a rate of rise of less than 0.07° C per hour. There was no difference between the epidural bupivacaine-only and the epidural bupivacaine-fentanyl groups in maternal tympanic membrane temperature measurements.

Several other investigators have documented similar patterns of temperature elevation in laboring women receiving epidural analgesia.[41,147-152] These studies typically have found the average rate of temperature increase to be approximately 0.1° C per hour of epidural analgesia, usually after a lag time of 4 to 5 hours. Other investigations have documented an increase in clinical fever in women with epidural analgesia, usually defined as temperature greater than 37.5° C or greater than 38° C (Table 37-1).* These studies have employed various study designs, most commonly observational investigations of women self-selecting the mode of analgesia. Selection bias, reflecting greater prevalence of risk factors for fever among women choosing epidural analgesia, undoubtedly has affected the results of these reports.[163] However, other study designs have confirmed the finding of greater risk for fever in women who receive epidural analgesia. In a natural experiment, in which epidural analgesia was rapidly introduced in a facility in which it was previously unavailable, clinical fever markedly increased after epidural analgesia was widely available.[147] In addition, eight randomized controlled trials, in which women were randomly assigned to receive epidural analgesia or parenteral opioids (or nonpharmacologic analgesia in one study[155]), also confirmed an increase in clinical fever in women who were randomized to receive epidural analgesia.[152,155,156,158-162] Only one study examined fever as a primary outcome.[155] Meta-analysis of six trials found a relative risk (RR) for fever of 3.34 (95% confidence interval, 2.63 to 4.23) for epidural compared with nonepidural or no labor analgesia.[164] Most trials have investigated epidural labor analgesia, but at least one trial specifically investigated combined spinal-epidural (CSE) analgesia.[155]

Originally viewed as two separate phenomena, the slow progressive temperature rise observed by Fusi[145] and Camann[146] and the clinical fever observed in other studies may be manifestations of the same process. Two investigations have concluded that the slow rise may actually be an artifact caused by averaging the temperature curves of women who develop clinical fever with those who remain afebrile (see Figure 23-7).[165,166] Frölich et al.[167] compared

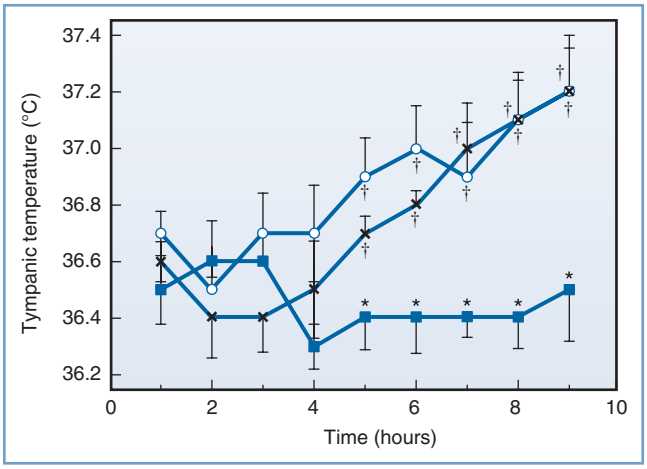

FIGURE 37-3 ■ Mean (SE) tympanic temperatures during labor in three groups of patients: Epidural bupivacaine-fentanyl (*open circles*), epidural bupivacaine-only (x), and parenteral opioid (*blue squares*) groups. **P* < .01 compared with the epidural group; †*P* < .01 compared with the pre–epidural analgesia temperature. (From Camann WR, Hortvet LA, Hughes N, et al. Maternal temperature regulation during extradural analgesia for labour. Br J Anaesth 1991; 657:565-8.)

*References 24, 41, 52, 147-151, 153-162.

TABLE 37-1 **Incidence of Clinical Fever in Women with Epidural Labor Analgesia**

Study	Study Design	Definition of Fever (°C)	Epidural Group % (n/N)	Nonepidural Group % (n/N)	*P* Value
Lieberman[150]	Observational	> 38	14.5 (152/1047)	1.0 (6/610)	< .001
Mayer[41]	Observational	≥ 37.8	20.4 (39/191)	2.1 (2/96)	< .001
Kaul[157]	Observational	> 38	6.6 (61/922)	0 (0/255)	< .001
Dashe[154]	Observational[a]	≥ 38	46.3 (37/80)	26.1 (18/69)	.01
Vinson[148]	Observational	≥ 37.5	26.8 (11/41)	8.3 (3/36)	.05
		> 38	14.6 (6/41)	0 (0/36)	.03
Herbst[151]	Observational	≥ 38	6.4 (44/683)	1.2 (28/2426)	< .001
Ploeckinger[149]	Observational	> 38	1.6 (17/1056)	0.2 (11/6261)	< .005
Agakidis[153]	Observational	≥ 38	11.3 (54/480)	0.8 (4/480)	< .0001
Riley[52]	Observational	> 38	22.7 (34/150)	6.0 (3/50)	.009
Greenwell[24]	Observational	> 37.5	44.8 (1246/2784)	14.6 (62/425)	< .0001
		> 38	19.2 (535/2784)	2.4 (10/425)	< .0001
Yancey[147]	Natural experiment[b]	≥ 37.5	26.2 (150/572)	8.2 (41/498)	< .01
		≥ 38	11.0 (63/572)	0.6 (3/498)	< .01
Ramin[160]	RCT[c]	≥ 38	22.7 (98/432)	4.8 (21/437)	< .001
Sharma[162]	RCT[c,d]	> 38	23.9 (58/243)	6.2 (16/259)	< .0001
Sharma[161]	RCT[e]	≥ 38	33.2 (75/226)	6.9 (16/233)	< .001
Lucas[159]	RCT[f]	≥ 38	20.4 (76/372)	7.1 (26/366)	< .001
Halpern[156]	RCT	> 38	15.3 (19/124)	8.5 (10/118)	.10
Nafisi[158]	RCT	≥ 38	21.8 (43/197)	6.6 (13/198)	< .001
Evron[173]	RCT[g]	≥ 38	10.5 (15/148)	2.3 (1/44)	.09
de Orange[155]	RCT[h]	≥ 38	14.3 (5/35)	0 (0/35)	.027

RCT, randomized controlled trial.
[a]All patients had ruptured membranes > 6 h; outcome included fever up to 6 h postpartum.
[b]Natural experiment (impact study) compared two time periods, before and after the introduction of on-demand labor epidural analgesia to a single institution. The "after" period is reported as the epidural group (83% of nulliparous women received epidural analgesia); the "before" period is reported as the nonepidural group (1% received epidural analgesia).
[c]Fever was reported for protocol-compliant women only.
[d]Data from this investigation were reanalyzed by Philip et al.[152]
[e]Only nulliparous women participated in the study.
[f]The study included parturients with gestational hypertension or preeclampsia; the percentages were recalculated from n/N reported in the publication.
[g]The epidural group comprised three groups: (1) epidural analgesia only, (2) epidural analgesia with intravenous remifentanil, and (3) epidural analgesia with intravenous acetaminophen.
[h]Patients were randomized to receive combined-spinal epidural (CSE) analgesia or nonpharmacologic analgesia.

the slope of the temperature-time curves in women before and after receiving epidural analgesia and found no difference. They examined only women who did not develop a temperature greater than 38° C, and thus their finding supports the observation that epidural analgesia affects temperature in only a subset of women who develop clinical fever. These findings imply that an understanding of the nature of the relationship between epidural analgesia and overt fever is the key to understanding hyperthermia during labor in these patients.

Etiology

The mechanisms by which epidural analgesia produces maternal hyperthermia during labor remain unclear, and at least three types of explanation are plausible: thermoregulatory factors, effects of systemic opioids in patients not receiving epidural analgesia, and inflammation.[163]

Thermoregulatory factors that may play a role include ambient temperature, impaired heat dissipation, and increased heat production. Fusi et al.[145] attributed the maternal pyrexia to the high ambient temperature (24° C to 26° C) found in most British delivery rooms. However, other investigators have failed to find an association between ambient temperature and maternal[148] or fetal[8] temperature. Alternatively, epidural analgesia may impair heat-dissipating mechanisms. Decreased sweating and the lack of hyperventilation that follow the provision of effective epidural pain relief may predispose laboring women to pyrexia.[145,146,168] In volunteers, epidural anesthesia raised the sweating threshold by 0.55° C.[169] Moreover, epidural analgesia attenuates the significant increase in oxygen consumption observed during uterine contractions and the even greater increase observed during expulsive efforts.[170] This lack of increase in ventilation in the setting of increased energy expenditure may manifest as increased temperature in the laboring patient. Finally, the high incidence of shivering among laboring women who receive epidural analgesia may predispose them to the development of fever. Gleeson et al.[39] found that laboring patients who shivered after the administration of epidural analgesia developed pyrexia as early as 1 hour

after initiation of neuroblockade, compared with more than 4 hours after initiation neuroblockade in patients who did not shiver. Moreover, the maximum temperature was higher and the incidence of clinical fever was three times more common in the women who shivered.[39] Some shivering and sweating in labor has been demonstrated to be nonthermoregulatory (i.e., not accompanied by changes in core temperature or vasomotor tone).[40] However, it is not clear whether shivering is a cause or an effect of factors increasing body temperature.

Parenteral **opioids** administered to women for labor analgesia might suppress fever that would otherwise have been apparent. In a nonpregnant volunteer study, fever was induced by the injection of interleukin-2.[171] Epidural analgesia with ropivacaine with or without epidural fentanyl did not affect the magnitude of the fever, but intravenous fentanyl markedly attenuated the rise in temperature.[171] However, in one large retrospective study,[172] differences in intravenous nalbuphine use did not explain the increased occurrence of fever among those receiving epidural analgesia. Evron et al.[173] randomized laboring women to receive epidural ropivacaine, intravenous remifentanil, both drugs, or epidural ropivacaine and intravenous acetaminophen. They identified fever (temperature ≥ 38° C) in 14% of the ropivacaine group, 8% in the ropivacaine and remifentanil group, 8% in the ropivacaine and acetaminophen group, and 1% in the remifentanil group. Taken together, these investigations suggest that any fever-suppressing effect of parenteral opioids is relatively weak and is seen only with μ-opioid receptor agonists.

The predominant theory to date holds that **inflammation**, perhaps of a noninfectious etiology, is responsible for epidural analgesia–associated fever. Several lines of evidence support this mechanism. First, women who are more likely to request epidural analgesia during labor also are more likely to have other risk factors for fever during labor. These may include nulliparity,[151,174] premature rupture of membranes,[175] prolonged rupture of membranes,[148,151,174] induction of labor,[175] unfavorable cervical examination at admission,[175] prostaglandin exposure,[175] prolonged labor,[8,146,148,151] obesity, higher temperature on admission,[151] early chorioamnionitis,[151] and possibly more cervical examinations.[46,175,176]

Second, women with epidural analgesia and fever more frequently demonstrate placental inflammation. In a case-control study, Vallejo et al.[177] compared women without epidural analgesia and with clinical chorioamnionitis (temperature ≥ 38° C and clinical manifestations) to two groups of women who received epidural analgesia, one with and the other without clinical chorioamnionitis. The diagnosis of chorioamnionitis was confirmed histologically. Not surprisingly, fever was far more common in the women with chorioamnionitis. In fact, the incidence of fever in women with epidural analgesia but without chorioamnionitis was only 1%.[177] Similarly, Dashe et al.[154] analyzed the records and placental pathology of 149 women who delivered more than 6 hours after membrane rupture. They found an increased incidence of fever (temperature ≥ 38° C) in the 54% of their subjects who received epidural analgesia. However, histologic evidence of placental inflammation was also more common among epidural analgesia–exposed women. In the absence of placental inflammation, the incidence of maternal fever was equivalent in the epidural analgesia–exposed and unexposed patients (11% and 9%, respectively).[154]

Importantly, the placental inflammation associated with epidural analgesia–associated fever may not indicate bacterial infection. Riley et al.[52] examined the placentas of 200 women, 150 of whom received epidural analgesia, who had participated in two previous randomized trials of the presence of birthing assistants. The authors attempted to culture bacteria from the placentas, as well as to detect bacterial DNA by the polymerase chain reaction; they also measured serum interleukin concentrations. Fever was more common in women who received epidural analgesia than in those who did not (23% versus 6%, respectively; $P = .009$), but the incidence of infection was low in both groups (4.7% versus 4.0%, respectively; $P > .99$). An admission interleukin-6 (IL-6) level greater than 11 pg/mL predicted development of fever, irrespective of analgesic choice, and IL-6 levels increased more over the course of labor in women choosing epidural analgesia, irrespective of development of fever.

A third line of evidence supporting an inflammatory mechanism of epidural analgesia–associated fever is that biomarkers of inflammation are more common in women with epidural analgesia who develop fever. Goetzl et al.[178] randomized women with epidural analgesia to receive acetaminophen or placebo in labor. The incidence of fever (temperature > 38° C) was identical in the two groups. They demonstrated elevated maternal serum and umbilical cord blood markers of inflammation (IL-6) in febrile women. Pathologic examination of the placenta was not reported.[178] As discussed earlier, Riley et al.[52] also found higher IL-6 levels in women receiving epidural analgesia and in women developing fever regardless of whether they received epidural analgesia. In a second trial, Goetzl et al.[179] were able to demonstrate suppression of epidural analgesia–associated fever with high-dose maternal corticosteroid therapy (methylprednisolone 100 mg every 4 hours). Umbilical cord blood IL-6 levels were lower in corticosteroid-treated patients, indicating suppression of inflammation. However, neonatal bacteremia was significantly increased by corticosteroid exposure.[179] In a small and likely underpowered trial, Wang et al.[180] randomized low-risk parturients with epidural analgesia to receive bupivacaine and fentanyl alone or combined with epidural dexamethasone 0.2 mg/mL. They observed no difference in the incidence of overt fever or placental inflammation but a reduction in mean temperature in the dexamethasone group. Maternal and umbilical cord blood IL-6 levels were reduced in the corticosteroid group, although the differences were not significant. Fetal condition was excellent in both groups.

The mechanism by which epidural analgesia might induce inflammation in a subgroup of women remains unclear. In nonrandomized investigations, differences in patient factors among women selecting epidural analgesia may indicate confounding risk factors for inflammation. Even in randomized trials, differences in obstetric management could also confound the association, because it

is not possible to blind the treatment group in trials of epidural analgesia.[163] For example, epidural analgesia is associated with greater use of oxytocin in randomized trials, and it is conceivable that women randomly assigned to receive epidural analgesia may also receive earlier artificial rupture of membranes, more frequent cervical examinations, and greater use of internal monitoring in order to titrate oxytocin administration.[52,152] Conversely, a direct action of epidural local anesthetic in stimulating inflammation has been proposed, with the effect mediated through activation of the vanilloid receptor TRPV1.[181]

Clinical Impact

Epidural analgesia–associated maternal hyperthermia has become a subject of significant controversy. As discussed earlier, maternal fever attributed to clinical chorioamnionitis and other infection is associated with adverse neonatal condition as well as more severe neurologic injuries, including seizures, encephalopathy, and cerebral palsy. However, the effect of epidural analgesia–associated fever has not been specifically elucidated. In randomized trials comparing epidural and nonepidural analgesia, neonatal condition as measured by umbilical arterial acidosis or 5-minute Apgar score is consistently better in the epidural analgesia groups and neonatal intensive care unit admission does not differ between groups.[164] In a large retrospective analysis, epidural analgesia with fever was associated with adverse neonatal outcomes, but in the absence of fever epidural analgesia was not.[24] To date, no evidence has linked noninfectious epidural analgesia–associated fever to severe neonatal adverse outcomes.

It is possible that the mother and neonate may be placed at risk *indirectly* as a result of the interventions triggered by the occurrence of maternal fever.[41,150] For example, antibiotic administration is more likely in the setting of maternal fever. Mayer et al.[41] retrospectively analyzed the records of 300 low-risk nulliparous women who received systemic opioids, epidural analgesia, or both and identified an increased incidence of both fever (≥ 37.8°C) and antibiotic administration among the two groups who received epidural analgesia. Nonetheless, only 5 of 10 patients with culture- or pathology-proven chorioamnionitis developed fever and none had fever as the *only* presenting sign or symptom. The authors suggested that obstetricians seek additional evidence of infection before treating all maternal fever with antibiotics.

In another retrospective study, Lieberman et al.[150] reanalyzed the records of 1657 low-risk nulliparous women originally enrolled in a trial of active management of labor.[182] They, too, found a higher incidence of maternal temperature (> 38°C) in parturients who received epidural analgesia compared with those who did not (15% versus 1%, respectively). Neonates in the epidural group had a higher incidence of sepsis evaluation (34% versus 10%, respectively) and antibiotic treatment (15% versus 4%, respectively) compared with neonates in the nonepidural group. The incidence of actual neonatal sepsis was very low in both groups (0.3% and 0.2%, respectively). As in all studies in which women self-select their analgesia, the women receiving epidural analgesia were already at risk for intrapartum fever. For example, they had larger infants, longer labors, and a twofold increase in the rate of induction of labor.[150] Moreover, the active labor management protocol mandated frequent cervical examinations and early amniotomy, which may have increased the risk for fever.[183] Of interest, two thirds of the sepsis evaluations occurred in infants of mothers who did *not* have intrapartum fever.[150,183]

To further elucidate the relationship between epidural analgesia and neonatal sepsis evaluation, the same group reanalyzed the subcohort of women[182] admitted in spontaneous labor, in whom intrapartum temperature remained below 38°C throughout labor.[184] Epidural analgesia was associated with both major (rupture of membranes > 24 hours, FHR > 160 beats/min) and minor criteria (maternal temperature > 37.5°C, rupture of membranes 12 to 24 hours) for sepsis evaluation. It is likely that many of the features of labor that led to sepsis evaluations also predisposed women to choose epidural analgesia.

Subsequent work by other investigators has suggested the role of maternal temperature elevation as the key feature related to neonatal sepsis evaluations. Philip et al.[152] demonstrated that women randomized to receive epidural analgesia had a higher incidence of fever (≥ 38°C) than those randomized to receive intravenous analgesia (15% versus 4%, respectively). Neonatal sepsis evaluations were also much more common in women with fever than in those without (96% versus 13%, respectively). However, within both the febrile and the afebrile cohorts, the incidence of neonatal sepsis evaluation was independent of analgesic type. The authors concluded[152]:

> *… our results indicate that in the absence of maternal fever, epidural analgesia during labor has no bearing on the need for such neonatal management and therefore should not be considered a predictor per se for neonatal sepsis evaluations. We attribute this finding to the minimization of ascertainment bias as a result of randomization of analgesia.*

Other investigators have highlighted the importance of neonatal practice style in determining the rate of sepsis evaluations. Yancey et al.[147] studied the rates of maternal fever and neonatal sepsis evaluation during a period in which epidural analgesia use rapidly increased from 1% to 83% after the introduction of a round-the-clock, on-demand epidural analgesia service. The incidence of fever greater than 37.5°C increased threefold, and fever greater than 38°C increased 18-fold after the introduction of epidural analgesia, although numerous indices of the patients' admission status and intrapartum obstetric management did not change. The incidence of screening neonatal blood counts and blood cultures increased modestly (RR, 1.5 and 1.7, respectively), but there was no change in antibiotic treatment. The authors contrasted their results to those of Lieberman[150] and attributed the difference to neonatal practice patterns that did not require antibiotic therapy solely on the basis of maternal fever or antibiotic exposure.[147]

Kaul et al.[157] also emphasized neonatologists' practice style. They analyzed the records of 1177 nulliparous women and their neonates. Women with epidural analgesia had an increased risk for fever compared with women who received parenteral opioid analgesia (7% versus 0%, respectively), but multivariate logistic regression failed to demonstrate a significant association between epidural analgesia or maternal fever and neonatal sepsis evaluation. In contrast to Lieberman et al.,[150] the authors attributed the lack of effect of epidural analgesia to more stringent guidelines for neonatal sepsis evaluation that required at least one neonatal sign or symptom of infection regardless of the maternal condition.[157]

The ability of epidural analgesia to stimulate maternal fever is likely a real phenomenon and not purely an artifact of higher-risk patients selecting epidural analgesia more frequently. Because of the growing evidence that maternal inflammation and infection, manifesting as fever, can be detrimental to the fetal brain, anesthesiologists cannot dismiss this unique physiologic effect as a mere curiosity. Further study to elucidate the link between epidural analgesia, pregnancy and labor, and fever is crucial to developing effective and safe strategies to minimize this link. In addition, attention must be paid to the indirect effects of maternal fever on the clinical decision-making of obstetricians and neonatologists to minimize unnecessary maternal and fetal interventions. In the meantime, if maternal pyrexia occurs, good clinical practice dictates that efforts be made to lower maternal temperature and identify and treat a presumed maternal infection.

NEURAXIAL ANESTHESIA IN THE FEBRILE OR INFECTED PATIENT

Clinicians have long suspected an association between the performance of dural puncture during a period of bacteremia and the subsequent development of meningitis. Some clinicians have feared that diagnostic lumbar puncture may cause meningitis rather than aid in its diagnosis. They reasoned that lumbar puncture may disrupt the rich venous plexus surrounding the spinal cord and allow the direct introduction of infected blood into the CNS by the spinal needle. Alternatively, others have speculated that disruption of the dural barrier may permit hematogenous spread of infection into the CNS without direct vessel trauma. Similar concerns apply to the performance of neuraxial anesthesia and the development of spinal-epidural abscess (see Chapter 32). Administration of continuous epidural analgesia often results in blood vessel trauma, and it includes the introduction of a foreign body. Theoretically, this technique could produce a nidus for subsequent infection.

Laboratory Studies

Carp and Bailey[185] performed a study to assess the risk for meningitis after the performance of dural puncture in bacteremic rodents. In this study, rats were made bacteremic by producing a flank abscess using *E. coli* bacteria. The bacteremia was similar in magnitude to that which occurs during the early phase of sepsis in humans. Cisternal dural puncture was performed after the onset of bacteremia. After 24 hours, the cisterna magna was drained surgically, and the cerebrospinal fluid (CSF) was cultured for evidence of meningitis. Of the 40 animals that underwent dural puncture during *E. coli* bacteremia, 12 developed meningitis (Table 37-2). None of the 40 bacteremic animals *not* subjected to dural puncture developed meningitis. Furthermore, dural puncture did not result in infection in the 30 animals without bacteremia. Importantly, *none* of the 30 bacteremic animals given a dose of gentamicin 15 minutes before dural puncture developed meningitis.

TABLE 37-2 The Association between Bacteremia and the Recovery of *Escherichia coli* from Cerebrospinal Fluid after Dural Puncture in Rats

n	Bacteremia (CFU/mL)*	Gentamicin†	Dural Puncture	CSF *E. coli*‡
40	40 ± 22 (5-100)	No	Yes	12/40§
40	48 ± 25‖ (2-100)	No	No	0/40
30	0 (0)	No	Yes	0/30
30	49 ± 35 (5-110)	Yes	Yes	0/30

*Data expressed as mean ± SD (range in parentheses).
†Gentamicin administered before dural puncture.
‡Data expressed as the number of animals in which *E. coli* cultured from spinal fluid per total number of animals in that group.
§$P < .05$ compared with other groups.
‖Not significantly different from that in the bacteremic groups undergoing cisternal puncture.
CFU, colony-forming unit(s); *CSF,* cerebrospinal fluid; *n,* number of rats in each group.
Modified from Carp H, Bailey S. The association between meningitis and dural puncture in bacteremic rats. Anesthesiology 1992; 76:739-42.

This study is consistent with earlier laboratory studies that observed the development of meningitis after the performance of dural puncture in bacteremic laboratory animals.[186,187] Although animal models of disease permit careful control of experimental conditions, these studies do not duplicate clinical conditions. Thus, there are limitations in the application of the rat study[185] to clinical practice. First, the level of bacteremia produced in the rats exceeded the transient, low-grade bacteremia that often occurs clinically. Also, these animals most likely had hemodynamic and metabolic changes characteristic of early sepsis. Second, although *E. coli* is a common cause of bacteremia in surgical and obstetric patients, it is an uncommon cause of meningitis. Third, the relative size of the dural tear produced by the 26-gauge needle used in this study is greater in rats than humans. Fourth, the cisternal site of dural puncture is not used clinically. Fifth, spinal and epidural anesthesia involves the injection of local anesthetics, and these drugs appear to be bacteriostatic.[188] Finally, the investigators knew the identity of the

organism (*E. coli*) and also knew that it was susceptible to gentamicin.

In summary, this study suggests that high-grade bacteremia may increase the risk for meningitis after dural puncture. However, antibiotic therapy before dural puncture appears to reduce if not eliminate this risk.

Clinical Studies

At least six retrospective clinical studies have evaluated *diagnostic lumbar puncture* and the risk for meningitis.[189-194] (These studies did not evaluate the risk of neuraxial anesthesia or analgesia.) These reports provided conflicting conclusions regarding the risk for meningitis after the performance of dural puncture in bacteremic patients. Two studies suggested an association between dural puncture and meningitis.[189,192] However, both studies had serious methodologic flaws. One study was performed during an epidemic of meningitis.[189] Although the authors observed a high rate of meningitis after lumbar puncture, they did not evaluate a comparable control group who did not undergo lumbar puncture. Teele et al.[192] reported an association between lumbar puncture and meningitis only in bacteremic children younger than 1 year of age. However, they acknowledged the possibility that clinical judgment might have prompted their pediatricians to perform diagnostic lumbar puncture in children with incipient meningitis before the CSF provided diagnostic evidence of infection.

The remaining four studies clearly did not support an association between dural puncture and meningitis.[190,191,193,194] Shapiro et al.[194] concluded:

> *The development of bacterial meningitis in children with occult bacteremia is strongly associated with the species of bacteria that causes the infection, but not with a lumbar puncture.…Children with high-density bacteremia may appear to be more severely ill than children who have bacteremia with lower concentrations of bacteria, and therefore may be more likely to undergo a lumbar puncture.*

In an editorial, Chestnut[195] stated, "Physicians often perform diagnostic lumbar puncture in patients with fever and/or bacteremia of unknown origin. If dural puncture during bacteremia results in meningitis, one would expect that unequivocal clinical data should exist." However, no epidemiologic study has clearly established a causal relationship between the performance of dural puncture during bacteremia and the subsequent development of meningitis or epidural abscess. Part of the uncertainty regarding the risk of dural puncture results from awareness that processes other than meningeal integrity may help protect against the occurrence of CNS infection. For example, as many as 35% of epidural catheters used postoperatively are colonized by bacteria,[196] but epidural abscess is a *very rare* complication. Some anesthesiologists have cited anecdotal reports of meningitis after spinal anesthesia during presumed, but not documented, bacteremia as evidence that dural puncture may cause meningitis.[197-200] In one of these reports, the physicians used reusable equipment and the source of infection was traced to inadequately sterilized supplies.[197] The use of sterile, disposable equipment and strict attention to aseptic technique have largely eliminated these factors as a source of infection.

Some evidence points to external contamination as the source of meningitis after spinal anesthesia (see Chapter 32).[201-204] Rubin[203] reported six cases of meningitis after spinal anesthesia over a 5-year period; all procedures were performed by the same anesthesiologist and the infections were all caused by the same organism. Videira et al.[205] reported three cases of meningitis after 38,128 spinal anesthetics (1 : 12,709). In two cases, streptococci presumed to be skin or nasopharyngeal flora were cultured. The authors concluded that lapses in sterile technique may have been responsible for the meningitis. Poor attention to asepsis was also apparently responsible for three cases of meningitis reported in a 3-year period in a single hospital.[206] In one case, the offending organism was cultured from the nose of the anesthesiologist performing the procedure. A 2012 outbreak of fungal meningitis in patients receiving otherwise uncomplicated epidural steroid injections was traced to contaminated methylprednisolone.[207]

Several reports have described the occurrence of meningitis after CSE analgesia in obstetric patients.[208-210] None of these patients was febrile during the CSE procedure. Furthermore, in the cases with positive CSF cultures, the authors concluded that contamination by skin flora was the most likely mechanism of infection. In general, evidence does not support a greater risk for meningitis with the CSE technique than with other neuraxial procedures, but rather a reporting bias involving complications of a relatively new technique.[211]

Large epidemiologic studies have found a very low incidence of CNS infection after the administration of neuraxial anesthesia. Dripps and Vandam[212] prospectively studied 8460 patients who received 10,098 spinal anesthetics between 1948 and 1951. Similarly, Phillips et al.[213] reported the administration of spinal anesthesia to 10,440 patients between 1964 and 1966. A large number of the patients in both studies underwent obstetric or urologic procedures. Undoubtedly some patients had bacteremia during or after the performance of spinal anesthesia. However, neither study reported a single case of CNS infection.[212,213]

Some evidence supports a lower frequency of infectious complications in obstetric patients than in general surgical patients. A 10-year review in Sweden of 1,260,000 spinal anesthetics and 450,000 epidural procedures (including 200,000 labor analgesia procedures) found 29 cases of meningitis and 13 epidural abscesses. Among the obstetric patients, there were no episodes of meningitis and one abscess.[214] Similarly, four reviews that included a total of more than 500,000 obstetric patients who received epidural anesthesia reported no cases of meningitis and two cases of epidural infection.[215-218] A 2009 national audit conducted in the United Kingdom gathered data on all central neuraxial procedures over a 1-year period (707,425 total cases and 320,425 obstetric cases).[219] Three cases of meningitis and 15 epidural abscesses were reported, but no meningitis and only one abscess was observed in the obstetric population.

Undoubtedly some parturients are bacteremic during the administration of epidural or spinal anesthesia, given the frequency with which parturients develop fever and infection during labor. For example, Blanco et al.[50] found a 1% incidence of bacteremia in a random sample of patients on the labor ward. Other studies have noted an incidence of bacteremia ranging from 2.3% to 12% in parturients with chorioamnionitis.[47,49,51] Unfortunately, there are no good predictive factors for identifying the subgroup of febrile patients with chorioamnionitis who are bacteremic at the time of anesthesia. The severity of fever does not reliably predict the likelihood of bacteremia in these patients.[220] For example, Blanco et al.[50] reported that 86 (49%) of 176 patients with documented bacteremia had a temperature below 38.8° C. Furthermore, Bader et al.[220] reported no significant difference in the mean temperatures of bacteremic and nonbacteremic patients with chorioamnionitis. Similarly, in a study of 146 women with chorioamnionitis, Goodman et al.[51] found no differences in temperature, leukocytosis, or maternal symptoms between patients with positive and negative blood cultures.

Bader et al.[220] retrospectively observed no cases of CNS infection after the administration of epidural or spinal anesthesia for labor and/or cesarean delivery in 279 patients with chorioamnionitis. Only 43 of these 279 women received antibiotic therapy before the administration of neuraxial anesthesia. At least three women had positive blood cultures consistent with bacteremia, and none of these three women received antibiotics before the administration of anesthesia. Similarly, Goodman et al.[51] found no cases of meningitis or epidural abscess among 531 patients with chorioamnionitis (proven by culture or pathologic examination) who received epidural (n = 517) or spinal (n = 14) anesthesia. Eleven of 45 patients with fever before initiation of the neuraxial procedure, and 174 of 229 patients with preexisting leukocytosis, received no antibiotics before instrumentation of the epidural or subarachnoid space.

Together, these clinical studies suggest that meningitis and epidural abscess are rare complications of epidural or spinal anesthesia. Furthermore, bacteremia itself does not appear to increase the risk for CNS infection after the administration of neuraxial anesthesia. However, published studies of neuraxial anesthesia in patients with chorioamnionitis were small and retrospective. Given the infrequent occurrence of CNS infection among noninfected patients undergoing neuraxial anesthesia, none of these studies was sufficiently large to exclude the possibility that chorioamnionitis increases the risk for meningitis or epidural abscess. Moreover, the retrospective study design introduces the possibility of selection bias; anesthesia providers may have avoided neuraxial anesthesia in the sickest patients with chorioamnionitis.

Recommendations

In our judgment, the anesthesiologist may safely administer spinal or epidural anesthesia to healthy patients at risk for bacteremia. The anesthesiologist need not avoid administration of neuraxial anesthesia in patients at risk for transient, low-grade bacteremia after the administration of anesthesia. Moreover, appropriate antibiotic therapy may lessen the risk for meningitis or epidural abscess in patients with established infection. In our practice, we administer spinal or epidural anesthesia to patients with evidence of systemic infection, provided that appropriate antibiotic therapy has begun. Thus, it often is appropriate for the anesthesia provider to request the initiation of antibiotic therapy before administration of analgesia/anesthesia. Finally, although the choice of anesthesia must be individualized, it seems prudent to avoid spinal or epidural anesthesia in untreated patients with overt clinical signs of sepsis.

Chestnut reviewed this subject and concluded[195]:

> *We do not give regional [neuraxial] anesthesia in the absence of other relevant information. Rather, we provide care for febrile patients who require anesthesia for labor, delivery, or emergency surgery. When one considers the risks of infection with regional anesthesia, one should ask: What are the alternatives? What are the consequences of withholding regional anesthesia in a febrile patient? For example, what is the greater risk in a febrile parturient: meningitis or epidural abscess after spinal or epidural anesthesia, or failed intubation and aspiration during general anesthesia?*

Finally, both physicians and patients should recognize that most cases of meningitis and epidural abscess occur spontaneously. Eng and Seligman[191] concluded, "Even if an appropriate temporal sequence…is documented…one cannot differentiate spontaneous meningitis from lumbar puncture–induced meningitis in the individual patient."

GENITAL HERPES INFECTION

Herpes simplex virus type 2 (HSV-2) causes locally recurring disease that is characterized by asymptomatic periods interrupted by episodes of viral reactivation from sites in the sensory ganglia.[221] Genital herpes infection typically presents as painful vesicular or papular lesions on the skin or mucous membranes of the genital tract, including the labia, vulva, perineum, cervix, and urethra.[222] Primary maternal HSV-2 infection is associated with transient viremia,[222] and up to 2% of pregnant women will be primarily infected during gestation.[221] Epidemiologic evidence suggests that HSV-1, formerly associated only with perioral lesions (herpes labialis), is now the predominant cause of new genital herpes infections in some populations.[223] Patients with primary infection may have systemic symptoms, including fever, headache, and lymphadenopathy, although asymptomatic primary infection is common. Hepatitis, aseptic meningitis, encephalitis, and cauda equina syndrome are uncommon complications of primary genital herpes infection. During recurrent (i.e., secondary) infection, maternal antibodies prevent the recurrence of viremia. Thus systemic symptoms are less severe—or do not occur at all—during episodes of recurrent infection. However, recurrent infection may result in severe symptoms localized to the site of the lesions on the external genitalia. Prodromal symptoms, including vulvar pain or burning, often

precede development of recurrent lesions. Unfortunately, asymptomatic shedding of the virus also may occur in the genital tract.[221,222]

Interaction with Pregnancy

During the first 20 weeks of pregnancy, primary genital herpes infection may be associated with an increased risk for pregnancy loss,[224] although contemporary cohort studies have disputed the risk for fetal death.[225] However, the major obstetric concern is the potential for transmission of the virus to the infant at the time of birth. The infant may become infected in one of two ways.[222] First, infection can occur as the fetus comes in direct contact with the virus during vaginal delivery. Second, intrauterine infection can occur by ascent of the organism after rupture of membranes. Neonatal HSV infection is a life-threatening infection with the potential for permanent CNS sequelae.[221,222,224,226] The severity of the neonatal infection may be reduced by the early initiation of antiviral therapy. Meta-analysis of seven randomized trials of antepartum antiviral therapy with acyclovir or valacyclovir demonstrated a reduction in the presence of active genital lesions at delivery (RR, 0.28) and requirement for cesarean delivery (RR, 0.30).[227] However, these trials could not demonstrate a reduction in neonatal herpes infection (there were no cases in any trial), and failure of suppressive therapy to prevent such transmission has been reported.[226]

Retrospective studies suggest that the risk for neonatal HSV infection associated with a primary maternal infection is much greater than that associated with recurrent maternal infection or asymptomatic shedding of the virus.[224,228-230] The risk for transmission in the setting of active recurrent herpes has been estimated at 3% and in infected women without genital lesions at delivery at 2 per 10,000.[221] Most likely there is a greater risk that the infant will be exposed to the virus during episodes of primary maternal infection; in recurrent herpes there is evidence that passive transfer of antibodies to HSV from the mother to the fetus is protective.

Obstetric Management

A large epidemiologic study of 58,362 women provided direct evidence that cesarean delivery dramatically reduces the overall risk for HSV transmission to the neonate when HSV cultures of the cervix and external genitalia taken at the time of labor were positive (OR, 0.14).[228] Other risk factors included maternal HSV seronegativity, positive cervical culture, use of invasive obstetric monitoring, and HSV-1 (compared with HSV-2) infection.[228]

The ACOG has reviewed the obstetric management of parturients with HSV infections and has concluded the following[221]:

> *Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate an impending outbreak. The incidence of neonatal disease is low when there is recurrent maternal disease, but cesarean delivery is recommended because of the potentially serious nature of the disease.…In patients with active HSV infection and ruptured membranes at or near term, a cesarean delivery should be performed as soon as the necessary personnel and equipment can be readied. There is no evidence that there is a duration of rupture of membranes beyond which the fetus does not benefit from cesarean delivery.…In pregnancies remote from term, especially in women with recurrent disease, there is increasing support for continuing the pregnancy to gain benefit from time and use of corticosteroids. There is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV.*

Of interest, the mothers of most infants infected with HSV have no history of HSV infection and no obvious lesions at the time of delivery.[221,230] Previously, it was thought that antenatal viral cultures could predict asymptomatic viral shedding at the time of delivery and reduce the incidence of neonatal infection. Unfortunately, there is little correlation between antepartum HSV culture results and viral shedding at the time of delivery, even in women with a history of previous HSV infection.[230] Thus, the ACOG concluded that there was no evidence for cost-effectiveness of various antenatal screening protocols.[221]

Anesthetic Management

There are at least five published retrospective studies of the use of neuraxial anesthesia in patients with genital HSV infection. These studies reported no serious neurologic sequelae related to the use of neuraxial anesthesia.[231-235] However, most of the patients in these studies had recurrent (secondary) infection. Two studies[232,233] were limited to patients with recurrent infection, and a third report[231] did not indicate whether the patients had primary or recurrent infection. Bader et al.[234] reported outcomes for 169 women with genital herpes infection who underwent cesarean delivery. Five of the 169 women in this study had primary infections, and three of these women received spinal anesthesia. Of the three women, one had transient, postoperative weakness of the left leg. The authors[234] stated, "None of the cases of primary infection had associated systemic symptoms; it is therefore possible that some of these cases were actually misdiagnosed recurrent infections. The safety of regional anesthesia in patients with primary HSV infection remains unclear."

Viremia may accompany primary episodes of genital herpes infection. However, viremia rarely complicates recurrent episodes of genital herpes infection. It is unlikely that a spinal or epidural needle could introduce virus into the CNS in patients with recurrent genital herpes infection. Thus, a consensus exists that it is safe to administer spinal or epidural anesthesia to women with recurrent genital herpes infection and no systemic symptoms. There are insufficient data to allow a definitive recommendation regarding the safety of neuraxial anesthesia in patients with primary infection who may be viremic. If the anesthesia provider is confronted with a patient with primary infection, the theoretical risk for

CNS infection should be weighed against the risks of alternative methods of analgesia and anesthesia.

Finally, several studies have suggested that spinal or epidural administration of morphine, commonly administered for postcesarean delivery analgesia, increases the incidence of **recurrence of oral HSV infection**. This phenomenon was confirmed in randomized prospective trials for both epidural[236] and intrathecal[237] morphine. The cause is unknown, but some investigators have speculated that pruritus and scratching play a role in reactivation of oral lesions. Boyle[238] concluded that facial pruritus is a marker of the migration of morphine to the trigeminal nucleus but not the cause of HSV recrudescence. He suggested that immunologic modulation by the opioid within this ganglion is the primary cause of the viral reactivation. Substantial evidence now supports this mechanism.[239] A case of HSV-1 meningitis after unintentional dural puncture and passage of an intrathecal catheter has been reported.[240] The patient underwent cesarean delivery with spinal bupivacaine, fentanyl, and morphine; the authors suggested reactivation of HSV-1 due to morphine and the presence of the intrathecal catheter may have contributed to the infection.[240] To our knowledge, there are no reports suggesting that epidural or intrathecal administration of opioids increases the risk for recurrent *genital* herpes infection or neonatal herpes infection.

KEY POINTS

- Fever may be produced by endogenous pyrogens released from immune effector cells in response to infection.
- Fetal temperature typically is slightly higher than maternal temperature.
- Modest maternal fever does not seem to adversely affect the fetus, but maternal infection and other inflammatory states may cause fetal neurologic injury.
- Pyelonephritis and chorioamnionitis are the antepartum infections most likely to result in maternal and perinatal morbidity and mortality. Septic shock is an uncommon but devastating complication of maternal infection that demands aggressive hemodynamic support, broad-spectrum antibiotic therapy, and, in some cases, surgical intervention.
- Epidural analgesia increases the risk for maternal fever during labor in a subset of women. The mechanism is unclear but most likely related to a noninfectious inflammatory process. It is unknown whether epidural analgesia–associated fever places the fetus at risk for neurologic injury; however, no study has directly linked maternal fever associated with epidural analgesia to adverse effects on the fetus or neonate. Epidural fever may prompt neonatologists to evaluate neonates for possible sepsis.
- The anesthesiologist may safely administer epidural or spinal analgesia or anesthesia to patients at risk for transient bacteremia.
- The anesthesiologist may safely administer epidural or spinal anesthesia to patients with established infection, provided there is no evidence of frank sepsis. However, it seems prudent to begin antibiotic therapy before the administration of anesthesia.
- Recurrent genital herpes infection does not contraindicate the administration of neuraxial anesthesia.
- Spinal and epidural morphine administration is associated with reactivation of oral herpes simplex virus.

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CHAPTER 38

Antepartum and Postpartum Hemorrhage

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CHAPTER OUTLINE

Obstetric hemorrhage is the most common cause of maternal mortality worldwide, accounting for 25% of maternal deaths.[1] The World Health Organization estimates that severe hemorrhage complicates 10.5% of live births globally and carries with it a case-fatality rate of 1%.[1] The rates of maternal death and death due to hemorrhage vary widely throughout various regions of the world (see Chapter 40).[1-3] In the United States, hemorrhage accounts for 12.5% of pregnancy-related deaths (1.8 pregnancy-related deaths due to hemorrhage per 100,000 live births).[4] Data from the United Kingdom indicate death from peripartum hemorrhage occurs in 0.39 per 100,000 maternities.[5] Hemorrhage is the most common cause for admission of an obstetric patient to an intensive care unit and is a risk factor for myocardial ischemia and infarction and stroke.[6-8] A 2010 investigation demonstrated that organ dysfunction complicates 16% of cases of major obstetric hemorrhage (defined as transfusion of 5 or more units of packed red blood cells [PRBCs]).[9]

Evidence indicates hemorrhage rates and severe morbidity due to hemorrhage are increasing in the United States and other high-resource countries, owing primarily to increases in postpartum, rather than antepartum, hemorrhage.[10-13] The explanation for this acceleration is not entirely clear but appears to be related to rising rates of postpartum uterine atony as well as increases in abnormal placentation coincident with the rise in cesarean delivery rates.[10,11,14,15]

The majority of hemorrhage-related adverse outcomes are considered preventable.[5,16,17] Common provider-related shortcomings include failure to recognize risk factors, failure to accurately estimate the extent of blood loss, and failure to initiate treatment in a timely fashion. It is essential that clinicians develop an appreciation for the rapidity with which obstetric patients can become unstable, and that anesthesiologists—often the only physicians on the labor and delivery unit with specific training in resuscitation and critical care—become involved early in the care of bleeding patients. Timely and effective communication among all obstetric caregivers is imperative.

MECHANISMS OF HEMOSTASIS

Uterine contraction, stimulated by endogenous oxytocic substances released after delivery, represents the primary mechanism for controlling blood loss at parturition. Uterine tetany creates shearing forces that cleave the placenta from the uterine wall through the layer of the uterine decidua (see Figure 4-3). In addition, uterine contraction constricts the spiral arteries and placental veins spanning the myometrium and supplying the placental bed.

After disruption of vascular integrity, mechanisms of coagulation include (1) platelet aggregation and plug formation, (2) local vasoconstriction, (3) clot polymerization, and (4) fibrous tissue fortification of the clot. Platelet activation and aggregation occur rapidly after endothelial damage. Activated platelets release adenosine diphosphate (ADP), serotonin, catecholamines, and other factors that promote local vasoconstriction and hemostasis. These factors also activate the coagulation cascade. The

end result of the cascade is conversion of fibrinogen to fibrin and stabilization of the blood clot (see Chapter 44).

Anesthesia providers, obstetricians, midwives, and labor nurses frequently underestimate blood loss at delivery.[18] Heavy bleeding is associated with larger errors in estimated blood loss, and this underestimation may lead to inadequate replacement of intravascular volume.[18] Tachycardia and hypotension are late signs of hypovolemia, particularly in healthy young patients (Table 38-1); therefore, constant vigilance is necessary to ensure accurate estimation of blood loss and adequate resuscitation. Fluid and transfusion therapy is best guided by continual reassessment of maternal vital signs, urine output, hemoglobin concentration, and acid-base balance.

ANTEPARTUM HEMORRHAGE

Antepartum vaginal bleeding may occur in as many as 25% of pregnant women; fortunately, only a fraction of these patients experience life-threatening hemorrhage.[19] The majority of cases occur during the first trimester. The causes of antepartum hemorrhage range from cervicitis to abnormalities in placentation, including placenta previa and placental abruption. The greatest threat of antepartum hemorrhage is not to the mother but to her fetus. Several decades ago, vaginal bleeding during the second and third trimesters was associated with perinatal mortality rates as high as 80%. More recent data suggest that antepartum bleeding secondary to placenta previa and placental abruption is responsible for perinatal mortality rates of 2.3% and 12%, respectively.[20-22]

Placenta Previa

Placenta previa is present when the placenta implants in advance of the fetal presenting part. Further classification can be made on the basis of the relationship between the placenta and the cervical os. A **total placenta previa** completely covers the cervical os. A **partial placenta previa** covers part but not all of the os. A **marginal placenta previa** lies within 2 cm of, but does not cover, the cervical os (Figure 38-1).

Epidemiology

The incidence of placenta previa is 4.0 per 1000 pregnancies.[23,24] The exact cause is unclear, but prior uterine trauma (e.g., scar from prior cesarean delivery) is a common element. The placenta may implant in the scarred area, which typically includes the lower uterine segment. Conditions associated with placenta previa

TABLE 38-1 **Advanced Trauma Life Support (ATLS) Classification of Shock**

	Class 1	Class 2	Class 3	Class 4
Blood loss (%)*	< 15	15-30	30-40	> 40
Heart rate (beats/min)	< 100	> 100	> 120	> 140
Systolic blood pressure (mm Hg)	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	> 35
Mental state	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

*Percent total blood volume.

From American College of Surgeons Trauma Committee. Advanced Trauma Life Support for Doctors. 8th edition. Chicago, American College of Surgeons, 2008.

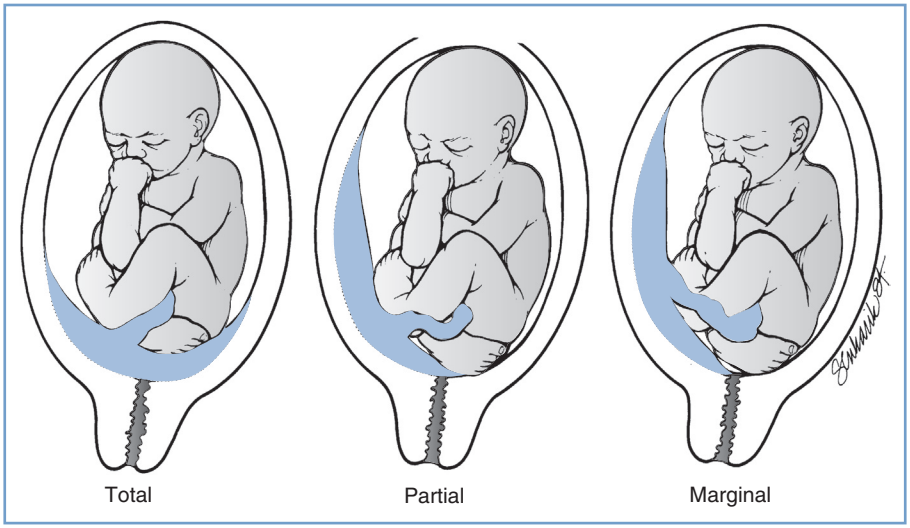

FIGURE 38-1 ■ **Three variations of placenta previa.** (From Benedetti TJ. Obstetric hemorrhage. In Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: Normal and Problem Pregnancies. 4th edition. New York, Churchill Livingstone, 2001:516.)

include multiparity, advanced maternal age, smoking history, male fetus, previous cesarean delivery or other uterine surgery, and previous placenta previa.[23] The presence of placenta previa increases the likelihood that the patient will require a peripartum hysterectomy.[25]

Diagnosis

Transvaginal ultrasonography has become the gold standard for diagnosis of placenta previa; the distance from the placental edge to the internal os is measured and predicts the likelihood of antepartum hemorrhage and need for cesarean delivery.[26,27] Advances in ultrasonography have made the **double setup examination** (i.e., vaginal examination with all personnel ready for immediate cesarean delivery) nearly obsolete in modern obstetric practice. Magnetic resonance imaging (MRI) is also useful for the diagnosis of placenta previa, but its use is not practical in most cases of antepartum hemorrhage.

The classic clinical sign of placenta previa is painless vaginal bleeding during the second or third trimester. The first episode of bleeding typically occurs preterm and is not related to any particular inciting event. The lack of abdominal pain and/or absence of abnormal uterine tone helps distinguish this event from placental abruption. The absence of these factors does not exclude abruption, however, and patients with placenta previa are at risk for coexisting placental abruption.[24]

Obstetric Management

Obstetric management is based on the severity of vaginal bleeding and the maturity and status of the fetus. Active labor, persistent bleeding, a mature fetus (≥ 36 weeks' gestational age), or nonreassuring fetal status should prompt delivery.[28] The fetus is at risk from two distinct pathophysiologic processes: (1) progressive or sudden placental separation that causes uteroplacental insufficiency and (2) preterm delivery and its sequelae. The first episode of bleeding characteristically stops spontaneously and rarely causes maternal shock or fetal compromise. Expectant management in the hospital has been shown to prolong pregnancy by an average of 4 weeks after the initial bleeding episode.[28] Maternal vital signs are assessed frequently, and the hemoglobin concentration is checked at regular intervals. Fetal evaluation involves frequent performance of a nonstress test or biophysical profile, ultrasonographic assessment of fetal growth, and fetal lung maturity studies as indicated. Hemorrhage may be prevented by limitations on physical activity and avoidance of vaginal examinations and coitus, although the evidence supporting these measures is limited.

Outpatient management has resulted in good outcome in carefully selected patients.[29] Outpatient management is reserved for stable patients without bleeding in the previous 48 hours who have both telephone access and the ability to be transported quickly to the hospital. Expectant management requires immediate access to a medical center with 24-hour obstetric and anesthesia coverage and a neonatal intensive care unit.[28]

In most cases of placenta previa diagnosed between 24 and 34 weeks' gestation, a corticosteroid (e.g., betamethasone) is administered to accelerate fetal lung maturity.[28] A significant number of patients with placenta previa have preterm labor, which may provoke bleeding. Obstetricians may administer tocolytic therapy to decrease preterm contractions, with the goal to stabilize antepartum bleeding. Ritodrine has been shown to prolong pregnancy in women with placenta previa, but no studies have confirmed any decrease in the frequency or severity of vaginal bleeding.[28,30] Obstetricians must balance the potential cardiovascular consequences of tocolytic therapy in the event of maternal hemorrhage against the consequences of preterm delivery. Tocolytic therapy is not recommended for patients with uncontrolled hemorrhage or those in whom placental abruption is suspected. Although expectant management reduces the risk for prematurity, it does not eliminate it, and prematurity remains the most common cause of neonatal mortality and morbidity, especially if bleeding begins before 20 weeks' gestation.[31]

Fetuses of women with placenta previa may be at risk for other complications, including asymmetric fetal growth restriction (also known as intrauterine growth restriction).[32] Several factors may account for the association between placenta previa and fetal growth restriction. First, the lower uterine segment may be less vascular than normal sites of placental implantation. Second, the placenta often is adherent to an area of fibrosis tissue. Third, patients with placenta previa have a higher incidence of first-trimester bleeding, which may promote a partial placental separation, reducing the surface area for placental exchange. Fourth, although the blood loss from placenta previa is almost entirely maternal, trauma to the placenta with vaginal examination or coitus may result in some fetal blood loss, which could retard fetal growth.[32] Some studies have reported a higher incidence of congenital anomalies in the fetuses of women with placenta previa.[20]

Anesthetic Management

All patients admitted with antepartum vaginal bleeding should be evaluated by an anesthesia provider on arrival. Special consideration should be given to the airway examination, intravascular volume assessment, and history of previous cesarean delivery or other procedures that create a uterine scar. Volume resuscitation should be initiated using a non–dextrose-containing balanced salt solution (e.g., lactated Ringer's, normal saline). Women with placenta previa may remain hospitalized for some time prior to delivery, and at least one intravenous catheter should be maintained if bleeding is recurrent or imminent delivery is anticipated. For women without recurrent bleeding, consideration may be given to either deferring venous access entirely or placing a peripherally-inserted central catheter (PICC) for drug administration so that other peripheral veins are preserved for large-bore intravenous catheter access in the event of hemorrhagic emergency. Hemoglobin concentration measurement may be indicated after a bleeding episode. A blood type and screen, and for women who are actively bleeding, a blood type and crossmatch, should be maintained. The American Association of Blood Banks (AABB) recommends repeating such tests every 3 days in pregnant women owing to the small but finite risk for developing a new alloantibody

during pregnancy.[33] This recommendation is written into the U.S. Code of Federal Regulations.[34] The use of lower-extremity sequential compression devices may decrease the risk for venous thromboembolism in patients on bed rest. Pharmacologic prophylaxis is not commonly used because of the risk for bleeding.

Double Setup Examination. The accuracy of ultrasonography for the identification of placenta previa has almost eliminated the need for double setup examination, but a few patients still require it (e.g., morbidly obese patients who cannot be adequately evaluated with ultrasonography). The examination is performed in the operating room. All members of the obstetric care team, including the anesthesia provider, obstetrician, and pediatrician, make full preparation for cesarean delivery. Full preparation consists of application of maternal monitors, insertion of two large-bore intravenous cannulas, administration of a nonparticulate antacid, and sterile preparation and draping of the abdomen. The obstetrician subsequently performs a careful vaginal examination. A cesarean delivery is performed if significant bleeding occurs or if the obstetrician confirms the presence of total placenta previa in a woman with a mature fetus.

Cesarean Delivery. Experts recommend that women with a placental edge-to-internal os distance greater than 1 cm be offered a trial of labor; the risk for antepartum hemorrhage and need for cesarean delivery during labor are low in this setting.[26] Parturients with total previa, placental edge-to-internal os distance less than 1 cm, and/or significant bleeding will require abdominal delivery, as will some patients with nonreassuring fetal status. The choice of anesthetic technique depends on the indication and urgency for delivery, the severity of maternal hypovolemia, and the obstetric history (e.g., prior cesarean delivery).

Surveys of obstetric anesthesiologists show that neuraxial anesthesia is preferred in patients with placenta previa without active bleeding or intravascular volume deficit.[35] Patients who have placenta previa—without active preoperative bleeding—remain at risk for increased intraoperative blood loss for at least three reasons. First, the obstetrician may injure an anteriorly located placenta during uterine incision. Second, after delivery, the lower uterine segment implantation site, lacking uterine muscle compared with the fundus, does not contract as well as the normal fundal implantation site. Third, a patient with placenta previa is at increased risk for placenta accreta, especially if there is a history of previous cesarean delivery (Table 38-2).[25] For these reasons, two large-bore intravenous cannulas should be placed before the start of either elective or emergency cesarean delivery. No consensus exists on the need for blood product availability in these patients, but it seems prudent to order at least a blood type and screen. If preoperative imaging indicates the possibility of a placenta accreta, preparation for massive blood loss should be undertaken (see later discussion).

A randomized controlled trial comparing epidural with general anesthesia for cesarean delivery in women with placenta previa in the absence of active bleeding demonstrated that epidural anesthesia was associated with (1) more stable blood pressure after delivery and (2) lower transfusion rates and transfusion volumes with similar hematocrit measurements the day after surgery.[36] Operative times, estimated blood loss, urine output, and neonatal Apgar scores were similar in the two groups.[36] Combined spinal-epidural anesthesia, or even single-shot spinal anesthesia, is considered acceptable for patients without active bleeding provided that there is both a low risk for placenta accreta and a low risk for difficult airway management should intraoperative conversion to general anesthesia become necessary.

Patients with placenta previa and active preoperative bleeding represent a significant challenge for the anesthesia care team. Frequently, such patients have just presented to the hospital and there is minimal time for evaluation. In these cases, patient evaluation, resuscitation, and preparation for operative delivery all proceed simultaneously. Because the placental site is the source of hemorrhage, the bleeding may continue unabated until the placenta is removed and the uterus contracts. Preoperative evaluation requires careful assessment of the parturient's airway and intravascular volume. Two large-bore intravenous catheters should be placed, and blood products should be ordered as necessary. Blood administration sets, fluid warmers, and equipment for invasive monitoring should be immediately available. Initially, non–dextrose-containing crystalloid or colloid is infused rapidly. In some cases, the patient requires transfusion before completion of the blood crossmatch, and type-specific blood or type O, Rh-negative blood must be administered.

Rapid-sequence induction of general anesthesia is the preferred technique for bleeding patients. The choice of intravenous induction agent depends on the degree of cardiovascular instability. In patients with severe hypovolemic shock, tracheal intubation may be accomplished without an induction agent, although this situation is rare. A low dose of propofol should be administered in women with ongoing hemorrhage; in the case of *severe* ongoing hemorrhage it may be best to avoid propofol. Ketamine and etomidate are useful alternative induction agents for hemodynamically unstable patients. Ketamine 0.5 to 1.0 mg/kg has an excellent record of safety and

TABLE 38-2 **Risk for Placenta Accreta in Patients with Placenta Previa: Relationship to Number of Prior Cesarean Deliveries**

Number of Prior Cesarean Deliveries	% of Patients with Placenta Accreta
0	3
1	11
2	40
3	61
4 or more	67

Modified from Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol 2006; 107:1226-3.

efficacy in obstetric anesthesia practice. Emergence phenomena such as hallucinations and nightmares are uncommon when the dose does not exceed 1 mg/kg. Ketamine may cause myocardial depression, which may result in hypotension in patients with severe hypovolemia. Etomidate 0.3 mg/kg causes minimal cardiac depression and is safe for use in obstetric patients.[37] A low dose is appropriate in patients with severe hemorrhage. Disadvantages of etomidate include venous irritation, myoclonus, and possible adrenal suppression.[38]

The agent(s) chosen for maintenance of anesthesia depends on maternal cardiovascular stability. In patients with modest bleeding and no fetal compromise, 50% nitrous oxide in oxygen can be administered with a low concentration of a volatile halogenated agent before delivery to prevent maternal awareness. The concentration of nitrous oxide can be reduced or omitted in cases of severe maternal hemorrhage or fetal compromise. In these cases, scopolamine or a benzodiazepine such as midazolam may be administered to ensure amnesia.

Oxytocin should be administered by intravenous infusion immediately after delivery. The relatively amuscular lower uterine segment implantation site does not contract as efficiently as the uterine fundus. If bleeding continues, it may be best to discontinue the volatile halogenated agent after delivery and to substitute 70% nitrous oxide and an intravenous opioid or ketamine. These drugs, along with small doses of midazolam, can be administered without causing significant uterine relaxation or cardiovascular depression. A low-dose infusion of propofol and/or ketamine may be considered, with the caution that propofol causes decreased uterine contractility in a dose-dependent manner.[39,40] Some anesthesia providers contend that bispectral index (BIS) monitoring may be useful in lowering the risk for intraoperative awareness in cases in which the volatile anesthetic agent has been discontinued, although this issue is a matter of some dispute.

If the placenta does not separate easily, a placenta accreta may exist. In such cases, massive blood loss and the need for cesarean hysterectomy should be anticipated (see later discussion). The need for invasive hemodynamic monitoring varies among patients. An indwelling arterial catheter is useful for patients with hemodynamic instability or for those who require frequent determination of hematocrit and blood gas measurements. Coagulopathy rarely occurs with placenta previa.

Placental Abruption

Placental abruption is defined as complete or partial separation of the placenta from the decidua basalis before delivery of the fetus. Maternal hemorrhage may be revealed by vaginal bleeding or may be concealed behind the placenta. Fetal compromise occurs because of the loss of placental surface area for maternal-fetal exchange of oxygen and nutrients.[41]

Epidemiology

Placental abruption complicates 0.4% to 1.0% of pregnancies, and the incidence is increasing, particularly among African-American women in the United States.[21,42-44] The causes are not well understood, but several conditions are known risk factors for abruption (Box 38-1).[42,43] Patients hospitalized for both acute and chronic respiratory diseases are at risk for placental abruption for unclear reasons.[45]

BOX 38-1 Conditions Associated with Placental Abruption

Obstetric Conditions

- Advanced maternal age
- Multiparity
- Preeclampsia
- Premature rupture of membranes
- Chorioamnionitis

Maternal Comorbidities

- Hypertension
- Acute or chronic respiratory illness
- Substance abuse
- Maternal cocaine use
- Maternal or paternal tobacco use

Trauma

- Direct (i.e., blunt abdominal)
- Indirect (e.g., acceleration/deceleration injury)

Diagnosis

The classic presentation of abruption consists of vaginal bleeding, uterine tenderness, and increased uterine activity; however, not all of these symptoms are always present. In cases of concealed abruption, vaginal bleeding may be absent and gross underestimation of maternal hypovolemia can occur. Bleeding may be painless.[41] In some cases, abruption may manifest as idiopathic preterm labor. Patients may have a variety of nonreassuring fetal heart rate (FHR) patterns, including bradycardia, late or variable decelerations, and/or loss of variability.[41] The diagnosis of placental abruption is primarily clinical, but in a subset of cases, ultrasonography may help confirm it. Ultrasonography is highly specific for placental abruption (96%), but it is not very sensitive (24%).[46] It is also useful for determining placental location, which can exclude placenta previa as a cause of vaginal bleeding.[41] The ultrasonographic examination can ascertain whether retroplacental or subchorionic hematoma is present. Normal findings do not exclude the diagnosis of placental abruption.

Pathophysiology

Complications of placental abruption include hemorrhagic shock, coagulopathy, and fetal compromise or demise. One third of coagulopathies in pregnancy are attributable to abruption, and coagulopathy is associated with fetal demise.[47] Placental tissue displays tissue factor and other procoagulant substances on cell membranes, and it is surmised that when bleeding at the decidual-placental interface (i.e., abruption) occurs, these

thromboplastic substances are released into the central circulation, resulting in consumptive coagulopathy and disseminated intravascular coagulation (DIC).[48]

Although some cases of abruption occur acutely (e.g., in the setting of trauma), many abruptions complicate chronic, long-standing placental abnormalities. Investigators have noted strong associations between abruption, fetal growth restriction, and preeclampsia, and all three conditions share similar risk factors.[49] Naeye et al.[50] prospectively studied more than 53,000 deliveries and found that decidual necrosis at the placental margin and large placental infarcts were the most common abnormalities among patients who suffered placental abruption and fetal demise. Infants who died had 14% less placental weight, 8% less body weight, and 3% shorter body length than surviving control infants of the same gestational age. In addition, histologic evidence of shallow trophoblastic invasion of the spiral arteries supports the conclusion that "ischemic placental disease" may underlie chronic placental hypoxia, leading to preeclampsia, fetal growth restriction, and abruption.[49]

The major risks for the fetus are hypoxia and prematurity. Fetal oxygenation depends on adequate maternal oxygen-carrying capacity, uteroplacental blood flow, and transplacental exchange. Separation of all or part of the placenta reduces gas exchange surface area and can lead to fetal death. The risk for intrauterine fetal demise increases as the detachment area increases, particularly when the location of bleeding is retroplacental rather than subchorionic.[41,51,52] Inadequate transplacental oxygen exchange is exacerbated by maternal hypotension, which decreases uteroplacental blood flow. Ananth and Wilcox[21] reviewed outcomes for 7.5 million pregnancies in the United States; the perinatal mortality rate associated with placental abruption was 12%. The high mortality rate is due in large part to the fact that infants of mothers with placental abruption are five times more likely to be delivered preterm.[21]

Obstetric Management

If the diagnosis of abruption is suspected, the practitioner should insert a large-bore intravenous catheter and obtain blood for assessment of hematocrit, coagulation status, and type and crossmatch. When assessing volume status, the clinician must remain aware of the possibility of hemorrhage concealed behind the placenta. Placement of a urethral catheter to monitor urine output may help the physician assess the adequacy of renal perfusion. The definitive treatment is delivery of the infant and placenta, but the degree of maternal and fetal compromise and estimated gestational age determine the timing and route of delivery.[41] If the fetus is at or near term and both maternal and fetal status are reassuring, vaginal delivery may be appropriate. If the patient is preterm, the extent of abruption is minimal, and the mother and fetus show no signs of compromise, the patient may be hospitalized and the pregnancy allowed to continue to optimize fetal maturation. The obstetrician may administer a corticosteroid to promote fetal lung maturity. If the mother develops hemodynamic instability or coagulopathy, or fetal status becomes nonreassuring, urgent cesarean delivery may become necessary. Vaginal delivery is preferred for patients with intrauterine fetal demise.[41]

Anesthetic Management

The anesthesia provider should consider the severity of the abruption and the urgency of delivery in planning anesthetic management.

Labor and Vaginal Delivery. Neuraxial labor analgesia may be offered in the setting of abruption provided that hypovolemia has been treated and coagulation status is normal. The appropriateness of neuraxial analgesia with its accompanying sympathectomy in patients at risk for extension of abruption and further hemorrhage has been questioned; however, the risk that neuraxial analgesia will worsen hemorrhage-associated tachycardia and hypotension can be mitigated by appropriate intravascular volume replacement and use of vasopressors. Close monitoring is required for evidence of further bleeding and changes in intravascular volume status. A coagulopathic patient may present for vaginal delivery, particularly in the setting of fetal demise. In this case, intravenous patient-controlled opioid analgesia should be offered.

Cesarean Delivery. Similar anesthetic considerations pertain to the administration of neuraxial anesthesia for cesarean delivery. Spinal, combined-spinal epidural, or epidural anesthesia may be administered in stable patients in whom intravascular volume status is adequate and coagulation studies are normal. General anesthesia is preferred for most cases of urgent cesarean delivery accompanied by unstable maternal status, a nonreassuring FHR pattern, or both. Propofol may precipitate severe hypotension in patients with unrecognized hypovolemia; ketamine and etomidate may represent better options for the patient with unknown or decreased intravascular volume.

Aggressive volume resuscitation is critical. Either crystalloid or colloid may be used; the choice is less important than adequate restoration of intravascular volume. In cases of severe hemorrhage, insertion of an intra-arterial catheter may aid prompt recognition of hypotension and allow for frequent blood sampling and assessment of anemia and coagulation status. Patients with abruption are at risk for persistent hemorrhage after delivery from uterine atony or coagulopathy; after delivery, oxytocin should be infused promptly to prevent uterine atony. Persistent uterine atony requires the administration of other uterotonic drugs (see later discussion). Red blood cells (RBCs) and coagulation factors should be replaced as indicated by laboratory studies. Experts recommend aggressive monitoring and early replacement of coagulation factors, especially fibrinogen, to minimize the developing coagulopathy.[53]

Most parturients recover quickly and completely after delivery. A minority of postpartum patients, notably those who have prolonged hypotension or coagulopathy, and who need massive blood volume and blood product replacement, are best monitored in a multidisciplinary intensive care unit.

BOX 38-2 Conditions Associated with Uterine Rupture

Obstetric Conditions

- Prior uterine surgery
- Induction of labor
- High-dose oxytocin induction
- Prostaglandin induction
- Grand multiparity (> 5)
- Morbidly adherent placenta
- Congenital uterine anomaly (e.g., bicornuate uterus)

Maternal Comorbidities

- Connective tissue disorder (e.g., Ehlers-Danlos syndrome)

Trauma

Obstetric

- Forceps application/rotation
- Internal podalic version
- Excessive fundal pressure

Nonobstetric

- Blunt
- Penetrating

Uterine Rupture

Epidemiology

Rupture of the gravid uterus can be disastrous for both the mother and the fetus. Fortunately, it does not occur often. Previous uterine surgery (e.g., cesarean delivery or myomectomy) increases the risk, but the incidence of true uterine rupture after cesarean delivery is still low, occurring at a rate of less than 1%.[54,55] Uterine rupture is rare in the primigravid woman or the woman with an unscarred uterus, but it does occur.[55] Box 38-2 lists additional conditions that have been associated with uterine rupture.[55,56] Very rarely, uterine rupture occurs without explanation.[57]

Rupture of a previous uterine scar may occur in the absence of labor. In a review of records from a large multistate hospital system, nearly half of all true uterine ruptures occurred in the absence of a history of cesarean delivery, and 22% of ruptures occurred in the absence of labor.[58] Lydon-Rochelle et al.[59] undertook a population-based retrospective analysis of more than 20,000 women who had undergone one previous cesarean delivery. The risk for rupture among nonlaboring women was 1.6 per 1000. Among women in spontaneous labor the risk increased approximately threefold to 5.2 per 1000; among women undergoing induction of labor the risk increased nearly fivefold to 7.7 per 1000; and among women undergoing prostaglandin induction the risk increased almost 16-fold to 24.5 per 1000. Additional risk factors for uterine rupture during a trial of labor after cesarean (TOLAC) include post-term gestation (≥ 42 weeks), birth weight greater than 4000 g, maternal age older than 35 years, and maternal height greater than 164 cm.[54]

Because of variation in nomenclature and severity, accurate determination of maternal and fetal morbidity secondary to uterine rupture is difficult. The most common variety of uterine scar disruption is separation or dehiscence, some cases of which are asymptomatic. **Uterine scar dehiscence** is defined as a uterine wall defect that does not result in excessive hemorrhage or FHR abnormalities and does not require emergency cesarean delivery or postpartum laparotomy. In contrast, **uterine rupture**, less common than dehiscence, refers to a uterine wall defect with maternal hemorrhage and/or fetal compromise sufficient to require emergency cesarean delivery or postpartum laparotomy.

The rupture of a classical uterine incision scar (a vertical incision involving the muscular uterine fundus) is associated with greater morbidity and mortality than rupture of a low transverse uterine incision scar because the anterior uterine wall is highly vascular and may include the area of placental implantation. Lateral extension of the rupture can involve the major uterine vessels and is typically associated with massive bleeding. Maternal death secondary to uterine rupture is rare, although there were three deaths attributed to uterine rupture in the 2006 to 2008 triennial report from the United Kingdom.[5] In Sweden between 1983 and 2001, Kaczmarczyk et al.[54] estimated that the neonatal mortality rate associated with uterine rupture was approximately 5%.

Diagnosis

The variable presentation of uterine rupture may cause diagnostic difficulty. Abdominal pain and an abnormal FHR pattern are the two most common presenting signs of uterine rupture,[60] but neither is 100% sensitive. One retrospective study reported the occurrence of abdominal pain in 17% of patients; an FHR abnormality was the first sign of uterine rupture in 87% of patients (see Chapter 19).[61] Other presenting signs include vaginal bleeding, uterine hypertonia, cessation of labor, maternal hypotension, loss of the fetal station, decrease in cervical dilation, or a change in fetal presentation. Breakthrough pain during neuraxial labor analgesia may also indicate uterine rupture.[62]

Obstetric Management

Treatment options for uterine rupture include repair of the uterus, arterial ligation, and hysterectomy. Uterine repair is appropriate for most cases of separation of a prior low transverse uterine scar and for some cases of rupture of a classical incision. However, the risk for rupture in a future pregnancy remains. A disadvantage of arterial ligation is that it may not control the bleeding and may delay definitive treatment. Hysterectomy may be required for some cases of uterine rupture.[56]

Anesthetic Management

Patient evaluation and resuscitation are initiated while the patient is being prepared for emergency laparotomy. If rupture has occurred antepartum, fetal compromise is likely. General anesthesia is often necessary, except in some stable patients with preexisting epidural labor analgesia. Aggressive volume replacement is essential,

and transfusion may be necessary. Urine output should be monitored. Invasive hemodynamic monitoring may be appropriate if there is uncertainty about the intravascular volume status.

Vasa Previa

Vasa previa is defined as the velamentous insertion of the fetal vessels over the cervical os (i.e., the fetal vessels traverse the fetal membranes ahead of the fetal presenting part). Thus, the fetal vessels are not protected by the placenta or the umbilical cord. Rupture of the membranes is often accompanied by tearing of a fetal vessel, which may lead to exsanguination of the fetus.

Epidemiology

Vasa previa occurs rarely (1 in 2500 to 1 in 5000 deliveries).[28] Because it involves the loss of fetal blood, vasa previa is associated with a high fetal mortality rate (nearly 60% if vasa previa is unrecognized).[63] The blood volume of the fetus at term is approximately 80 to 100 mL/kg. Therefore, the amount of blood that can be lost without fetal death is small. In addition, the vulnerable fetal vessels may be compressed by the fetal presenting part, resulting in fetal hypoxia and death. Risk factors for vasa previa include the presence of placenta previa or low-lying placenta in the second trimester, placental accessory lobes, *in vitro* fertilization, and multiple gestation.[28]

Diagnosis

Ultrasonography can be used to visualize the velamentous insertion of the vessels, and transvaginal color Doppler imaging can confirm the diagnosis.[28,63] Vasa previa should be suspected whenever bleeding occurs with rupture of membranes, particularly if the rupture is accompanied by FHR decelerations or fetal bradycardia. Hemorrhage can also occur without rupture of membranes, making the diagnosis more difficult. Rarely, vasa previa can be diagnosed via digital cervical examination or amnioscopy. The diagnosis of vasa previa can be confirmed through examination of the shed blood for evidence of fetal hemoglobin (e.g., Kleihauer-Betke test); however, when bleeding occurs, the emergency nature of vasa previa usually precludes such diagnostic confirmation.

Obstetric Management

Prenatal diagnosis confers a neonatal survival benefit. Oyelese et al.[63] conducted a retrospective study of 155 pregnancies complicated by vasa previa. Neonatal mortality was 3% when the vasa previa was diagnosed antenatally and 56% when it was not. The authors recommended ultrasonographic examination with transvaginal color Doppler in patients at risk for vasa previa. The management of vasa previa is directed solely toward ensuring fetal survival. Some authors advocate hospitalization of the patient between 30 and 32 weeks' gestation to ensure prompt delivery if rupture of membranes should occur; consideration should be given to the administration of a corticosteroid to promote fetal lung maturity.[28] Timing of delivery reflects a balance between the risks of preterm delivery and the risk for vessel rupture if the pregnancy is allowed to continue. Robinson and Grobman[64] compared delivery timing strategies for women with vasa previa and calculated that the best fetal outcomes occurred with elective delivery between 34 and 35 weeks' gestation. They further determined that confirmation of fetal lung maturity via amniocentesis was not necessary.[64]

Ruptured vasa previa is a true obstetric emergency that requires immediate delivery of the fetus, almost always by the abdominal route. Neonatal resuscitation requires immediate attention to neonatal volume replacement with colloid, balanced salt solutions, and blood.

Anesthetic Management

The choice of anesthetic technique depends on the urgency of the cesarean delivery. In many cases, general anesthesia is necessary for prompt delivery.

POSTPARTUM HEMORRHAGE

Conflicting definitions of postpartum hemorrhage exist; however, the most commonly accepted definition is more than 500 mL blood loss after vaginal delivery or more than 1000 mL after cesarean delivery.[1,65] These values may have low clinical utility because they are only slightly higher than the average blood loss for each type of delivery. Postpartum hemorrhage can also be inferred clinically (albeit retrospectively) from a 10% decrease in hematocrit from admission to the postpartum period or the need to administer PRBCs owing to postpartum blood loss.

Postpartum hemorrhage is the most common cause of maternal mortality worldwide and an important contributor to maternal death in the United States.[1,2,4] The incidence of postpartum hemorrhage varies widely throughout different regions of the world[2]; in the United States the current rate of postpartum hemorrhage is approximately 3%.[10,11] Postpartum hemorrhage, severe postpartum hemorrhage, and the attendant morbidity and mortality from hemorrhage are increasing in incidence.[10,11] Between 1994 and 2006 the transfusion rate for postpartum hemorrhage more than doubled.[10] The explanation for this acceleration is not entirely clear but appears to be related to rising rates of postpartum uterine atony as well as increases in the incidence of abnormal placentation, both coincident with the rise in cesarean delivery rates.[10,11,14,15] Other factors may include the rising rates of obstetric interventions, such as induction and augmentation of labor,[66-68] and the increasing prevalence of obesity,[69-71] multiple gestation,[67,72] hypertensive diseases of pregnancy,[73] and advanced maternal age.[12,74] However, the rising prevalence of these risk factors does not entirely explain the upward trend in postpartum hemorrhage that has been observed.[10,11]

Primary postpartum hemorrhage occurs during the first 24 hours, and secondary postpartum hemorrhage occurs between 24 hours and 6 weeks after delivery.[75] Primary postpartum hemorrhage is more likely to result in maternal morbidity or mortality. Figure 38-2 provides

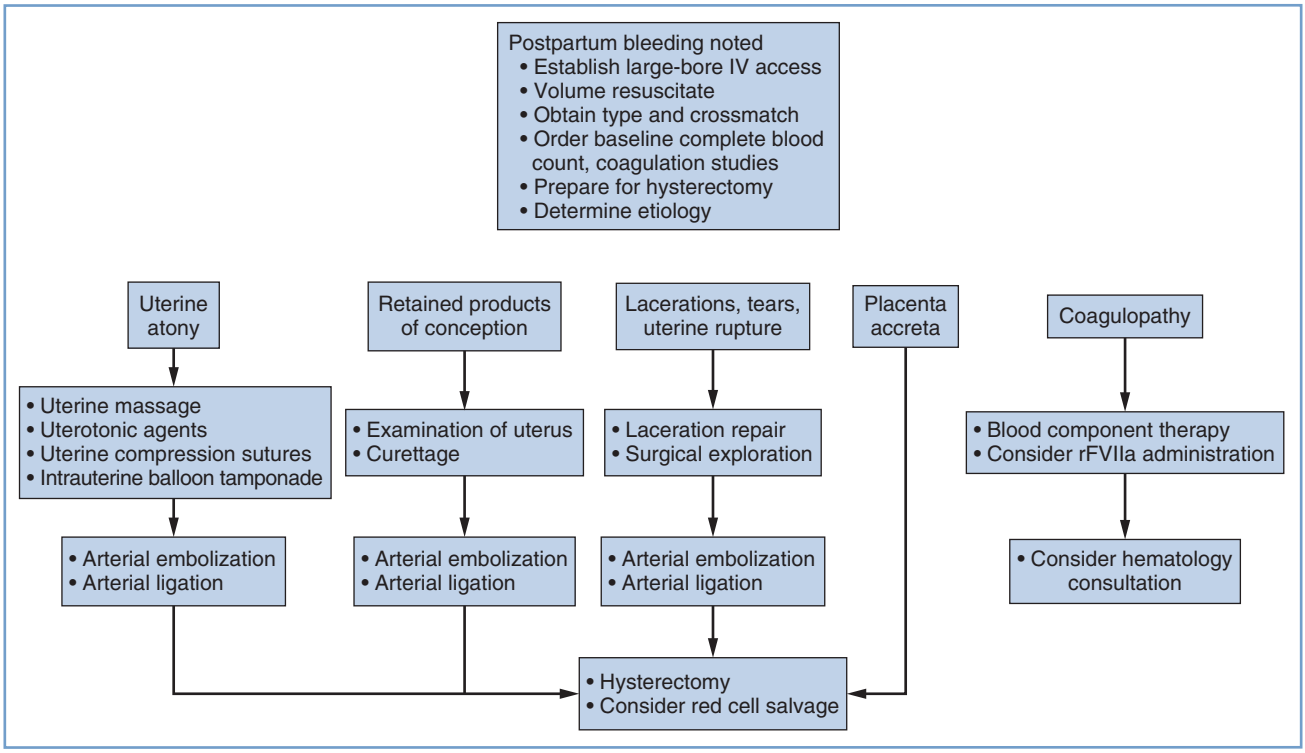

FIGURE 38-2 ■ Management options for postpartum hemorrhage. *IV,* intravenous.

an overview of the obstetric management of postpartum hemorrhage.

Uterine Atony

Epidemiology

Uterine atony is the most common cause of severe postpartum hemorrhage, accounting for approximately 80% of cases.[10,11] In addition to normal hemostatic mechanisms, postpartum hemostasis involves the release of endogenous uterotonic agents—primarily oxytocin and prostaglandins—that contract the uterus and constrict uterine vessels. Uterine atony represents a failure of this process. In addition, parturients with obstetric hemorrhage may have uterine arteries that are relatively unresponsive to vasoconstrictor substances.[76] Box 38-3 lists conditions associated with uterine atony.

Diagnosis

A soft, poorly contractile uterus and vaginal bleeding are the most common findings in patients with uterine atony. The absence of vaginal bleeding does not exclude this disorder because the atonic, engorged uterus may contain more than 1000 mL of blood. Unrecognized bleeding may manifest initially as tachycardia; worsening hypovolemia eventually leads to hypotension (see Table 38-1).

Obstetric and Anesthetic Management

Prophylaxis. The American College of Obstetricians and Gynecologists (ACOG) recommends prophylactic administration of uterotonic agents to prevent uterine atony.[75] **Active management of the third stage of labor**, including uterine massage and oxytocin administration, decreases blood loss and transfusion requirements compared with expectant management.[77,78]

BOX 38-3 Conditions Associated with Uterine Atony

Obstetric Management
- Cesarean delivery
- Induced labor
- Augmented labor

Obstetric Conditions
- Multiple gestation
- Macrosomia
- Polyhydramnios
- High parity
- Prolonged labor
- Precipitous labor
- Chorioamnionitis

Maternal Comorbidities
- Advanced maternal age
- Hypertensive disease
- Diabetes

Other
- Tocolytic drugs*
- High concentration of volatile halogenated anesthetic agent

*β-adrenergic agonists, magnesium sulfate.

Oxytocin is the first-line drug for prophylaxis and treatment of uterine atony after delivery of a third-trimester pregnancy. The number of high-affinity receptors for oxytocin increases greatly near term; alternative uterotonics are more effective in the first and second trimesters of pregnancy. Endogenous oxytocin is a 9-amino acid polypeptide produced in the posterior pituitary. The exogenous form of the drug (Pitocin, Syntocinon) is a synthetic preparation with a rapid onset and short half-life. Unfortunately, exogenous oxytocin can be associated with serious side effects, including tachycardia, hypotension, myocardial ischemia, and, rarely, death, especially in hypovolemic or other hemodynamically compromised women[79-83]; many of these adverse effects are directly related to the dose of oxytocin.[84,85] Preeclamptic women may be less able to tolerate high doses of oxytocin than healthy women.[86] In addition, high doses of oxytocin administered concomitantly with large volumes of intravenous fluids, especially those containing free water, can lead to hyponatremia, seizures, and coma because of oxytocin's structural similarity to vasopressin.[87]

The dose of oxytocin required to generate satisfactory uterine tone after delivery is lower than previously thought (see Chapter 26). In a study of nonlaboring women undergoing elective cesarean delivery, the ED_{90} of bolus dose oxytocin for satisfactory uterine tone within 3 minutes of delivery was 0.35 international units (IU)[88]; The ED_{90} was approximately 3 IU in laboring women undergoing cesarean delivery for labor arrest after labor augmentation with oxytocin.[89] The ED_{90} of oxytocin administered via infusion without a bolus dose in nonlaboring women was approximately 0.3 IU/min for 1 hour.[90] Munn et al.[91] randomized women undergoing a cesarean delivery during labor to receive a prophylactic infusion of oxytocin at 2.67 IU/min or 0.33 IU/min for 30 minutes after delivery; the higher dose was associated with less need for secondary uterotonics (19% versus 39%, respectively; $P < .001$); however, the high dose may be associated with clinically significant tachycardia and hypotension (see later discussion).

Oxytocin is rapidly metabolized by hepatic oxytocinases and cleared in the urine and bile, resulting in a half-life of less than 6 minutes. Consequently, a prolonged intravenous infusion may be more effective than bolus administration in preventing uterine atony. In an international randomized, controlled trial, Sheehan et al.[92] found that the addition of a 4-hour maintenance infusion of 0.17 IU/min (after an initial 5-IU bolus dose) decreased the need for secondary uterotonics compared with a 5-IU bolus dose alone.[92] King et al.[93] studied women at high risk for postcesarean uterine atony and demonstrated that administering a 5-IU bolus of oxytocin before a 1.3-IU/min infusion did not provide benefit compared with an infusion without a bolus. Administration of phenylephrine with oxytocin can mitigate the adverse hemodynamic consequences of oxytocin,[94] but phenylephrine may not be necessary as long as an oxytocin bolus dose is avoided and the infusion rate is maintained below 1 IU/min, the threshold at which hemodynamic consequences become apparent.[84]

Data demonstrating lower oxytocin dose requirements than previously assumed and awareness of the dangers of high-dose administration call into question the common practice of injecting 10 to 40 IU of oxytocin into a 1-liter crystalloid solution and infusing the solution at an unspecified rate, often "wide open" (i.e., gravity-dependent flow). The doses administered with this method may approach those achieved with bolus administration. At my institution, my colleagues and I administer prophylactic oxytocin at a rate of 0.3 IU/min (the ED_{90}) and increase the rate to 0.6 IU/min (twice the ED_{90}) if there is inadequate response. The maximum beneficial oxytocin infusion rate to treat persistent uterine atony is unknown.

Carbetocin is an alternative synthetic oxytocin-receptor agonist available in Canada, the United Kingdom, and other developed countries but not the United States. A meta-analysis comparing carbetocin with oxytocin suggests that carbetocin reduces the need for secondary uterotonics[95]; this difference may reflect the fact that equipotent dosing regimens have not been determined. Carbetocin has a longer duration of action than oxytocin; therefore, prolonged infusion is not necessary.

Treatment. Despite preventive measures, postpartum uterine atony may occur. A multidisciplinary response to atony is imperative. General resuscitative measures include (1) additional large-bore intravenous access, (2) intravenous administration of crystalloid and colloid solutions and vasopressors, (3) laboratory determination of hemoglobin concentration or hematocrit and assessment of coagulation status, and (4) blood bank preparation of blood products for transfusion. Bimanual compression and massage of the uterus and continued infusion of oxytocin may be helpful in restoring uterine tone. Unfortunately, few high-quality data exist to guide therapy if these management strategies fail; current practice relies on expert opinion and clinical judgment. In the case of inadequate response to oxytocin, additional uterotonic agents should be employed. Three classes of drugs are currently available for the treatment of uterine atony: oxytocin, ergot alkaloids, and prostaglandins (Table 38-3).

The **ergot alkaloids** comprise one class of drugs used for the treatment of uterine atony. The natural ergot alkaloids are produced by a fungus that commonly infests rye and other grains. Ergonovine and methylergonovine (a semisynthetic preparation) are the two ergot alkaloids currently available for use; their pharmacologic profiles are identical. Ergot alkaloids are unstable unless they are refrigerated.[96] Both drugs are dispensed in ampules containing 0.2 mg. They have a rapid onset when administered via the intramuscular route. Bolus intravenous administration is **not** recommended. The uterotonic effect usually lasts for 2 to 4 hours.

Both drugs rapidly produce tetanic uterine contractions and for this reason are restricted to postpartum use. The mechanism of action is poorly understood, but the uterotonic effect is most likely mediated by alpha-adrenergic receptor stimulation.[97] Parenteral administration of an ergot alkaloid is associated with a high incidence of nausea and vomiting.[98] Administration by any route may cause serious cardiovascular system derangements, including vasoconstriction, hypertension,[98] myocardial ischemia and infarction due to

TABLE 38-3 **Drug Therapy for Uterine Atony**

Agent	Dose and Route	Relative Contraindications	Side Effects	Notes
Oxytocin	0.3-0.6 IU/min IV infusion	None	Tachycardia Hypotension Myocardial ischemia Free water retention	Short duration of effect
Ergonovine or methylergonovine	0.2 mg IM	Hypertension Preeclampsia Coronary artery disease	Nausea and vomiting Arteriolar constriction Hypertension	Long duration of action May be repeated once after 1 h
15-Methylprostaglandin $F_{2\alpha}$	0.25 mg IM	Reactive airway disease Pulmonary hypertension Hypoxemia	Fever Chills Nausea and vomiting Diarrhea Bronchoconstriction	May be repeated every 15 min up to 2 mg
Misoprostol	600-1000 μg per rectum, sublingual, or buccal	None	Fever Chills Nausea and vomiting Diarrhea	Off-label use

IM, intramuscular; *IV,* intravenous.

coronary vasospasm,[99-101] cerebrovascular accidents,[102] seizures,[102] and even death.[99,103] Patients at greatest risk are those with preexisting hypertension; however, sudden and marked hypertension may also occur in previously normotensive patients. The combination of an ergot alkaloid followed by a vasopressor has been reported to lead to exaggerated hypertension.[104] Relative contraindications to the use of ergot alkaloids include hypertension, preeclampsia, peripheral vascular disease, and ischemic heart disease. Treatment of ergot-induced vasoconstriction and hypertension may require administration of a potent vasodilator such as nitroglycerin or sodium nitroprusside. Blood pressure and the electrocardiogram should be monitored closely after administration.

Prostaglandins of the E and F families have gained wide acceptance as escalation therapy when high-dose oxytocin is inadequate. Concentrations of endogenous prostaglandins increase during labor, but levels do not peak until the time of placental separation. It is hypothesized that uterine atony may represent a failure of prostaglandin concentrations to increase during the third stage of labor in some women.[105,106] Prostaglandins increase myometrial intracellular free calcium concentration,[107] ultimately leading to an increase in myosin light-chain kinase activity. Common side effects noted after administration of prostaglandins include fever, chills, diarrhea, nausea, and vomiting.[108,109]

A prostaglandin commonly used for the treatment of refractory uterine atony is **15-methyl prostaglandin $F_{2\alpha}$,** or carboprost; its administration may succeed in controlling hemorrhage when all other pharmacologic treatments have failed.[108,110] The recommended dose is 0.25 mg (250 μg) administered intramuscularly, which may be repeated every 15 to 30 minutes; the total dose should not exceed 2 mg (eight doses). Unfortunately, this valuable agent may precipitate bronchospasm, abnormal ventilation-perfusion ratio, increased intrapulmonary shunt fraction, and hypoxemia in susceptible patients.[111,112]

Misoprostol is a prostaglandin E_1 analogue that has been used successfully for cervical ripening and induction of labor. Misoprostol is thermostable in tropical conditions and does not require intravenous access for administration; prophylactic misoprostol administration reduced the incidence of postpartum hemorrhage compared with placebo.[113] These characteristics make it an attractive alternative to oxytocin and ergot alkaloids in low-resource areas, where the rate of maternal mortality from hemorrhage is high[1,2,113]; however, parenteral oxytocin is more effective for postpartum hemorrhage prophylaxis than misoprostol (relative risk [RR] of hemorrhage, 1.34; 95% confidence interval [CI], 1.16 to 1.55).[113]

Whether misoprostol can also decrease bleeding in patients with postpartum uterine atony unresponsive to conventional uterotonics is unclear.[114] A large international randomized controlled trial failed to identify any benefit of misoprostol 600 μg administered sublingually in addition to oxytocin for treatment of postpartum hemorrhage.[109] A second randomized controlled trial suggested that misoprostol may be less effective than the combined administration of ergometrine and oxytocin for the treatment of postpartum hemorrhage.[115] A dose of 600 to 1000 μg per rectum is commonly administered; administration via the oral, buccal, and sublingual routes has been described.[75,113,114] Like other prostaglandins, misoprostol may be associated with fever, chills, nausea, vomiting, and diarrhea.[109,113,114] Misoprostol may have a more favorable side effect profile than ergonovine or 15-methyl prostaglandin $F_{2\alpha}$ in patients with hypertension and/or reactive airway disease.

If hemorrhage and atony persist despite aggressive administration of multiple classes of uterotonic drugs, invasive techniques must be considered. Invasive techniques include intrauterine balloon tamponade, uterine compression sutures, embolization of the arteries supplying the uterus, surgical ligation of arteries, and cesarean hysterectomy (see later discussion).

Genital Trauma

The most common childbirth injuries are lacerations and hematomas of the perineum, vagina, and cervix. Most

injuries have minimal consequence, but some puerperal lacerations and hematomas are associated with significant hemorrhage, either immediate or delayed.[116] Prompt recognition and treatment can minimize morbidity and mortality.[116] Genital tract lacerations should be suspected in all patients who have vaginal bleeding despite a firm, contracted uterus. The cervix and vagina must be inspected carefully in these patients. Computed tomography (CT) and/or MRI may be useful in detecting the presence, location, and extent of suspected hematoma.[117] Pelvic hematomas may be divided into four types: vaginal, vulvar, vulvovaginal, and retroperitoneal.[116]

Vaginal hematomas result from soft tissue injury during delivery, and they may involve bleeding from the descending branch of the uterine artery.[116,118] The use of forceps or vacuum extraction increases the risk.[118] A study in Sweden of all cases of vaginal hematoma from 1987 to 2000 found a prevalence of approximately 1 in 1240 deliveries.[119] The investigators identified nulliparity, advanced maternal age, and neonatal birth weight exceeding 4000 g as risk factors for vaginal hematoma. Other risk factors may include prolonged second stage of labor, multiple gestation, preeclampsia, and vulvovaginal varicosities.[116]

Vulvar hematomas commonly involve branches of the pudendal artery.[116] Injury is usually suggested by extreme pain or clinical manifestations of hypovolemia secondary to blood loss.[116] Small vaginal or vulvar hematomas that are not enlarging may be observed and treated conservatively with ice packs and oral analgesics. Large hematomas should be incised and evacuated. Bleeding vessels should be ligated. Often no specific bleeding source can be identified. The successful use of arterial embolization to decrease bleeding and aid in surgical management of genital tract hematomas has recently been reported.[118] Volume resuscitation and transfusion may be necessary.[116]

Retroperitoneal hematomas are the least common and most dangerous hematomas associated with childbirth. A retroperitoneal hemorrhage occurs after laceration of one of the branches of the hypogastric artery. Injury typically occurs during cesarean delivery or rarely after rupture of a low transverse uterine scar during labor. These hematomas may be large and may extend as far as the kidneys.

The symptoms of concealed bleeding depend on the size of the hematoma and the rate at which it forms. In some instances, abrupt hypotension may be the first sign of bleeding. The diagnosis of a retroperitoneal hematoma must be considered whenever a postpartum patient has an unexpected decrease in hematocrit or unexplained tachycardia and hypotension. Other signs and symptoms are restlessness, lower abdominal pain, a tender mass above the inguinal ligament that displaces a firm uterus to the contralateral side, and vaginal bleeding with hypotension out of proportion to the external blood loss. Ileus, unilateral leg edema, urinary retention, and hematuria also may occur.[116] A high index of suspicion is needed; in obese women it may be especially difficult to examine the abdomen for signs of retroperitoneal hematoma.

Occasionally, a retroperitoneal hematoma may be self-limiting and need no surgical intervention. Life-threatening hematomas require exploratory laparotomy and ligation of the hypogastric vessels. Fliegner[120] reported that 38 of 39 patients with a broad ligament hematoma received a blood transfusion. The average amount administered was 4000 mL. Eight (21%) of the patients required a hysterectomy.

Anesthetic Management

Choice of anesthetic technique for the repair of genital lacerations and evacuation of pelvic hematomas depends on the affected area, surgical requirements, volume/hemodynamic status of the patient, and urgency of the procedure. Local infiltration and a small dose of intravenous opioid suffice for drainage of some vulvar hematomas; however, repair of extensive lacerations and drainage of vaginal hematomas require significant levels of analgesia or anesthesia. Pudendal nerve block may not be technically feasible because of anatomic distortion or severe pain from the hematoma. Low doses of ketamine (10-mg boluses, not exceeding a total dose of 0.5 mg/kg) may suffice to produce sedation and analgesia with minimal risk for altering airway reflexes. Spinal or epidural anesthesia may be necessary, although the clinician should exercise caution initiating (or extending) a neuraxial block in a hypovolemic patient. In some cases, general anesthesia with tracheal intubation may be necessary. Exploratory laparotomy for a retroperitoneal hematoma typically requires the administration of general anesthesia.

Retained Placenta

Retained placenta is defined as failure to deliver the placenta completely within 30 minutes after delivery of the infant and occurs in approximately 3% of vaginal deliveries.[121,122] Retained placenta is a leading cause of both primary and secondary postpartum hemorrhage. The risk for postpartum hemorrhage increases significantly if the interval between delivery of the infant and the placenta exceeds 30 minutes.[121] The severity of bleeding ranges from minimal to severe and can be life-threatening and require transfusion.[122] Risk factors for retained placenta include history of retained placenta, preterm delivery, oxytocin use during labor, preeclampsia, and nulliparity.[121,122]

Obstetric Management

Treatment of retained placenta during the early postpartum period often involves manual removal and inspection of the placenta. Curettage may be required. After removal of the placenta, uterine tone should be augmented with oxytocin and the patient should be observed for evidence of recurrent hemorrhage.

Anesthetic Management

Choice of anesthetic technique depends on the degree of hemorrhage. In some cases, the administration of small amounts of sedatives and analgesics is adequate to allow examination and manual placental extraction by a skilled obstetrician. Neuraxial anesthesia may be considered in patients who are not bleeding severely and who are

hemodynamically stable. This may be accomplished with either administration of additional local anesthetic through an existing labor epidural catheter or initiation of spinal anesthesia. General anesthesia sometimes becomes necessary, particularly in patients who are hemodynamically unstable.

In some cases, the obstetrician requires uterine relaxation to facilitate manual removal of the placenta. Historically, anesthesia providers have performed rapid-sequence induction of general anesthesia, followed by the administration of a high dose of volatile halogenated agent to relax the uterus. Equipotent doses of halothane, sevoflurane, and desflurane depress uterine contractility equally and in a dose-dependent manner. In a study of isolated human uterine muscle, an equi-anesthetic concentration of isoflurane was a less effective uterine relaxant than the other volatile agents.[123] Uterine contractility is decreased by 50% with administration of approximately 1.5 minimum alveolar concentration (MAC) of a volatile anesthetic agent.[123] The induction of general anesthesia and administration of a volatile halogenated agent results in rapid onset of uterine relaxation, and discontinuation of the volatile agent results in rapid offset when uterine relaxation is no longer necessary. However, induction of general anesthesia in a parturient entails risk for failed ventilation, failed tracheal intubation, and/or aspiration of gastric contents.

Alternatively, **nitroglycerin** may be administered for uterine relaxation. Nitroglycerin provides a rapid onset of reliable smooth muscle relaxation and a short plasma half-life (2 to 3 minutes).[124,125] Nitroglycerin has been administered for various obstetric emergencies without clinically significant side effects.[125] Peng et al.[126] described successful removal of retained placenta in 15 parturients after administration of intravenous nitroglycerin 500 μg. DeSimone et al.[127] used a substantially smaller dose of nitroglycerin (50 to 100 μg) with similar results; all patients were managed successfully without the need for induction of general anesthesia. Nitroglycerin may also be administered sublingually via spray or tablet. A double-blind, randomized, controlled study compared sublingual nitroglycerin with placebo for management of retained placenta[128]; the placenta was delivered successfully within 5 minutes in all 12 of the parturients who received nitroglycerin, compared with only 1 of the 12 who received placebo. Nitroglycerin most likely produces uterine smooth muscle relaxation by releasing nitric oxide; it may require the presence of placental tissue to be effective.[129]

Uterine Inversion

Epidemiology

Uterine inversion, or the turning inside-out of all or part of the uterus, is a rare but potentially disastrous event. It is associated with severe postpartum hemorrhage, and hemodynamic instability may be worsened by concurrent vagal reflex–mediated bradycardia. Inversions may be acute or chronic, but only acute peripartum inversions involve the obstetric anesthesia provider. The reported incidence of this disorder varies widely; recent reports suggest an incidence of approximately 1 in 2500 deliveries.[130]

Risk factors for uterine inversion include uterine atony, a short umbilical cord, uterine anomalies, and overly aggressive management of the third stage of labor, including maneuvers such as inappropriate fundal pressure or excessive umbilical cord traction.[130] Uterotonic therapy can convert a partial inversion to a complete inversion. An abnormally implanted placenta (i.e., placenta accreta) may be first recognized when uterine inversion occurs.

Diagnosis

Many cases of uterine inversion are obvious because of hemorrhage and a mass in the vagina, but others may not be readily apparent. Inversion should be suspected in all cases of postpartum hemorrhage. Ultrasonographic examination may show characteristic findings, such as an echolucent zone within an echogenic mass filling the uterine cavity on transverse view.[131] Historically, obstetricians have stated that the shock is out of proportion to the blood loss, but an underestimation of obstetric hemorrhage is more likely. An incomplete inversion not protruding through the introitus is more likely to result in missed or delayed diagnosis.[116]

Obstetric Management

Immediate replacement of the uterus, even before removal of the placenta, is the treatment goal, but it may be difficult to achieve. The appropriate technique for correcting an inversion has been described.[130] All uterotonic drugs should be discontinued immediately. The obstetrician should attempt to right the inversion by applying pressure through the vagina to the uterine fundus; ring forceps may be used on the cervix to apply countertraction. Early diagnosis and prompt correction may reduce the morbidity and mortality associated with uterine inversion.

Anesthetic Management

Often, uterine tone precludes replacement of the uterus, and uterine relaxation is necessary for successful uterine reduction.[130] The use of nitroglycerin to facilitate relaxation and replacement of the uterus has been reported.[132,133] Fairly large intravenous doses (200 to 250 μg) may be required, and the anesthesiologist typically will need to support the circulation with intravenous fluids and vasopressors. Administration of general anesthesia with a volatile halogenated agent may become necessary, not only for uterine relaxation but also to prepare for laparotomy should it become necessary to correct the inversion. Once the uterus has been replaced, a firm, well-contracted uterus is desired.[130] Oxytocin should be infused, and additional uterotonic drugs may be needed.

Placenta Accreta

Placenta accreta is defined as a placenta that in whole or in part invades the uterine wall and is inseparable from it.[134] Three types of placenta accreta occur (Figure 38-3).

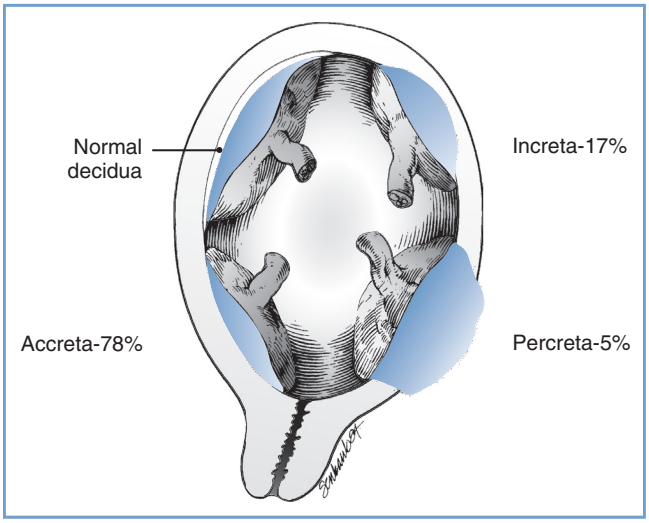

FIGURE 38-3 ■ Uteroplacental relationships found in abnormal placentation. (From Francois KE, Foley MR. Antepartum and postpartum hemorrhage. In Gabbe SG, Niebyl JR, Simpson JL, et al., editors. Obstetrics: Normal and Problem Pregnancies. 6th edition. Philadelphia, Elsevier Saunders, 2012:424.)

Placenta accreta vera is defined as adherence of the basal plate of the placenta directly to uterine myometrium without an intervening decidual layer. **Placenta increta** refers to a placenta in which chorionic villi invade the myometrium. **Placenta percreta** represents invasion through the myometrium into serosa and sometimes into adjacent organs, most often the bladder.[134]

Epidemiology

Evidence suggests that the incidence of placenta accreta is rising, primarily because of the increasing cesarean delivery rate. Between 1994 and 2007 the rate of peripartum hysterectomy for abnormal placentation increased by 20% in the United States, an increase entirely explained by adjustment for the rising prevalence of previous cesarean delivery among childbearing women.[15] The percentage of U.S. cesarean deliveries increased from 20.7% in 1997 to 32.9% in 2009, owing to increases in both primary and repeat cesarean deliveries and a decrease in the TOLAC rate.[135-137] Fortunately, the cesarean delivery rate remained stable between 2009 and 2012.[138]

Previous cesarean delivery or other uterine surgery increases the risk for both placenta previa and accreta. The combination of placenta previa with previous cesarean delivery synergistically increases the risk for coexisting placenta accreta, particularly if the placenta is anterior and overlies the uterine scar. In a prospective multicenter observational study, Silver et al.[25] determined the relationship between placenta accreta, placenta previa, and previous cesarean delivery. Placenta previa with no prior uterine surgery conferred a 3% risk for placenta accreta. In women with placenta previa and one previous cesarean delivery, the risk for placenta accreta was 11%. In patients with placenta previa and a history of two previous cesarean deliveries, the incidence of placenta accreta was increased to 40%. The incidence of placenta accreta was over 60% in women with placenta previa and a history of three or more previous cesarean deliveries (see Table 38-2). Another study noted a relationship between the extent of uterine wall invasion and the number of previous cesarean deliveries.[139]

Diagnosis

In some cases of placenta accreta the condition is first suspected at vaginal delivery, when the obstetrician notes difficulty in separating the placenta. The definitive diagnosis is then made at laparotomy. Antenatal diagnosis of placenta accreta facilitates effective planning. Antenatal diagnosis is associated with less maternal and neonatal morbidity, including decreased blood loss at delivery and transfusion of fewer units of blood products.[140] Ultrasonography is a useful screening tool in patients with placenta previa and/or previous cesarean delivery and is the primary imaging modality used for making the diagnosis of placenta accreta. However, among women at risk for placenta accreta, ultrasonography has imperfect sensitivity and specificity.[134] Some evidence suggests that MRI may help confirm the diagnosis in at-risk patients with inconclusive ultrasonographic examinations.[141]

Obstetric Management

The ACOG advises that providers working at small hospitals without adequate blood bank supplies consider transferring patients with placenta accreta to a tertiary care facility.[134] Patients treated at institutions with a 24-hour in-house obstetrician and anesthesiologist, immediate availability of a gynecologic oncologist, a fully stocked blood bank, and interventional radiology services suffer less morbidity than those treated at hospitals without these services.[142] Planned delivery with all of the necessary multidisciplinary collaborators present compared with emergency delivery is associated with less maternal morbidity, including fewer transfusions, complications, and intensive care unit admissions. Some cases of vaginal bleeding remote from term resolve spontaneously, and expectant management may prolong the duration of pregnancy, at least into the third trimester. However, the risk for severe antenatal bleeding increases as gestational length increases.[142] Timing of delivery therefore involves balancing this risk against the neonatal risks of preterm delivery. Institutions that manage women with suspected placenta accreta expectantly must have the capacity to mobilize the entire perioperative team at any time.

Most patients with known placenta accreta should undergo planned preterm cesarean delivery and hysterectomy with the placenta left *in situ* because attempts to remove the placenta are likely to initiate hemorrhage. Because the positive predictive value of ultrasonography may be low, the ACOG advises that it is reasonable to await spontaneous placental delivery in some cases, but manual removal of the placenta should be avoided.[134] Preoperative placement of ureteral stents may minimize urinary tract injury.[134] A midline vertical skin incision may provide optimal surgical exposure; it may be necessary to modify the uterine incision to avoid cutting through the placenta.

The preoperative insertion of **internal iliac artery balloon catheters** is controversial. Optimally, the

balloons are inflated after delivery as a means to provide a less bloody surgical field and decrease blood loss and transfusion requirements. Retrospective cohort studies have reported conflicting data regarding effects of balloon catheter placement on estimated blood loss, transfusion requirements, and duration of the surgical procedure.[143-146] The largest of these studies compared 59 patients who had placement of preoperative balloon catheters with 58 who did not and determined there was lower mean estimated blood loss, fewer cases with estimated blood loss greater than 2500 mL, and fewer massive transfusions in the balloon group.[146]

Multiple complications can arise from the placement of these devices, some of them involving serious disruptions of the vasculature and lower extremity ischemia.[144,146-148] Introduction of the arterial catheters (without inflation) can cause fetal bradycardia, necessitating emergency delivery.[149] If employed, therefore, internal iliac artery balloon catheters should be placed in the operating room to avoid dislodgement during transport and to allow for rapid delivery should fetal compromise occur. Authors of a recent review of the literature opined that current evidence, confined to case reports, case series, and small retrospective studies, is inadequate to guide clinical decision-making.[150] The Society of Maternal-Fetal Medicine (SMFM) recommends reserving the use of prophylactic intra-arterial balloon catheters for well-counseled women with a strong desire for fertility preservation, those who decline blood products, and those with unresectable placenta percreta.[151]

Two forms of conservative therapy for placenta accreta have been described. In selected patients with a partial placenta accreta, small focal areas of placental invasion may be managed by curettage and oversewing. Alternatively, it may be possible to leave the intact placenta *in situ*, close the uterus and abdomen, and await spontaneous placental involution.[152-154] However, conservatively managed patients often require additional therapies such as internal iliac artery balloon inflation, embolization, or methotrexate. Some patients treated in this way have subsequently had successful pregnancies[152]; however, complications have been reported, including secondary hemorrhage, subsequent need for hysterectomy, and sepsis.[152,154] The ACOG considers planned peripartum hysterectomy to be the management of choice for patients with placenta accreta and cautions the obstetrician to reserve uterine conservation strategies for hemodynamically stable patients who strongly desire future fertility.[134]

Anesthetic Management

Anesthetic management is similar to other cases of severe postpartum hemorrhage and peripartum hysterectomy (see later discussion). Preoperative suspicion for placental implantation abnormalities should alert the anesthesia provider to the potential for massive blood loss. One group of investigators reported that estimated blood loss exceeded 2000 mL in 66% of cases of placenta accreta, 5000 mL in 15%, 10,000 mL in 6.5%, and 20,000 mL in 3% of cases.[155] Initial blood loss may be minimal but can rapidly become torrential if the placental bed is disturbed or if the surgeons encounter unavoidable placental tissue during the course of the hysterectomy.

Invasive Treatment Options

Regardless of the cause of obstetric hemorrhage, first-line conservative measures may fail to control bleeding. In these cases, invasive procedures must be performed promptly to avoid severe morbidity and mortality. Second-line options include intrauterine balloon tamponade, uterine compression sutures, angiographic arterial embolization, and uterine artery and/or internal iliac artery ligation, performed in an attempt to avoid hysterectomy. Unfortunately, no randomized controlled trials assessing relative efficacy and safety of these options exist to guide management.[156,157]

Intrauterine balloon tamponade is a conservative method for controlling postpartum hemorrhage, especially when uterine atony or lower uterine segment bleeding is suspected.[75] A 2007 systematic review reported the technique is successful (no need for additional therapy) 84% of the time,[156] and a prospective evaluation reported a success rate of 81%.[158] A variety of devices have been used, including a balloon specifically designed for this purpose.[159] An intrauterine balloon can be deployed quickly, requires minimal analgesia for both insertion and removal, and preserves fertility. Failure is easily recognized and commonly attributed to prolapse though a partially open cervix; in such cases, the balloon may be replaced and secured by applying bilateral ring forceps to the cervix[160] or by placing a cervical cerclage.[161] Few complications have been reported, although concerns for infection exist.[156,157] A case report described uterine rupture after curettage and subsequent tamponade balloon placement.[162]

Uterine compression sutures (e.g., B-Lynch suture[163]) are most useful in cases of refractory uterine atony but have also been used in cases of retained placenta and accreta.[156,157] A systematic review—based mostly on case reports and case series and therefore subject to reporting bias—estimated a 92% success rate for this procedure,[156] but the success rate (avoidance of hysterectomy) in a prospective population-based trial was more modest (75%).[164] The suture may slip off of the uterine fundus and fail to provide compression.[157] Placement of compression sutures may preserve fertility; however, data are lacking on the long-term effects on fertility and pregnancy outcomes. Complications include infection, uterine necrosis, and suture erosion.[157]

Angiographic arterial embolization may be appropriate if moderate blood loss continues and if the patient is stable for transport to the interventional radiology suite. The uterine arteries, which are branches of the anterior trunk of the internal iliac arteries, provide the primary blood supply to the uterus. The ovarian and vaginal arteries also make a sizable contribution to uterine blood flow during pregnancy. During angiography the radiologist can identify the vessels responsible for bleeding and embolize these vessels effectively with gelatin sponge pledgets (Gelfoam). A small percentage of cases may require placement of a metallic coil in addition to gelatin sponges. The gelatin sponge is a temporary

occlusive agent, and flow through these vessels returns over time, preserving both the uterus and fertility.[165] Published success rates in emergently controlling postpartum hemorrhage with this approach vary between 70% and 100%.[156,157] Successful treatment of acute postpartum hemorrhage with this modality requires rapid access to an angiography facility and a skilled interventional radiologist. The patient must be observed and monitored carefully while undergoing the procedure. Ischemic complications of embolization therapy have been reported, but the risk is reduced with the use of selective techniques.[156,166,167]

Bilateral surgical ligation of the uterine arteries (O'Leary sutures) may be used to control bleeding at laparotomy. In the case of failure to control bleeding, the surgeon may proceed with a more complex procedure that involves ligation of the tubo-ovarian and ascending and descending uterine arteries. Internal iliac artery ligation may also be considered, although it is more difficult to perform.[157] Reported success rates are highly variable, and it appears that arterial ligation is being used less often than in the past.[75] The rich collateral circulation of the uterus at term most likely contributes to failure to control bleeding, as does the challenging nature of the procedure itself. Engorgement of pelvic viscera, variability in vascular anatomy, and the increased blood flow during pregnancy contribute to the risk of complications when this approach is used. Successful surgical ligation permits preservation of fertility. Ischemic complications and neuropathy have been reported.[156]

Peripartum Hysterectomy

Peripartum hysterectomy is the definitive treatment for postpartum hemorrhage unresponsive to medical and other invasive therapies. The two most common indications for this procedure are uterine atony and placenta accreta.[15] Between 1994 and 2007 the overall rate of peripartum hysterectomy increased by 15% in the United States, because of a 130% increase in hysterectomy for atony and a 23% increase in hysterectomy for placental implantation abnormalities.[15] The increase in hysterectomy for placental abnormalities is almost entirely explained by an increase in the cesarean delivery rate.[15] Parturients with a history of previous cesarean delivery are more than five times as likely to require a peripartum hysterectomy than those without this history, and risk for hysterectomy rises progressively with an increasing number of previous cesarean deliveries.[15,25] The incidence of peripartum hysterectomy due to uterine rupture has declined in the United States because the rate of TOLAC has declined.[15] Elective peripartum hysterectomy may also be undertaken for concurrent gynecologic abnormalities, especially malignancies.

Peripartum hysterectomy is a technically challenging operation; the uterus is enlarged, exposure may be difficult, the vessels are engorged, and the pregnant uterus receives a rich collateral blood supply. The presence of dense adhesions from previous surgeries can further complicate the surgery. A 2010 systematic review of emergency postpartum hysterectomy for hemorrhage revealed a perioperative morbidity rate of 56% and a mortality rate of 2.6%.[168] Compared with nonobstetric hysterectomy, patients undergoing obstetric hysterectomy are more likely to suffer postoperative hemorrhage and require blood transfusion, have intraoperative urinary tract injury, and experience perioperative complications such as wound infection, venous thromboembolism, and cardiovascular and other medical complications.[169] Mortality is more than 25 times higher in peripartum than nonperipartum hysterectomy.[169]

Transfusion is required in 44% or more of patients.[168] Emergency peripartum hysterectomy is associated with increased blood loss, worse coagulopathy, and increased transfusion rates compared with elective peripartum hysterectomy.[170] A multicenter review showed that the mean blood loss for emergency obstetric hysterectomy was 2526 mL, with a mean transfusion requirement of 6.6 units of PRBCs; in elective procedures, the mean blood loss was 1319 mL and the average replacement was 1.6 units of PRBCs (Table 38-4).[170]

Owing to the challenging technical aspects of the procedure, the obstetrician may elect to perform a subtotal hysterectomy, wherein the cervix is left *in situ*. Subtotal approaches are associated with fewer urinary tract and other operative injuries and a shorter length of stay,[168,169] but greater mean transfusion requirements and more frequent rates of reoperation than total hysterectomy.[169] Subtotal hysterectomy is not appropriate for patients with bleeding from the cervix, lower uterine segment, or both (e.g., implantation of the placenta on the lower uterine segment).

Manual compression of the aorta can be a lifesaving procedure in the event of catastrophic obstetric hemorrhage.[171] Effective aortic compression against a vertebral body in the upper abdomen should decrease blood flow to the pelvis, thereby allowing hemodynamic and hemostatic resuscitation and surgical control.[172] An aortic cross-clamp requires vascular surgery expertise and retroperitoneal dissection but may be necessary to achieve hemostasis. Mild cardiac and renal dysfunction have been noted in nonobstetric patients if the aortic cross-clamp time exceeds 50 minutes[173]; if a prolonged clamp time is required, the anesthesiologist should prepare for lactic acidosis and hemodynamic instability at the time the clamp is released. Advanced surgical techniques to control friable, engorged blood vessels include felt or Teflon pledgets to buttress sutures, the rapid application of straight clamps, and the application of high-pressure surgical sealants.[172,174]

Anesthetic Management. Anesthesia for peripartum hysterectomy is frequently challenging because massive blood loss may occur unpredictably.[175] An experienced, skilled team is invaluable and critical to a successful outcome. An experienced team may elect neuraxial anesthesia in a properly prepared patient. Intraperitoneal manipulation, dissection, and traction may exceed similar maneuvers required with cesarean delivery alone, leading to pain, nausea, and vomiting. Maintenance of a T4 sensory level of anesthesia and judicious sedation may reduce the need for intraoperative conversion to general anesthesia. In a multicenter study of peripartum hysterectomy, none of the 12 patients who received continuous

TABLE 38-4 Operative Management and Complications of Elective versus Emergency Obstetric Hysterectomies

	Elective (N = 21)	Emergency (N = 21)	*P* Value
Anesthesia			
Epidural	8	4	
Spinal	0	1	
General	13	16	
Operative time (min)	137 ± 55	148 ± 62	NS
Hysterectomy			NS
Total	21	19	
Subtotal	0	2	
Estimated blood loss (mL)	1319 ± 396	2526 ± 1240	< .001
Intraoperative hypotension	6 (29%)	13 (62%)	< .05
Intraoperative crystalloid (mL)	4062 ± 1512	5374 ± 2340	< .05
Intraoperative transfusion	7 (33%)	17 (81%)	< .01
Intraoperative or postoperative transfusion	10 (48%)	18 (86%)	< .01
Total units transfused	1.6 ± 1.9	6.6 ± 5.4	< .001
Discharge hematocrit (%)	30 ± 4	30 ± 4	NS
Intraoperative injury			
Ureteral	1 (5%)	0	NS
Cystotomy	1 (5%)	0	NS
Reoperation required	0	1 (5%)	NS
Days in hospital	5.5 ± 1.3	7.3 ± 4.3	< .05
Mortality	0	0	NS

NS, not significant.
Values are n or mean ± SD.
Modified from Chestnut DH, Dewan DM, Redick LF, et al. Anesthetic management for obstetric hysterectomy: a multi-institutional study. Anesthesiology 1989; 70:607-10.

epidural anesthesia for elective or emergency hysterectomy required intraoperative induction of general anesthesia.[170]

Single-shot spinal anesthesia is unlikely to provide anesthesia of sufficient duration for an unanticipated hysterectomy. Indications for induction of general anesthesia at the beginning of a cesarean hysterectomy include anticipated difficult airway management, antepartum hemorrhage with hemodynamic instability, and known placenta percreta, which may increase the risk for massive hemorrhage and complex surgery.

Patients who have delivered vaginally with preexisting epidural labor analgesia may be managed successfully with extension of epidural blockade, but careful consideration of hemodynamic status should precede the administration of local anesthetics into the epidural space. Animal models suggest that sympatholysis established before the onset of hemorrhage reduces excessive catecholamine response to blood loss and may improve survival.[176] However, the induction of sympatholysis during hemorrhage may compromise end-organ perfusion and even precipitate cardiopulmonary arrest.

As the magnitude of blood loss increases, general anesthesia becomes the anesthetic technique of choice. First, severely hypotensive patients may require tracheal intubation for airway protection. Second, large fluid shifts and massive transfusion may adversely affect oxygenation so that control of ventilation via an endotracheal tube becomes necessary. Third, these same fluid shifts increase airway edema, potentially making failed ventilation/failed tracheal intubation more likely as the surgery proceeds. Fourth, the massive transfusion of blood products often results in the need for coadministration of potent vasopressors and calcium chloride and, thus, central venous access; the placement of a central venous catheter may be more easily accomplished after the induction of general anesthesia. In all cases, patients at risk for peripartum hysterectomy managed with neuraxial anesthesia should be informed in advance that intraoperative discomfort or severe hemorrhage may mandate the intraoperative induction of general anesthesia.

The induction of general anesthesia in the setting of severe hemorrhage requires careful use of small doses of nondepressant induction agents such as ketamine or etomidate. The circulation should be supported with replacement of intravascular volume and vasopressors as needed. A review of maternal deaths from postpartum hemorrhage in France revealed that 5 of 38 deaths followed cardiac arrest on induction of general anesthesia.[177]

Regardless of the anesthetic technique used, two or more large-bore intravenous catheters should be inserted. Invasive blood pressure monitoring may aid in the prompt recognition of hypotension and provide access for frequent blood draws. The blood bank should be alerted to the possible need for massive transfusion. At least 4 units of PRBCs should be immediately available, with additional blood products, including plasma and cryoprecipitate, readily available without delay. The ACOG recommends consideration of intraoperative blood salvage in cases of placenta accreta (see later discussion).[75,134] Vasoactive drugs (e.g., phenylephrine, epinephrine) should be available. Fluid warmers, a forced-air body warmer, and

equipment for rapid infusion of fluids and blood products should be accessible if the care team is anticipating and managing significant blood loss. Teamwork and precise communication are indispensable.

RESPONSE TO HEMORRHAGE

Prevention of Mortality

Data from the U.K. Confidential Enquiry into Maternal and Child Health and the French Confidential Enquiry into Maternal Death reveal that maternal deaths from hemorrhage in high-resource settings are often preventable and associated with substandard care.[5,177] Berg et al.[16] reported that whereas only 40% of all pregnancy-related deaths in the state of North Carolina between 1995 and 1999 were considered preventable, a staggering 93% of deaths due to hemorrhage were judged preventable. The most important factor in preventability of deaths from hemorrhage was management that did not meet the expected standard of care the review committee believed should have been available.[16]

Delays in diagnosis and treatment of postpartum hemorrhage increase the severity of hemorrhage.[17,178,179] In a retrospective structured chart review of 63 women who suffered severe obstetric hemorrhage (defined by > 3 units blood transfused and intensive care unit admission), Della Torre et al.[17] identified clinically significant delays in the diagnosis of hemorrhage in 23% of cases and delays in treatment in 38% of cases. A multicenter cohort study in France evaluated all women who developed postpartum hemorrhage due to uterine atony after vaginal birth to determine risk factors for progression to severe postpartum hemorrhage (defined by a decrease in hemoglobin concentration > 4 g/dL).[179] Patients were more likely to develop severe hemorrhage if oxytocin administration, manual exploration of the uterus, or both were delayed. Delays of more than 10 minutes in summoning either an obstetrician or an anesthesiologist also increased the odds of severity, presumably by delaying treatment. Interestingly, epidural labor analgesia protected against severe hemorrhage, in all likelihood by allowing for more rapid and thorough uterine exploration.[179]

Delays in care most likely result from several factors, including difficulties in accurately estimating blood loss and in diagnosing maternal hypovolemia and shock, lack of aggressive monitoring and treatment of coagulopathy, and poor coordination of team responses.

Practitioners often underestimate the amount of blood loss, with the degree of underestimation increasing as blood loss volume increases (Figure 38-4).[180-183] Accuracy of blood loss estimation can be improved with the use of calibrated collection drapes.[18,184] Clinician education using simulated scenarios with known blood volumes enhances estimation accuracy.[181,183,185] Separation of nonblood fluids (i.e., switching the suction canister after evacuation of amniotic fluid) and weighing pads and bedding may improve assessment. It is imperative that clinicians have a low threshold for the diagnosis of postpartum hemorrhage.

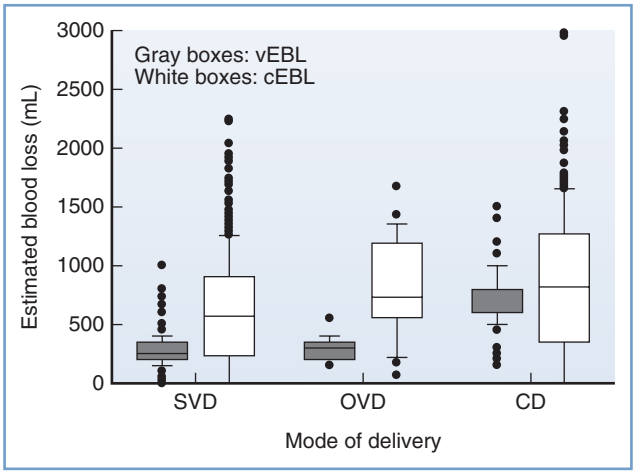

FIGURE 38-4 ■ The visually estimated blood loss (vEBL) and calculated estimated blood loss (cEBL) by mode of delivery. The boxes illustrate the 25th, 50th, and 75th percentiles and the whiskers illustrate the 10th and 95th percentiles. Calculated estimated blood loss was derived by multiplying the calculated maternal blood volume by the percent of blood volume lost, where calculated maternal blood volume = 0.75 × {[maternal height in inches × 50] + [maternal weight in pounds x 25]} and percent of blood volume lost = {predelivery hematocrit – postdelivery hematocrit}/predelivery hematocrit. vEBL was statistically different from cEBL for each degree of laceration and for all modes of delivery, demonstrating an underestimation of vEBL with increasing cEBL. *SVD,* spontaneous vaginal delivery; *OVD,* operative vaginal delivery; *CD,* cesarean delivery. (From Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008; 199:519.e1-7.)

A second potential explanation for delays in diagnosis and treatment relates to difficulties in diagnosing hypovolemic shock in healthy young patients. The American College of Surgeons Trauma Committee's Advanced Trauma Life Support (ATLS) system defines four stages of hypovolemic shock based on degree of blood loss (see Table 38-1).[186] Obstetric patients are often mildly tachycardic, and worrisome rates of tachycardia (> 120 beats per minute) may not develop until the patient has lost 30% to 40% of her total blood volume. Similarly, hypotension and mental status changes are late signs. Findings such as these have led to the use of a modified early obstetric warning system (MEOWS) to detect impending adverse events (Table 38-5).[187] Physiologic variables such as vital signs, oxygenation, and mental status are monitored regularly, and thresholds that trigger clinical evaluation are defined. MEOWS is not specific to hemorrhage. It has a positive predictive value of 39% and a negative predictive value of 98% in predicting maternal morbidity.[187] It is not known whether hemorrhage-specific modifications to the MEOWS would improve outcomes in the setting of obstetric hemorrhage.

Another issue that may lead to delays in care is the speed with which coagulopathy develops in the setting of obstetric hemorrhage. The rapid consumption of coagulation factors, especially fibrinogen, during obstetric hemorrhage has prompted experts to recommend early monitoring for, and aggressive treatment of, coagulopathy, especially hypofibrinogenemia.[53,188] Postpartum hemorrhage and other placental bed bleeding such as

TABLE 38-5 Trigger Thresholds for MEOWS Parameters

	Red Trigger*	Yellow Trigger*
Temperature (°C)	< 35 or > 38	35-36
Systolic blood pressure (mm Hg)	< 90 or > 160	150-160 or 90-100
Diastolic blood pressure (mm Hg)	> 100	90-100
Heart rate (beats/min)	< 40 or > 120	100-120 or 40-50
Respiratory rate (breaths/min)	< 10 or > 30	21-30
Oxygen saturation (%)	< 95	—
Pain score†	—	2-3
Neurologic response‡	Unresponsive, pain	Voice

MEOWS, modified early obstetric warning system.
*A trigger is defined as a single markedly abnormal observation (red trigger) or the simultaneous combination of two mildly abnormal observations (yellow trigger). A trigger prompts urgent medical assessment.
†*Pain scores:* 0 = no pain at rest or movement; 1 = no pain at rest, slight pain on movement; 2 = intermittent pain at rest, moderate pain on movement; 3 = moderate pain at rest, severe pain on movement.
‡*Neurologic responses:* Alert: patient is alert and conscious; Verbal: patient responds to verbal stimulation; Pain: patient responds to painful stimulation; Unresponsive: patient is unresponsive to any stimulus.
From Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia 2012; 67:12-8.

abruption appear to trigger a coagulopathy disproportionate to the amount of blood loss or dilution of coagulation factors (see later discussion). Once coagulopathy develops, the requirement for additional resources (e.g., blood products) accelerates. The institutional system(s) by which personnel and resources are rapidly activated must be clearly defined in advance.[171,189]

Protocols and Team Approach

Because early delays in care during postpartum hemorrhage worsen outcomes, protocols have been introduced that focus on early recognition and treatment; specifically, protocols emphasize team responses, the accurate estimation of blood loss, recognition of early signs of hypovolemic shock, early monitoring for anemia and coagulopathy, and appropriate transfusion of blood products. A number of protocols have been implemented and published, including a detailed obstetric hemorrhage "kit" by the California Maternal Quality Care Collaborative.[190]

The combination of protocols and team practice drills that emphasize these elements has been shown to decrease the severity of hemorrhage and, in some cases, mortality.[191-193] Shields et al.[193] introduced a postpartum hemorrhage protocol with practice drills and subsequently performed a follow-up study to determine whether introduction of the protocol reduced severity of hemorrhage and/or need for transfusion. All obstetric patients were assessed on admission to the hospital for risk for bleeding, and patients deemed at increased risk had blood samples sent to the blood bank for type and screen or type and crossmatch. Blood loss after delivery was estimated by weighing all absorbent material, adding the liquid contents of fluid collection devices, and subtracting the nonblood fluid volume (e.g., amniotic fluid). After delivery, each patient was assigned to one of four stages of increasing acuity, depending on estimated blood loss and changes in hemodynamic status. Higher stages of acuity directed the team of caregivers to summon help, to advance progressively through pharmacologic and surgical interventions to control the source of bleeding, and to simultaneously intensify hemodynamic and hemostatic support. In the preprotocol period, only 33% of patients were successfully treated in the earliest stage of hemorrhage (stage 1), compared with 82% in the postprotocol period ($P = .02$). Similarly, among patients who progressed to moderate hemorrhage (stage 2), 8% were successfully treated at that stage in the preprotocol period, compared with 50% in the postprotocol group ($P = .02$). Transfusion rates declined and there was a trend toward less DIC in the postprotocol period.[193]

Introduction of these types of protocols and drills has positive effects on sentinel events and malpractice payments.[194] Additionally, *in situ* drills may uncover latent systems errors that can subsequently be corrected.[195,196] The Joint Commission has called for clinicians to identify triggers that warn of excessive blood loss and hemodynamic instability early in the course of hemorrhage and to develop protocols for responding to such triggers; they recommend drills for obstetric hemorrhage, noting that these team exercises can be used for training staff as well as identifying and fixing systems problems.[197]

TRANSFUSION THERAPY

Despite advances in the prevention, diagnosis, and treatment of the hemorrhagic complications of pregnancy, the potential for significant blood loss remains. All physicians who provide care for pregnant women should understand the indications, risks, and benefits of transfusion. Transfusion may be indicated for treatment of severe anemia after moderate obstetric hemorrhage or to preserve life during massive hemorrhage.

The AABB recommends restrictive transfusion strategies after moderate hemorrhage in otherwise hemodynamically stable adults.[198] This advice is based on consideration of the risks of anemia compared to the risks of transfusion. Randomized controlled trials have failed to demonstrate benefits for liberal compared with restrictive RBC transfusion strategies. Additional considerations arise from concern about resource utilization and the costs associated with transfusion.

Risks and Benefits

Risk of Anemia

Blood oxygen content and oxygen delivery to the tissues are a function of hemoglobin concentration; however, compensatory physiologic responses offset the negative

effect of anemia on oxygen transport, especially if euvolemia is maintained with crystalloid or colloid intravascular volume expansion after moderate hemorrhage. Tachycardia and increased stroke volume combine to increase cardiac output, and blood viscosity and systemic vascular resistance decrease, augmenting blood flow to the tissues. Additionally, tissue oxygen extraction increases. Experience with patients who refuse transfusion indicate that these compensatory mechanisms are usually adequate to compensate for moderate blood loss; no increase in mortality is observed as long as hemoglobin concentration remains greater than 5.0 g/dL.[199] Weiskopf et al.[200] studied the effects of acute normovolemic hemodilution on oxygen delivery and extraction. As hemoglobin concentration fell, systemic vascular resistance decreased and heart rate, stroke volume, and cardiac index increased. Oxygen transport rate and mixed venous oxyhemoglobin saturation did not decrease until hemoglobin concentration levels reached 5.0 g/dL. Plasma lactate did not accumulate, leading the authors to conclude that transport of oxygen was not compromised during anemia of this magnitude. These measurements were made in healthy, nonpregnant patients and volunteers who were at rest; extrapolation of these results to sick or pregnant patients may not be warranted. Anemia carries increased risks in patients with cardiovascular disease.[201]

Postpartum anemia is associated with fatigue. However, fatigue is transient, and within 1 week fatigue and health-related quality of life scores are similar between postpartum patients who were anemic at discharge and those who were not.[202] Transfusion of 1 or 2 units of PRBCs to moderately anemic parturients has no effect on length of hospital stay.[203] Jonsson et al.[204] investigated the correlation between postoperative hematocrit and wound tissue oxygenation and wound collagen deposition. There was no correlation until the hematocrit fell below 15%, most likely because compensatory responses to anemia mitigate the effects of low oxygen content. The effect of moderate anemia on breastfeeding is unknown.

Risks of Transfusion

Blood product transfusion is associated with known risks (see Table 55-2). **Transfusion-associated circulatory overload** (TACO) occurs in 1% to 6% of transfused patients.[205-207] TACO sometimes develops in young patients and may follow the transfusion of as little as 1 unit of PRBCs.[208] The likelihood of TACO increases with larger amounts of plasma transfused[205] and may occur during the correction of the coagulopathy that accompanies severe hemorrhage and massive transfusion.

Transfusion-related acute lung injury (TRALI) is defined as a new acute lung injury (ALI) that occurs within 6 hours of transfusion in a patient without an alternative risk factor for ALI. It is accompanied by hypoxemia and radiographic evidence of pulmonary edema in the absence of circulatory overload (Box 38-4).[209] TRALI results when human leukocyte antigen (HLA) class I and II neutrophil or possibly monocyte antibodies in donor plasma prime and activate recipient white blood cells (WBCs) to cause an ALI. This WBC activation leads to increased pulmonary microvascular permeability and interstitial and alveolar edema and extravasated neutrophils in the alveolar spaces.[210] Multiparous female donors are more likely to carry the offending antibodies.[211] In 2006, U.S. blood collection agencies instituted male-only donor plasma transfusion policies, and the TRALI rate has fallen to approximately one third of its prior level (approximately 1 case per 12,000 transfused units).[211] Multicomponent apheresis collection techniques also decreased the risk for TRALI.[210]

BOX 38-4 Recommended Criteria for TRALI and Possible TRALI

TRALI Criteria

- Acute lung injury
  - Acute onset
  - Hypoxemia
    Research setting: $PaO_2/FIO_2 \leq 300$ or $SpO_2 < 90\%$ on room air
    Nonresearch setting: $PaO_2/FIO_2 \leq 300$ or $SpO_2 < 90\%$ on room air or other clinical evidence of hypoxemia
  - Bilateral infiltrates on frontal chest radiograph
  - No evidence of left atrial hypertension (i.e., circulatory overload)
- No preexisting acute lung injury before transfusion
- Occurs during or within 6 h of transfusion
- No temporal relationship to an alternative risk factor for acute lung injury

Possible TRALI Criteria

- Acute lung injury
- No preexisting acute lung injury before transfusion
- Occurs during or within 6 h of transfusion
- A clear temporal relationship to an alternative risk factor for acute lung injury

TRALI, transfusion-related acute lung injury.
From Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004; 44:1774-89.

Allogeneic RBC administration also risks **transfusion-related immunomodulation** (TRIM). The mechanisms for development of TRIM are incompletely understood, but subsequent to RBC transfusion, the host develops immune tolerance and a period of generalized immune suppression. Consequences of immune tolerance and suppression include an increased incidence of nosocomial infection, postoperative infection, and cancer recurrence.[212] In addition, microchimerism, whereby donor cells/DNA persist in the host for several years, occurs and predisposes the recipient to autoimmune illnesses.[212] There is some suggestion that TRIM increases the lifetime risk for nonsolid cell malignancies.[213] These consequences are more likely to manifest as time passes and therefore may be more likely to affect young obstetric patients than older patients. Leukoreduction may have a modest role in mitigating TRIM.[210]

The risk for **viral transmission** because of allogeneic blood transfusion continues to decrease with thorough donor screening and use of nucleic acid amplification testing (nucleic acid technology [NAT]).[214] The residual risk for transmission after both NAT and serologic testing

of donor blood is approximately 1 in 2 million for both human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[198,214,215] NAT is not routinely used to test for hepatitis B virus (HBV). Instead, donor screening for hepatitis B surface antigen (HBsAg) and anti-core (HBc) antibody have greatly reduced the risk for transmission of HBV; the current risk for transmission with a blood transfusion is 1 in 350,000.[198,214] The transfusion transmission of Creutzfeldt-Jakob disease has been reported. Because of the long incubation period of this prion, symptoms may not be evident for several years after transfusion.[216] Levels of infectivity are believed to be very low.[214] The first case of West Nile virus transmitted via a blood transfusion was identified in 2002; since 2003, routine blood screening has been implemented, virtually eliminating this risk.[214] Cytomegalovirus (CMV) is carried in the monocytes of asymptomatic donors and may be transmitted to uninfected recipients of blood transfusions.[217] Most of the subsequent infections are asymptomatic or mild, but CMV infection of an immunocompromised patient and/or fetus or neonate can lead to serious sequelae. The transmission rate may be as high as 30% without preventive techniques. The risk for transmission of CMV is reduced to 1.3% if seronegative blood is transferred[218] and to 2.5% with the use of leukodepleted PRBCs.[219] In 2000, a Canadian consensus conference concluded that these two methods of preventing post-transfusion CMV infection can be used interchangeably.[217]

Bacterial contamination occasionally occurs. Because platelets may undergo conformational changes at temperatures below 18° C, they are stored at 20° C to 24° C. This warmer storage temperature (compared with that used for PRBCs) increases the risk for bacterial proliferation. In 2004, the AABB mandated testing of all platelets for bacterial contamination. Use of culture-negative platelets has resulted in a reduction in the risk of septic transfusion to 1 in 75,000.[220]

Hemolytic transfusion reaction is a rare complication; it occurs most commonly as a result of accidental administration of ABO-incompatible blood.[198] Acute intravascular hemolysis typically results in fever, chills, nausea, flushing, and chest and flank pain. These symptoms are masked by general anesthesia. Signs that may manifest during general anesthesia include hypotension, tachycardia, DIC, and hemoglobinuria.[221] Immediate supportive care consists of discontinuation of the transfusion, treatment of hypotension and hyperkalemia, administration of a diuretic, and alkalinization of the urine. Assays for urine and plasma hemoglobin concentration and antibody screening confirm the diagnosis. A second crossmatch must be performed.

The biochemical and additional changes that occur during blood storage can lead to complications in the recipient, particularly when blood products are infused rapidly, as during massive transfusion for severe hemorrhage. The anticoagulant used for blood collection and storage contains citrate, which binds ionized calcium. Citrate is rapidly metabolized in the liver and typically does *not* lead to significant **hypocalcemia**. In patients who are hypothermic, have liver disease, or require rapid infusion of multiple units of blood products, however, citrate may accumulate and cause a decrease in ionized calcium. The concentration of citrate is seven times higher in fresh frozen plasma (FFP) and platelets than in PRBCs.[222] Hypocalcemia results in reduced cardiac contractility, hypotension, and elevated central venous pressure.[223]

Plasma potassium concentration increases in stored blood. Transfused potassium usually moves intracellularly or is excreted in the urine. However, rapid infusion of multiple units of blood can lead to **hyperkalemia**, particularly in the hypothermic acidotic patient.[223] Blood maintained at 4° C also can contribute to **hypothermia**, especially if the patient is anesthetized in a cold operating room. The decreased pH of stored blood is caused by the addition of citrate-phosphate-dextrose and the accumulation of lactic and pyruvic acids as a result of RBC metabolism and glycolysis. Despite the lower pH, transfusion of large amounts of stored blood rarely causes acidosis as long as tissue perfusion remains normal.[223]

Transfusion Strategies

Several randomized controlled trials have compared the use of restrictive and liberal transfusion practices, based on lower or higher hemoglobin triggers.[224] These trials uniformly failed to demonstrate benefit to a liberal strategy and suggested that using higher hemoglobin triggers may cause harm.[224-227] A 2012 meta-analysis that examined the effect of restrictive compared with liberal transfusion triggers on various outcomes[228] found that the use of lower hemoglobin triggers reduced the risk of receiving an RBC transfusion (RR, 0.61; 95% CI, 0.52 to 0.72), reduced the volume of RBC transfused, and did not impact the rate of adverse events such as myocardial infarction, other cardiac events, or stroke. Furthermore, restrictive strategies were associated with a reduction of in-hospital mortality (RR, 0.77; 95% CI, 0.62 to 0.95) and a trend toward lower 30-day mortality (RR, 0.85; 95% CI, 0.70 to 1.03). There are no published randomized controlled trials examining low versus high transfusion triggers in obstetric patients. Among a series of 117 women with major obstetric hemorrhage (5 units or more of packed PRBCs transfused), a hematocrit nadir below 20% was associated with end organ injury.[9]

The indications for, and appropriateness of, RBC transfusion have been recently reevaluated because of (1) concerns for transfusion-related complications, (2) appreciation of the body's mechanisms for compensating for anemia, and (3) the results of the randomized trials indicating no benefit to early transfusion. The AABB recommends that RBC transfusion not be considered in euvolemic, hemodynamically stable patients until the hemoglobin concentration reaches 7 g/dL, or 8 g/dL in patients with cardiovascular disease.[198] The AABB further advises that transfusion be guided by symptoms and not by hemoglobin concentration triggers alone.[198]

Practices vary widely[229] and often deviate from these guidelines. In a retrospective chart review, Butwick et al.[230] found no specific documented indication for transfusion in 34% of obstetric patients who received a transfusion. Additionally, 18% had a pretransfusion hemoglobin concentration greater than 8 g/dL. Parker

et al.[231] documented that 31% of obstetric transfusions administered over a 1-year period occurred despite a hemoglobin concentration greater than 7 g/dL in the absence of ongoing bleeding or symptomatic anemia. Similarly, Fong et al.[232] reported that 24% of transfusions administered to patients undergoing cesarean delivery were inappropriate, based on a preadministration hemoglobin concentration higher than 7 mg/dL. Finally, in a review of 33,795 obstetric-related admissions from 1994 to 2002, Silverman et al.[233] found that 32% of RBC transfusions were not appropriate when judged against institutional guidelines.

The AABB guidelines do not address transfusion in parturients.[198] Similarly, the ACOG is silent on this issue. Given current evidence in nonobstetric patients and the lack of data in obstetric patients (who are generally young and healthy), it seems reasonable that transfusion should be considered in obstetric patients with a hemoglobin concentration less than 7 g/dL or clinical evidence of inadequate oxygen-carrying capacity. Moreover, ongoing blood loss should prompt transfusion in some patients with a hemoglobin concentration greater than 7 g/dL.

The need to obtain a blood type and screen for all parturients on admission is controversial. Some clinicians suggest that this test is not necessary in patients with no identifiable risk factors for peripartum hemorrhage. Ransom et al.[234] found that only 0.8 per 1000 low-risk patients undergoing cesarean delivery required a blood transfusion. They concluded that a routine type and screen in low-risk patients is not cost-effective. However, many anesthesia providers believe that the potential need for transfusion, and the occasional patient who develops an antibody from fetal antigen exposure during pregnancy, warrants the routine performance of a blood type and screen. The American Society of Anesthesiologists (ASA) Practice Guidelines for Obstetric Anesthesia state that the decision to perform a type and screen should be based on maternal history, anticipated hemorrhagic complications, and local institutional policies.[235] It is not necessary for all parturients to undergo a type and crossmatch, although it may be prudent to obtain a crossmatch for patients with risk factors for bleeding.[235] In addition, patients with a positive antibody screen should have a blood sample sent for crossmatch to avoid a delay in obtaining blood products should the need arise.

If blood is required quickly and the results of antibody screening are not available, the safest option is to administer ABO- and Rh-specific blood. If the blood type is unknown and blood products are required immediately, type O Rh-negative blood can be administered.

Blood Conservation Techniques

Iron deficiency is common in childbearing women because erythropoiesis occurs in the fetus at the expense of maternal iron stores. Oral iron therapy is a mainstay of anemia prevention and treatment in pregnant women. Unfortunately, oral therapy is not well-tolerated and therefore many patients may be noncompliant; others may have reduced gastrointestinal absorption.[236] Vitamin C enhances iron absorption.[236] In cases of malabsorption, intravenous iron administration may be required. Intravenous therapy more quickly and reliably corrects anemia than oral iron therapy,[237] including anemia in postpartum women.[238] Low-molecular-weight iron dextran is recommended for this purpose because it is associated with few serious adverse effects, in contrast to older iron preparations.[239] Erythropoietin stimulates bone marrow erythropoiesis but has been associated with venous thromboembolism in vulnerable populations.[240] Its use is not well studied in pregnancy.

The potential advantages of autologous blood transfusion include avoiding the risks of some transfusion-related adverse events and reduction of demands on the blood supply. The three methods of autologous transfusion are (1) preoperative (antepartum) donation, (2) normovolemic hemodilution, and (3) intraoperative blood salvage. Preoperative autologous donation causes anemia, may not reduce the risk of allogeneic transfusion, cannot be used in emergencies, and is not cost-effective because of difficulties in predicting transfusion need in obstetric patients, even those with traditional risk factors for hemorrhage.[241,242] Normovolemic hemodilution may also induce anemia and may not reduce the risk of allogeneic transfusion.[242,243] Experts do not endorse the routine use of either of these two techniques in obstetric patients.[242]

Intraoperative blood salvage is a technique of scavenging blood lost during surgery, processing it by centrifugation, washing and filtering, and administering the scavenged, autologous RBCs back to the patient. Red blood cells that are salvaged, processed, and transfused have an excellent survival rate. This procedure, which can rapidly provide large quantities of autologous blood, is widely used in cardiovascular and general surgery and is acceptable to many Jehovah's Witness patients.[244] Employment of cell salvage diminishes the need for allogeneic transfusion and postoperative anemia after cesarean delivery.[245]

Contamination of salvaged blood with bacteria, fat, bowel contents, or various pharmacologic agents represents a relative contraindication to the technique.[246] In the past, the use of intraoperative blood salvage in obstetric patients has been limited, in part, by concern that blood processing may not adequately remove amniotic fluid, fetal debris, or fetal cells and that reinfusion might precipitate amniotic fluid embolism. However, modern salvaging processes efficiently remove these contaminants.[246,247] *In vitro* studies demonstrate that washing and filtration remove tissue factor, which is implicated in the pathophysiology of amniotic fluid embolism, from salvaged products.[248] In addition, combining these processes with the use of a leukocyte-depletion filter greatly reduces fetal squames and other fetal debris.[249,250] Waters et al.[250] demonstrated that fetal squamous cell concentration in postfiltration scavenged blood is equal to that in maternal venous blood. In all cases of potential contamination, a double suction setup is recommended.[246,247] In this setup, one suction line, connected to the general suction system, removes grossly contaminated fluid immediately after amniotomy and delivery, before a second suction line delivers blood to the salvaging system.

The cell scavenging system does not distinguish between maternal and fetal red cells, and the transfusion of washed blood is likely to expose the mother to a greater

amount of fetal RBCs than commonly occurs during delivery.[249,250] In one series, the median fetal red cell transfusion (contamination) volume was 0.8 mL, ranging from 0.2 to 12.9 mL.[251] Isoimmunization of the mother is possible, and anti-D immune globulin should be administered as guided by Kleihauer-Betke testing.[246,247]

Reports of clinical experience with cell salvage in obstetric patients have accumulated over recent years; more than 650 cases have been published describing its use in obstetric patients without adverse sequelae.[251-253] Few controlled trials have been published. Rebarber et al.[254] performed a retrospective, multicenter study of 139 patients in whom autologous blood transfusion was performed during cesarean delivery between 1988 and 1997. The volume of autotransfused blood ranged from 200 to 11,250 mL. The investigators identified no cases of acute respiratory distress syndrome or amniotic fluid embolism, and the incidence of other complications (e.g., DIC) in these patients was not different from the incidence in 87 control patients who underwent similar surgical procedures without autotransfusion in the same hospitals. In a randomized study of women undergoing cesarean delivery, Rainaldi et al.[245] observed that 34 patients who underwent intraoperative salvage and re-infusion of autologous blood (mean ± SD volume, 363 ± 153 mL) required less allogeneic blood and had a shorter hospital stay than the control group. The authors of one case report attributed maternal death to cell salvage-induced amniotic fluid embolism.[255] Many authorities do not accept the cause of death as amniotic fluid embolism because the patient was quite ill with severe preeclampsia, HELLP syndrome, and coagulopathy and the postmortem examination was inconclusive concerning the diagnosis of amniotic fluid embolism.

Intraoperative blood salvage during cesarean delivery is widely regarded as safe in the United Kingdom[242,247] and is gaining acceptance in the United States. The ACOG has stated that in cases of suspected placenta accreta, "cell saver technology should be considered if available."[75] The ASA Practice Guidelines for Obstetric Anesthesia recommend that "in cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell salvage should be considered if available."[235]

Many authorities advocate this technique as a potential solution to the worsening shortage of banked blood, increased cost of allogeneic blood transfusion, and concern about transfusion-related infections and clerical errors.[246,247,249] Waters et al.[256] performed an economic analysis of the use of cell salvage in obstetrics and calculated that its cost-effectiveness may depend, in part, on an institution's case volume and the expected volume of blood lost per case. Fong et al.[232] have suggested that the use of intraoperative blood salvage might reduce exposure to allogeneic blood in almost half of obstetric patients who require transfusion and might eliminate exposure to allogeneic blood altogether in 14% to 25% of patients.

Treatment of Massive Blood Loss

In the initial resuscitation of the hemorrhaging patient, warmed non–dextrose-containing crystalloid (e.g., lactated Ringer's solution, normal saline) and/or colloid (e.g., 5% albumin) solutions are acceptable choices for volume replacement. During massive hemorrhage, blood replacement therapy becomes necessary. A coagulopathy can develop rapidly in the bleeding obstetric patient, because of hemostatic factor consumption, exsanguination, dilution, or hyperfibrinolysis. Dilutional coagulopathy results from the replacement of blood loss with crystalloid and PRBCs, which dilutes coagulation factors and platelets. Sustained hemorrhage may also lead to DIC with simultaneous accelerated consumption and fibrinolysis, resulting in worsening hemorrhage (see later discussion). Pregnancy-related pathologic processes commonly associated with DIC include amniotic fluid embolism, placental abruption, uterine infection, intrauterine fetal demise, and severe postpartum hemorrhage.

Blood Products

Allogeneic blood can be transfused as whole blood or component products. Whole blood would be an ideal choice for maintaining intravascular volume in the setting of massive hemorrhage. Alexander et al.[257] performed a population-based observational study of 1540 obstetric patients who required transfusion. The authors compared outcomes among patients who received only whole blood (43%), only PRBCs (39%), or multicomponent therapy (19%). Whole blood was associated with lower rates of acute tubular necrosis than the two other transfusion practices. However, few donor units are kept as whole blood in the modern blood bank. The high demand for blood components such as platelets, FFP, and cryoprecipitate necessitates that more than 90% of donor blood be fractionated into blood components. Blood component therapy provides the patient with only those products that are required and helps extend the shelf-life of each unit of donor blood because derivatives from one unit of blood can be used to treat several patients. Characteristics of commonly administered blood products are summarized in Table 38-6. During massive resuscitation, care must be taken to avoid hypothermia, acidosis, and hypocalcemia, because these conditions contribute to coagulopathy.

PRBC units are prepared by removing plasma from whole blood and replacing it with additives to improve red cell survival. These units are packaged with preservatives and anticoagulant (citrate, phosphate, dextrose, adenine) and have a 42-day shelf-life. Each unit has volume of approximately 300 mL with a hematocrit of 70%. Transfusion of 1 unit of PRBC increases the hemoglobin concentration by approximately 1 mg/dL in the absence of ongoing bleeding.

A unit of **fresh frozen plasma** has a volume of approximately 250 mL and contains coagulation factors. Transfusion of FFP is indicated when replacement of coagulation factors is necessary to achieve hemostasis, as may occur during massive transfusion or in the presence of DIC. Administration of FFP may be considered for correction of microvascular bleeding if the prothrombin time (PT) is more than 1.5 times normal, the international normalized ratio (INR) is greater than 2.0, or the activated partial thromboplastin time (aPTT) is more

TABLE 38-6 **Characteristics of Blood Components**

Component	Dose	Volume Per Dose	Shelf Life	Storage Conditions	Expected Response
Packed red blood cells	1 unit	250-325 mL	21-42 days	1°C to 6°C	1 g/dL increase in hemoglobin concentration
Fresh frozen plasma	Factor replacement: 10-15 mL/kg	200 mL	Frozen: 1 yr Thawed: 24 h	Frozen: ≤ –18°C Thawed 1°C to 10°C	Correction of PT, aPTT, INR by replacement of coagulation factors
Platelets	4-6 units of pooled whole blood–derived platelets or one unit of apheresis platelets	200-250 mL	5 days	20°C to 24°C with continuous and gentle agitation	Increase in platelet count of 30,000-60,000/mm^3
Cryoprecipitate	10 pooled units	100 mL	Frozen: 1 yr Thawed/pooled: 4 h	Frozen: ≤ –18°C Thawed: 1°C to 10°C	Increase in levels of fibrinogen, von Willebrand factor, factor VIII, factor XIII

aPTT, activated partial thromboplastin time; *INR,* international normalized ratio; *PT,* prothrombin time.
Modified from Sanford K, Roseff S. A surgeon's guide to blood banking and transfusion medicine. In: Spiess BD, Spence RK, Shander A, editors. Perioperative Transfusion Medicine, 2nd edition. Philadelphia, Lippincott Williams and Wilkins, 2006: 179-98.

than two times normal.[221] FFP should not be used to treat hypovolemia or as a protein supplement. One unit of FFP per 20 kg of body weight (or 10 to 15 mL/kg body weight) is an appropriate initial dose.[221] The prophylactic use of FFP is not effective for decreasing blood loss in patients at risk for massive blood loss.[222]

Cryoprecipitate is prepared from thawed FFP and contains fibrinogen, factor VIII, von Willebrand factor, fibronectin, and factor XIII. In the setting of postpartum hemorrhage, cryoprecipitate is used to replace fibrinogen, which is rapidly consumed during obstetric hemorrhage. Normal pregnancy is a hypercoagulable state,[258,259] and coagulation activity peaks at the time of parturition[260,261] because of an increase in circulating tissue factor concentration and enhancement of the tissue factor–dependent coagulation pathway.[262] It is postulated that tissue factor and other procoagulant substances are released from the placental implantation site at the time of placental separation, augmenting thrombin formation and serving an important hemostatic function after delivery.[48] In the setting of continued bleeding from the placental bed, these thromboplastic substances may continue to enter the circulation and, in severe cases, may lead to a consumptive coagulopathy and DIC.[48]

The consumption of fibrinogen appears to play a central role in the pathophysiology of peripartum hemorrhage.[263] Charbit et al.[188] prospectively identified 128 patients who had postpartum hemorrhage and classified the hemorrhage as severe (decrease in hemoglobin concentration of ≥ 4 g/dL, transfusion of ≥ 4 units PRBCs, or invasive hemostatic intervention required) or nonsevere.[188] At the time postpartum hemorrhage was diagnosed, patients who subsequently developed severe hemorrhage had lower fibrinogen, prothrombin, factor V, and antithrombin levels compared with patients without severe hemorrhage. These early differences were most marked for fibrinogen. A fibrinogen concentration less than 200 mg/dL at the time hemorrhage was diagnosed had a 100% positive predictive value for severe hemorrhage; a fibrinogen concentration greater than 400 mg/dL had a 79% negative predictive value for severe hemorrhage. The coagulation changes were consistent with a consumptive coagulopathy because they were accompanied by increases in thrombin-antithrombin complexes and D-dimer levels, both markers of excessive coagulation. Furthermore, because the fall in fibrinogen concentration was twice the fall in hemoglobin concentration, it was believed that dilution did not account for the difference in fibrinogen levels between the two groups. Other investigators have confirmed that decreases in fibrinogen correlate better than other hemostatic measures with the severity of hemorrhage.[264,265]

The alarmingly rapid consumption of coagulation factors, especially fibrinogen, during obstetric hemorrhage has prompted experts to recommend early monitoring for, and aggressive treatment of, hypofibrinogenemia with rapid central laboratory or point-of-care testing.[266-268] During active hemorrhage, clinicians should attempt to maintain the fibrinogen concentration higher than 150 to 200 mg/dL.[268] Each *dose* of cryoprecipitate supplied by most blood banks contains 5 to 10 single-donor units of cryoprecipitate, and each unit of cryoprecipitate contains approximately twice the fibrinogen of 1 unit of FFP. Therefore, the most efficient method to replace fibrinogen during obstetric hemorrhage may be to administer cryoprecipitate.[269] In a multicenter prospective cohort study of trauma victims (n = 1175), administration of cryoprecipitate compared with large doses of FFP was associated with a decreased risk for multiorgan failure.[270] In a small case series of obstetric hemorrhage associated with hypofibrinogenemia, fibrinogen concentrate was used to restore fibrinogen levels.[271] This product is currently approved for the treatment of acute bleeding in individuals with congenital hypofibrinogenemia. Further study is required to clarify its role in the treatment of the acquired hypofibrinogenemia associated with obstetric hemorrhage.[263,270]

Thrombocytopenia may develop after massive transfusion secondary to dilution or in association with obstetric comorbidities such as HELLP syndrome. **Platelet**

transfusion may be necessary if hemorrhage is accompanied by a platelet count less than 50,000/mm^3.[221] In nonbleeding patients, a transfusion trigger of 20,000/mm^3 has traditionally been suggested, although many clinicians prefer to administer platelets before the platelet count decreases to this value.[272] Platelet dysfunction associated with bleeding may also necessitate platelet administration.[221] One unit of donor platelets increases the platelet count by 5000 to 10,000/mm^3 in the average adult. The blood bank typically provides pooled random-donor platelets or single-donor apheresis platelets obtained from an ABO- and Rh-compatible donor, although ABO compatibility is not essential. One unit of apheresis platelets is equivalent to 4 to 6 units of pooled platelets.

The optimal **FFP:PRBC transfusion ratio** remains a topic of research and debate. Borgman et al.[273] sought to characterize the relationship between this ratio and survival in a retrospective review of combat victims in Iraq between 2003 and 2005. The investigators identified 246 patients who required massive transfusion and separated them into low (median ratio 1:8), medium (median ratio 1:2.5), and high (median ratio 1:1.4) FFP:PRBC ratio groups. A high FFP:PRBC ratio was independently associated with increased odds of survival after correcting for confounders (odds ratio, 8.6; 95%, CI 2.1 to 35.2). After publication of these data, some experts recommended a 1:1 FFP:PRBC ratio during massive hemorrhage. However, many authors,[274] including Borgman et al.,[273] pointed out the well-known limitations of retrospective data, which include the potential existence of unidentified confounders. These authors have articulated the fact that deaths in the low-ratio group occurred much earlier than deaths in the high-ratio group, raising the possibility that those in the low-ratio group had more severe injuries and died before FFP could be thawed and administered (e.g., survivor bias). Indeed, if the analysis is adjusted for survivor bias, the survival benefit associated with high FFP:PRBC ratio disappears.[274,275] Furthermore, a study in civilian trauma victims identified a FFP:PRBC ratio of 1:2 to 1:3 as optimal for survival.[276] However, the extrapolation of data from young male trauma victims to bleeding parturients seems fraught with potential for error.

A 2013 publication described the retrospective review of records from 142 women who had postpartum hemorrhage and required transfusion within 6 hours of delivery.[277] Patients were divided into two groups based on their response to sulprostone therapy: those in whom bleeding was controlled with sulprostone alone and those who required advanced interventional procedures. Propensity score analysis revealed that a high FFP:PRBC ratio (> 1:2) was associated with fewer requirements for interventional procedures. Retrospective studies such as these can only demonstrate an association between the FFP:PRBC ratio and outcome and cannot infer cause and effect. Investigators have uniformly called for high-quality randomized trials to adequately define the optimal FFP:PRBC ratio during resuscitation for massive hemorrhage.[273,275-278]

Many blood banks have in place **massive transfusion protocols** whereby blood products are delivered to the operating room in fixed ratios, sometimes in a cooler or refrigerator.[279] Such protocols allow the blood bank to more quickly provide component products[280] and may encourage clinicians to more effectively prevent and/or treat coagulopathy. A massive transfusion protocol for postpartum hemorrhage has been described (Figure 38-5).[281]

Recombinant Activated Factor VII

A number of reports have described the administration of recombinant activated factor VII (rFVIIa) for hemorrhage and coagulopathy unresponsive to conventional blood product resuscitation.[282] Factor VIIa binds not only to tissue factor but also with low affinity to the thrombin-activated platelet. This low-affinity binding to the activated platelet allows direct activation of factor X to Xa on the surface of the activated platelet, bypassing the normal need for factors VIIIa and IXa. Activation of factor X leads to a small thrombin burst. This thrombin, in turn, activates more platelets. Additionally, rFVIIa enhances platelet aggregation and adhesion. Recombinant activated factor VII is currently approved in the United States for the treatment and prophylaxis of bleeding in patients with hemophilia A and B with inhibitors to factors VIII and IX, acquired hemophilia, and congenital factor VII deficiency. However, its use has been reported off-label for multiple clinical scenarios, including the following: platelet disorders; severe liver disease; major trauma; cardiac, prostate, and liver surgery; stroke; and postpartum hemorrhage.[236,283] Greater numbers of patients are being treated with rFVIIa each year, and the majority of treated patients are receiving the drug for off-label indications.[284]

No randomized controlled trials investigating the use of rFVIIa in the setting of obstetric hemorrhage have been published; most recommendations are therefore based on case report or case series data. Franchini et al.[285] compiled 9 reports of 272 obstetric patients who received rFVIIa. A 10th report described a registry of 105 patients who received rFVIIa for postpartum hemorrhage in Australia and New Zealand.[286] Of the 377 patients included in these 10 reports, 82% were judged by their practitioners to have had a positive treatment response (bleeding decreased or stopped) after one or more doses of rFVIIa. These data are difficult to interpret. Variation in underlying pathology existed; 49% of patients underwent cesarean delivery, and 51% underwent vaginal delivery. Nineteen percent had vaginal or uterine lacerations, 25% had placental abnormalities, and 8% had retained placenta. Additionally, the doses were not standardized and there were no criteria for the administration of rFVIIa, nor were there criteria for what constituted a positive response. Most patients received simultaneous therapy with other traditional therapies such as FFP and cryoprecipitate administration. These circumstances make judgments regarding response to rFVIIa unreliable and uncontrolled; thus, a high likelihood for bias exists. Several authors have called for randomized placebo-controlled trials of rFVIIa use for postpartum hemorrhage, but such a trial will be difficult to undertake given the low incidence and unpredictability of massive obstetric hemorrhage.

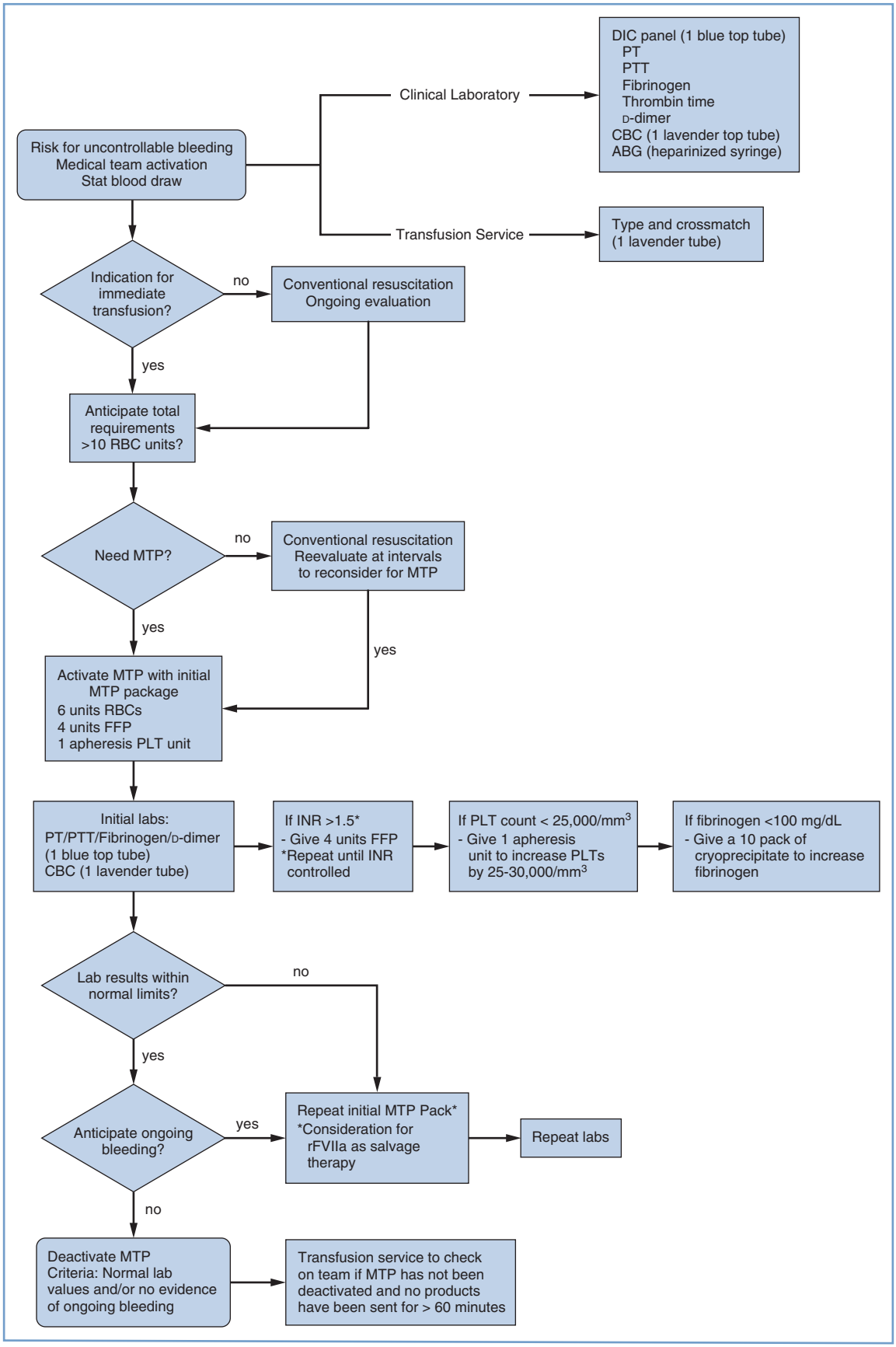

FIGURE 38-5 ■ Sample algorithm for a massive transfusion protocol for the labor and delivery unit. *ABG,* arterial blood gas; *CBC,* complete blood cell count; *DIC,* disseminated intravascular coagulation; *FFP,* fresh frozen plasma; *INR,* international normalized ratio; *MTP,* massive transfusion protocol; *PLT,* platelet; *PT,* prothrombin time; *RBC,* red blood cells; *rFVIIA,* recombinant activated factor VII. (Modified from Burtelow M, Riley E, Druzin M, et al. How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. Transfusion 2007; 47:1564-72.)

There is concern that rFVIIa may increase the likelihood of thromboembolic events. The true incidence is not known. Arterial events (e.g., myocardial infarction, cerebral thrombosis) are more likely than venous events[287,288] and are dose[287] and age dependent.[288] Among the 377 reported cases of rFVIIa administered for postpartum hemorrhage, eight patients developed venous thromboembolism, one suffered myocardial infarction, and one had a thrombotic cerebrovascular accident, suggesting a thrombotic complication frequency of 2.7% in the postpartum period. However, severe obstetric hemorrhage and peripartum hysterectomy are known to increase the risk for thrombotic complications; thus, this frequency cannot support or refute any causal relationship with rFVIIa. Leighton et al.[289] advise against rFVIIa administration in the setting of amniotic fluid embolism because tissue factor may play a role in its pathophysiology and thrombotic complications may be increased.

Given the unknown efficacy and safety of rFVIIa, as well as its high cost, rFVIIa is not recommended for routine use in obstetric practice. In 2005, an American panel, based on type II evidence (obtained from well-designed, nonrandomized trials or cohort or case-control analytic trials), judged the use of rFVIIa for treatment of postpartum hemorrhage as appropriate only when bleeding continued despite clotting factor replacement.[290] The ASA guidelines recommend consideration of rFVIIa therapy if "traditional well-tested options for treating microvascular bleeding (i.e., coagulopathy) have been exhausted."[221] In addition, maintenance of normothermia and correction of acidosis are necessary for optimal rFVIIa activity; optimization of platelet count, fibrinogen, and serum calcium are also advisable as rFVIIa requires these substances to be effective.

Antifibrinolytic Therapy

It has been suggested that antifibrinolytic therapies such as tranexamic acid may be useful in treating postpartum hemorrhage–associated coagulopathy.[291] A meta-analysis of six randomized trials comparing tranexamic acid with placebo administered shortly after birth demonstrated that tranexamic acid was associated with a nonsignificant reduction in blood loss of 33 mL.[292] In five of the six trials, tranexamic acid was administered prophylactically. The sixth trial enrolled women who had lost at least 800 mL after vaginal delivery; tranexamic acid reduced the total blood loss over the subsequent 6 hours by 50 mL (170 mL versus 221 mL, $P = .04$).[293] A large international placebo-controlled trial of tranexamic acid therapy in the setting of postpartum hemorrhage is ongoing.[294] Tranexamic acid may be most beneficial for women who demonstrate hyperfibrinolysis based on hemostatic monitoring such as thromboelastography.[263,268]

KEY POINTS

- Obstetric hemorrhage is the most common cause of maternal mortality worldwide and a leading contributor to maternal mortality in developed nations.
- Most severe morbidity and mortality that occurs secondary to obstetric hemorrhage is considered preventable and is due to delays in recognition and treatment.
- The visual estimate of vaginal bleeding often underestimates true blood loss; training clinicians, separation of amniotic fluid, use of calibrated drapes, and weighing pads and bedding improves estimation accuracy.
- Hypotension and tachycardia are late signs in hypovolemic shock.
- Antepartum hemorrhage usually represents a greater threat to the fetus than to the mother.
- Postpartum hemorrhage is increasing in both rate and severity in the developed world, mostly due to an increase in the incidence of uterine atony.
- Uterine atony is the most common cause of postpartum hemorrhage.
- The incidence of placenta accreta is increasing as a result of the higher cesarean delivery rate.
- Peripartum hysterectomy is increasing in frequency because of an increase in the incidence of both uterine atony and placenta accreta.
- Patients with placenta accreta are at high risk for massive hemorrhage and should be managed only in facilities with multidisciplinary specialists, including interventional radiologists and a well-staffed blood bank.
- Team responses that emphasize the accurate estimation of blood loss, early warning signs of shock, and rapid response to blood loss and coagulopathy are associated with less maternal morbidity.
- Coagulopathy develops quickly during bleeding from the placental bed, and may be out of proportion to blood loss or dilution because of the rapid consumption of fibrinogen.
- Intraoperative blood salvage may be lifesaving in cases of intractable hemorrhage, if banked blood is not available, or if the patient refuses banked blood.
- The safety and efficacy of recombinant activated factor VII therapy has not been fully evaluated in the treatment of obstetric hemorrhage.

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CHAPTER 39

Embolic Disorders

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CHAPTER OUTLINE

Embolic disease during pregnancy includes amniotic fluid embolism, venous thromboembolism, and venous air embolism. Each of these entities varies in its incidence, clinical course, and consequences. Embolic events account for almost one fifth of all maternal deaths in the United States.[1] Early recognition, diagnosis, and treatment are necessary to reduce associated morbidity and to avoid mortality.

AMNIOTIC FLUID EMBOLISM

Death attributable to an amniotic fluid embolism (AFE) was first reported by Meyer in 1926.[2] Early reports described a syndrome of fatal peripartum shock attributed to emboli of amniotic fluid mechanically obstructing the maternal pulmonary circulation.[3] Although the pathophysiology of this disease remains poorly understood, current evidence suggests that emboli alone are insufficient to precipitate this infrequent, idiosyncratic, and devastating condition. Rather, fetal material in the maternal circulation has the potential to trigger a massive cascade of inflammatory and hemostatic reactions that culminate in cardiopulmonary collapse and disseminated intravascular coagulation.

Epidemiology

The incidence of amniotic fluid embolism is difficult to establish because (1) AFE is a diagnosis of exclusion, (2) there is no universally accepted definition for identifying cases of AFE, and (3) differing ascertainment methods yield divergent rates of AFE. Registry data from the United Kingdom suggest an event rate between 0.8 and 2 per 100,000 deliveries.[4,5] Cross-sectional analyses of administrative data in Australia and the United States suggest higher rates—3.3 and 7.7 per 100,000 deliveries, respectively.[6,7] A systematic review published in 2009 estimated that the pooled incidence of AFE in North America was approximately 1:15,200 (95% confidence interval [CI], 1:13,900 to 1:16,700), whereas the incidence in Europe was three times lower at 1:53,800 (95% CI, 1:48,800 to 1:59,900).[8] This heterogeneity likely reflects variations in ascertainment procedures, rather than true differences by continent of origin. One limitation of analyses of secondary databases is that the diagnosis of AFE may not have been validated. For example, one regional surveillance system in Australia has developed the capacity to systematically review records for all cases identified from administrative data. By only counting those women who experienced one of the cardinal symptoms of AFE, with no other potential explanation, the reported incidence decreased from 6.3 to 3.3 cases per 100,000 pregnancies.[9]

Risk Factors

Maternal demographic factors such as older age and race or ethnicity have been associated with AFE in population-based studies.[5,7] Other obstetric factors such as abnormal placentation, placental abruption, eclampsia, multiple gestation, induction of labor, artificial or spontaneous rupture of membranes, and operative delivery have also been associated with AFE.[5,7,10-12] Because nonreassuring fetal heart rate (FHR) tracings can complicate AFE in labor, cesarean delivery may be a consequence,

rather than cause, of intrapartum AFE. Nonetheless, a strong association between cesarean birth and postpartum AFE persists among women in the United Kingdom Obstetric Surveillance System (UKOSS) dataset (adjusted odds ratio, 8.8).[5] The proportion of excess postpartum AFE events associated with cesarean delivery (the population-proportional attributable risk for cesarean delivery) from the UKOSS dataset was estimated to be 62%.[5]

Pathophysiology

In 1941, Drs. Steiner and Lushbaugh, two pathologists from the University of Chicago, described a case series of eight autopsies after fatal intrapartum shock.[3] Examination of lung tissue from these cases revealed embolic material of squamous cells, mucin, meconium, and amorphous eosinophilic material.[3] Because all of these patients were described as having tumultuous labors with stronger than usual uterine contractions, it was presumed that the forceful contractions loosened or tore the placenta and forced the emboli into the maternal circulation.[3] Yet, periods of uterine tachysystole are the least likely times for maternoplacental exchange of embolic material to occur as uterine blood flow ceases.[13] The tachysystole is probably a result of endogenous norepinephrine release and, therefore, is likely temporally related to, but not causative for, embolic material transfer.[13]

Large intravenous boluses of human meconium suspended in human amniotic fluid can precipitate cardiovascular collapse in rabbits and dogs,[3] but injection of autologous amniotic fluid fails to reproduce the AFE syndrome in many animal models.[14] The passage of fetal squames, lanugo hair, and mucin into the maternal pelvic vasculature appears to be a common event at term,[15] and fetal material has been identified in pulmonary arterial samples aspirated from critically ill women who did not have AFE.[16-18]

The exact trigger for the reaction in women with AFE is not known but may be a rare pathologic fetal antigen or a common antigen presented in an unusual way—in amount, timing, or frequency of entry into the maternal circulation.[19] AFE appears to be a systemic inflammatory response associated with the inappropriate release of endogenous inflammatory mediators.[20] Whatever the trigger, several maternal endogenous mediators appear to play an important role in the initial reaction, including arachidonic acid metabolites (i.e., thromboxane, prostaglandins, leukotrienes, endothelins).[20]

Approximately 40% of women in a United States national AFE registry had a history of allergy or atopy, leading some authors to suggest an anaphylactoid mechanism.[12] In support of this theory, the symptoms of AFE could be blocked by the administration of a leukotriene inhibitor in a rabbit model.[21] However, a series of case reports now suggests that levels of tryptase and histamine are not dramatically or universally elevated among women experiencing the AFE syndrome.[22,23] Although mast cell degranulation may contribute to the pathophysiology of AFE, this effect may be a secondary product of the inflammatory cascade, rather than causal, and thus the term *anaphylactoid syndrome of pregnancy* may be a misnomer.[23]

Other immune-mediated mechanisms have also been implicated in AFE. A case-control study demonstrated low levels of the complement components C3 and C4 among women diagnosed with AFE compared with controls, suggesting that complement activation may also contribute to the inflammatory cascade.[22] Whether complement plays a primary[19] or secondary role[24] in the AFE syndrome is unknown. A heat-stable pressor agent in meconium has been suggested as another possible mediator of AFE; in a goat model this agent caused a circulatory response similar to that seen in human AFE.[25]

Alternatively, the hemodynamic consequences of AFE could derive from activation of the coagulation system, mediated through platelet activation. Fetal squamous cells and syncytiotrophoblasts display high concentrations of tissue factor and phosphatidylserine.[26-28] Tissue factor irreversibly aggregates platelets,[29] leading to platelet degranulation, which releases thromboxane, serotonin, and additional mediators that amplify the immunologic systems. Serotonin is a potent pulmonary vasoconstrictor that produces vasodilation in the systemic vasculature and may lead to early right-sided heart failure in the AFE syndrome.[27,30,31]

Coagulopathy develops in the majority of women who survive the initial cardiovascular collapse.[12,32] One proposed mechanism involves tissue factor. As pregnancy progresses, increasing amounts of tissue factor, a potent procoagulant, accumulates in the amniotic fluid.[27,28] Tissue factor binds factor VII, thus activating the extrinsic pathway and triggering clotting by activating factor X, with the subsequent development of a consumptive coagulopathy.[27] A second possible mechanism is that amniotic fluid has a thromboplastin-like effect, which induces platelet aggregation, releases platelet factor III, and activates the clotting cascade.[33] Other components of amniotic fluid, the amniochorion, and the placenta have also been implicated in contributing to the coagulopathy. Uterine atony, whether due to a specific myometrial depressant or from uterine hypoperfusion, may exacerbate hemorrhage and consumptive coagulopathy in AFE.[34]

There is conflicting evidence regarding whether the bleeding seen in AFE is due primarily to a consumptive coagulopathy versus massive fibrinolysis. In one *in vitro* study, investigators added 10 to 60 μL of clear autologous amniotic fluid to 330 μL of blood from volunteers undergoing uneventful cesarean delivery.[35] Thromboelastographic analysis of the specimens revealed accelerated clot formation but no evidence of fibrinolysis. However, because of the rapid and severe hypofibrinogenemia observed during AFE, some investigators have suggested that severe hyperfibrinolysis is also present.[36] Future work is necessary to further refine our understanding of the coagulopathy that accompanies AFE.

Clinical Presentation

Whereas the classic presentation of AFE includes acute respiratory distress, cardiovascular collapse, and coagulopathy near the time of delivery, a broad range of AFE syndromes have been described in situations in which other diagnoses were excluded (Table 39-1).[12,20,37]

Currently, the UKOSS provides the most comprehensive prospective surveillance for amniotic fluid embolism in the world. All hospitals in the United Kingdom with a consultant-led maternity unit report all suspected cases of AFE, along with monthly delivery volume data, for central review and reporting.[5,38] Cases of AFE are defined using either *clinical criteria* that include acute hypotension, cardiac arrest, acute hypoxemia, and/or coagulopathy in the absence of any other potential explanation for the symptoms and signs observed, or *pathologic evidence* indicating the presence of fetal squames or hair in the maternal lungs. All women in the UKOSS registry demonstrated at least one cardinal feature of AFE, including shortness of breath, hypotension, coagulopathy, maternal hemorrhage, or premonitory symptoms (see Table 39-1).[5]

A national registry in the United States accepted voluntary submissions of medical records for patients with suspected AFE beginning in 1988. The diagnosis of AFE was confirmed based on meeting all entry criteria outlined in Box 39-1. Data for 46 confirmed cases of AFE were last published in 1995.[12]

AFE most often occurs during labor; intrapartum events comprise 56% of cases in the UKOSS registry[5] and 70% in the U.S. registry.[12] In the U.S. registry, seizure and dyspnea were the two most common presenting symptoms in women who collapsed before delivery.[12] Maternal symptoms may precede FHR changes, as shown in Figure 39-1. Fetal bradycardia, or the abrupt onset of variable decelerations that progress to fetal bradycardia, may also herald AFE in labor.[12]

AFE can present after abdominal trauma,[39] after first-trimester abortion,[40] in the second trimester,[41] at the time of delivery,[12] and in the postpartum period.[42] Although acknowledging that AFE has been reported up to 48 hours postpartum,[34] both the U.S. and U.K. registries require the diagnosis of AFE to be made within 30 minutes of delivery.[4,12]

Close inspection of hemodynamic data reveals a biphasic cardiovascular response during AFE. During the

TABLE 39-1 Features of Amniotic Fluid Embolism at Presentation

	Percent Exhibiting Feature (n = 60)*	Percent Exhibiting Feature as First Symptom or Sign (n = 60)*
Maternal hemorrhage†	65%	2%
Hypotension†	63%	8%
Shortness of breath†	62%	20%
Coagulopathy†	62%	0%
Premonitory symptoms† (i.e., restlessness, agitation, numbness, tingling)	47%	30%
Acute fetal compromise	43%	20%
Cardiac arrest	40%	8%
Dysrhythmias	27%	5%
Seizure	15%	7%

*Some women had multiple features; therefore, the totals are greater than 100%.
†Cardinal feature of amniotic fluid embolism. Twenty-seven percent of women experienced at least four of the five cardinal features.
Data from Knight M, Tuffnell D, Brocklehurst P, et al. Incidence and risk factors for amniotic-fluid embolism. Obstet Gynecol 2010; 115:910-7.

BOX 39-1 United States Amniotic Fluid Embolism Registry Entry Criteria

1. Acute hypotension or cardiac arrest
2. Acute hypoxia (dyspnea, cyanosis, respiratory arrest)
3. Coagulopathy (laboratory evidence or hemorrhage without an alternative explanation)
4. Onset of the above during labor, cesarean delivery, dilation and evacuation, or within 30 minutes postpartum
5. Absence of an alternative explanation for the observed signs/symptoms

Modified from Clark SL, Hankins GD, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995; 172:1158-67.

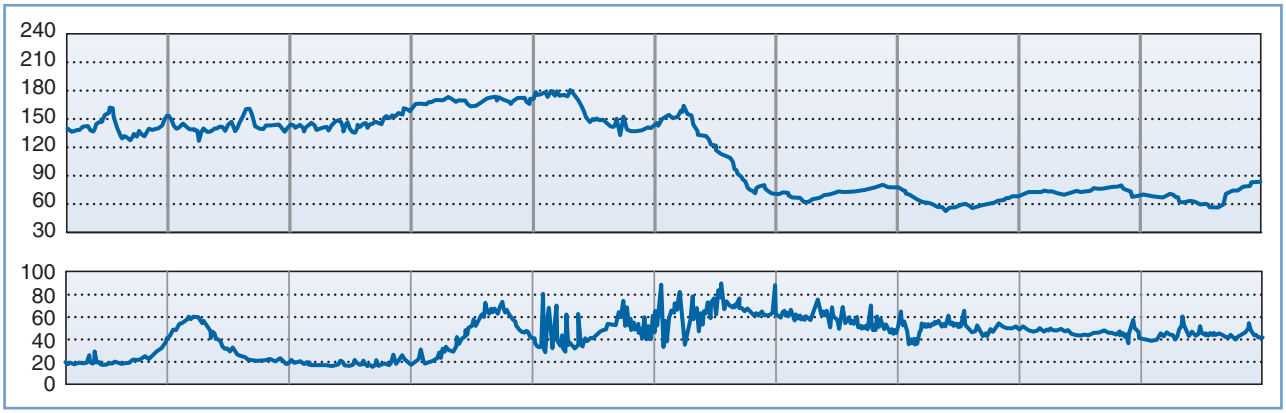

FIGURE 39-1 ■ Fetal heart rate tracing in a patient with amniotic fluid embolism. Maternal symptoms began just before the onset of spontaneous uterine hypertonus and fetal bradycardia. (Modified from Clark SL, Hankins GDV, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995; 172:1158-67.)

initial phase, acute pulmonary hypertension results in right ventricular dilation, a decrease in cardiac output, and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch resulting in oxygen desaturation. Early arterial blood gas analysis may demonstrate evidence of profound shunt.[12] In the U.S. registry, 11 of 17 patients with a blood gas sample drawn within 30 minutes of the acute event demonstrated an initial Pao_2 less than 30 mm Hg while breathing an Fio_2 of 100%.[12] Release of endogenous catecholamines may produce a brief period of systemic hypertension and uterine tachysystole that precedes hypotension or cardiac arrest.[12] Electrocardiographic findings are nonspecific and vary from ST-wave and T-wave abnormalities to arrhythmias or asystole. A chest radiograph may show diffuse bilateral heterogeneous or homogenous areas of opacity.

Echocardiography typically demonstrates a dilated, akinetic right ventricle, pulmonary hypertension, and a normally-contracting left ventricle with a nearly obliterated cavity.[43,44] Initially, right ventricular failure leads to right ventricular dilation, which compresses the left ventricle and impedes left ventricular filling and cardiac output.[43,44] A second phase commences when right ventricular function improves,[44] typically 15 to 30 minutes after the initial event. At this point, left ventricular failure may persist due to ischemic injury to the left ventricle,[45] or direct myocardial depression,[34] and is accompanied by decreased systemic ventricular resistance, decreased left ventricular stroke index, and pulmonary edema.[46,47] Women who survive to the second phase may also experience hemorrhage and disseminated intravascular coagulopathy. Laboratory analysis may reveal anemia, thrombocytopenia, prolonged prothrombin time or activated partial thromboplastin time (aPTT) or both, and decreased fibrinogen levels.[12,34] In a minority of cases there is massive hemorrhage and disseminated intravascular coagulopathy without preceding cardiopulmonary collapse.[37]

Because many of the signs and symptoms are nonspecific, the differential diagnosis for AFE is extensive and should include nonobstetric, obstetric, and anesthetic causes (Box 39-2). Even though the time course and clinical presentation of many of these competing diagnoses are similar, only amniotic fluid embolism and placental abruption result in a relatively sudden onset of consumptive coagulopathy after maternal collapse. However, partial AFE syndromes have been described in the literature.[20] Therefore, the absence of coagulopathy should not exclude the possibility of AFE.

BOX 39-2 Differential Diagnosis of Amniotic Fluid Embolism

Nonobstetric
- Myocardial infarction
- Pulmonary embolism
- Aspiration
- Sepsis
- Anaphylaxis
- Venous air embolism

Obstetric
- Placental abruption
- Eclampsia
- Uterine rupture or laceration
- Uterine atony

Anesthetic
- High neuraxial blockade ("total spinal")
- Local anesthetic systemic toxicity
- Medication error

Confirmatory Tests

To date, there is no definitive test to confirm the diagnosis of AFE, although the UKOSS considers the finding of fetal material in the maternal pulmonary vasculature at autopsy to be pathognomonic for AFE.[5] However, fetal squamous cells and trophoblasts are commonly found in the maternal circulation of healthy parturients. Furthermore, differentiating between maternal and fetal cells histologically is challenging.[18] Clinicians should therefore not place invasive monitors solely for the purpose of aspirating cells of fetal origin.

Several biochemical markers have been suggested. Although some of these may be promising based on preliminary data and theoretical understanding of AFE, studies of test performance are limited by delayed sample acquisition and small sample size owing to the rarity and unpredictability of the AFE syndrome.

Several markers suggest an anaphylactic/anaphylactoid mechanism. Mast cells release tryptase and histamine during degranulation; tryptase has been used as a marker for anaphylaxis because its half-life is longer than that of histamine. Elevations in serum tryptase have been reported in some parturients with AFE.[23] However, a case series found normal tryptase and urinary histamine levels in nine women with presumed AFE.[22] Pulmonary mast cell counts have also been suggested; however, this measurement can only be obtained using immunohistochemistry at autopsy and therefore is of limited applicability in the clinical setting. In one observational study, the mean pulmonary mast cell count per fixed area for parturients who died of AFE was similar to that of parturients who died of anaphylactic shock but was higher than the mean counts in both pregnant and nonpregnant control patients.[48] These data, together with the finding of minimal to no elevation in serum tryptase, suggest that pulmonary mast cell degranulation may be a secondary process in AFE.[23]

Complement activation may cause mast cell degranulation, and there is some evidence supporting widespread complement activation, and depressed C3 and C4 levels, in AFE.[22] However, because complement is activated during acute respiratory distress syndrome and other inflammatory states, results are not specific for AFE. Zinc coproporphyrin[49] and sialyl Tn antigen[22] are two biomarkers that are components of meconium and have been associated with the AFE syndrome. Sialyl Tn is a mucinous glycoprotein that originates in the fetal gastrointestinal tract and is also associated with mucinous gastrointestinal tumors. Most recently, insulin-like

growth factor–binding protein-1 (IGFBP-1) was identified as a sensitive and specific biomarker for AFE in a case-control study conducted in 13 delivery centers in France.[50] IGFBP-1 levels exceeded 104.5 µg/L in 23 of 25 women with AFE and remained below 95 µg/L in all patients with postpartum hemorrhage due to atony, thrombotic pulmonary embolism, or uncomplicated labor. A single false-positive result was found in a woman with acute fatty liver of pregnancy. Based on the median concentration of IGFBP-1 in the amniotic fluid and blood samples, the investigators estimated that 6 to 92 mL of amniotic fluid passed into the maternal circulation in women who experienced the AFE syndrome.[50]

Management

Although no single intervention has been shown to reliably reverse the AFE syndrome, prompt recognition and aggressive resuscitation may improve maternal and fetal outcomes. Maternal resuscitation should focus on three priorities: (1) maintenance of oxygenation; (2) hemodynamic support; and (3) correction of coagulopathy (Box 39-3).

On diagnosis of AFE, 100% oxygen should be delivered to the patient. Given the risk for coagulopathy and hemorrhage, large-bore intravenous access is warranted. An arterial line and central venous pressure catheter may facilitate hemodynamic monitoring, blood sampling, and vasopressor administration. Transesophageal echocardiography may be useful to guide volume resuscitation and selection of appropriate vasopressor therapy.

In addition to standard resuscitative measures, other management strategies have been reported for AFE. The use of cardiopulmonary bypass, extracorporeal membrane oxygenation, continuous hemofiltration, and exchange transfusions have all been described in the literature.[5,43,51] It is speculated that these technologies may filter amniotic fluid or vasoactive mediators from the systemic circulation. Strategies for management of the early right-sided heart failure seen in AFE include inhaled nitric oxide, prostacyclin, right ventricular assist devices, and vasopressors such as vasopressin, dobutamine, and milrinone.[52,53] The use of extracorporal membrane oxygenation and intra-aortic balloon counterpulsation has also been reported for management of left-sided heart failure.[54]

In AFE, intact neonatal survival is related to the time interval from the onset of maternal compromise to delivery.[12] In the event of maternal cardiopulmonary arrest, the American Heart Association recommends that delivery of the fetus should occur within 5 minutes to increase the probability of good outcomes for both the mother and her neonate.[55] Although the operating room may provide a more favorable environment for surgery and resuscitation, simulation studies have suggested that resuscitation quality and the arrest-to-delivery interval both suffer with maternal transport[56,57]; therefore, strong consideration should be given to performing a bedside perimortem cesarean delivery.

Because coagulopathy will likely ensue for the majority of AFE survivors, the obstetric and anesthesia providers should activate a massive transfusion protocol as soon as AFE is suspected. Blood and component therapy should be guided by the clinical presentation (see Chapter 38). Close communication with the blood bank is paramount because large quantities of blood products may be needed. Analysis of the U.K. registry demonstrated that patients who developed a coagulopathy received between 12 and 106 units of blood products.[4] Potential pharmacologic therapies for the coagulopathy associated with AFE include antifibrinolytic agents (e.g., tranexamic acid, aprotinin), recombinant factor VIIa (rVIIa), prothrombin complex concentrate, and fibrinogen concentrate.[36,58,59]

The use of rVIIa to treat intractable hemorrhage in the AFE syndrome is controversial. The use is off-label in obstetric hemorrhage (see Chapter 38). Recombinant factor VIIa binds to tissue factor and initiates clotting via the extrinsic pathway. Although individual case reports have described improvement in hemostasis, rVIIa has been associated with thrombotic complications. A meta-analysis of 25 trials involving 3849 nonobstetric bleeding patients without hemophilia found a significant increase in arterial thromboembolic events among patients who received rVIIa (relative risk [RR], 1.45; 95% CI, 1.02 to 2.05).[60]

A case-controlled study based on a systematic review of case reports of women with the AFE syndrome identified a twofold increase in risk for death or permanent

BOX 39-3 Management of Amniotic Fluid Embolism

Airway

- Administer 100% oxygen.
- Intubate the trachea and support ventilation as needed.

Cardiovascular Support

- Start chest compressions if indicated.
- Ensure left uterine displacement to relieve aortocaval compression if appropriate.
- Administer fluids and vasopressors.
- Establish large-bore intravenous access.
- Consider invasive pressure monitoring.

Fetus

- Monitor fetal well-being.
- Expedite delivery for nonreassuring status in a viable fetus or in the event of maternal cardiopulmonary arrest in the second half of pregnancy (i.e., perimortem cesarean delivery).

Hemostatic Support

- Activate the obstetric hemorrhage protocol and massive transfusion protocol.*
- Send blood for serial laboratory assessment to monitor for coagulopathy and electrolyte disturbances.
- Provide blood component therapy as indicated.
- Ensure normothermia.

Postresuscitation Care

- Notify the intensive care unit of the potential admission.

*See Chapter 38.

disability among 16 women treated with rVIIa compared with 28 control patients who underwent surgery to control bleeding but did not receive rVIIa.[58] Among survivors, treatment with rVIIa was associated with more permanent disability (risk ratio, 4.0; 95% CI, 1.5 to 10.4), largely attributed to thrombosis in major organs.[58] An unmeasured increase in severity of disease in the treatment group compared with the control group could explain these dismal results because the population of patients who did not survive to the time of operation was excluded from the analysis. In this case-controlled study of case reports,[58] 50% of parturients treated with rVIIa survived, whereas in the 2010 UKOSS dataset,[5] 93% of the parturients treated with rVIIa survived (n = 14). However, the UKOSS data did not report neurologic outcomes or thromboembolic complications.[5] The differences in outcomes between these two studies may be explained in part by differing definitions of AFE and differences in case ascertainment. Only five cases in the case-controlled study[58] were peer-reviewed publications; the remainder were obtained from abstracts presented at national meetings and from registry data.

Maternal and Perinatal Outcomes

The maternal mortality ratio associated with AFE has been reported between 0.5 and 1.7 deaths per 100,000 live births.[8] AFE accounted for 7.5% of pregnancy-related deaths in the United States between 1998 and 2005.[1] The case-fatality rate from the UKOSS data was 20% (95% CI, 11 to 32),[5] significantly lower than the reported fatality rate of 61% in the 1988 to 1994 analysis of the U.S. AFE registry.[12] In the UKOSS dataset, patients who died of AFE were more likely to be from ethnic minority groups than were survivors, even after adjusting for confounders such as age, socioeconomic status, obesity, and parity (adjusted odds ratio [aOR], 11.8; 95% CI, 1.4 to 99.5).[5] Similar racial/ethnic disparities were seen in the United States.[1] Improvements in the management of critically ill parturients may have contributed to the decline in the case-fatality rate observed in the two studies, but the disparity in outcomes by race or ethnicity suggests further systems improvements are necessary.

Cardiac arrest complicated 87% of AFE cases reported to the U.S. registry but only 40% of cases identified by UKOSS.[5,12] This difference may reflect more comprehensive ascertainment in the United Kingdom that captures less severe cases; alternatively, improvements in early recognition and management of AFE over the past 15 years may explain improved outcomes recently reported from the United Kingdom compared with those previously published from the U.S. registry.

Neurologic outcomes for survivors are poor. The 1995 analysis of the U.S. registry reported a 15% overall rate of intact neurologic survival, with only 8% neurologically intact after cardiac arrest.[5,12] Neonates have a high overall survival rate, with approximately 80% of infants surviving,[5,12] but also have low rates of intact neurologic survival, with only 39% of survivors neurologically intact.[12] Intact neurologic survival for infants is related to the cardiac arrest-to-delivery interval; delays of greater than 15 minutes are associated with worse outcomes.[12]

Recurrent AFE has not been reported.

THROMBOEMBOLIC DISORDERS

Incidence

Venous thromboembolic events (VTE) in pregnancy refer to deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). The incidence of pregnancy-related thromboembolic events is 1.0 to 1.7 events per 1,000 pregnancies.[61-63] The range of reported incidences may reflect differing study designs and diagnostic criteria for thromboembolism, in addition to biologic differences among populations. Analysis of administrative data from a nationally representative sample of United States hospital admissions that included 9,058,162 pregnancy admissions and 73,834 postpartum admissions demonstrated 1.36 cases of DVT and 0.36 cases of PTE per 1,000 deliveries.[61] Fifteen to 24 percent of pregnant women with an untreated DVT develop a PTE.[61,64,65]

There is a fivefold greater odds of thromboembolic events during pregnancy (odds ratio [OR], 4.6; 95% CI, 2.7 to 7.8), and a 60-times greater odds in the postpartum period (95% CI, 26.5 to 135.9) than in nonpregnant patients.[66] Study results conflict as to whether there is an increased risk by trimester. A meta-analysis of 12 studies that evaluated the period of risk for DVT in pregnancy found that 21.9% of antepartum DVTs develop in the first trimester (95% CI, 17.4 to 27.3), 33.7% in the second trimester (95% CI, 28.1 to 39.8), and 47.6% in the third trimester (95% CI, 39.2% to 56.2%).[67] The highest risk for thromboembolic events occurs postpartum. Analysis of data from a 30-year population-based cohort (n = 50,080 births) revealed that the risk for both DVT and PTE was highest in the first week postpartum (incidence rate, 3573 per 100,000 woman-years [95% CI, 2475 to 4993 per 100,000]), with a progressive decline thereafter.[68]

Overall, the incidence of DVT appears to be stable or decreasing while the incidence of PTE appears to be increasing.[63,68] Despite the increased incidence of PTE, mortality from venous thromboembolism is decreasing.[1,62,69,70] From 1985 to 2005, the leading cause of direct maternal deaths, as reported by the Confidential Enquiries into Maternal Deaths in the United Kingdom (CMACE), was PTE.[69] In the most recent report (2006-2008), the overall rate of maternal death decreased compared with the previous triennium, largely as a result of the decreased rate of deaths due to PTE; PTE was no longer the leading cause of direct maternal deaths.[69] This change is likely the result of early recognition of at-risk patients, as well as the increasing use of protocols for peripartum thromboprophylaxis. Ten percent of all maternal deaths in the Centers for Disease Control and Prevention (CDC) Pregnancy Mortality Surveillance System from 1998 to 2005, and 15% of all direct deaths in the 2006 to 2008 CMACE report, were attributable to PTE.[1,69]

Risk Factors

The two most important risk factors for thromboembolic events in pregnancy and the postpartum period are a previous history of thromboembolism and a diagnosis of thrombophilia.[61,63,70] Essentially all known thrombophilias increase risk for VTE in pregnancy, with the greatest risk increase noted in women homozygous for the factor V Leiden mutation.[71] Antenatal immobilization and obesity are the most important modifiable risk factors for VTE,[72] and their combination has a multiplicative effect.[73] In the most recent CMACE report, 81% of the 16 patients who died of PTE were either overweight or obese.[69] Compared with vaginal birth, cesarean delivery essentially doubles the risk for postpartum venous thromboembolism, with greater increases noted for unplanned, as opposed to elective, cesarean delivery.[61-63] The American College of Chest Physicians has defined major and minor risk factors for postcesarean VTE (Box 39-4).[74]

BOX 39-4 Risk Factors for Venous Thromboembolism in the Postpartum Period

Major Risk Factors: presence of at least *one* risk factor*

- Immobility (strict bed rest for ≥ 1 week in the antepartum period)
- Previous venous thromboembolism
- Preeclampsia with fetal growth restriction
- Thrombophilia
  - Antithrombin III deficiency
  - Factor V Leiden (homozygous or heterozygous)
  - Prothrombin G20210A (homozygous or heterozygous)
- Medical conditions
  - Systematic lupus erythematous
  - Heart disease
  - Sickle cell disease
- Postpartum hemorrhage ≥ 1000 mL *and* surgery
- Blood transfusion
- Postpartum infection

Minor Risk Factors: presence of at least *two* risk factors*

- Body mass index > 30 kg/m^2
- Emergency cesarean delivery
- Multiple pregnancy
- Postpartum hemorrhage > 1000 mL
- Smoking > 10 cigarettes/day
- Fetal growth restriction
- Thrombophilia
  - Protein C deficiency
  - Protein S deficiency
- Preeclampsia

*The presence of at least one major risk factor or two minor risk factors is an indication for prophylactic therapy for venous thromboembolism (see text).

Modified from Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e691S-736S.

Pathophysiology

Virchow's triad describes three factors that contribute to an increased risk for thromboembolism: (1) **venous stasis**, (2) **vascular damage**, and (3) **hypercoagulability**. The incidence of each factor is increased during pregnancy or in the postpartum period. Venous stasis occurs due to venocaval compression and possibly decreased mobility later in pregnancy. Separation of the placenta from the uterine wall traumatizes the endometrium, which accelerates the coagulation cascade. Finally, pregnancy is a relatively hypercoagulable state, associated with enhanced platelet turnover, coagulation, and fibrinolysis.[75,76] Thrombin generation and the concentration of clotting factors increase during pregnancy, including factors I (fibrinogen), V, VII, VIII, IX, X, and XII.[75] Platelet count typically remains unchanged or is decreased during pregnancy. Fibrinolytic activity decreases during the 48 hours after delivery and enhances clot stability in the early postpartum period.[75]

The prognosis of PTE depends on the following factors: (1) the size and number of emboli; (2) concurrent cardiopulmonary function; (3) the rate of clot fragmentation and lysis; (4) the presence or absence of a source for recurrent emboli; and (5) the location of the embolism (proximal or main pulmonary artery embolism is more symptomatic than segmental embolization).[77] Massive PTE can occlude the pulmonary vasculature and precipitate cardiopulmonary arrest; smaller emboli may also lead to cardiopulmonary failure by triggering pulmonary arterial vasospasm[78] and secondary pulmonary edema.[79] Local platelets embedded in the clot release serotonin, adenosine diphosphate, and thrombin, factors that promote both vasoconstriction and bronchoconstriction.[80] Redistribution in pulmonary blood flow leads to "hyperperfusion" of otherwise low $\dot{V}/\dot{Q}$ zones in unaffected areas of the lung; the resulting intrapulmonary shunts can generate hypoxemia disproportionate to the cross-sectional area occluded by clot.[81] At the same time, regional hypoxic pulmonary vasoconstriction exacerbates pulmonary hypertension initiated by mechanical and humoral factors. Intracardiac shunting may develop when elevated right ventricular pressure forces blood across a probe-patent foramen ovale. Elevated pulmonary venous pressure and aggressive intravenous volume replacement may disrupt capillary integrity and exacerbate pulmonary edema.[79]

The increase in right ventricular pressure leads to right ventricular dilation, with increased wall tension and oxygen demand, and a leftward shift of the interventricular septum.[78] Compression of the left ventricle combined with a decrease in preload impairs left ventricular function, cardiac output, and coronary arterial perfusion, with eventual myocardial ischemia and cardiopulmonary failure.

Deep Vein Thrombosis

Clinical Presentation

The signs and symptoms of DVT are nonspecific and often mimic normal symptoms of pregnancy, specifically lower leg edema and pain. A systematic review of the

anatomic distribution of DVT in symptomatic pregnant patients (six studies, pooled n = 124) identified left leg thrombus in 88% of pregnant women in whom the side of the DVT was reported.[82] Most thrombi were proximally located in the iliac or femoral veins or both. This distribution is different from the anatomic distribution seen in nonpregnant patients, who are more likely to have thrombi in the distal calf vessels.[82] A prospective observational study of serial ultrasonographic examinations in pregnant women (n = 24) found an increase in vessel diameter and a decrease in flow velocity in the proximal deep leg veins with increasing gestation; this finding was most notable in the common femoral vein.[83] The flow velocity was slower in the left leg than in the right leg, presumably owing to uterine compression of the left iliac vein where it crosses the right iliac artery.[83]

TABLE 39-2 **Physical Findings in Pulmonary Embolism**

Finding	Patients Affected (%)
Tachypnea	85
Tachycardia	40
Fever	45
Accentuated second heart sound	50
Localized rales	60
Thrombophlebitis	40
Supraventricular dysrhythmia	15

Modified from Spence TH. Pulmonary embolization syndrome. In Civetta JM, Taylor RW, Kirby RR, editors. Critical Care. Philadelphia, JB Lippincott, 1988:1091-102.

Diagnosis

For patients with new-onset signs or symptoms suggestive of DVT, the American College of Obstetricians and Gynecologists (ACOG) recommends compression ultrasonography of proximal veins as the initial diagnostic test.[84] If the test is negative, and involvement of the iliac vessels is not suspected, no further action other than routine surveillance is necessary. A positive result warrants treatment (see later discussion). If the results are negative or equivocal, and iliac vein thrombosis is suspected, clinicians may opt for magnetic resonance imaging or presumptive anticoagulation.[84]

The D-dimer test is useful in nonpregnant patients because it has a high sensitivity and a high negative predictive value. Unfortunately, D-dimer levels are increased in pregnancy, making interpretation of elevated levels difficult in pregnant women. In one prospective, longitudinal study, serial D-dimer levels were evaluated in 89 healthy pregnant women; values exceeded the normal nonpregnant reference range in all but one woman in the third trimester.[85] Therefore, the D-dimer test is not currently recommended for diagnosis of DVT in pregnancy[84]; however, future work may delineate pregnancy-specific thresholds.

Pulmonary Thromboembolism

Clinical Presentation

Clinical suspicion for PTE is critical to ensure timely diagnosis and treatment (Table 39-2). Physical signs and symptoms may be subtle and limited to symptoms (e.g., shortness of breath) that mimic normal pregnancy. Palpitations, anxiety, chest pain that may be pleuritic, cyanosis, diaphoresis, and cough with or without hemoptysis may all indicate PTE. Physical examination of the patient commonly reveals tachypnea, crackles, decreased breath sounds (more common than rhonchi or wheezing), and tachycardia. Signs of right ventricular failure, including an accentuated or split second heart sound, jugular venous distention, a parasternal heave, and hepatic enlargement, may be apparent. The electrocardiogram may show signs of right ventricular strain, including a right-axis shift, P pulmonale, ST-segment abnormalities, and T-wave inversion, as well as supraventricular arrhythmias. One or more of the signs of DVT (calf or thigh edema, erythema, tenderness, palpable cord) generally accompanies the pulmonary or cardiovascular findings.[64,77] Despite the observation that pulmonary shunt is a common feature of PTE, as many as 30% of all patients with a pulmonary embolus have an arterial Pao_2 greater than 80 mm Hg, and the diagnosis of PTE cannot be excluded on the basis of an apparently normal Pao_2.[77]

Invasive hemodynamic monitoring typically demonstrates (1) normal to low (< 15 mm Hg) pulmonary artery occlusion pressure, (2) increased mean pulmonary artery pressure (although typically < 35 mm Hg), and (3) increased (> 8 mm Hg) central venous pressure.[79] Calculated pulmonary vascular resistance typically is more than 2.5 times normal resistance; right ventricular failure occurs when the mean pulmonary artery pressure exceeds 35 to 45 mm Hg.[79] Left ventricular failure may occur secondary to poor left ventricular filling and arterial hypoxemia.

Diagnosis

There are no validated risk criteria, such as the Wells or Geneva criteria, for pregnant patients, which makes diagnosis of PTE in pregnancy challenging. If the pregnant patient has signs or symptoms suggestive of DVT in addition to the signs or symptoms of PTE, compression ultrasonography should be done. If the results are positive, treatment should ensue; however, if results are negative, further imaging is necessary. In the absence of symptoms of DVT, or if compression ultrasonography of the legs is negative, the choice of the next diagnostic test to be performed is controversial. Factors such as the likelihood of a nondiscriminatory test and the radiation exposure to both mother and fetus must be considered in decision-making.

The American Thoracic Society developed an evidence-based guideline for the evaluation of suspected PTE, which has been endorsed by the ACOG.[86] A diagnostic algorithm for suspected PTE is shown in Figure 39-2. If there are no signs or symptoms of DVT, a chest radiograph should be performed, both to exclude

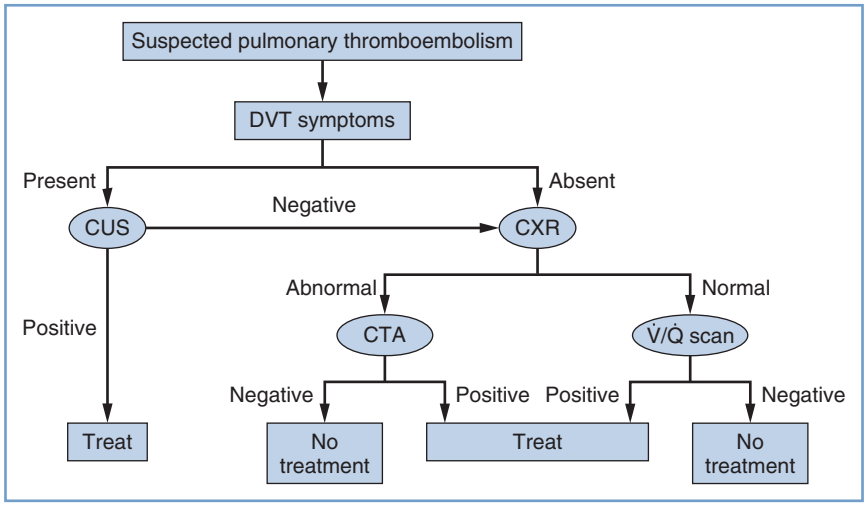

FIGURE 39-2 ■ Diagnostic algorithm for workup of suspected pulmonary thromboembolism during pregnancy. *CTA,* computed tomography pulmonary angiography; *CUS,* compression ultrasonography; *CXR,* chest radiograph; *DVT,* deep vein thrombosis; *V̇/Q̇ scan,* ventilation-perfusion scan.

alternative diagnoses, and to guide decision-making for the next most appropriate test. If the chest radiograph is normal, V̇/Q̇ scanning should be performed.[86] A retrospective study of 304 women who underwent computed tomographic angiography (CTA) or V̇/Q̇ scanning at a single institution between 2001 and 2006 demonstrated that pregnant women with a normal chest radiograph have a fivefold higher rate of a nondiagnostic result from a CTA compared with a V̇/Q̇ scan (RR, 5.3; 95% CI, 2.1 to 13.8).[87] The use of chest radiography as a screening procedure may also minimize the amount of radiation to which a pregnant woman and her fetus are exposed if the pregnant patient is a candidate for V̇/Q̇ scanning.[86] If the chest radiograph is abnormal, CTA is the next appropriate test because the proportion of nondiagnostic V̇/Q̇ scans in the presence of an abnormal chest radiograph has been reported to be as high as 48%.[88] If either the V̇/Q̇ scan or CTA is positive, anticoagulation should ensue. The use of magnetic resonance pulmonary angiography has not been validated in the pregnant population. A new diagnosis modality, V̇/Q̇ single-photon emission computed tomography (SPECT), has recently been introduced[89,90]; however, to date, the V̇/Q̇ SPECT has not been evaluated in pregnant women.

Perhaps the greatest concern with diagnostic imaging for PTE is maternal and fetal exposure to ionizing radiation. The teratogenic effects of ionizing radiation are discussed in Chapter 17).[91] Both V̇/Q̇ scanning and CTA are associated with low-doses of fetal radiation exposure (< 1 mGy). V̇/Q̇ scanning delivers a higher *fetal* dose of radiation than CTA; however, the *maternal* radiation exposure is higher with CTA, particularly radiation to the breast tissue. A patient's lifetime breast cancer risk may increase as much as 14% after CTA.[92]

Management of Thromboembolic Disorders

Anticoagulation

All women with a new-onset thromboembolic event in pregnancy should be therapeutically anticoagulated.[84] Patients with a previous history of thrombosis, certain high-risk populations, such as patients with acquired or inherited thrombophilias, or patients with a mechanical heart valve should be anticoagulated during pregnancy as well as the postpartum period. The ACOG practice bulletin on thromboembolism in pregnancy outlines which patients should receive prophylactic or therapeutic anticoagulation.[84]

Although the exact dose and regimen for anticoagulation remain controversial, two classes of drugs are typically used to initiate anticoagulation: **low-molecular-weight heparin (LMWH)** and **unfractionated heparin (UFH)** (see Chapter 44). Table 39-3 lists anticoagulation regimens commonly used in pregnancy. The ACOG does not make a distinction between UFH and LMWH for initiation of anticoagulation[84]; however, the American College of Chest Physicians recommends LMWH for prophylactic and therapeutic anticoagulation for pregnant women instead of UFH.[74]

LMWH has an enhanced ratio of antithrombotic (anti–factor Xa) to anticoagulant (anti–factor IIa) activity when compared with UFH and does not affect aPTT measurement.[93] A 2005 systematic review (64 studies, pooled n = 2777) evaluated the efficacy and safety of LMWH in pregnancy. The rate of VTE was 0.9% (95% CI, 0.6% to 1.3%), the rate of significant maternal bleeding was 2.0% (95% CI, 1.5% to 2.6%), and there were no reported cases of heparin-induced thrombocytopenia when LMWH was used for any indication in pregnancy.[93]

TABLE 39-3 Commonly Used Anticoagulation Regimens during Pregnancy

Drug	Dose
Prophylactic LMWH	Enoxaparin 40 mg SC once daily Dalteparin 5000 units SC once daily Tinzaparin 4500 units SC once daily
Therapeutic LMWH (weight-adjusted treatment dose)	Enoxaparin 1 mg/kg q12h Dalteparin 200 units/kg once daily Tinzaparin 175 units/kg once daily Dalteparin 100 units/kg q12h
Prophylactic UFH	UFH 5000-10,000 units SC q12h
Therapeutic UFH (weight-adjusted treatment dose)	UFH 10,000 units or more SC q12h adjusted to target aPTT (1.5-2.5 times the normal range 6 h after injection)
Postpartum anticoagulation	Prophylactic LMWH/UFH for 4-6 wk *or* Vitamin K antagonists for 4-6 wk (target INR 2.0-3.0). Therapy must overlap with LMWH/UFH until INR ≥ 2.0 for 2 days

aPTT, activated partial thromboplastin time; *INR,* international normalized ratio; *LMWH,* low-molecular weight heparin; *SC,* subcutaneous; *UFH,* unfractionated heparin.

Modified from American College of Obstetricians and Gynecologists. Thromboembolism in pregnancy. ACOG Practice Bulletin No. 123. Washington, DC. (Obstet Gynecol 2011; 118:718-28.)

An older systematic review (1999) did not find any significant increase in osteoporosis in pregnant women treated with LMWH compared with nonpregnant controls.[94]

The pharmacokinetics of LMWH are altered during pregnancy[95]; however, dose adjustment is not routinely required for prophylactic therapy.[84] When LMWH is used for therapeutic anticoagulation, dosing can be adjusted based on anti–factor Xa activity; the desired peak level is 0.6 to 1.0 U/mL measured 4 hours after injection.[84] Thromboelastography provides an alternative method to assess LMWH activity. Carroll et al.[96] demonstrated that the delta reaction time (ΔR) measured by thromboelastography correlates with anti–factor Xa levels in the pregnant woman and allows LMWH doses to be adjusted to ensure anticoagulation or, conversely, confirms the absence of anticoagulation. LMWH is cleared by the kidney; therefore, dose reduction may be required in patients with renal failure.

UFH therapy may be used to initiate anticoagulation or to maintain therapy as the patient nears delivery (see later discussion). UFH exerts its anticoagulant activity by binding to antithrombin III and potentiates inactivation of other coagulation factors, including thrombin (IIa), factors IXa, Xa, XIa, and XIIa, and kallikrein. Typically, UFH is administered as a subcutaneous injection for both prophylactic and therapeutic therapy. Intravenous therapy becomes necessary when PTE causes hemodynamic instability; it is initiated with a bolus dose and maintained by infusion titrated to a therapeutic aPTT value. The aPTT measured 6 hours after an injection or dose adjustment should be maintained at 1.5 to 2.5 times the normal range.[84] In pregnancy, the bioavailability of UFH decreases owing to an increase in heparin-binding proteins, increased plasma volume, increased renal clearance, and increased degradation by plasma heparinases.[97] Based on pharmacodynamic studies, 5000 units of subcutaneous heparin are often inadequate to achieve *prophylactic* serum anti–factor Xa levels in the second half of pregnancy.[98] Thus, for therapeutic anticoagulation, the ACOG currently recommends UFH 10,000 units subcutaneous twice daily, with aPTT monitoring and dose adjustment.[84]

In patients who develop heparin-induced thrombocytopenia, or severe cutaneous reactions to heparin, fondaparinux is the preferred anticoagulant owing to minimal cross-reactivity with UFH.[84] Anticoagulation with other classes of drugs such as vitamin K antagonists, thienopyridines, direct factor Xa inhibitors, and direct thrombin inhibitors is possible in pregnancy, but the use of these medications is less common. Additionally, animal studies with rivaroxaban, a direct factor Xa inhibitor, and dabigatran, a direct thrombin inhibitor, have found teratogenic effects, reduced fetal viability, hemorrhagic changes, and placental abnormalities; thus, their use in pregnancy is not recommended.[99]

Antithrombotic Therapy and Anesthetic Implications

The greatest concern with neuraxial procedures in anticoagulated patients is spinal or epidural hematoma. A meta-analysis of the incidence of epidural hematoma in obstetric patients (8 studies, pooled n = 1.1 million) found an incidence of 1:183,000.[100] Notwithstanding the very low incidence, the consequences of a spinal-epidural hematoma can be devastating. The American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines include a summary of 16 cases of spinal hematoma after neuraxial anesthesia in obstetric patients; approximately half of the cases had some form of permanent motor or sensory dysfunction.[101]

A case report and literature review published in 2005 described six published cases of spontaneous epidural hematoma in pregnancy.[102] One proposed cause is that a pressure differential exists between the low-pressure epidural space and central venous pressure and that an increase in central venous pressure relative to the pressure in the epidural space leads to spontaneous rupture of the venous wall.[102] Case reports of spontaneous epidural hematoma in anticoagulated pregnant women, including patients with preeclampsia, have been reported.[103,104]

In 2010, ASRA published updated guidelines for regional anesthesia in patients receiving antithrombotic or thrombolytic therapy.[101] Among other topics, the updated guidelines address antithrombotic therapy during pregnancy. Owing to the relative paucity of outcome data in pregnant women, the ASRA suggests following the guidelines for surgical patients when developing clinical policy for obstetric patients with regard to initiation of neuraxial procedures and postpartum thromboprophylaxis (Table 39-4).[101] The ASRA guidelines do not make recommendations for patients receiving doses of more than 10,000 units of UFH daily or for patients

TABLE 39-4 Time Interval for Administration of Neuraxial Anesthesia after Anticoagulation

Therapy	American Society of Regional Anesthesia and Pain Medicine[101]	European Society of Anaesthesiology[105]
SC UFH, prophylactic	No delay*	4-6 h[†‡]
SC UFH, therapeutic	No recommendation*[‡]	8-12 h[‡§]
LMWH, prophylactic	10-12 h	12 h
LMWH, therapeutic	24 h	24 h

LMWH, low-molecular weight heparin; *SC,* subcutaneous; *UFH,* unfractionated heparin.
*No contraindication to neuraxial procedures with twice-daily dosing *and* total daily dose < 10,000 units.
[†]UFH ≤ 15,000 units/day.
[‡]Check platelet count if UFH therapy for more than 4 days (American Society of Regional Anesthesia and Pain Medicine) or more than 5 days (European Society of Anaesthesiology).
[§]Check activated partial thromboplastin time (aPTT) or activated clotting time (ACT) before initiation of neuraxial procedure.

receiving UFH more than twice daily. These guidelines differ somewhat from those of the European Society of Anaesthesiology.[101,105]

For patients being treated with UFH for more than 4 days, a platelet count should be assessed before initiation of neuraxial anesthesia procedures.[101] Measurement of aPTT is not necessary in patients receiving prophylactic UFH (≤ 5000 units twice a day) but may be indicated in patients receiving a large dose. Protamine reversal of UFH to facilitate more rapid administration of neuraxial anesthesia is not recommended. Further, protamine reversal of LMWH also is not recommended because it is unpredictable in reversing LMWH-induced anti–factor Xa activity.[101] If anticoagulant dosing is provided outside the ranges specifically addressed by the ASRA guidelines, individualized risk-benefit assessment is necessary to ascertain the best timing for initiation of neuraxial procedures. In some cases, confirmation of coagulation parameters (e.g., aPTT, anti–factor Xa level) within the normal range before initiation of neuraxial anesthesia may help to clarify the relative risk/benefit ratio for an individual patient.[101]

Other anticoagulant medications sometimes administered to pregnant women include aspirin, warfarin, and newer anticoagulant medications. In patients receiving warfarin therapy, the ASRA recommends discontinuing warfarin therapy for 4 to 5 days and waiting for normalization of the international normalized ratio (INR). Neuraxial catheters are *not* recommended in patients receiving fondaparinux, and neuraxial techniques are *not* recommended in patients anticoagulated with direct thrombin inhibitors. Treatment with thrombolytics is an absolute contraindication to neuraxial anesthesia.[101] By contrast, there is no contraindication to neuraxial anesthesia in patients who have received nonsteroidal anti-inflammatory drugs or aspirin if these drugs are used alone.[101]

If a patient is not a candidate for neuraxial anesthesia, noninvasive analgesic methods (e.g., intravenous opioids) should be offered for labor, and general anesthesia should be performed for operative procedures, including cesarean delivery.

The following anticoagulation strategies will help to facilitate safe and timely neuraxial analgesia/anesthesia for parturients[101]:

1. Women taking oral anticoagulants should transition to LMWH or UFH no later than 36 weeks' gestation.
2. LMWH should be discontinued 36 hours before planned delivery; the patient should be converted to UFH if necessary.
3. Intravenous UFH should be discontinued 4 to 6 hours before planned delivery.

Postpartum, prophylactic anticoagulation with LMWH or UFH can begin 12 hours after vaginal delivery or 2 hours* after neuraxial catheter removal, whichever occurs later. A 24-hour delay is required for the first dose of UFH or LMWH if (1) the patient underwent a cesarean delivery, (2) therapeutic dosing is required (regardless of the mode of delivery), or (3) blood was present during needle or catheter placement.[101] The ASRA postpartum dosing recommendations differ from the guidelines of the ACOG and other international guidelines, including those of the Royal College of Obstetricians and Gynaecologists.[84,106] Therefore, a multidisciplinary institutional review of anticoagulation policies is advisable.

Because of the risk for epidural hematoma—even in the absence of neuraxial procedures—anesthesiologists, obstetricians, and nursing staff must remain vigilant for signs and symptoms of epidural hematoma. These include (1) severe, unremitting backache; (2) neurologic deficit, including bowel or bladder dysfunction or radiculopathy; (3) tenderness over the spinous or paraspinous area; and (4) unexplained fever.[107] Suspicion of epidural hematoma should lead to immediate diagnostic imaging of the spinal cord and neurosurgical consultation for possible spinal cord decompression. Neurologic recovery is a function of the severity of preoperative deficits, the duration of maximum deficit, and the interval between symptom onset and surgery; better outcomes are associated with a shorter symptom onset-to-surgery interval.[108] A high index of suspicion is necessary because neurologic dysfunction may mimic local anesthetic-induced effects.[109]

Risks of general anesthesia in the anticoagulated patient include airway bleeding. Laryngoscopy and tracheal intubation should be as atraumatic as possible. The anesthesia provider should be aware that placement of nasopharyngeal and oropharyngeal airways, gastric tubes, and other devices (e.g., temperature probes, stethoscopes)

*The U.S. Food and Drug Administration recommends waiting at least 4 hours after removal of a neuraxial catheter before administering a postprocedure dose of LMWH. (U.S. Food and Drug Administration. Low molecular weight heparins: drug safety communication—recommendations to decrease risk of spinal column bleeding and paralysis. November 6, 2013. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm373918.htm. Accessed November 2013.)

carries the tangible risk for traumatic hemorrhage. Emergency surgery may necessitate the administration of protamine or the transfusion of blood products (e.g., plasma, platelets) to reverse anticoagulation and reduce the risk for hemorrhage during and after surgery.

Prevention of Thromboembolic Events

Given the morbidity and mortality associated with thromboembolic events, there is great interest in identifying and implementing strategies to reduce their occurrence. Several risk-stratification strategies have been proposed to prevent thromboembolic events, although these are based on expert opinion.[74,106,110] A meta-analysis published in 2010 found that there was insufficient evidence on which to base recommendations for thromboprophylaxis in pregnancy and the postpartum period.[111] The American College of Chest Physicians recommends the following for postcesarean delivery thromboprophylaxis based on the risk factors outlined in Box 39-4[74]:

- For patients without any risk factors for VTE, no thrombosis prophylaxis other than early mobilization should be used.
- For women at increased risk for VTE because of the presence of one major or at least two minor risk factors, pharmacologic thromboprophylaxis with prophylactic LMWH should be used; mechanical prophylaxis should be initiated in women with contraindications to anticoagulants.
- For women at very high risk for VTE who have multiple additional risk factors for VTE in the puerperium, prophylactic LMWH should be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone.
- For women in whom significant risk factors persist after delivery, extended prophylaxis (up to 6 weeks postpartum) is recommended.

One decision-analysis study modeled the safety and efficacy of thromboprophylaxis with intermittent pneumatic compression stockings at cesarean delivery compared with universal subcutaneous heparin prophylaxis. The use of the pneumatic compression stockings was the preferred strategy because universal heparin prophylaxis would be associated with 13 cases of heparin-induced thrombocytopenia or hemorrhage for each VTE prevented.[112] The reduction in VTE risk was similar between pneumatic compression stockings and universal heparin use.[112] Casele and Grobman[113] found intermittent pneumatic compression stockings to be cost-effective when compared with no thromboprophylaxis after cesarean delivery. Regardless of whether thromboprophylaxis is initiated in the hospital or not, women are at the highest risk for thrombotic events in the first week postpartum.[68] Therefore, careful postdischarge planning and evaluation of VTE risk are equally important to inpatient management.

VENOUS AIR EMBOLISM

Venous air embolism (VAE) is a recognized complication of many surgical procedures.[114] The first study of VAE during cesarean delivery was published in 1987.[115] Subsequent research has revealed that VAE is a common occurrence during cesarean delivery. Most air emboli are small, but volumes greater than 200 to 300 mL, or 3 to 5 mL/kg, may be lethal.[114] Early recognition and appropriate management are necessary for avoiding adverse outcomes.

TABLE 39-5 Methods to Detect Venous Air Embolism

Method of Detection	Sensitivity	Volume of Air Detected (mL/kg)
Transesophageal echocardiography	High	0.02
Precordial Doppler	High	0.05
Pulmonary artery catheter	High	0.25
Expired CO_2	Moderate	0.5
Expired nitrogen	Moderate	0.5

Modified from Mirski MA, Lele AV, Fitzsimmons L, Toung TJK. Diagnosis and treatment of vascular air embolism. Anesthesiology 2007; 106:164-77.

Incidence

The reported incidence of VAE during cesarean delivery varies depending on the method used to ascertain the presence of air (Table 39-5). The most sensitive monitors detect volumes of air as low as 0.02 mL/kg.[114] Studies that have used precordial Doppler monitoring in patients undergoing cesarean delivery with neuraxial anesthesia have found incidence rates ranging from 10% to 65%.[115-119] One study used precordial Doppler monitoring to detect VAE and correlated the Doppler findings with transthoracic echocardiographic evidence of intracardiac air. Of the 42 patients who underwent cesarean delivery with neuraxial anesthesia, 11 (26%) had evidence of VAE, with perfect agreement between the Doppler and the echocardiographic monitoring (kappa = 1.0).[117] One study of healthy parturients undergoing elective cesarean delivery under general anesthesia found that 29 of 30 parturients had evidence of intraoperative VAE.[120] The authors defined VAE as a 0.1% increase from the baseline of expired nitrogen concentration (equivalent to 0.25 to 1.0 mL/kg venous air).[120] Although the volume of entrained air may be lower with general anesthesia using positive-pressure ventilation than spontaneous ventilation,[121] the use of prophylactic positive end-expiratory pressure has not been shown to decrease the incidence of VAE in a neurosurgical population.[122]

The incidence of VAE does not appear to vary with maternal position. The Trendelenburg position could produce a pressure gradient between the right side of the heart and open venous sinuses in the surgical field. A meta-analysis of two randomized controlled trials, which compared 5 to 10 degrees reverse Trendelenburg position with supine positioning for cesarean delivery (pooled n = 130) found no difference in the incidence of air embolism (RR, 0.95; 95% CI, 0.65 to 1.26).[123]

The majority of VAE episodes are subclinical. The true incidence of fatal VAE in the obstetric population is

unknown. One estimate using data on maternal deaths from the National Center for Health Statistics from 1974 to 1978 found that 25 of 2475 deaths were attributable to air embolism.[124] More recent published estimates in the United States have not reported VAE as a cause of maternal death.[1] In the most CMACE report from the United Kingdom, only 1 of 261 deaths was attributed to VAE.[69] This death occurred during intercourse 2 weeks postpartum.[69] This case highlights that VAE may occur in the nonoperative setting. Venous air embolism has been reported during pregnancy during vaginal examinations and during orogenital sex.[125,126]

Pathophysiology

A pressure gradient as small as −5 cm H_2O between the surgical field and the heart allows a significant amount of air to be entrained into the venous circulation. Immediately after placental separation, the raw endometrial surface appears to be a location of significant air entrainment; almost all episodes of VAE during cesarean delivery are noted after the delivery of the placenta.[118] In the noncesarean delivery setting, pressurized air in the vagina is believed to traverse the cervical canal, dissect around fetal membranes (if present), and enter the maternal circulation via subplacental sinuses.[127]

Small volumes of air can precipitate pulmonary vasospasm via a pathophysiology that mimics that of other embolic phenomena. Vasoactive mediators or mechanical obstruction of small vessels appear to induce pulmonary vasoconstriction that leads to $\dot{V}/\dot{Q}$ mismatch, hypoxemia, right-sided heart failure, arrhythmias, and hypotension. Fluid resuscitation and increased hydrostatic pressure may provoke interstitial pulmonary edema. A paradoxical air embolus into the arterial circulation (by means of a patent foramen ovale) can lead to cardiovascular and neurologic sequelae and morbidity. Large volumes of air (> 3 mL/kg) can generate cardiovascular collapse by creating an "air lock" that causes right ventricular outflow tract obstruction.

Clinical Presentation

Most air emboli are subclinical with no sequelae; however, massive VAE can manifest as a sudden, dramatic, and devastating event with hypotension, hypoxemia, and even cardiac arrest.[128] In awake patients receiving neuraxial anesthesia, transient episodes of hypoxemia, dyspnea, or chest pain during uterine repair suggest VAE.[115,116,118,119] In the patient receiving general anesthesia, evidence of VAE may be limited to hypoxemia and a slight decrease in end-tidal CO_2.[114] VAE may be more frequent when the uterus is exteriorized than when it is repaired within the abdomen, either owing to vertical elevation relative to the heart or traction on the uterus that opens venous sinuses.[118,119] Clinically significant air emboli may be associated with hypotension, heart rate or rhythm changes, evidence of right-sided heart strain on the electrocardiogram, an increase in central venous pressure, and/or an increase in pulmonary artery pressure. Electrocardiographic changes consistent with myocardial ischemia (e.g., ST-segment depression) are relatively common during cesarean delivery,[129,130] but the clinical significance of ST-segment depression and its relationship to VAE remain unclear.

A precordial stethoscope may detect a pathognomonic "millwheel murmur." Transesophageal echocardiography may detect air in the right atria or the pulmonary artery. However, several small case series failed to identify VAE using echocardiography at the time of ST-segment depression during cesarean delivery.[129] More recent evidence suggests that ST-segment depression in the immediate postdelivery period may be associated with rapid oxytocin administration.[131,132]

Management

The clinician should consider VAE in women who complain of intraoperative chest pain or dyspnea or experience sudden hypoxemia, hypotension, or arrhythmia during cesarean delivery. Although continuous precordial Doppler monitoring has been recommended by some experts,[114] the rarity of hemodynamically significant VAE suggests that targeted use in high-risk patients (e.g., women with a known intracardiac shunt) may be more appropriate than routine application. Transthoracic or transesophageal echocardiography may help to confirm a diagnosis of VAE, to exclude alternative causes of hemodynamic instability, and to guide appropriate clinical management. Regardless, clinical suspicion of VAE should prompt appropriate management (Box 39-5).

Currently, there are no data to support central line insertion for air aspiration from the right side of the heart, but central line placement may be indicated to deliver potent vasopressors.[114] Position changes to limit air entrainment are recommended. However, in a canine study of resuscitation positioning after a 2.5 mL/kg VAE,[133] repositioning animals to direct air to the dependent portion of the right side of the heart did not improve cardiac function or survival; thus, this maneuver is not

BOX 39-5 Resuscitation of the Obstetric Patient with Massive Venous Air Embolism

Air
- Prevent further air entrainment (e.g., flood the surgical field with saline solution, lower the surgical field relative to the heart if tolerated).

Airway
- Administer 100% oxygen; discontinue nitrous oxide; intubate the trachea and support ventilation as needed.

Cardiovascular Support
- Support circulation with chest compressions, intravascular volume expansion, and vasopressors as needed.

Fetus
- Expedite delivery.

Postresuscitation Care
- Evaluate for intracerebral air and consider hyperbaric oxygen therapy if indicated.

recommended. The use of the Valsalva maneuver and positive-end expiratory pressure should be avoided because an increase in right atrial pressure may result in a paradoxical embolism. In patients with delayed emergence from anesthesia, computed tomography or magnetic resonance imaging may be considered to evaluate for intracerebral air. Hyperbaric oxygen may improve neurologic outcomes if instituted within 6 hours of intracerebral air embolism.[134]

KEY POINTS

- Embolic disorders are a major cause of maternal morbidity and mortality.
- Early recognition, diagnosis, and therapy may reduce the incidence of morbidity and mortality associated with embolic disorders.
- Amniotic fluid embolism is a diagnosis of exclusion. It may occur at any time during labor or delivery, as well as antepartum or postpartum.
- During pulmonary embolic phenomena, hemostatic and immunologic mediators may trigger a cascade of physiologic derangements disproportionate to the cross-sectional area of occluded lung tissue.
- Pregnant patients are at fivefold higher risk than nonpregnant patients for pulmonary thromboembolism. The third trimester and first postpartum week are the periods of highest risk.
- Several prophylactic and therapeutic anticoagulation regimens exist for patients with venous thromboembolism or those at increased risk for thromboembolism; anesthesia providers should be aware of the safety implications of anticoagulation therapy on the timing of initiation of neuraxial anesthesia and neuraxial catheter removal.
- Venous air embolism is a common occurrence during cesarean delivery. Most of the emboli are small, transient, and benign. Massive venous air embolism is rare during vaginal or cesarean delivery but can be fatal.

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CHAPTER 40

Maternal Mortality

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CHAPTER OUTLINE

GLOBAL MATERNAL MORTALITY

Globally in 2010, 287,000 women died while pregnant or within 42 days of the end of pregnancy.[1] This number corresponds to a ratio of 210 maternal deaths per 100,000 live births and to a 1-in-180 lifetime risk for maternal death for each girl entering her childbearing years (Table 40-1).[1] According to the World Health Organization (WHO), "No issue is more central to global well-being than maternal and perinatal health. Every individual, every family and every community is at some point intimately involved in pregnancy and the success of childbirth."[2]

Definitions for maternal death are listed in Table 40-2, and measures of maternal mortality are listed in Table 40-3. More than 99% of maternal deaths occur in developing countries, with 85% in either sub-Saharan Africa or South Asia (see Table 40-1). As part of the Millennium Development Goals,[1] the international community committed to reduce the **maternal mortality ratio (MMR)** by 75% between 1990 and 2015,[1] from 400 to less than 100 per 100,000 live births. Between 1990 and 2010, the global MMR fell by 47%, with the greatest reductions demonstrated in East Asia (69%), North Africa (66%), and South Asia (64%).[1] Although the MMR declined 41% in sub-Saharan Africa, the lifetime risk for maternal death remains unacceptably high, at 1 in 39.[1] There is considerable regional variation. Within sub-Saharan Africa, the highest MMRs are in Chad (1100) and Somalia (1000) and represent rates that are 10-fold higher than the lowest ratios in the region.[1]

Leading Causes

Hemorrhage, hypertensive disorders of pregnancy, and **sepsis** account for more than half of global maternal deaths and for slightly more than a third of deaths in the developed world.[3] Hemorrhage is the leading cause of maternal death in both Africa and Asia (Table 40-4). Hypertensive disorders represent the leading cause in Latin America and the Caribbean.[3] Infection and sepsis may be substantially underestimated in regions where laboratory diagnostic tests are unavailable.[4] In one Malawi hospital with full laboratory capabilities, infection played a primary role in almost three fourths of all maternal deaths.[5]

Anemia and **obstructed labor** each cause approximately one tenth of maternal deaths in Asia.[3] Anemia is associated with (1) iron and other micronutrient deficiencies, (2) pregnancy intervals of less than 1 year, (3) adolescent pregnancy, (4) hemoglobinopathy, (5) urinary tract infection, (6) human immunodeficiency virus (HIV) infection, (7) parasitic infections including malaria, and (8) recurrent antepartum hemorrhage.[6-8] Anemia can cause lethal congestive heart failure in pregnancy[7] and also increases the risk for maternal death from other complications, particularly hemorrhage and infection.[6]

Obstructed labor is an important cause of maternal death in communities in which early adolescent pregnancy is common, childhood malnutrition leads to small maternal pelves, and operative delivery is unavailable.[9] Maternal mortality from obstructed labor is largely the result of uterine rupture or ascending genital tract infection.[9,10] Prolonged pressure on the pelvic outlet can lead to tissue necrosis and obstetric fistula, which is thought to affect between 2 and 3.5 million women worldwide.[11,12]

HIV/acquired immune deficiency syndrome (AIDS) increases vulnerability to both nonobstetric infection (e.g., tuberculosis, malaria) and obstetric complications (e.g., hemorrhage, pregnancy-related sepsis, septic abortion).[13,14] The WHO attributed 6.5% of

TABLE 40-1 Estimates of Maternal Mortality Ratio (MMR), Number of Maternal Deaths, and Lifetime Risk by United Nations Millennium Development Goal Regions, 2010

Region	MMR[a]	Range of MMR Uncertainty		No. of Maternal Deaths[a]	Lifetime Risk for Maternal Death,[a] 1 in:
		LOWER ESTIMATE	UPPER ESTIMATE		
World	210	170	300	287,000	180
Developed Regions[b]	16	14	18	2200	3800
Developing Regions	240	190	330	284,000	150
Northern Africa[c]	78	52	120	2800	470
Sub-Saharan Africa[d]	500	400	750	162,000	39
Eastern Asia[e]	37	24	58	6400	1700
Southern Asia[f]	220	150	310	83,000	160
Southeastern Asia[g]	150	100	220	17,000	290
Western Asia[h]	71	48	110	3500	430
Caucasus & Central Asia[i]	46	37	62	750	850
Latin America[j]	72	61	88	7400	580
Caribbean[k]	190	140	290	1400	220
Oceania[l]	200	98	430	520	130

[a]The MMR, number of maternal deaths, and lifetime risk have been rounded according to the following scheme: < 100, no rounding; 100-999, rounded to nearest 10; 1000-9999, rounded to nearest 100; and > 10,000, rounded to nearest 1000.
[b]Albania, Australia, Belarus, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the former Yugoslav Republic of Macedonia, Ukraine, United Kingdom of Great Britain and Northern Ireland, and the United States of America.
[c]Algeria, Egypt, Libya, Morocco, Tunisia.
[d]Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.
[e]China, Democratic People's Republic of Korea, Mongolia, Republic of Korea.
[f]Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan, Sri Lanka.
[g]Cambodia, Indonesia, Lao People's Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Vietnam.
[h]Bahrain, Iraq, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, West Bank and Gaza Strip (territory), Yemen.
[i]Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan.
[j]Argentina, Belize, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, Venezuela (Bolivarian Republic of).
[k]Bahamas, Barbados, Cuba, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago.
[l]Fiji, Micronesia (Federated States of), Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu.
Reproduced from World Health Organization. Trends in Maternal Mortality 1990-2010: Estimates Developed by WHO, UNICEF, and UNFPA. Geneva, Department of Reproductive Health and Research, 2012.

maternal deaths in 2010 to HIV/AIDS.[1] In contrast, the Institute of Health Metrics and Evaluation estimated that one in five maternal deaths in 2011 would not have occurred in the absence of the HIV epidemic, based on statistical models that account for the prevalence of HIV within a population.[15,16] In countries most severely affected, including Botswana, Malawi, Namibia, South Africa, Swaziland, and Zimbabwe, MMRs increased between 1990 and 2000, but they have since begun to decline as antiretroviral therapy becomes increasingly available.[1,15,16]

Maternal deaths attributed to **unsafe abortion** account for 13% of maternal deaths worldwide (47,000 in 2008).[17] The WHO defines *unsafe abortion* as "a procedure for terminating an unintended pregnancy either by individuals without the necessary skills or in an environment that does not conform to minimum medical standards, or both."[17,18] Worldwide, 49% of abortions were unsafe in 2008, compared with 44% in 1995.[19] The case-fatality rate (460 maternal deaths per 100,000 unsafe abortions) and the absolute number of maternal deaths per year (28,500) are highest in sub-Saharan Africa.[17,20]

Early marriage (before age 18 years) has been identified as a major health risk for girls, increasing their exposure to domestic violence, coercion, pregnancy, and sexually transmitted diseases such as HIV/AIDS.[21-23] Girls younger than 15 years are five times more likely to die in childbirth than women in their 20s,[24] and pregnancy is among the leading causes of death worldwide for girls ages 15 to 19.[25] Early childbearing also increases the likelihood of **high parity birth** (≥ 5) later in life. With a threefold increase in the MMR, high parity is the most important demographic risk for maternal death because it remains so common, accounting for 29% of births globally between 1990 and 2005.[26] **Advanced maternal age** is less common globally but increases individual risk

TABLE 40-2 Glossary of Terms Used in Discussions of Maternal Mortality

Source	Term	Definition*
World Health Organization	Maternal death	Death of women while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. ICD-10 A34, O00-O95, O98-O99[1]
	Direct maternal death	Death resulting from obstetric complications of the pregnant state (pregnancy, labor, and the puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above. A34, O00-O95[1]
	Indirect maternal death	Deaths resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes but was aggravated by physiologic effects of pregnancy. O98-O99[1]
	Late maternal death	The death of a woman from direct or indirect obstetric causes more than 42 days but less than 1 year after termination of pregnancy. O96-O97[1]
	Pregnancy-related death	Deaths occurring in women while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death.
U.S. Centers for Disease Control and Prevention, Pregnancy Mortality Surveillance System[2]	Pregnancy-associated death	Death of a woman while pregnant or within 1 year of termination of pregnancy, irrespective of cause.
	Pregnancy-related death	Death of a woman while pregnant or within 1 year of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by her pregnancy or its management, but not from accidental or incidental causes.
	Non–pregnancy-related death	Death of a woman while pregnant or within 1 year of termination of pregnancy, due to a cause unrelated to pregnancy.

*Numbers after some definitions indicate cause of death codes.

[1]*ICD-10,* International Statistical Classification of Diseases and Related Health Problems: 10th revision.

[2]*From Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol 2010; 116:1302-9.*

TABLE 40-3 Measures of Maternal Mortality

Maternal Mortality Measure	Definitions	Reports Using the Measure
Maternal mortality ratio (MMR)	Direct and indirect maternal deaths, but not late maternal deaths, per 100,000 live births	WHO[1]
Maternal mortality rate	Direct and indirect maternal deaths, but not late maternal deaths, per 100,000 maternities (pregnancies resulting in a live birth or stillbirth ≥ 20 weeks gestational age)	UK CEMD[63]
Pregnancy-related mortality ratio (PRMR)	Pregnancy-related deaths per 100,000 live births	US CDC PMSS[75]
Lifetime risk for maternal death	The lifetime risk for maternal death takes into account both the probability of becoming pregnant and the probability of dying as a result of that pregnancy cumulated across a woman's reproductive years	WHO[1]

UK CEMD, The United Kingdom Confidential Enquiry into Maternal Death; *US CDC PMSS,* U.S. Centers for Disease Control and Prevention Pregnancy Mortality Surveillance System; *WHO,* World Health Organization.

TABLE 40-4 The Five Leading Causes of Maternal Death by Region

Africa		*Asia*		*Latin America and the Caribbean*		*Developed Countries**	
Hemorrhage	33.9%	Hemorrhage	30.8%	Hypertensive disorders	25.7%	Other direct causes of death	21.3%
Other indirect causes of death	16.7%	Anemia	12.8%	Hemorrhage	20.8%	Hypertensive disorders	16.1%
Sepsis/infection	9.7%	Other indirect causes of death	12.5%	Obstructed labor	13.4%	Embolism	14.9%
Hypertensive disorders	9.1%	Sepsis/infection	11.6%	Abortion	12.0%	Other indirect causes of death	14.4%
HIV/AIDS	6.2%	Obstructed labor	9.4%	Unclassified deaths	11.7%	Hemorrhage	13.4%

*Europe, North America, Australia, New Zealand, Japan.

Data from Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367:1066-74.

for maternal death as much as fourfold for women aged 35 years or older and as much as eightfold after age 40.[27]

Anesthesia providers working in the developing world must contend with profound limitations in staffing, equipment, and other resources.[14,28-33] In addition, patients who labor at home may face a variety of social and environmental obstacles to reach a facility with the capacity to provide comprehensive emergency obstetric care,[34-36] and many arrive at these facilities in septic or hemorrhagic shock.[37,38] Cesarean delivery is the most common major surgical procedure in Africa,[39] and perioperative maternal mortality is estimated to be between 1.2% and 2%.[40-42] As many as one third of deaths that occur within 24 hours of surgery have been attributed to anesthesia, mainly because of airway problems with general anesthesia or hemodynamic collapse with neuraxial anesthesia.[14,28,29,43] Peripartum deaths have also been attributed to limited availability or affordability of blood products.[32,40,43,44] The number of maternal perioperative deaths likely pales in comparison with maternal deaths that result from the unmet need for lifesaving obstetric procedures, including cesarean delivery.[45]

Strategies to reduce global maternal mortality include (1) improvement in family planning services and a reduction in the performance of unsafe abortion[46,47]; (2) community-based education focused on safe birth practices and indications for transfer to a higher level of care[48-51]; and (3) development of the infrastructure needed to provide timely emergency obstetric care, including the performance of indicated cesarean delivery (and safe administration of anesthesia) by trained care providers, who can also provide resuscitation of women in whom shock develops secondary to hemorrhage or infection.[52-57] Limited human, political, and economic capital mandate ongoing rigorous evaluation of the effectiveness of future programmatic efforts.[58,59] Cluster randomized trials to evaluate these strategies are beginning to appear[48,49,51] and suggest that certain interventions succeed only when deployed as part of an integrated, context-specific and culturally sensitive program.[55] For example, training traditional birth attendants to identify and manage complications may only improve maternal and perinatal outcomes if accompanied by ongoing training, resource support, and effective referral pathways to emergency obstetric care.[60]

MATERNAL MORTALITY IN THE DEVELOPED WORLD

In developed regions of the world, the reported MMR has traditionally fluctuated around 10 per 100,000 live births.[61] As of 2010, the WHO has reported an MMR of 16 (95% confidence interval [CI], 14 to 18). This apparent increase reflects increases documented primarily in the United States, as well as expansion of the developed world to include Cyprus, Israel, the Republic of Moldova, Belarus, the Russian Federation, and Ukraine.[1]

The most comprehensive maternal surveillance system in the world is the **Confidential Enquiry into Maternal Deaths (CEMD)** in the United Kingdom.* Triennial reports of CEMD in England and Wales extend back to 1952 and have covered the entire United Kingdom since the 1985 to 1987 report. By government mandate, all maternal deaths are subject to this enquiry, and health professionals have a duty to provide all requested information.[62,63] Once a case is identified, practitioners are asked to provide (1) a full account of the circumstances leading up to the woman's death, (2) all supporting records, (3) any clinical or other lessons that have been learned, and (4) details of any actions that may have been taken as a result.[62,63] Regional assessors review the files to ensure completeness before removing identifying information. Central assessors compile the cases and produce the triennial reports. The reports focus on both medical and nonmedical recommendations for action to improve safety for future pregnant women.

The CEMD reports include both the internationally defined MMR and the U.K.-defined maternal mortality rate (see Table 40-3). The numerator for the U.K.-defined maternal mortality rate includes all deaths that in the opinion of the central assessors are related to pregnancy, including some causes that are not internationally coded as maternity related (e.g., suicide attributed to postpartum depression). The denominator includes all pregnancies that resulted in a live birth or stillbirth after 20 weeks' gestation. The international MMR is calculated strictly from data coded on death certificates; the U.K. maternal mortality rate includes all deaths identified through active surveillance. As a result, the 2006 to 2008 internationally defined MMR for the United Kingdom (6.69 per 100,000 live births) is significantly lower than the 2006 through 2008 maternal mortality rate (11.39 per 100,000 maternities).[63,64]

National confidential enquiry reports are now published by many other countries, including Australia,[65] France,[66] the Netherlands,[67] New Zealand,[68] and South Africa.[14]

In the United States, the **National Center for Health Statistics (NCHS)** has provided maternal death counts since 1900 and MMRs since 1915.[69] Accuracy is limited because (1) the system relies on death certificates rather than active surveillance, (2) the certification of death is the legal responsibility of individual states, and (3) the process of maternal death ascertainment varies by state.

The U.S. MMR reported by the NCHS declined from more than 600 deaths per 100,000 live births in 1915 to fewer than 10 deaths per 100,000 live births by 1980 (Figure 40-1).[69] Throughout the 1980s and 1990s, the MMR oscillated between 6.6 and 9.2. Then in 1999, the MMR began to increase, reaching 16.6 in 2009 (Figure 40-2).[70] Improvements in ascertainment explain

*The Confidential Enquiries into Maternal Death have been overseen by a series of organizations in recent years, including The Confidential Enquiry in Maternal and Child Health (CEMACH), the Center for Maternal and Child Enquiries (CMACE), and, most recently, Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom (MBRRACE-UK), led by the National Perinatal Epidemiology Unit (NPEU) at the University of Oxford. Future reports are planned on an annual basis starting in 2014.

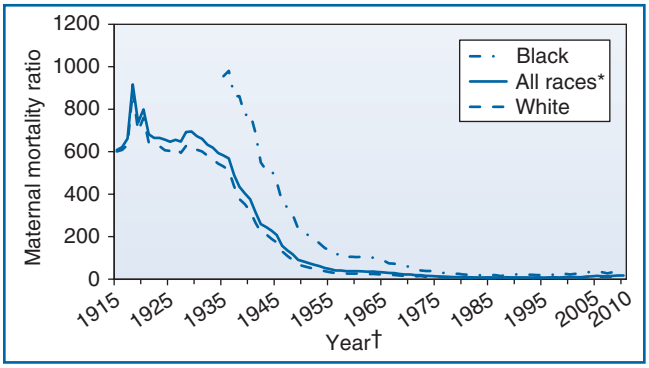

FIGURE 40-1 ■ U.S. maternal mortality ratios by race, 1915 to 2010.[69,70,155-158] *Includes races other than white and black. †For 1915 to 1934, data on black race not available.

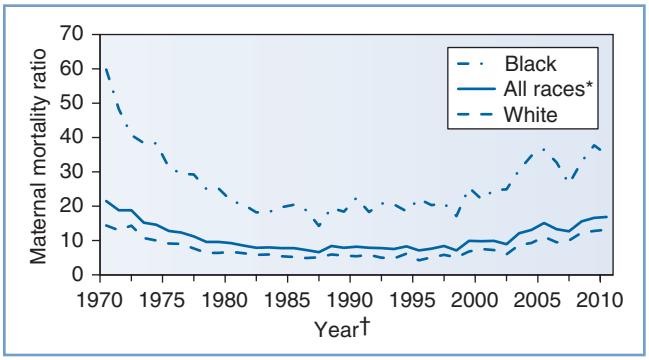

FIGURE 40-2 ■ U.S. maternal mortality ratios by race, 1970 to 2010.[69,70,155-158] *Includes races other than white and black. †Beginning in 1989, race for live births tabulated according to race of mother, not child.

BOX 40-1 Pregnancy Questions, U.S. Standard Certificate of Death, 2003 Revision

If female:
- Not pregnant within the past year
- Pregnant at the time of death
- Not pregnant, but pregnant within 42 days of death
- Not pregnant, but pregnant 42 days to 1 year before death
- Unknown if pregnant within the past year

Reprinted from National Center for Health Statistics. United States Standard Certificate of Death—Rev. 11/2003. Available at www.cdc.gov/nchs/data/dvs/DEATH11-03final-acc.pdf. Accessed June 2012.[159]

some of the increase. In 1999, the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) replaced the ICD-9 as the coding system for U.S. death certificates and liberalized the criteria by which pregnancy could be linked with death. Growing numbers of states perform electronic matches among women's death certificates, live birth certificates, and fetal death files. In addition, increasing numbers of states have adopted the 2003 revision of the U.S. Standard Certificate of Death, which introduced questions about pregnancy status at the time of death (Box 40-1). By 2005, 19 states had adopted the standard pregnancy questions; the MMR calculated from vital records in these states was 17.3, compared with 10.7 from states without any questions about pregnancy on the state death certificate.[71]

In 1987, the Centers for Disease Control and Prevention (CDC) partnered with state health departments and the American College of Obstetricians and Gynecologists (ACOG) to form the **Pregnancy Mortality Surveillance System (PMSS).**[72] To capture maternal deaths more completely, the PMSS recommended that states develop an active surveillance system and collect death certificates and matching live birth or fetal death certificates for all pregnancy-associated deaths (defined in Table 40-2). These certificates are forwarded to the CDC, where clinically experienced epidemiologists manually review the certificates to identify all pregnancy-related deaths (defined in Table 40-2). Similar surveillance enhancement procedures have been estimated to improve case ascertainment by between 22% and 93%.[73] The pregnancy-related mortality ratio (PRMR) includes deaths that took place up to a year after the end of pregnancy and, according to the PMSS, increased from 10.3 in 1991 to 16.8 in 2003 before returning to 15.4 in 2005.[74,75] Documentation of pregnancy on the death certificate increases ascertainment further. In 2005, among the 19 states with death certificates that include the standard pregnancy questions, the combination of data from the NCHS and the PMSS suggests an MMR of 19.7 and a PRMR of 22.3.[71]

Leading Causes

According to a 2006 systematic review of data from Europe, North America, Australia, New Zealand, and Japan, **hypertensive disorders of pregnancy, embolic disorders,** and **hemorrhage** together account for slightly less than half of maternal deaths in the developed world (see Table 40-4).[3] **Indirect deaths** account for another 14%.[3]

Indirect deaths have exceeded direct deaths in the United Kingdom since 1997, with cardiac disease being the most common category of death. Similar patterns are seen in the United States, where the combination of cardiovascular conditions and cardiomyopathy comprised 23% of all pregnancy-related deaths between 1998 and 2005 and cerebrovascular accidents and noncardiovascular medical conditions represented another 20%.[75] Cause-specific mortality ratios are shown in Table 40-e1 (available online at expertconsult.com). Cardiomyopathy, including both peripartum and other types of cardiomyopathy, is the leading diagnosis underlying maternal cardiac death in both the United States and the United Kingdom.[63,75]

Venous thromboembolism was the leading direct cause of maternal death in the United Kingdom for many years (see online Table 40-e1), but a national campaign to improve venous thromboembolism prophylaxis heralded a 60% reduction in the cause-specific mortality ratio to 0.79 per 100,000 in the 2006 to 2008 CEMD report.[63,76,77]

TABLE 40-e1 **Ratios of Leading Causes of Maternal Death in the United States (1987-2007) and United Kingdom (1988-2008)**

Cause of Death	*United States**				*United Kingdom†*						
	1987-1990	1991-1997	1998-2005	2006-2007	1988-1990	1991-1993	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008
Hypertensive disorders of pregnancy	1.61	1.82	1.79	1.67	1.35	0.95	1.00	0.94	0.85	0.90	0.96
Obstetric hemorrhage	2.62	2.09	1.81	1.79	1.95	1.34	1.42	1.12	1.50	1.32	0.87
First trimester	*1.00*	*0.65*	*0.49*	—	*0.89*	*0.52*	*0.64*	*0.70*	*0.60*	*0.52*	*0.48*
Venous thromboembolism	0.99	1.17	1.48	1.64	1.40	1.51	2.18	1.65	1.50	1.94	0.79
Amniotic fluid embolism	0.70	0.99	1.09	0.84	0.47	0.43	0.77	0.38	0.25	0.80	0.57
Infection/sepsis	1.20	1.51	1.55	1.67	0.72	0.65	0.73	0.85	0.65	0.85	1.13
Cardiovascular diseases	—	—	3.48	3.94	0.76	1.60	1.77	1.65	2.20	2.27	2.31
Cardiomyopathy	0.52	0.88	*1.68*	*1.90*	—	—	*0.27*	*0.47*	*0.40*	*0.05*	*0.57*
Other cardiovascular disease	—	—	*1.80*	*2.04*	—	—	*1.50*	*1.18*	*1.80*	*2.22*	*1.74*
Cerebrovascular disease	—	0.54	0.91	0.80	1.27	1.08	2.14	1.60	2.00	1.75	1.57
Anesthesia complications	0.23	0.18	0.17	0.09	0.17	0.35	0.05	0.14	0.30	0.28	0.31
Psychiatric causes	—	—	—	—	—	—	0.41	0.71	0.80	0.85	0.57
Other direct causes	—	—	—	—	0.51	0.66	0.05	0.14	0.35	0.14	0.04
Other medical conditions	—	2.10	1.80	2.04	—	—	0.41	1.23	1.05	1.32	0.70
Unknown	1.16	0.08	0.30	0.84	—	—	—	—	—	—	—
Overall mortality ratio	9.13	11.47	14.51	15.08	10.08	9.85	12.19	11.40	13.07	13.95	11.39

*United States: Cause-specific mortality ratio includes death during pregnancy and up to 1 year after the end of pregnancy per 100,000 live births. Data from references 1 to 4 below.
†United Kingdom: Cause-specific mortality ratio includes deaths during pregnancy and up to 1 year after the end of pregnancy per 100,000 pregnancies lasting at least 20 weeks' gestation.
Italicized numbers represent subcategories of the numbers listed above. Data from reference 5 below.

References

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During this period, **sepsis** due to **genital tract infection** emerged as the leading cause of direct obstetric death in the United Kingdom and was largely attributed to community-acquired group A streptococcal disease.[63,64] Current recommendations focus on early warning scoring systems to identify vital sign derangements that could indicate systemic infection, standardized management according to the *Surviving Sepsis Campaign*, and early involvement of anesthesiologists and intensivists.[63,78] More detail is provided in Chapters 37 and 55.

In the United States between 1998 and 2005, seven conditions each accounted for 10% to 13% of all pregnancy-related deaths, including hemorrhage, hypertensive disorders of pregnancy, sepsis, thrombotic pulmonary embolism, cardiomyopathy, other cardiovascular disorders, and noncardiovascular medical disorders (see online Table 40-e1).[75]

Injury-related deaths are considered pregnancy-associated but not pregnancy-related; they are discussed in Chapter 55.

Risk Factors

Detailed descriptions of hypertensive disorders of pregnancy, obstetric sepsis, maternal hemorrhage, embolic disorders, and cardiovascular diseases in pregnancy are provided in Chapters 36, 37, 38, 39, and 42, respectively. Common clinical and sociodemographic factors that increase the risk for maternal death from all of these complications are discussed in this chapter (see later discussion).

Advanced maternal age increases maternal risk,[79] with a linear trend evident for each 5-year increase in maternal age beyond 34 years.[63] In the United States between 1998 and 2005, the PRMR among women 40 years of age and older was 166.9 for black women (compared with 24.8 for black women 20 to 24 years of age) and 40.0 for white women (compared with 7.5 for white women 20 to 24 years of age).[75] Based on data from the PMSS for the years 1991 through 1999, the association between age and mortality persisted after data were controlled for parity, prenatal care, race, and education.[79] Among older black women (≥ 40 years), the excess risks were greatest for hypertensive disorders of pregnancy, infection, cerebrovascular accident, and other medical conditions. Among older white women, the greatest excess risks for death were due to hemorrhage, cardiomyopathy, embolic disorders, and other medical conditions.[79]

In the United States, **black or African-American race** significantly correlates with the risk for death. Non-Hispanic black women experience a PRMR that is 3.5-fold higher than non-Hispanic white women. Based on death certificate data (1999 to 2009), disparities are most dramatic for deaths associated with ectopic pregnancy (black-to-white ratio of 4.8), cardiomyopathy (4.2), and deaths from complications of anesthesia (2.9).[70] In a case series of anesthesia-related maternal deaths in Michigan published in 2007, six of eight deaths occurred among non-Hispanic black women in Detroit, suggesting a profound concentration of maternal risk.[80] The disparity in maternal mortality between black and white women persists after data are controlled for maternal age, income, and receipt of prenatal care[81] and appears to be related to a higher case-fatality rate.[82]

Other racial and ethnic groups also experience increased risk.[63] In the United States between 1999 and 2009, in comparison with non-Hispanic white women, the MMR was 80% higher for American Indian or Alaska Native women.[70] In England, black African, black Caribbean, Indian, Pakistani, and Chinese women have higher relative risks of death than white women.[63,83]

Immigrants, asylum seekers, and non-native speakers appear to be particularly vulnerable to both maternal death and substandard care, based on data from the United Kingdom and the Netherlands.[63,67,83,84] In the United States, Hispanic and Asian/Pacific Islander immigrants face increased risk compared with women of these same racial/ethnic groups born in the United States.[85] Significant regional variation has been identified in France, with increased risk noted for women delivering in Paris (adjusted odds ratio [AOR], 1.6; 95% CI, 1.2 to 2.0) and the overseas districts (AOR, 3.5; 95% CI, 2.4 to 5.0) compared with continental France.[86] Differences in behavior, biology, environmental conditions, social circumstances, and the quality of clinical care may contribute to disparities in outcomes for sociodemographically vulnerable populations.[63,86,87]

Maternal obesity increases the risk for maternal death from a variety of causes, including pulmonary embolism, infection, preeclampsia, and anesthesia-related complications. Remarkably, there are limited epidemiologic data to establish this connection. Obesity is a common feature in case series of maternal deaths. In the 2006 to 2008 CEMD report from the United Kingdom, 49% of women who died were overweight or obese.[63] Among the subset of women experiencing severe obstetric complications (including eclampsia, pulmonary embolism, amniotic fluid embolism, acute fatty liver of pregnancy, and antenatal stroke), obesity (body mass index ≥ 30 kg/m^2) was associated with maternal death [AOR, 5.26; 95% CI, 1.15 to 6.46].[83]

Multifetal pregnancies increase maternal risk for a variety of complications, including preeclampsia, venous thromboembolism, heart failure, myocardial infarction, peripartum hemorrhage, and maternal death.[63,88-91] Compared with twin pregnancies, triplet and higher-order multiple pregnancies further increase maternal risk for preeclampsia, hemorrhage, and emergency peripartum hysterectomy.[89,90] In the United States between 1979 and 2000, the relative risk of death associated with a multifetal pregnancy was 3.6 (95% CI, 3.1 to 4.1) with threefold to fourfold increases in the cause-specific relative risk of death for embolism, hemorrhage, hypertensive disorders of pregnancy, infection, cardiomyopathy, and other medical conditions.[91]

Cesarean delivery has also been associated with an increased risk for maternal death; however, the association does not always reflect a causal relationship. Death can be a consequence of the indication for the operation rather than the mode of delivery itself. In an attempt to estimate the relative risk of death due to cesarean delivery, a population-based case-control study from France

focused on 65 maternal deaths after singleton births among low-risk women in whom complications developed only after delivery.[92] Cases were identified by the French National Confidential Enquiry on Maternal Deaths from 1996 through 2000.[92] These cases were compared with 10,244 singleton births to low-risk women identified through the French National Perinatal Survey conducted in 1998. After data were controlled for maternal age, nationality, parity, and preterm delivery, the AOR for increased risk for death with cesarean delivery was 3.64 (95% CI, 2.15 to 6.19). The increased risk was most dramatic for intrapartum cesarean deliveries (AOR, 4.58; 95% CI, 2.30 to 9.09) but persisted when cesarean delivery preceded labor (AOR, 2.42; 95% CI, 1.14 to 5.13).[92] Among women who underwent cesarean delivery, there was an increased risk for cause-specific maternal mortality from venous thromboembolism, puerperal infection, and complications of anesthesia. There was no difference in risk for death from postpartum hemorrhage or amniotic fluid embolism.

A cohort study of deliveries in Canada between 1991 and 2005 compared 46,766 planned cesarean deliveries for breech presentation with 2,292,420 planned vaginal deliveries in which labor was either spontaneous or induced.[93] Planned cesarean delivery increased the risk for postpartum cardiac arrest (AOR, 5.1; 95% CI, 4.1 to 6.3), major puerperal infection (AOR, 3.0; 95% CI, 2.7 to 3.4), anesthetic complications (AOR, 2.3; 95% CI, 2.0 to 2.6), and puerperal venous thromboembolism (AOR, 2.2; 95% CI, 1.5 to 3.4), but did not increase the risk for in-hospital maternal death ($P = .87$).[93]

A medical record review of all in-hospital maternal deaths that occurred in a sample of U.S. hospitals between 2000 and 2006 sought to identify evidence for a causal connection between mode of delivery and the mechanism of maternal death.[94] Among 1,461,270 live births, there were 95 maternal deaths (6.5 per 100,000). Although 61% of the deaths were associated with cesarean delivery, one third of these were perimortem cesarean deliveries in which the surgical procedure followed maternal cardiac arrest. Four deaths were thought to have been directly caused by cesarean delivery (attributed to hemorrhage or infection), with an additional seven deaths attributed to pulmonary thromboembolism after cesarean delivery. Two deaths were thought to have been causally related to vaginal delivery (one case of uterine inversion and one case of rupture of an unrecognized cerebral berry aneurysm during labor), and two deaths were attributed to pulmonary thromboembolism after vaginal delivery. Another 16 deaths were thought to have been potentially preventable had a cesarean delivery or an earlier cesarean delivery been performed (12 due to preeclampsia, 3 due to hemorrhage, and 1 due to sepsis).[94] The investigators concluded that a policy of universal thromboprophylaxis for all patients undergoing cesarean delivery would eliminate the increased risk for maternal death caused by cesarean delivery as opposed to vaginal delivery.[94]

Regardless of mode of delivery, risk appears to be particularly concentrated in women with preexisting medical conditions; pulmonary hypertension, malignancy, systemic lupus erythematosus, sickle cell disease, and major cardiovascular and renal disease all confer substantially increased risk for maternal death or end-organ injury.[95,96] Given the preponderance of indirect deaths documented in recent CEMD reports, central assessors have repeatedly recommended both preconception counseling and intensive multidisciplinary antepartum and intrapartum care for women with serious medical or mental health conditions that may be aggravated by pregnancy.[62,63] These conditions include congenital or acquired cardiac disease, obesity with a body mass index of 30 kg/m^2 or higher, epilepsy, diabetes, asthma, autoimmune disorders, renal or liver disease, HIV infection, and a personal or family history of severe mental illness.[62,63] The Joint Commission has advanced a similar proposal in the United States.[97]

Some **health system characteristics** have been associated with a higher risk for maternal death; they include (1) low maternal-fetal medicine specialist density[98] and (2) a single physician functioning as both the obstetrician and the anesthesia provider.[99]

Severe and Near-Miss Morbidity

Death is considered the extreme outcome of the following continuum of adverse pregnancy events: normal pregnancy → morbidity → severe morbidity → near-miss → death.[100] Approximately half of women experience some **morbidity** during pregnancy, most commonly anemia, urinary tract infection, mental health conditions, hypertensive disorders, and pelvic or perineal trauma.[101] Research has focused on severe morbidity, near-miss events, and maternal deaths to elucidate the patient, provider, and health system factors that lead to these adverse outcomes.

Severe maternal morbidity includes those complications that have the potential to evolve toward end-organ injury or maternal death; its estimated incidence depends on the health system evaluated, the method of ascertainment, and the definition of severe morbidity used.[102-105] Waterstone et al.[102] evaluated pregnancies in France between 1997 and 1998 for the presence of severe preeclampsia, severe hemorrhage, or sepsis; the combined incidence for these three conditions was 12.0 per 1000 deliveries (95% CI, 11.2 to 13.2). Zhang et al.[103] applied the same criteria across Western Europe and identified a combined European incidence for these three conditions of 9.5 per 1000 deliveries (95% CI, 9.1 to 9.9). Analyses of administrative codes (ICD-9 or ICD-10) for conditions that indicate severe obstetric morbidity in population-level data suggest rates of 8.1 per 1000 hospitalizations in the United States from 2004 to 2005, 13.8 per 1000 in Canada from 2003 to 2007, and 13.8 per 1000 deliveries in Australia in 2004.[106-109]

Near-miss morbidity occurs when a woman survives a life-threatening complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy.[110] The concept of a near-miss event evolved from early studies of pregnant patients who required intensive care.[111-113] Mantel et al.[114] proposed a definition that requires evidence of severe organ dysfunction,

intensive care unit admission, emergency hysterectomy, or an anesthetic accident such as failed intubation. On the basis of these criteria, a meta-analysis of 11 studies suggests a ratio of 4.2 near-misses per 1000 deliveries (95% CI, 4.0 to 4.4).[115] Geller et al.[116] validated a five-factor scoring system consisting of organ system failure (5 points), intensive care unit admission (4 points), transfusion of more than 3 units of blood products (3 points), extended intubation (2 points), and surgical intervention (1 point); a total score higher than 7 points defines a near-miss event. According to this scoring system, the incidence of a near-miss event was approximately 0.2 per 1000 deliveries in a perinatal tertiary care center in Chicago between 1995 and 2001.[116]

Maternal near-miss morbidity has also been defined using administrative data by combining ICD-9 codes for diagnoses indicating end-organ injury with either a prolonged length of stay (> 99th percentile) or transfer to a second health care facility.[95] Based on this administrative data definition, the incidence of near-miss maternal morbidity or maternal death in the United States between 2003 and 2006 was 1.3 per 1000 hospitalizations for delivery.[95]

The WHO Working Group on Maternal Mortality and Morbidity Classification determined that end-organ injury represents the most epidemiologically sound way to identify near-miss morbidity.[117] In 2009 the WHO proposed a panel of clinical, laboratory-based, or management-based criteria to identify maternal end-organ injury (see Box 40-e1 available at expertconsult.com).[110,118] Cecatti et al.[119] applied the WHO near-miss criteria to all ICU admissions in a tertiary care facility in Brazil between 2002 and 2007 and found a near-miss morbidity ratio of 14.7 events per 1000 live births, a MMR of 125 deaths per 100,000 live births, and a maternal near-miss-to-mortality ratio of 10.7:1.

Preventability has emerged as an important concept in maternal mortality and near-miss morbidity reviews because the opportunities for prevention identified from these reviews can be used to prioritize changes in clinical policy and health system improvements.[64,97,120] The Perinatal and Maternal Mortality Review Committee in New Zealand proposed a comprehensive list of contributory factors, including those attributed to the health care organization, personnel, technology and equipment, the environment and geography, and patient-level barriers to accessing or engaging with care.[68] Although contributory factors may be identified in the majority of maternal deaths, multiple reviews suggest that only 20% to 45% were likely preventable.[66,68,116,121,122] In a case-control study of maternal death, near-miss events, and severe morbidity, Geller et al.[122] identified a higher proportion of preventability among deaths and near-miss events compared with cases of severe morbidity (41% and 45% versus 17%) and suggested that provider-level improvements in medical care among women who develop severe morbidities represent the most frequent opportunities to prevent both near-miss events and maternal deaths. Across various reviews, the highest rates of preventability are noted among ethnic minorities[63,67] and among deaths attributed to hemorrhage, hypertensive disorders of pregnancy, and sepsis or infection.[63,123]

Anesthesia-Related Maternal Mortality

Anesthesia-related maternal mortality has been defined as "death attributable to anesthesia, either as the result of medications used, method chosen, or the technical maneuvers performed, whether iatrogenic in origin or resulting from an abnormal patient response."[124] A death may be considered anesthesia-related if it can be uniquely attributed to an anesthetic complication.[80] Actual case reports often include layers of comorbidities, anesthetic complications, and problems with nonanesthetic care; these cases may be considered anesthesia-related if optimal anesthetic care would likely have averted the death.[80] If optimal anesthetic care in combination with improvements in obstetric or medical management would likely have saved the woman's life, then the death may be considered anesthesia-contributing.[80] In some cases, the anesthetic complication is tragic but incidental (e.g., failed intubation during advanced cardiac life support for massive pulmonary embolism).

Anesthesia-related maternal death is extremely rare in the developed world. Table 40-5 shows recent MMRs attributed to anesthesia in the United States and the United Kingdom. Comparable ratios reported elsewhere in recent years include 1.4 per million live births in France for the years 2001 through 2006 and 1.0 per million in the Netherlands for the years 1993 through 2005.[66,67] Active surveillance in the United Kingdom may

TABLE 40-5 Anesthesia-Related Maternal Mortality Ratios in the United States and the United Kingdom, 1979-2008*

Triennium	United States (95% CI)	United Kingdom (95% CI)
1979-1981	4.3 (3.1-5.7)	8.7 (5.5-13.2)†
1982-1984	3.3 (2.3-4.5)	7.2 (4.3-11.4)†
1985-1987	2.3 (1.5-3.4)	2.6 (1.2-5.8)
1988-1990	1.7 (1.1-2.7)	1.7 (0.7-4.4)
1991-1993	1.4 (0.8-2.2)	3.5 (1.8-6.8)
1994-1996	1.1 (0.6-1.9)	0.5 (0.1-2.6)
1997-1999	1.2 (0.7-2.0)	1.4 (0.5-4.2)
2000-2002	1.0 (0.5-1.7)	3.0 (1.4-6.6)
2003-2005	Not available	2.8 (1.3-6.2)
2006-2008	Not available	3.1 (1.5-6.4)

CI, confidence interval.

*Reported rates refer to the risk for anesthesia-related death during pregnancy or up to 1 year after delivery per million live births in the United States or per million maternities in the United Kingdom.

†Rates for England and Wales only.

U.S. data from Hawkins JL, Chang J, Palmer SK, et al. Anesthesia-related maternal mortality in the United States: 1979-2002. Obstet Gynecol 2011; 117:69-74; U.K. data from Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. Br J Obstet Gynaecol 2011; 118(Suppl 1):1-203.

BOX 40-e1 The WHO Maternal Near-Miss Criteria

Clinical Criteria

- Acute cyanosis
- Gasping[a]
- Respiratory rate > 40 or < 6/min
- Shock[b]
- Oliguria nonresponsive to fluids or diuretics[c]
- Clotting failure[d]
- Loss of consciousness lasting ≥ 12 hours[e]
- Loss of consciousness *and* absence of pulse/heart beat
- Stroke[f]
- Uncontrollable fit/total paralysis[g]
- Jaundice in the presence of preeclampsia[h]

Laboratory-Based Criteria

- Oxygen saturation < 90% for ≥ 60 minutes
- Pa_{O_2}/F_{IO_2} < 200 mm Hg
- Creatinine ≥ 300 µmol/L or ≥ 3.5 mg/dL
- Bilirubin > 100 µmol/L or > 6.0 mg/dL
- pH < 7.1
- Lactate > 5
- Acute thrombocytopenia (< 50,000 platelets)
- Loss of consciousness *and* the presence of glucose and ketoacids in urine

Management-Based Criteria

- Hysterectomy after infection or hemorrhage
- Use of continuous vasoactive drugs[i]
- Transfusion of ≥ 5 units of red blood cells
- Intubation and ventilation for ≥ 60 minutes not related to anesthesia
- Dialysis for acute renal failure
- Cardiopulmonary resuscitation

[a] *Gasping* is a terminal respiratory pattern and the breath is convulsively and audibly caught.

[b] *Shock* is a persistent severe hypotension, defined as a systolic blood pressure < 90 mm Hg for ≥ 60 minutes with a pulse rate at least 120 despite aggressive fluid replacement (> 2 L).

[c] *Oliguria* is defined as a urinary output < 30 mL/h for 4 h or < 400 mL/24 h.

[d] *Clotting failure* can be assessed by the bedside clotting test or absence of clotting from the IV site after 7 to 10 minutes.

[e] *Loss of consciousness* is a profound alteration of mental state that involves complete or near-complete lack of responsiveness to external stimuli. It is defined as a Coma Glasgow Scale < 10 (moderate or severe coma).

[f] *Stroke* is a neurologic deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours.

[g] Condition in which the brain is in a state of continuous seizure.

[h] *Preeclampsia* is defined as the presence of hypertension associated with proteinuria. *Hypertension* is defined as a blood pressure of at least 140 mm Hg (systolic) or at least 90 mm Hg (diastolic) on at least two occasions and at least 4 to 6 h apart after the 20th week of gestation in women known to be normotensive before pregnancy. *Proteinuria* is defined as excretion of 300 mg or more of protein every 24 hours. If 24-h urine samples are not available, proteinuria is defined as a protein concentration of 300 mg/L or more (≥ 1+ on dipstick) in at least two random urine samples taken at least 4 to 6 hours apart.

[i] For instance, continuous use of any dose of dopamine, epinephrine, or norepinephrine.

Reproduced from Say L, Souza JP, Pattinson RC. Maternal near miss—towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol 2009; 23:287-96.

TABLE 40-6 **Case-Fatality Rates per Million Anesthetics for Cesarean Delivery in the United States (95% CI)**

Year of Death	General	Neuraxial	Risk Ratios
1979-1984	20.0 (17.7-22.7)	8.6 (7.8-9.4)	2.3 (1.9-2.9)
1985-1990	32.3 (25.9-49.3)	1.9 (1.8-2.0)	16.7 (12.9-21.8)
1991-1996	16.8 (8.9-28.7)	2.5 (1.2-4.5)	6.7 (3.0-14.9)
1997-2002	6.5 (2.1-15.3)	3.8 (2.3-6.1)	1.7 (0.6-4.6)

CI, confidence interval.
Data from Hawkins JL, Chang J, Palmer SK, et al. Anesthesia-related maternal mortality in the United States: 1979-2002. Obstet Gynecol 2011; 117:69-74.

be particularly effective at comprehensive identification of anesthesia-related maternal deaths.

A number of clinical and sociodemographic factors commonly appear among cases of anesthesia-related maternal death and may play a causal role in the mechanism of death. These include (1) maternal obesity; (2) patient refusal of neuraxial anesthesia; (3) remote anesthetic location; (4) delay in anesthesia provider consultation; (5) insufficient multidisciplinary planning, communication, and coordination; and (6) inadequate supervision of care.[62,63,80,124-126] In the United States, the relative risk of anesthesia-related maternal death appears to be increased for African-American women.[80,124,127]

Anesthesia-related maternal deaths are distributed throughout the perioperative period and follow both neuraxial and general anesthesia, primarily administered for cesarean delivery, but occasionally for vaginal delivery or another obstetric or nonobstetric surgical procedure.[62,80,126, 127] Case-fatality rates according to mode of anesthesia for cesarean delivery are presented in Table 40-6. To generate these estimates, the authors identified cases from death certificate data collected by the PMSS and estimated the total number of anesthetics delivered based on the national incidence of cesarean delivery and the proportions of cesarean deliveries completed with neuraxial and general anesthesia according to national surveys of anesthesia providers.[127,128]

Anesthesia-related maternal deaths are almost always preventable,[62-64,80,126,129] as evidenced by both individual case analysis and review of historical trends. The relative risks of general and neuraxial anesthesia for cesarean delivery in the United States have shifted over time, reflecting three major safety initiatives in anesthesia practice (see Table 40-6).[130] The first initiative addressed the hazard of **local anesthetic systemic toxicity (LAST),** identified as a major problem in a series of editorials published in the early 1980s.[131,132] In response, in 1984, the U.S. Food and Drug Administration recommended that bupivacaine 0.75% not be used for epidural anesthesia in obstetric patients. Also, anesthesiologists developed a series of safety procedures to avoid the unintentional intravascular administration of a toxic dose of local anesthetic through an epidural catheter. Case-fatality rates for neuraxial anesthesia subsequently declined 78% between the years 1979 through 1984 and 1985 through 1990 (see Table 40-6). Despite this improvement in prevention, LAST remains a rare and potentially lethal complication in obstetric anesthesia, with recent events attributed to drug error by nonanesthesia providers, cumulative dosing above the toxic threshold, epidural catheter migration, and single-shot transversus abdominis plane (TAP) blocks.[62,133-135] Lipid emulsion is now recommended as part of a comprehensive resuscitation strategy.[136,137]

The second initiative involved a shift toward **greater use of neuraxial anesthesia for cesarean delivery.**[128] Between 1985 and 1990, the relative risk of general anesthesia compared with neuraxial anesthesia for cesarean delivery was 16.7 (see Table 40-6), and much of the increase in risk was attributed to failed intubation or aspiration of gastric contents during induction of general anesthesia or both. In response, anesthesia providers now reserve general anesthesia for specific indications, including (1) emergency cesarean delivery with insufficient time to establish neuraxial anesthesia; (2) medical conditions that make neuraxial anesthesia unsafe, such as maternal coagulopathy, hemorrhagic shock, and septic shock; and (3) failed neuraxial anesthesia with intraoperative pain.[138]

The third initiative introduced a series of **protocols and devices to improve the safety of general anesthesia.**[130] Pulse oximetry and capnography have been widely credited with the decline in the incidence of unrecognized esophageal intubation.[139] Failed intubation algorithms, extraglottic airway devices (particularly the laryngeal mask airway), and a heightened focus on simulation and practice have impelled a transformation in airway management toward a clear focus on effective oxygenation and ventilation as well as ongoing preparation for airway emergencies.[64,140,141] Consequently, the case-fatality rate for general anesthesia decreased by 80% between the years 1985 through 1990 and 1997 through 2002 (see Table 40-6).[127] Nevertheless, recent series continue to report deaths from difficult intubation, unrecognized esophageal intubation, pulmonary aspiration of gastric contents (both with anesthetic induction and emergence), postextubation airway obstruction, and postoperative respiratory arrest attributed to opioids or other respiratory depressants.* Strategies to limit the risk for airway misadventure are discussed in Chapters 29 and 30.

The relative risk of general anesthesia in comparison with neuraxial anesthesia has fallen since 1990 and was estimated to be 1.7 (95% CI, 0.6 to 4.6) between 1997 and 2002.[127] In contemporary anesthesia practice, both general anesthesia and neuraxial anesthesia carry remote, but tangible risks for maternal death.

Why do women die of neuraxial anesthesia? **High neuraxial block** was the leading cause of anesthesia-related maternal death among women receiving neuraxial anesthesia for cesarean delivery in the United States between 1997 and 2002.[127] It was also the leading cause

*See references 62, 63, 80, 125, 127, 142.

of legal claims for maternal death or permanent brain injury filed between 1990 and 2003 (n = 15/25; 60%), with the majority of these attributed to unrecognized intrathecal catheters intended for the epidural space.[142] Single-shot spinal anesthesia administered after failed epidural anesthesia for cesarean delivery represents a second clinical scenario associated with high neuraxial block.[143] More details on high neuraxial block and its management may be found in Chapters 23 and 26.

Potentially lethal **infectious complications of neuraxial block** include meningitis, encephalitis, and neuraxial abscess.[144-146] The CEMD 2006 to 2008 report included a case of acute hemorrhagic disseminated leukoencephalitis attributed to thoracolumbar spinal canal empyema.[63] Current guidelines stress the importance of strict aseptic technique during neuraxial block administration, as well as appropriate monitoring and management for any infectious complications that may develop.[147,148] Further details are available in Chapter 32.

Other series suggest that neuraxial cardiac arrest and hypotensive arrest may be important mechanisms by which neuraxial anesthesia can lead to maternal death.[14,149] Prevention likely depends on careful attention to intravascular volume status, as well as the prompt, aggressive treatment of maternal hypotension to prevent reflex-mediated bradycardia and cardiovascular collapse.[150] Finally, perioperative respiratory arrest can result from neuraxial opioids or intravenous opioids or other respiratory depressants administered during or after neuraxial anesthesia.[62,80]

Further efforts to improve maternal safety must include a comprehensive approach to **high-quality perioperative patient care.** Timely preanesthesia evaluation and ongoing communication with obstetric providers are essential to limit the number of patients who require emergency administration of anesthesia without sufficient evaluation and preparation. Problems with **postoperative care** have long been recognized[151] but appear to account for a growing proportion of perioperative maternal deaths,[61,62,125,126] particularly those attributed to respiratory events, hemorrhage, and maternal sepsis.[67,68,87,143,145] The physiology of pregnancy and the compensatory physiologic responses that occur in young pregnant women may obscure early signs of septic or hemorrhagic shock. **Early warning scoring systems** may facilitate the early identification of women who have, or are beginning to develop, a critical illness.[62,63,97,126,152] Postanesthesia and postpartum care are commonly provided by labor and delivery nurses (as opposed to perianesthesia care nurses[153]) with limited training and experience with major anesthetic complications, noninvasive ventilation, and advanced cardiopulmonary life support.[154]

Fortunately, severe morbidity and mortality are rare in obstetrics; as an unfortunate consequence of this rarity, individual clinical experience with serious adverse events will always be limited. Simulation may be an effective strategy for all obstetric and anesthesia providers to prepare for a wide variety of obstetric emergencies, including postoperative airway obstruction, failed intubation, eclampsia, anaphylaxis, maternal cardiac arrest, and maternal hemorrhage. Chapter 11 details additional strategies to enhance patient safety.

KEY POINTS

- Ninety-nine percent of maternal deaths worldwide occur in developing countries. More than half of global maternal deaths are attributed to direct obstetric causes, including maternal hemorrhage, hypertensive disorders of pregnancy, and infection.
- In the developed world, 16 women die per 100,000 live births. In the United States, the maternal mortality ratio is increasing; in 2009, 16.6 women died per 100,000 live births.
- Advanced maternal age, maternal obesity, multiple gestation, cesarean delivery, and nonwhite race increase the risk for maternal death.
- Hypertensive disorders of pregnancy, embolic disorders, and hemorrhage together account for just under half of maternal deaths in the developed world but appear to be eclipsed by indirect deaths in some countries.
- Death is considered the extreme outcome of the following continuum of adverse pregnancy events: normal pregnancy → morbidity → severe morbidity → near-miss → death.
- In the developed world, the anesthesia-related maternal mortality ratio is estimated to range between 1 and 3 per million live births.
- Anesthesia safety for obstetric patients depends on the provision of high-quality perioperative patient care.

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PART X

THE PARTURIENT WITH SYSTEMIC DISEASE

Donald Caton, MD

John Snow, the London physician who twice anesthetized Queen Victoria for childbirth, made the first notes of an anesthetic administered to a parturient with systemic disease. On February 12, 1852, he was called to anesthetize a 23-year-old pregnant woman with osteosarcoma of the left shoulder. Her labor had begun 6 hours earlier. As Snow describes it, "the chloroform was not given to the extent of causing unconsciousness but it removed the suffering and caused fits of laughter in the patient after each time of inhaling it for the first half hour." The child was stillborn, "ill-nourished and small." From the child's condition, Snow believed that it had been dead for some time. He noted that the woman died a few weeks later.[1]

Snow wrote extensively about anesthesia. He was acutely aware that systemic disease affected the patient's response to anesthesia. In his last book, published posthumously, he described in detail various physical conditions that influenced a patient's response. Snow stated, "The comparative strength of debility of the patient has considerable influence on the way in which chloroform acts. Usually the more feeble the patient is, whether from illness, or from any other cause, the more quietly does he become insensible."[2] Snow's approach to patients with systemic disease was the same as that used today. The management of the parturient with severe diseases did not become a significant clinical problem until the twentieth century, when medical care had improved to the point that such a patient could survive into adulthood and become pregnant with a reasonable chance of carrying a child into the third trimester. Snow's experience with this seriously ill patient was probably unique for his day.[3]

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CHAPTER 41

Autoimmune Disorders

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CHAPTER OUTLINE

In the late 19th century Ehrlich proposed the dictum of *horror autotoxicus*, the belief that immunity is directed against foreign material and never against one's own body. The demonstration of autoantibodies in the 1950s disproved the theory and demonstrated the failure of self-tolerance.[1] Autoimmunity has been described in more than 40 disorders, and it may result in chronic illness and severe disability.

The cause of autoimmunity involves genetic and environmental factors, and consequently the classification of autoimmune diseases has been controversial. The traditional clinical classification recognizes immune responses that are directed against a particular antigen and are limited to a particular organ or cell type (**organ-specific disease**), and those that are directed against a range of antigens that produce multisystem involvement (**systemic disease**). Some examples are shown in Box 41-1. Classification now incorporates a "spectrum of autoimmunity" from low-level (possibly beneficial to self) to high-level (clearly detrimental to self) autoimmunity.[2]

The pathogenesis of autoimmunity is complex. A genetic predisposition underlies abnormal reactivity of B cells and immunoglobulins, T-cell receptors, and genes within the major histocompatibility complex (MHC).[3] Specific allotypes within the MHC are associated with certain diseases; for example, HLA-DR2 is strongly positively associated with **systemic lupus erythematosus (SLE)** but negatively associated with **diabetes mellitus type 1,** HLA-DR4 is associated with **rheumatoid arthritis** and **diabetes mellitus type 1,** and HLA-B27 is associated with **ankylosing spondylitis.** Recent work using genome-wide association studies has identified genetic associations between single nucleotide polymorphisms (SNPs) and autoimmune conditions[4] and may lead to a new classification of autoimmune disease.[5] Meta-analyses of HLA subclasses show similar associations with autoimmunity.[6]

Environmental factors may predispose to autoimmunity. Parasitic infection may reduce the incidence of autoimmunity, whereas bacterial infection with *Klebsiella* may predispose to ankylosing spondylitis. Drug-induced SLE is well described.

Sex hormones, notably the androgen-estrogen balance and its effect on cytokine production, have been implicated in the development of autoimmunity.[7] Autoimmune disorders are more common in women than men, with the highest incidence of several conditions occurring during the childbearing years; occasionally, the initial diagnosis is made during pregnancy. During normal pregnancy, altered immune function allows

BOX 41-1 Classification of Some Autoimmune Diseases

Organ-Specific Disease

- ***Neurologic:*** Myasthenia gravis, autoimmune peripheral neuropathy, Hashimoto's encephalopathy, temporal arteritis
- ***Hematologic:*** Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, cold agglutinin disease
- ***Skin:*** Vitiligo, pemphigus vulgaris, alopecia areata, autoimmune urticaria, psoriasis
- ***Gastrointestinal:*** Crohn's disease, celiac disease, autoimmune hepatitis, primary biliary cirrhosis, ulcerative colitis
- ***Endocrine***: Hashimoto's thyroiditis, Addison's disease, diabetes mellitus type 1, Graves' disease
- ***Skeleton***: Ankylosing spondylitis, psoriatic arthropathy
- ***Cardiovascular***: Autoimmune cardiomyopathy
- ***Renal***: Goodpasture's syndrome

Systemic Disease

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Multiple sclerosis
- Sjögren's syndrome
- Dermatomyositis
- Scleroderma
- Polymyositis
- Mixed connective tissue disease
- Wegener's granulomatosis

maternal tolerance of the fetal allograft. Both mother and fetus produce immunologic factors that inhibit maternal cell-mediated immunity,[8,9] prevent rejection of the fetus, and limit the expression of autoimmunity. Conversely, the high estrogen environment of pregnancy may enhance immune function.[10] Although this may protect the mother and fetus from peripartum infection, it increases the likelihood of autoimmune conditions.

Systemic lupus erythematosus, lupus anticoagulant, scleroderma, and **polymyositis/dermatomyositis** are discussed in this chapter. Other autoimmune disorders are discussed elsewhere in this text, including **diabetes mellitus type 1** (see Chapter 43) **autoimmune thrombocytopenic purpura** and **autoimmune hemolytic anemia** (see Chapter 44), **rheumatoid arthritis** and **ankylosing spondylitis** (see Chapter 48), and **myasthenia gravis** (see Chapter 49).

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition and Epidemiology

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease of unknown etiology that is characterized by the production of autoantibodies against nuclear, cytoplasmic, and cell membrane antigens. Although SLE may occur at any age, it is recognized most commonly in women during their childbearing years, with a female-to-male ratio of 9:1. African-Americans, Asians, and Native Americans are affected more often than whites.[11] An estimated 1 in 1200 deliveries occur in women with SLE.[12]

BOX 41-2 Diagnostic Criteria for Systemic Lupus Erythematosus

- Malar rash (butterfly rash over malar region)
- Discoid rash (erythematous, raised patches with scaling)
- Photosensitivity
- Oral ulceration
- Arthritis
- Serositis (pleuritis or pericarditis)
- Renal disorder (persistent proteinuria or cellular casts)
- Neurologic disorder (seizures or psychosis)
- Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
- Immunologic disorder (anti-DNA, anti-Sm nuclear antigen, anticardiolipin antibodies, lupus anticoagulant, or false-positive syphilis test)
- Antinuclear antibody

From Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-7; and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40:1725.

Pathophysiology

The etiology of SLE remains unclear. The principal mechanism is thought to be an immune complex disease involving IgG antibodies to double-stranded DNA and other nuclear proteins. Intracellular autoantigens are released by necrotic and apoptotic cells, leading to aberrant sensitization against these antigens. Impaired clearance of apoptotic cells and prolonged exposure to nuclear autoantigens may be involved.[13] Affected individuals have both hyperactivity of the antibody-producing B cells and defects of the helper and suppressor T cells.[14] Genetic defects of immune regulation and possibly environmental triggers including viruses and bacteria lead to a proliferation of B cells capable of producing autoantibodies. More than 30 classes of antigens have been identified as targets of these antibodies. A variety of antigen-antibody immune complexes are formed, followed by secondary inflammatory responses. Deposition of immune complexes and continued inflammation within the glomerulus may lead to irreversible renal injury. Deposits also occur within the skin, choroid plexus, and other endothelial surfaces, with or without an inflammatory response. However, SLE is not simply an immune complex disorder because some autoantibodies actively bind to erythrocytes, granulocytes, lymphocytes, and macrophages, leading to their removal from the circulation.[11]

Diagnosis

Clinical manifestations of SLE are diverse, owing to the widespread antigenic targets. Box 41-2 outlines objective criteria for the diagnosis of SLE.[15,16] Although epidemiologic studies require the presence of four or more of these criteria, the clinical diagnosis may be suspected if fewer features are present without another explanation. Typically, the diagnosis of SLE is made

before conception, but in 20% of cases the initial diagnosis is made during pregnancy.[17]

Effect of Pregnancy

Although pregnancy does not worsen the long-term course of SLE,[18,19] disease activity may increase during pregnancy.[20,21] A preconception history of nephritis predicts adverse maternal outcome.[22] The risk for significant disease activity during pregnancy is increased sevenfold if active disease is present in the 6 months before conception.[23] Assessments using the SLE Disease Activity Index found that 50% to 65% of women with active disease had deterioration during pregnancy in both retrospective[24] and prospective[25] studies. Such flares occur most commonly in the second and third trimesters and the puerperium and are not more severe than those in nonpregnant patients; most respond to conservative management.

Effect on the Mother

Most women with SLE do not have renal impairment at conception, possibly because renal insufficiency impairs fertility. If lupus nephritis does preexist, deterioration in renal function may occur during pregnancy. This is generally mild and reversible, but 12% of pregnant women with SLE suffer irreversible progression of renal dysfunction.[26,27] Long-term glomerular filtration rate may be preserved.[28]

The presence of hypertension, edema, and proteinuria in both lupus nephritis and preeclampsia makes distinguishing between the two difficult. It is not clear whether preeclampsia is more common in patients with SLE, but a large meta-analysis suggests an association between lupus nephritis and preeclampsia.[29] The distinction is critical because treatments are different (immunosuppressive therapy for lupus nephritis versus delivery for preeclampsia). Increased serum uric acid concentration, proteinuria without active urinary sediment, and liver enzyme abnormalities suggest preeclampsia rather than SLE.

SLE may cause thrombocytopenia. When thrombocytopenia occurs in a pregnant woman, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and disseminated intravascular coagulation must also be considered. Anemia, a common manifestation of SLE, must be differentiated from nutritional anemia and the physiologic anemia of late pregnancy.

Ligamentous relaxation often occurs during late pregnancy and may worsen the pain of lupus arthritis. Patients with SLE occasionally require joint replacement, most commonly of the femoral head. These prostheses may become painful, dislocated, or infected during pregnancy.[30] Neurologic complications of SLE are rare during pregnancy but include seizures, chorea gravidarum, and stroke.

Effect on the Fetus

Maternal SLE impairs fetal survival and increases the risk for preterm delivery. A systematic review of papers published between 1980 and 2009 showed that preterm delivery occurred in 39.4% of 2751 pregnancies in 1842 patients.[29] In the Hopkins Lupus Pregnancy Cohort, preterm birth occurred in 38 of 57 (67%) pregnancies in women with moderate to severe active SLE, compared with 68 of 210 (32%) pregnancies in women with inactive or mild active SLE.[31] Improved perinatal management and control of disease activity has reduced the rate of fetal loss from 43% (between 1960 and 1965) to 17% (between 2000 and 2003).[32] Data from California showed a preterm delivery rate in SLE that was six times higher than that found in the general population.[33]

Neonatal lupus erythematosus (NLE) is a syndrome that results from maternal autoantibodies against Ro (SS-A) or La (SS-B) crossing the placenta and binding to fetal tissue. These autoantibodies are found in up to 87% of patients with SLE,[34] but NLE occurs in only a small proportion of patients. The condition is generally benign and self-limiting, and reversible manifestations such as cutaneous lupus, elevation in aminotransferase levels, and thrombocytopenia resolve as maternal antibodies disappear from the neonatal circulation within 8 months of birth. Anti-Ro/anti-La antibodies may bind to fetal cardiac conduction cells *in utero*, leading to cell death and irreversible fetal heart block. Neonatal congenital heart block occurs in 2% of neonates when anti-Ro antibody is detected in the mother.[35] Fetal echocardiography reveals atrioventricular dissociation, cardiac dilation, and pericardial effusion. Treatment includes prompt delivery, newborn cardiac pacing, antepartum administration of dexamethasone, and consideration of apheresis to remove maternal antibodies.[36]

Medical Management

Optimally, women with SLE should delay pregnancy until their disease has been quiescent for at least 6 months, and they should be taking "acceptably safe" medications at the time of conception.[21,23,27,37] Medications with acceptable safety are used to minimize disease activity during gestation.

Disease-modifying antirheumatic drugs (DMARDs) and immunosuppressive agents form the mainstay of treatment. Antimalarial drugs are frequently used to reduce SLE activity.[38] Discontinuation of **hydroxychloroquinine** just before conception or in early pregnancy leads to a significant increase in disease activity.[39] A systematic review of English literature (1982-2007) found that antimalarial drugs, particularly hydroxychloroquinine, prevent lupus flares; increase long-term survival; contribute to protection against irreversible organ damage, thrombosis, and bone loss; and have low toxicity.[40] Hydroxychloroquinine should be continued in all women who were taking it before conception and may be used to treat flares during gestation. In contrast, **mycophenolate mofetil** should be discontinued before conception owing to the risk for teratogenicity. **Azathioprine** is an acceptable substitute and should be continued if used before conception.[21,23] The fetal liver does not express the enzyme necessary to convert azathioprine to its active form,[41] but maternal use of azathioprine has been associated with reversible neonatal lymphopenia, depressed serum immunoglobulin levels, and decreased thymic size in the newborn.[41,42]

Corticosteroids may be used to treat flares of SLE disease activity. Antenatal exposure to low-dose **prednisone** (< 20 mg daily) appears to be safe, and most children develop normally. However, there is concern that prolonged fetal exposure to other corticosteroids such as **dexamethasone** or **betamethasone** may lead to fetal growth restriction and abnormal neuronal development.[43] Corticosteroid therapy may precipitate gestational diabetes, and patients should be monitored for evidence of glucose intolerance. Striae, gastrointestinal ulceration, and bone demineralization may complicate long-term corticosteroid therapy. Affected patients should receive postprandial and bedtime antacids.[44] The pediatrician should be alerted to the possibility of neonatal adrenal suppression.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and stronger analgesics may be used to manage lupus arthritis. Although there is no evidence of teratogenicity with these agents,[41] concern exists that NSAIDs may cause premature closure of the fetal ductus arteriosus,[45] impairment of maternal and neonatal hemostasis,[46] and adverse effects on maternal renal function.

Obstetric Management

Patients with SLE are at increased risk for intrauterine fetal death and preterm delivery. Estimation of the gestational age is obtained with ultrasonography at the first prenatal visit and again at 20 weeks' gestation. Continued surveillance consists of nonstress testing, biophysical profile measurement, and/or umbilical artery Doppler velocimetry beginning at 26 to 28 weeks' gestation and performed weekly until delivery.[27]

The coexistence of antiphospholipid antibodies predicts a much higher maternal and fetal risk. Maternal serologic markers are checked regularly, together with platelet count, creatinine clearance, 24-hour urine protein level, and presence or absence of anti-Ro/anti-La antibodies.[47] Platelet count measurement is repeated monthly. If anti-Ro/anti-La antibodies are detected or the fetal heart rate is 60 beats per minute without variability in the second trimester, fetal echocardiography and fetal heart rate testing are performed to check for signs of congenital heart block or failure.[48] Thromboprophylaxis is important in patients with **antiphospholipid syndrome** (see later discussion). In normal pregnancy, serial complement levels gradually increase. However, declining levels of C3 and C4 suggest active disease and lupus nephritis.[21] Aspirin resistance may predict adverse maternal and neonatal outcome.[49] Regular assessment of blood pressure, weight gain, and proteinuria is performed to detect the development of preeclampsia.

The timing and route of delivery are individualized. Although vaginal delivery is preferred, the cesarean delivery rate in parturients with SLE is 40%.[12]

Anesthetic Management

The obstetrician, rheumatologist, and anesthesiologist should formulate a joint plan for delivery. Maternal organ system involvement, current disease severity, and particularly the presence of flares must be assessed.[50]

Pericarditis is common in patients with SLE and is typically asymptomatic. A history of dyspnea on exertion or unexplained tachycardia may suggest pericarditis or **myocarditis. Cardiac tamponade** has been reported.[51] Prolongation of the PR interval or nonspecific T-wave changes may be seen on the electrocardiogram. Coronary artery vasculitis, accelerated atherosclerosis leading to **myocardial ischemia,** and even **myocardial infarction** in young women have been reported.[52,53]

An echocardiographic study in 69 patients with SLE showed a high incidence of **valvular abnormalities,** including valvular thickening in 51%, vegetations in 43%, regurgitation in 25%, and stenosis in 4%.[54] Current American Heart Association guidelines recommend antibiotic prophylaxis only for patients at highest risk for infective endocarditis in whom there is both significant risk and consequence of infection.[55] Prophylactic antibiotics are not recommended for women with common valvular lesions undergoing genitourinary procedures, including vaginal delivery, but are specifically indicated for those with previous infective endocarditis, unrepaired cyanotic congenital heart disease, implanted prosthetic material or devices, or a history of cardiac transplantation with cardiac valvulopathy.

The prevalence and progression of **pulmonary hypertension** in 28 patients with SLE has been studied.[56] The prevalence increased from 14% at initial evaluation to 43% 5 years later. Epidural anesthesia for cesarean delivery in parturients with pulmonary hypertension has been reported (see Chapter 42). The abrupt onset of sympathetic blockade and decreased venous return may cause precipitous systemic hypotension and hypoxemia. One report described the administration of general anesthesia in a parturient with SLE and pulmonary hypertension, with coexisting SLE-related restrictive lung disease, pulmonary edema, and orthopnea.[57] In one report of three parturients with pulmonary hypertension secondary to SLE and antiphospholipid syndrome, two died of right-sided heart failure within 48 hours of delivery.[58]

Subclinical **pleuritis** is common, but significant **pleural effusions** occur rarely. Patients may suffer from **infectious pneumonia** or **lupus pneumonitis.** The latter condition is characterized by fleeting hemorrhagic infiltrates that may become consolidated. **Pulmonary embolism** and **diaphragmatic dysfunction** have been reported.[52]

Central and peripheral sensorimotor and autonomic neuropathies are observed in as many as 25% of patients with SLE.[59] **Vocal cord palsy** has been reported in SLE.[50,60] These deficits should be documented before the administration of either neuraxial or general anesthesia. **Migraine headache** and **cerebral vasculitis** resulting from SLE must be considered in the differential diagnosis of a postpartum headache. **Psychological disorders** and frank **psychosis** can occur during disease flares.[11,61] **Seizures** can occur, especially if chronic anticonvulsant medications are discontinued inadvertently.

Hematologic abnormalities, including **anemia, thrombocytopenia,** and **coagulopathy,** should be documented. An abnormality of the activated partial thromboplastin time (aPTT), which is not corrected with a 1 : 1 control plasma mix, suggests the presence of either lupus

anticoagulant (a coexistent but separate disease entity) or, more rarely, true autoantibodies against specific coagulation factors (e.g., VIII, IX, XII). Lupus anticoagulant is a laboratory artifact that does *not* cause clinical coagulopathy. True coagulation factor autoantibodies (or inhibitors) may result in a significant bleeding diathesis, which contraindicates the administration of neuraxial anesthesia.

Long-term use of NSAIDs leads to qualitative platelet abnormalities but has rarely been associated with epidural or subdural hematoma, and the role of NSAIDs in causing spinal epidural hematoma remains conjectural.[62,63] In a prospective study of 924 patients undergoing orthopedic procedures with spinal or epidural anesthesia, preoperative antiplatelet medications were taken by 39% of these patients; no cases of spinal epidural hematoma were observed.[64] The same investigators similarly studied 1035 patients undergoing epidural steroid injection.[65] NSAID use was reported by 32% of patients undergoing chronic pain management; there were no cases of spinal hematoma. In the CLASP study, a large, multicenter randomized trial, 9364 pregnant women received either low-dose aspirin (60 mg daily) or placebo for prevention and treatment of preeclampsia.[66] Of 5000 enrollees, at least 1069 patients received epidural analgesia, and no cases of epidural hematoma were observed.[67] Determination of the bleeding time before neuraxial injection in patients taking aspirin or NSAIDs is no longer indicated. Measurement of thromboelastography has been suggested as an alternative but is not widely available.[68]

Atypical blood antibodies may complicate crossmatching of blood for patients with SLE. Additional time should be allowed for this possibility.

Prosthetic orthopedic joints should be positioned carefully during vaginal or cesarean delivery. Lupus arthritis rarely involves the cervical spine. Women who have undergone long-term corticosteroid therapy should receive a peripartum stress dose of a corticosteroid.

ANTIPHOSPHOLIPID SYNDROME

Definition and Epidemiology

The antiphospholipid syndrome (APS, also known as Hughes' syndrome) was first recognized in the early 1980s[69-71] and classified by international consensus in 2005.[72] It is a *prothrombotic* disorder characterized by the presence of two autoantibodies, lupus anticoagulant and anticardiolipin antibody. Affected patients are at risk for both arterial and venous thrombosis. Patients with SLE may show lupus anticoagulant (34%) and anticardiolipin antibody (44%).[73] However, APS is a distinct and separate entity from SLE. A long-term cohort study found that among patients with APS, only 11 of 128 (8%) had SLE.[74]

The population prevalence of APS is unclear. In 1990, commenting on the volume of publications on APS, Harris[75] remarked that the syndrome "probably occurs less frequently than the number of papers published on the subject." But in 2007, with greater clinical recognition, Hughes predicted that the prevalence of APS will exceed that of SLE.[70]

Pathophysiology

APS is characterized by two important misnomers. First, the antiphospholipid antibodies do not bind directly to phospholipids but to phospholipid-binding plasma proteins such as β_2-glycoprotein I, prothrombin, and annexin V. Second, the lupus anticoagulant has no true anticoagulant activity *in vivo* but is a laboratory artifact that affects phospholipid-dependent coagulation assays: the aPTT, the kaolin clotting time (KCT), the tissue thromboplastin inhibition (TTI) test, and the dilute Russell viper venom time (dRVVT). These times remain prolonged even when the tests are repeated with a 1:1 mixture of the patient's plasma and control plasma. The prothrombin time (PT) typically is normal. Lupus anticoagulant appears to block *in vitro* assembly of prothrombinase (a phospholipid complex), thus preventing the conversion of prothrombin to thrombin. True bleeding associated with lupus anticoagulant is extremely rare and, in most cases, is caused by an underlying factor deficiency or inhibitor.[76]

Contrary to expectation, lupus anticoagulant and anticardiolipin antibody are associated with both arterial and venous **thrombotic events.** The current model by which this thrombotic tendency occurs involves antiphospholipid antibodies binding to β_2-glycoprotein I, which then bind to glycoprotein Ibα on platelets, monocytes, and endothelial cells. These complexes cause platelet adhesion, expression of prothrombotic molecules, and local complement activation.[76,77]

Diagnosis

The diagnosis of APS depends on a clinical history of unexplained recurrent venous or arterial thrombosis, pregnancy loss, and laboratory evidence of anticardiolipin antibody or lupus anticoagulant.[72] The latter is demonstrated by (1) evidence of abnormal phospholipid-dependent coagulation (elevated aPTT), (2) evidence that this abnormality is caused by an inhibitor rather than a factor deficiency (elevated aPTT with 1:1 mix), and (3) proof that the inhibitor is directed against phospholipid rather than specific coagulation factors. Antibodies should be demonstrable on two occasions separated by 12 weeks.[78] The presence of lupus anticoagulant, anticardiolipin (aCL), and anti-β_2-glycoprotein I (aβ2GPI) antibodies ("triple positivity") with a clinical diagnosis of APS predicts severe disease.[79] Results from different laboratories show considerable variability, and guidelines on diagnostic criteria have been published.[80] Tests for syphilis detect the antiphospholipid antibodies present in syphilis, and consequently the Venereal Disease Research Laboratory (VDRL) and Wasserman test results are often falsely positive.

Effect on the Mother

Pregnant women with APS are at risk for **venous and arterial thrombosis, pulmonary embolism, myocardial infarction, cerebral infarction** and **fetal loss.** Cohort studies suggest that contemporary management strategies may improve maternal outcome. In 130 women with APS followed over a 3-year period, 48%

experienced at least one of the following disorders: **transient ischemic attack, peripheral thrombosis** (of which one fourth occurred in pregnancy and the puerperium), **stroke, amaurosis fugax, autoimmune thrombocytopenia,** and **SLE.**[81] Women who were diagnosed with APS on the basis of recurrent pregnancy loss and evidence of antiphospholipid antibody, but without prior thrombotic events, rarely suffered thrombosis during pregnancy.[82] A history of thromboembolic events significantly worsens prognosis and increases the likelihood of future events, an effect ameliorated by the use of oral anticoagulants.[83] Thrombocytopenia, present in one fourth of patients with APS, may require splenectomy.[84] **Catastrophic APS,** an accelerated form of the condition that results in multisystem organ thrombosis and failure, may be triggered by pregnancy in 4% of cases.[85]

Effect on the Fetus

Pregnant women with APS are at high risk for intrauterine fetal death. Early studies showed that only 7.5% of pregnancies resulted in the delivery of a live newborn,[86] whereas recent reports have shown live-birth rates up to 100%.[87] Pregnant women with lupus anticoagulant, aCL, and aβ2GPI antibody titers greater than four times the upper limit of normal have a twofold increase in risk for fetal loss, when compared with women with positive titers only (35% versus 77% live-birth rate).[88] Placental infarction is the apparent mechanism of mortality, and most fetal deaths occur during mid and late pregnancy. There is no high-level evidence to guide management of pregnant women with high antibody titers.[89]

Most infants born to women with APS do not have an increased rate of neonatal or childhood complications,[90] although cases of antiphospholipid-related **fetal and neonatal thrombosis** (mainly cerebral thrombosis) have been reported.[91]

Medical and Obstetric Management

Fetal survival and maternal thrombotic risk may be improved when affected pregnant women are treated with low-dose aspirin and heparin. A 2005 meta-analysis found that combined treatment with unfractionated heparin and aspirin can reduce pregnancy loss by 54%.[92] Recommendations on investigation and management of APS have been made.[93] Women with more than three unexplained pregnancy losses before 10 weeks' gestation should be tested for antiphospholipid antibodies; women with APS and recurrent pregnancy loss should receive prophylactic doses of **heparin** and **low-dose aspirin** throughout pregnancy, and administration for 6 to 8 weeks postpartum should be considered. A history of APS with thrombosis may require full anticoagulation throughout pregnancy and the postpartum period. A meta-analysis suggested that unfractionated heparin in combination with aspirin increases the live-birth rate in women with APS, but the benefit of **low-molecular-weight heparin (LMWH)** is unclear; neither type of heparin crosses the placental barrier.[94]

Catastrophic antiphospholipid syndrome (CAPS or Asherson's syndrome) occurs in 1% of patients with APS.[85] Diagnosis requires the presence of antiphospholipid antibodies with involvement of at least three organs and rapid onset and progression of disease. Mortality is as high as 50%.[72] Aggressive treatment with full anticoagulation, antibiotic cover for a precipitating bacterial infection, intravenous corticosteroids and immunoglobulins, and plasma exchange may be required. Severe **thrombocytopenia** may respond to **rituximab.**

Anesthetic Management

Management of the patient with antiphospholipid antibodies is similar to that of the patient with SLE. Coexisting autoimmune disorders, secondary organ involvement, and thrombotic phenomena should be evaluated. The term *lupus anticoagulant* is a misnomer (as discussed earlier) and does *not* warrant withholding neuraxial anesthesia. Infrequently, antiphospholipid antibodies can cause coagulation factor deficiencies, and in such patients neuraxial anesthesia is relatively contraindicated. In the absence of an underlying coagulation deficit or anticoagulant therapy, the prolonged aPTT does *not* suggest a bleeding tendency, and neuraxial anesthesia may be administered safely.

The anesthetic management of pregnancies complicated by APS has been reviewed.[95,96] All subjects received aspirin (75 to 150 mg daily) throughout pregnancy, and aspirin therapy alone was not considered a contraindication to neuraxial anesthesia. In parturients who received thromboprophylaxis with standard unfractionated heparin, spinal or epidural anesthesia was administered 4 hours after the last dose of heparin. The use of LMWH for thromboprophylaxis precludes administration of neuraxial anesthesia until at least 12 hours have elapsed since the time of the last dose.[97] Further, therapeutic anticoagulation with high-dose LMWH precludes the administration of neuraxial anesthesia until at least 24 hours have elapsed since the time of the last dose (see Chapters 39 and 44). The use of **thromboelastography** to document clearance of heparin before administration of neuraxial anesthesia in parturients with lupus anticoagulant has been described.[98]

If fetal compromise secondary to multi-infarct placental insufficiency exists, hypotension from sympathetic blockade should be prevented. Neuraxial anesthesia with an epidural, intrathecal, or combined spinal-epidural technique is not contraindicated, provided that blood pressure is closely controlled. Parturients with APS who undergo general anesthesia are at risk for venous thrombosis. Compression stockings, warm intravenous fluids, and early ambulation should be used, whereas hypothermia and dehydration should be avoided.[95,96,99] There is no evidence that a "walking epidural" confers benefit.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Definition and Epidemiology

Systemic sclerosis or scleroderma is a chronic progressive autoimmune disease of unknown etiology characterized by deposition of fibrous connective tissue in the skin and

other tissues, microvascular changes, and chronic inflammation. It is a heterogeneous disorder and may be in the form of **limited** or **diffuse cutaneous scleroderma.** A subset of patients exhibit systemic sclerosis without cutaneous involvement.[100]

The annual incidence of scleroderma in the United States is 19 per million. The prevalence is 240 per million, which is four to nine times greater than the reported global prevalence. Scleroderma is almost five times more common among women than men and occurs primarily between 30 and 50 years of age.[101]

Pathophysiology

The stimulus for fibroblasts to produce excessive collagen and other matrix constituents is unknown; however, their accumulation leads to microvascular obliteration and fibrosis in the skin and other target organs. Endothelial cells undergo vasomotor and permeability changes, producing cyclic vasoconstriction-vasodilation and edema. Patients with scleroderma produce autoantibodies against nuclear and centromere structures, although their significance is unclear. Scleroderma exhibits a strong female predilection, a steep rise in incidence after the childbearing years, and features that are similar to graft-versus-host disease after bone marrow transplantation, prompting some to postulate that microchimerism may be involved in its pathogenesis. Fetal cells gain access to the maternal circulation during gestation and may be detected in maternal blood for decades after delivery. After some unknown stimulus (that possibly includes environmental factors), these fetal cells may differentiate and initiate a reaction similar to graft-versus-host disease.[102,103]

Diagnosis

Raynaud's phenomenon, characterized by cyclic pallor and cyanosis of the digits in response to cold or emotion, is a common prodrome to scleroderma, with 1% of patients progressing to scleroderma. The triad of Raynaud's phenomenon, nonpitting edema, and hidebound skin establishes the diagnosis of scleroderma.

Limited cutaneous scleroderma, also termed **CREST syndrome,** involves calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. Skin involvement is limited to the hands, face, and feet in this form of the disease. The more extensive clinical manifestations of diffuse cutaneous scleroderma are summarized in Box 41-3.

BOX 41-3 Manifestations of Diffuse Cutaneous Systemic Sclerosis

Skin
- Raynaud's phenomenon
- Nonpitting edema
- Hidebound skin (involves all but back and buttocks)

Gastrointestinal
- Hypomotility
- Dysphagia
- Reflux esophagitis
- Postprandial fullness
- Constipation
- Abdominal pain
- Intermittent diarrhea
- Malnutrition
- Ileus

Pulmonary
- Interstitial fibrosis
- Pleuritis
- Pulmonary hypertension

Renal
- Proteinuria
- Renal insufficiency and failure
- Malignant hypertension

Cardiac
- Chronic pericardial effusion
- Myocardial ischemia and infarction
- Conduction disturbances
- Heart failure

Musculoskeletal
- Arthritis (symmetric, small joints)
- Myopathy
- Muscle wasting

Other
- Peripheral or cranial neuropathy
- Facial pain
- Trigeminal neuralgia
- Keratoconjunctivitis sicca
- Xerostomia
- Absence of anticentromere antibodies

From LeRoy EC. Systemic sclerosis (scleroderma). In Wyngaarden JB, Smith LH, Bennett JC, editors. Cecil Textbook of Medicine. 19th edition. Philadelphia, WB Saunders, 1992:1530-5.

Effect of Pregnancy

Progression of scleroderma tends to be slow. More than 70% of patients with diffuse cutaneous scleroderma and more than 90% of those with limited cutaneous scleroderma are alive 15 years after diagnosis.[104] Renal failure and malignant hypertension are the most common causes of death. Successive reviews by Steen[105-107] indicate that improvements in management allow patients with scleroderma to have successful maternal and fetal outcomes. Maternal symptoms were unchanged in 62% of pregnancies and improved in 20%. In the other 18% of pregnancies, esophageal reflux, cardiac arrhythmias, arthritis, skin thickening, and/or renal crisis occurred or worsened.[105-107] Deterioration of renal function is of greatest concern.[108]

Effect on Pregnancy and the Fetus

The frequency of preterm births and small-for-dates infants is higher in pregnant women with scleroderma.[108] Preterm birth occurs in 25% of pregnancies (compared with 5% in control pregnancies), and most preterm deliveries occur in women with unstable diffuse scleroderma of less than 4 years' duration. Miscarriage occurs

more commonly in women with long-standing diffuse scleroderma.[105]

Medical Management

Management is symptomatic rather than curative, and is directed toward slowing end-organ damage. When lifestyle alterations (e.g., avoidance of cold, cessation of smoking) are no longer effective, management may include **calcium entry–blocking agents** for skin manifestations, **proton-pump inhibitors** and occasionally **esophageal dilation** for gastrointestinal tract symptoms, and **phosphodiesterase inhibitors** and **prostaglandins** for pulmonary arterial hypertension. No disease modification benefits have been shown by administration of **penicillamine, methotrexate,** or other immunosuppressive agents (other than the use of glucocorticoids for inflammatory myositis).[109,110]

Drugs with unproven or potential teratogenicity are relatively contraindicated during pregnancy. However, **angiotensin-converting enzyme (ACE) inhibitors** are the agents of choice for treating scleroderma-associated renal crisis and malignant hypertension, despite the potential for fetal teratogenicity, renal atresia, pulmonary hypoplasia, anhydramnios, and fetopathy.[106] ACE inhibitors provide the only effective control of hypertension during scleroderma-associated renal crisis and should be started immediately if maternal hypertension occurs. Their use should be avoided if hypertension or overt renal crisis is not present.

Nitric oxide donors and possibly **heparin** may provide some protection against placental dysfunction in pregnant women with scleroderma.[111]

Obstetric Management

Pregnant women with scleroderma should be specifically evaluated for evidence of renal, pulmonary, and cardiac dysfunction. Preterm delivery or termination of pregnancy may be required in the presence of advanced or rapidly progressive disease. Frequent assessment of renal function and intensive observation for the onset of systemic or pulmonary hypertension, cardiac dysfunction, and fetal compromise, combined with improvements in monitoring and treatment, allow most mothers to deliver healthy infants. Obstructive uropathy may result from an enlarging uterus trapped within a noncompliant abdomen.[112] Uterine and cervical wall thickening may lead to ineffective uterine contractions or cervical dystocia at delivery.[107] Even the tightest abdominal skin usually heals if cesarean delivery is necessary.[107]

Anesthetic Management

The pregnant woman with scleroderma presents several challenges to the anesthesia provider and should be assessed before labor and delivery. Early multidisciplinary involvement is required.

History and physical examination should be directed toward detection of underlying systemic dysfunction. Laboratory tests include complete blood cell count, coagulation screen, electrolyte concentrations and creatinine clearance, arterial blood gas analysis, urinalysis, and urine protein determination. An electrocardiogram and pulmonary function testing should be performed in all patients. Echocardiography is increasingly used to assess ventricular dysfunction, pericardial and pleural effusions, and pulmonary hypertension.[113] Particular attention should be paid to arterial pulses, noninvasive blood pressure measurement, peripheral venous access, extent of Raynaud's phenomenon involvement, and special positioning requirements.

Severe limitation of mouth opening caused by hidebound perioral skin may make direct laryngoscopy impossible and mandates careful airway assessment.[114] Maximal mouth opening, the ability to sublux the mandible, visualization of oropharyngeal structures, degree of atlanto-occipital joint extension, and presence of oral or nasal telangiectases should be checked and a determination made as to whether direct laryngoscopy will be difficult if general anesthesia is required.[115] The patient should be prepared for the possibility of an awake tracheal intubation. Specialized airway equipment (e.g., fiberoptic laryngoscope, videolaryngoscope, emergency cricothyrotomy set) should be immediately available. The changes in graded intubation scores that occur during labor should also be borne in mind.[116]

Epidural anesthesia has been used successfully in parturients with scleroderma.[117,118] Early administration of epidural analgesia in laboring women in whom tracheal intubation is likely to be difficult is to be encouraged. Even when severe diffuse cutaneous involvement is present, the skin of the lumbar back is spared. Spinal anesthesia for cesarean delivery complicated by precipitous hypotension in a parturient with scleroderma has been reported.[119] Recovery was uneventful in this woman, with full return of motor function within 3.5 hours. However, prolonged duration of regional anesthesia has been observed in some patients with scleroderma. An axillary block performed with 1% lidocaine with epinephrine was reported to have persisted for 24 hours,[120] a digital nerve block performed with 1% lidocaine without epinephrine persisted for 10 hours,[121] and a sciatic nerve block persisted for 16 hours.[122] Prolonged epidural anesthesia with 2% 2-chloroprocaine has also been reported.[123]

Unduly prolonged analgesia and anesthesia may be due to reduced uptake of the local anesthetic agent as a consequence of microvasculature changes. This is not a contraindication to neuraxial techniques but should prompt the use of small incremental boluses of the local anesthetic agent. The patient should be warned of the possibility of prolonged neural blockade. Because continuous infusion techniques may result in the administration of an excessive dose with prolonged neural blockade, incremental bolus or patient-controlled injection techniques may be preferable. Whether this consideration makes epidural (with the ability to titrate the dose) rather than spinal anesthesia preferable for cesarean delivery is unclear.

If cesarean delivery is required, the decision to use epidural or general anesthesia depends on the urgency of delivery, anticipated airway difficulty, and the operator skills. Gastric hypomotility increases the risk for esophageal reflux and aspiration. Diffuse cutaneous involvement

may indicate the need for central venous catheterization if venous access is difficult, and for invasive arterial monitoring if noninvasive blood pressure measurement is inaccurate. Radial artery catheterization is contraindicated in patients with Raynaud's phenomenon because of the risk for hand ischemia. Brachial artery catheterization may be necessary. Pulmonary artery catheterization may be indicated in the presence of cardiac dysfunction or pulmonary hypertension.[124] The use of noninvasive assessment of cardiac function with transthoracic echocardiography is likely to increase.[125] Warming of the patient, and especially of the extremities affected by Raynaud's phenomenon, is required. Scleroderma reduces tear production, and the eyes should be protected against corneal abrasions.

POLYMYOSITIS AND DERMATOMYOSITIS

Definition and Epidemiology

Polymyositis and **dermatomyositis** represent two members of a larger disease group, the idiopathic inflammatory myopathic diseases. Polymyositis is characterized by nonsuppurative inflammation of muscle, primarily skeletal muscles of the proximal limbs, neck, and pharynx. This inflammation leads to symmetric weakness, atrophy, and fibrosis of affected muscle groups. Dermatomyositis represents the same disorder, with the addition of a characteristic heliotrope eruption (blue-purple discoloration of the upper eyelid) and Gottron's papules (raised, scaly, violet eruptions over the knuckles). These disorders are quite rare, with a prevalence of 10 per million and an annual incidence of 5.5 per million. Women are affected twice as often as men. The age at onset is bimodal, with peaks before puberty and during the fifth decade.[126]

Pathophysiology

Both polymyositis and dermatomyositis are associated with other autoimmune disorders, notably scleroderma. The etiology of inflammatory muscle disease is unknown and probably multifactorial. An initial insult mediated by viral or other infectious agent, or exposure to environmental substances, may lead to initial muscle damage in genetically susceptible individuals. This initial process may then trigger an autoimmune response involving chronic muscle inflammation. A viral etiology is suggested by seasonal and geographic clustering of new cases. However, viral genomic material has not been identified in affected muscle tissue. Many drugs, including lipid-lowering drugs in the statin group and antiretroviral drugs, are associated with the development of myopathy. The presence of cellular infiltrates within affected muscle tissue and complement-mediated capillary damage are features of inflammatory muscle diseases. More than 12 autoantibodies have been identified within affected individuals. Underlying malignancy has been associated with both polymyositis and dermatomyositis, although causality is unclear; the association is stronger for dermatomyositis than polymyositis.[126,127]

BOX 41-4 Diagnostic Criteria for Polymyositis and Dermatomyositis

POLYMYOSITIS

- Symmetric weakness of proximal muscles
- Histologic evidence of muscle inflammation and necrosis
- Elevation of serum skeletal muscle enzymes
- Electromyographic evidence of myopathy

DERMATOMYOSITIS

- Three or four of the above, plus heliotrope eruption or Gottron's papules

From Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975; 292:403-7.

Diagnosis

The diagnostic criteria proposed by Bohan and Peter remain the standard of classification for polymyositis and dermatomyositis (Box 41-4).[128] After exclusion of other conditions that can mimic polymyositis or dermatomyositis, clinical features together with electromyographic and laboratory evidence of myositis (both through blood tests and muscle biopsy) establish the diagnosis. Serum creatine kinase concentration correlates with disease activity. Variable systemic involvement may be present. Pharyngeal muscle involvement leads to **dysphagia** and **reflux,** and most patients exhibit **impairment of gastric and esophageal motility.**[129] Pulmonary involvement is present in 50% of patients with polymyositis/dermatomyositis, and **chronic aspiration pneumonitis** and **pneumonia** are the most common pulmonary manifestations. **Pulmonary fibrosis** is present in 30% of patients and may rarely lead to **pulmonary hypertension.**[130,131] **Myositis of the respiratory muscles** may cause respiratory insufficiency. **Cardiac involvement** includes nonspecific repolarization abnormalities, conduction disturbances, arrhythmias, coronary artery vasculitis, and, rarely, heart failure.[132] **Arthritis** generally involves the small joints of the hands and fingers. Renal or hematologic involvement is rare. The onset of a pregnancy-associated form of dermatomyositis has been described postpartum.[133]

Effect of Pregnancy

Reports of polymyositis or dermatomyositis during pregnancy are rare. Ishii et al.[134] reviewed 12 reports of 29 pregnancies during a 30-year period. In 11 (40%) of the patients, the initial diagnosis was made during gestation or the immediate postpartum period. Pregnancy may be a trigger for induction of dermatomyositis in some women. Among the 18 patients with previously diagnosed disease, the disease remained inactive in 11 (61%) of the patients, and 2 (11%) had an exacerbation of disease activity.

Effect on the Fetus

Fetal survival is affected by concurrent polymyositis/dermatomyositis. In a literature review, 10 of 29 (32%)

pregnancies ended with fetal death or spontaneous abortion; eight infants (26%) were delivered preterm.[134] Fetal outcome was strongly influenced by disease activity. Of the women who had minimal disease activity, nearly 60% delivered healthy newborns at term. Silva et al.[135] observed a similar correlation between outcome and disease activity in four pregnancies in four women with polymyositis/dermatomyositis, two with active disease and fetal death and two with disease remission and uneventful outcome.

Medical and Obstetric Management

Pregnancy should be planned during periods of disease inactivity. Serum creatine kinase, glutamic oxaloacetic transaminase, and aldolase determinations can guide this decision.

Glucocorticoid treatment is the mainstay of medical management of active disease. Efficacy of steroids has not been demonstrated in controlled studies, but improvement in muscle strength and decreased creatine kinase concentration are usually seen after 1 to 2 months of either continuous or pulsed steroid therapy. **Methotrexate, azathioprine,** and **intravenous immunoglobulin** may be beneficial; there is limited evidence for their use and safety in pregnant patients.[136-138] Obstetric management involves frequent monitoring of disease activity and fetal well-being.

Anesthetic Management

Anesthetic management of the pregnant woman with polymyositis/dermatomyositis begins with the evaluation of disease activity and underlying cardiopulmonary involvement. If muscle weakness is present, spirometry should be performed to determine whether respiratory muscles are affected. Maximum breathing capacity and peak expiratory flow rate are the most helpful measurements. Pharyngeal weakness may cause chronic aspiration and pulmonary diffusion defects. Arterial blood gas analysis and a chest radiograph should be obtained in patients with a history of aspiration. An electrocardiogram should be obtained to exclude conduction abnormalities and arrhythmias.

Use of neuraxial anesthesia in a patient with muscle weakness requires caution because excessive cephalad spread may further impair intercostal muscle function and lead to ventilatory failure. Abdominal muscle paralysis may slow progress of the second stage of labor. Careful epidural administration of a dilute solution of local anesthetic should provide effective pain relief without adverse effect on the progress of labor. Intrathecal opioid administration is an attractive, alternative method of labor analgesia in these patients.

Patients with polymyositis/dermatomyositis may exhibit **atypical responses to muscle relaxants.** A short-lived thumb contracture after **succinylcholine** administration in a child with dermatomyositis has been reported.[139] Direct laryngoscopy was not impaired, the contracture resolved in 3 minutes, and normal neuromuscular recovery occurred. Plasma potassium concentration increased by 20%, although this response is similar to that seen in normal subjects after succinylcholine administration. Prolonged paralysis of 50 minutes after succinylcholine administration in a patient with dermatomyositis has been noted.[140] The patient was found to be homozygous for an atypical pseudocholinesterase. Of four other patients with dermatomyositis in whom dibucaine numbers were measured, one was heterozygous for atypical pseudocholinesterase. The occurrence of benign contractures and the possibility of atypical pseudocholinesterase do not preclude the use of succinylcholine if it is required for cesarean delivery, although newer agents such as rocuronium may provide an alternative. Neuromuscular recovery should be documented before extubation. Some investigators have advocated the avoidance of agents known to trigger malignant hyperthermia in patients with polymyositis/dermatomyositis and elevated creatine kinase levels.[141,142] This approach is speculative and is not supported by published clinical experience.

An atypical response to **nondepolarizing muscle relaxants** has been reported. A case of prolonged paralysis (9.5 hours) after administration of vecuronium in a patient with polymyositis has been reported.[143] Underlying malignancy with associated **myasthenic syndrome** can prolong neuromuscular blockade. Other reports of nondepolarizing neuromuscular blockade in patients with polymyositis/dermatomyositis have indicated a normal response and recovery.[142,144,145] Parturients who have undergone long-term corticosteroid therapy should receive a peripartum stress dose of a corticosteroid.

KEY POINTS

- Pregnancy does not worsen the long-term course of autoimmune disorders.
- Autoimmune disorders can lead to renal, cardiac, and pulmonary dysfunction.
- Systemic lupus erythematosus can result in maternal thrombocytopenia.
- Systemic lupus erythematosus is associated with a higher incidence of spontaneous abortion, intrauterine fetal demise, and preterm delivery.
- Antiphospholipid syndrome is characterized by the presence of the autoantibodies lupus anticoagulant and anticardiolipin antibody.
- The term *lupus anticoagulant* is a misnomer because it has no true anticoagulant activity *in vivo.*
- Patients with lupus anticoagulant do *not* have a bleeding tendency in the absence of an underlying coagulation disorder and can safely receive neuraxial anesthesia.
- Patients with scleroderma are at increased risk for difficult airway management.
- Scleroderma can prolong the duration of neuraxial anesthesia.
- The severity of polymyositis/dermatomyositis affects fetal survival.

- Patients with polymyositis/dermatomyositis may have an atypical response to succinylcholine.
- Neuraxial anesthesia must be administered cautiously to parturients with polymyositis/dermatomyositis and intercostal muscle weakness.

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CHAPTER 42

Cardiovascular Disease

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CHAPTER OUTLINE

Evidence suggests that gender has a significant impact on cardiovascular disease. The etiology of coronary thrombosis causing acute myocardial infarction is different in women than in men. Plaque erosion, rather than plaque rupture, occurs at a higher rate in women than in men. Coronary artery diameter is smaller in women,[1] and women frequently develop more diffuse atherosclerosis than men. Female aortas appear to be stiffer due to underlying fibrosis or remodeling. Women have more microvascular coronary artery dysfunction than men and frequently demonstrate impaired coronary artery vasodilator response.

Autoimmune rheumatic diseases are associated with premature atherosclerosis; vasculitides such as Takayasu's arteritis, temporal arteritis, rheumatoid vasculitis, lupus vasculitis, and polymyalgia rheumatica are all more common in women than in men. During exercise stress testing, women more often have atypical and nonanginal pain than men, who more often have typical angina.[2] Women with acute myocardial infarction more frequently do not have chest pain, especially women who have the infarction at a younger age. In-hospital mortality for acute myocardial infarction is higher for women than for men.[3] Although women who have non–ST-segment elevation myocardial infarction have a worse risk profile than men, the infarction is frequently treated less aggressively.[4] Yet women are more likely than men to summon emergency medical services during a myocardial infarction.

Whether women have worse outcome after percutaneous coronary intervention has been a matter of debate.[5] At the time of presentation for both percutaneous and surgical coronary revascularization procedures, women are older than men and have more cardiovascular risk factors and comorbid conditions.[5] Older studies demonstrated worse overall outcome in women than in men; however, more recent studies have demonstrated a narrowing or disappearance of the gender outcome gap. Similarly, several studies have demonstrated that female gender was an independent predictor of coronary artery bypass (CABG) operative mortality. However, after extensive baseline risk adjustment, outcomes after CABG or aortic valve replacement have been reported to be similar for men and women.

The number of pregnancies has been associated with the future risk for coronary artery disease[6] and progression of atherosclerosis.[7] Hypertensive disorders of pregnancy, preeclampsia, and gestational diabetes mellitus are risk factors for future development of cardiovascular disease.[8,9] Earlier identification of these women with an increased lifetime risk for developing cardiovascular disease may present a unique opportunity for prevention of subsequent cardiovascular events.

Historically, rheumatic mitral stenosis represented the most common cardiac condition encountered in pregnant women. This disease continues to be a major problem in the developing world and in certain immigrant populations in the United States. In the industrialized countries, congenital heart disease has become the most common cardiac condition complicating pregnancy. This demographic change is a result of significant advances in the treatment of complex congenital heart conditions and survival of these patients into childbearing age. In the United States, maternal mortality due to hemorrhage and hypertensive disorders of pregnancy has declined, whereas mortality due to cardiovascular conditions has steadily increased.[10]

The optimal management of women with cardiovascular disease begins *before* conception. Normal physiologic changes of pregnancy may exacerbate preexisting cardiovascular disease. For most women with heart disease, pregnancy is associated with favorable outcome; however, even with modern advances in treatment and monitoring, there remains a high incidence of morbidity and mortality for some conditions. Thus, for some women, it may be advisable to avoid pregnancy.

There is significant individual variability in the severity of specific cardiovascular disease entities. Additionally, several cardiovascular conditions may be simultaneously present in one individual. Management may be further complicated by the presence of noncardiovascular pathologic processes. The anesthetic management of the parturient with cardiovascular disease should be individualized, and a multidisciplinary team should plan peripartum care. Some case reports and small series have described the anesthetic management of these patients, but, in general, few data justify choosing one anesthetic technique over another. Therefore, the anesthesiologist must have a thorough understanding of the normal physiologic changes of pregnancy as well as the individual parturient's pathophysiology, and then plan anesthetic management that best achieves the desired hemodynamic goals. Optimal *analgesia* is often an important part of safe childbirth in these patients.

The anesthetic care of women with cardiovascular disease does not end with labor and delivery; rather, it continues postpartum when the physiologic changes of pregnancy may be at their greatest. Inadequate postpartum analgesia may be associated with hypertension and tachycardia. Postoperative shivering increases oxygen consumption and may cause myocardial ischemia in patients with limited cardiac reserve.

CARDIOVASCULAR PHYSIOLOGIC CHANGES OF PREGNANCY

The **electrocardiogram (ECG)** typically changes during pregnancy. During the third trimester, the enlarging gravid uterus causes upward and lateral rotation of the heart, which may result in left-axis deviation of 15 to 20 degrees. Overall, however, the QRS axis is quite variable during pregnancy. At rest, nonspecific ST-segment and T-wave changes are very common during normal pregnancy.[11] Exercise in healthy pregnant women does not cause distinctive ECG changes when compared with nonpregnant subjects.

No repolarization abnormalities are observed with uncomplicated vaginal delivery. ST-segment *elevation* is never seen in normal pregnancy and should always be considered pathologic. ST-segment *depression* is seen in 25% to 81% of parturients undergoing cesarean delivery, regardless of the type of anesthesia. Oxytocin administration during the third stage of labor has been associated

with ST-segment depression.[12,13] However, these oxytocin-associated ECG changes are not associated with myocardial damage. Whether these ECG changes are caused by underlying ischemia or some other mechanism remains unclear.[14]

Left ventricular mass increases during normal pregnancy.[15,16] The increase in left ventricular mass is greater in multiple gestation than in singleton gestation.[17] Preeclampsia also results in a greater increase in left ventricular mass.[18]

Plasma lipid concentrations, including total serum cholesterol, triglycerides, and low-density lipoprotein cholesterol concentrations, increase during pregnancy.[19] Obese pregnant women have an even greater increase in plasma lipids. This increase in plasma lipids results in part from insulin resistance and an increase in estrogen levels during pregnancy. The effects of these physiologic changes in plasma lipid concentrations on long-term cardiovascular outcomes are unclear.

Brain natriuretic peptide (BNP) is a natriuretic hormone synthesized primarily in the heart ventricles. BNP levels increase as a response to increased filling pressures in patients with heart failure. Physiologically, BNP has hypotensive, diuretic, and natriuretic effects. During uncomplicated normal pregnancy, BNP levels are unchanged (< 20 pg/mL).[20] The lack of change in BNP levels during normal pregnancy suggests that the heart adapts to the increased volume load associated with pregnancy. By contrast, BNP levels are increased in preeclamptic women[20] and in pregnant women with heart disease.[21] A correlation exists between BNP and the increases in left ventricular mass and end-diastolic and end-systolic volumes observed in preeclampsia.[18] The increase in BNP with fluid administration in preeclamptic women further confirms that this hormone is secreted in response to increased intracavitary pressures. Intravenous fluid administration does not increase BNP levels in healthy women.[22,23] BNP is elevated in women with complex congenital heart disease, but it varies considerably among anomalies. Therefore, its use for individual patient management remains unclear.[24]

Cardiac enzyme levels may be altered by pregnancy or pregnancy-associated disease. Myocardial cell death is associated with elevation of sensitive and specific cardiac biomarkers—creatine kinase MB fraction (CK-MB) and cardiac troponins.[25] Cardiac troponin levels are not elevated above the upper limits of normal during uncomplicated pregnancy. Troponin levels are elevated in women with gestational hypertension or preeclampsia.[26,27] By contrast, CK-MB levels may be elevated up to two to four times the upper limit of normal owing to the presence of these enzymes in the uterus and placenta (see Figure 47-1). Thus, elevated CK-MB levels are not specific for the diagnosis of myocardial infarction during pregnancy.[27,28] In patients with preeclampsia who have concurrent myocardial infarction, the observed troponin levels are higher than expected for the underlying preeclampsia.[29] Heterophil antibody interference with the troponin assay may cause a false-positive increase in troponin levels during pregnancy. However, both CK-MB and troponin are sensitive markers for the diagnosis of myocardial infarction during pregnancy.

Cardiac output increases as early as 5 weeks' gestation and continues to increase throughout the second trimester until it is approximately 50% greater than nonpregnant values (see Figure 2-1). Cardiac output does not change from this level during the third trimester; it may actually be reported as decreased in the third trimester if measurements are made in the supine position, which causes aortocaval compression. Both an increase in heart rate and stroke volume contribute to the increase in cardiac output. Distribution of cardiac output to the uterine circulation increases from 1% in the nonpregnant state to 12% during the second half of pregnancy (see Chapter 2).

CARDIAC EXAMINATION DURING PREGNANCY

Pregnant women frequently complain of mild dyspnea at rest and exertion; on occasion, exercise tolerance is decreased. Therefore, it is important to recognize normal changes in the physical examination associated with pregnancy (Table 42-1).

Resting heart rate is higher in pregnancy, and peripheral pulses are "well filled" with rapid upstroke and collapse, primarily owing to lower systemic vascular resistance (SVR). The central venous pressure remains unchanged during pregnancy, and any elevation of jugular venous pressure is an abnormal finding. Basilar rales may be heard on lung auscultation; however, these are no longer heard after deep inspiration, a brief breath-hold, or a cough. These evanescent rales likely result from basilar atelectasis.

The heart examination during pregnancy is altered as a result of uterine enlargement. Consequently, the point of maximum impulse (left ventricular apex) is displaced superiorly and laterally during advanced pregnancy. It remains crisp, well defined, and hyperdynamic. In thin women, the right ventricular impulse may become visible owing to an increase in circulating blood volume and the proximity of this chamber to the anterior chest wall.

Recognition of normal auscultatory changes helps distinguish pathologic from physiologic changes. New murmurs are heard in more than 90% of pregnant women. The loudest murmurs are heard between 15 and 25 weeks' gestation; murmur intensity decreases toward term and increases again during labor and the early postpartum period. This peripartum increase in murmurs is followed by a gradual decrease; most of these pregnancy-associated murmurs are no longer appreciated by 6 weeks postpartum.[30] Importantly, there is no correlation between the disappearance of physiologic murmurs of pregnancy and the return of cardiac output and blood volume to prepregnancy levels.[31]

The first heart sound (S1) becomes louder and is widely split owing to early closure of the mitral valve during pregnancy. The second heart sound (S2) is unchanged. It is quite common to appreciate the third heart sound (S3), although considerable expertise and a quiet environment are necessary because of the presence of underlying tachycardia and an increased basal respiratory rate. The fourth heart sound (S4) is rarely

TABLE 42-1 **Cardiovascular Physical Examination in Pregnancy**

Feature	Normal Pregnancy	Implication of Abnormal Findings
Jugular venous pressure	Normal	Any elevation warrants further evaluation of volume status
Carotid pulse	Normal upstroke Normal volume	Decreased or delayed upstroke (aortic stenosis), bifid pulse (hypertrophic cardiomyopathy)
Peripheral pulses	Well filled	Diminished or delayed (aortic stenosis, left ventricular outflow obstruction)
Point of maximum impulse	Crisp, slightly laterally displaced	Any enlargement or more than slight lateral displacement warrants further evaluation.
S1	Louder and widely split	
S2	Unchanged	Soft/absent/paradoxically split (aortic stenosis) Loud P2, fixed split (pulmonary hypertension)
S3	Normally present	
S4	Rarely heard	
Aortic stenosis murmur	Increased	
Aortic regurgitation murmur	Decreased	Helpful to confirm physical examination findings with echocardiography
Mitral stenosis murmur	Increased	
Mitral regurgitation murmur	Decreased	
Hypertrophic cardiomyopathy murmur	Decreased	Not all hypertrophic cardiomyopathies have obstructive murmurs; helpful to confirm with echocardiography
Peripheral edema	Mild edema normally present	Asymmetric edema warrants further evaluation
Stigmata of Marfan syndrome		Risk for aortic dissection
Stigmata of Turner syndrome		Risk for aortic dissection

LV, left ventricle.

appreciated. Owing to increased cardiac output and increased flow through cardiac valves, a systolic ejection murmur, usually soft (grade 2 to 3/6), is appreciated over the upper sternal border and the right side of the heart.

The murmurs of aortic and mitral regurgitation generally decrease and may become inaudible during pregnancy owing to the decrease in SVR. However, administration of phenylephrine or development of hypertension during pregnancy, both of which increase the SVR, increases the intensity of these murmurs.[32]

The murmur associated with aortic stenosis increases in intensity during pregnancy from increased flow through the stenotic valve. A diminished carotid upstroke, soft or inaudible S2, and a grade 4/6 murmur are almost always indicative of severe aortic stenosis. An audible, physiologic split S2 almost invariably rules out severe aortic stenosis. Diastolic murmurs during pregnancy are almost always associated with an underlying pathologic process.

The murmur of hypertrophic cardiomyopathy may have decreased intensity because the pregnancy-associated increase in intravascular volume may result in decreased outflow tract obstruction. The murmur of an atrial septal defect may become more audible during pregnancy.

Mammary souffle ("soo-fuhl") is a noncardiac sound; it describes the continuous hum heard over the breasts. It becomes audible during late pregnancy and lactation, and it disappears at the end of lactation.

Most pregnant women display some degree of peripheral edema, in part owing to uterine compression of the inferior vena cava, which impedes venous return. This physiologic edema is symmetric and decreases with leg elevation and the left lateral decubitus position. The pathologic edema of preeclampsia should be differentiated from the physiologic edema of pregnancy. Asymmetric lower extremity edema is almost invariably pathologic. A tender and warm lower extremity may suggest deep vein thrombosis or cellulitis.

Funduscopic examination in pregnancy may help differentiate chronic hypertension from hypertensive disease of pregnancy (preeclampsia/eclampsia) and may identify changes due to long-standing diabetes.

It is important to look for stigmata of Marfan syndrome. Tall stature, large arm span, or other stigmata may alert the practitioner to the presence of a previously undiagnosed condition. Patients with Marfan syndrome frequently demonstrate scoliosis and may have dural ectasia. Turner syndrome is characterized by short stature and webbed neck. Both conditions predispose pregnant women to aortic dissection (see later discussion).

CARDIAC RISK PREDICTION

The New York Heart Association (NYHA)[33] and Heart Failure Stage[34] classifications describe symptoms and predict risk in the nonpregnant population (Box 42-1). Several classifications have been proposed to specifically predict cardiac risk during pregnancy (Boxes 42-2, 42-3, and 42-4).[35-38] These classifications may help predict the individual pregnant woman's cardiac risk and, combined with the clinical constellation and results of cardiac imaging, may help guide clinical management.[35,37-39] Implementation of a standardized and guideline-based approach to care, based on risk assessment, provides consistency in treating pregnant women with cardiac disease.

Maternal cardiac disease is associated with an increased incidence of **neonatal complications**. The most widely

BOX 42-1 New York Heart Association (NYHA) Functional Classification of Heart Failure

Classification of Heart Failure

Class I

No limitation of physical activity

Class II

Mild limitation of physical activity; regular physical activity causes symptoms

Class III

Marked limitation of physical activity; no symptoms at rest; minimal activity causes symptoms

Class IV

Symptoms at rest

Stages in the Development of Heart Failure

Stage A

At risk for heart failure but without structural heart disease or symptoms (e.g., hypertension, coronary artery disease, obesity)

Stage B

Structural heart disease but without signs or symptoms (e.g., previous myocardial infarction, asymptomatic valvular heart disease)

Stage C

Structural heart disease with prior or current symptoms of heart failure (e.g., known structural heart disease and symptoms)

Stage D

Refractory heart failure (e.g., marked symptoms at rest with maximal medical therapy)

Modified from Kosman CE, editor. New York Heart Association. Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis. 6th edition. Boston, Brown and Co., 1964; and Hunt SA, Abraham WT, Chin MH, et al. Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:e391-479.

BOX 42-2 CARPREG (CARdiac Disease in PREGnancy) System for Predicting Maternal Cardiovascular Events

Prior cardiac event (1 point)
- Heart failure
- Transient ischemic attack
- Cerebrovascular accident
- Arrhythmia

NYHA > class II or cyanosis (1 point)
Mitral valve area < 2 cm^2 (1 point)
Aortic valve area < 1.5 cm^2 (1 point)
Left ventricular outflow tract gradient > 30 mm Hg (1 point)
Ejection fraction < 40% (1 point)

CARPREG Points	Cardiac Complication Rate
0	5%
1	27%
2	75%

Points are added and the total score reflects the predicted cardiac event rate.
NYHA, New York Heart Association.
Modified from Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001; 104:515-21.

BOX 42-3 ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking) for Predicting Maternal Cardiovascular Events

History of arrhythmia (1.5 points)
Use of cardiac medications before pregnancy (1.5 points)
NYHA > class II (0.75 point)
Left-sided heart obstruction (peak gradient > 50 mm Hg or aortic valve area < 1.0 cm^2) (2.5 points)
Systemic atrioventricular valve regurgitation (moderate/severe) (0.75 point)
Pulmonic atrioventricular valve regurgitation (moderate/severe) (0.75 point)
Mechanical valve prosthesis (4.25 points)
Repaired or unrepaired cyanotic heart disease (1.0 point)

ZAHARA Points	Cardiac Complication Rate
0-0.5	2.9%
0.51-1.50	7.5%
1.51-2.50	17.5%
2.51-3.50	43.1%
≥ 3.51	70.0%

Points are added and the total score reflects the predicted cardiac event rate.
NYHA, New York Heart Association.
Modified from Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010; 31:2124-32.

accepted associations are cyanosis, NYHA functional class greater than II, presence of a mechanical valve prosthesis, heparin or warfarin use during pregnancy, multiple gestation, smoking during pregnancy, left-sided heart obstruction, and use of cardiac medications before pregnancy.[35,39]

CARDIOVASCULAR IMAGING DURING PREGNANCY

Echocardiography

Echocardiography allows for safe and noninvasive assessment of heart structure and function. Both transthoracic and transesophageal echocardiography can be performed at any stage of pregnancy. Echocardiography helps predict overall cardiac risk and guides anesthetic management in pregnant women with cardiac disease. Echocardiography also allows assessment of intravascular volume

BOX 42-4 Modified World Health Organization Cardiac Risk Assessment

Class I (no increase or a mild increase in morbidity)

- Mild pulmonic stenosis
- PDA
- Mitral valve prolapse
- Repaired ASD, VSD, PDA, anomalous pulmonary venous return

Class II (small increase in maternal mortality, moderate increase in maternal morbidity)

- Unrepaired ASD or VSD
- Repaired tetralogy of Fallot
- Most arrhythmias
- Mild left ventricular dysfunction
- Hypertrophic cardiomyopathy
- Marfan syndrome without aortic dilation
- Bicuspid aortic valve with aortic diameter < 45 mm

Class III (significant increase in maternal mortality and severe increase in maternal morbidity)

- Mechanical valve(s)
- Systemic right ventricle
- Fontan circulation
- Unrepaired cyanotic heart disease
- Complex congenital heart disease
- Marfan syndrome with aortic dilation 40 to 45 mm
- Bicuspid aortic valve with aortic dilation 45 to 50 mm

Class IV (pregnancy is not recommended or is contraindicated)

- Pulmonary artery hypertension of any cause
- Severe left ventricular dysfunction
- Previous peripartum cardiomyopathy with residual left ventricular dysfunction
- Severe mitral stenosis
- Severe aortic stenosis
- Marfan syndrome with aortic dilation > 45 mm
- Bicuspid aortic valve with aortic dilation > 50 mm
- Severe unrepaired aortic coarctation

PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect.

Modified from Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart 2006; 92:1520-5; and Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. European Society of Cardiology guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 2011; 32:3147-97.

and may obviate the need for right-sided heart catheterization to determine ventricular filling pressures.

One of the most commonly used echocardiographic assessments of left ventricular function—left ventricular ejection fraction—remains unchanged during pregnancy. Echocardiographic measurements of cardiac output increase during pregnancy owing to increases in stroke volume and heart rate. Importantly, stroke work is increased during pregnancy, which is consistent with augmented myocardial fiber function. Both the right and left ventricular chamber size are increased in end diastole and end systole, and the heart becomes more globular. This increase in chamber size results in increased left ventricular end-systolic and end-diastolic volumes and is accompanied by an increase in left ventricular wall thickness (eccentric left ventricular hypertrophy). These parameters return to baseline within 3 to 6 months postpartum.[40] Left ventricular end-diastolic and end-systolic volumes are further increased with multiple gestation; the stroke volume is increased an additional 15%. Combined with a small additional increase in heart rate, this change results in a 20% greater increase in maternal cardiac output with multiple gestation compared with singleton gestation.[17]

Left atrial size is increased during pregnancy[16]; the increase is even greater with multiple gestation than with singleton gestation.[17] Preeclampsia results in an adaptive concentric hypertrophy and an increase in left ventricular mass due to increased afterload.

In normal pregnancy, left ventricular diastolic function is increased in the first two trimesters and declines in the third trimester.[15] Twenty percent of women with preeclampsia have evidence of global diastolic dysfunction.[41] Diastolic function is most commonly assessed echocardiographically by evaluating mitral valve inflow, pulmonary venous flow, and myocardial tissue motion (tissue Doppler imaging).

Cardiac Magnetic Resonance Imaging

The risks of magnetic resonance imaging (MRI) in pregnant women are similar to those in nonpregnant patients. The *potential* risks to the fetus are teratogenicity and acoustic damage. There are no published reports of untoward fetal effects resulting from MRI in pregnant women. Owing to limited evidence on safety during organogenesis, it may be prudent to limit use of MRI during the first trimester. Cardiac magnetic resonance (CMR) imaging should be performed during pregnancy only after consideration of both the maternal and fetal benefits and risks. However, given the quality of images and diagnostic yield, CMR is preferable to any other modality that uses ionizing radiation. Gadolinium use during pregnancy should be avoided; it should be used only if absolutely required. Gadolinium is a pregnancy category C drug; it crosses the placenta and has been shown to be teratogenic in animal studies.

Left- and Right-Sided Heart Catheterization

Left-sided heart catheterization remains the gold standard for diagnosis of coronary artery disease, and it can be performed at any time during pregnancy. Radial arterial access is preferable to femoral access because it is associated with earlier ambulation, increased patient comfort, and a significant reduction in access-related bleeding complications. Additionally, during the procedure, the left lateral decubitus position can be more easily maintained with radial access. Cardiologists should strictly adhere to the ALARA principle (as low as reasonably achievable) to limit both maternal and fetal ionizing radiation exposure.

The use of pulmonary artery catheterization has significantly declined in the United States in recent

years. Similar information can be obtained noninvasively by transthoracic or transesophageal echocardiography. However, thermodilution and Fick cardiac output measurements can be obtained only with the use of a pulmonary artery catheter. Similarly, right-sided heart catheterization is required for vasoreactivity testing in patients with pulmonary hypertension. Historically, pulmonary artery catheterization has helped guide fluid management in women with severe preeclampsia and eclampsia, particularly those who develop renal failure and pulmonary edema (see Chapter 36). In the future, ventricular filling in these patients may be assessed noninvasively with the bedside use of portable, hand-held transthoracic echocardiography devices.

Iodinated Contrast Use during Pregnancy

The use of iodinated contrast media in pregnant women appears safe. To date, there have been no reports of fetal teratogenic or mutagenic effects after maternal administration of iodinated contrast media. Free iodide in the contrast medium administered to the mother may depress fetal, and subsequently neonatal, thyroid function. Therefore, it has been suggested that neonatal thyroid function be checked during the first week postpartum. Minimal amounts of iodinated contrast media are excreted in breast milk; even smaller amounts are absorbed by the neonate's gastrointestinal tract. The slight potential risk associated with absorption of contrast medium is thought to be insufficient to recommend interruption of breast-feeding after maternal administration of iodinated contrast media.

Computed Tomographic Angiography

Multidetector computed tomography (CT) allows noninvasive imaging of the coronary arteries along with cardiac structure and function. Use of contemporary CT with aggressive dose-reduction techniques can significantly limit the radiation dose. The overall radiation dose of coronary CT angiography may be equivalent to, or even lower than, radiation doses delivered with conventional invasive coronary angiography. Although soft cardiac structures not seen by conventional coronary angiography are well visualized by CT angiography, the intravenous contrast medium load is greater with CT angiography, and coronary intervention cannot be performed at the time of imaging. Thus, in pregnancy, invasive coronary angiography appears preferable under most circumstances.

Ionizing Radiation Risks to the Fetus

The ionizing radiation dose to the fetus can be limited by the use of echocardiography, intracardiac echocardiography, and markedly reduced fluoroscopy frame rates. Because the fetus is not directly within the radiation beam for cardiac procedures, the fetal exposure occurs through indirect scatter radiation. Therefore, external shielding of the fetus is ineffective. The fetal radiation dose cannot be measured and is therefore estimated. It is reassuring that the estimated fetal doses are low. Nonetheless, the safest approach is to avoid ionizing radiation during pregnancy if possible, and to assess both the maternal and fetal risks and benefits before deciding on the most appropriate imaging modality.

CARDIAC DRUGS AND PREGNANCY

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the mainstay of coronary artery disease treatment, left ventricular dysfunction, and hypertension in nonpregnant patients. These drugs are particularly useful in nonpregnant patients with diabetes mellitus.

In the first trimester, the use of ACE inhibitors has been associated with an increased risk for fetal cardiovascular and central nervous system malformations. Use of ACE inhibitors during the second and third trimesters of pregnancy has also been associated with adverse fetal and neonatal outcomes as a result of the ACE inhibitors' effect on fetal renal vascular tone. These drugs cause fetal kidney malfunction and decreased fetal urine output, which results in oligohydramnios. Positional limb deformities, skull ossification retardation, and lung hypoplasia are seen with ACE inhibitor–associated oligohydramnios. These effects are not thought to be caused by fetal exposure to ACE inhibitors during the first trimester. Thus, despite the exceptionally useful profile of ACE inhibitors in nonpregnant patients with cardiovascular disease, their use in pregnancy is contraindicated (pregnancy category D) (see Chapter 14).[42]

Angiotensin Receptor–Blocking Agents

Fewer data are available on the use of angiotensin receptor–blocking agents in pregnancy. Nonetheless, given the adverse outcomes associated with use of ACE inhibitors in pregnancy and the mechanism of action of angiotensin receptor–blocking agents, the use of these drugs is not recommended in pregnancy.[42]

Beta-adrenergic Receptor Antagonists

Beta-adrenergic receptor antagonists are often used for treatment of coronary artery disease, myocardial infarction, hypertension, many arrhythmias, and a wide spectrum of cardiomyopathies. There is no evidence that beta-adrenergic receptor antagonists are teratogenic. Prolonged and high-dose use of these drugs has been associated with fetal growth restriction (also known as intrauterine growth restriction); however, the overall risk is likely small.[42] Neonatal bradycardia, hypotension, and hyperglycemia are rarely encountered.

Calcium Entry–Blocking Agents

First-trimester maternal use of **verapamil** and **diltiazem** is likely not teratogenic. Both drugs appear to be safe and effective treatments for cardiac arrhythmias in the second and third trimesters.[42] The use of **amlodipine**, a

dihydropyridine calcium entry–blocking agent, appears safe during pregnancy.[42]

Other Drugs

Hydralazine is used in the treatment of cardiomyopathy and is also an excellent antihypertensive agent. It has a long track record of safe use during pregnancy.[42]

The use of **nitrates** for treatment of angina during pregnancy appears safe. Nitrates likely can be safely used long term in pregnant women with cardiomyopathy.[42]

Digoxin is quite useful for the treatment of various cardiomyopathies and some arrhythmias. Digoxin freely crosses the placenta, but its use has not been associated with congenital abnormalities or untoward fetal effects.[42] Digoxin's pharmacokinetics are altered during pregnancy, and attention to blood levels is recommended.

Eptifibatide, tirofiban, and abciximab are potent intravenous platelet aggregation inhibitors **(IIB/IIIA receptor inhibitors)** used to inhibit platelet aggregation during percutaneous coronary intervention. Both the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the European Society of Anaesthesiology (ESA) guidelines strongly advise avoidance of neuraxial anesthesia until platelet function has recovered after administration of these agents.[43,44]

Statins interrupt cholesterol synthesis and result in a lowering of plasma cholesterol levels. The widespread use of statins (which are associated with exceptionally robust cardiovascular outcome data) has transformed the treatment of coronary artery disease. Nonetheless, given the critical importance of cholesterol synthesis in the normal development of the embryo and placenta, and thus their potential for teratogenicity, statins are contraindicated in pregnancy (pregnancy category X).[42]

Thiazide diuretics do not appear to be teratogenic. Long-term use may result in a reduction in uteroplacental perfusion, which may be associated with fetal growth restriction and oligohydramnios.[42] Neonatal hypoglycemia and thrombocytopenia have been reported.

Loop diuretics are likely not teratogenic.[42] Similar to thiazide diuretics, fetal growth restriction may be associated with long-term use during pregnancy. **Spironolactone** is an aldosterone antagonist frequently used in the treatment of patients with congestive heart failure and cardiomyopathy, but because of its antiandrogenic potential its use during pregnancy is not recommended.[42]

AORTIC DISEASES AND AORTIC DISSECTION

The cardiovascular changes of pregnancy may to lead to increased arterial wall tension and intimal shear forces. However, the full impact of pregnancy on changes in aortic wall structure is not fully understood. Estrogen-induced changes in collagen deposition, as well as circulating elastases and relaxin, may weaken the aortic media and thus predispose the aorta to dissection during pregnancy. Approximately half of aortic dissections and ruptures in women younger than 40 years of age are associated with pregnancy.[45] Dissection of the ascending aorta (Stanford type A or DeBakey type I or II) is a surgical emergency, whereas dissection of the descending aorta (Stanford type B or DeBakey type III) is predominantly treated medically.

Conditions that predispose women to aortic dissection during pregnancy include Marfan syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve,[46] Turner syndrome, and non–Marfan syndrome–associated familial thoracic aneurysms.[47] Aortic dissection has been associated with preeclampsia and chronic hypertension in pregnancy.[48] Most aortic dissections that occur during pregnancy are type A (ascending aorta); the average aortic diameter at the time of dissection is 4.8 cm.[49] The majority of dissections occur in the third trimester of pregnancy, but aortic dissections may also occur at the time of delivery or in the early postpartum period. It has been hypothesized that contraction of the uterus causes outflow resistance, thus predisposing to aortic dissection after delivery.

Marfan Syndrome

Marfan syndrome is an autosomal-dominant connective tissue disorder. The penetrance is high, but the expression is variable. Marfan syndrome is caused by a mutation in the *FBN1* gene encoding fibrillin-1, a glycoprotein. Sporadic mutations are seen in approximately 25% of patients without a family history of this syndrome. Aortic dilation and aortic dissection contribute significantly to cardiovascular complications in these patients. In addition to aortic disease, affected patients often have valvular disease (e.g., aortic regurgitation, mitral regurgitation, mitral valve prolapse). Aortic dissection has been observed during pregnancy and in the peripartum period.[50,51] Most patients have type A aortic dissection; type B aortic dissection and abdominal aortic aneurysm are less commonly seen.

Based on observational studies, current guidelines recommend that women with Marfan syndrome who are planning pregnancy undergo replacement of the ascending aorta and the aortic root if the diameter is greater than 4.0 cm (class IIa, level of evidence C).[47,52] The aortic root dilation rate increases during pregnancy and does not return to baseline after delivery. Subsequent pregnancies further increase the aortic dilation rate.[53]

Aortic Disease Associated with a Bicuspid Aortic Valve

Bicuspid aortic valve has been associated with dissection during pregnancy.[46] Affected women are slightly younger, and the dissection occurs earlier in pregnancy than in patients with Marfan syndrome.[49] Because the disease is familial, first-degree relatives of patients with a bicuspid aortic valve should be screened for this disease.[54]

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is an inherited connective tissue disorder. Ehlers-Danlos syndrome type IV has been associated with severe complications and maternal mortality. Rupture of the bowel, aorta, vena cava, and uterus may

occur.[47] Pregnancy outcomes in patients with Ehlers-Danlos syndrome types I, II, and III are generally favorable, although these women have a higher incidence of pelvic instability, preterm delivery, perineal lacerations, and postpartum hemorrhage than the general population.[55]

Turner Syndrome

Turner syndrome is caused by complete or partial absence of an X chromosome. In addition to short stature, webbed neck, and characteristic facial features, Turner syndrome is associated with aortic coarctation and hypertension. During pregnancy, the syndrome is associated with aortic dissection.[56,57] Moreover, approximately 30% of patients with Turner syndrome have a bicuspid aortic valve, which is also a risk factor for aortic dissection. Preconception echocardiographic evaluation of patients with Turner syndrome is recommended.[47,58] Given the frequent aortic abnormalities in these patients, preconception MRI is also recommended. Cesarean delivery is frequently required in these patients because of cephalopelvic disproportion.[58]

Management

Given the inherent risk for aortic dissection, parturients with aortic disease should deliver in a center that has immediate access to a cardiothoracic surgeon with expertise in aortic endovascular repair techniques.[59] Current guidelines are based on expert opinion, case reports, and current standard of care (level C evidence) (Box 42-5; Table 42-2). The 2010 American College of Cardiology (ACC) Foundation/American Heart Association (AHA) guidelines recommend the following for pregnant women with chronic aortic dilation: (1) strict blood pressure control; (2) monthly or bimonthly echocardiographic measurement of aortic dimension; (3) cesarean delivery in women with significant aortic enlargement, dissection, or severe aortic valve regurgitation; and (4) prophylactic surgery in the setting of progressive aortic dilation and/or advancing aortic valve regurgitation.[47]

All patients with Marfan syndrome should receive beta-adrenergic receptor antagonist therapy throughout pregnancy to decrease the rate of aortic dilation.[47,60] The risk for major aortic complications during pregnancy appears low if the aortic root diameter is less than 4.0 cm.[47] In the event of a type A aortic dissection in the first or second trimester, surgical repair should be performed with the knowledge of fetal risk during hypothermic circulatory arrest. If the dissection occurs in the third trimester and the fetus is deemed viable, an urgent cesarean delivery followed by aortic surgery may be performed.

Both neuraxial[61,62] and general anesthesia[63] may be safely performed in these patients, with emphasis on meticulous blood pressure stability and control. Invasive blood pressure monitoring is recommended to facilitate tight hemodynamic control. Dural ectasia and scoliosis may complicate neuraxial anesthetic techniques in parturients with Marfan syndrome.[64] The increase in lumbar cerebrospinal fluid volume associated with dural ectasia may cause unpredictable and inadequate spread of intrathecal local anesthetic solutions; thus, it may be prudent to obtain lumbar spine MRI before planned pregnancy.

BOX 42-5 Management of Chronic Aortic Diseases in Pregnancy*

Class I†

- Women should be counseled about the risk for aortic dissection as well as the heritable nature of the disease before pregnancy.
- Strict blood pressure control, specifically to prevent stage 2 hypertension, is recommended.‡
- Monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions are recommended to detect aortic expansion.
- For imaging of pregnant women, magnetic resonance imaging (without gadolinium) is recommended over computed tomography to avoid both maternal and fetal radiation exposure. Transesophageal echocardiography is an option for imaging of the thoracic aorta.
- Women should be delivered in a center where cardiothoracic surgery is available.

Class IIa†

- Cesarean delivery is reasonable for patients with significant aortic enlargement, dissection, or severe aortic valve regurgitation.

Class IIb†

- If progressive aortic dilation and/or advancing aortic valve regurgitation is documented, prophylactic surgery may be considered.

*All recommendations are *Level of Evidence C* (very limited populations have been evaluated and recommendations are based on consensus opinion of exerts, case studies, or standard of care).
†Class I: Procedure/treatment should be performed/administered; Class IIa: It is reasonable to perform procedure/administer treatment; Class IIb: Procedure/treatment may be considered.
‡Stage 2 hypertension: blood pressure ≥ 160/100 mm Hg.
Modified from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. Circulation 2010; 121:e266-369.

CONGENITAL HEART DISEASE

Atrial Septal Defect

Patients with an atrial septal defect may remain asymptomatic until the fourth decade of life. Not infrequently, women with an atrial septal defect may become symptomatic during pregnancy. The most common defect is the secundum-type atrial septal defect (80%), whereas the primum, sinus venosus, and coronary sinus types of atrial septal defect are less common. Right ventricular overload leads to pulmonary hypertension and Eisenmenger syndrome in less than 5% of patients with an atrial septal defect. In women with both an atrial septal

TABLE 42-2 **Anesthetic Considerations for Specific Cardiovascular Pathologic Processes**

Disease	Modifier	Anesthetic Considerations	Monitoring
Ascending aortic dilation/aneurysm	Bicuspid aortic valve Marfan syndrome Turner syndrome	Meticulous attention to blood pressure control Maintain beta-adrenergic receptor antagonist therapy Possible dural ectasia (Marfan syndrome) may increase risk for failed spinal anesthesia	Low threshold for invasive blood pressure monitoring
Unrepaired ASD	PAP < 40 mm Hg	Pregnancy/labor usually well tolerated Meticulous attention to de-airing all venous access tubing Consider potential for air embolism with loss-of-resistance-to-air epidural technique	
	PAP ≥ 40 mm Hg	High-risk group Maintain preload Positive-pressure ventilation decreases preload and increases intrathoracic pressure, which is deleterious to RV function	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring
Repaired ASD	PAP < 40 mm Hg	Pregnancy well tolerated	
	PAP ≥ 40 mm Hg	High-risk group Maintain preload Positive-pressure ventilation decreases preload and increases intrathoracic pressure, which is deleterious to RV function	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring May require pulmonary vasodilators
Unrepaired or repaired VSD	PAP < 40 mm Hg	Pregnancy well tolerated	
	PAP ≥ 40 mm Hg	High-risk group	Invasive blood pressure monitoring. Central venous access/filling pressure monitoring May require pulmonary vasodilators
Patent ductus arteriosus		Pregnancy well tolerated	Echocardiographic evaluation to rule out pulmonary hypertension (rare)
Fontan repair		Meticulous attention to preload; low and high preload poorly tolerated Positive-pressure ventilation is poorly tolerated because increased intrathoracic pressure impedes venous return	Continuous telemetry monitoring indicated because of high incidence of arrhythmias
Transposition of the great arteries	Complete/repaired	Caution with preload due to propensity for RV dysfunction Meticulous attention to preload in the early postpartum period	Low threshold for central venous access/filling pressure monitoring in patients with RV dysfunction Continuous telemetry monitoring indicated because of high incidence of arrhythmias
	Congenitally corrected	Pregnancy well tolerated	Echocardiographic assessment of ventricular function is helpful
Ebstein's anomaly		Pregnancy well tolerated with normal RV function May have associated ASD detected by echocardiography (see above for ASD considerations)	Low threshold for continuous telemetry monitoring because of high incidence of arrhythmias

Continued

TABLE 42-2 **Anesthetic Considerations for Specific Cardiovascular Pathologic Processes—cont'd**

Disease	Modifier	Anesthetic Considerations	Monitoring
Tetralogy of Fallot (repaired)		Pregnancy well tolerated	Echocardiographic assessment of RV structure, function, and evidence of pulmonary hypertension
Pulmonary hypertension	Mild-moderate	Attention to preload	Low threshold for central venous access/filling pressure monitoring
	Severe	Very high-risk group Maintain SVR Maintain preload/venous return Prevent/treat pain, hypoxemia, hypercarbia, and acidosis Avoid myocardial depression	Multidisciplinary approach Echocardiography May require pulmonary vasodilators Invasive blood pressure monitoring Central venous access/filling pressure monitoring Caution with pulmonary artery catheterization without fluoroscopic guidance
Aortic stenosis	Transvalvular gradient < 25 mm Hg, valve area > 1.5 cm^2, normal LV function	Neuraxial anesthesia generally well tolerated Attentive preservation of preload and afterload Monitor closely for volume overload during the first 24 hours after delivery	Low threshold for invasive blood pressure monitoring
	Transvalvular gradient ≥ 25 mm Hg, valve area < 1.0 cm^2, LV dysfunction	High-risk group Consider risks/benefits of neuraxial versus general anesthesia Avoid myocardial depressants and vasodilators Meticulously maintain preload and afterload Avoid abrupt decrease in SVR with sympathectomy Maintain sinus rhythm Address new-onset atrial fibrillation (rate control, consider cardioversion). Monitor very closely for volume overload during first 24 hours after delivery	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring
Mitral stenosis	Valve area > 1.5 cm^2, gradient < 5 mm Hg, no pulmonary hypertension	Neuraxial anesthesia generally well tolerated Maintain sinus rhythm and prevent tachycardia Increase in preload is not well tolerated Address new-onset atrial fibrillation (rate control, consider cardioversion) Monitor closely for volume overload during first 24 hours after delivery	Low threshold for central venous access/filling pressure monitoring
	Valve area ≤ 1.5 cm^2, gradient ≥ 5 mm Hg, pulmonary hypertension	High-risk group Consider percutaneous mitral valvuloplasty prior to labor/delivery Maintain sinus rhythm and prevent tachycardia Increase in preload is not well tolerated Address new-onset atrial fibrillation (rate control, consider cardioversion) Prevent/treat pain, hypoxemia, hypercarbia, and acidosis	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring

TABLE 42-2 **Anesthetic Considerations for Specific Cardiovascular Pathologic Processes—cont'd**

Disease	Modifier	Anesthetic Considerations	Monitoring
Pulmonary stenosis	Mild-moderate	Pregnancy well tolerated	
	Severe	High-risk group Consider balloon valvuloplasty Prevent tachycardia Mitigate increase in pulmonary artery resistance (e.g., hypoxemia, positive-pressure ventilation)	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring
Hypertrophic cardiomyopathy	Without LVOT obstruction	Pregnancy well tolerated	
	With LVOT obstruction	Maintain beta-adrenergic receptor antagonist therapy Low preload and low afterload worsen outflow gradient Treat hypotension with phenylephrine Maintain sinus rhythm and prevent tachycardia Address new-onset atrial fibrillation (rate control, consider cardioversion)	Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring Echocardiography helpful to follow outflow tract gradient
Cardiac tamponade		Meticulous attention to preload Maintain spontaneous ventilation Positive-pressure ventilation is deleterious to preload Volatile anesthetic agents depress ventricular function	Invasive blood pressure monitoring Central venous access/filling pressure monitoring

All patients with cardiovascular disease should labor in the lateral position to decrease aortocaval compression. Central venous pressure monitoring should be performed above the diaphragm.

ASD, atrial septal defect; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *PAP,* pulmonary artery pressure; *RV,* right ventricle; *SVR,* systemic vascular resistance; *VSD,* ventricular septal defect.

defect and Eisenmenger syndrome, pregnancy carries a significant risk for both maternal and fetal mortality, and is not recommended.[54,65] In the absence of pulmonary hypertension, pregnancy is overwhelmingly well tolerated in women with an atrial septal defect.

Cardiac complications are similar in women with unrepaired and repaired atrial septal defects. Preeclampsia, fetal demise, and small-for-gestational-age infants are more common in pregnant women with an unrepaired atrial septal defect than in the general obstetric population.[66] Pregnant women with an atrial septal defect are more likely to develop supraventricular and ventricular arrhythmias than women who are not pregnant.[67]

The risk for paradoxical embolism is increased in patients with an unrepaired atrial septal defect. It is critically important to ensure that intravenous catheters are de-aired.[54] Transesophageal echocardiography demonstrates the presence of microbubbles in the right-sided cardiac chambers within 15 seconds of the epidural injection of air or fluid.[68] Therefore, it seems prudent to avoid using the loss-of-resistance-to-air technique to identify the epidural space (see Table 42-2). Both neuraxial and general anesthesia are appropriate for patients with a repaired or unrepaired atrial septal defect.

Ventricular Septal Defect

There are four types of ventricular septal defects; the most common type is a perimembranous ventricular septal defect. Pregnancy is well tolerated in women with a repaired ventricular septal defect or a small ventricular septal defect in the absence of pulmonary hypertension. An unrepaired ventricular septal defect with Eisenmenger syndrome is associated with a high risk for maternal cardiac complications (see later discussion). Pregnancy is not recommended in patients with a ventricular septal defect and Eisenmenger syndrome.[54,65] Preeclampsia is encountered more frequently in women with an unrepaired ventricular septal defect.[69] Echocardiography allows assessment of right-sided pressures and shunt fraction.

Patent Ductus Arteriosus

Pregnancy is well tolerated in patients with patent ductus arteriosus, and complications are rare.[70] A left-to-right shunt may cause pulmonary hypertension. Pregnancy is not recommended in women with patent ductus arteriosus with Eisenmenger syndrome.[54,65]

Coarctation of the Aorta

Women with repaired coarctation of the aorta tolerate pregnancy well. Systemic arterial hypertension is often observed during labor. The coarctation may be associated with a bicuspid aortic valve in more than half the patients.[71] Prepregnancy evaluation of the coarctation, including the residual degree of obstruction[72] and associated anomalies (e.g., bicuspid aortic valve), is recommended.[54]

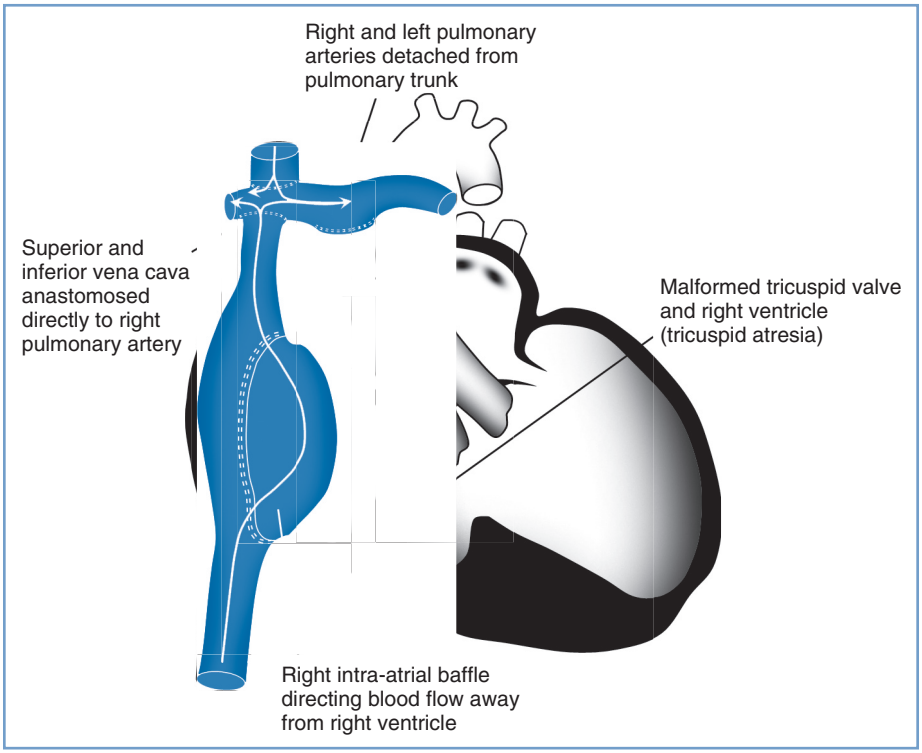

FIGURE 42-1 ■ Schematic depiction of a Fontan repair. There is no functional right ventricle. The white lines with arrows represent the pathway of venous blood returning to the heart. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Vaginal delivery with neuraxial anesthesia is the preferred mode of delivery; cesarean delivery is reserved for obstetric indications.[73-75] Epidural anesthesia has been successfully administered in a patient with an uncorrected coarctation.[76] One report described the use of remifentanil to control blood pressure during administration of general anesthesia for cesarean delivery.[77]

Fontan Repair

The Fontan repair is a surgical procedure that establishes blood flow from the venous system to the pulmonary artery by bypassing the right ventricle (Figure 42-1). It can be performed for valvular defects such as tricuspid or pulmonic atresia, or other anomalies with a single ventricle. Because there is no functional right ventricle, blood flow from the periphery to the lungs occurs at *very low* pressure gradients. Owing to the presence of surgical scar tissue in the atrium, patients with a Fontan repair are prone to supraventricular and, less commonly, ventricular arrhythmias.[78,79] The Fontan repair is associated with the highest prevalence of arrhythmias during pregnancy of any congenital heart condition.[39] Deterioration in the NYHA functional status during pregnancy can occur.[79]

Administration of neuraxial analgesia/anesthesia for labor and vaginal delivery[80] and emergency cesarean delivery[81] has been described.[82] Administration of neuraxial anesthesia, with meticulous attention to maintenance of normal intravascular preload, appears to be the preferred anesthetic technique for cesarean delivery. Use of neuraxial anesthesia avoids the adverse effects of myocardial depression and positive-pressure ventilation on the Fontan circulation, which lacks a functioning right ventricle (see Table 42-2).[80,81]

Transposition of the Great Arteries

Transposition of the great arteries comprises two distinct groups: complete transposition of the great arteries (d-transposition) and congenitally corrected transposition of the great arteries (l-transposition). In both conditions, the aorta originates from the right ventricle and the pulmonary artery originates from the left ventricle. Complete transposition of the great arteries manifests as neonatal cyanosis.

Pregnant women born with d-transposition of the great arteries have undergone surgical correction—traditionally an *atrial* switch procedure (Senning or Mustard) or the more contemporary *arterial* switch procedure (Jatene or Rastelli). In the atrial switch procedure, the right ventricle functions as the systemic ventricle. Atrial arrhythmias, right ventricular (systemic ventricle) dysfunction, tricuspid regurgitation (systemic atrioventricular valve), atrial baffle obstruction or leaks, and pulmonary hypertension are some of the long-term complications of the traditional atrial switch surgical repair of d-transposition of the great arteries.[65] The advantage of the Jatene and Rastelli procedures is that the left ventricle functions as the systemic ventricle. However, myocardial ischemia may occur after arterial

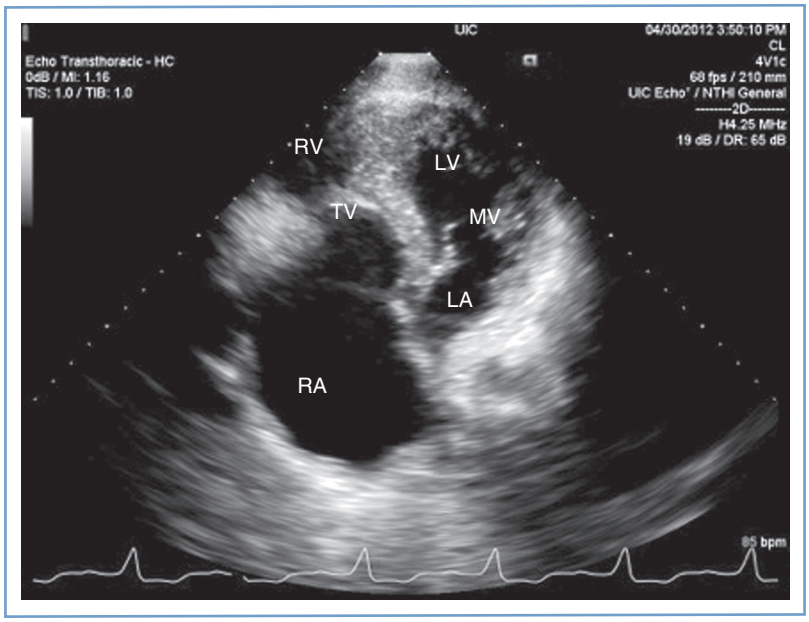

FIGURE 42-2 ■ Echocardiographic image of Ebstein's anomaly. The right atrium is markedly enlarged. *RA,* right atrium; *RV,* right ventricle; *TV,* tricuspid valve; *LA,* left atrium; *MV,* mitral valve; *LV,* left ventricle. (Courtesy Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)

switch operations, because the coronary arteries are reimplanted during these procedures.[83]

All women with repaired d-transposition of the great arteries require detailed echocardiography and, ideally, CMR imaging before planned pregnancy.[54,65] Owing to the propensity for arrhythmias in these patients,[39,84] continuous telemetry monitoring during labor and delivery seems appropriate. Women who have undergone the Mustard operation tolerate pregnancy well[85,86]; however, there is a risk for right ventricular dysfunction[84,87] that may be irreversible.[88] The physiologic changes of pregnancy and/or the natural progression of disease result in an increased right ventricular volume in pregnant women who have undergone a Mustard procedure.[85,88] There are limited data about pregnancy in patients who have undergone an arterial switch operation. Overall, pregnancy outcomes after arterial switch operations appear favorable.[89]

Patients with congenitally corrected transposition (l-transposition) of the great arteries tolerate pregnancy well.[90-92] Thorough echocardiographic evaluation before and throughout pregnancy is advisable.[54,65,83]

Both neuraxial and general anesthesia appear to be reasonable options for parturients with surgically corrected and congenitally corrected transposition of the great arteries (see Table 42-2). Successful cesarean delivery with general anesthesia has been reported in a parturient with d-transposition of the great arteries corrected with a Jatene procedure.[93]

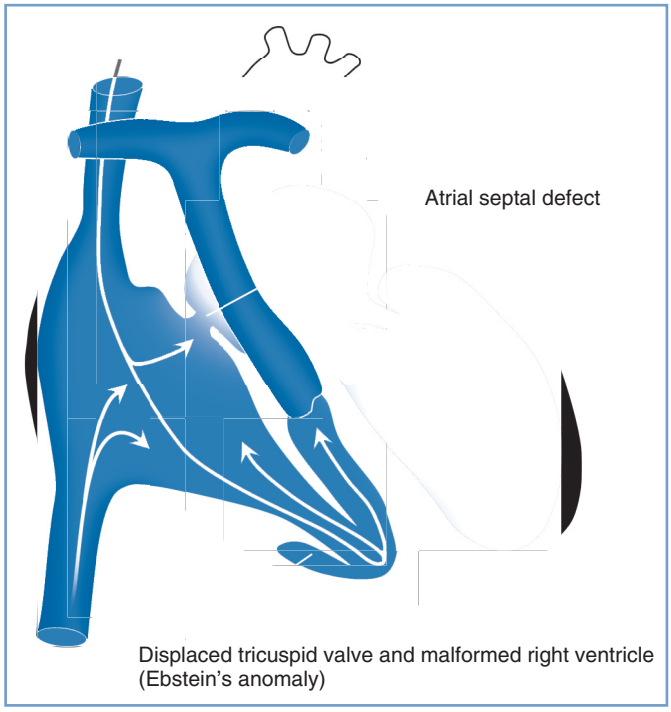

FIGURE 42-3 ■ Schematic depiction of Ebstein's anomaly and atrial septal defect. An atrial septal defect is present in more than one third of patients with Ebstein's anomaly. The white lines with arrows represent the pathway of venous blood returning to the heart. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Ebstein's Anomaly

In Ebstein's anomaly the tricuspid valve is displaced toward the apex of the right ventricle, which results in severe tricuspid regurgitation and right atrial enlargement (Figures 42-2 and 42-3). It is commonly associated with an atrial septal defect and preexcitation syndromes. Accessory pathways result in arrhythmias in approximately 30% of patients; the most commonly observed arrhythmias include atrial tachycardia, atrial flutter, and atrial fibrillation. Pregnancy appears to be well tolerated

in patients with Ebstein's anomaly, especially in women with preserved ventricular function (see Table 42-2).[65,94,95] Patients with a concomitant atrial septal defect and cyanosis have an increased risk for fetal loss and low infant birth weight.[54]

Tetralogy of Fallot

Unrepaired tetralogy of Fallot consists of a ventricular septal defect, an aorta that overrides the ventricular septal defect, and right ventricular outflow tract obstruction (infundibular, valvular, or both), with resulting right ventricular hypertrophy.[54,65] Most women born with tetralogy of Fallot in the United States now present in pregnancy with surgically repaired tetralogy of Fallot. Unrepaired tetralogy of Fallot is rarely seen in developed countries; pregnancy is associated with significant risk in patients with unrepaired defects and is not recommended.[54,65]

During surgical repair the ventricular septal defect is closed and the right ventricular outflow obstruction is repaired. After surgery, important considerations include residual pulmonic valve insufficiency and resulting right ventricular dilation and dysfunction. The preanesthesia evaluation of these patients should include detailed echocardiographic evaluation of cardiac structure and function. Preferably, preconception CMR imaging should be performed because it provides superior imaging of the right-sided chambers. Patients with repaired tetralogy of Fallot are at risk for atrial and ventricular arrhythmias. Sudden cardiac death has been observed late after repair.[96]

Women with repaired tetralogy of Fallot and well-compensated hemodynamic function tolerate pregnancy well (see Table 42-2).[97-99] However, the presence of pulmonary hypertension, right ventricular dysfunction, right ventricular dilation, and/or pulmonic regurgitation predisposes these patients to adverse peripartum complications such as arrhythmias and right-sided heart failure.[65,99,100]

The safe management of neuraxial analgesia/anesthesia for labor and vaginal or cesarean delivery has been described in parturients with repaired tetralogy of Fallot and a wide range of residual pathologic processes.[101] In patients with unrepaired tetralogy of Fallot or tetralogy of Fallot with residual pathology, the anesthesiologist should avoid a decrease in SVR, which worsens the severity of the right-to-left shunt. It is also important to maintain adequate intravascular volume and venous return. In the presence of right ventricular compromise, high filling pressures are needed to enhance right ventricular performance and ensure adequate pulmonary blood flow. Administration of neuraxial analgesia during early labor (low-dose local anesthetic-opioid epidural analgesia or opioid-only intrathecal analgesia) may attenuate the surge of catecholamines and subsequent hemodynamic instability. It may be advisable to choose a titratable neuraxial technique for cesarean delivery (epidural or low-dose sequential spinal-epidural anesthesia [see Chapter 26]) to avoid the abrupt decrease in SVR associated with single-shot spinal anesthesia.

BOX 42-6 Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension owing to left-sided heart disease
3. Pulmonary hypertension owing to lung disease and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms

Updated classification from the 4th World Symposium on Pulmonary Hypertension (Dana Point, CA, 2008). Modified from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54:S43-54.

PULMONARY HYPERTENSION

Box 42-6 outlines the current classification of pulmonary hypertension. Group 1 (pulmonary arterial hypertension) includes idiopathic pulmonary arterial hypertension and pulmonary hypertension due to congenital heart disease.[102] Other clinical conditions associated with group 1 pulmonary hypertension include connective tissue disease, human immunodeficiency virus (HIV) infection, portal hypertension, drugs/toxins (e.g., anorectics, methamphetamine, cocaine), and hemoglobinopathies (e.g., sickle cell disease).[102-104]

All of these conditions are associated with exceptionally high maternal mortality. Older studies reported maternal mortality rates as high as 56%[105]; however, more contemporary studies have demonstrated some improvement in maternal mortality, with rates ranging from 17% to 33%.[106] Nonetheless, pregnancy should be discouraged in women with pulmonary hypertension.

Normal mean pulmonary artery pressure (PAP) at rest is 14 ± 3 mm Hg (upper limit of normal = 20 mm Hg). Pulmonary arterial hypertension is defined as a mean PAP greater than 25 mm Hg with a *normal* pulmonary artery occlusion pressure (PAOP) (≤ 15 mm Hg) and pulmonary vascular resistance greater than 3 Wood* units.[103,104] In contrast, in "postcapillary" pulmonary hypertension due to left-sided heart failure (group 2), PAOP is *elevated* (> 15 mm Hg). Increased pulmonary vascular resistance results in right ventricular overload, which is followed by right ventricular hypertrophy. Right ventricular hypertrophy progresses to dilation of the right-sided chambers, eventually leading to right ventricular failure and death.[104]

A loud pulmonic heart sound (P2) can be heard on physical examination. The second heart sound is widely split owing to delayed closure of the pulmonic valve resulting from high right-sided pressures (pulmonary valve closes *after* the aortic valve). A right-sided

*Wood unit, unit of measure of vascular resistance (mm Hg • min/L); multiply by 80 to convert to dyne•s•cm^{-5}.

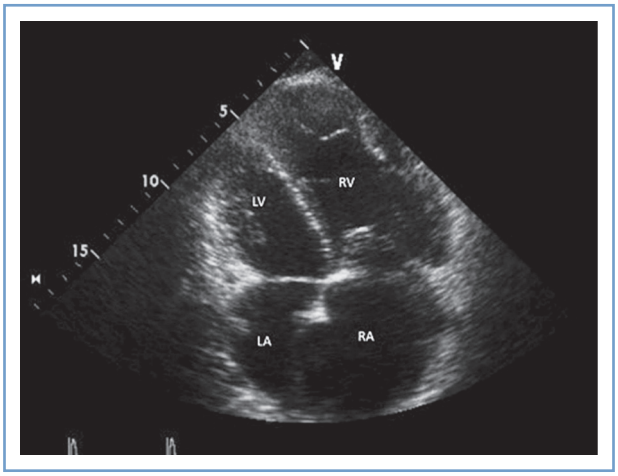

FIGURE 42-4 ■ Echocardiographic image of pulmonary hypertension with severe right-chamber enlargement. The RV basal measurement is 55 mm (upper limit of normal 42 mm); the RA minor axis dimension is 70 mm (upper limit of normal 44 mm). *RA,* right atrium; *LA,* left atrium; *RV,* right ventricle; *LV,* left ventricle. (Courtesy Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)

holosystolic murmur of tricuspid regurgitation is frequently appreciated. Palpation of the precordium demonstrates the classic right ventricular heave. The most commonly encountered ECG findings in patients with pulmonary hypertension are right-axis deviation and right ventricular hypertrophy.

Echocardiography helps establish the diagnosis and prognosis of pulmonary hypertension because it demonstrates the degree of right ventricular hypertrophy and allows estimation of pulmonary artery pressure by assessing the velocity of the tricuspid regurgitant jet (Figure 42-4). Echocardiography also allows assessment of right ventricular function.

Echocardiographic assessment of right-sided pressures may be inaccurate; therefore, invasive right-sided—and frequently left-sided—heart catheterization is required for the definitive diagnosis of pulmonary arterial hypertension. Right-sided heart catheterization allows pressure measurements, thermodilution and Fick cardiac output determination, and vasoreactivity testing. Vasoreactivity testing is usually performed with inhaled nitric oxide or intravenous infusion of sodium nitroprusside, epoprostenol, or adenosine in the cardiac catheterization laboratory. Patients who achieve a decrease in mean PAP of 10 mm Hg or more and achieve a mean PAP of 40 mm Hg or less, without a decrease in cardiac output, are "positive acute responders."[103,104] Patients with a positive response have a better prognosis and may respond to oral therapy with a calcium entry–blocking agent.[103]

Eisenmenger Syndrome

In patients with an anatomic shunt between the systemic and pulmonary circulations at the atrial, ventricular, or aortopulmonary artery level, a left-to-right shunt initially causes increased pulmonary blood flow. Over time, pulmonary vascular resistance increases and pulmonary hypertension develops. The development of pulmonary hypertension results, at least in part, from endothelial dysfunction and vascular remodeling of the pulmonary vascular bed. This increase in pulmonary vascular resistance causes reversal of the shunt (from left-to-right to right-to-left), which results in hypoxemia and cyanosis. This anatomic and physiologic scenario is referred to as *Eisenmenger syndrome*.

Maternal mortality in women with Eisenmenger syndrome is exceptionally high (i.e., 30% to 50%).[105,106] The cardiovascular physiologic changes of pregnancy present a significant hemodynamic challenge for women with pulmonary hypertension and may lead to development of right ventricular failure. The peripartum period, with its rapid fluid shifts and increased oxygen demand, is particularly challenging. Death usually occurs peripartum or postpartum. In a systematic review of case reports of pulmonary hypertension associated with congenital heart disease published between 1997 and 2007 (n = 29),[106] all eight maternal deaths occurred postpartum (range, 0 to 24 days after delivery).

Women with Eisenmenger syndrome often cannot respond to the increased oxygen demands of pregnancy. The normal pregnancy-related decrease in pulmonary vascular resistance does not occur because pulmonary vascular resistance is fixed. In addition, the normal pregnancy-associated decrease in SVR tends to exacerbate the severity of the right-to-left shunt. These changes, together with the normal pregnancy-associated decrease in functional residual capacity, predispose women with Eisenmenger syndrome to hypoxemia. Maternal hypoxemia leads to a high incidence of fetal growth restriction and fetal demise. With contemporary drug therapy, cardiac imaging, and collaborative care, successful pregnancy has been described in patients with Eisenmenger syndrome.[106]

Pulmonary arterial hypertension due to congenital heart disease can be caused by a number of unrepaired congenital heart defects with a left-to-right shunt. Eisenmenger syndrome is associated with ventricular septal defect, atrial septal defect, patent ductus arteriosus, and atrioventricular septal defect (also referred to as endocardial cushion defect). More rarely encountered congenital heart defects (e.g., partial or total anomalous pulmonary venous return, transposition of the great arteries) may also lead to pulmonary arterial hypertension and Eisenmenger syndrome.[54]

Medical and Obstetric Management

Pregnant women with pulmonary hypertension should receive multidisciplinary care in a referral center. Diuretics are frequently needed to manage volume overload in patients with pulmonary arterial hypertension. Diuretics may be particularly helpful in the immediate postpartum period, when uterine contraction and autotransfusion cause an increase in ventricular preload. Dobutamine infusion may help improve right ventricular function. It is unclear whether all of these patients should receive thromboprophylaxis. Both hemorrhage and thromboembolism are causes of maternal mortality.[106]

Therapy for pulmonary arterial hypertension includes general supportive measures, assessment of vasoreactivity, and administration of vasoactive drugs.[104] Inhaled **nitric oxide** selectively dilates the pulmonary vasculature. Case reports have described the successful use of nitric oxide for vaginal and cesarean deliveries in parturients with pulmonary arterial hypertension.[107-109] Epoprostenol, treprostinil, and iloprost are **prostacyclins** used in the treatment of pulmonary hypertension. Successful pregnancy has been described in patients with pulmonary arterial hypertension treated with epoprostenol.[110-113] Similarly, sildenafil, a **phosphodiesterase type-5 inhibitor**, has been successfully used in pregnant women with pulmonary arterial hypertension.[114,115] **Endothelin receptor antagonists** (e.g., bosentan, ambrisentan) are likely teratogenic, and therefore their use is contraindicated during pregnancy.

The optimal mode of delivery in patients with pulmonary hypertension is unknown. In a systematic review that included reports from 1978 to 1996,[105] operative delivery was an independent risk factor for maternal mortality. In contrast, the mode of delivery was not identified as a risk factor for maternal death in a systematic review that included more recent cases.[106] Cesarean delivery is associated with larger changes in intravascular volume, more bleeding complications and blood loss, and a greater risk for thromboembolism; therefore, it seems reasonable to reserve cesarean delivery for obstetric indications.

Anesthetic Management

The primary goals of anesthetic management are (1) maintenance of adequate SVR; (2) maintenance of intravascular volume and venous return; (3) avoidance of aortocaval compression; (4) prevention of pain, hypoxemia, hypercarbia, and acidosis, which may increase pulmonary vascular resistance; and (5) avoidance of myocardial depression during general anesthesia (see Table 42-2).

Current evidence on choice of anesthetic technique for patients with pulmonary arterial hypertension is based on case reports and series from high-volume referral centers. The use of both general[113,116] and epidural anesthesia[117,118] has been reported.[119] Neuraxial (epidural and combined spinal-epidural) anesthesia with use of pulmonary vasodilators in highly specialized centers appears to be associated with favorable overall outcomes.[120,121] In published case reports, cautious administration of epidural anesthesia did not affect the shunt flow in parturients with Eisenmenger syndrome. Slowly titrated epidural or combined spinal-epidural anesthesia eliminates the undesirable effects of myocardial depression and positive-pressure ventilation (with its associated decrease in preload) associated with general anesthesia.

Intravascular volume assessment in patients with pulmonary arterial hypertension is of utmost importance. It is likely best achieved with central venous pressure monitoring; pulmonary artery catheterization without the use of fluoroscopy is technically challenging owing to the frequent presence of tricuspid regurgitation and right-sided chamber enlargement in these patients. Pulmonary artery catheterization has not been shown to improve outcome. Both transthoracic and transesophageal echocardiography are very helpful, and invasive blood pressure monitoring is indispensable. Because patients with pulmonary arterial hypertension frequently require systemic anticoagulation, the choice of anesthesia in these patients is best determined by a multidisciplinary team.

Because of its ease of administration, nitric oxide can be readily administered in the urgent setting. Nitric oxide has been administered during epidural anesthesia for emergency cesarean delivery using a noninvasive ventilation device.[122] Successful cesarean delivery with inhaled iloprost and slowly titrated epidural anesthesia has been reported.[123,124]

Given the high rate of postpartum mortality, patients should be monitored in an intensive care setting for a number of days postpartum.

INFECTIVE ENDOCARDITIS

Endocarditis during pregnancy is rare. It is most frequently associated with intravenous drug use or preexisting structural heart and valve abnormalities (e.g., rheumatic valvular disease, congenital heart disease). Maternal and fetal mortality rates are both high (range, 15% to 25%, respectively).[125]

Antibiotic Prophylaxis

Currently, the ACC, the AHA, and the American College of Obstetricians and Gynecologists (ACOG)[126] do not recommend antibiotic prophylaxis during vaginal or cesarean delivery in the absence of structural heart disease.[54,127,128] In patients with congenital heart disease and the *highest* risk for adverse outcomes, it is *reasonable* to administer antibiotic prophylaxis against infective endocarditis before *vaginal* delivery at the time of membrane rupture.[54] High-risk patients include those with one or more of the following: (1) a prosthetic cardiac valve or a valve repaired with prosthetic material, (2) unrepaired or palliated cyanotic congenital heart disease, and (3) surgically constructed palliative shunts and conduits (Box 42-7). In patients with one of these high-risk conditions who have an established infection (e.g., chorioamnionitis), the underlying infection should be treated. Additional antibiotics specific to endocarditis prophylaxis are not recommended.[126] Mitral valve prolapse is *not* an indication for antibiotic prophylaxis. It is important to note that the level of evidence for these recommendations is C (consensus opinion of experts, case studies, standard of care). In young women of childbearing age, there is no difference in the rate of prosthetic valve endocarditis with mechanical or bioprosthetic valves.

Diagnosis and Treatment

The diagnosis of endocarditis rests on a very high index of suspicion, physical examination, laboratory findings, and cardiac imaging. The modified Duke criteria are the most widely accepted criteria for the diagnosis of endocarditis (Box 42-8). Patients with endocarditis may have

BOX 42-7 High-Risk Cardiac Conditions for Which Antibiotic Endocarditis Prophylaxis for Vaginal Delivery at Time of Membrane Rupture is Reasonable

- Prosthetic heart valve
- Prosthetic material used for heart valve repair
- History of infective endocarditis
- Unrepaired cyanotic congenital heart disease
- Repaired congenital disease
  - Palliative shunts and/or conduits
  - Prosthetic material or percutaneously inserted devices/material during the first 6 months after the procedure
  - Residual defects in proximity to prosthetic material or percutaneously inserted device
- Cardiac transplantation recipient with valvulopathy

Modified from American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation 2007; 116:1736-54.

BOX 42-8 Modified Duke Criteria for the Diagnosis of Bacterial Endocarditis

Major Criteria

- Positive blood culture with typical infective endocarditis microorganism
- Evidence of endocardial involvement with positive echocardiogram

Minor Criteria

- Predisposing factor: known cardiac lesion, recreational drug injection
- Fever > 38° C
- Evidence of embolism: arterial emboli, pulmonary infarcts, Janeway lesions, conjunctival hemorrhage
- Immunologic problems: glomerulonephritis, Osler's nodes
- Positive blood culture (with an atypical microorganism that does not meet a major criterion) or serologic evidence of infection with organism consistent with infective endocarditis but not satisfying a major criterion

The diagnosis of infective endocarditis is confirmed if two major criteria, one major and three minor criteria, or five minor criteria are present.

Modified from Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994; 96:200-9.

negative blood cultures. Therefore, absence of bacterial growth in blood cultures does not automatically rule out endocarditis.

In addition to systemic antibiotic therapy, valve replacement may be required in pregnant women with endocarditis. Alternatively, successful treatment with aggressive antibiotic therapy has been described.

Neuraxial Anesthesia in Patients with Systemic Infection

The safety of neuraxial anesthesia in patients with systemic infection has been debated for many years (see Chapter 37).[129] Neurologic complications after spinal or epidural anesthesia are rare in large observational series[130,131]; however, there is general agreement that patients with *untreated* systemic infection should *not* receive neuraxial anesthesia.

Published data and clinical experience suggest that spinal anesthesia may be safely administered in patients who have received antibiotic treatment and are responding to treatment at the time of dural puncture. Similarly, it is likely that epidural anesthesia may be safely administered to patients with treated systemic infection.[129] In patients with endocarditis, bacteremia may seed the epidural space and cause epidural abscess in the absence of neuraxial anesthesia. Similarly, meningitis is a recognized neurologic complication of endocarditis. Therefore, it may be difficult to determine whether the neuraxial procedure contributed to the development of the infection if meningitis or epidural abscess should develop in a patient with endocarditis receiving neuraxial anesthesia.

IMPLANTABLE CARDIAC DEVICES

Permanent and Temporary Pacemakers

Permanent pacemakers implanted before pregnancy are occasionally encountered. Pregnancy and labor and delivery are generally well tolerated in these patients.[132,133]

Advanced second-degree (two or more nonconducted P waves) or third-degree atrioventricular block is rare in pregnant women and is most commonly seen in patients with congenital heart disease. Recommendations are inconsistent as to whether temporary pacing is required for labor and delivery.[134-138] Some of the principal indications for pacemaker placement (e.g., symptomatic bradycardia, periods of asystole greater than 3 seconds, escape rhythms below the atrioventricular node with rates < 40 beats per minute) also appear to be appropriate indications for parturients; the decision to electively place either a temporary or permanent device should be made by a multidisciplinary team. Patients who develop hemodynamic instability due to bradycardia should receive a temporary venous pacemaker. Transcutaneous pacing is an attractive alternative, but it is uncomfortable for prolonged use. Because the majority of patients requiring temporary pacing have underlying congenital heart disease, it is critically important to understand the cardiac anatomy before placing the venous pacemaker to minimize complications such as perforation or valve injury.

Implantable Cardioverter-Defibrillators

Pacemaker and implantable cardioverter-defibrillator (ICD) implantation during pregnancy may be performed with echocardiographic guidance, thus reducing fetal radiation exposure. A wearable automatic defibrillator is an attractive option for pregnant women, because it may

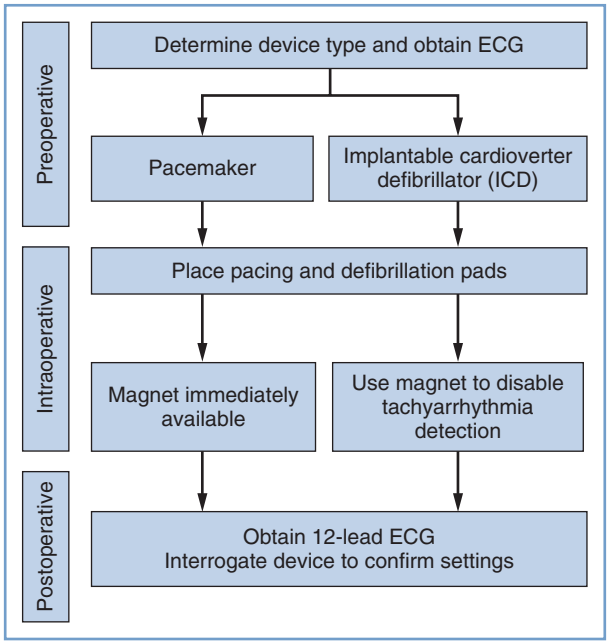

FIGURE 42-5 ■ A suggested perioperative approach to the management of implantable cardiac devices during cesarean delivery. *ECG,* electrocardiogram.

allow ICD implantation to be postponed until after delivery. In the future, ICDs that are placed entirely within a subcutaneous pocket may be offered to pregnant women and eliminate the need for fetal radiation exposure.

Women with previously placed ICDs usually tolerate pregnancy and delivery well. Pregnancy does not increase the risk for ICD-related complications, and it does not increase the number of ICD discharges. Rather, the severity of underlying structural heart disease determines the overall complication rate.[139] Case reports suggest that pregnant women tolerate ICD shocks as well as nonpregnant women.[139,140]

Peripartum Management

Pacemakers and ICDs should be interrogated before or during pregnancy and before and after labor and vaginal or cesarean delivery (Figure 42-5). The type of device, manufacturer, and model should be documented. The indication for the device, the patient's underlying rhythm, and whether the patient is pacemaker dependent should be identified. Given the complexity of contemporary pacing and ICD devices, it is imperative to perform this evaluation in collaboration with an electrophysiologist or a cardiologist familiar with device management. It is helpful to obtain a 12-lead ECG before and after delivery and before and after any change in device programming.

The response of the device to magnet placement and removal should be known. It is important to recognize that different devices may respond quite differently to magnet placement. Most pacemakers will pace in an asynchronous mode after application of an external magnet. For most ICDs, the magnet will disable tachycardia detection (i.e., the device will not deliver a shock for ventricular tachycardia or ventricular fibrillation), but the magnet will *not* alter the pacing mode and rate settings. Magnets do *not* change bradycardia pacing settings for ICDs.

Because of the variability of pacemaker design from different manufacturers, and the highly sophisticated programming settings, peripartum device management should be individualized. Management is best planned before labor and delivery using a collaborative approach. For operative obstetric procedures, electromagnetic interference is unlikely given the distance of the site of surgery from the implanted device. Because pacemaker electrical activity can occur without resulting ventricular contraction, monitoring patients with an implantable cardiac device includes continuous ECG *together with* either plethysmography (pulse oximetry) or invasive blood pressure monitoring to ascertain the presence of a pulse.

For all procedures in patients with a pacemaker, a magnet should be immediately available. Immediate availability of external pacing and defibrillation capability is mandatory for all patients regardless of the type of device and urgency of the surgery. For most obstetric surgeries, it is recommended that devices *not* be reprogrammed and that ICDs *not* be deactivated by reprogramming. If deactivation of an ICD is necessary, the patient must remain in a monitored setting with external defibrillation pads placed on the patient until it is confirmed that the ICD has been reactivated. If the ICD is not deactivated by reprogramming, a magnet should be placed over the device intraoperatively to disable tachyarrhythmia detection. Removal of the magnet will restore previous ICD settings.

In patients with a pacemaker or an ICD, central intravenous catheter placement in the upper body needs to be performed with extreme caution so as not to damage or entangle device leads; this is particularly important in leads that were recently inserted (< 3 months earlier).

ADULT ARRHYTHMIAS

The incidence of arrhythmias is increased during pregnancy in patients with and without structural heart disease. The mechanisms have been attributed to atrial[16] and ventricular stretch[40] due to increased intravascular volume as well as the increase in resting heart rate. Additionally, autonomic and hormonal changes of pregnancy have been proposed as putative mechanisms.

Palpitations are frequent during pregnancy, and Holter monitoring often reveals premature atrial and ventricular contractions. The frequency of ectopy decreases after delivery. Interestingly, there is no correlation between symptomatic palpitations and frequency of underlying arrhythmias.[141] Therefore, no treatment is needed in asymptomatic patients with **premature atrial contractions** or **premature ventricular contractions**. Substances such as caffeine, alcohol, and cocaine should be discontinued, and treatment with a beta-adrenergic receptor antagonist may be considered in symptomatic patients.

Women who have been diagnosed with an arrhythmia before pregnancy frequently develop an exacerbation of

arrhythmia during pregnancy. Recurrence of a preexisting arrhythmia is associated with adverse fetal events.[142]

Supraventricular Arrhythmias

Overall, **supraventricular tachycardia** (SVT) during pregnancy is rare, with an estimated 24 episodes/100,000 pregnancies.[143] It is unclear whether pregnancy increases the risk for new-onset supraventricular tachycardia,[144,145] although the first onset of **paroxysmal supraventricular tachycardia** during pregnancy is unusual. Symptoms of supraventricular tachycardia may be exacerbated during pregnancy.[144]

Premature atrial contractions are frequently encountered during pregnancy. Their frequency generally decreases in the postpartum period.[141] Premature atrial contractions are overwhelmingly benign and rarely cause significant palpitations. Symptomatic patients can be treated with a low dose of a beta-adrenergic receptor antagonist.

Atrial fibrillation is encountered rarely during pregnancy. Rate and/or rhythm control along with prevention of thromboembolism are the mainstays of treatment of atrial fibrillation. The ventricular rate can be successfully controlled with digoxin, a beta-adrenergic receptor antagonist, or a nondihydropyridine calcium entry–blocking agent.[146] Alternatively, quinidine, sotalol, flecainide, or amiodarone may be used to control rapid ventricular response. These drugs also allow for pharmacologic cardioversion of atrial fibrillation. Although restoration of sinus rhythm reduces the risk for thromboembolism and may provide considerable short-term hemodynamic advantages in certain patients, the impact of a rhythm-control treatment strategy on long-term outcome is unclear.

Because atrial fibrillation during pregnancy most frequently results from underlying structural heart disease (rheumatic mitral stenosis or congenital heart disease), systemic anticoagulation during pregnancy is recommended. There is extensive published experience with the use of unfractionated heparin and warfarin during pregnancy; limited data are available with low-molecular-weight heparin (LMWH).

Use of the CHADS2 score[147] facilitates risk stratification for predicting stroke and thromboembolism associated with atrial fibrillation. This risk stratification provides guidance for choice of anticoagulation.[146] Points are assigned for the presence of six risk factors: **C**ongestive heart failure (1 point), **H**ypertension (1 point), **A**ge 75 years or older (1 point), **D**iabetes mellitus (1 point), and prior **S**troke/transient ischemic accident and thromboembolism (2 points). Patients at low risk for stroke generally receive aspirin, whereas those at high risk receive oral anticoagulation with warfarin or a newer oral anticoagulant (e.g., dabigatran, apixiban, rivaroxaban). There are no published reports of the use of these newer oral anticoagulants in pregnant women.

Atrial flutter is an organized macro-reentrant arrhythmia rarely seen during pregnancy. The atrial rate is usually 300 beats per minute; ventricular rate control may be difficult to achieve medically. Electric cardioversion is recommended for unstable patients, although pharmacologic cardioversion with ibutilide during pregnancy has been reported.[148]

Atrial tachycardia most frequently results from increased automaticity of atrial cells. Incessant atrial tachycardia has been successfully ablated during pregnancy.

Ventricular preexcitation syndromes (e.g., Wolff-Parkinson-White syndrome) are rarely encountered in pregnancy; these patients are usually identified at a younger age and have undergone highly effective electrophysiologic treatment. A few case reports suggest that preexcitation syndromes may be associated with an increased rate of supraventricular arrhythmias during pregnancy.

Ventricular Arrhythmias

Ventricular arrhythmias are commonly associated with underlying structural heart disease. The diagnostic evaluation warrants a baseline ECG and echocardiography. During pregnancy, peripartum cardiomyopathy as cause of ventricular arrhythmias needs to be ruled out.

Idiopathic ventricular tachycardia is most commonly monomorphic, originating from the right ventricular outflow tract. New-onset idiopathic ventricular tachycardia during pregnancy has been reported in a very small series of patients. These reported arrhythmias were catecholamine sensitive and responsive to beta-adrenergic receptor antagonist therapy.[149] Idiopathic ventricular tachycardia may also be sensitive to treatment with verapamil[150] or isoproterenol.[151] Polymorphic ventricular tachycardia[152] and electrical storm with Brugada syndrome[153] have also been reported during pregnancy.

Sudden cardiac death due to idiopathic ventricular tachycardia has been described in pregnant women with hypertrophic cardiomyopathy.[154-156] Sustained idiopathic ventricular tachycardia, successfully treated with lidocaine infusion, has been described in patients with repaired tetralogy of Fallot.

Congenital Long QT Syndrome

The congenital long QT syndrome is caused by mutations in cardiac ion channels resulting in prolongation of ventricular repolarization. The clinical spectrum ranges from a lack of symptoms to arrhythmia-associated syncope and sudden cardiac death. Risk for cardiac events (syncope, arrhythmias, or death) is decreased in pregnant women with long QT syndrome, due at least in part to the increase in heart rate that occurs during pregnancy.[157] Compared with the 40-week prepregnancy period, the 40-week postpartum period has been associated with an increased risk for ventricular tachycardia in women with long QT syndrome.[158] Different long QT syndrome genotypes may have different risks associated with pregnancy. The LQT2 genotype is associated with a higher rate of cardiac events in the 9-month postpartum period than the LQT1 and LQT3 genotypes.[157,159] Prophylactic treatment with a beta-adrenergic receptor antagonist is recommended during pregnancy and postpartum in patients with long QT syndrome.[157,160]

Antiarrhythmic Drugs

The risk for adverse fetal effects of antiarrhythmic drugs should be assessed on an individual basis (see Chapter 14). Beta-adrenergic receptor antagonists, amiodarone, and sotalol are effective in preventing idiopathic ventricular tachycardia during pregnancy. Fetal exposure to amiodarone (pregnancy category D) has been associated with hypothyroidism and, possibly, fetal growth restriction. Sotalol is classified as pregnancy category B and appears safe. Because sotalol is a beta-adrenergic receptor antagonist, its use may be associated with neonatal bradycardia and hypoglycemia.

Electric Cardioversion

Life-threatening or hemodynamically unstable arrhythmias should be terminated by electric cardioversion.[146,160] **Defibrillation** refers to administration of electric energy to terminate ventricular fibrillation. By contrast, **synchronized cardioversion** is delivery of an electric shock synchronized to the QRS complex. Synchronized cardioversion is administered for supraventricular rhythms (i.e., atrial fibrillation, atrial flutter, atrial tachycardia) as well as for monomorphic ventricular tachycardia with a pulse.[146] Pulseless ventricular tachycardia and polymorphic ventricular tachycardia should be treated with **unsynchronized cardioversion**.

Electric cardioversion can be performed safely throughout pregnancy without apparent adverse effects on fetal hemodynamic function.[161,162] Nonetheless, it is prudent to monitor the fetal heart rate (FHR) during cardioversion.[163] Current guidelines recommend the use of a biphasic defibrillator. Ventricular fibrillation can be successfully terminated with biphasic devices that use lower energy than is required with monophasic devices. Biphasic automatic external defibrillators (AEDs) are more effective in terminating ventricular fibrillation with lower energy than older monophasic devices.

If hemodynamically significant or severely symptomatic arrhythmias develop during pregnancy, electrophysiologic interventional management may be performed. Successful **radiofrequency catheter-based ablation** has been reported in pregnant women with no or minimal ionizing radiation exposure.

Patients usually require anesthesia care for cardioversion. The risk for pulmonary aspiration of gastric contents associated with sedation (with an unprotected airway) should be weighed against the risks associated with general anesthesia and tracheal intubation. The judicious use of sedation rather than general anesthesia is usually preferred. A benzodiazepine or propofol can provide satisfactory sedation and amnesia. Regardless of whether sedation or general anesthesia is selected, a nonparticulate oral antacid should be administered; administration of a histamine-2 (H_2)-receptor antagonist to increase gastric pH should also be considered. The use of metoclopramide in these patients is controversial owing to its possible association with tachyarrhythmias.

Maintenance of Sinus Rhythm

Development of atrial fibrillation may cause significant hemodynamic compromise, particularly in pregnant women with stenotic valvular lesions (aortic stenosis or mitral stenosis) or hypertrophic cardiomyopathy with its associated diastolic dysfunction. Hemodynamic compromise results from the diminished diastolic filling time and loss of the atrial contraction contribution to ventricular filling. Maintenance of sinus rhythm and strict rate control have *not* been shown to be beneficial in older (nonpregnant) patients with paroxysmal or permanent atrial fibrillation. However, published studies are largely not applicable to pregnant women, and it seems reasonable to maintain sinus rhythm and control heart rate in this population. Rate control is particularly important in patients with stenotic valvular lesions and hypertrophic cardiomyopathy because the hemodynamic condition of these patients may quickly deteriorate in the presence of tachycardia.

MYOCARDIAL INFARCTION

The term *myocardial infarction* signifies myocardial cell death caused by ischemia.[25] Myocardial infarction is diagnosed by clinical signs and symptoms, ECG patterns, elevation of biomarkers (CK-MB fraction, troponin), and various imaging modalities (echocardiography, radionuclide imaging, CMR imaging, CT). The current Universal Classification of Myocardial Infarction recognizes five types of myocardial infarction (Box 42-9).[25]

Myocardial infarction during pregnancy is rare; the estimated incidence is 2.8 to 6.2 per 100,000 deliveries.[164,165] It occurs most commonly in the third trimester or the immediate postpartum period. Myocardial infarction during pregnancy is associated with maternal use of tobacco, dyslipidemia, family history of myocardial infarction, hypertension, African race, Hispanic ethnicity, and diabetes. Contemporary evidence suggests that the maternal mortality rate from myocardial infarction during pregnancy is approximately 5%.[165]

Acute coronary syndrome is an encompassing term used to describe unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Unstable angina is differentiated from NSTEMI by lack of elevation of cardiac biomarkers. Compared with unstable angina or NSTEMI, STEMI is an emergency and requires early reperfusion; a "door-to-balloon" interval of less than 90 minutes is optimal.

Only 40% of pregnant patients with myocardial infarction have evidence of coronary artery atherosclerosis (type I myocardial infarction); spontaneous coronary artery dissection (type II myocardial infarction) is observed in as many as 27% of patients. Angiographically normal coronary arteries are seen in 13% of patients[166]; in these cases, myocardial infarction likely results from coronary artery spasm or embolism. Spasm can be spontaneous, or it can be due to cocaine or ergot alkaloids. Septic and metastatic neoplastic coronary embolism after abortion have been described. Atherosclerosis is more

BOX 42-9 Universal Classification of Myocardial Infarction

Type 1—Spontaneous Myocardial Infarction

Due to atherosclerosis and plaque rupture/erosion resulting in intracoronary thrombus formation

Type 2—Myocardial Infarction due to Ischemic Imbalance

Due to conditions other than atherosclerosis (e.g., supply-demand mismatch, coronary vasospasm, coronary embolism, coronary dissection, stress of noncardiac surgery)

Type 3—Cardiac Death due to Myocardial Infarction

Cardiac death highly suggestive of myocardial infarction without the availability of biomarker confirmation

Type 4a—Myocardial Infarction related to Percutaneous Coronary Intervention

Due to distal plaque embolization, side-branch occlusion, and directly related to coronary intervention (e.g., stenting or balloon angioplasty)

Type 4b—Myocardial Infarction due to Stent Thrombosis

Detected by autopsy or angiography

Type 5—Myocardial Infarction due to Coronary Artery Bypass Grafting (CABG)

Cardiac biomarker elevation associated with surgical revascularization procedure

Modified from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012; 60:1581-98.

commonly the cause of myocardial infarction in the antepartum period than in the peripartum or postpartum period, whereas coronary artery dissection is observed more frequently in the peripartum and postpartum periods.[166] It has been hypothesized that the high rate of spontaneous coronary artery dissection is related to hormonal changes of pregnancy.

Cesarean delivery is commonly associated with ischemic-appearing ST-segment depression.[14,167-170] These changes have been attributed, at least in part, to oxytocin administration (see earlier discussion).[12,13] ST-segment elevation is *not* a normal occurrence during labor and delivery or with any type of intrapartum anesthesia. Hence, ST-segment elevation should always be considered abnormal, and ST-segment depression should be carefully evaluated.

CK-MB fraction may be elevated during normal pregnancy and labor (see Figure 47-1); thus, measurement of this enzyme is less useful for the diagnosis of myocardial infarction in pregnant women than in nonpregnant women.[28] An elevated troponin level is much more specific, although troponin may be elevated in patients with gestational hypertension and preeclampsia/eclampsia.[26,27] Both markers are quite sensitive for the diagnosis of myocardial infarction.

Percutaneous Coronary Intervention

STEMI during pregnancy should be treated with primary percutaneous coronary intervention. Although successfully used in anecdotal reports, use of thrombolytic therapy for STEMI in pregnant women should be reserved for rare instances. Radial arterial access for the percutaneous coronary intervention procedure is preferable because it has fewer bleeding complications and a lower mortality rate than femoral arterial access. Systemic anticoagulation with unfractionated heparin appears most reasonable owing to its short half-life, the availability of activated clotting time (ACT) monitoring, and the ability to rapidly reverse its anticoagulant effect. Importantly, larger doses of heparin are needed to achieve the desired level of anticoagulation in pregnant women than in nonpregnant patients. Anticoagulation for percutaneous coronary intervention can be achieved with low-molecular weight heparin, although inability to rapidly assess its anticoagulant effect and its altered pharmacokinetics during pregnancy are major disadvantages.

Percutaneous coronary interventions for treatment of myocardial infarction include conventional "plain old balloon angioplasty" and stent placement. An advantage of conventional balloon angioplasty is that it does not require dual antiplatelet therapy; however, placement of a stent is associated with a lower risk for abrupt vessel closure in the short term and a lower long-term risk for restenosis.

Dual antiplatelet therapy is mandatory after placement of a coronary artery stent to prevent stent thrombosis (Table 42-3). This therapy consists of both aspirin (81 to 325 mg daily) and clopidogrel. Clopidogrel can be substituted with a newer agent (e.g., prasugrel, ticagrelor) in specific nonpregnant patients. However, the safety and efficacy of these newer antiplatelet agents in pregnancy are unknown.

Stent Type Choice

In patients with a nonacute coronary syndrome (e.g., chronic stable angina), bare-metal stents require a minimum of 1 month of dual antiplatelet therapy, whereas drug-eluting stents require a minimum of 12 months. When either bare-metal stents or drug-eluting stents are placed in a patient with any *acute* coronary syndrome (e.g., unstable angina, NSTEMI, STEMI), 12 months of dual antiplatelet therapy is recommended. The advantage of drug-eluting stents is a decreased risk for in-stent restenosis than occurs with bare-metal stents. Drug-eluting stents elute an antiproliferative agent (everolimus, sirolimus, paclitaxel) into the arterial wall and reduce the neointimal proliferation that causes in-stent restenosis. However, the stent strut endothelialization process is slower with drug-eluting stents than with bare-metal stents; thus, a longer duration of dual antiplatelet therapy is required to prevent stent thrombosis. Overall rates of death and myocardial infarction are similar with drug-eluting and bare-metal stents. The risk for stent thrombosis may be lower with contemporary drug-eluting stents than with bare-metal stents. Newer-generation drug-eluting stents may allow for earlier discontinuation of dual antiplatelet therapy.

TABLE 42-3 **Dual Antiplatelet Therapy Recommendations**

		Percutaneous Coronary Intervention (PCI)		
		BALLOON ANGIOPLASTY	BARE-METAL STENT	DRUG-ELUTING STENT
Nonacute Coronary Syndrome	Aspirin	Indefinitely	Indefinitely	Indefinitely
	Clopidogrel	None	1 month	12 months
Acute Coronary Syndrome*	Aspirin	Indefinitely	Indefinitely	Indefinitely
	Clopidogrel	12 months	12 months†	12 months

*Acute coronary syndrome includes unstable angina, non–ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction.
†If necessary for the safe care of the obstetric patient, dual antiplatelet therapy can be discontinued 1 month after placement of a bare-metal stent.

Dual Antiplatelet Therapy

Bare-metal stents allow for discontinuation of dual antiplatelet therapy 1 month after percutaneous coronary intervention, if necessary, even in the setting of acute coronary syndrome (see Table 42-3). This may be advantageous in pregnant women who are at risk for intrapartum and postpartum hemorrhage. Therefore, most interventional cardiologists will place a bare-metal stent in a pregnant woman with acute coronary syndrome. Although it appears reasonable to continue dual antiplatelet therapy as long as feasible in a pregnant woman with acute coronary syndrome, there are little data on the optimal duration of dual antiplatelet therapy in this unique clinical setting. Continuing research is being performed to determine the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention in the nonpregnant population.

It is not advisable to perform neuraxial anesthesia in patients receiving dual antiplatelet therapy.[43] After clopidogrel is discontinued, aspirin should be continued indefinitely in patients with any type of stent. Both spinal and epidural anesthesia can be performed safely in patients receiving aspirin. Clopidogrel should be discontinued 7 days before performance of neuraxial anesthesia.[43]

Aspirin crosses the placenta. A 2002 meta-analysis found no *overall* increase in the risk for congenital malformations when aspirin was administered in the first trimester; however, a twofold increase in the risk for gastroschisis was observed.[171] Another meta-analysis that evaluated the use of aspirin for prevention of preeclampsia found no evidence of increased risk for fetal growth restriction, pregnancy loss, or neonatal hemorrhage.[172] Most evidence suggests that aspirin use is safe during pregnancy.[173]

Coronary Artery Anomalies

Coronary artery anomalies occur in approximately 1% of the general population. Coronary artery anomalies are frequently associated with congenital heart disease such as d-transposition of the great arteries and tetralogy of Fallot.

There are numerous types of coronary anomalies, and most are benign. The two most common clinically significant anomalies are (1) a left main coronary artery that originates from the right coronary cusp and (2) a right coronary artery that originates from the left coronary cusp. External mechanical compression of those anomalous coronary vessels may cause myocardial ischemia and eventually lead to arrhythmias. The resulting ischemia and arrhythmias have been associated with sudden cardiac death. The effect of the physiologic changes of pregnancy in women with coronary artery anomalies has not been well studied.

VALVULAR HEART DISEASE

Pregnancy and its associated changes in cardiovascular physiology present a unique clinical challenge to women with underlying valvular heart disease. The general management principles for pregnant women with valvular heart disease are directed toward specific hemodynamic goals and the need for anticoagulation in patients with a mechanical valve.

Aortic Stenosis

The most common cause of aortic stenosis in pregnant women is a congenital bicuspid aortic valve. Less common causes/types of aortic stenosis include rheumatic, supravalvular, and subvalvular aortic stenosis.[174] Rheumatic aortic stenosis is invariably associated with some degree of mitral valve involvement. The hemodynamic implications of the various causes of aortic stenosis are similar. Calcific aortic stenosis of an anatomically normal tricuspid aortic valve occurs much later in life and is unlikely to be encountered in women of childbearing age.

Bicuspid aortic valve, the most common congenital heart defect, occurs in 0.5% to 2% of the population; women are affected four times less commonly than men. It is heritable; therefore, first-degree relatives of patients with a bicuspid aortic valve should be screened.[54] Bicuspid aortic valve is associated with accelerated and premature valve stenosis as well as aortic valve regurgitation. Symptoms of aortic stenosis (dyspnea on exertion, chest pain, syncope) generally present in the third and fourth decades of life. Importantly, patients with a bicuspid

TABLE 42-4 Severity Classification of Valvular Lesions

	Normal	Mild	Moderate	Severe
Aortic Stenosis				
Valve area (cm^2)	3.0-4.0	> 1.5	1.0-1.5	< 1.0
Mean gradient (mm Hg)		< 25	25-40	> 40
Jet velocity (m/sec)		< 3.0	3.0-4.0	> 4.0
Mitral Stenosis				
Valve area (cm^2)	4.0-6.0	> 1.5	1.0-1.5	< 1.0
Mean gradient (mm Hg)		< 5	5-10	> 10
Pulmonary artery systolic pressure (mm Hg)		< 30	30-50	> 50

Modified from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008; 52:e1-142.

aortic valve have underlying aortic root pathology in the media that is associated with aortic root dilation, thus predisposing to ascending root dissection.[49]

The normal aortic valve area is 3.0 to 4.0 cm^2 (Table 42-4). There is no pressure gradient across a normal aortic valve with normal resting cardiac output. Patients generally develop symptoms when the valve area is less than 1.0 cm^2 and the pressure gradient across the valve is greater than 40 mm Hg. The published definition of severe aortic stenosis varies. An aortic valve area less than 1.0 to 1.5 cm^2 and a mean valve gradient of 25 to 50 mm Hg generally define the group of patients with a high risk for cardiovascular complications due to aortic stenosis.[35,36,38,60]

Classically, the aortic valve area is estimated invasively in the cardiac catheterization laboratory using the Gorlin equation. Forward cardiac output is determined by thermodilution and/or Fick methods, and left ventricular and aortic pressures are simultaneously recorded. Doppler velocity measurements during echocardiography allow noninvasive estimation of aortic valve area using the continuity equation.

Using both these methods, the estimated transvalvular *gradient* increases during pregnancy because of the physiologic increase in cardiac output. The calculated valve *area* remains unchanged, however, because both the Gorlin equation and the continuity equation take cardiac output into account. The echocardiographic dimensionless *valve index* is useful in pregnant women as well as other patients; it takes into account both left ventricular outflow velocity and the aortic velocity. Because both velocities are increased during pregnancy, the dimensionless index and estimated valve area remain unchanged during pregnancy.

The severity of aortic stenosis affects maternal risk during pregnancy. *Mild* and *moderate* aortic stenosis are associated with favorable pregnancy outcomes.[174-176] Women with *severe* aortic stenosis experience frequent cardiac complications during pregnancy (e.g., worsening NYHA functional class, pulmonary edema, congestive heart failure, arrhythmias, hospitalization). The reported rates of these complications during pregnancy vary widely (e.g., heart failure and pulmonary edema 4% to 78%, arrhythmias 2% to 33%, hospitalization rate as high as 78%). Mortality is rare, however.[174,175,177] Additionally, women with severe disease are more likely to require a cardiac intervention (balloon valvuloplasty, valve replacement) during pregnancy or immediately postpartum. Percutaneous balloon valvuloplasty of the aortic valve is a palliative procedure that allows completion of pregnancy before definitive repair.

Obstetric and Anesthetic Management

Labor and assisted vaginal delivery are preferred. Cesarean delivery is reserved for obstetric indications.

Whether general or neuraxial anesthesia is more appropriate for parturients with aortic stenosis has been a matter of debate.[178-180] Historically, neuraxial anesthesia has been thought to be relatively contraindicated in patients with aortic stenosis; the simultaneous decrease in preload and afterload associated with neuraxial anesthesia may be particularly hazardous in these patients. However, case reports have documented successful administration of neuraxial anesthesia (spinal,[181] continuous spinal,[182] combined spinal-epidural,[180,183] epidural[184]) and general anesthesia[185,186] with favorable maternal and neonatal outcomes.

The choice between neuraxial and general anesthesia should not be made based on the aortic valve gradient or aortic valve area alone. The preanesthetic assessment should include physical examination, symptom evaluation, and comprehensive assessment of the right and left ventricular structure and function, as well as the structure and function of other cardiac valves. The presence or absence of pulmonary hypertension should also be determined.

Echocardiography offers indispensable information regarding left and right ventricular ejection fraction, left ventricular wall thickness, pulmonary artery pressure, presence of aortic insufficiency, mitral valvular structure and function, and aortic root size. Serial assessment of the aortic valve area before and during pregnancy is very helpful in managing these patients. Patients with normal right and left ventricular function are more likely to tolerate fluid shifts and the depressant effects of general anesthetic agents. If left ventricular dysfunction develops in the presence of aortic stenosis, a condition referred to as **low-output**, **low-gradient aortic stenosis** may be present.

The presence of pulmonary hypertension, right ventricular dysfunction, or mitral regurgitation is associated with greater dependence on preload and may unfavorably affect the hemodynamic response to neuraxial anesthesia. Patients with a dilated aortic root will likely benefit from gradual blood pressure changes, because aortic root dilation has been associated with aortic dissection. Left ventricular hypertrophy, frequently present with aortic stenosis, is associated with significant diastolic

dysfunction and may impede left ventricular filling. The presence of left ventricular hypertrophy will render these patients more sensitive to the adverse effects of decreased preload, tachycardia, and the development of congestive heart failure, especially in the setting of acute-onset atrial fibrillation. Aortic regurgitation is quite common in patients with a bicuspid aortic value. The ventricles are exposed to both pressure and volume overload, further complicating hemodynamic management and response to anesthesia.

The goals of anesthetic management are (1) maintenance of a normal heart rate, sinus rhythm, and adequate systemic vascular resistance; (2) maintenance of intravascular volume and venous return; (3) avoidance of aortocaval compression; and (4) avoidance of myocardial depression during general anesthesia (see Table 42-2). In the absence of prospective randomized trials in this patient population, current clinical evidence suggests that either neuraxial analgesia/anesthesia or general anesthesia is safe for patients with mild or moderate aortic stenosis with normal right and left ventricular ejection fraction and the absence of other significant valvular lesions or pulmonary hypertension. Neuraxial anesthetic techniques that allow gradual titration of anesthesia seem advantageous in these patients.

In patients with severe aortic stenosis, general anesthesia remains the gold standard. Although published reports have described successful administration of neuraxial anesthesia for labor and vaginal and cesarean delivery in women with severe aortic stenosis, the influence of publication bias in these reports cannot be excluded. In contemporary obstetric anesthesiology practice, an opioid-based neuraxial labor analgesia technique, along with alternative forms of analgesia (e.g., pudendal nerve block, intravenous opioids) is well tolerated in parturients with severe aortic stenosis. A slowly dosed, low-concentration local anesthetic epidural technique, chosen to mitigate the untoward effects of sympathectomy, may be safely performed with vigilant blood pressure monitoring. The anesthesiologist may choose to avoid use of an epinephrine-containing local anesthetic solution because the unintentional intravenous injection of epinephrine can precipitate tachycardia; further, systemic absorption of epinephrine can diminish SVR and reduce venous return. General anesthesia may be the best choice for cesarean delivery in patients with severe aortic stenosis and other significant valvular lesions, pulmonary hypertension, and/or left ventricular dysfunction. Induction of anesthesia with a combination of etomidate and a moderate dose of a lipid-soluble opioid may be preferable to agents that cause myocardial depression and vasodilation (propofol, thiopental) and tachycardia (ketamine). Anesthesia can be maintained with an opioid and a low-dose volatile anesthetic technique.

Peripartum invasive arterial blood pressure monitoring is recommended for parturients with moderate and severe aortic stenosis. Pulmonary artery catheterization is unlikely to provide much clinical benefit in this patient population. Development of atrial fibrillation with rapid ventricular response is deleterious in these patients because it decreases diastolic filling time and eliminates the atrial component of left ventricular filling. If new-onset atrial fibrillation results in hypotension or pulmonary edema, sinus rhythm should be promptly restored.

Aortic Regurgitation

The most common etiology of chronic aortic regurgitation in pregnant women is a degenerated bicuspid aortic value; rheumatic aortic regurgitation occurs less frequently. Dilation of the ascending aorta and the resulting aortic leaflet separation may also result in aortic regurgitation. Most commonly, aortic root dilation results from cystic medial necrosis associated with Marfan syndrome, or it occurs in association with a bicuspid aortic value. Chronic aortic regurgitation is generally well tolerated during pregnancy, especially in patients with preserved left ventricular ejection fraction.[187,188] The physiologic changes of pregnancy (increased heart rate resulting in a shorter duration of diastole, as well as reduced SVR) contribute to an overall reduction in regurgitant aortic flow.

Although patients with chronic aortic regurgitation can compensate for the hemodynamic stress over time, patients with acute aortic regurgitation are frequently very ill and may require surgery. Endocarditis is the most common etiology of acute aortic regurgitation during pregnancy. Ascending aortic dissection may also result in severe acute aortic regurgitation. Affected patients may require valve replacement during pregnancy.

Anesthetic Management

The goals of anesthetic management are (1) maintenance of a normal to slightly elevated heart rate, (2) prevention of an increase in SVR, (3) avoidance of aortocaval compression, and (4) avoidance of myocardial depression during general anesthesia (see Table 42-2).

Antepartum echocardiography may guide decisions regarding the choice of anesthesia and monitoring. Patients with chronic, compensated aortic insufficiency and normal ejection fraction tolerate the hemodynamic changes of pregnancy well; however, patients with left ventricular dysfunction will likely require careful assessment of volume status and pulmonary artery pressures during labor and delivery. Traditionally, a pulmonary artery catheter has been used for this purpose. In the future, transthoracic echocardiography will likely be used for this purpose.

The degree of aortic insufficiency, concomitant involvement of the mitral valve, and the size of the aortic root help define hemodynamic goals. Patients with a bicuspid aortic valve may have simultaneous aortic stenosis and aortic regurgitation. Both neuraxial analgesia/anesthesia and general anesthesia can be safely performed in patients with aortic regurgitation and preserved left ventricular ejection fraction. Severe aortic insufficiency with left ventricular dysfunction is not a contraindication for neuraxial anesthesia. Initiation of neuraxial analgesia during early labor may mitigate pain-associated increases in SVR that can be deleterious in patients with aortic regurgitation. Intra-aortic balloon pump placement is contraindicated in patients with aortic regurgitation because its use increases regurgitant flow.

Mitral Stenosis

Mitral stenosis frequently becomes symptomatic during pregnancy owing to the increase in maternal blood volume and heart rate. Increased blood volume with decreased diastolic filling time can result in pulmonary edema. Additionally, mitral stenosis predisposes patients to development of atrial tachyarrhythmias (atrial fibrillation, atrial flutter) as well as thromboembolic complications, with or without atrial arrhythmias. The underlying hypercoagulable state of pregnancy also increases the risk for thromboembolic complications in patients with mitral stenosis. Therefore, systemic anticoagulation is recommended for the duration of pregnancy and postpartum.

The etiology of mitral stenosis is almost invariably rheumatic.[175,189] Severe mitral stenosis is defined as a valve area less than 1.0 cm^2 (see Table 42-4). In addition to valve area, a mean value gradient of greater than 10 mm Hg and a mean PAP greater than 50 mm Hg are used to define severe mitral stenosis. Transmitral valve gradients measured by echocardiography increase during pregnancy.[190]

Poor functional status NYHA (e.g., III to IV) portends a greater risk for adverse outcomes.[60,191,192] When possible, preconception treatment of symptomatic moderate or severe mitral stenosis is preferred.[38,60] The procedure of choice is percutaneous balloon mitral valvuloplasty. Suitability for percutaneous balloon valvuloplasty is determined by an echocardiography-based scoring system, which takes into account valve calcification and mobility as well as valvular and subvalvular thickening.[193]

For patients who require percutaneous valvuloplasty during pregnancy, the procedure is ideally performed after 12 to 14 weeks' gestation to minimize fetal radiation exposure during the period of organogenesis. If the patient can be stabilized with medical management, delaying the procedure to 26 to 30 weeks' gestation will reduce the risk for preterm birth. Open surgical mitral valve commissurotomy is associated with higher rates of fetal mortality than percutaneous valvuloplasty (38% versus 5%).[194]

Standard medical therapy during pregnancy includes a reduction in activity level (e.g., bed rest), beta-adrenergic receptor antagonist and diuretic therapy, and anticoagulation.

Obstetric and Anesthetic Management

Cesarean delivery is typically reserved for obstetric indications. Vaginal delivery is usually assisted, because the Valsalva maneuver during the second stage of labor may result in a sudden increase in central venous pressure. Regardless of the method of delivery, patients are at risk for hemodynamic compromise and pulmonary edema immediately after delivery because uterine contraction results in autotransfusion.[195] Therefore, these patients usually require postpartum intensive care.

Neuraxial analgesia/anesthesia for labor and vaginal or cesarean delivery can be safely performed in patients with mitral stenosis.[189,196] The important anesthetic goals are (1) maintenance of a low-normal heart rate and preservation of sinus rhythm; (2) aggressive treatment of atrial fibrillation, if present; (3) avoidance of aortocaval compression; (4) maintenance of venous return; (5) maintenance of adequate SVR; and (6) prevention of pain, hypoxemia, hypercarbia, and acidosis, which may increase pulmonary vascular resistance (see Table 42-2).

Parturients with mitral stenosis are at risk for both intrapartum and postpartum hemodynamic compromise and pulmonary edema. Invasive hemodynamic monitoring is often helpful, and close peripartum monitoring of filling pressures is important. Echocardiographic assessment of right-sided pressures appears to somewhat overestimate true pressures; therefore, in selected patients with severe mitral stenosis, a pulmonary artery catheter may help guide fluid management. The decision to place a pulmonary artery catheter should be guided by assessment of NYHA functional status, right ventricular function, pulmonary artery pressure, and severity of symptoms related to mitral stenosis before pregnancy.

Adequate analgesia during the first stage of labor is essential. Intrathecal administration of a lipid-soluble opioid during the first stage of labor provides excellent analgesia without causing sympathetic blockade. Neuraxial administration of an opioid with a small dose of local anesthetic may provide satisfactory analgesia for the second stage of labor. Hypotension should be treated with a direct-acting vasoconstrictor (phenylephrine).

Neuraxial anesthesia for cesarean delivery is best administered with a titratable technique (epidural anesthesia, sequential combined spinal-epidural anesthesia), judicious intravenous fluid administration, and titration of phenylephrine to maintain hemodynamic stability. During induction and maintenance of general anesthesia, tachycardia should be prevented by administration of a beta-adrenergic receptor antagonist and/or an opioid. After delivery, care should be taken with the administration of the uterotonic agent 15-methyl prostaglandin-F_{2a}, because it may increase pulmonary vascular resistance.

Mitral Regurgitation

Mitral regurgitation is generally well tolerated during pregnancy. Nonetheless, some evidence suggests that the volume overload associated with pregnancy may induce unfavorable structural alterations in women with mitral regurgitation.[197] Both neuraxial and general anesthesia are well tolerated. Chronic mitral regurgitation may be associated with left ventricular dysfunction; thus, echocardiographic assessment of left ventricular function helps guide anesthetic and fluid management. The goals of anesthetic management in patients with mitral regurgitation include (1) prevention of an increase in SVR, (2) maintenance of a normal to slightly increased heart rate, (3) maintenance of sinus rhythm, (4) aggressive treatment of acute atrial fibrillation, (5) avoidance of aortocaval compression, (6) maintenance of venous return, (7) prevention of an increase in central venous volume, (8) avoidance of myocardial depression during general anesthesia, and (9) prevention of pain, hypoxemia, hypercarbia, and acidosis, which may increase pulmonary vascular resistance (see Table 42-2).

Mitral Valve Prolapse Syndrome

Historically, prior to the contemporary understanding of the complex three-dimensional echocardiographic anatomy of the mitral valve, mitral valve prolapse tended to be overdiagnosed. Currently, the term *mitral valve prolapse* should be restricted to conditions in which the free margin of the anterior, posterior, or both leaflets of the mitral valve is displaced superior to the annular plane of the mitral valve.[198] With these diagnostic criteria, the prevalence of mitral valve prolapse in the general population is 2% to 3%, with no female preponderance.[199] Mitral valve prolapse is a heterogeneous disorder with various causes and associations, including familial and degenerative or myxomatous disorders, Marfan syndrome, Ehlers-Danlos syndrome, a redundant papillary chordal apparatus, and many other diseases.[200] Varying degrees of mitral regurgitation can be associated with this condition. There is some overlap between the strictly defined mitral valve prolapse syndrome and mitral regurgitation. Therefore, along with history and physical examination, echocardiography plays a central role in the diagnosis, treatment, and ongoing assessment of these patients.

The overall clinical course in patients with mitral valve prolapse is excellent.[201] Pregnancy and vaginal or cesarean delivery with either neuraxial or general anesthesia are well tolerated. Patients with moderate or severe mitral regurgitation and/or depressed left ventricular function are at increased risk for morbidity and mortality.[202] The recommendations for anesthetic management of parturients with mitral regurgitation and/or left ventricular dysfunction also apply to patients with these conditions associated with mitral value prolapse. Antibiotic endocarditis prophylaxis is not recommended.[127]

Tricuspid Stenosis and Regurgitation

Rheumatic **tricuspid stenosis** is rarely encountered in pregnancy; most frequently, it accompanies rheumatic mitral stenosis. Clinically, it is associated with dyspnea, pulmonary hypertension, and congestive heart failure. Successful treatment with balloon valvuloplasty has been described.

Tricuspid regurgitation is rarely found in isolation during pregnancy. Functional tricuspid regurgitation is often observed in normal pregnancy with little clinical consequence. Severe tricuspid regurgitation is often associated with congenital heart disease such as Ebstein's anomaly. Overall, pregnancy is well tolerated in the presence of tricuspid regurgitation. Affected patients may be susceptible to hypotension with a decrease in preload.[60]

Pulmonic Stenosis and Regurgitation

Pregnancy is well tolerated in patients with **pulmonic stenosis**, and isolated pulmonic stenosis has not been found to affect maternal and fetal outcomes[203] (see Table 42-2). In a small series of cases, affected patients had normal right ventricular function and only mild symptoms on initial presentation.[203] Nonetheless, valvuloplasty is recommended in asymptomatic nonpregnant patients with pulmonic stenosis and a transpulmonic valve gradient greater than 40 mm Hg and in symptomatic nonpregnant patients with a gradient greater than 30 mm Hg.[60]

Pulmonic regurgitation occurs infrequently as an isolated valvular lesion; it is most commonly associated with congenital heart disease, such as repaired tetralogy of Fallot[100] or repaired pulmonic stenosis. Physiologic pulmonic regurgitation is commonly seen during pregnancy.[204] Overall, pregnancy and labor are well tolerated in the presence of mild or moderate pulmonic regurgitation; however, severe pulmonic regurgitation is highly associated with maternal cardiac events during pregnancy.[205,206] Right-sided heart failure due to pulmonic regurgitation occurs more commonly in patients with multiple gestation, pulmonary artery stenosis distal to the left and right pulmonary arteries, preexisting right ventricular systolic dysfunction, and/or right ventricular hypertrophy.[206]

Prosthetic Heart Valves

Bioprosthetic Valves

The advantage of bioprosthetic valves is that long-term systemic anticoagulation is not required. It is unclear whether pregnancy, with its associated cardiovascular changes, accelerates bioprosthetic valve structural degeneration. Several studies observed complications related to valve deterioration, most of which required reoperation during pregnancy or shortly after delivery.[207-211] Other studies reported little or no impact of pregnancy on valve structural deterioration.[212-216] Hence, although a bioprosthetic valve simplifies the required anticoagulant regimen during pregnancy, it may expose the mother to a high risk for reoperation and associated operative mortality (ranging from 3.8%[213] to 8.7%[217]). The 10-year incidence of valve replacement or valve-related death ranges from 50% to 80% in young women of childbearing age.[213,215,217] The risk for valve failure appears higher in the mitral position than in the aortic position.[215] Bioprosthetic homografts appear to be more durable than heterografts. Autografts have a better hemodynamic profile than heterografts.

Anticoagulation for Patients with a Mechanical Valve

All patients with a mechanical valve require systemic anticoagulation. Mechanical valves have a higher risk for thromboembolism than bioprosthetic valves. Valves in the mitral position have a higher risk for thromboembolism than valves in the aortic position. A higher risk for mechanical valve thromboembolic complications has been observed during pregnancy.[218] No large prospective randomized trials have examined the use of various anticoagulation strategies for pregnant women with a mechanical valve. Additionally, newer prosthetic valve designs may have a lower risk for thromboembolism than older models. The current anticoagulation recommendations are based on expert consensus guidelines from three major professional organizations: the ACC/AHA,[60] the American College of Chest Physicians (ACCP),[173,219] and

the European Society of Cardiology (ESC).[38] Differences among these guidelines are summarized in Table 42-5.

Warfarin. In patients with a mechanical valve, anticoagulation with warfarin is associated with lower rates of thromboembolic complications and maternal death than is heparin.[220] Warfarin crosses the placenta. Use of warfarin between 6 and 12 weeks' gestation has been associated with embryopathy; therefore, consensus guidelines have recommended substitution with unfractionated heparin or LMWH during this period.[220] Additionally, the use of warfarin at any time during pregnancy has been associated with fetal wasting, central nervous system abnormalities, and fetal hemorrhagic complications.[173]

Warfarin anticoagulation effect is monitored by periodic assessment of the international normalized ratio (INR). Low-dose aspirin may be safely administered in addition to warfarin. Warfarin should be discontinued before delivery; in patients with a mechanical heart valve, heparin must be substituted.

Warfarin anticoagulation should be stopped for 4 to 5 days and the INR measured immediately before administration of a neuraxial block (see Chapter 44). Concurrent administration of other anticoagulants or antiplatelet agents increases the risk for bleeding complications. After delivery, patients with a mechanical valve typically require bridging to warfarin; the type of anesthesia and timing of neuraxial catheter removal may significantly affect the timing of anticoagulation after delivery.[43,44]

Unfractionated Heparin. Unfractionated heparin does not cross the placenta and therefore is safer for the fetus than warfarin. However, use of unfractionated heparin in the first trimester and close to term has been associated with an increased risk for valve thrombosis.[220] Unfractionated heparin can be administered subcutaneously or as a continuous intravenous infusion. Its therapeutic efficacy is monitored with the aPTT. Heparin requirements are higher during pregnancy due to underlying physiologic changes (e.g., increased levels of heparin-binding proteins, factor VIII, fibrinogen). The incidence of heparin-induced thrombocytopenia is three times higher in women than in men.

Intravenous unfractionated heparin should be discontinued 4 to 6 hours before administration of a neuraxial anesthetic technique or anticipated delivery (see Chapter 44).[43] The aPTT should be determined to verify normalization of coagulation function, and a platelet count should be checked to rule out heparin-induced thrombocytopenia. An indwelling neuraxial catheter can be removed 2 to 4 hours after the last dose of unfractionated heparin. Unfractionated heparin can be restarted 1 hour after removal of a neuraxial catheter.

Low-Molecular-Weight Heparin. LMWH does not cross the placenta and is administered subcutaneously for most indications. The pharmacokinetics of LMWH are altered in pregnancy. Use of LMWH for thromboprophylaxis during pregnancy has been associated with mechanical valve thrombosis.[221-224] The efficacy of LMWH can be monitored with anti–factor Xa levels. *Peak* anti–factor Xa levels should be checked 4 to 6 hours after LMWH administration in pregnant women with a mechanical valve. Importantly, in pregnant women with a mechanical valve, the required doses of LMWH are considered *therapeutic* and are therefore higher than those required for deep vein thrombosis prophylaxis. Additional monitoring of trough anti–factor Xa levels may allow further refinement of management. In the absence of anti–factor Xa monitoring, therapeutic use of LMWH in pregnant women with a mechanical valve is not advisable.[38]

A neuraxial block should not be performed until at least 24 hours have elapsed after the last dose of LMWH. Anti–factor Xa levels do not predict the risk for bleeding. Other anticoagulants or antiplatelet agents coadministered with LMWH increase the risk for bleeding complications. After delivery, LMWH should not be administered until at least 24 hours have elapsed after performance of the neuraxial block procedure (see Chapter 44).[43] After removal of a neuraxial catheter, at least 4 hours should elapse before administration of the next dose of LMWH (see Table 42-5).

New Anticoagulants. There are no published reports of the use of new oral anticoagulants in pregnancy. Therefore, use of oral **direct thrombin inhibitors** (dabigatran) or oral **anti–factor Xa inhibitors** (apixiban, rivaroxaban) cannot be recommended during pregnancy.

There are no published reports of the administration of **bivalirudin** during pregnancy; the use of **argatroban** during pregnancy has been described.[225] The current ASRA guidelines recommend against neuraxial anesthesia administration in patients receiving direct thrombin inhibitors.[43]

Neuraxial Anesthesia in Patients with a Mechanical Valve. No published observational or prospective randomized trials have investigated the use of neuraxial anesthetic techniques in patients with a mechanical heart valve who require systemic anticoagulation. Therefore, current clinical practice is guided by consensus guidelines.[43,44,226,227] Systemic anticoagulation may affect the choice and timing of anesthesia, and the neuraxial anesthetic technique and timing of catheter removal may influence the choice and timing of resumption of systemic anticoagulation after vaginal or cesarean delivery. Therapeutic anticoagulation is usually not resumed for at least 12 hours *after* delivery. The choice and timing of the anesthetic technique should be developed in discussion with the patient, the cardiologist, and the obstetrician, with consideration of consensus guidelines (see Table 39-4).

CARDIOMYOPATHIES

Heart Failure Nomenclature

Accurate description of patients with heart failure is important for diagnostic, therapeutic, and prognostic purposes. It is helpful to broadly describe symptoms of heart *failure* as **new-onset (acute)** or **chronic**. **Acute-on-chronic** heart failure describes patients with

TABLE 42-5 **Major Professional Society Guidelines for Anticoagulation in Pregnant Patients with Mechanical Valve(s)**

	American College of Cardiology/American Heart Association*	European Society of Cardiology†	American College of Chest Physicians‡
Warfarin	May discontinue warfarin at 6-12 weeks' gestation per patient preference and substitute UFH or LMWH	May consider continuing low-dose warfarin (< 5 mg daily) throughout pregnancy with informed patient consent	UFH or LMWH until 13 weeks' gestation, then warfarin In high-risk patients (older generation valves in mitral position, previous thromboembolism) continue warfarin throughout pregnancy
INR goal	Aortic and mitral valve: 3.0 (range, 2.5-3.5)	No recommendation	Aortic valve: 2.5 (range, 2.0-3.0) Mitral valve: 3.0 (range, 2.5-3.5)
Unfractionated heparin	Continuous infusion or dose-adjusted subcutaneous administration twice daily	In high-risk patients, continuous infusion	Subcutaneous administration twice daily
aPTT goal	aPTT 6 h after subcutaneous injection: twice control value	aPTT 4-6 h after subcutaneous injection: twice control value	Mid-interval aPTT (6 h after injection): twice control or anti–factor Xa level of 0.35-0.70 U/mL
Low-molecular-weight heparin	Subcutaneous administration twice daily	Subcutaneous administration twice daily	May give adjusted dose of LMWH throughout pregnancy, twice daily
Anti–factor Xa level goal	Maintain peak level 0.7-1.2 U/mL 4-6 h after administration	Maintain peak level 0.8-1.2 U/mL 4-6 h after administration	Maintain manufacturer's recommended peak anti–factor Xa level (approximately 1.0 U/mL) 4 h after administration
Aspirin	Low-dose aspirin (75-100 mg daily) reasonable in second and third trimesters in addition to warfarin or heparin	Not recommended	Low-dose aspirin (75-100 mg daily) added to thromboprophylactic regimen for patients with valves at high risk for thromboembolism
Peripartum§	Discontinue warfarin 2-3 weeks before planned delivery and start continuous intravenous UFH	Discontinue warfarin at 36 weeks' gestation and start dose-adjusted UFH or LMWH. Replace LWMH at least 36 h before planned delivery and substitute with UFH. Discontinue UFH 4-6 h before planned delivery	Discontinue warfarin close to delivery; replace with UFH or LMWH

aPTT, activated partial thromboplastin time; *INR,* international normalized ratio; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

*Modified from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines J Am Coll Cardiol 2008; 52:e1-142.

†Modified from Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011; 32:3147-97.

‡Modified from Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e691S-736S and Whitlock RP, Sun JC, Fremes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e576S-600S.

§For resumption of anticoagulation in the postoperative period, the 2010 American Society of Regional Anesthesia and Pain Medicine Practice Advisory[43] recommends the following: (1) Warfarin: The indwelling neuraxial catheter should be removed when the INR is less than 1.5. (2) UFH: The indwelling neuraxial catheter should be removed 2 to 4 hours after the last dose of UFH, after checking the patient's coagulation status (aPTT). The next dose of UFH should not be given until at least 1 hour has elapsed after removal of the catheter. (3) LMWH: The first therapeutic dose should not be administered until 24 hours after the initiation of the neuraxial procedure and until at least 2 hours after removal of the indwelling neuraxial catheter. The U.S. Food and Drug Administration recommends waiting at least 4 hours after removal of a neuraxial catheter before administering a postprocedure dose of LMWH. (U.S. Food and Drug Administration. *Low Molecular Weight Heparins: Drug Safety Communication—Recommendations to Decrease Risk of Spinal Column Bleeding and Paralysis. November 6, 2013.* Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm373918.htm. Accessed November 2013.)

worsening symptoms after an earlier diagnosis of heart failure.

Heart failure can be separated into **left sided** (predominantly pulmonary congestion and pulmonary edema) and **right sided** (predominantly peripheral edema). **Biventricular** heart failure describes symptoms that result from both right and left ventricular involvement.

Assessment of ventricular function allows for differentiation between **systolic** and **diastolic** heart *dysfunction*. Arbitrarily, left ventricular dysfunction is defined by a left ventricular ejection fraction less than 45% to 50%.

Left ventricular systolic dysfunction (decreased ejection fraction) is not synonymous with left-sided heart failure because patients may be largely asymptomatic, even with left ventricular ejection fraction less than 30%. Similarly, diastolic dysfunction is not synonymous with diastolic heart failure. Diastolic heart failure is more accurately described as **heart failure with preserved ejection fraction (HFpEF)**.

The NYHA classification describes patients' *functional status* (see Box 42-1), and the functional status can change over time. In contrast, the *staging classification* of heart failure recognizes that heart failure is a progressive condition and may manifest as variable symptoms over time.[34,228] Both classifications remain highly useful in clinical practice.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a unique cardiomyopathy of unknown cause that occurs during pregnancy or the postpartum period.[229-231] The *timing* of development of heart failure is important to help exclude other causes of heart failure. To make the diagnosis of peripartum cardiomyopathy, the development of heart failure should occur in the last month of pregnancy or within 5 months of delivery (Box 42-10). Other identifiable causes of heart failure should be excluded, and the absence of other recognizable cardiac disease prior to the last month of pregnancy should be verified. Echocardiographic diagnostic criteria include (1) left ventricular ejection fraction less than 45% (and/or M-mode fractional shortening < 30%) and (2) end-diastolic left ventricular dimension greater than 27 mm/m^2 body surface area.[232] Some women develop cardiomyopathy before the last month of pregnancy. This condition is referred to as *pregnancy-associated cardiomyopathy*. Its clinical signs, symptoms, and outcomes are similar to those for peripartum cardiomyopathy.[233]

BOX 42-10 Diagnostic Criteria for Peripartum Cardiomyopathy

Traditional Criteria

- Onset of heart failure during the last month of pregnancy or within 5 months of delivery
- No other identifiable cause of heart failure
- No known heart disease before pregnancy

Echocardiographic Criteria

- Left ventricular ejection fraction < 45%
- Fractional shortening < 30%
- Left ventricular end-diastolic volume ≥ 27 mm/m^2

Modified from Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA 2000; 283:1183-88; and Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol 1999; 94:311-6.

The incidence of peripartum cardiomyopathy varies around the world and has been reported to be as high as 1 in 300 live births in Haiti[234] and 1 per 3000 to 4000 live births in the United States.[229,235] The cause(s) for such regional variation are unclear. Risk factors for peripartum cardiomyopathy include African race, multiparity, multiple gestation, preeclampsia, gestational hypertension, use of tocolytic agents, cocaine abuse, and age older than 30 years.

The etiology of this relatively rare condition remains unclear; several possible causes have been proposed, including underlying myocarditis, apoptosis, inflammation, pathologic maternal immune response to fetal antigens, effects of prolactin, viral triggers, and hereditary/familial factors.

Patients with peripartum cardiomyopathy have typical signs and symptoms of systolic heart failure. On clinical examination, the apical impulse is displaced laterally and an S3 gallop is appreciated. Because of left ventricular enlargement (Figure 42-6) and changes in ventricular cavity geometry, functional mitral regurgitation is frequently seen. Peripartum cardiomyopathy is primarily a diagnosis of exclusion, and the symptoms may be disguised as physiologic changes of pregnancy; thus, the use of echocardiography helps confirm the diagnosis. Right-sided heart pressures can almost always be assessed by echocardiography; hence, right-sided heart catheterization is rarely necessary. Left-sided heart catheterization may be necessary to assess the coronary arteries. However, given that the risk for ischemic cardiomyopathy in pregnancy is very low, and because coronary angiography results in fetal radiation exposure, left-sided heart catheterization is infrequently used to make the diagnosis. Ischemic cardiomyopathy is typically accompanied by regional wall motion abnormalities, whereas peripartum or nonischemic cardiomyopathy typically results in a global decrease in contractility.

Medical management of peripartum cardiomyopathy rests on basic treatment paradigms for congestive heart failure and dilated cardiomyopathy (see later discussion). Compared with other forms of nonischemic cardiomyopathy (e.g., infiltrative or HIV-related), peripartum cardiomyopathy has a better prognosis, with a 94% 5-year survival rate in the United States.[236] Recovery of left ventricular function occurs in slightly more than half of the affected women.[233] Black women are 6.4 times more likely to die of peripartum cardiomyopathy than white women. In contrast, in Haiti the 2-year mortality is 15.4% and only a fourth of the patients experience normalization of left ventricular function.[234]

The risk for subsequent pregnancy is substantially higher in women who do not recover normal left ventricular function.[237] In a series of 44 women with peripartum cardiomyopathy, the maternal mortality rate in subsequent pregnancies was 19% in women with

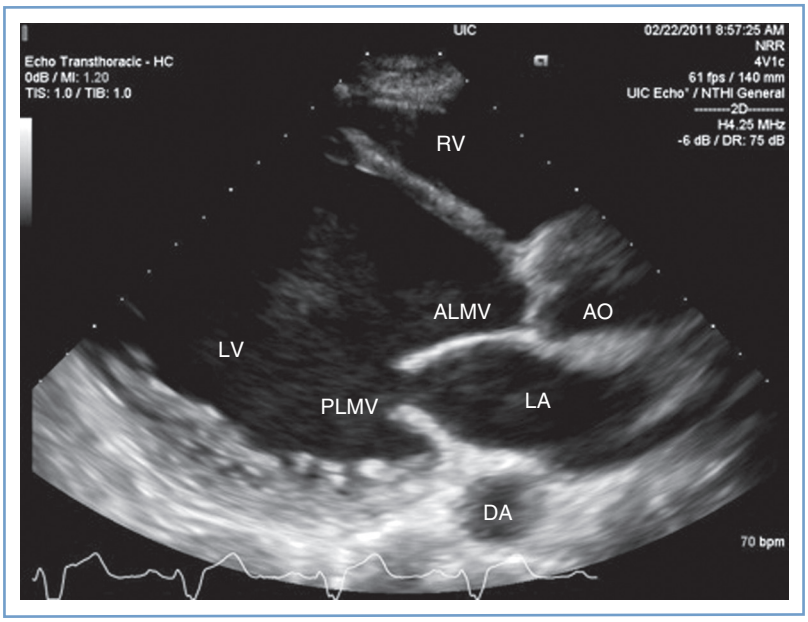

FIGURE 42-6 ■ Echocardiographic image of dilated cardiomyopathy. *RV,* right ventricle; *LA,* left atrium; *LV,* left ventricle; *ALMV,* anterior leaflet of the mitral valve; *PLMV,* posterior leaflet of the mitral valve; *AO,* aorta; *DA,* descending aorta. (Courtesy Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)

persistent left ventricular dysfunction compared with 0% in women without residual dysfunction.[237] Therefore, subsequent pregnancy should be discouraged if left ventricular function has not recovered. Even in patients with normalized left ventricular function, careful counseling is advised owing to a significant risk for recurrence of left ventricular dysfunction in a subsequent pregnancy.[38]

Obstetric and Anesthetic Management

Obstetric management involves expedient delivery after stabilization of the mother; in most cases, cesarean delivery is reserved for obstetric indications. Continuous spinal anesthesia[238] and combined spinal-epidural anesthesia[239,240] have been safely administered in patients with severe peripartum cardiomyopathy. Given the intravascular fluid shifts associated with labor, delivery, and the immediate postpartum period, invasive blood pressure and central venous pressure monitoring are recommended. Neuraxial anesthesia appears ideally suited for these patients because it results in a beneficial decrease in both preload and afterload. Particular attention should be paid to the immediate postpartum period when autotransfusion combined with the regression of neuraxial anesthesia may cause worsening of heart failure.

Other Nonischemic Cardiomyopathies

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is relatively common, with a prevalence estimated at 1 in 500. It is an autosomal dominant disorder associated with various forms of left ventricular hypertrophy; the risk that an affected patient will transmit the disease to offspring is 50%. Additionally, hypertrophic cardiomyopathy mutations are highly penetrant. Preconception genetic counseling is recommended.[154]

The complications that result from hypertrophic cardiomyopathy can be separated into two categories: mechanical and electrophysiologic. The mechanical consequences relate to left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, and development of heart failure. The electrophysiologic complications include atrial and ventricular arrhythmias and, most important, the risk for sudden cardiac death. The myocardial ischemia observed in patients with hypertrophic cardiomyopathy, often at ages younger than expected, is caused by supply-demand mismatch rather than coronary atherosclerosis. Hypertrophic cardiomyopathy is associated with disorganized myocardial architecture, myocardial disarray, and fibrosis (Figure 42-7).

One of the hallmarks of hypertrophic cardiomyopathy is the dynamic left ventricular outflow tract obstruction. The obstruction gradient typically increases after a premature ventricular contraction. One third of patients have left ventricular outflow tract obstruction at rest, one third have a physiologically provocable gradient, and one third have no gradient (nonobstructive form of hypertrophic cardiomyopathy). A gradient of 30 mm Hg or more is clinically significant.[241]

Pregnant women with hypertrophic cardiomyopathy may have dyspnea, fatigue, angina, palpitations, and/or syncope. Symptoms of congestive heart failure are rarely seen in patients in sinus rhythm; these symptoms are more frequently encountered when atrial fibrillation is present.

On physical examination the classic obstructive systolic murmur is heard at the apex (grade 3 to 4/6), and it radiates to the left sternal border. Although most patients will have a displaced and forceful left ventricular impulse, the presence of a murmur depends on the degree and

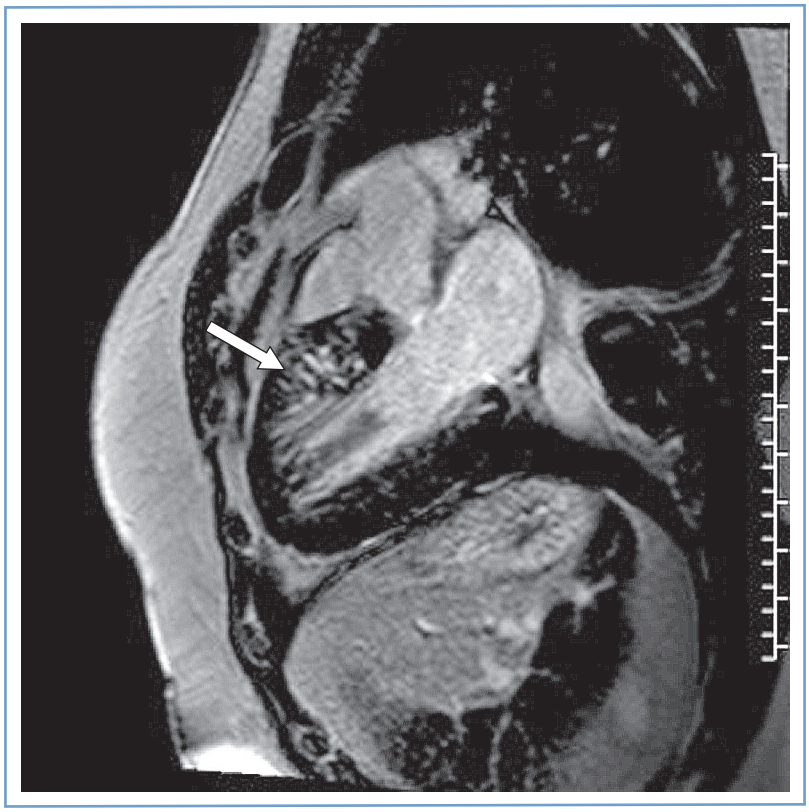

FIGURE 42-7 ■ Cardiac magnetic resonance image of hypertrophic cardiomyopathy with myocardial scar. Arrow shows scar with delayed enhancement with gadolinium in the hypertrophied myocardium. (Courtesy Dr. Afshin Farzaneh-Far, University of Illinois at Chicago, Chicago, IL.)

type of obstruction. The intensity of a hypertrophic cardiomyopathy murmur increases with a Valsalva maneuver or standing (decreased preload or afterload causes more obstruction), and it decreases with squatting (increased afterload causes less obstruction). Invasive arterial pressure monitoring allows recognition of a *bifid* arterial pulse waveform.

The ECG is abnormal in the vast majority of patients and demonstrates an increase in voltage, T-wave inversions, and pathologic Q waves. ECG abnormalities correlate poorly with the severity of hypertrophic cardiomyopathy.[155] Transthoracic echocardiography is indispensable for making the diagnosis, determining prognosis, and guiding management decisions.[154] Diagnostic criteria include a septal thickness greater than 15 mm and an increased septal-to-posterior wall thickness ratio (1.3). Systolic anterior motion of the mitral valve has a specificity of 98% for hypertrophic cardiomyopathy. Left ventricular outflow tract obstruction is apparent during Doppler interrogation; the continuous wave tracing has a classic "dagger-shaped" contour (Figure 42-8). In addition, echocardiography allows identification of various morphologic variants and assessment of the extent of hypertrophy. A wall thickness of 30 mm or greater is associated with a high risk for sudden cardiac death.[242] Patients with a gradient of 50 mm Hg or greater are at highest risk for complications.[154]

Fortuitously, the increase in blood volume allows most patients with hypertrophic cardiomyopathy to tolerate pregnancy well.[156,243,244] Both asymptomatic and symptomatic women with hypertrophic cardiomyopathy should continue taking a beta-adrenergic receptor antagonist throughout pregnancy and the peripartum period.[154]

Patients with hypertrophic cardiomyopathy are at increased risk for developing atrial fibrillation. Treatment of atrial fibrillation rests on rate and rhythm control as well as systemic anticoagulation to prevent thromboembolic stroke. Rate control can alleviate symptoms; beta-adrenergic receptor antagonists and nondihydropyridine calcium entry–blocking agents (e.g., verapamil, diltiazem) provide best results. Digoxin is less effective in controlling rate and may be harmful in patients with hypertrophic cardiomyopathy in the absence of atrial fibrillation.[154] Amiodarone can be successfully used for rate control in patients with hypertrophic cardiomyopathy. Rhythm control can be attempted pharmacologically with amiodarone and sotalol. In patients with a rapid ventricular response and significant hemodynamic compromise, electric cardioversion should be performed.

Obstetric and Anesthetic Management. Traditionally, general anesthesia has been considered the anesthetic technique of choice for parturients with hypertrophic cardiomyopathy.[245-249] It avoids a precipitous decrease in preload, and the negative inotropic effect of inhalation anesthetic agents may help reduce the degree of dynamic obstruction (see Table 42-2). No prospective controlled trials have compared general anesthesia with neuraxial anesthesia in parturients with hypertrophic cardiomyopathy; numerous case reports have described

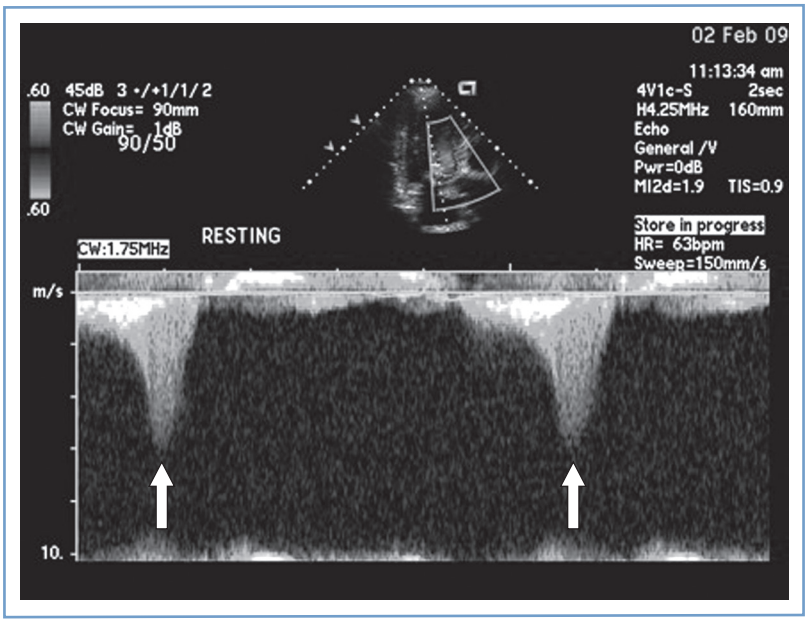

FIGURE 42-8 ■ Dynamic left ventricular outflow obstruction in hypertrophic cardiomyopathy. Continuous wave Doppler tracing in left ventricular outflow tract displays typical late-peaking ("dagger-shaped") contour of dynamic outflow obstruction (*arrows*). (Courtesy Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)

successful use of neuraxial anesthesia in these patients.[250-257] Given that hypertrophic cardiomyopathy is a heterogeneous condition, and given the high likelihood of selection and publication bias in these case reports, it is difficult to make generalized recommendations for these patients. In deciding whether to administer general or neuraxial anesthesia, it is important to recognize the degree of left ventricular outflow tract obstruction. For cesarean delivery, it appears reasonable to recommend general anesthesia for patients with a gradient of 50 mm Hg or greater or for those with symptoms of heart failure during pregnancy. In asymptomatic parturients with a lower gradient, slowly titrated neuraxial analgesia/anesthesia appears safe.

Because a decrease in preload is expected to increase the degree of left ventricular outflow tract obstruction, central venous pressure monitoring seems reasonable. Similarly, invasive arterial blood pressure monitoring may be helpful. Transthoracic echocardiography facilitates assessment of intravascular volume. Beta-adrenergic receptor antagonists decrease myocardial contractility and decrease the severity of left ventricular outflow tract obstruction. Phenylephrine is the drug of choice for the treatment of hypotension. Inotropic agents (e.g., dopamine, dobutamine) may be harmful in these patients.[154] Rapid administration of intravenous oxytocin has been associated with hypotension; slow administration is therefore recommended.

Stress-Induced Cardiomyopathy

Stress-induced cardiomyopathy, also known as *takotsubo cardiomyopathy*, *broken heart syndrome*, or *apical ballooning syndrome*, is a transient cardiomyopathy with typical left ventricular systolic dysfunction of the apical and midcavity segments.[258] The basal ventricular segments are frequently hyperkinetic and may cause left ventricular outflow tract obstruction. Affected patients typically do not have underlying coronary artery disease. Stress-induced cardiomyopathy occurs predominantly in postmenopausal women in the seventh and eight decades of life and is frequently associated with emotional and physical stressors. It has also been described during pregnancy in the setting of emotional and physical triggers, postpartum depression, and administration of pharmacologic triggers such as ergot alkaloids. It has been reported in the absence of apparent triggers[259] during otherwise uncomplicated spinal anesthesia for cesarean delivery.[260,261]

Clinically, patients have chest pain, dyspnea, and symptoms of left ventricular systolic dysfunction and heart failure. ECG abnormalities are frequently observed in left precordial leads and may mimic STEMI due to plaque rupture. Coronary angiography is required to rule out STEMI; ventriculography or echocardiography allows recognition and characterization of wall motion abnormalities. The most critical differential diagnoses are STEMI and peripartum cardiomyopathy. When treating patients who develop shock, it is critically important to determine the degree of left ventricular outflow tract obstruction. Shock without left ventricular outflow tract obstruction can be treated in standard fashion with an inotropic agent. Patients with left ventricular outflow tract obstruction require optimization of intravascular volume and administration of a beta-adrenergic receptor antagonist; use of an intra-aortic balloon pump may be necessary to relieve the obstruction.

Dilated and Other Cardiomyopathies

In women with **idiopathic** or **anthracycline-induced cardiomyopathy,** pregnancy is associated with a high risk for adverse maternal, fetal, and neonatal outcomes.

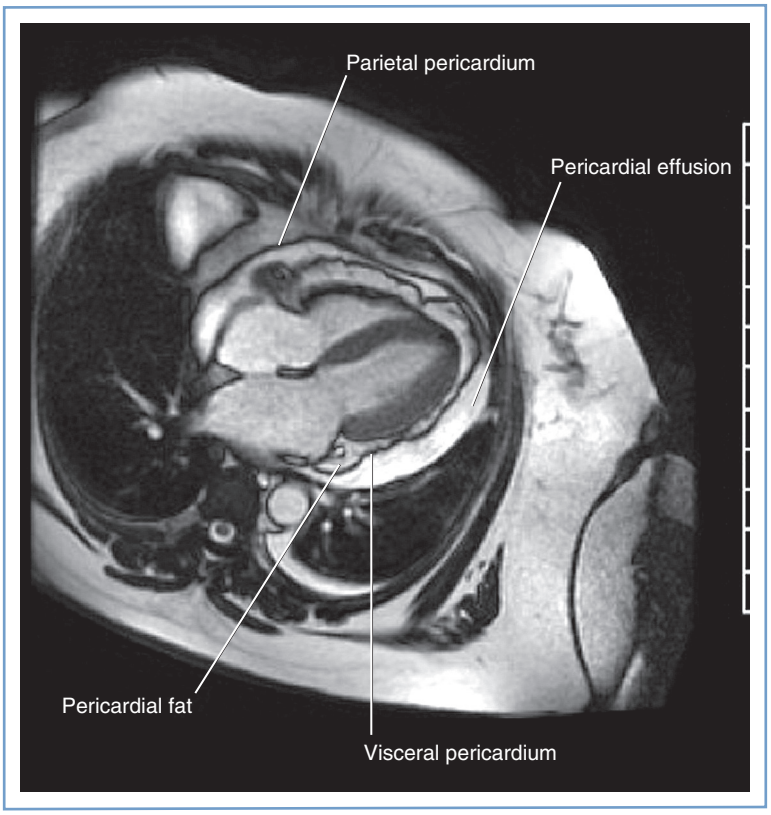

FIGURE 42-9 ■ Cardiac magnetic resonance image of pericardial effusion. (Courtesy Dr. Afshin Farzaneh-Far, University of Illinois at Chicago, Chicago, IL.)

Pregnancy appears to unfavorably affect the short-term course of these cardiomyopathies. The NYHA functional status and ejection fraction may predict outcomes in this population.[262] Other causes of cardiomyopathy during pregnancy include **cocaine abuse** and **hemochromatosis**; the latter results in an infiltrative cardiomyopathy.

Rapid atrial or ventricular rates due to arrhythmia can cause **tachycardia-induced cardiomyopathy**. This cardiomyopathy is a potentially reversible condition that has been described in pregnancy[263] and successfully treated with radiofrequency ablation.[264,265] Differentiation from other forms of cardiomyopathy may be difficult, but it is important from a prognostic standpoint.

Medical Management of Heart Failure

Principles of heart failure management for pregnant patients are similar to those for nonpregnant patients with two notable exceptions: angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blocking agents and aldosterone antagonists (spironolactone, eplerenone) should *not* be used in pregnant women. A beta-adrenergic receptor antagonist should be administered, and hydralazine can be substituted for ACE inhibitors/angiotensin receptor blocking agents. Digoxin use is safe in pregnancy. Loop diuretics and sodium restriction are indicated to prevent or treat volume overload. In patients with decompensated heart failure, treatment with intravenous nitroglycerin and dopamine or dobutamine is indicated.

Ventricular Assist Devices

Anecdotal reports have described ventricular assist device use during pregnancy. A successful completion of pregnancy with cesarean delivery in a patient with a ventricular assist device has been reported.[266] In another patient with myocardial infarction and subsequent severe left ventricular dysfunction, a ventricular assist device was placed, although pregnancy was not recognized at the time of placement; fetal death subsequently ensued.[267] The preconception presence of a ventricular assist device remains a contraindication to pregnancy.

PERICARDIAL DISEASE

Pericardial Effusion

Asymptomatic pericardial effusions are frequently found in otherwise healthy pregnant women (Figure 42-9). A pericardial effusion may be seen in 15% to 20% of pregnancies in the first and second trimester; this rate increases to approximately 40% in the third trimester. The effusion is seen more often in nulliparous women than in parous women.[268] These effusions are transudative and disappear within 2 months after delivery. Treatment is rarely required. Physical signs of tamponade or pulsus paradoxus are rarely seen. Similarly, electrical alternans is not seen on the ECG.

Acute Pericarditis

Pericarditis remains a clinical diagnosis confirmed by ECG and echocardiography. Patients typically have precordial pain that improves with sitting and learning forward. A pericardial friction rub may be appreciated on physical examination; this finding is frequently evanescent, and repeat examinations may be required. ECG findings consist of diffuse concave ST-segment elevations. Diffuse PR interval depression is frequently seen except in lead aVR, which demonstrates near-pathognomonic PR-interval elevation. Echocardiography may demonstrate various degrees of pericardial effusion. Importantly, the presence of a pericardial effusion is not synonymous with pericarditis because pericarditis remains a clinical diagnosis.

The etiology of acute pericarditis during pregnancy is most likely similar to that in the general population. A viral etiology is most common. Less common causes include tuberculosis, connective tissue disease (e.g., systemic lupus erythematosus), and neoplasm.

Treatment of pericarditis in the general population includes nonsteroidal anti-inflammatory drugs, glucocorticoids, colchicine, and, rarely, immunosuppressant drugs. During pregnancy, the maternal and fetal risks and benefits of these agents should be weighed carefully.

Cardiac Tamponade

Therapeutic and diagnostic pericardiocentesis or a surgical pericardial window can be safely performed during pregnancy. However, echocardiographic rather than fluoroscopic guidance is preferred because it avoids fetal radiation exposure.

Constrictive Pericarditis

Constrictive pericarditis is a condition in which a noncompliant pericardium prevents filling of the right- and left-sided heart chambers; specific hemodynamic features include equalization and elevation of both left and right ventricular diastolic pressures, preserved systolic function, and a "dip and plateau" pattern of the ventricular pressure tracing. Potential causes of constrictive pericarditis during pregnancy include previous irradiation, recurrent pericarditis due to rheumatoid arthritis, tuberculosis, and neoplasm. Patients may be asymptomatic before pregnancy; the physiologic changes of pregnancy may exacerbate the condition.

Anesthetic Management

Constrictive physiology and cardiac tamponade share some common pathophysiologic features that are important for the conduct of anesthesia (see Table 42-2). Impaired filling of the right side of the heart results from either a noncompliant pericardium (constrictive physiology) or pericardial fluid (tamponade physiology). Cardiac output is reduced by any intervention that reduces preload (e.g., aortocaval compression, sympathectomy with neuraxial anesthesia, positive-pressure ventilation with general anesthesia). Therefore, maintenance of preload is critically important; this goal can be achieved with central venous pressure monitoring, slowly titrated neuraxial anesthesia, and avoidance of positive-pressure ventilation. Invasive blood pressure monitoring is recommended.

CARDIOPULMONARY RESUSCITATION DURING PREGNANCY

Cardiac arrest during pregnancy is rare; it occurs in 1 in 20,000 to 30,000 pregnancies. Overall survival rates are poorer than expected compared with other clinical arrest scenarios.[269,270] The reversible causes of cardiac arrest during pregnancy are similar to those in nonpregnant patients. Additional causes specific to pregnancy include amniotic fluid embolism, eclampsia, placental abruption, and uterine atony (see Box 55-5).

Standard Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) principles apply to these patients. However, anatomic and physiologic changes of pregnancy require several specific modifications to the resuscitation protocol (Box 42-11; see also Box 55-5).[269] The hands performing chest compressions should be placed slightly higher on the sternum because the abdominal contents and the diaphragm are displaced cephalad during the third trimester of pregnancy. Intravenous access should be obtained above the diaphragm. In pregnant patients, aortocaval compression reduces the cardiac output that results from chest compressions. Although it is typically advised to tilt the patient 15 to 30 degrees to facilitate left uterine displacement and optimize venous return and cardiac output, such a maneuver may impede the effectiveness of chest compressions. Therefore, current guidelines advocate manual left uterine displacement rather than the usual whole-body tilt (see Figure 55-2). If this technique is not successful, a firm wedge

BOX 42-11 Modifications of Cardiopulmonary Resuscitation in Pregnancy

- Left uterine displacement (15 to 30 degrees)
- Airway
  - Consider airway edema associated with pregnancy
- Breathing
  - Be aware of the impact of decreased functional residual capacity in pregnancy
- Circulation
  - Perform chest compressions higher on the sternum than in nonpregnant patients
- Defibrillation
  - May use automated external defibrillator (AED)
  - Apply same energies as in nonpregnant patients
  - Remove all fetal monitoring probes and leads
- Drugs
  - Drugs (and doses) are the same as those used in nonpregnant patients

Modified from Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: Cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122:S829-61.

may be placed under a resuscitation board to tilt the patient approximately 30 degrees. In the field, the responder may use his or her knees to tilt the patient.

If spontaneous circulation does not return within 4 minutes of cardiac arrest, hysterotomy or cesarean delivery should be performed, with the goal of achieving delivery within 5 minutes of cardiac arrest. The primary purpose of cesarean delivery is to improve the chance of maternal survival, but timely delivery also improves the chances of infant survival.

Defibrillation should be performed based on current ACLS protocols. Transthoracic impedance is not changed during pregnancy, and the standard recommended electric energies should be used. Both cardioversion and defibrillation are considered safe at all stages of pregnancy. External and internal fetal monitoring probes and leads should be removed before defibrillation or cardioversion.

An intra-aortic balloon pump, a percutaneous left ventricular assist device, cardiopulmonary bypass, and extracorporeal membrane oxygenation have been successfully used in pregnant women with cardiac arrest; favorable outcomes have been reported. Therapeutic hypothermia has also been used after cardiac arrest during pregnancy, with successful delivery and favorable neonatal outcome.

PREGNANCY AFTER HEART TRANSPLANTATION

The first successful pregnancy in a heart transplant recipient was described in 1988. Subsequently, several reports have documented the feasibility and relative safety of pregnancy and delivery in female heart transplant recipients.[271,272] Successful patient management requires an interdisciplinary team approach.

The transplanted heart is denervated and the increase in cardiac output with pregnancy primarily results from an increase in stroke volume rather than heart rate. Because the risk for acute rejection is not increased in pregnant patients with a heart transplant, the immunosuppressant medications should be maintained at the lowest possible dose. The risk for infection is greater in patients receiving immunosuppression therapy. The AHA considers the presence of valvulopathy in heart transplant recipients a high-risk lesion for the development of bacterial endocarditis. Thus, given the unfavorable outcomes in heart transplant recipients who develop endocarditis, it appears reasonable to recommend antibiotic endocarditis prophylaxis at the time of membrane rupture for these parturients undergoing labor and vaginal delivery (see Box 42-7).[127]

Cardiac transplant vasculopathy is a disease specific to transplanted hearts; it consists of concentric and longitudinal intimal hyperplasia in the coronary arteries. In contrast, native coronary atherosclerosis manifests as focal, noncircumferential lesions. After malignancy, cardiac transplant vasculopathy constitutes the second most common cause of death 1 year after heart transplantation. Therefore, monitoring for ischemia appears prudent in these patients, especially because they may not present with classic anginal symptoms owing to denervation of the transplanted heart.

Baseline echocardiography allows assessment of ejection fraction and the presence of transplant valvulopathy. Most parturients with a heart transplant with a normal ejection fraction and normal right-sided pressures tolerate labor and delivery well; both neuraxial and general anesthesia are acceptable. Peripartum immunosuppression therapy should be managed by a multidisciplinary team.

CARDIOPULMONARY BYPASS DURING PREGNANCY

In the current era, maternal mortality associated with elective cardiopulmonary bypass during pregnancy is comparable to that for nonpregnant women.[273] Fetal mortality remains high (16% to 33%),[274-276] although some series report excellent fetal outcomes.[277] The optimal timing of cardiopulmonary bypass appears to be the second trimester of pregnancy. Procedures performed immediately after delivery and on an emergency basis appear to confer added risk for maternal mortality. The degree of hypothermia is associated with poor fetal outcome. There is no evidence that anesthesia *per se* contributes to adverse maternal or fetal outcomes in this setting.[273] The need for intraoperative FHR monitoring is universally accepted. Measures to lower fetal mortality include normothermic cardiopulmonary bypass with flow rates in excess of 2.4 L/min/m^2 while maintaining mean arterial blood pressure above 70 to 75 mm Hg. Left uterine displacement and maintenance of hematocrit greater than 28% are recommended.

KEY POINTS

- Heart disease is the primary medical cause of nonobstetric maternal mortality.
- Congenital heart disease is the cause of 60% to 80% of cases of cardiac disorders in pregnant women in developed countries such as the United States.
- The management of most forms of congenital heart disease, including Eisenmenger syndrome, rarely requires pulmonary artery catheterization.
- Intrathecal administration of a lipophilic opioid is an excellent choice of intrapartum analgesia for women who may not tolerate decreased systemic vascular resistance and decreased venous return.
- Cardiac lesions do not represent an absolute contraindication to the use of neuraxial anesthesia, assuming that the induction of anesthesia proceeds slowly and the potentially adverse hemodynamic changes are corrected promptly. Single-shot spinal anesthesia can

produce circulatory collapse in parturients with severe aortic stenosis, primary pulmonary hypertension, and Eisenmenger syndrome.

- The treatment of most arrhythmias during pregnancy is similar to that for nonpregnant women.
- When cardiopulmonary resuscitation is required during pregnancy, the standard advanced cardiac life support protocols should be used. Left uterine displacement should be employed to prevent aortocaval compression and a reduction in preload. Choice of drugs (and doses) as well as indications for defibrillation are the same as those for nonpregnant adult women. After 20 weeks' gestation, early hysterotomy and uterine evacuation may be necessary to facilitate resuscitation of the mother. Rescuers should be prepared to proceed with cesarean delivery if spontaneous circulation does not return within 4 minutes of cardiac arrest.
- Infective endocarditis prophylaxis is not recommended for vaginal or cesarean delivery except in patients with cardiac conditions at highest risk for endocarditis.

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CHAPTER 49

Neurologic and Neuromuscular Disease

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CHAPTER OUTLINE

The choice of anesthetic technique for pregnant women with neurologic disease requires knowledge of the pathophysiology of the disorder and an understanding of controversies involved in the diagnosis and management of the disease. If a patient's neurologic condition deteriorates postpartum, the cause may be unclear and the anesthetic technique may be blamed unfairly. There are limited published data on specific neurologic and neuromuscular disorders in pregnant women. However, few of these disorders contraindicate the use of neuraxial anesthesia. In most cases, the obstetrician should obtain early antepartum consultation from an anesthesiologist. Early

consultation allows accurate antepartum documentation of the extent and pattern of the neurologic deficit as well as discussion and formulation of the anesthetic plan with the patient, her obstetrician, and a neurologist or neurosurgeon.

Because patients with a wide variety of neurologic disorders will present for preoperative evaluation, the following thought process will assist the clinician with completing a proper evaluation and formulating an anesthetic plan.

What is the basic pathophysiology of the particular neurologic disorder? Neurologic disorders may be stable, progressive, or relapsing/recurrent. It is important to understand the common disease patterns. The potential for progression of the disease after delivery will depend on the pattern of progression and underlying pathophysiology and on the effect of pregnancy on disease progression.

What is the patient's history and current findings after neurologic examination? A history should include the onset date and current course of the disorder. Symptoms related to neurologic issues should be documented (e.g., seizure type and frequency, deficits after cerebrovascular events, cognitive deficits). A basic physical examination should be conducted to document existing deficit patterns, including cognitive dysfunction (e.g., ability to understand and cooperate), deficits involving vision, hearing, speech, and swallowing; respiratory symptoms; and weakness and sensory deficits in the head and neck, trunk, and extremities. Motor and sensory deficits are classified as mild, moderate, or severe, with a description of the affected area. Special attention should be directed to limitations in ambulatory ability (e.g., bed-bound, wheelchair, walking with assistance) or positioning.

What are the current treatments and what testing results are available? Documentation of medical and nonmedical therapies is essential. For some disorders (e.g., myasthenia gravis), documentation of the timing of treatment is also critical. In most cases, specific laboratory testing will not influence management and outcome. However, pulmonary function testing should be considered in patients with neurologic disorders that result in significant respiratory compromise; the findings may assist the anesthesiologist in making decisions about anesthetic management.

What is the impact of the neurologic disorder on other organ systems (e.g., cardiac, respiratory, airway)? The patient's neurologic disease may affect organ systems that are relevant to the anesthetic plan. For example, central core disease is associated with a risk for malignant hyperthermia. In addition, progressive neurologic disorders may significantly compromise the patient's respiratory status, thereby increasing the risks associated with neuraxial and general anesthesia.

What are the potential impacts, risks, or benefits of particular anesthetic options based on the disease's pathophysiology, symptoms, and treatment? Can treatment be initiated antepartum or before delivery that will improve outcome? For most rare neurologic disorders there is limited evidence on which to base decisions about anesthetic management. In these cases, the anesthesiologist should consider the disease's basic pathophysiology and its possible direct and indirect interactions with specific anesthetic techniques. Encouraging the obstetrician to send these patients for early antepartum consultation will enable the anesthesiologist to obtain formal input from a neurologist or other consultant if necessary. A multidisciplinary discussion that includes the patient may be necessary to weigh the risks and benefits of specific obstetric and anesthesia plans.

In all cases, accurate documentation of the responses to the previous questions will greatly assist the team providing analgesic or anesthetic care for these patients. Some of the more common neurologic conditions are addressed in this chapter, and the existing literature is surveyed relative to the peripartum management of these patients. This knowledge allows the anesthesiologist an opportunity to formulate a safe and rational anesthetic plan as well as enable an appropriate discussion with the patient regarding the risks and benefits of particular anesthetic options.

MULTIPLE SCLEROSIS

Multiple sclerosis is a major cause of neurologic disability in young adults. The prevalence of the disorder varies with the population. Recent data suggest that the prevalence of the disease is increasing, especially in females, and may be as high as 300 per 100,000 in some parts of North America.[1] Both environmental and genetic factors appear to play a role in the incidence and prevalence of disease.

The disease is characterized by variable neurologic disabilities with two general patterns of presentation: (1) **exacerbating remitting**, which accounts for 85% of cases, in which attacks appear abruptly and resolve over several months, and (2) **chronic progressive**, in which continued deterioration occurs over time.[2] The relapse rate varies significantly among patients, averaging approximately 0.4 attacks per year; this rate reflects the large proportion of patients with relapsing/remitting disease. The deficits tend to become more progressive and debilitating over time. Environmental factors (e.g., stress, infection, increased body temperature) may provoke a relapse. Most relapses reproduce previously experienced neurologic deficits, which can manifest as pyramidal, cerebellar, or brainstem symptoms.

The etiology remains unclear. There is a clinically significant heritable component, and alleles in the HLA locus have been identified as risk factors for multiple sclerosis.[3] Pathologic findings include inflammation and loss of myelin in the central nervous system (CNS). It is possible that the disease results from a yet undetermined combination of genetic predisposition and exposure to specific environmental factors.

The more common symptoms include motor weakness, impaired vision, ataxia, bladder and bowel dysfunction, and emotional lability. Cerebrospinal fluid (CSF) immunoglobulin and lymphocyte concentrations are increased, and magnetic resonance imaging (MRI) studies demonstrate white matter plaques. Lesions may be documented by the demonstration of prolonged evoked potentials in areas of involvement.

There is no cure. Immunosuppressive therapies may hasten recovery from a relapse, but no evidence suggests

that these agents influence the progressive course of the disease. Administration of interferon-beta may significantly reduce the relapse rate and retard disability; however, an increased risk for fetal loss and low birth weight (LBW) has been observed with the use of this therapy during the first trimester of pregnancy.[4] In contrast, administration of intravenous immunoglobulin may reduce the risk for relapse and has no known adverse effects on pregnancy outcome.[5] Acute relapses during pregnancy can be treated with intravenous corticosteroids, although their use may be associated with maternal glucose intolerance and neonatal adrenal suppression.[6]

Interaction with Pregnancy

Evidence regarding the effect of multiple sclerosis on pregnancy is conflicting. In one cohort study that compared 198 affected women with 1584 healthy women, the number of maternal complications was not higher in women with multiple sclerosis.[7] However, infants delivered of women with multiple sclerosis appear to be at greater risk for meconium aspiration, even though the presence of moderate to heavy meconium is not significantly increased.[7] This finding may reflect an intrauterine environment in patients with multiple sclerosis that is more susceptible to acute hypoxic events.[7] A subsequent cohort study of 649 pregnancies in women with multiple sclerosis concluded that infants of these women were more likely to be small for gestational age; this outcome was also attributed to a suboptimal intrauterine environment.[8] Moreover, this study found that mothers with multiple sclerosis were more likely to undergo induction of labor and operative delivery, possibly as a result of neuromuscular weakness and spasticity.

In a 2011 meta-analysis of reports of pregnant women with multiple sclerosis, the relapse rate was lower during pregnancy than before or after pregnancy.[9] It is unclear whether the prevalence of cesarean deliveries, spontaneous abortions, preterm births, and LBW neonates is higher in women with multiple sclerosis than in healthy women, although the rates did not reach levels that would warrant great concern.

Data from prospective studies suggest that the rate of relapse increases during the first 3 months postpartum in comparison with the year before pregnancy.[10] Relapses during this period were more likely in women who had higher relapse rates in the year before pregnancy or during pregnancy. Stress, exhaustion, infection, the loss of antenatal immunosuppression, and the postpartum decline in concentrations of reproductive hormones may account for the higher postpartum relapse rate. Treatment with immunologically active agents (e.g., interferon-beta) may result in a decreased postpartum relapse rate, but data are limited.[10]

Pregnancy does not negatively affect the long-term outcome of multiple sclerosis. Rather, at least one study has suggested that parturition may have a slightly favorable effect on long-term disease activity.[11] Data are conflicting as to whether exclusive breast-feeding is associated with a lower risk for relapse than partial or no breast-feeding.[12,13]

Anesthetic Management

The anesthesiologist should assess the patient's level of compromise, document the pattern of deficits, and give special attention to respiratory involvement. Historically, the optimal route of anesthesia in patients with multiple sclerosis has been controversial. Most anesthesia providers have considered general anesthesia to be safe, although published data are limited.[14,15] Many anesthesia providers have been reluctant to administer neuraxial anesthesia because the effect of local anesthetic drugs on the course of the disease is unclear. Some anesthesiologists have expressed concern that neuraxial anesthesia may expose demyelinated areas of the spinal cord to potentially neurotoxic effects of local anesthetic agents. Several animal studies have investigated the histologic effects of local anesthetic agents on the normal spinal cord. In one study, subarachnoid injection of small doses of a local anesthetic agent produced no histologic changes in the spinal cord or meninges.[16] Injection of very large doses caused reversible inflammatory and degenerative changes, but all changes resolved within 14 days of injection.

Diagnostic lumbar puncture is not associated with a higher rate of relapse.[17] Two small reports have implicated spinal anesthesia in the exacerbation of multiple sclerosis.[15,18] Bamford et al.[15] described one case of relapse after the administration of spinal anesthesia in 9 patients, and Stenuit and Marchand[18] identified two cases of relapse after the administration of spinal anesthesia in 19 patients. The relationship of these relapses to spinal anesthesia or other postoperative conditions (e.g., stress, infection, hyperpyrexia) known to exacerbate multiple sclerosis is unclear.

There are few published data on the use of epidural anesthesia in patients with multiple sclerosis. Warren et al.[19] reported minor exacerbations after the administration of epidural anesthesia for two separate vaginal deliveries in one patient. Crawford et al.[20] reported one postoperative relapse in 50 nonobstetric and 7 obstetric patients who received epidural analgesia. Confavreux et al.[21] reported a study of 269 pregnancies in 254 women with multiple sclerosis, of whom 42 received epidural analgesia. They noted that epidural analgesia did not have an adverse effect on the rate of relapse or on the progression of disability in these patients. Bader et al.[22] retrospectively evaluated 32 pregnancies in women with multiple sclerosis; they observed that women who received epidural anesthesia for vaginal delivery did not have a higher incidence of relapse than those who received only local infiltration anesthesia. In a prospective study of 227 women who had multiple sclerosis for at least 1 year before conception, of whom 42 received epidural analgesia during labor, no adverse effect of epidural analgesia on the rate of relapse or the progression of disability was identified.[10]

Bader et al.[22] observed that all of the women who experienced a relapse after epidural anesthesia had received a concentration of bupivacaine greater than 0.25%. The concentration of local anesthetic in the CSF progressively increases during prolonged administration of epidural anesthesia, and the authors suggested that the higher concentration may overwhelm the protective effect of

dilution within the CSF. An alternative explanation is that women who require a higher concentration of neuraxial local anesthetic may have more stressful labor. However, these observations suggest that anesthesia providers should use a dilute solution of local anesthetic for epidural analgesia during labor, when possible.

The addition of an opioid reduces the total dose of local anesthetic required for epidural analgesia during labor. Berger and Ontell[23] reported the administration of intrathecal morphine, which was added to low-dose tetracaine for surgical anesthesia and postoperative analgesia, and observed no exacerbation of multiple sclerosis at 1 and 6 months after surgery. Leigh et al.[24] described the successful use of intrathecal diamorphine for postoperative analgesia in a patient with multiple sclerosis who underwent a laparotomy.

The administration of neuraxial anesthesia for cesarean delivery is controversial. Because the operation is of limited duration, multiple doses of local anesthetic are typically not needed, so a progressive increase in CSF concentration of local anesthetic over time is less likely. In light of the significant benefits of neuraxial techniques for intraoperative anesthesia and postoperative analgesia, either spinal or epidural anesthesia is the principal anesthetic technique used for cesarean delivery in patients with multiple sclerosis in many institutions, including my own.

In summary, published data do not contraindicate the use of neuraxial anesthetic techniques for labor analgesia or operative anesthesia. The patient should be aware that there is a higher incidence of relapse during the postpartum period, even without the use of neuraxial analgesia or anesthesia. In addition, when anesthetic techniques are used, the type of anesthesia selected does not appear to influence the relapse rate. Neither pregnancy nor anesthesia appears to have a negative influence on the long-term course of the disease. The willingness of anesthesiologists to use neuraxial techniques in pregnant patients with multiple sclerosis is reflected in a survey of obstetric anesthesiologists published in 2006.[25] The majority (91%) of respondents had seen fewer than 10 cases of multiple sclerosis in the past 10 years; 79% and 98% of anesthesiologists indicated they would perform a neuraxial anesthetic technique for labor and elective cesarean delivery, respectively.

HEADACHE DURING PREGNANCY

Headaches are among the most frequently observed neurologic symptoms during pregnancy (Table 49-1). Tension headaches, migraine headaches, and headaches associated with hypertension in pregnancy, including preeclampsia, are commonly observed during pregnancy. A pregnant patient with a history of chronic headaches who reports new or different symptoms should be closely evaluated to exclude serious etiologies such as preeclampsia, tumor, or intracranial vascular malformation. Symptoms of concern include sudden onset, intense severity, altered mental status, meningeal signs, fever, vomiting, and any localizing or lateralizing abnormality.

Tension Headache

Tension or muscle contraction headaches are the most common type of headache observed during pregnancy.[26] The symptoms typically consist of dull, persistent pain that extends over the entire head. The onset is usually gradual, but the symptoms may persist for long periods. Although the etiology is unknown, this type of headache is believed to be associated with stress rather than hormonal changes. These headaches are more common in women, are frequently associated with anxiety, and may be a symptom of postpartum depression.[27]

Treatment

In the nonpregnant patient, treatment of tension headaches may involve acetaminophen, aspirin, opioids, tricyclic antidepressants, and benzodiazepines. In the pregnant

TABLE 49-1 **Headache during Pregnancy**

Etiology	Symptoms	Pattern	Treatment
Tension headache	Dull, widespread headache	Increased incidence during peripartum period	Analgesics Tricyclic antidepressants
Migraine headache	Frontotemporal throbbing Prodrome of scotomata	Improvement in 79% of patients during pregnancy	Ergotamine contraindicated during pregnancy Promethazine Beta-adrenergic receptor antagonist for prophylaxis
Preeclampsia	Generalized headache Occasional scotomata and/or blurred vision	Occurrence during pregnancy and occasionally postpartum	Blood pressure control Delivery
Meningeal irritation (subarachnoid hemorrhage, meningitis)	Generalized headache	Increased risk for subarachnoid hemorrhage during pregnancy	Based on etiology
Brain tumor	Variable	No increase in incidence during pregnancy, possible increased growth rate	Based on etiology
Idiopathic intracranial hypertension	Generalized headache Visual symptoms	Increased incidence and worsened symptoms during pregnancy	Typically remits within 1 to 3 months or after childbirth

patient, acetaminophen should be used as a first-line analgesic. Caffeine may be contained in combination analgesic products (e.g., Fioricet, Fiorinal). The American College of Obstetricians and Gynecologists (ACOG) has stated that, at the current time, there is no clear evidence that caffeine exposure increases the risk for fetal growth restriction (also known as intrauterine growth restriction).[28] Because a final conclusion regarding risk of high caffeine intake and miscarriage cannot be made, the ACOG recommends moderate caffeine intake (< 200 mg/d) during pregnancy. Limited data suggest that butalbital is not associated with congenital anomalies.[29] Ergot alkaloids (e.g., ergotamine) are contraindicated during pregnancy; these agents may cause marked increases in uterine tone, which may compromise placental perfusion and fetal oxygenation.[29] Use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be limited during the third trimester because of concerns about their association with premature closure of the fetal ductus arteriosus and prolongation of pregnancy. Although a 2013 review did not find evidence that first-trimester exposure to benzodiazepines is associated with an increased risk for congenital malformations,[30] these drugs are not usually used to treat headache during pregnancy. Opioids and tricyclic antidepressants have a long record of safe use during pregnancy; one study suggested that tricyclic antidepressants do not have detrimental effects on the neurodevelopment of children exposed *in utero*.[31]

Obstetric and Anesthetic Management

Pregnancy is not likely to reduce the frequency or severity of tension headaches because they are not hormonally mediated. Obstetric and anesthetic management are rarely affected by the presence of tension headaches, although a history of chronic tension headaches has been associated with an increased risk for placental abruption (adjusted odds ratio, 1.60).[32]

Migraine Headache

Migraine headaches are classically described as unilateral, throbbing headaches sometimes accompanied by nausea and vomiting. The duration varies from hours to days. Visual disturbances (e.g., scotomata) typically precede the onset of these headaches, and focal neurologic symptoms (e.g., aphasia, hemiplegia) may also occur. Most investigators favor neurovascular vasospasm, followed by cerebral vasodilation, as a cause of these headaches; a primary vascular disorder or a disturbance in the noradrenergic nervous system also may be involved. Patients appear to be more susceptible to symptoms when serotonin levels are low.

The 1-year period prevalence of migraine headache in the United States is 3.9% for men and 5.1% for women.[33] Prevalence is higher in middle life, between the ages of 30 and 59 years. Hormonal influences have a strong association with these headaches; estrogen withdrawal is associated with an exacerbation of symptoms.[34] After delivery, the reduction in hormonal concentrations coincides with an increase in migraine symptoms.[35] In a prospective study of 208 Japanese women,[36] 85% of women had headache regression during pregnancy; no patient had worsening of headache symptoms during pregnancy. More than 50% of women experienced recurrence of migraine headache in the first postpartum month; breastfeeding was protective against the recurrence of headache.

Treatment

In nonpregnant patients, therapy often involves ergotamine tartrate, typically in combination with caffeine (e.g., Cafergot, Migergot). However, ergot alkaloids are contraindicated during pregnancy because of associated uterotonic effects and possible (but unproven) teratogenic effects.[29,35,37] In general, acetaminophen is the first-line treatment during pregnancy. Combination therapy with agents containing caffeine and/or butalbital can be used with caution; the caffeine component should be limited to a dose less than 200 mg/day (see earlier discussion). Use of NSAIDs should be limited during the third trimester because of concerns about their association with premature closure of the ductus arteriosus, oligohydramnios, and prolongation of pregnancy. Beta-adrenergic receptor antagonists (e.g., propranolol) may be used for prophylaxis; however, owing to their ability to cross the placenta, these agents should be used only when a patient's symptoms are severe. Occasionally, calcium entry–blocking agents are used. The use of sumatriptan or other selective serotonin agonists is controversial. A higher incidence of congenital anomalies has been observed after administration of high doses of sumatriptan in animals[37]; however, in a review of human studies, no evidence of any specific adverse effect of sumatriptan on pregnancy outcome was found.[38]

Obstetric and Anesthetic Management

Women with a history of migraines have a higher risk for developing gestational hypertension or preeclampsia (adjusted odds ratio, 2.85).[37,39] In addition, patients with a lifetime history of migraine have been reported to have a twofold increased risk for placental abruption.

Cerebral ischemia has been reported after the administration of terbutaline in pregnant patients with migraine. Rosene et al.[40] recommended that physicians avoid the administration of terbutaline in pregnant women with a history of vascular headache.

There are no published data on the relationship between intrapartum anesthesia and postpartum migraine headaches.

SPINAL CORD INJURY

Worldwide, there are large geographic differences in the incidence, prevalence, and lethality of spinal cord injuries.[41] In the United States, traumatic spinal cord injuries occur with an incidence of 23.7 to 77.0 per million population per year; the prevalence per million inhabitants is 473 to 1800.[41] Improved handling and stabilization of victims at the site of an accident and the availability of

extensive rehabilitation services have resulted in a higher number of women who present for obstetric care after spinal cord injury than in the past.

Patient disability and residual function depend on the anatomic location of the injury.[42] Cord injuries below S2 involve mainly bladder, bowel, and sexual functions. Affected patients have relaxed perineal muscles, and women with such injuries experience pain during labor. Women with a lesion above T10 do not experience labor pain. Patients with a lesion above T6 have varying levels of respiratory compromise and are at risk for autonomic hyperreflexia (see later discussion).

Spinal shock, defined as transient sensorimotor dysfunction resolving in less than 24 hours, may develop in about half of spinal cord–injured patients.[43] Neurogenic shock consists of hemodynamic and sensorimotor abnormalities and is characterized by flaccid paralysis with loss of tendon and autonomic reflexes for weeks to months.[43] Patients with neurogenic shock lose vasomotor tone, temperature regulation, sweating, and piloerection in the parts of the body below the lesion. Pulmonary edema, hemodynamic instability, and circulatory collapse can develop in the absence of brainstem regulation of vasomotor tone. Patients are at risk for aspiration, infection, and other pulmonary complications. Paraplegic patients may have a compensatory tachycardia, whereas quadriplegic patients may have bradycardia due to unopposed vagal tone.

After a variable period, the patient progresses to a chronic stage in which reflex activity is regained. In most cases, this return of reflex activity occurs within 1 to 6 weeks after the injury; rarely, return of reflex activity may take several months. This stage is characterized by disuse atrophy, flexor spasms, and an exaggeration of reflexes. The **mass motor reflex** results from the absence of central inhibitory mechanisms. A stimulus that normally would cause the contraction of a few muscle units leads to the widespread spasm of entire muscle groups. The mass motor reflex can occur with any level of spinal cord injury. It may occur with autonomic hyperreflexia in a patient with a lesion above T6.[44]

Approximately 85% of patients with chronic spinal cord injuries at or above T6 experience the syndrome of **autonomic hyperreflexia.**[43] This is a life-threatening complication that results from the absence of central inhibition on the sympathetic neurons in the cord below the injury. Noxious stimuli, bladder or bowel distention, and uterine contractions result in afferent transmission by means of the dorsal spinal root (Figure 49-1).[45] These afferent neurons synapse with sympathetic neurons, and the impulse is propagated both cephalad and caudad in the sympathetic chain, without central inhibition. The propagation results in extreme sympathetic hyperactivity and severe systemic hypertension secondary to vasoconstriction below the level of the lesion. In response, the reflex arcs involving the baroreceptors of the aortic and carotid bodies lead to bradycardia and vasodilation above the level of the lesion. In patients with lesions of T6 and above, these compensatory mechanisms are insufficient to compensate for the severe hypertension. Intracranial hemorrhage, arrhythmias, and myocardial infarction occur in some cases. A variety of agents have been used

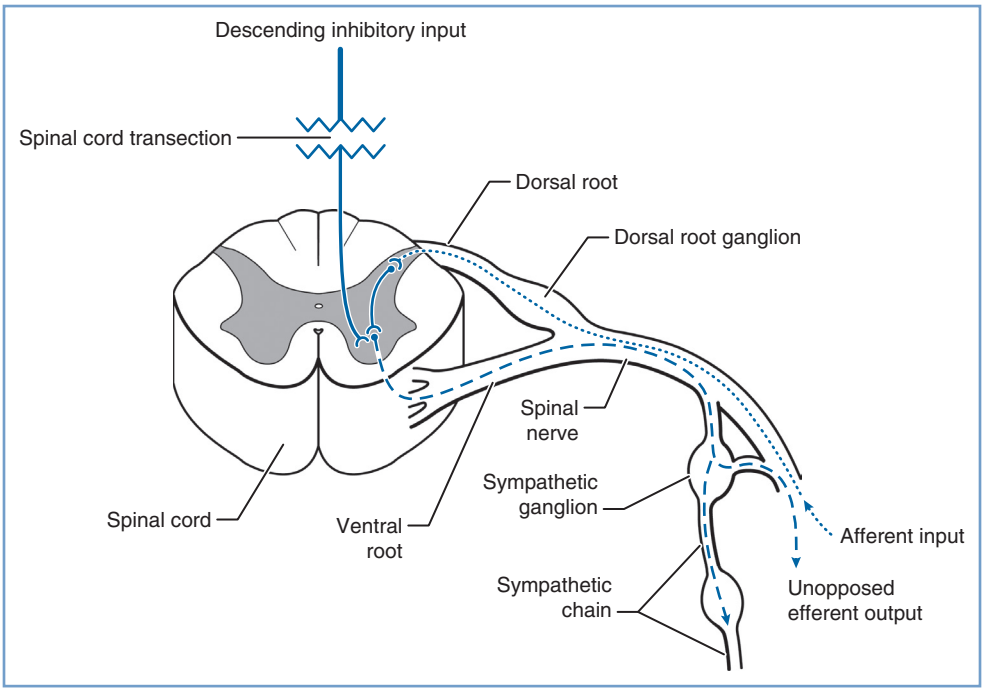

FIGURE 49-1 ■ Noxious stimuli enter the dorsal horn of the spinal cord through the dorsal spinal root (*dotted line*). These afferent neurons synapse either directly or by means of interneurons (*solid line*) with sympathetic neurons in the intermediolateral columns of the lateral horns, which then project through the anterior roots to the paraspinal sympathetic chain (*dashed line*). The impulse is propagated peripherally at that spinal level and also travels both cephalad and caudad in the sympathetic chain, exiting at multiple thoracic and lumbar levels (*dashed line*) and resulting in sympathetic hyperactivity. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

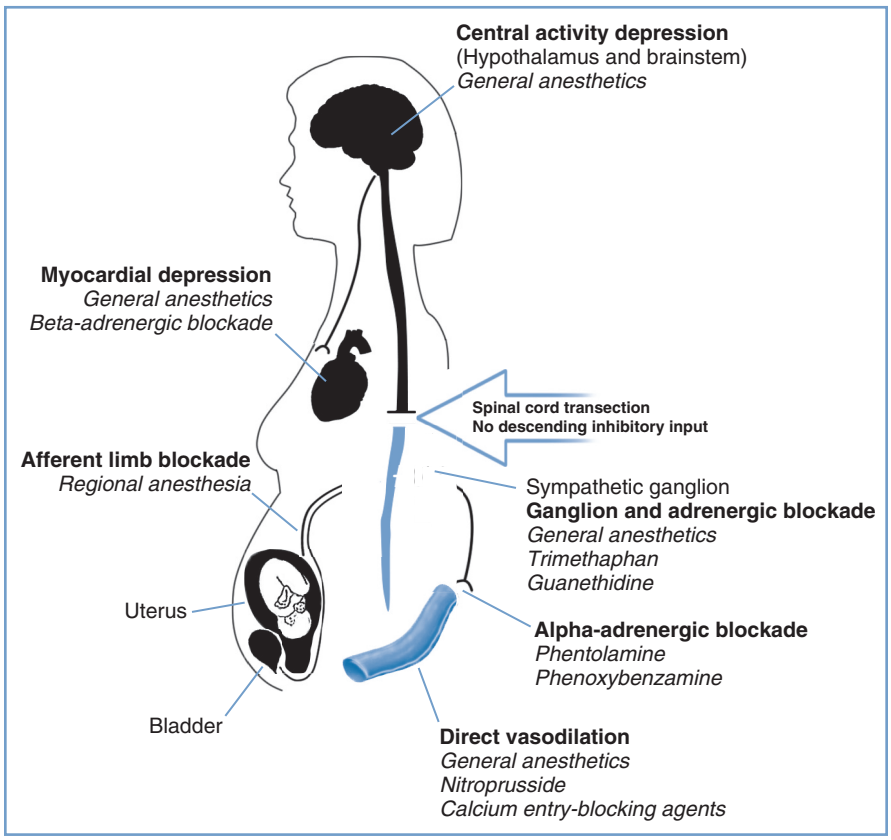

FIGURE 49-2 ■ Sites of action for agents used in the control of hypertension associated with autonomic hyperreflexia. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

for control of the hypertension of autonomic hyperreflexia (Figure 49-2).

Obstetric Management

Pregnancy may aggravate many of the medical complications of spinal cord injury (Box 49-1).[45] The loss of both functional residual capacity and expiratory reserve volume during pregnancy may increase the likelihood of respiratory compromise associated with spinal cord injury. Pregnancy increases the risks for thromboembolic phenomena and urinary tract infection. Loss of sympathetic tone below the level of the lesion renders pregnant patients with spinal cord injury particularly prone to orthostatic hypotension, which may result in a decrease in uteroplacental perfusion. Uterine contractions can stimulate autonomic hyperreflexia, and the resultant vasoconstriction can result in fetal hypoxia and bradycardia. In pregnant women, autonomic hyperreflexia occurs most commonly during labor.

Women with a lesion above T11 may have a higher risk for preterm labor.[42] Because these women do not experience labor pain, obstetric management includes weekly cervical examinations during the third trimester. Vaginal delivery is preferred. The use of assisted vaginal delivery may be necessary because of the parturient's inability to push.[42] In a study of 52 pregnancies in spinal cord–injured women, 9 of 12 patients with lesions above T5 had symptoms of autonomic hyperreflexia. The cesarean delivery rate was 47% for women with lesions above T5 and 26% for women with lesions at T5 or below.[46]

BOX 49-1 Medical Complications of Spinal Cord Injury Aggravated by Pregnancy

Pulmonary
- Decreased respiratory reserve
- Atelectasis and pneumonia
- Impaired cough

Hematologic
- Anemia
- Deep vein thrombosis
- Thromboembolic phenomena

Urogenital
- Chronic urinary tract infections
- Urinary tract calculi
- Proteinuria
- Renal insufficiency

Dermatologic
- Decubitus ulcers

Cardiovascular
- Hypertension
- Autonomic hyperreflexia

From Crosby E, St. Jean B, Reid D, Elliot RD. Obstetric anaesthesia and analgesia in chronic spinal cord-injured women. Can J Anaesth 1992; 39:487-94.

Preterm delivery occurred in 19% of patients. Autonomic hyperreflexia may affect uteroplacental blood flow, necessitating careful monitoring of the fetal heart rate (FHR).

Anesthetic Management

Women with spinal cord lesions at or above T6 are at risk for autonomic hyperreflexia. This syndrome can be distinguished from other causes of intrapartum hypertension by the occurrence of cyclic hypertension (i.e., blood pressure increases during contractions and decreases between contractions). The ACOG[47] recommends continuous hemodynamic monitoring during labor for all patients at risk for autonomic hyperreflexia.

Administration of neuraxial anesthesia is the most common method for prevention or treatment of autonomic hyperreflexia during labor and delivery. Spinal anesthesia has effectively controlled blood pressure in paraplegic patients undergoing general surgical procedures.[48] Although some anesthesiologists contend that distortion of the vertebral column in paraplegic patients makes it more difficult to predict and control the level of spinal anesthesia, published data do not lend support to this argument.[48] If spinal anesthesia is chosen, insertion of an intrathecal catheter and use of a continuous technique may be appropriate; this approach may allow careful titration of the resulting neuroblockade.

Most obstetric anesthesiologists prefer the use of epidural analgesia for the prevention or treatment of autonomic hyperreflexia during labor and delivery. Consideration also should be given to providing epidural analgesia after vaginal delivery to minimize the possibility of autonomic hyperreflexia, which has been reported to occur in response to pain as late as 5 days after delivery.[49]

Case reports have described the successful epidural administration of 0.25% or 0.5% bupivacaine or the administration of combined spinal-epidural (CSE) anesthesia for the mitigation of autonomic hyperreflexia.[50-52] Baraka[53] reported the successful use of epidural meperidine, an opioid with local anesthetic qualities, in avoiding the signs of autonomic hyperreflexia. Abouleish et al.[54] observed that epidural fentanyl alone did not effectively treat the hypertension of autonomic hyperreflexia, but the addition of 0.25% bupivacaine led to a decrease in blood pressure to baseline levels. Maehama et al.[55] described the successful use of magnesium sulfate for management of autonomic hyperreflexia during labor.

Patients with spinal cord injury often have a low baseline blood pressure and some hemodynamic instability. Placement of an intra-arterial catheter before induction of anesthesia allows the continuous assessment of blood pressure.

Positioning for neuraxial block may be difficult; the anesthesiologist should consider performing the block with the patient in a lateral position because the sitting position may cause hypotension from venous pooling in the lower body. Therapeutic doses of a local anesthetic agent should be administered cautiously with the understanding that the cephalad level of the sensory block can be fully assessed only if it is higher than the level of the spinal cord lesion. As a result, the typical epidural test dose may not identify unintentional subarachnoid injection in a patient with spinal cord injury. Neuraxial blockade can be partially assessed by evaluating segmental reflexes below the level of the lesion. For example, the anesthesiologist can lightly stroke each side of the abdomen above and below the umbilicus, looking for contraction of the abdominal muscles and deviation of the umbilicus toward the stimulus. Reflexes are absent below the level of the block. In some patients with spastic paresis at baseline, the level of anesthesia may be confirmed by the conversion of spastic paresis to flaccid paresis.[50] A decline in blood pressure may also herald the onset of neuraxial blockade. Using a nerve stimulator connected to a saline-filled, wire-reinforced epidural catheter was found to be a reliable and relatively simple method of confirming catheter placement in the epidural space.[56]

Alternative means of treating autonomic hyperreflexia should be available if neuraxial anesthesia is not successful. Antihypertensive medications such as magnesium sulfate or arteriolar vasodilators may be effective, recognizing that hypotension can result in decreased uterine blood flow.[46] Careful titration of nitroprusside, noting the potential for fetal/neonatal cyanide intoxication, or beta-adrenergic receptor blockade, may also be useful. The anesthesiologist should recognize that increased vagal activity during autonomic hyperreflexia can result in electrocardiographic changes including first- and second-degree atrioventricular block and sinus arrest.[57]

If cesarean delivery is necessary, epidural or spinal anesthesia can be administered. Spinal anesthesia is generally associated with a more rapid onset and a more unpredictable level of neuroblockade and can lead to significant hypotension.[58] The effect of neuraxial blockade on respiratory function may be less severe with epidural anesthesia than with spinal anesthesia.

Severe respiratory insufficiency or technical difficulties with neuraxial anesthesia may necessitate the use of general anesthesia.[59] If general anesthesia is required, a depolarizing muscle relaxant such as succinylcholine should not be given during the period of denervation injury. By a conservative definition, this period begins 24 hours after the injury and lasts for 1 year. The use of succinylcholine during this period of denervation injury may cause severe hyperkalemia[60]; therefore, a nondepolarizing muscle relaxant should be used to facilitate laryngoscopy and tracheal intubation.

MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder characterized by episodes of muscle weakness that are made worse by activity. Its prevalence is 50 to 125 cases per million. Women are twice as likely to have the disease as men, and the onset is earlier (second or third decade in women versus the sixth or seventh decade in men).[61] Myasthenia gravis has been classified according to severity as follows[61]:

I. Ocular myasthenia
II. Mild generalized myasthenia; may include ocular, oropharyngeal, and respiratory involvement
III. Moderate generalized disease

IV. Severe generalized weakness
V. Defined by requirement for tracheal intubation, with or without mechanical ventilation

Myasthenia gravis results from an abnormality in autoimmune regulation, which leads to the production of antibodies against the nicotinic acetylcholine receptor on the neuromuscular end plate of skeletal muscle. The result is receptor destruction as well as antibody-induced blockade of the remaining acetylcholine receptors.[62] Smooth muscle and cardiac muscle are not affected. Thymic hyperplasia is common, and thymic tumors occur in approximately 10% of patients. There is an association between myasthenia gravis and other autoimmune disorders, such as rheumatoid arthritis and polymyositis. In general, an early age at onset and an extended duration of purely ocular myasthenia are good prognostic signs.

Medical Management

Treatment involves a thymectomy, administration of anticholinesterase medications and/or immunosuppressive agents, and plasmapheresis. A thymectomy improves the disease course in approximately 96% of patients; 46% of these patients undergo complete remission, and an additional 50% are asymptomatic or experience improvement with therapy.[63] In addition, a thymectomy appears to exert a favorable influence on the outcome of pregnancy.[64] One study noted decreased maternal and perinatal morbidity as well as less frequent clinical exacerbations in patients who had undergone thymectomy.[64]

Anticholinesterase drugs, which inhibit the breakdown of acetylcholine, are the mainstay of therapy. Decreased muscle weakness within minutes of administering an intravenous dose of edrophonium (10 mg) confirms the diagnosis of myasthenia gravis. Physostigmine crosses the blood-brain barrier and is not used for long-term therapy. Neostigmine and pyridostigmine are quaternary ammonium compounds that do not cross the blood-brain barrier. These drugs may be administered orally or intravenously. In general, pyridostigmine is preferred because it has less severe muscarinic side effects.[65]

Corticosteroids and azathioprine have been used with some success. Plasmapheresis can be especially helpful for patients in crisis. One study noted that preoperative plasmapheresis resulted in less need for mechanical ventilation and less time in the intensive care unit postoperatively.[66]

Myasthenia gravis can manifest in two types of crises. A **cholinergic crisis** results from an excess of the muscarinic effects of anticholinesterase medications combined with a poor response to anticholinesterase therapy. Symptoms include muscle weakness, respiratory difficulty or failure, increased sweating, salivation, bronchial secretions, and miosis. In contrast, a **myasthenic crisis** results from a worsening of the disease; its symptoms include more severe muscle weakness, including the respiratory muscles. These two crises can be distinguished by the administration of edrophonium. The symptoms do not improve if the crisis is cholinergic. In contrast, improvement indicates a myasthenic crisis and the need for a higher dose of anticholinesterase medication.

Many drugs can cause a worsening of myasthenic symptoms. These patients are extremely sensitive to drugs that potentiate muscle weakness.[67] These agents include neuromuscular blocking agents, quinidine, propranolol, aminoglycoside antibiotics, and tocolytic agents such as magnesium sulfate[68,69] and terbutaline. One case report noted worsened symptoms after the maternal administration of betamethasone.[70]

Obstetric Management

The course of myasthenia gravis during pregnancy varies. In general, approximately 29% of cases improve, 41% worsen, and 30% show no change.[71] Approximately 30% of patients experience a relapse postpartum. The highest chance of exacerbations occurs in the first trimester and in the acute postpartum period.[72]

Myasthenia gravis increases the rates of pregnancy wastage, preterm labor, and maternal mortality and morbidity.[72,73] In 1991 Plauché[71] estimated that maternal mortality is approximately 40 per 1000 live births and perinatal mortality is approximately 68 per 1000 births. Maternal mortality risk is inversely proportional to the duration of myasthenia gravis, with the highest risk occurring in the first year; consequently, myasthenic women are sometimes counseled to delay childbirth for the first few years after diagnosis.[73]

The maternal physiologic changes of pregnancy, including alterations in drug absorption, increases in blood volume, and changes in renal clearance, may require adjustments in the doses of anticholinesterase drugs. However, in the presence of a myasthenic crisis, aggressive intravenous therapy is essential, even during labor. Anticholinesterase agents are quaternary ammonium compounds that undergo minimal placental transfer but have known uterotonic effects[73]; thus, uterine activity should be monitored during the administration of these drugs. Each patient should be monitored carefully for progressive respiratory compromise secondary to diaphragmatic elevation during pregnancy. Vital capacity can be measured to monitor fatigue during labor. The treatment of the myasthenic patient with preeclampsia or preterm labor is problematic because the use of magnesium sulfate for maternal seizure prophylaxis or fetal neuroprotection may be associated with a significant increase in maternal and fetal muscle weakness.[72]

The uterus consists of smooth muscle; therefore, myasthenia gravis should not affect the first stage of labor. However, the second stage of labor often requires the use of striated muscle and consequently an assisted (e.g., vacuum or forceps) vaginal delivery may be required.

Maternal antibodies to the acetylcholine receptor are transferred across the placenta. Neonatal myasthenia gravis occurs in approximately 16% of infants of mothers with myasthenia gravis.[64,71] Physiologic variations in the levels of alpha-fetoprotein, which can block the binding of the antibody to the acetylcholine receptor, can alter the clinical course of myasthenia during pregnancy.[74] The rapid decrease in alpha-fetoprotein concentrations in the neonate after birth may be responsible for transient symptoms of myasthenia (e.g., feeding problems, hypotonia, respiratory difficulty) within the first 4 days of

life.[72] The symptoms abate as the antibodies are metabolized, with resolution typically occurring within 2 to 4 weeks; however, anticholinesterase therapy may be required during the interim.

Anesthetic Management

Myasthenia gravis patients should undergo early antepartum consultation with an anesthesiologist. This evaluation should assess the extent of bulbar and respiratory involvement and overall baseline muscle strength. Pulmonary function testing should be performed in patients with evidence of respiratory compromise. In a study of surgical patients, the presence of bulbar symptoms, a preoperative serum level of antiacetylcholine receptor antibody greater than 100 nmol/L, and intraoperative blood loss greater than 1000 mL were risk factors for having a postoperative myasthenic crisis.[75]

Patients with respiratory compromise may be more susceptible to opioid-induced respiratory depression, and consideration should be given to minimizing or avoiding opioids when possible. Neuraxial techniques are the preferred method for labor analgesia in patients with myasthenia gravis, given their association with low pain scores and high maternal satisfaction, even without the addition of opioids.[76] The use of anticholinesterase drugs may prolong the half-life of ester local anesthetic agents.

Neuraxial anesthetic techniques are preferred for cesarean delivery unless the patient has significant bulbar involvement or respiratory compromise. The use of bilevel positive airway pressure for ventilatory support in patients with moderate respiratory compromise may improve the safety of neuraxial anesthesia.[77]

In the patient with severe bulbar involvement or respiratory compromise, it may be prudent to secure the airway before surgery. Sodium thiopental, ketamine, and propofol have been used successfully for the induction of general anesthesia in patients with myasthenia gravis.[73,77,78] Depolarizing muscle relaxants (e.g., succinylcholine) have an unpredictable effect in these patients, with affected and unaffected muscles being more sensitive and resistant to these agents, respectively.[63] However, the commonly administered dose of succinylcholine (1 to 1.5 mg/kg), which is three to five times the effective dose in 95% of normal patients, will most likely provide adequate relaxation even for resistant muscles. Anticholinesterase agents and plasmapheresis cause decreases in the activity of plasma cholinesterase and may cause delays in succinylcholine hydrolysis.

Myasthenic patients are extremely sensitive to nondepolarizing muscle relaxants. If a nondepolarizing muscle relaxant must be given, the anesthesia provider should administer a small amount of an agent with a short half-life (e.g., rocuronium, atracurium, vecuronium).[63] Mivacurium is metabolized via plasma pseudocholinesterase, which may be inhibited by pyridostigmine. In general, greater disease severity corresponds with enhanced sensitivity to nondepolarizing muscle relaxants, necessitating the use of clinical judgment and neuromuscular monitoring to determine the amount and timing of drug doses. Myasthenia may prevent a full-strength contraction with nerve stimulation; therefore, a control train-of-four stimulus test should be performed before paralysis for later comparison. For nondepolarizing agents, approximately 50% of the standard dose may be adequate, and a prolonged recovery should be anticipated. Small doses of neostigmine may be given cautiously for the reversal of neuromuscular blockade.

After delivery, fluid shifts and decreased maternal alpha-fetoprotein concentrations may necessitate an adjustment of anticholinesterase drug doses. Some patients who receive general anesthesia require postoperative ventilation. The following factors are predictive of an increased risk for postoperative ventilation: (1) female gender, (2) $FEF_{25\%-75\%}$ (forced expiratory flow during the middle half of the forced vital capacity) less than 3.3 L/sec and less than 85% of that predicted, (3) FVC (forced vital capacity) less than 2.6 L/sec and less than 78% of that predicted, and (4) $MEF_{50\%}$ (maximal expiratory flow at 50% of expired vital capacity) less than 3.9 L/sec and less than 80% of that predicted.[79]

EPILEPSY

Epilepsy is a condition characterized by recurrent seizure activity in the absence of metabolic disorders or acute brain disease. The classification scheme for epileptic seizures is evolving; however, most seizures are grouped into the two major types: partial and generalized.[80,81] In partial seizures, the excess neuronal discharge is thought to originate in one region of the cerebral cortex; in generalized seizures, the discharge occurs bilaterally and involves the entire cortex.

Medical Management

A variety of antiepileptic agents are used for seizure therapy, depending on the type of seizure and clinical response (Table 49-2). A variety of adverse effects have been reported with these agents, including early-onset events (e.g., somnolence, dizziness, hypersensitivity, rash, gastrointestinal symptoms) and late-onset events (e.g., depression, leukopenia, aplastic anemia, thrombocytopenia, megaloblastic anemia, hyponatremia).[81]

Prognosis for medical control of seizures is good for patients with generalized seizure disorders; as many as 2% to 40% of newly diagnosed epilepsy patients become seizure-free without or with minimal antiepileptic drug therapy.[82] Two of three newly treated epilepsy patients will eventually enter long-term remission (5 years or more without a seizure).[82] However, about one third of patients will have an intermittent pattern (early remission with late recurrence or late remission). Finally, the standard mortality ratio for patients with epilepsy (observed number of deaths in the study compared with the general population) is consistently increased in the first several years after the diagnosis of epilepsy.

Interaction with Pregnancy

Three to five births per thousand occur in women with epilepsy.[83] A 2009 systematic review by the American Academy of Neurology and American Epilepsy Society

TABLE 49-2 Epilepsy Drugs

Antiepilepsy Drug	Enzyme Inducer*	Enzyme Inhibitor†	Target Dose (mg/d)	Target Plasma Concentration (mg/L)‡
Carbamazepine	Yes	No	600-1200 bid or tid	3-12
Clobazam	No	No	10-20 bid	–
Felbamate	No	No	2400-3600 bid or tid	20-45
Gabapentin	No	No	900-2400 bid or tid	–
Lamotrigine	Yes	Yes	100-400 qd or bid	2-15
Levetiracetam	No	No	1000-3000 bid	–
Oxcarbazepine	Yes	No	800-1800 bid or tid	7.5-20 (MHD)
Phenobarbital	Yes	No	50-200 qd or bid	10-40
Phenytoin	Yes	No	200-300 bid or tid	5-25
Pregabalin§	No	No	150-600 bid or tid	–
Primidone	Yes	No	500-750 tid	10-40 (PHB)
Tiagabine			36-60 tid	–
Topiramate	Yes¶	No	100-400 bid	–
Valproate	No	Yes	600-1500 bid (slow release) or tid	40-120
Vigabatrin§	No	No	500-3000 bid	–
Zonisamide§	No	No	300	–

MHD, monohydroxy derivative; *PHD,* phenobarbital.
*Enzyme inducer of the CYP cytochrome P450 system.
†Enzyme inhibitor of the CYP cytochrome P450 and uridine diphosphate glucuronyl transferase systems.
‡Dash (–) indicates not relevant.
§Dose should be reduced in patients with renal dysfunction.
¶For doses > 200 mg/d.
From Elger CE, Schmidt D. Modern management of epilepsy: a practical approach. Epilepsy Behav 2008; 12:501-39.

concluded that there is insufficient evidence to determine whether seizure frequency changes during pregnancy.[84] Women who are free of seizures for at least 9 months to 1 year before pregnancy have a probability of 84% to 92% of remaining seizure-free during pregnancy.[84]

Optimizing antiseizure therapy before pregnancy is critical. Because of the teratogenic aspects of many antiepileptic agents, some physicians consider withdrawal of these drugs after 2 years without seizures and recommend waiting at least 6 additional months after withdrawal before attempting to conceive. Substituting new antiepileptic agents after conception is not recommended.

A variety of causes have been proposed for the increase in seizure frequency observed in some pregnant women (Table 49-3). Higher estrogen concentrations in pregnancy lower the seizure threshold.[85] Greater sodium and water retention, alkalosis secondary to hyperventilation, sleep deprivation, and increased stress and anxiety also have been suggested as mechanisms.[86] In addition, anticonvulsant drug levels can decrease during pregnancy, often despite the administration of a larger dose[87]; this may be partially explained by the decreased plasma protein binding and greater drug clearance observed during pregnancy.[88] The American Academy of Neurology and American Epilepsy Society concluded that monitoring of lamotrigine, carbamazepine, and phenytoin levels should be considered during pregnancy. Monitoring of levetiracetam and oxcarbazepine (and its active metabolite, monohydroxy derivative) may be considered, and monitoring of other antiepileptic agents should not be discouraged despite limited data regarding their pharmacokinetic behavior during pregnancy.[89]

TABLE 49-3 Possible Causes of Increased Seizure Frequency during Pregnancy

Mechanism	Examples
Hormonal	Changes in levels of estrogen (proconvulsant) and progesterone (anticonvulsant)
Metabolic	Increased water and sodium retention
Psychological	Stress, sleep deprivation
Pharmacokinetics	Increase in liver metabolism, renal clearance, or volume of distribution
Physiologic	Decreased gastrointestinal absorption

Maternal seizures can have devastating consequences. Hypoxia and acidosis that occur during a generalized seizure can result in fetal compromise or intrauterine fetal death. During the past three decades, the overall risk for obstetric complications in epileptic women has declined. Although some studies have suggested an increased risk for hypertension in pregnancy (including preeclampsia), bleeding, and preterm birth, a systematic review concluded that evidence is inconclusive.[84] However, women with epilepsy may have a moderately increased risk for cesarean delivery.[84]

Fetuses and neonates of women with epilepsy are approximately twice as likely to have adverse pregnancy

outcomes, including intrauterine fetal death, cesarean delivery, 1-minute Apgar score less than 7, neonatal and perinatal death, LBW, and abnormal development.[90] Antiepilepsy drugs taken in the first trimester of pregnancy are associated with an increased risk for major *congenital malformations*.[83,90,91] Data are insufficient to judge whether *in utero* exposure to antiepileptic agents in general increases the risk for *cognitive impairment* in the offspring of women with epilepsy, although there is some evidence that the risk may be increased for specific drugs.[83,91] Specifically, *in utero* exposure to valproate has been associated with maladaptive childhood behavior and autism.[91]

The risk for congenital malformations in women with epilepsy receiving antiepileptic drug monotherapy is 4% to 6%[90,91] Malformations have been associated with all currently used therapeutic modalities; those most often observed are cleft lip and palate and cardiac, neural tube, and urogenital defects (hypospadias).[91]

Certain drugs have been associated with a higher relative risk for congenital defects than others. Data from prospective studies indicate that valproate in particular is associated with significantly higher rates of major malformations.[83,91] Animal studies suggest that newer agents (e.g., lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, pregabalin) have less teratogenic effect in animals, but adequate human studies have not been performed.[91] Lamotrigine may be less teratogenic in humans than other antiepileptic agents, although neonates with orofacial clefts have been reported in association with its use.[92] Collaborative international registries are collecting more information regarding the dose-dependent effects of antiepileptic agents during pregnancy, particularly information regarding the newer drugs.[93] Several studies suggest that maternal folic acid supplementation before conception may decrease the risk for major congenital abnormalities in the offspring of women with epilepsy on antiepileptic therapy.[89]

Tomson and Battino[91] reviewed data from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and made the following suggestions: (1) before conception select the most appropriate agent for the woman's type of epilepsy, (2) select the drug with the lowest teratogenic potential, (3) aim for monotherapy with the lowest effective dose, (4) whenever possible avoid valproate, and (5) if possible avoid valproate at doses of 700 mg/d and higher.

Neonates of mothers undergoing long-term antiepileptic therapy may be at risk for deficiencies in vitamin K–dependent clotting factors or other coagulation defects, despite the absence of clinically evident maternal coagulation abnormalities.[89] Enzyme-inducing antiepileptic agents (e.g., phenytoin, phenobarbital, carbamazepine) can cross the placenta and may increase the rate of oxidative degradation of vitamin K in the fetus. Affected infants are at risk for neonatal hemorrhage and respond to vitamin K (1 mg) given intramuscularly at birth. The administration of prenatal vitamin K to epileptic women with long-term exposure to these particular antiepileptic agents has not been conclusively shown to reduce the risk for neonatal hemorrhage.[89]

Anesthetic Management

There are significant interactions between antiepileptic drugs and anesthetic agents.[94] Carbamazepine, phenytoin, phenobarbital, and primidone are potent inducers of the cytochrome P450 enzymes in hepatic metabolism (see Table 49-2), which may result in decreased plasma concentrations of many medications, including beta-adrenergic receptor antagonists and calcium entry–blocking agents.[81]

Serum levels of antiepileptic drugs should be checked if therapeutic levels are known (see Table 49-2). Drug doses should not be missed during the peripartum period. If the patient experiences a seizure during labor, airway protection and support of ventilation are essential. Small doses of a benzodiazepine, propofol, or sodium thiopental arrest most seizures. Fetal bradycardia may necessitate immediate delivery.

Oral antiepileptic therapies should be continued whenever possible throughout the peripartum period. Unfortunately many of the agents are not available in parenteral forms. If oral agents cannot be taken, conversion to a parenteral agent such as phenytoin may be required. In general, antiepileptic agents have sedating properties and some are known to induce liver enzymes; this feature could potentially lead to more rapid breakdown of anesthetic agents that are metabolized by the liver.

The presence of epilepsy is not a contraindication to the administration of neuraxial analgesia or anesthesia. In a retrospective review of 100 epileptic obstetric patients, 19 received general anesthesia, 48 received spinal anesthesia, 21 received epidural or caudal anesthesia, and 12 received pudendal nerve block.[95] Of the 5 women who had a postpartum seizure, 4 had received spinal anesthesia and 1 had received general anesthesia with enflurane. No seizures occurred in patients who received epidural or caudal anesthesia. Although antiepileptic drugs have been associated with adverse effects on the coagulation system, Manohar et al.[96] observed no abnormal clotting parameters or platelet counts preoperatively in a series of patients with epilepsy undergoing surgery.

If general anesthesia is necessary, it seems prudent to avoid drugs such as ketamine and meperidine, which may lower the seizure threshold.[86,97] Sevoflurane has stronger epileptogenic properties than isoflurane, but co-administration of nitrous oxide and hyperventilation both counteract this effect.[98] Low doses of propofol also have been shown to cause activation of the electrocorticogram in epileptic patients, but at higher doses burst suppression was induced.[99] The highest incidence of seizure activity with induction of anesthesia is believed to occur with etomidate, followed by thiopental, methohexital, and propofol. Ketamine may also facilitate seizures at low dosages, but at high doses each of these induction agents acts as an anticonvulsant.[94] Induction of general anesthesia can be performed with propofol or sodium thiopental and succinylcholine, and anesthesia may be maintained with a mixture of oxygen, nitrous oxide, and isoflurane. One study noted that some patients who receive phenytoin are resistant to vecuronium but not to atracurium.[100]

MYOTONIA AND MYOTONIC DYSTROPHY

Myotonia is the general term used to describe a prolonged contraction of certain muscles after stimulation, which is followed by a delay in relaxation. **Myotonic dystrophies** are a genetically and phenotypically heterogeneous group of neuromuscular disorders caused by expansion defects in nucleotide sequences, principally on chromosome 19.[101] Based on clinical ascertainment, the estimated prevalence of myotonic dystrophy is about 1 in 8000; however, prevalence estimates vary widely.[101] As the most common form of myotonic disorders, myotonic dystrophies manifest in two distinct forms with different nucleotide sequences, DM1 and DM2. Both DM1 and DM2 are multisystem disorders characterized by skeletal muscle weakness and myotonia, cardiac conduction abnormalities, cataracts, hypogammaglobulinemia, and insulin resistance. DM1, also known as Steinert's disease, is generally more severe and exists in congenital, juvenile, and adult forms, whereas only an adult form has been identified for DM2.[101]

Myotonias can involve specific muscles, typically the hand, facial, masseter, and pretibial muscles, which become dystrophic or wasted. The disorder is slowly progressive with continual deterioration and gradual involvement of pharyngeal and laryngeal muscles, proximal limb muscles, and the diaphragm. Uterine smooth muscle is affected, and cardiac conduction abnormalities are often present. Patients typically succumb to either pulmonary or cardiac failure.

Congenital myotonic dystrophy is a severe form of myotonic dystrophy (DM1) that manifests early in infancy with hypotonia and feeding difficulties.[102] Myotonia becomes apparent during the first few years of life. In most cases the mother has myotonic dystrophy.

Myotonia congenita is a milder familial disorder characterized by myotonia of the skeletal muscles; multisystem involvement does not occur.[103] Unlike myotonic dystrophy, cardiac abnormalities are not present and smooth muscles are not affected. In some cases, muscle hypertrophy rather than wasting occurs. This disorder can be compatible with long life. It is distinguished from DM1 and DM2 by characteristic clinical features and an absence of significant histopathology in the muscle biopsy specimen. Myotonia congenita is characterized by dysfunction of the chloride channel.

Central core disease is a rare disorder in which muscle biopsies demonstrate the absence of oxidative enzyme activity in the longitudinal axis of the muscle fiber (i.e., the "central core"). Affected individuals have proximal muscle weakness and often scoliosis. This disease is caused by mutations in the skeletal muscle ryanodine receptor gene (*RYR1*) at chromosome 19q13.1, which has been associated with malignant hyperthermia.[104] Many patients with central core disease test positive for the malignant hyperthermia susceptibility trait on the caffeine-halothane contracture test (*in vitro* contracture test) (see Chapter 47); these patients should be considered at risk for malignant hyperthermia when exposed to triggering agents (i.e., succinylcholine, volatile halogenated agents).[104] Some patients with multiminicore and nemaline rod myopathy may also be at risk for malignant hyperthermia.[105]

Drugs such as quinine and mexiletine are most commonly used to relieve myotonic symptoms.[101-103] Corticosteroids, phenytoin, and tocainide also have been prescribed.

Obstetric Management

In patients with myotonic dystrophy, symptoms of weakness and myotonia usually remain unchanged during pregnancy; however, in a minority of women, symptoms worsen during pregnancy but generally resolve after delivery.[106] Antepartum evaluation should include pulmonary function testing, to assess the severity of restrictive lung disease due to muscle wasting, and an electrocardiogram, which may reveal conduction abnormalities.

There may be a higher risk for preterm labor in patients with myotonic dystrophy. Other complications of pregnancy include polyhydramnios (secondary to reduced fetal swallowing) and an increased risk for placenta previa.[107] Magnesium sulfate has been reported to cause respiratory compromise.[108] Poor uterine contractions may result in prolonged labor, uterine atony, and an increased risk for postpartum hemorrhage.[109,110] Muscle weakness may result in a prolonged second stage of labor and a higher incidence of operative delivery.[107] The neonate also may have respiratory distress if affected by congenital myotonic dystrophy.

There are reports of patients with myotonia congenita who experience temporary worsening of symptoms during pregnancy.[111] Obstetric problems have not been described, most likely because this disease involves skeletal muscle only; uterine smooth muscle is not affected in these patients.

Anesthetic Management

Patients with myotonic disorders may be especially sensitive to the respiratory depressant effects of opioid analgesic and general anesthetic agents.[112] Sedative-hypnotic agents should be used with caution; in some cases, opioids or sedatives may precipitate apnea. Thus, neuraxial anesthesia is preferred for labor and vaginal or cesarean delivery. Both spinal and epidural anesthesia have been used successfully in patients with myotonic dystrophy.[113-115] Although the clinical characteristics of myotonic dystrophy DM2 are generally more benign than DM1, anesthesiologists should be aware that both may be associated with dysphagia, cardiomyopathy, and cardiac conduction abnormalities.[116]

The prolonged contractions witnessed in patients with myotonia are due to an intrinsic muscle disorder that is not relieved by spinal or epidural anesthesia; however, infiltration with a local anesthetic agent may partially release contractions. Cold external temperatures and shivering are known triggers of myotonia, so the patient should be kept warm. Some anesthesiologists recommend the cautious administration of intrathecal or epidural opioids for their anti-shivering effect.[113] Patients

with myotonic dystrophy have a high incidence of pulmonary complications after general anesthesia.[117]

If general anesthesia is required, it is prudent to limit the use of opioids and carefully titrate muscle relaxants to mitigate the risk for postoperative pulmonary complications.[118] Depolarizing agents such as succinylcholine should be avoided because fasciculations may trigger myotonia,[119] thereby making ventilation and tracheal intubation difficult. By contrast, patients with myotonic dystrophy appear to have a normal response to nondepolarizing muscle relaxants. Regardless, careful neuromuscular monitoring is essential, particularly in those with significant baseline muscle weakness. Patients receiving quinine may require a smaller dose of a nondepolarizing muscle relaxant. In a review of dystrophic myotonias and their possible association with malignant hyperthermia, Parness et al.[120] concluded that susceptibility to malignant hyperthermia in this group of patients is similar to that of the general population. Patients with central core disease should be assumed to be susceptible to malignant hyperthermia.[104]

MUSCULAR DYSTROPHY

Muscular dystrophy is a group of disorders characterized by a progressive degeneration of skeletal muscle with intact innervation.[121] Research on the subsarcolemmal muscle fiber protein dystrophin has led to a reclassification of these disorders. Analysis of dystrophin quality and quantity can be used diagnostically before and during pregnancy and can identify carriers in some cases.

Duchenne and **Becker muscular dystrophies** are transmitted as X-linked recessive disorders and occur almost exclusively in males. The most common muscular dystrophies affecting females are fascioscapulohumeral dystrophy and limb-girdle dystrophies. **Fascioscapulohumeral dystrophy** is an autosomal dominant, slowly progressive disorder that primarily involves the muscles of the shoulders and face.[121] Over time the pelvic and pretibial muscles may be affected. Tachycardia and arrhythmias have been infrequently reported. **Limb-girdle dystrophies** involve slow degeneration of the shoulder and pelvic muscles.[121] The inheritance pattern and severity of these diseases are variable. Cardiac conduction disorders and cardiomyopathies occur in some affected patients.

Obstetric Management

The classification of the muscular dystrophies is defined by DNA and dystrophin analysis. The presentations of these dystrophinopathies are variable, and the overall management is guided by the presence and severity of symptoms. If significant weakness is present, pulmonary function testing should be obtained to assess the extent of restrictive disease. An antepartum electrocardiogram and echocardiogram should also be considered. Pregnant women with muscular dystrophies may have an increased incidence of operative delivery; the presence of severe pelvic wasting may necessitate an instrumental vaginal or cesarean delivery.[122,123] In a series of pregnant women with fascioscapulohumeral dystrophy, increased rates of LBW infants and operative deliveries were observed; the disorder worsened in 24% of these pregnancies and generally did not resolve after delivery.[122] A larger study of the course of pregnancy in women with hereditary neuromuscular disorders reported a high rate (27%) of abnormal fetal presentation in women with limb-girdle muscular dystrophy, especially in chair-bound patients.[106] About half of patients with limb-girdle muscular dystrophy reported a deterioration of symptoms during and after pregnancy.

Anesthetic Management

Limb-girdle muscular dystrophy is associated with various cardiac abnormalities, including cardiomyopathies and conduction abnormalities. Reduced lung function and respiratory compromise can be exacerbated by the physiologic changes of pregnancy; one report of a parturient with limb-girdle muscular dystrophy noted the requirement of noninvasive positive-pressure ventilation during the third trimester of pregnancy for progression of severe restrictive pulmonary disease.[124] Neuraxial techniques are preferred for labor analgesia and cesarean delivery anesthesia. Severe disease may result in both airway abnormalities and spinal deformities, which may complicate the administration of either general or neuraxial anesthesia. Severe kyphoscoliosis during pregnancy can prevent adaptive hyperventilation and gradually result in respiratory insufficiency.[125]

Whereas most females are asymptomatic carriers of the abnormal gene for muscular dystrophies, approximately 2.5% of female carriers have symptoms of the disease—although usually in milder forms than those witnessed in men.[126] There are reported cases of muscular dystrophy associated with "malignant hyperthermia." In a systematic review, Gurnaney et al.[127] summarized reported cases of patients with muscular dystrophy who developed hyperthermia, tachycardia, rhabdomyolysis, and hyperkalemia after exposure to succinylcholine and/or volatile anesthetic agents. However, none of these patients had other classic signs of malignant hyperthermia or evidence of hypermetabolism. The mechanism for this response is not well understood but may be related to the ability of these agents to exacerbate instability and permeability of dystrophin-deficient muscle membranes.[127] Although the authors concluded that muscular dystrophy patients are unlikely to be at increased risk for malignant hyperthermia, they recommended that volatile anesthetic agents be used cautiously because of the risk for severe rhabdomyolysis. Succinylcholine may lead to hyperkalemia because of up-regulation of extrajunctional acetylcholine receptors or as a result of rhabdomyolysis. Thus, succinylcholine should not be administered to patients with known muscular dystrophy. In general, these patients have a normal response to nondepolarizing muscle relaxants, but careful neuromuscular monitoring is needed, especially in patients with severe muscle wasting.

THE PHAKOMATOSES (NEUROCUTANEOUS SYNDROMES)

The phakomatoses are congenital disorders that manifest as CNS and cutaneous abnormalities. Structures of ectodermal origin such as skin, nervous system, and eyes are commonly affected.[128] The diseases are classified into three main groups: neurofibromatoses, tuberous sclerosis, and angiomatoses with CNS abnormalities (Box 49-2). The most common phakomatoses are neurofibromatosis types 1 and 2, tuberous sclerosis, Sturge-Weber disease, and von Hippel-Lindau disease. Abnormalities of the brain and spinal cord can have significant implications for anesthetic management.

Neurofibromatosis

Neurofibromatosis occurs as a result of excessive proliferation of neural crest elements such as Schwann cells, melanocytes, and fibroblasts. Clinical manifestations include hyperpigmented lesions (*café-au-lait* spots) accompanied by a variety of cutaneous and subcutaneous tumors. This disorder is now believed to exist in two distinct forms with gene abnormalities on two different chromosomes. Neurofibromatosis type 1, the "classic" form, has an incidence of approximately 1 in 3000. The severity and progression of the disease are variable, with the neurologic symptoms depending on the location of the tumors. Intracranial tumors and paraspinal neurofibromas are a cause of concern and may require surgical excision. The risk for pheochromocytoma is greater in these patients.[129] Neurofibromatosis type 2 is a less common, more recently discovered, form of the disease with fewer cutaneous lesions. Acoustic neuromas as well as other cranial or spinal neurofibromas, meningiomas, and gliomas may be present.

BOX 49-2 The Congenital Neuroectodermoses

True Phakomatoses

- Tuberous sclerosis
- Neurofibromatosis
  - Type 1 (classical)
  - Type 2 (acoustic)
  - Familial schwannomatosis

Cutaneous Angiomatosis with Abnormalities of the Central Nervous System

- Sturge-Weber syndrome (meningofacial or encephalofacial angiomatosis with cerebral calcification)
- Dermatomal hemangiomas and spinal vascular malformations
- Epidural nervus (linear sebaceous nevus) syndrome
- Osler-Rendu-Weber disease (hereditary hemorrhagic telangiectasia)
- von Hippel-Lindau disease
- Ataxia-telangiectasia (Louis-Bar disease)
- Fabry disease

Modified from Ropper AH, Samuels MA. Adams and Victor's Principles of Neurology. 9th edition. New York, McGraw Hill, 2009: online version Chapter 38.

Obstetric Management

Pregnancy may exacerbate the disease by increasing tumor growth.[130] Regression occurs after delivery in some women. Although early, small studies suggested an increased risk for obstetric complications in women with type 1 neurofibromatosis, a review of 247 pregnancies did not confirm a higher rate of preeclampsia, preterm delivery, fetal growth restriction, spontaneous abortion, or perinatal mortality compared with healthy women.[130] The high cesarean delivery rate (36%) was associated with pregnancy-related complications of the disease, including the compression of the birth canal by pelvic neurofibromas.[130] The presence of intracranial masses may be problematic during labor and vaginal delivery, particularly with the increased intracranial pressure (ICP) that occurs with the Valsalva maneuver during the second stage of labor.

Anesthetic Management

An anesthesiologist should thoroughly assess the patient's current symptoms and known lesions, particularly if they involve neck and laryngeal tumors; these tumors are common, particularly in patients with neurofibromatosis type 1.[131]

Neuraxial anesthetic techniques can be used for labor analgesia and operative anesthesia in most patients with the disorder. However, severe kyphoscoliosis owing to the presence of paraspinal tumors may complicate the administration of neuraxial anesthesia. The presence of asymptomatic paraspinal and intracranial tumors has prompted some anesthesiologists to suggest that neuraxial anesthesia should be administered only after careful clinical and radiographic evaluations.[132]

The use of muscle relaxants in these patients is controversial, because both increased and decreased sensitivity to succinylcholine has been reported; increased sensitivity to nondepolarizing agents has been reported as well.[133-135] However, a number of investigators observed only minimal alterations in dose response to both depolarizing and nondepolarizing muscle relaxants in these patients and have recommended no alterations in the dose of drug.[133]

Tuberous Sclerosis

Tuberous sclerosis is a phakomatosis characterized by epilepsy, mental retardation, and adenoma sebaceum.[136] The brain shows abnormal growth of glial cells in hamartomas called tubers. Hamartomatous tumors can occur in multiple organs, including the heart, kidneys, liver, and lungs. The inheritance pattern is autosomal dominant with a variable expression, and the disease is slowly progressive.

Obstetric and Anesthetic Management

There are few reports of pregnancy in women with tuberous sclerosis. The obstetrician and anesthesiologist should know the locations of lesions in an individual patient. Hemorrhage into the tumors, renal failure,

and hypertension may complicate pregnancy.[137] Renal involvement appears to represent an important prognostic factor during pregnancy, and spontaneous rupture of a renal angiomyolipoma has been reported.[138] Published reports have included several patients who required cesarean delivery.[137,138] Factors that could potentially impact anesthetic management of these patients include the presence of cardiac and renal tumors (angiomyolipomas), spinal and intracranial tubers, epilepsy, pharyngeal tumors, and pulmonary involvement.[139] Cardiac rhabdomyosarcomas have been reported to occur in over 60% of children with this disorder. These tumors generally regress with age, but arrhythmias and cardiac failure from ventricular obstruction may occur. In the presence of known elevated ICP from cerebral lesions, some anesthesiologists believe that neuraxial anesthesia is contraindicated. Imaging should be considered before administration of neuraxial blockade if intracranial or spinal lesions are suspected. In addition, the airway should be assessed closely for the presence of oral tubers, which have been described in approximately 15% of these patients.

Cutaneous Angiomatosis with Central Nervous System Abnormalities

One group of phakomatoses consists of disorders in which a cutaneous vascular anomaly is accompanied by CNS abnormalities (see Box 49-2).[140] There are few reports of pregnancy in patients with these disorders. Patients may have neurologic problems related to hemangiomas of the CNS. Cesarean delivery with epidural anesthesia has been reported in a patient with spinal hemangiomas.[141] The presence of widespread varicosities in these disorders may result in a chronically low ventricular preload; if a significant increase in preload occurs during the peripartum period, cardiac overload and peripartum cardiomyopathy may occur.[142]

ACUTE IDIOPATHIC POLYNEURITIS (GUILLAIN-BARRÉ SYNDROME)

Acute idiopathic polyneuritis, also known as Guillain-Barré syndrome, is an inflammatory demyelinating illness with a reported incidence of approximately 1 case per 100,000 persons per year.[143] In 60% of patients, a viral illness precedes neurologic symptoms by 1 to 3 weeks. Cases also have occurred after the administration of antirabies and influenza vaccines.

Patients with this disorder initially have weakness in the limbs, followed by the trunk, neck, and facial muscles. Loss of reflexes, total motor paralysis, and respiratory failure can occur. Sensory loss typically is not detectable. Symptoms peak at 2 to 3 weeks. The majority of patients recover completely; approximately 10% of patients have severe residual disability, and in 3% the syndrome is fatal.[143]

Slowing of nerve conduction occurs. Pathologic changes include lymphoid cellular infiltration and areas of demyelination that most likely result from a cell-mediated immunologic reaction against peripheral nerves. Autonomic nervous system involvement and dysfunction may occur.

Treatment is largely supportive and may include mechanical ventilatory support. Plasmapheresis reduces the duration of illness when instituted during the evolution phase and has been used safely during pregnancy.[143,144]

Obstetric Management

The incidence of this syndrome appears to be lower in pregnant women than in nonpregnant women. Using data from several nationwide registries, Jiang et al.[145] found that the age-adjusted relative risk of Guillain-Barré syndrome appears to be decreased during pregnancy but increases in the first 3 postpartum months. In severe cases, the risk for preterm labor is increased and neurologic deterioration may occur after delivery.[146] Termination of pregnancy does not appear to improve the course of the disease, but induction of labor may be indicated if autonomic dysfunction occurs. Instrumental vaginal delivery may be necessary.[146]

Anesthetic Management

Anesthetic management depends on patient status at the time of delivery; epidural, spinal, and CSE techniques have been described in patients with Guillain-Barré syndrome.[147-149] However, some anesthesiologists have expressed concern regarding the use of neuraxial techniques in these patients, citing the theoretical potential for neurologic changes as a result of anesthetic toxicity or immunologic modulation. Steiner et al.[150] implicated epidural anesthesia as a trigger of Guillain-Barré syndrome in four patients; Wiertlewski et al.[148] reported the immediate worsening of neurologic status after delivery in a pregnant patient with Guillain-Barré syndrome who had received epidural anesthesia. These reports did not establish a causal relationship between the disease and neuraxial anesthesia techniques, nor did they properly acknowledge the increased frequency of Guillain-Barré syndrome in the postpartum period.

If general anesthesia is necessary in a patient with Guillain-Barré syndrome, succinylcholine most likely should be avoided because of the risk for hyperkalemia in patients with acute muscle wasting. Careful titration of nondepolarizing muscle relaxants is also necessary.

The parturient with a history of remote Guillain-Barré syndrome may have persistent diminished respiratory reserve, even in the absence of obvious residual disability.[151] Pulmonary evaluation should be considered before the administration of anesthesia. Approximately 5% of patients experience a relapse, with a small number of cases progressing to a chronic disorder.

POLIOMYELITIS

Poliomyelitis is a disease caused by a picornavirus that is transmitted by the fecal-oral route. Most cases are asymptomatic or are accompanied by mild systemic symptoms. More severe symptoms and nervous system involvement

occur in approximately 1% of patients.[152] Motor neurons in the cerebral cortex, brainstem, and spinal cord are affected. Asymmetric flaccid paralysis develops over several days. Bulbar paralysis is more common in young adults. The CSF findings are consistent with viral meningitis. Recovery occurs 3 to 4 months after onset, most likely from motor axon terminal sprouting that reinnervates the previously denervated muscle fibers; however, residual deficits often persist.

A slowly progressive syndrome called **postpoliomyelitis muscular atrophy** may develop as many as 40 years after the acute illness. Klingman et al.[153] speculated that the increased functional demands on the surviving neurons or the motor axon terminal sprouts eventually result in their death. Others believe that this syndrome results from a reactivation of the initial viral infection.[154]

Obstetric Management

Currently, polio is a cause for concern only in countries with ineffective vaccination programs. Although the poliovirus vaccine has been available since the 1950s, the last phase of poliomyelitis eradication has been difficult; as of 2011, transmission of the disease continues in countries such as such as Nigeria, India, Pakistan, and Afghanistan.[155] The oral form of the vaccination does not appear to have harmful effects on fetal development and can be used if vaccination is required during pregnancy.[156] In the past, a history of poliomyelitis was believed to affect labor and delivery only if residual deficits resulted in pelvic asymmetry or an inability to push effectively[157]; however, more recent data suggest a higher incidence of preeclampsia, maternal renal dysfunction, LBW infants, perinatal death, and cesarean delivery in poliomyelitis survivors.[158] Some of these adverse outcomes may be related to chronic pulmonary issues or mechanical obstruction during labor.

Anesthetic Management

A complete preanesthetic evaluation should be performed for the presence of respiratory impairment, sleep apnea, swallowing difficulties, and other neurologic and motor deficits in all parturients with a history of poliomyelitis.[152] Some anesthesiologists have feared that administration of neuraxial anesthesia in patients with a history of poliomyelitis might cause reactivation of the virus or postpoliomyelitis and muscular atrophy. However, there is no evidence that neuraxial analgesia or anesthesia worsens symptoms in these patients. Crawford et al.[147] reported the successful use of epidural analgesia with no adverse complications in patients with a history of poliomyelitis. Rezende et al.[159] reported a series of 123 patients with a history of poliomyelitis undergoing 162 surgical procedures and observed postoperatively for 22 months; neuraxial blockade was used in 64% of cases, with no patients exhibiting worsening of neurologic symptoms. Anesthetic considerations in these patients should include assessment for pulmonary restrictive disease as well as anatomic issues that may make neuraxial techniques difficult.[160,161] A study from India reported that about one third of pregnancies complicated by kyphoscoliosis occurred in patients with a history of poliomyelitis in infancy.[161] Radiographic imaging has been successfully used to guide spinal needle placement in these patients.

Suneel et al.[162] reported a patient with a history of poliomyelitis who developed muscle weakness after general anesthesia that responded to additional neostigmine, suggesting that these patients may have a low threshold for the effects of neuromuscular blocking agents. For the patient with poliomyelitis in whom general anesthesia is needed, some anesthesiologists have suggested the use of a decreased dose of a short-acting nondepolarizing muscle relaxant in lieu of succinylcholine, which may provoke severe acute hyperkalemia.[163]

BRAIN NEOPLASMS

Intracranial neoplasms vary in incidence, histology, clinical presentation, and prognosis (Table 49-4).[164] Brain neoplasms in pregnant women appear to occur with the same relative frequency as in nonpregnant women; however, the physiologic alterations that occur during pregnancy can have profound implications for symptomatology and management.

Gliomas are the most common intracranial neoplasms, accounting for approximately 39% of all primary intracranial tumors.[165] These tumors, which result from anaplasia of astrocytes, exhibit diversity in invasive potential and include glioblastoma multiforme, astrocytomas, ependymomas, and oligodendrocytomas. Glioblastoma multiforme is the most lethal, whereas oligodendrocytomas have a better prognosis.

Meningiomas account for approximately one third of all primary brain tumors.[165] These benign tumors originate from the dura mater or arachnoid. Surgery typically is curative.

TABLE 49-4 **Classification of Brain Tumors in Women**

Histologic Type	Percentage of all Diagnosed Tumors
Benign	
Meningioma	35
Schwannoma	7
Pituitary neoplasms	7
Malignant	
Gliomas:	
Low-grade astrocytoma	3
Glioblastoma multiforme (plus high-grade astrocytoma)	23
Other astrocytoma	8
Other	5
Lymphoma	2
Medulloblastoma	2
Other brain neoplasms	8

Modified from Swensen R, Kirsch W. Brain neoplasms in women: a review. Clin Obstet Gynecol 2002; 45:904-27.

Pituitary adenomas account for 7% of diagnosed primary brain neoplasms, but postmortem studies suggest a significantly higher incidence.[165] Only a small fraction of these tumors cause symptoms (e.g., visual field deficits). These tumors may secrete prolactin, growth hormone, or adrenocorticotropic hormone. Growth of pituitary tumors is physically limited by the sella turcica of the sphenoid bone and, in a cephalad orientation, the hypothalamus. Compression of the hypothalamus or pituitary may result in respective decreases in the production or release of vasopressin, leading to diabetes insipidus. Bromocriptine often provides effective medical therapy for prolactin-secreting adenomas. Irradiation and surgery also represent effective therapies, and the prognosis is generally good.

Schwannomas, also called **neurinomas,** account for 7% of all brain tumors.[165] These lesions originate in the Schwann cells surrounding the nerve. Clinical presentation depends on the location of the tumor. Acoustic neuromas result when the eighth cranial nerve is involved; these lesions are often seen in patients with neurofibromatosis. The treatment is surgical excision.

Metastatic carcinomas account for a significant number of brain neoplasms.[165] Common primary cancers include those of the lung, breast, and colon. Prognosis and therapy depend on the tumor of origin.

Brain tumors share several pathophysiologic features. Neurologic deficits can result from a mass effect or increased ICP, even if the tumor is benign. Brain edema, which may result from a combination of vasogenic and cytotoxic mechanisms, is a prominent feature of cerebral neoplasms.

The potential for herniation must be considered in any patient with a mass lesion. The brain is divided into three basic compartments. The falx cerebri separates the cerebrum into right and left halves, and the tentorium isolates the cerebellum. High pressure from a mass can cause shifts from one compartment to another with devastating effects.

Obstetric Management

The incidence of primary brain tumors first manifesting in pregnancy does not appear to be greater than that in aged-matched, nonpregnant women.[165] Approximately 9% of patients with **choriocarcinoma** have brain metastases at the time of diagnosis.[166] In one epidemiologic study, patients with primary brain tumors had a higher incidence of spontaneous abortion, possibly because of hormonal factors.[167] A 2012 study using a retrospective cohort from the National Inpatient Sample reported an increased rate of maternal mortality, cesarean delivery, and preterm labor in patients with malignant brain tumors, and an increased rate of preterm labor and cesarean delivery in patients with benign brain tumors.[168] Pregnancy complications were significantly more likely to occur in patients having a neurosurgical procedure during their admission.

Although pregnancy does not affect the incidence of brain tumors, some of these lesions appear to grow faster during pregnancy. Visual field defects from pituitary adenomas worsen as a result of tumor enlargement during pregnancy, and symptoms have been observed to improve during the postpartum period.[169] Edema and the increased blood volume may account for some of these symptoms. Pregnancy-induced hormonal changes also may play a role because estrogen and progesterone receptors are present in meningiomas and some gliomas.[170]

Diagnosis during pregnancy requires intracranial imaging. In general, MRI is preferred because it avoids the use of ionizing radiation. MRI may require the use of gadolinium-based contrast agents. Gadolinium has the advantage compared with other contrast agents of not containing iodine, and studies demonstrating adverse fetal effects are lacking in humans. However, gadolinium appears rapidly in the fetal bladder and amniotic fluid, from where it may be swallowed by the fetus and absorbed from the gastrointestinal tract. Its fetal half-life is unknown. The American College of Radiology has stated that the "decision to administer a gadolinium-based MR contrast agent to pregnant patients should be accompanied by a well-documented and thoughtful risk-benefit analysis."[171]

Management during pregnancy depends on the nature of the tumor. Surgery for benign tumors (e.g., meningiomas) with mild symptoms can often be delayed until after delivery. Women with more aggressive, malignant tumors or with tumors causing seizures or severe visual impairment may require urgent surgery during pregnancy to avoid acute neurologic deterioration. Delivery also may be recommended as soon as reasonable fetal survival can be expected, sometimes by cesarean delivery immediately before neurosurgery. For women with pregnancies far from fetal viability, radiation therapy or stereotactic radiosurgery can be considered. Cranial radiation therapy is generally administered as a first therapeutic procedure to reduce the size of the mass in cases of aggressive neoplasm. However, radiation therapy, and particularly systemic chemotherapy, can pose significant hazards to the fetus, especially when administered during the first trimester.[165] Some women may opt for surgery after an elective abortion.

In the normal parturient, CSF pressure may increase significantly with painful uterine contractions.[172] In patients with an intracranial mass lesion, this situation could result in an increased risk for herniation. The location and size of the tumor should be assessed in the individual patient so that an appropriate delivery plan can be developed with multidisciplinary input. In general, either a pain-free second stage (with instrumental vaginal delivery to avoid pushing) or cesarean delivery may be appropriate.[173]

Anesthetic Management

The optimal anesthetic technique for labor analgesia and cesarean delivery anesthesia in the patient with an intracranial tumor is controversial. Epidural analgesia prevents the increase in ICP that can result with pushing during the second stage of labor.[174] Several published reports have described the successful use of labor epidural analgesia in women with intracranial neoplasms[174,175]; in addition, the use of spinal anesthesia for an emergency cesarean delivery in a patient with a glioblastoma has

been described.[176] However, in pregnant women with increased ICP, an unintentional dural puncture associated with an attempted epidural catheter placement can result in a fatal brain herniation.[177] As a consequence, many anesthesiologists favor general anesthesia for cesarean delivery in the patient with a brain neoplasm[178]; however, potential disadvantages of general anesthesia include (1) the loss of verbal and motor responses that facilitate neurologic assessment and (2) the risks of increased ICP with tracheal intubation and extubation.

Wang and Paech[179] have reviewed specific elements in the anesthetic management of the pregnant patient undergoing neurosurgery, many of which are also relevant to the patient with an intracranial tumor undergoing cesarean delivery. The induction of general anesthesia may consist of the administration of an induction dose of propofol or sodium thiopental and either a depolarizing or a rapid-acting nondepolarizing neuromuscular blocking agent. Some anesthesiologists avoid succinylcholine because it may cause a transient increase in ICP, but others consider this effect to be clinically insignificant.[179] A combination of a volatile halogenated agent (sevoflurane or isoflurane), nitrous oxide, and an opioid is commonly used for maintenance of anesthesia. The FHR should be monitored during intracranial surgery when possible.

To preserve cerebral and uteroplacental perfusion, hemodynamic stability should be maintained through appropriate fluid administration, avoidance of aortocaval compression, the prophylactic or early use of vasopressor drugs, and intra-arterial blood pressure monitoring instituted before induction of anesthesia.[179] In general, blood pressure should be kept close to baseline measurements; in the setting of an emergency neurosurgical procedure in a patient with increased ICP, a drop in blood pressure may compromise cerebral perfusion. Fluid management for intracranial surgery should involve administration of isonatremic, isotonic, and glucose-free intravenous solutions to reduce the risk for cerebral edema and hyperglycemia.[179] Mannitol administered to a pregnant woman slowly accumulates in the fetus, leading to fetal hyperosmolality and the subsequent physiologic changes of reduced fetal lung fluid production, decreased fetal urine production, and increased fetal plasma sodium concentrations[180,181]; however, mannitol in doses of 0.25 to 0.5 mg/kg has been reported in individual cases and appears to be associated with good maternal and fetal outcomes.[179] Furosemide is an alternative diuretic that also should be administered cautiously.

There may be some conflict between maternal and fetal interests in the patient with increased ICP. Moderate mechanical hyperventilation may be used to reduce the increased ICP that occurs in nonpregnant patients with a brain tumor or brain injury. Minute ventilation increases during normal pregnancy, resulting in a maternal $Paco_2$ of 28 to 32 mm Hg; additional hyperventilation and hypocapnia may cause uterine artery vasoconstriction and a leftward shift in the maternal oxyhemoglobin dissociation curve (see Chapter 2). For pregnant women with an acute increase in ICP, Wang and Paech[179] have suggested a target $Paco_2$ range of 25 to 30 mm Hg; however, data are currently insufficient to support evidence-based recommendations specific to pregnant women undergoing intracranial surgery. In pregnant patients with increased ICP, we recommend maintenance of maternal $Paco_2$ in the middle or at the lower end of the normal range for pregnancy. Management should be individualized according to the clinical setting.

When the decision is made to perform a cesarean delivery and brain tumor resection sequentially during a single anesthetic, hypertension should be avoided to prevent deleterious effects from tumor expansion. To avoid this complication during induction, some authors have used a combination of a high dose of fentanyl, thiopental, or propofol with succinylcholine.

A recent report of a patient with an unresected astroglioma undergoing cesarean delivery describes the postoperative use of transversus abdominis plane block to provide analgesia and reduce opioid requirements, thus reducing the risk for postoperative respiratory depression and potential exacerbation of ICP.[182] In cases for which it is considered optimal to initially perform neurosurgery and then allow completion of the pregnancy, neuraxial techniques may be considered for delivery. The patient should be assessed to determine if ICP is elevated because this may preclude the use of a neuraxial technique. After neurosurgery, a reduction in ICP from a CSF leak may cause intracranial hypotension and may make confirmation of correct spinal needle placement by identification of CSF difficult.[179]

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension, previously referred to as *pseudotumor cerebri* or *benign intracranial hypertension*, is defined as an increase in ICP with a normal CSF composition in the absence of hydrocephalus or a mass lesion.[183] The disorder most often occurs in obese women of childbearing age, suggesting that hormonal factors may play a role in the pathophysiology. The majority of patients have a headache, and in some cases visual symptoms occur. Over time the disorder generally improves, but there is a small risk for recurrence.

Traditional therapies have varied in efficacy; they include serial lumbar punctures and the administration of a carbonic anhydrase inhibitor and/or corticosteroid. Lumboperitoneal shunting may be required in severe cases with visual symptoms. Weight loss appears to improve the condition.

Interaction with Pregnancy

Symptoms of idiopathic intracranial hypertension worsen during pregnancy in 50% of cases and typically improve after delivery.[184] However, in the presence of severe maternal symptoms, the placement of an intracranial shunt can result in clinical improvement and normal perinatal outcomes.[185] Overall, this disorder does not seem to adversely affect maternal and perinatal outcomes.[186]

Anesthetic Management

Deliberate lumbar puncture represents a common form of treatment for idiopathic intracranial hypertension. Cerebellar tonsillar herniation does not occur because of the uniform, global increase in ICP. Paruchuri et al.[187] noted that there are only two published cases of cerebellar tonsillar herniation after diagnostic lumbar puncture in patients with this disorder. Both patients had severe headache, neck pain exacerbated by movement, and focal neurologic deficits. In the absence of these signs and symptoms, the anesthesia provider can provide neuraxial analgesia or anesthesia.[188]

Some anesthesiologists recommend the administration of general anesthesia for cesarean delivery in patients with *lumboperitoneal shunt*. They contend that local anesthetic agents that reach the subarachnoid space may escape into the peritoneum, making it difficult to achieve adequate anesthesia. Moreover, the performance of neuraxial anesthesia may result in trauma to the shunt catheter. Bédard et al.[189] reported the successful administration of epidural anesthesia in a preeclamptic patient with a lumboperitoneal shunt that had been placed for the treatment of idiopathic intracranial hypertension. Preoperative radiographic examination may help the anesthesia provider avoid needle placement near the catheter, although such imaging was not used in this published case. Provision of neuraxial anesthesia with an intrathecal catheter has been performed for both vaginal and cesarean delivery in parturients with idiopathic intracranial hypertension and a lumboperitoneal shunt; in one case, the intrathecal catheter provided both labor analgesia and temporary control of ICP.[190,191] Questions regarding the functional status of an *in situ* subarachnoid shunt or the possible (very rare) use of the shunt for the administration of spinal anesthesia should be discussed with neurologic or neurosurgical consultants.[192]

MATERNAL HYDROCEPHALUS WITH SHUNT

Hydrocephalus results from a variety of conditions. The most common are intracranial hemorrhage in preterm infants, fetal and neonatal infections, the Arnold-Chiari malformation, aqueductal stenosis, and the Dandy-Walker syndrome.[193] The Arnold-Chiari malformation consists of extension of a portion of cerebellar tissue into the cervical canal, with progressive hydrocephalus. The Dandy-Walker syndrome occurs with failure of development of the midline of the cerebellum, with resultant hydrocephalus of the fourth ventricle.

Ventriculoatrial or ventriculoperitoneal shunt catheters are placed for the treatment of many of these disorders. Because of advances in neonatal and neurosurgical care, hydrocephalic women with CSF shunt catheters are reaching childbearing age in increasing numbers.

Obstetric Management

Obstetric management depends on the presence of other medical and neurologic conditions. In general, although maternal shunt dependency carries a relatively high risk for complications for some patients, proper management can lead to normal pregnancy and delivery.[194] Neurologic complications may occur in as many as 76% of pregnant women with preexisting shunts, including severe headache, shunt obstruction, and increased ICP.[195] Most symptoms resolve postpartum.

Most pregnant women with intracranial shunt catheters can undergo labor and vaginal delivery; elective cesarean delivery is recommended only in the presence of severe neurologic symptoms or instability.

Anesthetic Management

Anesthetic management of the patient with hydrocephalus may depend on the location of the shunt. There has been concern that some of the local anesthetic agent entering the CSF may escape into the atrium or peritoneum, resulting in inadequate analgesia. However, both epidural and spinal anesthesia have been used in patients with lumboperitoneal, ventriculoatrial, and ventriculoperitoneal shunts (as discussed earlier).[189-191] The anesthetic technique chosen for an urgent sequential ventriculoperitoneal shunt revision and cesarean delivery must balance the needs of the maternal neurologic condition and the pregnancy.

Because of the risk for shunt infection, some physicians recommend preoperative use of a prophylactic antibiotic regimen similar to that used to prevent bacterial endocarditis.[196]

INTRACEREBRAL HEMORRHAGE

Cerebrovascular disease during pregnancy can result from three major mechanisms—hemorrhage, arterial infarction, and venous thrombosis. Intracerebral hemorrhage is most commonly associated with an arteriovenous malformation or aneurysm (Figure 49-3). Using data from the National Inpatient Sample (1995 to 2008), the

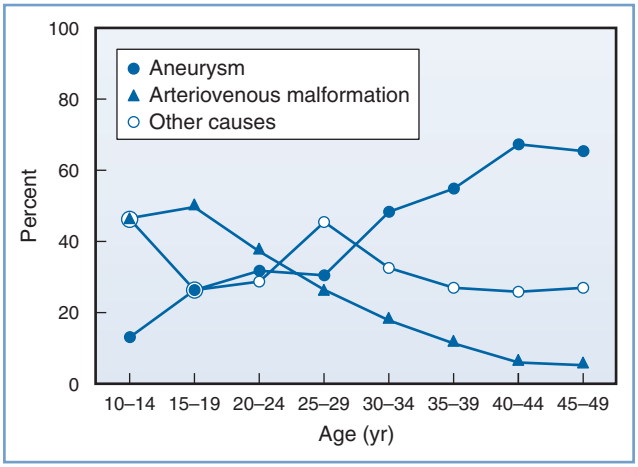

FIGURE 49-3 ■ Relative probability of major causes of subarachnoid hemorrhage for women stratified by age. (From Donaldson JO. Neurology of Pregnancy. 2nd edition. London, WB Saunders, 1989:139.)

prevalence of subarachnoid hemorrhage was 5.8 per 100,000 deliveries in women aged 15 to 44 years.[197] The ratio of hemorrhage from an arteriovenous malformation to that from an aneurysm was significantly higher in pregnant than in nonpregnant patients. The mortality rate was 10.6%; subarachnoid hemorrhage was associated with 4.1% of all pregnancy-related deaths.

Data are conflicting as to whether the aneurysm bleeding rate is higher during pregnancy.[198] Some authors have reported a progressive increase in the incidence of aneurysm bleeding throughout gestation and up to 6 weeks postpartum.[199] This interval corresponds with the period of physiologic increase in blood volume. In general, unruptured aneurysms diagnosed during pregnancy should be treated if they are symptomatic or enlarging.[200] The treatment of ruptured aneurysms during pregnancy should mimic treatment of aneurysms in nonpregnant patients.[200] The American Heart Association (AHA) guidelines for the management of aneurysmal subarachnoid hemorrhage include monitoring and controlling blood pressure (balancing the risk for stroke, rebleeding, and maintenance of cerebral perfusion pressure) and early surgical clipping or endovascular coiling.[201] Controversy exists as to whether endovascular coiling results in better outcomes than clipping. Although the AHA has suggested that "endovascular coiling can be beneficial," some experts argue that several factors may alter the risk-benefit ratio in pregnancy. These factors include (1) the need for exposure to ionizing radiation for coil placement, (2) the possible need for anticoagulation or use of antifibrinolytic agents, and (3) the increased rate of incomplete aneurysm occlusion associated with coiling compared with clipping.[196,202] Endovascular coiling has not been specifically studied in the pregnant population, although several cases of successful endovascular treatment of ruptured intracranial aneurysms in pregnant women have been reported.[200,203]

Bleeding from arteriovenous malformations has been reported to occur with equal or greater frequency with advancing gestational age.[196,199] The risk for hemorrhage from an arteriovenous malformation in pregnant women does not appear to differ from that in the general population, although the risk for bleeding appears greater during the second half of pregnancy and the first 6 postpartum weeks, corresponding to the period of high cardiac output.[196] The management of arteriovenous malformations in pregnancy does not differ from standard care of the nonpregnant patient. As with aneurysms, a multidisciplinary decision-making process allows planning based on the location of the lesion, the duration of pregnancy, and the relative risks of interventional and noninterventional methods of management. Management of arteriovascular malformations, including those that present during pregnancy, has increasingly shifted over the past decade from a surgical to an endovascular approach.

Obstetric Management

If the lesion has been treated surgically, the patient requires no special care during labor and delivery. For an untreated aneurysm or arteriovenous malformation, the hemodynamic stress occurring during labor and delivery should be minimized. Current data do not demonstrate a definite advantage of cesarean delivery over assisted vaginal delivery.[204] The decision about the method of delivery should be based on the individual patient and her pregnancy history. For labor and vaginal delivery, neuraxial analgesia and low outlet forceps or vacuum assistance may be used to shorten the second stage of labor and attenuate fluctuations in blood pressure.

Anesthetic Management

If the parturient has undergone surgical repair of either an aneurysm or arteriovenous malformation, anesthetic management need not differ from that for other obstetric patients. Hypertension should be avoided in the parturient with an untreated lesion. If vaginal delivery is planned, epidural or CSE analgesia should be considered. For cesarean delivery, either epidural or spinal anesthesia can be used. Some anesthesiologists contend that epidural anesthesia or sequential CSE anesthesia (e.g., initial use of a lower intrathecal drug dose, followed by block augmentation with epidural injection of local anesthetic) provides greater hemodynamic stability and is thus preferred for cesarean delivery. Interdisciplinary planning is important.[196,205]

In some cases, the neurosurgeon may ligate or excise the vascular lesion *during* pregnancy, *before* delivery. The anesthesiologist should consider the general principles of anesthetic management for pregnant women undergoing nonobstetric surgery (see Chapter 17) as well as the special considerations for pregnant women undergoing neurosurgery (as discussed earlier).[179] The risks for hypertension and intracranial bleeding, as well as the risk for aspiration should be considered during induction of anesthesia. It is critical to maintain stable blood pressure during induction of anesthesia, laryngoscopy, tracheal intubation, and extubation. The patient should receive adequate sedation before and after arrival in the operating room. Placement of an intra-arterial catheter is mandatory. The anesthesiologist may attenuate the hypertensive response to laryngoscopy and tracheal intubation by intravenous administration of esmolol, labetalol, lidocaine, nitroglycerin, nitroprusside, and/or an opioid (e.g., remifentanil). Succinylcholine can be used for tracheal intubation. Regardless of the choice of muscle relaxant, it is critical that laryngoscopy and tracheal intubation not be performed until the patient is anesthetized adequately.

The anesthesiologist may maintain anesthesia with nitrous oxide and modest doses of isoflurane and an opioid. Aggressive maternal hyperventilation may result in decreased uterine blood flow.[196] However, the anesthesiologist may use modest hyperventilation (e.g., $Paco_2$ of 28 to 30 mm Hg) as needed to reduce maternal ICP. The anesthesiologist should maintain left uterine displacement in patients beyond 20 weeks' gestation. Intraoperative FHR monitoring allows assessment of the fetal response to maternal general anesthesia and hyperventilation. At many institutions, including my own, intraoperative FHR monitoring is used beginning at 24 weeks' gestation, which corresponds to the onset of extrauterine neonatal viability. Typically, an obstetric nurse

monitors the FHR tracing during surgery and requests obstetric consultation if needed. An adverse change in the FHR tracing should prompt the anesthesiologist to ensure adequate maternal oxygenation, ventilation, and perfusion.

Use of deliberate hypotension may compromise uteroplacental perfusion, although its safe use has been reported during neurovascular intracranial surgery in pregnant women. There is no consensus regarding an acceptable or safe level of hypotension, or the ideal method for achieving hypotension, in these patients. The prolonged administration of large doses of nitroprusside may result in fetal cyanide toxicity, although short-term administration appears safe. Intraoperative FHR monitoring allows assessment of the fetal response to deliberate hypotension. Endovascular treatment with general anesthesia avoids the need for craniotomy and deliberate hypotension.

In some cases, the obstetrician and neurosurgeon may perform a combined procedure (e.g., a cesarean delivery followed by ligation or excision of the neurovascular lesion). Principles of anesthetic management are similar to those described earlier for intracranial neurovascular surgery during pregnancy.

Rarely, anesthesiologists may provide care for pregnant women who are receiving **extended somatic support** after brain death. Powner and Bernstein[206] reviewed 11 reports of 10 cases of brain death during pregnancy, in which somatic support was provided until successful delivery. Intracranial hemorrhage was the cause of maternal brain death in 6 of the 10 patients. The longest period of support was 107 days, from 15 to 32 weeks' gestation. All 10 infants survived. The authors concluded that preservation of uteroplacental blood flow is the most important priority during extended somatic support, but they acknowledged that this goal is difficult to achieve because of hemodynamic instability, the high prevalence of infection, and other adverse consequences (e.g., diabetes insipidus) associated with brain death.

CEREBRAL VEIN THROMBOSIS

Thrombosis of the cerebral veins and sinuses most often affects young adults and children; approximately 75% of the adult patients are women.[207] Thromboses commonly involve the cavernous sinus, lateral sinus, sagittal sinus, or cortical veins. Thrombosis of the cerebral veins causes venous obstruction with local effects, whereas thrombosis of the major sinuses causes intracranial hypertension. A prothrombotic risk factor or a direct cause can be identified in approximately 85% of patients. Pregnancy may be a precipitating factor for sinus thrombosis in a person with a genetically increased risk.[207]

Primary cerebral cortical vein thrombosis is the type of thrombosis most often seen in pregnancy. The estimated incidence of cerebral vein thrombosis during pregnancy is 12 cases per 100,000 deliveries in developed countries[208]; the incidence appears to be higher in some developing countries. Cerebral vein thrombosis occurs more frequently during the last trimester of pregnancy and in the second and third postpartum weeks.[208] Although the etiology is unclear, pregnancy may predispose patients to this condition because of at least two factors.[209] First, traumatic damage to the endothelial lining of vessels may occur during the second stage of labor. Second, pregnancy is a hypercoagulable state (see Chapters 2 and 39). Mechanical causes of sinus thrombosis may include head injury and lumbar puncture.[210] It has been postulated that low CSF pressure after a lumbar puncture causes the brain to shift downward, resulting in traction on the cortical veins and sinuses.

Patients with cerebral vein thrombosis may have headache, nausea and vomiting, and blurred vision. In more severe cases, lateralizing neurologic signs, lethargy, and seizures may occur. In severe cases, transtentorial herniation due to a focal mass effect can occur.

Care should be taken to differentiate cerebral vein thrombosis from post–dural puncture headache (PDPH).[209] In general, the headache associated with cerebral vein thrombosis is more diffuse in location. Earlier teaching suggested that the headache does not vary with position, but a 2007 review concluded that the nature of the headache may change over time and often manifests "as a positional headache that overlaps the usual timing…and treatment of PDPH in the parturient."[210]

Diagnosis can be confirmed by magnetic resonance (MR) venography. The American Heart Association/American Stroke Association published a set of management guidelines in 2011; the guidelines recommend full anticoagulation with unfractionated heparin (titrated to an activated partial thromboplastin time two times normal) or weight-adjusted low-molecular-weight heparin, continued for a minimum of 6 months' duration.[208]

Some patients with cerebral vein thrombosis may require anticonvulsant therapy. In some cases, residual neurologic deficits and seizures may persist.

Obstetric and Anesthetic Management

Cerebral vein thrombosis rarely occurs before delivery, although such an occurrence may prompt an urgent delivery if associated with maternal neurologic instability and fetal deterioration. Maternal anticoagulation contraindicates the administration of neuraxial anesthesia. The anesthesia provider should avoid systemic hypotension, which may reduce cerebral perfusion pressure and blood flow to injured areas already subjected to marginal perfusion. If the patient has an asymmetric cerebral hematoma, dural puncture may precipitate herniation of the brainstem. Thus, it seems preferable to administer general anesthesia for cesarean delivery, with special attention to the treatment of increased ICP. Cerebral venous thrombosis is a rare, but reported, complication after spinal and epidural anesthesia, presumably due to intracranial hypotension.[210]

MOTOR NEURON DISORDERS

Motor neuron diseases are a group of disorders characterized by progressive muscular weakness and atrophy.

These disorders may affect motor function alone or in conjunction with sensory deficits. There are few data on the course of these disorders in pregnant women. This discussion focuses on three of these disorders, amyotrophic lateral sclerosis and primary spinal muscular atrophy, which are pure motor neuron disorders, and peroneal muscular atrophy, which involves both motor and sensory degeneration. Currently there is no cure for any of these degenerative disorders.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis involves progressive degeneration of anterior horn cells with progressive atrophic weakness and hyperreflexia. Patients typically succumb to respiratory failure within 6 years of diagnosis.

This disease is seen more often in patients older than 50 years, but there are several reports of this disorder in pregnant women.[211,212] Physicians should assess and frequently monitor the patient's respiratory compromise throughout the peripartum period. Epidural analgesia and anesthesia have been used in these patients without evidence of worsened neurologic function postoperatively.[213,214] Patients with amyotrophic lateral sclerosis may be sensitive to the effects of nondepolarizing muscle relaxants.[215] The physiologic changes during late stages of pregnancy may worsen marginal respiratory status in these patients, and early cesarean delivery may be warranted.[216]

Spinal Muscular Atrophy

Like amyotrophic lateral sclerosis, primary spinal muscular atrophy involves degeneration of anterior horn cells. However, affected patients tend to be younger, and this disorder progresses more slowly. Some types are hereditary. Spinal muscular atrophy mainly involves the spinal cord, without involvement of the corticospinal tract. Marked kyphoscoliosis combined with truncal and limb weakness, especially involving the proximal musculature, can occur and result in significant ventilatory limitations.

Spinal muscular atrophy may be associated with an increased incidence of preterm labor.[217] One series noted that pregnancy was associated with an exacerbation of muscle weakness in 8 of 12 patients.[217] Epidural and spinal analgesia and anesthesia have been used successfully in patients with this disorder.[218,219] In children with this rare disorder, both general and regional anesthesia have been successfully used; special attention should be paid to postoperative respiratory function.[220]

Peroneal Muscular Atrophy

Peroneal muscular atrophy, also known as *Charcot-Marie-Tooth disease*, includes several inherited peripheral motor and sensory neuropathies; it is one of the most common inherited neuromuscular diseases.[221] It involves a progressive sensory and motor degeneration of peripheral nerves and roots. The peroneal nerve is affected early. The disorder progresses to involve all the nerves and muscles of the legs and finally the hands. Paresthesias are typically present. Restrictive pulmonary impairment, phrenic nerve dysfunction, diaphragmatic dysfunction, thoracic cage abnormalities, and sleep apnea have been described in association with peroneal muscular atrophy. Vocal cord dysfunction, possibly due to laryngeal nerve involvement, can also be present. Assessment of peripartum respiratory function is essential. Approximately 30% of patients with this disorder report deterioration in overall function during pregnancy, with approximately 20% indicating persistent postpartum deficits.[106]

A review of 108 deliveries found that women with this disorder have higher rates of abnormal fetal presentation, emergency operative delivery, and postpartum bleeding.[222] Both neuraxial and general anesthesia have been used for delivery.[223] Careful titration of muscle relaxants is essential if general anesthesia is employed.

ISOLATED MONONEUROPATHIES DURING PREGNANCY

Pregnancy is associated with an increased incidence of several specific mononeuropathies: Bell's palsy, carpal tunnel syndrome, and meralgia paresthetica.

Bell's Palsy

Bell's palsy is a syndrome of acute-onset paralysis of the facial nerve; it tends to present during the third trimester and the first few postpartum weeks. The incidence during pregnancy is approximately 3.3 times higher than that in nonpregnant women, which in turn is 2 to 4 times higher than that in men.[224] Some studies have suggested an association with preeclampsia, which may be based on increased interstitial edema.[225] Interestingly, Maloney[226] proposed that the smile of the famed portrait "The Mona Lisa" was the result of Leonardo da Vinci's anatomically precise rendering of a new mother affected by Bell's palsy during her pregnancy.

One study noted that pregnant patients whose symptoms progressed to complete facial paralysis within 10 days of onset were less likely to experience satisfactory recovery than a comparison group of nonpregnant patients.[227] Patients may benefit from a short course of prednisone.[228]

Dorsey and Camann[229] retrospectively reviewed 36 cases of Bell's palsy associated with pregnancy; 25 women experienced symptoms during the third trimester, and the remaining 11 had symptoms during the first week postpartum. Of the 36 women, 27 received spinal or epidural analgesia or anesthesia. There were no differences in incidence or progression of the Bell's palsy or maternal and fetal outcomes in relation to the type of anesthesia given; therefore, neuraxial analgesia or anesthesia does not appear to be contraindicated in patients with Bell's palsy.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is common during pregnancy; in a systematic review, the reported incidence ranged

from 0.8% to 70%.[230] The disorder results from compression of the median nerve in the flexor retinaculum at the wrist. Patients typically report paresthesias and weakness in the median nerve distribution, with symptoms worse in the morning on awakening from sleep. Symptoms have been reported to persist in approximately 50% and 30% of patients after 1 year and 3 years, respectively.[230] Patients may be treated with splinting of the wrists, although in severe cases, surgery may be required. In many cases, symptoms resolve spontaneously within the first 2 months postpartum and appear to correlate with losing the weight gained during pregnancy.[231]

Meralgia Paresthetica

Meralgia paresthetica involves sensory loss and paresthesias in the lateral thigh stemming from compression of the lateral femoral cutaneous nerve. Obesity and the exaggerated lordosis of pregnancy can stretch the nerve. Symptoms of meralgia paresthetica typically resolve within 3 months of delivery. This peripheral nerve palsy and other neurologic deficits are discussed more fully in Chapter 32.

KEY POINTS

- Symptoms of multiple sclerosis may worsen postpartum, regardless of the anesthetic technique used during delivery. However, the long-term prognosis of this disease is most likely unaffected by pregnancy.
- Multiple sclerosis does not contraindicate the use of neuraxial analgesia or anesthesia.
- Continuous epidural anesthesia is the method of choice for the prevention or treatment of autonomic hyperreflexia during labor and delivery in patients with spinal cord injury.
- Patients with myasthenia gravis require close surveillance during labor. Increasing muscle weakness may require an adjustment in the dosage of the anticholinesterase drug. Severe respiratory involvement may preclude the use of neuraxial anesthesia for cesarean delivery.
- The anesthesia provider should avoid succinylcholine in patients with myotonic dystrophy because fasciculations can trigger myotonia.
- Neuraxial analgesia or anesthesia does not appear to precipitate the onset of postpoliomyelitis muscular atrophy.
- Hemodynamic stability should be maintained in the parturient with an untreated intracranial aneurysm or arteriovenous malformation. Epidural anesthesia should be considered during labor and delivery.
- Bell's palsy, carpal tunnel syndrome, and meralgia paresthetica occur at higher rates during pregnancy. Symptoms typically resolve postpartum.

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CHAPTER 43

Endocrine Disorders

Richard N. Wissler, MD, PhD

CHAPTER OUTLINE

DIABETES MELLITUS

Definition and Epidemiology

Diabetes mellitus (DM) is a common metabolic disorder with a prevalence of 6.8% to 8.2% in the general adult population in the United States.[1,2] DM results from either an absolute deficiency in insulin secretion (type 1) or a combination of resistance to insulin in target tissues and inadequate insulin secretion (type 2).[3] Although a combination of genetic and environmental factors contributes to both types, type 1 DM is primarily an autoimmune disorder. Type 2 DM occurs primarily in obese individuals and accounts for 90% to 95% of cases of DM in the United States.[3] Gestational DM refers to DM or glucose intolerance that is first diagnosed during pregnancy. Gestational DM occurs in approximately 7% of pregnancies in the United States, reflecting a doubling of its prevalence between 1990 and 2000.[4,5]

Pathophysiology

Insulin is a peptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas. Insulin binds to specific cell-surface receptors in insulin-responsive target tissues (e.g., liver, skeletal muscle, fat). The intracellular effects of insulin are mediated by tyrosine kinase in the beta-subunit of the receptor through a cascade of distal protein kinase–mediated phosphorylations.[6,7] Normal hepatic glucose metabolism represents a balance between the effects of insulin and several "counterregulatory" hormones (e.g., glucagon, cortisol, epinephrine, growth hormone).[8] This control system for glucose homeostasis permits rapid adjustments in glucose metabolism in the fed and fasted states. Insulin is also an important anabolic regulator of lipid and amino acid metabolism (Figure 43-1). Insulin deficiency (absolute or relative) associated with DM results in abnormal metabolism of carbohydrates, lipids, and amino acids.

Acute and chronic complications occur in patients with DM (Box 43-1). The three major acute complications are diabetic ketoacidosis, hyperglycemic nonketotic state, and hypoglycemia. **Diabetic ketoacidosis (DKA)** occurs predominantly in patients with type 1 DM. DKA may develop with a new source of insulin resistance (e.g., infection, trauma, stress) and/or as a result of failure to administer usual insulin doses. DKA results from decreased uptake of glucose by insulin-responsive tissues and greater use of free fatty acids as a hepatic energy source. The lack of insulin favors lipolysis, beta-oxidation of free fatty acids in the liver, and hepatic formation of acetoacetate and beta-hydroxybutyrate from the excess acetyl-coenzyme A generated by fatty acid oxidation.[9] These biochemical events result in metabolic acidosis, hyperglycemia, and dehydration secondary to osmotic diuresis. Signs and symptoms of DKA include nausea, vomiting, weakness, tachypnea, hypotension, tachycardia, stupor, and acetone on the breath. The diagnosis of DKA depends on the laboratory findings of hyperglycemia, ketosis, and acidosis.[10]

Hyperglycemic nonketotic state (HNS) occurs predominantly in patients with type 2 DM. Laboratory findings in HNS are hyperglycemia (blood glucose level

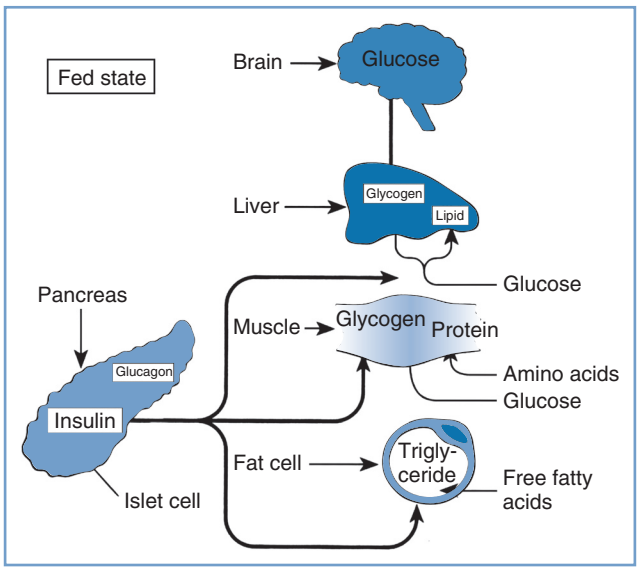

FIGURE 43-1 ■ Substrate use in the fed state, showing the role of insulin in the promotion of fuel storage. (From Kitabchi AE, Murphy MB. Diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma. Med Clin North Am 1988; 72:1545-63.)

BOX 43-1 Major Complications of Diabetes Mellitus

ACUTE

- Diabetic ketoacidosis
- Hyperglycemic nonketotic state
- Hypoglycemia

CHRONIC

Macrovascular (Atherosclerosis)

- Coronary
- Cerebrovascular
- Peripheral vascular

Microvascular

- Retinopathy
- Nephropathy

Neuropathy

- Autonomic
- Somatic

often > 600 mg/dL), hyperosmolarity (> 320 mOsm/kg), and moderate azotemia (serum blood urea nitrogen [BUN] often > 60 mg/dL), without ketonemia or significant acidosis.[10] The absence of significant ketosis in HNS may indicate an inhibition of lipolysis by hyperosmolarity or low levels of insulin. DKA and HNS are probably related conditions; inadequate insulin therapy and infection are the most common precipitating events for both.[10]

Hypoglycemia is a continuing health threat in diabetic patients, especially in patients receiving insulin therapy. Hypoglycemia results from an imbalance between insulin or oral hypoglycemic agents and available metabolic fuels. In hospitalized patients with DM, major risk factors for hypoglycemia include renal insufficiency and decreased caloric intake.[11] Symptomatic awareness of hypoglycemia and counterregulatory responses may be inadequate in some diabetic patients with autonomic neuropathy.[12] Problems with hypoglycemia awareness in patients receiving beta-adrenergic receptor antagonists can be minimized by using β_1-adrenergic receptor–selective antagonists.[13] Factitious hypoglycemia results from a deliberate, inappropriate self-administration of insulin or an oral hypoglycemic agent.[14]

In general, the prevalence of chronic complications increases with the duration of DM.[4,15] The Diabetes Control and Complications Trial, a randomized multicenter study of patients with type 1 DM, demonstrated a positive relationship between tight glucose control and a lower incidence or rate of progression of **retinopathy, nephropathy,** and **neuropathy**.[16] In a similar study of patients with type 2 DM—the U.K. Prospective Diabetes Study (UKPDS)—intensive glucose control lowered the incidence of microvascular complications but not of macrovascular complications or patient mortality.[17] In contrast, antihypertensive therapy reduced the incidence of macrovascular complications and mortality in patients with both type 2 DM and chronic hypertension.[17] DM may affect **cardiovascular function** as a result of coronary atherosclerosis, autonomic neuropathy, or development of a cardiomyopathy.[18]

BOX 43-2 Criteria for the Diagnosis of Diabetes Mellitus

1. Hemoglobin $A_{1c} \geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
   OR
2. Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*
   OR
3. Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.*
   OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL.

NGSP, National Glycohemoglobin Standardization Program; *DCCT*, Diabetes Control and Complications Trial.
*In the absence of unequivocal hyperglycemia, criteria 1 through 3 should be confirmed by repeat testing.
Modified from American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012; 35(Suppl 1):S64-71.

Clinical Presentation and Diagnosis

Box 43-2 lists the current diagnostic criteria for DM in *nonpregnant* patients.[4]

Gestational DM is associated with (1) advanced maternal age, (2) obesity, (3) family history of type 2 DM,

BOX 43-3 Screening and Diagnostic Strategies for Gestational Diabetes Mellitus

1. Screen for undiagnosed type 2 diabetes at the first prenatal visit, using standard diagnostic criteria (see Box 43-2), in those who are overweight (BMI ≥ 25 kg/m^2) and who have one or more of the following risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African race, Latino, Native American, Asian race, Pacific Islander)
   - Women who delivered an infant weighing > 9 lb (4 kg) or who were diagnosed with gestational diabetes
   - Hypertension (blood pressure ≥ 140/90 mm Hg or receiving therapy for hypertension)
   - High-density lipoprotein (HDL) cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Hemoglobin A_{1c} ≥ 5.7%, impaired fasting glucose level, or impaired glucose tolerance on previous testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - History of cardiovascular disease
2. In pregnant women not previously known to have diabetes, screen for gestational diabetes at 24-28 weeks' gestation, as follows:
   - Perform a 75-g oral glucose tolerance test (OGTT), with three plasma glucose measurements (fasting and 1 and 2 hours)
   - The OGTT should be performed in the morning after an overnight fast of at least 8 hours.
   - The diagnosis of gestational diabetes is made when any of the following plasma glucose measurements are exceeded:
     Fasting: ≥ 92 mg/dL (5.1 mmol/L)
     1-hour: ≥ 180 mg/dL (10.0 mmol/L)
     2-hour: ≥ 153 mg/dL (8.5 mmol/L)

BMI, body mass index.
Adapted from American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012; 35(Suppl 1):S11-63.

(4) prior history of gestational DM, (5) history of polycystic ovarian syndrome, (6) glycosuria, and/or (7) history of prior stillbirth, neonatal death, fetal malformation, or macrosomia. The clinical sensitivity of the medical history in detecting gestational DM is only 50%.[19] Box 43-3 lists the current recommendations of the American Diabetes Association (ADA) for screening and diagnosis of gestational DM.[4]

Several observational clinical studies, including the Hyperglycemia and Adverse Pregnancy Outcome Study,[20] have shown that adverse pregnancy outcomes are a continuous function of glucose intolerance in pregnancy. Based on these observations, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has proposed new diagnostic criteria for gestational DM as described in Box 43-3.[21] In this system, gestational DM is diagnosed if even one of the three blood glucose samples is elevated in a 2-hour oral glucose tolerance test. The ADA has approved the more inclusive IADPSG diagnostic criteria[4]; the new criteria are estimated to increase the diagnosed incidence of gestational diabetes to 16% to 18% of pregnant women.[22] However, the American College of Obstetricians and Gynecologists (ACOG) has not accepted the new criteria of the IADPSG/ADA. The ACOG continues to recommend a two-step diagnostic process; screening all women at 24 to 28 weeks' gestation followed by a 100-g, 3-hour oral glucose tolerance test for those who screen positive. With this conservative approach, the incidence of gestational DM is approximately 7%.[23] The current controversy between the IADPSG/ADA and the ACOG diagnostic criteria for gestational diabetes is centered on whether treatment of an expanded patient population is cost-effective and will improve outcomes.[22-26]

Glycosylated hemoglobin measurements are used as time-integrated estimates of glycemic control but not as a diagnostic test for DM. The normal range for hemoglobin A_{1c} in nondiabetic pregnant women is 4.0% to 5.5%, compared with 4.8% to 6.5% in nondiabetic nonpregnant women.[27]

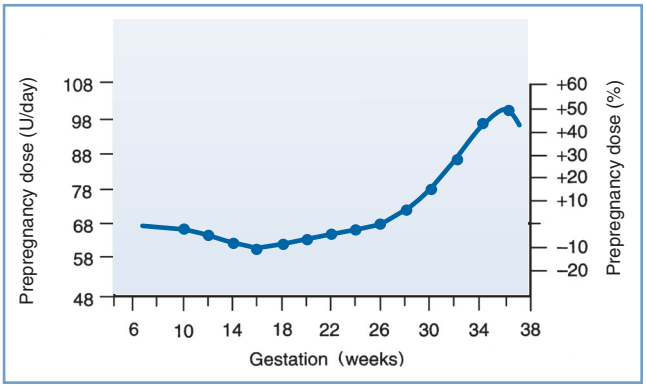

FIGURE 43-2 ■ **Insulin requirements in euglycemic women with type 1 diabetes mellitus during pregnancy.** (From Crombach G, Siebolds M, Mies R. Insulin use in pregnancy: clinical pharmacokinetic considerations. Clin Pharmacokinet 1993; 24:89-100.)

Interaction with Pregnancy

How Does Pregnancy Affect Diabetes Mellitus?

Pregnancy is characterized by progressive peripheral resistance to insulin at the receptor and postreceptor levels in the second and third trimesters (Figure 43-2).[28-30] The presumed mechanism involves an increase in counterregulatory hormones (e.g., placental lactogen, placental growth hormone, cortisol, progesterone) during pregnancy. The change in placental lactogen is a plausible mechanism, given that (1) a graph of serum lactogen levels during pregnancy is similar in shape to that of insulin requirements in pregnant women with type 1 DM and (2) placental lactogen has growth hormone–like activity. Also, maternal adipokines probably are important factors in insulin resistance of pregnancy[29]; they facilitate the provision of maternal fuels for the fetus.[30]

Gestational DM develops when a patient cannot mount a sufficient compensatory insulin response during pregnancy. In some patients, gestational DM can be viewed as a preclinical state of glucose intolerance that is not detectable before pregnancy. After delivery most patients return to normal glucose tolerance but remain at increased risk for DM (predominantly type 2) in later life.[31] The recurrence rate for gestational DM in a subsequent pregnancy is 35% to 70%.[32]

In patients with **pregestational DM,** insulin requirements progressively increase during pregnancy because of peripheral insulin resistance.[33] At term, the daily insulin requirement is approximately 1.0 insulin unit/kg, compared with 0.7 unit/kg before pregnancy.[33] Insulin requirements may be higher in pregnancies with multiple gestation.[34] During late pregnancy in normal healthy patients, basal and glucose-stimulated plasma insulin levels are twice the postpartum measurements.[30] These changes reflect pregnancy-related increases in pancreatic islet cell mass and glucose sensitivity, probably secondary to the net effect of competing progesterone and lactogenic hormone stimuli in the endocrine pancreas.[35,36] Near term, maternal overnight insulin requirements may decrease, presumably as a result of a "siphoning of maternal fuels" by the growing fetus during the overnight maternal fast.[37]

Endogenous plasma insulin concentrations during labor and delivery in nondiabetic parturients differ from exogenous insulin requirements in laboring diabetic women. In nondiabetic parturients, the plasma glucose concentration is only one of many factors that affect endogenous insulin secretion; glucose production and use are markedly higher during painful labor than postpartum.[38] Plasma insulin concentrations remain unchanged except for a brief increase during the third stage of labor and immediately postpartum.[38,39] This finding suggests that glucose use during labor is largely independent of insulin. The patterns of plasma insulin concentrations are similar in nondiabetic patients with and without analgesia (e.g., nitrous oxide, meperidine).[39]

In patients with type 1 DM, insulin requirements decrease with the onset of the first stage of labor.[40] These patients may require no additional insulin during the first stage of labor, although insulin requirements are modified by (1) the level of metabolic control before labor, (2) the residual effect of prior doses of subcutaneous insulin, and (3) the glucose infusion rate.[40,41] Insulin requirements increase during the second stage of labor via an unknown mechanism.[40,41] The use of epidural analgesia or oxytocin does not affect exogenous insulin requirements during the first and second stages of labor.[40] After delivery—either vaginal or cesarean—insulin requirements in women with type 1 DM decrease markedly for at least several days, although there is significant variability among individuals (Figure 43-3).[28,42] Presumably, the decreased insulin requirement results from loss of counterregulatory hormones produced by the placenta. Pituitary growth hormone responsiveness to hypoglycemia is blunted in late pregnancy and may contribute to impaired counterregulatory responses during the postpartum period.[43] Insulin requirements gradually return to prepregnancy levels within several weeks of delivery in women with type 1 DM.[37]

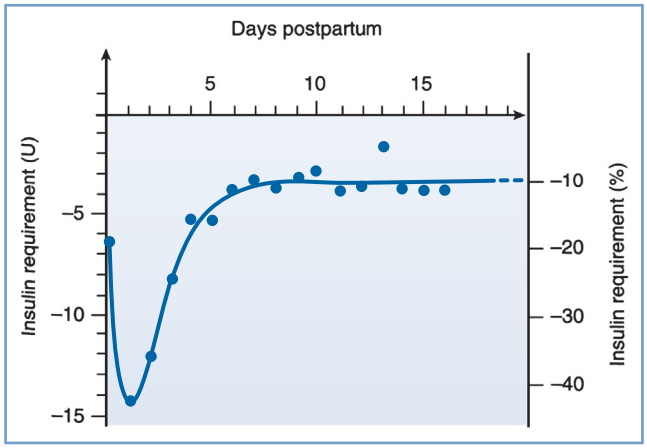

FIGURE 43-3 ■ Insulin requirements in the postpartum period. (From Crombach G, Siebolds M, Mies R. Insulin use in pregnancy: clinical pharmacokinetic considerations. Clin Pharmacokinet 1993; 24:89-100.)

Before the discovery of insulin in 1921, pregnancies were rare in diabetic patients. Insulin therapy improved the rate of survival in women with severe DM, allowing these women to reach childbearing age and become pregnant. Maternal outcomes improved, but fetal and neonatal morbidity and mortality remained high.[44]

In 1949, White[45] proposed a classification system for DM during pregnancy based on 439 consecutive cases. Physicians caring for pregnant diabetic patients should be familiar with the White system, which has endured with some modifications (Table 43-1). The system emphasizes the relationship among the duration of type 1 DM, vascular complications of type 1 DM, and poor fetal outcome.[46] In the 1950s, fetal survival rates were as follows: class A, 100%; class B, 67%; class C, 48%; class D, 32%, and class F, 3%.[46]

Diabetic Ketoacidosis. The incidence of DKA has decreased from 9% to between 1% and 2% of diabetic pregnancies,[47,48] probably as a result of improvements in medical care and patient education. Similarly, the incidence of perinatal and maternal mortality from DKA during pregnancy has decreased in the past several decades.[48,49] As is true for nonpregnant patients, DKA during pregnancy occurs predominantly in patients with type 1 DM. The higher risk for DKA during pregnancy reflects the metabolic adaptations of pregnancy, including peripheral insulin resistance.[28]

During pregnancy, DKA occurs most commonly during the second and third trimesters.[50] It is associated with (1) emesis, (2) infection, (3) poor compliance or noncompliance, (4) insulin pump failure, (5) use of beta-adrenergic receptor agonists, (6) use of corticosteroids, and (7) poor medical management.[48] The infection rate in pregnant women with pregestational type 1 DM is 3.2 times higher than that in nondiabetic pregnant women.[51] DKA may be the first clinical sign of type 1 DM during pregnancy.[52,53] Beta-adrenergic receptor agonists, which

TABLE 43-1 Modified White Classification of Diabetes Mellitus during Pregnancy

Class	Age at Onset of Diabetes (yr)		Duration of Diabetes (yr)	Vascular Disease	Insulin Required
Gestational Diabetes					
A_1	Any		Any	No	No
A_2	Any		Any	No	Yes
Pregestational Diabetes					
B	> 20		< 10	No	Yes
C	10-19	or	10-19	No	Yes
D*	< 10	or	> 20	Yes	Yes
F (nephropathy)	Any		Any	Yes	Yes
R (proliferative retinopathy)	Any		Any	Yes	Yes
T (status post–renal transplantation)	Any		Any	Yes	Yes
H (ischemic heart disease)	Any		Any	Yes	Yes

*Vascular disease in D is hypertension or benign retinopathy.
Modified from Landon MB, Gabbe SG. Diabetes mellitus and pregnancy. Obstet Gynecol Clin North Am 1992; 19:633-54.

are used to treat preterm labor, and corticosteroids, which are used to accelerate fetal lung maturity, both have counterregulatory pharmacologic effects that oppose insulin action. Beta-adrenergic agonist tocolytic therapy, with or without concurrent corticosteroid therapy, and by any route of administration, can precipitate DKA during pregnancy.[54] Beta-adrenergic receptor stimulation worsens glucose intolerance by stimulating glucagon secretion[55]; beta-adrenergic receptor agonists may be well tolerated in pregnant women with DM if higher insulin requirements are anticipated and doses are adjusted in response to frequent blood glucose determinations.[53,54]

Nonreassuring fetal heart rate patterns during episodes of maternal DKA have been described.[56] After appropriate medical management of maternal DKA, preterm uterine contractions stopped and fetal heart rate patterns normalized. The mechanism of fetal compromise during DKA is unclear, but it may be related to changes in uterine blood flow. Blechner et al.[57] demonstrated that uterine artery blood flow is reduced by acute maternal metabolic acidosis. A single case report demonstrated reversible redistribution of fetal blood flow during an episode of maternal DKA on the basis of Doppler pulsatility indices of the umbilical and middle cerebral arteries.[58]

There are three case reports of HNS during pregnancy.[59-61] No conclusion can be drawn about HNS and pregnancy, except that HNS rarely occurs during pregnancy.

Hypoglycemia. Hypoglycemia is a significant health risk for pregnant women with pregestational type 1 DM, occurring in 33% to 71% of these patients.[62-65] This rate is 3 to 15 times higher than that in similar groups of nonpregnant patients with type 1 DM[62,63]; 80% to 84% of severe hypoglycemia episodes occur before 20 weeks' gestation.[64,65] In one study, patients with pregestational type 2 DM or gestational DM requiring insulin therapy experienced no episodes of severe hypoglycemia.[63] The risk for hypoglycemia during pregnancy in patients with type 1 DM increases with tight glucose control.[62,64] This pattern mirrors the clinical experience in nonpregnant women with type 1 DM, in which a threefold rise in the occurrence of severe hypoglycemia results from tight insulin control.[66] In both pregnant and nonpregnant patients with type 1 DM, counterregulatory hormone responses to hypoglycemia are impaired after intensive insulin therapy.[67,68] Two small series suggest that acute mild to moderate maternal hypoglycemia is not associated with acute alterations in fetal well-being in pregnant women with type 1 DM.[67,69]

Other Complications. The relationship between pregnancy and the development of macrovascular complications of DM is largely unknown. Patients with pregestational type 1 DM have higher systolic and diastolic blood pressures during pregnancy, and they are three times more likely than nondiabetic control subjects to have **gestational hypertension**.[70,71] In women with pregestational type 1 DM, the risk for preeclampsia is increased with increased severity of diabetes (White classification), and proteinuria early in pregnancy is associated with an increased risk for adverse outcomes.[72] **Myocardial infarction** is a rare complication.[73] The effect of gestational hypertension on the progression of **atherosclerotic disease** in diabetic patients is unclear.

Pregnancy may accelerate the development of **proliferative retinopathy,** a microvascular complication of DM. Hyperglycemia and hypertension are also associated with the progression of retinopathy.[74,75] The onset of strict glycemic control may transiently exacerbate diabetic retinopathy in both pregnant and nonpregnant patients with type 1 DM. The Diabetes Control and Complications Trial demonstrated that strict glycemic control is justified in nonpregnant patients.[16]

In contrast to diabetic retinopathy, pregnancy does not accelerate the progression of diabetic **nephropathy**.[76] It is unclear whether pregnancy accelerates the progression of **somatic** or **autonomic neuropathy** in diabetic women.

How Does Diabetes Mellitus Affect the Mother and Fetus?

Both pregestational and gestational DM are associated with higher rates of gestational hypertension, polyhydramnios, and cesarean delivery.[47,76-78] The incidence of cesarean delivery is higher in women with pregestational DM than in women with gestational DM.[47,76,78] Trial of labor after cesarean delivery (TOLAC) in patients with gestational DM is associated with rates of operative vaginal delivery and repeat cesarean delivery that are higher than those found in nondiabetic controls.[79] Pregestational DM—but not gestational DM—is associated with a twofold to threefold increase in the incidence of **preterm labor and delivery**.[76,80]

Box 43-4 lists the fetal complications of maternal DM during pregnancy. **Fetal macrosomia** is a well-recognized complication of maternal DM. Most studies suggest that both pregestational DM and gestational DM result in an increased incidence of fetal macrosomia.[81-83] Depending on the definition of macrosomia (4000 g versus 4500 g), pregestational DM results in fetal macrosomia in 9% to 25% of women—a fourfold to sixfold higher rate than in nondiabetic controls.

Macrosomia results in an increased risk for **shoulder dystocia** and **birth trauma** with vaginal delivery.[77,84,85] Moreover, when comparisons are made within birth weight categories above 4000 g, pregnancies in diabetic women have a higher risk for shoulder dystocia than nondiabetic women.[86] The use of intensive insulin therapy may reduce the risk for birth trauma in women with pregestational DM.[87] Several mechanisms have been suggested for the development of fetal macrosomia in diabetic pregnancy. Maternal hyperglycemia can result in fetal hyperglycemia, with reactive fetal hyperinsulinemia and an anabolic response in the fetus.[88] Shoulder dystocia may reflect the excessive growth of the fetal trunk (relative to the fetal head) in response to fetal hyperinsulinemia.[89]

Women with pregestational DM are at increased risk for **fetal anomalies** (see Box 43-4). The incidence of major anomalies, estimated to be 6% to 10%, is five times higher than in nondiabetic controls.[47,90-92] Overall, cardiovascular anomalies are most common, followed by anomalies of the central nervous system (CNS). The caudal regression syndrome is uncommon, but it is 200 times more likely in diabetic than in nondiabetic pregnancies.[90] The incidence of major congenital anomalies in infants of women with gestational DM is 3% to 8%, which is lower than in infants of women with pregestational DM.[76]

Metabolic factors that may be involved in the development of fetal structural malformations in diabetic pregnancies include hyperglycemia, hypoglycemia, arachidonic acid, polyol pathways, mitochondrial dysfunction, and apoptosis.[92] Most fetal structural malformations that occur during diabetic pregnancies are likely to have a multifactorial etiology. However, hyperglycemia during the period of critical organogenesis before the seventh week after conception is probably the single strongest etiologic factor in diabetic women and may be associated with embryonic oxidative stress.[92,93]

Studies have suggested that patient education and strict glycemic control during the preconception period may reduce the rate of major congenital anomalies from 10% to 1% in patients with pregestational DM.[94] The latter figure is similar to the baseline risk for major structural malformations in the general population. Strict glycemic control initiated during the preconception period also increases the incidence of maternal hypoglycemic episodes. These studies suggest that hypoglycemia is not a significant factor in the etiology of human malformations, because the rate of anomalies decreased 10-fold despite hypoglycemic episodes.[94] Similarly, strict glycemic control before conception also has been associated with a threefold decrease in the incidence of spontaneous abortion in women with pregestational DM.[95] Dicker et al.[96] observed normal induced ovulation, *in vitro* fertilization, and early embryonic development in a small series of infertile patients with pregestational DM who attended a preconception diabetes clinic. However, only 36% of women with known pregestational DM receive appropriate medical care before conception.

During the 1950s to 1970s, the **perinatal mortality rate** in women with pregestational DM was 15% to 18%.[47] Subsequent studies noted a decrease to 2%, a rate similar to that in nondiabetic controls.[76] In contrast, one study noted a rate of 8%, three times greater than in nondiabetic controls.[83] If the entire population is considered, the perinatal mortality rate likely remains higher in patients with pregestational DM than in nondiabetic controls. The rate in patients with gestational DM is

BOX 43-4 Fetal Complications of Maternal Diabetes Mellitus

During Pregnancy and the Puerperium

Chronic

- Macrosomia
  - Shoulder dystocia
  - Birth injury or trauma
- Structural malformations
  - Central nervous system: anencephaly, encephalocele, meningomyelocele, spina bifida, holoprosencephaly
  - Cardiac: transposition of great vessels, ventricular septal defect, situs inversus, single ventricle, hypoplastic left ventricle
  - Skeletal: caudal regression
  - Renal: agenesis, multicystic dysplasia
  - Gastrointestinal: anal or rectal atresia, small left colon
  - Pulmonary: hypoplasia

Acute

- Intrauterine or neonatal death
- Neonatal respiratory distress syndrome
- Neonatal hypoglycemia
- Neonatal hyperbilirubinemia

After Pregnancy

- Glucose intolerance
- Possible impairment of cognitive development

intermediate between the rate in women with pregestational diabetes and the rate in nondiabetic controls.[76,83]

Historically, **intrauterine fetal death** was responsible for approximately 40% of the perinatal deaths in women with DM; 68% of the stillbirths occurred between 36 and 40 weeks' gestation.[45,83] In contemporary reports, the ratio of intrauterine deaths to neonatal deaths in diabetic pregnancies has varied from 0 to 1.0. Fetal macrosomia is a risk factor for intrauterine fetal demise in both diabetic and nondiabetic pregnancies. Recurrent episodes of intrauterine hypoxia can occur in diabetic pregnancies that end in stillbirth; episodes of hypoxia may reflect reduced uteroplacental blood flow and changes in fetal carbohydrate metabolism. **Congenital anomalies** have now emerged as the leading cause of perinatal mortality in diabetic pregnancies.[92] This change likely reflects better obstetric care during pregnancy, despite the lack of adequate glycemic control before conception.

Two series that involved women who delivered between 1950 and 1979 demonstrated an incidence of **neonatal respiratory distress syndrome (RDS)** in diabetic pregnancies that was 6 to 23 times that in nondiabetic controls.[47,97] Respiratory distress is more common among newborns who are delivered preterm or who are surgically delivered without labor. Later studies of patients with both pregestational and gestational DM have not demonstrated a significant difference in the incidence of neonatal RDS between diabetic and nondiabetic pregnancies.[76,98,99]

The level of glycemic control during pregnancy affects the amniotic fluid phospholipid profile. In pregnancies of patients with poorly controlled diabetes, there may be a higher incidence of immature amniotic fluid fetal lung profiles at 34 to 38 weeks' gestation without an increase in the rate of clinical respiratory distress syndrome.[99,100] In reliably dated pregnancies of diabetic patients, fetal lung maturity testing has little clinical benefit.[101]

Neonatal hypoglycemia occurs in 5% to 12% of cases of pregestational and gestational DM.[76] This represents a 6-fold to 16-fold higher risk for neonatal hypoglycemia than in nondiabetic controls. Neonatal hypoglycemia likely results from sustained fetal hyperinsulinemia in response to chronic intrauterine hyperglycemia. Clinical studies have demonstrated higher fetal insulin levels and exaggerated fetal insulin responses to acute maternal hyperglycemia in diabetic pregnancies.[102,103] An acute increase in maternal glucose concentration, as might occur if a dextrose-containing solution was used for intravenous hydration during administration of neuraxial anesthesia, can lead to reactive neonatal hypoglycemia, even in nondiabetic women.[104]

There is a twofold to fivefold higher incidence of **neonatal hyperbilirubinemia** in women with pregestational and gestational DM than in nondiabetic controls.[76] Other associated factors include the severity of gestational DM and excess maternal weight gain during pregnancy.[105,106] Both the etiology and the clinical significance of neonatal hyperbilirubinemia are unknown, although one study noted the absence of long-term morbidity.[76]

Offspring of diabetic mothers are at increased risk for development of **DM,** likely from a combination of genetic and intrauterine environmental factors. Despite the well-known association of type 1 DM with human leukocyte antigen markers, studies of monozygotic human twins have suggested that genetic factors have a greater role in type 2 DM than in type 1 DM (100% versus 20% to 50% concordance, respectively).[105] In addition, fathers with type 1 DM are five times more likely than mothers with the same disease to have a child with type 1 DM. The intrauterine environment also affects the development of glucose intolerance in offspring.[31]

Some investigators have suggested that **cognitive development** may be impaired in the children of diabetic mothers,[107] but this issue remains controversial.

Obstetric Management

Glycemic Control

Early, strict glycemic control is the best way to prevent fetal structural malformations in women with pregestational DM.[92,94] Determination of hemoglobin A_{1c} concentrations may help the physician determine the adequacy of preconceptional glycemic control.

During pregnancy, the patient should frequently determine capillary blood glucose concentration using a reflectance meter.[108] Continuous glucose monitoring systems (e.g., transdermal, subcutaneous) are more recent approaches.[109] Glucose determinations guide adjustments in diet and insulin therapy. In general, insulin requirements increase progressively during the second and third trimesters. Both maternal and perinatal outcomes seem to improve when maternal glycemic control approaches that observed in normal pregnancies. Opinions vary about the optimum target glucose concentration in patients with pregestational DM, but a fasting blood glucose concentration of 60 to 95 mg/dL seems appropriate. Of course, strict glycemic control increases the risk for maternal hypoglycemia.

Therapeutic insulin is available in several forms. Initially, insulin was isolated as a natural product from domestic animals (e.g., cattle, pigs). In the past 20 years, synthetic human insulin has become commercially available and has largely replaced beef and pork insulin in human medicine, with an expected decrease in immune reactions among human recipients.[110]

The goal of insulin therapy is to provide plasma insulin concentrations that lead to tight glucose control without hypoglycemia. This goal is facilitated by the availability of several insulin preparations with different subcutaneous absorption rates (Table 43-2).[109] Regular insulin can be administered by the intravenous or subcutaneous route. Regular insulin administered intravenously has a half-life of approximately 4 minutes.[111] Other native insulins listed in Table 43-2 (i.e., neutral protamine Hagedorn [NPH], the zinc suspensions lente and ultralente) represent chemical complexes of regular insulin with protamine or zinc; subcutaneous administration of these insulins is associated with slower absorption and onset of action. Lente and ultralente insulins have been replaced clinically by insulin analogues and are of only historical interest. An alternative therapeutic strategy is to administer a rapid-acting insulin by the subcutaneous route

TABLE 43-2 **Pharmacokinetics of Subcutaneous Insulin Administration in Nonpregnant Humans**

Insulin Preparations	Onset (h)	Peak (h)	Duration (h)
Short-Acting Class			
Regular	0.5	2-4	5-7
Lispro*	0.25	0.5-1.5	6-8
Aspart*	0.25	1-3	3-5
Glulisine*	0.25	1	4
Intermediate Class			
NPH	1-2	6-12	18-24
Lente	1-3	6-12	18-24
Long-Acting Class			
Ultralente	4-6	8-20	> 36
Glargine*	1.1	5	24

NPH, neutral protamine Hagedorn.
*Insulin analogue.
Adapted from Gabbe SG, Carpenter LB, Garrison EA. New strategies for glucose control in patients with type 1 and type 2 diabetes mellitus in pregnancy. Clin Obstet Gynecol 2007; 50:1014-24.

using a continuous programmable pump.[112] It is unclear whether continuous subcutaneous pump–administered insulin is clinically superior to intermittent subcutaneous injections of currently available insulins.[113,114]

Human insulin therapy has fundamentally changed in recent years through the development of insulin analogues.[115,116] These molecules have specific chemical substitutions in portions of the human insulin protein not involved in receptor binding. Both short-acting and long-acting insulin analogues are in clinical use. **Lispro** and **aspart** are rapid acting, with a more physiologic onset and offset than regular insulin. **Glargine** is relatively insoluble at neutral pH in the subcutaneous compartment. In contrast to ultralente insulin, subcutaneous glargine has a sustained release without an initial peak of activity. Lispro, aspart, and glargine have all been used safely during human pregnancy.

Because insulin requirements decrease abruptly at delivery, it is important to verify the times, doses, insulin preparations, and routes of administration in the 24 hours before delivery to avoid maternal postpartum hypoglycemia.

Management of **DKA** is similar in pregnant and nonpregnant women. It involves (1) intravenous hydration, (2) intravenous insulin, (3) treatment of the underlying cause of DKA, (4) careful monitoring of blood glucose and electrolyte levels, and (5) restriction of bicarbonate therapy to cases of extreme acidosis.[9,10,48] In addition, left uterine displacement should be maintained and supplemental oxygen should be administered. Initial management of the critically ill pregnant woman should focus on the effective management of DKA. Fetal compromise is likely to resolve with appropriate medical management.[56,57]

Diet and exercise are the initial therapeutic approaches for glycemic control in women with gestational DM. Insulin therapy is initiated if the fasting glucose measurement exceeds a threshold of 80 to 105 mg/dL.[23,117] In the past, oral hypoglycemic agents were not used extensively in pregnancy, primarily because of concerns about potential teratogenicity and fetal hyperinsulinemia. In current practice, many women with gestational DM are treated with glyburide, glipizide, or metformin.[118,119] Concerns about the long-term health implications of gestational diabetes have resulted in national initiatives for postpartum metabolic surveillance.[120,121] The goal is to identify and treat postpartum type 2 DM, with an emphasis on lifestyle interventions.

Timing of Delivery

Timing of delivery is important in the management of diabetic pregnancies. White[46] noted, "Our problem must [be] … to prevent premature delivery of the infant of the diabetic mother prior to the period of its viability … and, secondly, the termination of the pregnancy at the point of viability and before the dreaded late intrauterine accident can occur." Typically a nonstress test is performed twice weekly in patients with pregestational DM, beginning at 32 weeks' gestation.[122,123] A nonreactive nonstress test should prompt the performance of a fetal biophysical profile (see Chapter 6). Risk factors for abnormal fetal testing in diabetic pregnancies include maternal nephropathy, hypertension, and poor glycemic control.[124] No consensus exists regarding antepartum testing in women with well-controlled gestational DM.[23] Patients with poorly controlled gestational DM should probably undergo antepartum fetal surveillance similar to that in patients with pregestational DM.[23,117]

In the presence of reassuring fetal testing, delivery can be delayed until after 38 weeks' gestation.[122] If fetal testing is abnormal and amniotic fluid analysis indicates fetal pulmonary maturity, the fetus should be delivered as soon as possible. If fetal testing is abnormal but amniotic fluid analysis suggests that the fetal lungs are immature, decisions about the timing of delivery are more difficult.

The decision regarding the method of delivery requires consideration of estimated fetal weight, fetal condition, cervical dilation and effacement, and previous obstetric history. The obstetrician may choose elective cesarean delivery in the diabetic parturient with evidence of fetal macrosomia to decrease the risk for shoulder dystocia.

Anesthetic Management

Few studies exist concerning the anesthetic management of pregnant women with DM. In general, neuraxial analgesia is the preferred technique for labor and cesarean delivery, but clinical decisions about these patients must be guided by logical extensions of studies of nonpregnant diabetic patients and nondiabetic pregnant patients.

Preanesthetic evaluation of the woman with DM should include a history and physical examination that focuses on the identification of the acute and chronic complications of DM (see Box 43-1). There are

no published data on the relationship between the complications of DM and responses to anesthetic agents or on anesthetic outcomes in pregnant patients. In a study of nonpregnant diabetic patients, preoperative evidence of **autonomic cardiovascular dysfunction** was predictive of the need for a vasopressor during general anesthesia.[125] Because of the potential for hypotension during neuraxial anesthesia, noninvasive testing of autonomic function may be useful in obstetric patients with pregestational DM. For example, in nonpregnant diabetic patients the corrected QT interval on an electrocardiogram correlates with the severity of autonomic neuropathy.[126] Patients with evidence of autonomic dysfunction may benefit from more frequent blood pressure determinations and more vigorous intravenous hydration before and during the administration of neuraxial anesthesia. **Gastroparesis** is a manifestation of autonomic neuropathy in diabetic patients.[127] In nonpregnant diabetic patients, autonomic neuropathy is associated with a decreased cough reflex threshold and a higher incidence of obstructive sleep apnea.[128,129]

Several studies have examined the maternal, fetal, and neonatal effects of **neuraxial anesthesia** for cesarean delivery for women with pregestational DM.[130-133] Datta and Brown[130] observed that spinal anesthesia was associated with a slightly but significantly lower umbilical cord blood pH measurement at delivery in patients with pregestational DM than in similar patients who received general anesthesia for cesarean delivery. Subsequently, these investigators noted an association between fetal acidosis and peripartum maternal hypotension in patients with pregestational DM who received epidural anesthesia for cesarean delivery.[131] In both studies, acute maternal hyperglycemia—secondary to intravenous hydration with 5% dextrose before administration of neuraxial anesthesia—was a potentially confounding factor.[130]

Neonatal acidosis is *not* likely to occur during **spinal** or **epidural anesthesia** for cesarean delivery in diabetic parturients, provided that (1) maternal glycemic control is satisfactory, (2) the patient receives aggressive preanesthetic volume expansion with a non–dextrose-containing balanced salt solution, and (3) hypotension is treated promptly and aggressively.[132,133]

Thalme and Engstrom[134] demonstrated normal umbilical arterial blood pH measurements after the administration of **general anesthesia** in a small series of patients with pregestational DM.

After administration of epidural anesthesia for cesarean delivery, Ramanathan et al.[133] observed an increased incidence of neonatal hypoglycemia in patients with pregestational DM compared with nondiabetic controls (35% versus 7%, respectively). In this study, maternal glycemic control was fair (mean fasting plasma glucose level was 127 mg/dL), a non–dextrose-containing solution was used for intravenous hydration, and intravenous insulin therapy was adjusted on the basis of frequent blood glucose determinations. This study illustrates the neonate's vulnerability to hypoglycemia after a diabetic pregnancy despite meticulous anesthesia care at the time of delivery.

A single case report describes a parturient who received combined spinal-epidural labor analgesia and subsequently became hypoglycemic. The authors hypothesize that the rapid decrease in catecholamine levels from the resultant analgesia led to hypoglycemia.[135]

Maternal insulin requirements decrease with the onset of labor, increase again during the second stage of labor, and decrease markedly during the early postpartum period.[40,41] Intravenous insulin therapy is the most flexible method of treatment during this period of rapid change. Absorption of subcutaneous insulin may be unpredictable and may increase the risk for maternal hypoglycemia, especially during the postpartum period.[41] Moreover, strict glycemic control in pregnant women with type 1 DM increases the risk for maternal hypoglycemia as a result of impaired counterregulatory hormone responses (as discussed earlier).

Intravenous glucose and insulin infusions during the peripartum period should be titrated to maintain a maternal blood glucose concentration of 70 to 90 mg/dL. During active labor, the glucose requirement is 2.5 mg/kg/min or more.[38] For cesarean delivery with patients using subcutaneous insulin pumps, a preoperative strategy should be formulated for perioperative insulin pump management. This plan should identify the individual(s), other than the patient, who are experienced and knowledgeable in adjusting her insulin pump if the patient is not able to adjust it herself during surgery. Some patients and obstetricians prefer discontinuing the subcutaneous insulin pump preoperatively in favor of an intravenous insulin infusion. The preanesthetic evaluation is an excellent opportunity to discuss with the patient the expected changes in insulin requirements at the time of delivery. The preprocedure and postprocedure "time-outs" are excellent opportunities to discuss the plan for perioperative pump management and other diabetic management concerns with all team members.

Many perioperative strategies have been proposed for metabolic control in nonpregnant patients with DM.[136-138] No convincing evidence suggests that one clinical strategy for perioperative diabetic control is superior in terms of patient outcome. Frequent blood glucose measurements (e.g., at 30- to 60-minute intervals), followed by appropriate adjustment of glucose and insulin infusions, represent the cornerstone of optimal perioperative care in patients with DM.

There are no published data on the effects of DM on the pharmacokinetics and pharmacodynamics of anesthetic agents in pregnant women. In nonpregnant women, DM is associated with (1) a delayed onset of muscle relaxation with tubocurarine and (2) prolonged blockade with vecuronium.[139,140]

The **diabetic stiff-joint syndrome** has been associated with difficult direct laryngoscopy and tracheal intubation in patients with DM.[141,142] This syndrome occurs in patients with long-standing DM type 1 and is associated with nonfamilial short stature, joint contractures, and tight skin.[143] Limited movement of the atlantooccipital joint may result in difficult direct laryngoscopy and tracheal intubation. During the preanesthesia evaluation of patients with DM, the anesthesia provider can screen for the stiff-joint syndrome by looking for the "prayer sign" (Figure 43-4). Management is controversial. Some authorities recommend preanesthesia

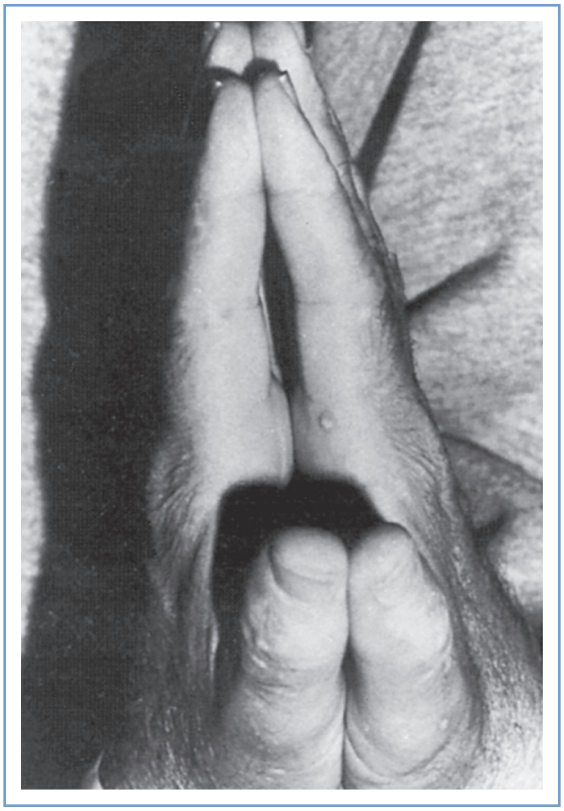

FIGURE 43-4 ■ Inability to approximate the palmar surfaces of the phalangeal joints despite maximal effort, secondary to diabetic stiff-joint syndrome. (From Hogan K, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988; 67:1162-5.)

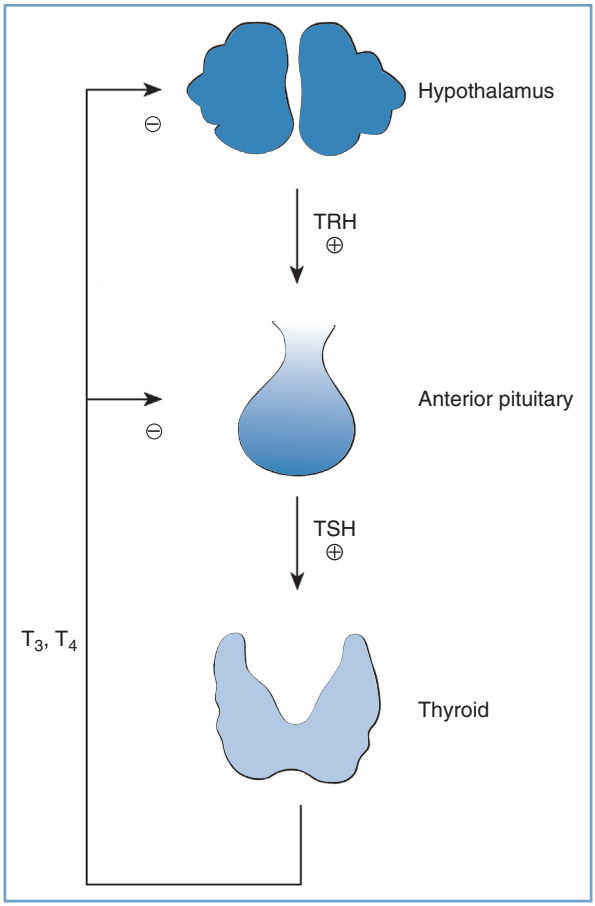

FIGURE 43-5 ■ Normal feedback control of thyroid hormone secretion. *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone; *T_3,* triiodothyronine; *T_4,* thyroxine. (From Davies PH, Franklyn JA. The effects of drugs on tests of thyroid function. Eur J Clin Pharmacol 1991; 40:439-51.)

flexion-extension radiographic studies of the cervical spine followed by awake tracheal intubation.[142] Others have expressed doubt about the clinical significance of this syndrome and the reported frequency of airway management problems.[144,145] The term **diabetic scleredema** is synonymous with stiff-joint syndrome. There is one case report of a pregnant patient with pregestational DM and diabetic scleredema who experienced anterior spinal artery syndrome after the administration of epidural anesthesia for cesarean delivery.[146] The author suggested that spinal cord vascular compression resulted from a combination of (1) preexisting microvascular disease, (2) an epidural space that was stiff because of connective tissue disease, and (3) administration of a large volume (i.e., 35 mL) of the local anesthetic agent. In patients with a history and physical examination that suggest diabetic stiff-joint syndrome, the anesthesia provider should consider two potential problems: (1) difficult direct laryngoscopy and tracheal intubation and (2) a noncompliant epidural space.

Infection is an important cause of morbidity in pregnant women with pregestational DM.[49] There are no published data regarding the incidence of CNS infection after the administration of neuraxial anesthesia in pregnant diabetic patients except for one case of fungal meningitis due to contaminated spinal anesthesia equipment.[147] Strict aseptic technique always should be used during the administration of neuraxial anesthesia.

THYROID DISORDERS

Thyroid Hormone Physiology

The follicular cells of the thyroid gland sequester iodine and synthesize thyroglobulin, an iodinated precursor protein. Thyroglobulin is secreted into the lumen of the microscopic thyroid follicles before it undergoes reuptake, proteolysis, and transfer to lysosomes, where it undergoes degradation.[148] This process results in the systemic release of the thyroid hormones: thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3). Reverse T_3 (3,3′,5′-triiodothyronine) is a structural variant with much less physiologic potency in most target organs.[149]

Thyroid hormone synthesis and release are controlled primarily by thyroid-stimulating hormone (TSH)—a trophic hormone from the pituitary—and the supply of iodine. The thyroid hormones normally participate in a negative feedback loop that regulates TSH secretion (Figure 43-5) and thyrotropin-releasing hormone production in the hypothalamus.[150]

Thyroid hormones are highly bound to protein in the blood. In euthyroid nonpregnant humans, the normal total serum concentrations of T_4 and T_3 are 50 to

150 nmol/L and 1.4 to 3.2 nmol/L, respectively.[151] The unbound or free fractions of T_4 and T_3 are 0.03% and 0.3% of total circulating T_4 and T_3, respectively.[152] Similar proportions of T_4 and T_3 are distributed among the three major plasma proteins that bind thyroid hormones, which are (1) thyroxine-binding globulin (70% to 80%), (2) thyroxine-binding prealbumin or transthyretin (10% to 20%), and (3) albumin (10% to 15%).[153,154] The serum concentration of unbound or free T_4 is typically the major determinant of thyroid hormone activity in target tissues. Thyroid hormones are temporarily inert while bound to plasma proteins. Changes in the concentrations of thyroxine-binding proteins can occur during various physiologic states (e.g., pregnancy) and disease processes. Thyroid hormone action does not change with fluctuations in the total concentration of T_4 as long as the concentration of free T_4 remains constant.

Thyroid hormone is an endocrine regulator in many target organs (e.g., liver, kidneys, skeletal and cardiac muscles, brain, pituitary, placenta).[155] The defined physiologic effects of thyroid hormones are mediated by regulation of specific gene products. These effects include (1) somatic and nervous system development, (2) calorigenesis, (3) augmented skeletal and cardiac muscle performance, (4) intermediary metabolism, and (5) feedback control.[156]

In target tissues, the molecular actions of T_4 begin with the enzymatic deiodination of T_4 to T_3. Iodothyronine deiodinase is widely distributed in the body and occurs in three molecular forms.[157] Only 20% of the daily T_3 production is secreted by the thyroid gland; the rest is formed by peripheral deiodination.[158] In the classic model of thyroid hormone action, T_3 enters the nuclei of target cells, binds to specific thyroid hormone receptors, and alters genomic transcription of specific proteins.[159] Research has now characterized other mechanisms of thyroid hormone action, including mitochondrial transcription and cytoplasmic or cell-surface nontranscriptional effects.[160,161] The thyroid hormone receptor belongs to a family of structurally related, intracellular ligand-binding proteins.[160] Variations in the number and types of thyroid hormone receptors, as well as receptor linkage to development- or tissue-specific genomic expressions, provide additional levels of physiologic control and vulnerability to disease processes.[157]

Antithyroid medications may affect single or multiple steps in thyroid hormone synthesis and release, as well as concentrations of plasma binding proteins, deiodinase activity, and peripheral uptake of thyroid hormones.[153,162,163]

Laboratory evaluation of thyroid function consists of two measurements. First, the serum concentration of free T_4 can be directly measured or indirectly calculated. Second, the serum concentration of TSH is measured to assess the negative feedback loop that controls the thyroid gland. The TSH concentration is judged as appropriate or inappropriate in the context of the serum concentration of free T_4.

During normal human pregnancy, the serum concentration of thyroxine-binding globulin (TBG) steadily increases until it reaches a plateau at 20 weeks' gestation, when it is 50% greater than the nonpregnant level.[151] The greater concentration of TBG results from a prolonged half-life—not higher synthesis—during pregnancy.[154] The normal pregnant woman is euthyroid because the serum concentrations of free T_4 and T_3 are in the normal or low-normal range for nonpregnant humans.[151] However, the increased concentration of TBG means that total serum concentrations of T_4 and T_3 during pregnancy are at or above the upper limit of normal for nonpregnant women.[151,164]

Human chorionic gonadotropin (hCG) is a placental protein that shares some structural features with TSH. The serum concentrations of TSH and hCG have an inverse relationship during normal human pregnancy,[151] reflecting the mild TSH-like activity that results from increased plasma concentrations of hCG during early pregnancy.[165,166]

Maternal iodine availability is decreased during pregnancy because of greater fetal uptake and increased maternal renal clearance.[167] In geographic areas with marginal iodine supplies, the lower availability may predispose the mother to goiter unless she receives dietary iodine supplementation.[151,168,169]

Hyperthyroidism

Definition and Epidemiology

Hyperthyroidism is defined as an abnormal increase in the serum concentration of unbound or free thyroid hormones. The prevalence of hyperthyroidism in the general population is 0.2% to 1.9%, with a female-to-male ratio of 10:1.[170,171] The etiology of hyperthyroidism is listed in Box 43-5. Graves' disease is responsible for 70% to 90% of cases; thyroiditis and the combined category of toxic adenoma and toxic multinodular goiter each account for approximately 5% of cases. There are multiple levels of interaction between the thyroid and reproductive endocrine systems in women, with specific implications for patients with hyperthyroidism and hypothyroidism.[172]

BOX 43-5 Etiology of Hyperthyroidism

Abnormal Thyroid Stimulation

- Graves' disease
- Gestational trophoblastic neoplasia
- Thyroid-stimulating hormone–secreting pituitary tumor

Intrinsic Thyroid Autonomy

- Toxic adenoma
- Toxic multinodular goiter

Inflammatory Disease

- Subacute thyroiditis

Extrinsic Hormone Source

- Ectopic thyroid tissue
- Thyroid hormone ingestion

Modified from Houston MS, Hay ID. Practical management of hyperthyroidism. Am Fam Physician 1990; 41:909-16.

Pathophysiology

Graves' disease is an autoimmune thyroid disease.[170,173] Its etiology is likely multifactorial and includes both **environmental** (e.g., stress, hormones) and **genetic** influences. Several autoantibodies against thyroid tissue have been described in patients with this disease. Autoantibodies directed against the TSH receptor in the thyroid gland may either augment or inhibit TSH action, depending on their binding specificities. These antibodies are called **thyroid receptor antibodies (TRAbs)**. The binding specificities of TRAbs in the blood of each patient with Graves' disease affect the net thyroid-stimulating activity. Autoantibodies against thyroid peroxidase, the sodium-iodine cotransporter, and thyroglobulin also have been described in patients with Graves' disease.

Among untreated patients with Graves' disease, approximately 20% undergo spontaneous remission.[173] However, the prognosis for individual patients cannot be predicted from results of clinical or laboratory examinations.

Clinical Presentation and Diagnosis

Hyperthyroidism presents as a physiologic state dominated by an increased metabolic rate. A hyperthyroid symptom scale has been developed on the basis of the following 10 clinical factors: nervousness, sweating, heat intolerance, hyperactivity, tremor, weakness, hyperdynamic precordium, diarrhea, appetite, and level of incapacitation.[174] This symptom scale has been useful to follow the clinical course of patients with Graves' disease. Exophthalmos or infiltrative ophthalmopathy is clinically apparent in most patients.[173-175] Other physical signs may occur at low frequency, including pretibial myxedema or dermopathy (1% to 2%) and nail changes or acropachy (< 1%). The infiltrative ophthalmopathy in Graves' disease is caused by enlargement of both the extraocular muscle bodies and intraorbital adipose tissue. The pathogenetic mechanism involves abnormal accumulation of hyaluronic acid and edema within these tissues; the orbital fibroblast appears to be the primary target cell of this autoimmune process.[175]

Hyperthyroidism stimulates the cardiovascular system in excess of the underlying increased metabolic rate, resulting in a hyperkinetic circulatory state.[163,176] Myocardial contractility, heart rate, stroke volume, and ventricular size all increase, and peripheral vascular resistance decreases in skin and muscle. Thyroid hormones can affect the ratio of alpha- and beta-adrenergic receptors in the heart.[176] Cardiomyopathy can be demonstrated during exercise in hyperthyroid patients, independent of beta-adrenergic receptors; it is reversible with normalization of thyroid function.[177]

The diagnosis of hyperthyroidism depends on increased serum concentrations of unbound or free T_4. The more common forms of hyperthyroidism (e.g., Graves' disease, toxic adenoma, toxic multinodular goiter) may be differentiated from the less common forms by a radioiodine uptake study.[171] The identification of TSH receptor autoantibodies may have some role in distinguishing Graves' disease from toxic adenoma or multinodular goiter.[173]

Interaction with Pregnancy

Normal human pregnancy is a euthyroid state, with normal serum concentrations of unbound or free T_4 despite increased serum concentrations of TBG and total T_4. During pregnancy, hyperthyroidism results from the same causes as in nonpregnant patients (see Box 43-5). Graves' disease is the leading cause of hyperthyroidism during pregnancy, with a prevalence of 0.2%, which is lower than in the general population.[178-180] The lower prevalence may reflect a beneficial effect of the immunotolerance of pregnancy on autoimmune disorders such as Graves' disease.[173] Human pregnancy is also associated with a change in the specificity of TSH receptor antibody activity from stimulatory to blocking activity.[181]

Gestational trophoblastic neoplasms are frequently associated with elevated serum hCG concentrations. High concentrations of hCG may possess significant thyroid-stimulating bioactivity because of the structural homology between hCG and TSH.[165,182] Transient hyperthyroidism during pregnancy has been reported in association with hyperemesis gravidarum; hyperthyroidism and hyperemesis gravidarum may be parallel disease processes in pregnancy, with elevated hCG as a shared mechanism.[183] Hyperthyroidism can, on rare occasions, result from two coincident disease processes (e.g., Graves' disease, struma ovarii) in both pregnant and nonpregnant women.[184]

Thyroid nodules occur in 4% to 7% of adults. Pregnancy is associated with increases in the number and size of thyroid nodules.[185] Pregnancy probably does not affect the development or progression of thyroid carcinoma, but this conclusion remains controversial.[186,187] Evaluation of a thyroid nodule that presents during pregnancy should include (1) measurement of serum TSH and free T_4 concentrations, (2) ultrasonographic examination to determine whether the lesion is cystic or solid, and (3) fine-needle aspiration or percutaneous needle biopsy. Malignant lesions, depending on the level of cellular differentiation, can be resected in the second trimester or observed until after delivery.[187] Radioactive iodine therapy should be delayed until the postpartum period.[186]

Medical and Surgical Management

Current therapies for Graves' disease in *nonpregnant* patients include radioactive iodine, antithyroid medications, and surgery.[170,171]

Radioactive iodine is administered orally as iodine-131 (^{131}I) in a dose range of 30 to 75 mCi.[188] All forms of iodine are sequestered by the thyroid gland, and ^{131}I exerts a therapeutic effect in Graves' disease primarily through local emission of beta radiation. In most patients with Graves' disease, hypothyroidism develops after a therapeutic dose of radioactive iodine, necessitating careful follow-up and long-term thyroid hormone replacement therapy. In nonpregnant patients, the long-term health risks of radioactive iodine therapy are minimal.[188] Radioactive iodine therapy is *contraindicated*

in pregnancy, because all forms of iodine readily cross the placenta to the fetus. Currently recommended treatment is to delay pregnancy for 4 to 6 months after radioactive iodine therapy, although ^{131}I has a half-life of only 8 days.[188]

Propylthiouracil and **methimazole** are the antithyroid medications used to treat Graves' disease.[163,189] These drugs interfere with the incorporation of iodine into thyroglobulin and with subsequent coupling reactions in the thyroid gland, and propylthiouracil inhibits iodothyronine deiodinase in peripheral tissues. Typical oral doses are 5 to 15 mg two times daily for methimazole and 100 to 150 mg three times daily for propylthiouracil. The long-term clinical strategy is to adjust the dose downward as tolerated. Some patients with Graves' disease experience remission after the administration of an antithyroid medication. Asymptomatic agranulocytosis, with an incidence of 0.03% to 0.5%, is a rare complication of antithyroid medications; onset typically occurs within 3 months of initiating therapy. Another rare complication of propylthiouracil, fulminant hepatic necrosis, prompted an FDA safety alert in 2009.[190] If treatment with antithyroid medications is unsatisfactory, *nonpregnant* patients may receive radioactive iodine.

Surgical therapy for Graves' disease is typically reserved for patients unable or unwilling to undergo treatment with radioactive iodine or antithyroid medications.[171,191] Controversy exists about the choice between subtotal and total thyroidectomy; the surgeon must weigh the risk for recurrent hyperthyroidism against that of permanent hypothyroidism requiring supplementation.[191] Perioperative complications of thyroid surgery include (1) unilateral or bilateral vocal cord paralysis secondary to laryngeal nerve injury, (2) wound hematoma, (3) pneumothorax, (4) hypoparathyroidism, and (5) thyroid storm.[191] Hypocalcemia secondary to acute hypoparathyroidism may manifest as laryngospasm during the postoperative period.[192]

Adjunctive therapies for hyperthyroidism include iodine, radiocontrast agents, lithium, and glucocorticoids.[163,170] Beta-adrenergic receptor antagonists also have been used to decrease cardiovascular responses to higher concentrations of thyroid hormones.

Thyroid Storm. Thyroid storm, also known as thyroid crisis, is a life-threatening exacerbation or decompensation of a preexisting hyperthyroid state.[193-196] It is a clinical diagnosis based on the following signs and symptoms: (1) fever, (2) mental and emotional disturbances, (3) tachycardia, (4) tachypnea, (5) diarrhea, (6) congestive heart failure, and (7) atrial fibrillation. Without treatment, thyroid storm may progress to coma, multiorgan system failure, and death. The mortality rate approached 100% in earlier series, but improved therapy has reduced the mortality rate to less than 20%.[195]

In most cases, thyroid storm is associated with a precipitating event in a patient with untreated or incompletely treated hyperthyroidism (Box 43-6). Historically, the precipitating events reflect the common serious medical illnesses of a given era[193,194-196]; cases of thyroid storm were categorized as "surgical" or "medical" depending on whether the exacerbation occurred during the perioperative period. With improved perioperative management, the incidence of *surgical* thyroid storm has decreased markedly, and this terminology is rarely used in contemporary medical practice.

BOX 43-6 Events Associated with Precipitation of Thyroid Storm

- Surgery
- Childbirth
- Trauma
- Iodinated contrast agents
- Treatment with iodine-131
- Emotional stress
- Pulmonary embolism
- Stroke
- Infection
- Diabetic ketoacidosis
- Hypoglycemia
- Congestive heart failure
- Bowel infarction

From Roth RN, McAuliffe MJ. Hyperthyroidism and thyroid storm. Emerg Med Clin North Am 1989; 7:873-83.

In the past, 2% to 7% of patients hospitalized for hyperthyroidism experienced thyroid storm.[193,194,196] The current incidence of thyroid storm in hyperthyroid patients is difficult to determine but appears to be much lower. Akamizu et al.[197] estimated that the incidence of thyroid storm in Japan was 0.2 per 100,000 hospitalized patients between 2004 and 2008.

The mechanism of the development of thyroid storm is unknown. On the basis of the clinical presentation and known precipitating events, one hypothesis is that it is caused by increases in thyroid hormone and catecholamine secretion. Limited data suggest that total serum concentrations of T_4 and T_3 do not increase during thyroid storm in hyperthyroid patients,[198] although one case report suggests otherwise.[199] Alternatively, the precipitating event in thyroid storm may augment thyroid hormone action by increasing the circulating free fraction of thyroid hormones. This hypothesis is supported by data that demonstrate higher serum concentrations of free T_4 during thyroid storm as well as by observations of changes in thyroid hormone binding during fever or systemic illness.[200]

Catecholamine secretion may also play a role in the development of thyroid storm. In hyperthyroid patients without thyroid storm, the endogenous secretion of epinephrine and norepinephrine is normal, as are the cardiovascular responses to exogenous epinephrine and isoproterenol.[201,202] These parameters have not been measured during episodes of thyroid storm, but symptoms respond well to medications that block the synthesis or receptor binding of beta-adrenergic receptor agonists.[194] The role of the sympathetic nervous system in thyroid storm is supported by historical observations that spinal anesthesia to the fourth thoracic dermatome level is therapeutic.[203] It is unclear whether thyroid storm can develop with baseline catecholamine secretions; a surge of catecholamines may be necessary to trigger this condition.

BOX 43-7 Treatment of Thyroid Storm

General Supportive Measures

- Cooling blanket and ice
- Chlorpromazine (25-50 mg IV) or meperidine (25-50 mg IV) to diminish shivering
- Intravenous hydration
- Glucose and electrolyte replacement
- Acetaminophen
- Oxygen
- Glucocorticoids: dexamethasone (2-4 mg IV q8h) or hydrocortisone (100 mg IV q8h)
- B-complex multivitamins

Reduction of Synthesis and Secretion of Thyroid Hormones

- Antithyroid medications: propylthiouracil (200-400 mg orally q6-8h) or methimazole (20-25 mg orally q6h)
- Iodine: sodium iodide (1 g IV or Lugol's solution 4-8 drops orally q6-8h) or supersaturated potassium iodide solution (5 drops orally q6h)
- Glucocorticoids

Reduction of Peripheral Conversion of Thyroxine (T_4) to 3,5,3′-Triiodothyronine (T_3)

- Propylthiouracil
- Glucocorticoids
- Radiographic contrast agents
- Propranolol

Decrease in the Metabolic Effects of Thyroid Hormones

- Beta-adrenergic receptor antagonists (propranolol, esmolol)

Other Therapeutic Maneuvers

- Plasma exchange

Diagnosis and Treatment of the Underlying Illness That Precipitated the Thyroid Storm

IV, intravenous.
Modified from Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006; 35:663-86.

Box 43-7 outlines the treatment of thyroid storm. Several points merit discussion. Glucocorticoid supplementation is listed as a general supportive measure because endogenous glucocorticoid production is impaired in patients with hyperthyroidism.[204] Glucocorticoids also inhibit both thyroid hormone production and the peripheral conversion of T_4 to T_3.[173] Propylthiouracil and methimazole reduce thyroid hormone production, but only propylthiouracil inhibits the peripheral conversion of T_4 to T_3 (as discussed earlier). In addition to the relief of many symptoms of hyperthyroidism, propranolol inhibits the peripheral conversion of T_4 to T_3. This latter property of propranolol is not related to its beta-adrenergic receptor blocking activity and is not shared by most other beta-adrenergic receptor antagonists.[205,206] Because of its dual action, propranolol is the beta-adrenergic receptor antagonist of choice in cases of thyroid storm. Esmolol also has been used successfully during the treatment of thyroid storm (see later discussion).[207,208]

Thyroid storm is an acute hypermetabolic state that may be difficult to distinguish clinically from malignant hyperthermia; rhabdomyolysis is one of the few features of the latter disorder that has not also been reported in thyroid storm.[209] Three cases of thyroid storm treated with dantrolene have been reported.[210-212] Two patients survived, but the third succumbed to multiorgan system failure that antedated the dantrolene therapy. In another case, a patient with known Graves' disease undergoing subtotal thyroidectomy had an intraoperative hypermetabolic crisis that was initially diagnosed and treated as thyroid storm. The correct diagnosis of malignant hyperthermia was made on the basis of subsequent blood gas analysis, and the patient was successfully treated with dantrolene.[213] Plasma exchange is another unusual but effective therapeutic option in cases of thyroid storm.[214]

In summary, treatment of thyroid storm consists of general supportive measures and the administration of glucocorticoids, propylthiouracil, sodium iodide, and propranolol. It is reasonable to delay iodine treatment until 1 hour after the administration of propylthiouracil to avoid increased iodine use by the thyroid gland.

Preoperative Preparation. The risk for thyroid storm during the perioperative period can be minimized by appropriate preparation of the hyperthyroid patient. Most cases of perioperative thyroid storm involve thyroid surgery. The preoperative therapeutic goals are to inhibit thyroid hormone synthesis and secretion in patients with preexisting hyperthyroidism and to decrease the vascularity of the thyroid gland. The four main therapies used in preoperative preparation are administration of (1) an antithyroid medication (primarily propylthiouracil), (2) a beta-adrenergic receptor antagonist, (3) a glucocorticoid, and (4) iodine.[163,191,215] Iodine inhibits thyroid hormone secretion more effectively in hyperthyroid patients than in euthyroid patients because the latter are capable of mounting a compensatory TSH response as serum T_4 levels decrease.[216]

In some patients, beta-adrenergic receptor blockade may be sufficient to prevent perioperative thyroid storm,[217] although thyroid storm has been reported after preoperative preparation with propranolol alone.[218] In some of these cases, patients probably did not receive effective beta-adrenergic receptor blockade. A 25% reduction in exercise-induced heart rate is a better indication of adequate beta-adrenergic receptor blockade than a change in the resting heart rate.[215] One advantage of beta-adrenergic receptor antagonists over antithyroid medications is the shorter time typically required for preoperative preparation: (i.e., 2 weeks versus 6 to 8 weeks, respectively).[217] Several investigators have recommended preoperative preparation with a beta-adrenergic receptor antagonist, with the addition of iodine beginning 10 days before surgery.[215,219] The use of beta-adrenergic receptor antagonists entails a risk for hypoglycemia in hyperthyroid patients, because they have reduced hepatic glucose reserves and nonspecific beta-adrenergic receptor blockade results in a pharmacologic blunting of counterregulatory sympathetic responses.[215]

No prospective randomized studies have compared the efficacy of various methods for preoperative preparation of hyperthyroid patients. A reasonable clinical approach would include the use of multiple therapeutic agents (e.g., a beta-adrenergic receptor antagonist, iodine, glucocorticoid), with the doses titrated to the clinical response of each patient. The clinical parameters may include exercise-induced heart rate, fine tremor, weight gain, and recovery of muscle strength.[163]

Elective surgery should not proceed without adequate preoperative preparation of hyperthyroid patients. In cases of emergency surgery, physicians should use the therapies discussed for the treatment of thyroid storm (as discussed earlier) (see Box 43-7).

Medical and Surgical Management during Pregnancy. All of the therapeutic options used in nonpregnant hyperthyroid patients should be efficacious in pregnant women. However, the potential effects on the fetus dictate modifications in the options for treatment of hyperthyroidism during pregnancy.

Radioactive iodine is *contraindicated* during pregnancy because iodine readily crosses the placenta to the fetus. Fetal effects of inadvertent maternal administration of ^{131}I vary with gestational age.[188] Before 10 weeks' gestation, the risk to the fetus is less well defined and likely approximates that of a low-level dose of radiation during early development[188]; after 10 weeks' gestation, however, the fetal thyroid gland can sequester iodine, and ^{131}I may destroy or significantly damage the gland.

The mainstays of therapy for hyperthyroidism during pregnancy are the antithyroid medications **propylthiouracil** and **methimazole,**[170,178,179,189] which cross the placenta much more easily than the maternal thyroid hormones—potentially inducing fetal hypothyroidism and goiter. Although these agents are similar in efficacy for treatment of hyperthyroidism during pregnancy,[179,189] propylthiouracil has been used more frequently than methimazole. Propylthiouracil is favored in the first trimester of pregnancy, owing to rare congenital anomalies reported with methimazole (e.g., scalp defects, choanal atresia, tracheoesophageal fistula).[187,220,221] After the first trimester, therapy can be switched to methimazole if there are concerns for hepatotoxicity with propylthiouracil.

Surgical therapy (e.g., subtotal thyroidectomy) is generally reserved for pregnant women in whom medical therapy has failed.[191] The pregnant woman should receive preoperative preparation with a beta-adrenergic receptor antagonist, a glucocorticoid, and iodine to minimize the risk for thyroid storm. Clinical data suggest that treating maternal Graves' disease with iodine does not result in fetal hypothyroidism,[222] implying that short-term preoperative maternal treatment with iodine should be safe for the fetus.

One national database study of pregnant women undergoing thyroid or parathyroid surgery demonstrated a threefold increase in general complications compared with age-matched nonpregnant controls.[223] In pregnant patients with Grave's disease, surgical thyroidectomy may lead to fetal hyperthyroidism through a combination of autoimmune and medication effects.[224]

During pregnancy, **thyroid storm** is a rare hypermetabolic event. Prior reports of a 2% to 4% incidence among pregnant patients are probably overestimates of the true incidence.[197] Most contemporary cases of thyroid storm during pregnancy occur in patients with undiagnosed or undertreated preexisting hyperthyroidism.[225-227] Precipitating events for thyroid storm during pregnancy include infection, thyroid cancer, normal labor, hemorrhage, cesarean delivery, and eclampsia.[225-228]

Treatment of thyroid storm is identical for both pregnant and nonpregnant patients (as discussed earlier) (see Box 43-7). Despite an association with fetal growth restriction (also known as intrauterine growth restriction) or preterm labor,[229] beta-adrenergic receptor antagonists are commonly prescribed during pregnancy. **Propranolol** is the most widely used beta-adrenergic receptor antagonist for treatment of thyroid storm.

Several case reports have described the use of the beta-adrenergic receptor antagonist **esmolol** for treatment of hyperthyroidism in both pregnant and nonpregnant patients,[207,208] although laboratory and clinical observations suggest that maternal administration of esmolol may result in fetal bradycardia and acidosis.[230,231] Esmolol may be considered when propranolol is contraindicated or the patient's hemodynamic status requires the use of a short-acting beta-adrenergic receptor antagonist. Esmolol is preferred for patients with a relative contraindication to nonspecific beta-adrenergic receptor blockade (e.g., asthma). Patients with significant cardiomyopathy from hyperthyroidism, who may be very sensitive to beta-adrenergic receptor blockade,[177,232,233] may benefit from esmolol because the dose can easily be titrated to the desired effect.[234] Hyperthyroid cardiomyopathy during pregnancy or the puerperium may require invasive monitoring and the use of multiple medications that require titration.[225,235,236] Esmolol's short half-life allows a rapid reversal of effect if needed. Untreated hyperthyroidism is associated with secondary pulmonary hypertension.[237]

In general, maternal and fetal interests are best served by optimal maternal therapy. When the physician opts for maternal therapy that could, in theory, adversely affect fetal well-being, the rationale should be documented in the medical record.

Obstetric Management

Poorly controlled hyperthyroidism during pregnancy increases the risks for severe preeclampsia in the mother and for low birth weight in the newborn.[238] Pregnant patients with treated hyperthyroidism have perinatal outcomes similar to those for euthyroid parturients.[239] The presence of hyperthyroidism does not affect the obstetric management of preeclampsia. In a retrospective study, Davis et al.[225] suggested that early diagnosis and treatment of hyperthyroidism during pregnancy is associated with better maternal and fetal outcomes.

The use of a nonselective beta-adrenergic receptor antagonist may precipitate or aggravate preterm labor. In women with Graves' disease, the placental transfer of antithyroid medications or thyroid-stimulating antibodies may result in the development of **fetal goiter**,[240] which can interfere with vaginal delivery or lead to airway

obstruction in the newborn. Fetal goiter can be diagnosed with ultrasonography; fetal hypothyroidism can be diagnosed with percutaneous umbilical cord blood sampling and can be treated with intra-amniotic injections of thyroxine.[241] In pregnant women with Graves' disease, maternal serum concentrations of TRAbs during the third trimester may predict neonatal thyroid function.[242]

Normal somatic and intellectual development have been reported in the children of hyperthyroid mothers treated with antithyroid medications[243]; such treatment does not contraindicate breast-feeding (see Chapter 14).[189]

Anesthetic Management

No prospective randomized studies have evaluated the efficacy or safety of various anesthetic techniques in patients with hyperthyroidism. The following features of hyperthyroidism may affect anesthetic management: (1) the hyperdynamic cardiovascular system and the possibility of cardiomyopathy, (2) partial airway obstruction secondary to an enlarged thyroid gland, (3) respiratory muscle weakness, and (4) electrolyte abnormalities.[163,244]

Halpern[245] described two patients with uncontrolled hyperthyroidism who required anesthesia for cesarean delivery and suggested that either neuraxial or general anesthesia can be safely administered in these parturients. On the basis of theoretical concerns, he suggested the omission of epinephrine from the epidural solution of local anesthetic agent and the use of an alpha-adrenergic receptor agonist (e.g., phenylephrine) for the treatment of hypotension. Earlier clinical studies in nonpregnant subjects with spontaneous hyperthyroidism, however, have shown normal hemodynamic responses to exogenous epinephrine, norepinephrine, phenylephrine, and clonidine.[246,247] It therefore appears safe to use epinephrine to minimize local anesthetic uptake and toxicity during the administration of epidural anesthesia in both euthyroid and hyperthyroid patients.

Hyperthyroid women should receive glucocorticoid supplementation because they have a relative deficiency of glucocorticoid reserves.[204] It seems prudent to avoid medications associated with tachycardia (e.g., ketamine, atropine).[163,245] Patients with Graves' disease may have exophthalmos and therefore may require additional care to prevent corneal abrasions during general anesthesia.[245] Some investigators have emphasized the efficacy of deep preoperative sedation in nonpregnant hyperthyroid patients.[163,203] The routine use of this technique in pregnant patients is not recommended because of the risks for maternal aspiration and neonatal depression.

Adequate preoperative preparation minimizes the risk for perioperative thyroid storm; when time permits, the goal is to make the patient euthyroid. In an emergency, the hyperthyroid patient can be prepared for surgery with oral propylthiouracil, an intravenous glucocorticoid, sodium iodide, and propranolol. The anesthesia provider should be prepared to treat perioperative thyroid storm (see Box 43-7).

Hypothyroidism

Definition and Epidemiology

Hypothyroidism is defined as an abnormal decrease in the serum concentration of unbound or free thyroid hormones. The prevalence of hypothyroidism in the general population is 0.1% to 2%, which is similar to that of hyperthyroidism.[248] Hypothyroidism is more common in women and the elderly. Screening tests for hypothyroidism in asymptomatic nonpregnant adults are not recommended by the American Academy of Family Physicians.[249] When clinically indicated, the preferred screening test is a sensitive assay for serum TSH.

Pathophysiology

The etiology of hypothyroidism can be divided into primary and secondary categories (Box 43-8); primary hypothyroidism is more common than secondary hypothyroidism. The clinical manifestations of hypothyroidism result from withdrawal of thyroid hormone from its many target organs and tissues.

BOX 43-8 Causes of Hypothyroidism

PRIMARY

Autoimmune

- Hashimoto's thyroiditis
- Atrophic hypothyroidism

Iatrogenic

- Radioiodine therapy for hyperthyroidism
- Subtotal thyroidectomy

Pharmacologic

- Iodine deficiency or excess
- Lithium
- Amiodarone
- Antithyroid drugs

Congenital

- Dyshormonogenesis
- Thyroid gland dysgenesis or agenesis

SECONDARY

Pituitary Dysfunction

- Irradiation
- Surgery
- Neoplasm
- Sheehan's syndrome
- Idiopathic

Hypothalamic Dysfunction

- Irradiation
- Granulomatous disease
- Neoplasm

From Gain LA. The diagnostic dilemmas of hyperthyroxinemia and hypothyroxinemia. Adv Intern Med 1988; 33:185-203.

Clinical Presentation and Diagnosis

The clinical presentation of hypothyroidism is dominated by constitutional signs and symptoms such as dry skin, decreased sweating, hoarseness, paresthesia, periorbital edema, and delayed reflexes.[250] A diagnosis of hypothyroidism may be suggested by detection of the following factors during the preanesthetic history and physical examination: (1) a history of neck irradiation or radioiodine therapy; (2) the use of lithium, iodine, amiodarone, antithyroid medications, or thyroid replacement medications; and (3) a history of thyroid surgery or the presence of a surgical scar overlying the site of the thyroid gland.

By definition, hypothyroidism is diagnosed by measuring a decreased serum concentration of unbound or free T_4. In the presence of an intact feedback loop, the serum concentration of TSH should be increased in patients with primary hypothyroidism. The serum TSH concentration is a more sensitive indicator of primary hypothyroidism than the serum T_4 concentration and is therefore the best initial laboratory test in a patient with suspected hypothyroidism.[248,249]

Interaction with Pregnancy

The prevalence of hypothyroidism during pregnancy is 0.3% to 0.5%.[251] This estimate is based on laboratory screening of all obstetric patients in a given geographic area. Pregnant women likely exhibit overt or symptomatic hypothyroidism at a much lower rate than nonpregnant women. Hypothyroid women have a lower fertility rate than euthyroid women; this difference reflects neuroendocrine and ovarian dysfunction.[172,252] The immunosuppressive effects of pregnancy may lead to a temporary improvement of Hashimoto's thyroiditis during pregnancy.

Medical Management

Hypothyroidism is treated by replacement therapy with oral thyroid hormones. The medication most commonly used in replacement therapy is **levothyroxine,**[253] which has a half-life of 7 days. Numerous studies have shown that the required replacement dose of thyroid hormone in hypothyroid women often increases during pregnancy.* Ideally, the increased dose of thyroid hormone replacement will begin as soon as pregnancy is recognized, and it will be titrated to serum TSH levels at 4-week intervals during the first half of pregnancy.[220,254,255]

Obstetric Management

Hypothyroidism is associated with an increased incidence of the following obstetric complications: anemia, preeclampsia, fetal growth restriction, gestational diabetes, preterm delivery, placental abruption, and postpartum hemorrhage.[178,251,256-258] However, several reports have emphasized successful pregnancy outcomes in some hypothyroid patients.[259,260] Early diagnosis and treatment of hypothyroidism appear to be associated with improved maternal and fetal well-being.

In most instances of maternal hypothyroidism, neonatal thyroid function is normal because fetal thyroid development is typically independent of maternal thyroid function. The fetus, however, depends on maternal thyroxine until the fetal thyroid system is fully functional at approximately 20 weeks' gestation. Therefore, maternal hypothyroidism in the first half of pregnancy may affect fetal brain development. In addition, fetal hypothyroidism during the second half of pregnancy may also affect normal maturation of the CNS.[261] With universal screening of neonates for hypothyroidism, these neonates should be readily identified. Published data suggest that cognitive development is relatively normal in hypothyroid infants who receive appropriate thyroid hormone replacement with an initial dose of 10 to 15 μg/kg/day.[262] Controversy continues on the issue of screening pregnant women for hypothyroidism with serum TSH levels. It is unclear whether screening should be universally applied to all pregnant women or restricted to a high-risk subgroup identified by medical history.[220,221,251,263-265] The current recommendations favor the second approach, but additional clinical studies are underway.[187,266,267]

Anesthetic Management

The clinical manifestations of hypothyroidism that may affect anesthetic management include the following[268-278]:

- Reversible myocardial dysfunction
- Coronary artery disease
- Reversible defects in hypoxic and hypercapnic ventilatory drives
- Obstructive sleep apnea
- Paresthesias
- Prolonged somatosensory-evoked potential central conduction time
- Abnormal peripheral nerve conduction
- Increased peripheral nociceptive thresholds
- Hyponatremia
- Decreased glucocorticoid reserves
- Anemia
- Abnormal coagulation factors and platelets

Hypothyroid patients may have an abnormal response to peripheral nerve stimulation that decreases the clinical use of a nerve stimulator during neuromuscular blockade.[279] Clinical studies of vasopressors in nonpregnant hypothyroid patients show normal responses to exogenous epinephrine and diminished responses to phenylephrine.[280,281]

Whether elective surgery should or should not be delayed in order to treat hypothyroidism adequately is controversial.[282] Patient safety issues may justify such a delay. For emergency procedures, anesthesia care should include glucocorticoid supplementation. **Myxedema** (hypothyroid) coma is likely the only circumstance in which acute intravenous thyroid hormone replacement is indicated.[195] In most hypothyroid patients, acute intravenous replacement therapy entails a significant risk for myocardial ischemia.[270]

No prospective randomized studies have compared the safety or efficacy of various anesthetic techniques in

*References 178, 180, 187, 220, 221, 248, 251.

pregnant or nonpregnant hypothyroid patients. Hypothyroidism is associated with qualitative platelet dysfunction and is a rare cause of acquired von Willebrand's disease.[278,283,284] The anesthesia provider should use findings from the history and physical examination as well as laboratory testing to verify the presence of normal coagulation before administering neuraxial anesthesia to the patient with severe untreated hypothyroidism. Although epidural hematoma represents a theoretical risk in such patients, there are no published reports of this complication in this patient population.

PHEOCHROMOCYTOMA

Definition and Epidemiology

Paragangliomas are a heterogeneous group of tumors that develop from neural crest–derived chromaffin cells.[285,286] Pheochromocytomas are paragangliomas that arise in the adrenal medulla (90%) or in the adjacent sympathetic nervous system tissues.[285,286] Extra-adrenal paragangliomas may develop from sympathetic or parasympathetic tissues and include such diverse neoplasms as glomus tumors, chemodectomas, carotid body tumors, and jugulotympanic tumors.[287] Pheochromocytomas occur bilaterally (e.g., in the medulla of both adrenal glands) in 5% to 10% of cases.[288] Approximately 10% of pheochromocytomas are malignant.[288,289] Histopathologic features are not reliable predictors of malignancy[290]; however, large tumor size, extra-adrenal location, and certain tumor susceptibility gene mutations (e.g., succinate dehydrogenase subunit B) are associated with malignant pheochromocytomas.[287]

Pheochromocytomas occur in 0.1% to 0.2% of hypertensive adults.[286] Men and women are affected relatively equally, and the peak incidence varies between the third and seventh decades of life.

Pheochromocytoma is one of the tumors found in two of the **multiple endocrine neoplasia (MEN)** syndromes, **MEN 2A** (e.g., medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma) and **MEN 2B** (e.g., medullary thyroid carcinoma, mucocutaneous neuromas, pheochromocytoma).[291] Other disease processes associated with pheochromocytoma include von Recklinghausen's disease, von Hippel–Lindau disease, Sturge-Weber syndrome, and tuberous sclerosis. At least 10 distinct genetic mutations have been identified in patients with paragangliomas; the estimated rate of the familial form of pheochromocytoma is 30%.[285,287] There is an evolving concept of combined genotype/biochemical phenotype classifications to predict the clinical behavior of pheochromocytomas in individual patients.[292]

Pathophysiology

The pathophysiology of pheochromocytoma is related almost entirely to the systemic effects of its endocrine secretory products, typically norepinephrine and epinephrine. Some pheochromocytomas may, however, secrete other catecholamines (e.g., dopamine, dihydroxyphenylalanine [DOPA]) or peptide hormones. In an individual patient, the clinical manifestations of pheochromocytoma represent the net systemic effects of the tumor's secretory products.

TABLE 43-3 Symptoms of Pheochromocytoma during Paroxysmal Attacks

Symptom	Patients Affected in Previous Series (%)		Patients Affected in Ross & Griffith Series (%)
	MEAN	RANGE	
Headache	59.9	43-80	57
Sweating	52.2	37-71	61
Palpitations	49.2	44-71	63
Pallor	42.9	42-44	43
Nausea	34.5	10-42	33
Tremor	33.5	30-38	13
Anxiety	28.9	15-72	30
Abdominal pain	25.8	5-62	14
Chest pain	25.0	19-50	0
Weakness	19.4	8-58	25
Dyspnea	17.0	15-39	23
Weight loss	16.5	14-23	7
Flushing	14.8	10-19	4
Visual disturbances	12.4	11-22	19

From Ross EJ, Griffith DN. The clinical presentation of phaeochromocytoma. Q J Med 1989; 71:485-96.

Clinical Presentation and Diagnosis

Patients with pheochromocytoma can have a variety of common or uncommon symptoms.[285-291] Patients typically have **paroxysmal symptoms** because of the episodic nature of hormone secretion by the tumor (Table 43-3). The most common symptoms are sweating, tachycardia, and headaches; one study suggested that the diagnosis of pheochromocytoma can be excluded with 99.9% certainty if a patient does not have these symptoms.[293] The attacks may remain the same or the symptoms may evolve over time.[289] Pallor is common and flushing is uncommon in patients with pheochromocytoma. Paroxysmal symptoms may be triggered by a wide variety of physical activities that patients learn to avoid.[289] Typically, these activities directly or indirectly increase the pressure around the tumor. As the tumor grows, the attacks may last longer and occur more frequently.[289]

The ability of pheochromocytomas to mimic other diseases has frustrated and confused several generations of physicians. In one series of patients with pheochromocytoma, 76% of the tumors were not diagnosed before autopsy.[289] Reports include numerous examples of pheochromocytomas that were initially confused with other medical or psychiatric disorders.[294-296] In addition to their systemic endocrine effects, pheochromocytomas can occasionally cause local abdominal symptoms.[297]

Hypertension is a common but not universal finding, occurring in 77% to 98% of patients with pheochromocytoma.[289] Although most patients have paroxysmal episodes of hypertension, half may also experience

sustained hypertension.[286] **Orthostatic hypotension** occurs in 70% of patients.[289,291] The presumed mechanisms for orthostatic hypotension are chronic vasoconstriction with intravascular volume depletion and impaired reflex responses secondary to receptor down-regulation or synaptic effects of circulating catecholamines.[289,291]

The current approach to the diagnosis of pheochromocytoma involves the following three steps: (1) biochemical testing for increased catecholamine secretion, (2) anatomic imaging, and (3) functional imaging.[285,286] Catecholamine secretion is evaluated by measuring norepinephrine and epinephrine or concentrations of their metabolites (normetanephrine, metanephrine, or vanillylmandelic acid) in plasma or urine samples. Although the relative merits of these laboratory tests have been debated for years, a consensus has emerged in favor of measuring the plasma concentration of free metanephrines as the initial laboratory test.[286,287,292,298-300]

Conversion of norepinephrine and epinephrine to the respective metanephrines by catecholamine-*O*-methyl transferase occurs to a large extent within the pheochromocytoma before secretion.[298] Several medical conditions may confound the diagnosis of pheochromocytoma by altering the plasma and urinary concentrations of catecholamine metabolites. These conditions include congestive heart failure, acute myocardial infarction, stroke, cocaine abuse, sleep apnea, and ethanol or clonidine withdrawal.[301] Medications that alter normal catecholamine secretion and metabolism include tricyclic antidepressants, acetaminophen, hydralazine, and beta-adrenergic receptor antagonists.[302] Chromogranin-A is a protein found with catecholamines inside secretory vesicles within pheochromocytoma and normal adrenal medullary cells. Originally, chromogranin-A was thought to be a packaging protein in secretory vesicles, but it is now recognized as a prohormone for several peptide hormones, including vasostatin.[303] The measurement of plasma concentrations of chromogranin-A is a confirmatory laboratory test for pheochromocytoma.[304,305]

For patients in whom initial laboratory findings are equivocal, a clonidine suppression test can be performed.[286,287] The basis of the test is that clonidine fails to suppress catecholamine secretion by pheochromocytoma cells.

After the laboratory diagnosis is confirmed, the pheochromocytoma is localized with anatomic and functional imaging.[306] The major anatomic imaging modalities are computed tomography (CT) and magnetic resonance imaging (MRI). Functional imaging relies on labeled compounds with a high affinity for pheochromocytoma cells. Meta-iodobenzylguanidine (MIBG) is an analogue of norepinephrine, and ^{123}I-MIBG is commonly used for scintigraphic localization. Positron emission tomography (PET) with either fluorine-18 (^{18}F)-fluoro-2-deoxy-D-glucose (^{18}F-FDG) or ^{18}F-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) can be used to localize pheochromocytomas.[306]

Interaction with Pregnancy

Pheochromocytoma is rare during pregnancy, with an overall incidence estimated to be less than 0.2 per 10,000 pregnancies.[307] Although pregnancy may accelerate the growth of some tumors, no data suggest that it does so for pheochromocytoma.[308] Both sporadic and familial types of pheochromocytoma, as well as benign and malignant forms, may occur during pregnancy. Case reports have demonstrated specific tumor susceptibility gene mutations in pregnant patients who have familial cases of pheochromocytoma.[309-312]

Clinical signs and symptoms of pheochromocytoma are similar in pregnant and nonpregnant patients.[307,313] Noninvasive hemodynamic measurements demonstrated intense vasoconstriction and decreased cardiac output during episodes of hypertension in two pregnant patients with pheochromocytoma.[314,315] The clinical recognition of pheochromocytoma during pregnancy is especially difficult because of its rarity and its similarity to preeclampsia, a common obstetric disease.[316,317] The diagnosis of pheochromocytoma before labor and delivery may reduce maternal mortality from 35% to near zero.[307] Easterling et al.[315] demonstrated that either an inverse relationship between blood pressure and heart rate or an increasing hematocrit during treatment with a beta-adrenergic receptor antagonist in a patient with suspected preeclampsia suggests the presence of pheochromocytoma. Pheochromocytoma may also manifest in the early postpartum period after an unremarkable vaginal delivery.[318,319]

Plasma concentrations of epinephrine, norepinephrine, and dopamine in normal pregnant women do not differ significantly from those in nonpregnant controls.[320] These data suggest that the same threshold levels can be used to interpret most laboratory test results (except urinary norepinephrine and normetanephrine) for the diagnosis of pheochromocytoma in pregnant and nonpregnant patients. During pregnancy, ultrasonography or MRI is most commonly used for anatomic imaging of pheochromocytomas.[306] One case report described functional PET/CT imaging of a pheochromocytoma during pregnancy using ^{18}F-FDG.[321] However, this imaging was delayed until 21 weeks' gestation to minimize the fetal radiation effects.

Medical and Surgical Management

Definitive therapy for pheochromocytoma is surgical resection of the tumor.[286,322] The greatest challenge in perioperative management is to prevent or effectively treat wide swings in hemodynamic measurements. The patient is at risk for severe hypertension during induction of anesthesia and surgical manipulation of the tumor; severe hypotension frequently occurs after excision of the tumor because of an abrupt decline in circulating concentrations of catecholamines.

Preoperative Preparation

The preoperative preparation of a patient with pheochromocytoma relies on pharmacologic therapy to return the patient to a near-normal physiologic state. Patients with a norepinephrine-dominant pheochromocytoma have intense peripheral vasoconstriction and severe intravascular volume depletion. In these patients, preoperative

preparation includes alpha-adrenergic receptor blockade and intravascular volume repletion.[286,323,324] The most commonly used alpha-adrenergic receptor antagonist is **phenoxybenzamine**. The initial dose is 10 mg orally twice a day, titrated upward to 40 to 50 mg twice a day. **Doxazosin, prazosin,** and **phentolamine** are other alpha-adrenergic receptor antagonists that have been used successfully.[323-325] Beta-adrenergic receptor antagonists may be added to treat arrhythmias, but their use must be preceded by effective alpha-adrenergic receptor blockade to prevent a paradoxical hypertensive response.[323,324] Beta-adrenergic receptor blockade must be individualized because patients with pheochromocytoma are at risk for catecholamine-induced cardiomyopathy.[326]

The administration of **nicardipine**, a calcium entry–blocking agent, is an alternative approach in the preoperative preparation of these patients.[324,327] **Metyrosine** is another therapeutic option that interferes with catecholamine synthesis; it has been used as an adjunct to preoperative alpha-adrenergic receptor blockade at doses of 250 to 1000 mg orally twice a day.[323,328] Patients whose symptoms or early responses to alpha-adrenergic receptor blockade suggest an epinephrine-dominant pheochromocytoma may need beta-adrenergic receptor blockade as primary preoperative therapy.[329]

Alpha-adrenergic receptor blockade with phenoxybenzamine is the most commonly used technique for preoperative preparation of the patient with pheochromocytoma.[286,323] Administration of a long-acting alpha-adrenergic receptor antagonist (e.g., phenoxybenzamine) may be desirable before tumor excision but can contribute to hypotension after tumor removal.[330] Prospective randomized studies comparing different methods of patient preparation have not been performed. A retrospective review of patients with pheochromocytoma who were treated preoperatively with phenoxybenzamine, prazosin, or doxazosin suggests that all of these agents are effective and safe.[331] Regardless of the method chosen, the patient must be prepared adequately for surgery. Adequate preparation could be the major reason for the recent decline in operative mortality in patients with pheochromocytoma. Hull[329] stated, "Emergency surgery to remove a phaeochromocytoma from an unprepared patient should never be contemplated." Roizen and Fleisher [332] have established four widely accepted criteria for adequate preoperative alpha-adrenergic receptor blockade in patients with pheochromocytoma (Box 43-9). Most patients require 10 to 14 days of treatment to meet these criteria.[319] Individual reports of rapid preoperative patient preparation techniques for pheochromocytoma resection (e.g., intravenous urapidil plus magnesium) will need additional confirmation before they become mainstream clinical practices.[333]

BOX 43-9 Criteria for Adequate Preoperative Alpha-Adrenergic Blockade in Patients with Pheochromocytoma

1. No in-hospital blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours before surgery. Arterial blood pressure can be measured every minute for 1 hour in a stressful environment (e.g., postanesthesia care unit). If no reading is greater than 165/90 mm Hg, this criterion is considered satisfied.
2. Orthostatic hypotension should be present, but blood pressure on standing should not be lower than 80/45 mm Hg.
3. The electrocardiogram should be free of ST-segment/T-wave changes that are not permanent.
4. No more than one premature ventricular contraction should occur every 5 minutes.

Modified from Roizen MF, Fleisher LA. Anesthetic implications of concurrent diseases. In Miller RD, editor. Anesthesia. 7th edition. New York, Churchill Livingstone, 2009:1067-149.

Intraoperative Management

Intraoperative management includes the treatment of episodic **hypertension** and **tachycardia** *before* excision and treatment of profound **hypotension** *after* excision. Many medications have been used successfully to manage intraoperative hypertension and tachycardia, including calcium entry–blocking agents, nitroprusside, nitroglycerin, esmolol, magnesium sulfate, dexmedetomidine, and adenosine.[324,327,334-339] Because of the episodic nature of catecholamine secretion and the change in cardiovascular status that occurs after tumor excision, the use of agents with a short duration of action may be advantageous. The successful use of various regimens implies that the intraoperative treatment of hypertension and tachycardia depends more on the vigilance and skill of the anesthesia provider than on the specific medication used.

Intraoperative monitoring of a patient with pheochromocytoma should include the use of standard monitors, an intra-arterial catheter, and a Foley catheter. Ongoing assessments of cardiac contractility and cardiac filling pressures and volumes facilitate the successful treatment of catecholamine-induced cardiomyopathy or postexcision hypotension. This information may be acquired via a pulmonary artery catheter or transesophageal echocardiography.[340] Laparoscopic resection of pheochromocytomas has almost completely replaced open surgical approaches, except for very large or malignant tumors.[341] Laparoscopic resection is associated with a shorter hospitalization and greater patient satisfaction.[342] In a small study, patients undergoing laparoscopic resection of a pheochromocytoma were randomized to receive one of two different intra-abdominal pressures during the carboperitoneum (either 8 to 10 or 15 mm Hg).[343] Patients with lower intra-abdominal pressure had less perioperative catecholamine release and fewer hemodynamic fluctuations than patients with higher intra-abdominal pressure. A retrospective review of 143 patients who underwent predominantly open resection of pheochromocytoma or paraganglioma at the Mayo Clinic from 1983 to 1996 showed a 25% incidence of sustained intraoperative hypertension but very few serious perioperative complications.[344]

Hypoglycemia may also be a serious problem after the resection of a pheochromocytoma.[345,346] Insulin secretion is inhibited by alpha-adrenergic receptor stimulation, and removal of the tumor may result in a rebound

of insulin release. Blood glucose concentration should be measured frequently after pheochromocytoma excision.

Medical therapy for pheochromocytoma is used only as a temporizing measure during pregnancy or in patients with inoperable or metastatic disease. Pheochromocytoma recurs in 6.5% of patients who have undergone complete surgical resection.[347]

Management during Pregnancy

When pheochromocytoma presents during pregnancy, surgical resection of the tumor is the preferred therapy.[307,314,348] A variety of clinical strategies have been associated with successful obstetric and surgical outcomes. They include (1) open or laparoscopic tumor resection at 16 to 23 weeks' gestation followed by vaginal or cesarean delivery at term,[349-352] (2) cesarean delivery with concurrent open tumor resection,[353] (3) cesarean delivery with open or laparoscopic tumor resection 2 to 8 weeks later,[313,354,355] and (4) vaginal delivery with laparoscopic tumor resection 6 weeks later.[349] A number of case reports describe successful laparoscopic resection of abdominal pheochromocytoma during pregnancy between 12 and 23 weeks' gestation with good maternal and fetal outcomes.[350,351,352] These reports include one robotic case and one set of twins. Before 24 weeks' gestation, surgery should proceed as soon as the patient is adequately prepared with adrenergic blockade.[322,356] After 24 weeks' gestation, the gravid uterus represents a mechanical obstruction to surgery for most abdominal pheochromocytomas. Women with pregnancy at this gestational age should receive adrenergic blockade for the remainder of the pregnancy, or until the tumor is removed.[322]

Phenoxybenzamine, the most widely used medication for preoperative preparation of the pregnant woman with pheochromocytoma, easily crosses the placenta.[356] A case series suggested that neonates should be monitored closely in an intensive care nursery after intrauterine exposure to phenoxybenzamine.[357] Other alpha-adrenergic receptor antagonists have been used successfully in pregnant patients with pheochromocytoma, including phentolamine, prazosin, and doxazosin.[307,348,358] Beta-adrenergic receptor blockade may be added if needed to control tachycardia or arrhythmias or to treat an epinephrine-dominant pheochromocytoma. Beta-adrenergic receptor antagonists that have been used successfully in pregnant patients with a pheochromocytoma include propranolol, atenolol, and metoprolol.[307,356,358] Clinical experience with metyrosine during pregnancy is very limited.[307] The current package insert lists metyrosine as a "pregnancy category C drug." Pending further assessment of safety during pregnancy, the use of metyrosine in pregnant women with pheochromocytoma should be restricted to those whose tumors are resistant to adrenergic blockade.

Medications that have been used successfully to control intraoperative hypertension and tachycardia in pregnant patients with pheochromocytoma include phentolamine, nitroprusside, nitroglycerin, magnesium sulfate, propranolol, remifentanil, esmolol, and hydralazine.[313,359,360] Esmolol, however, may not be an ideal medication during pregnancy (as discussed earlier).[228,229,230] The safety of maternal administration of nitroprusside has also been questioned because of possible fetal cyanide toxicity.[361] Adverse effects were noted in fetal lambs when high doses of nitroprusside were administered in pregnant ewes in which tachyphylaxis had developed.[361] Clinical case reports suggest that a low-dose maternal infusion of nitroprusside (approximately 1 μg/kg/min) should be safe during the peripartum period.[362,363] If maternal tachyphylaxis develops, nitroprusside should be discontinued and a different vasodilator used. Nitroprusside reduces uteroplacental vascular resistance in hypertensive sheep, and it antagonizes norepinephrine-induced uterine artery vasoconstriction in humans and guinea pigs.[364-366] These data suggest theoretical advantages for the perioperative use of nitroprusside in pregnant women with pheochromocytoma.

In summary, early diagnosis of pheochromocytoma during pregnancy and adequate adrenergic receptor blockade are essential to optimize maternal and fetal safety. Phenoxybenzamine is used for preoperative preparation of the pregnant patient. If beta-adrenergic receptor blockade is necessary, metoprolol can be used unless specifically contraindicated. During surgery, short-acting, titratable cardiovascular medications are preferred. Monitoring and therapy should be directed toward optimization of preload, afterload, and cardiac contractility for a patient with rapid changes in circulating concentrations of catecholamines. Attention to detail is likely more important than the choice of specific medications.

Obstetric Management

Pheochromocytoma during pregnancy is associated with an increased incidence of fetal death and fetal growth restriction.[307] The presumed mechanism is decreased uterine blood flow secondary to catecholamine secretion by the tumor; the metabolic activity of the placenta is an effective barrier to the transplacental passage of maternal catecholamines.[367] When pheochromocytoma is diagnosed and effective maternal alpha-adrenergic receptor blockade is instituted before delivery, the fetal death rate declines from 50% to near zero.[322]

Placental abruption has been reported in patients with pheochromocytoma.[368] From a hemodynamic standpoint, this process may be analogous to the occurrence of placental abruption in patients with acute cocaine intoxication.[369] Pheochromocytoma and preeclampsia may have overlapping clinical presentations; proteinuria, for example, occasionally occurs in patients with pheochromocytoma.[370]

To avoid the increased abdominal pressure on the tumor that can occur during active labor, cesarean delivery is preferred in patients with an unresected pheochromocytoma.[307,368]

Anesthetic Management

Preoperative preparation and intraoperative monitoring and management have already been discussed. A variety of general anesthetic agents as well as spinal and epidural anesthesia have been successfully used in nonpregnant

BOX 43-10 Perioperative Medications to Avoid in Patients with Pheochromocytoma

- Atracurium
- Droperidol
- Glucocorticoids
- Metoclopramide
- Morphine
- Pancuronium
- Pentazocine
- Succinylcholine
- Vancomycin

These medications may, either directly or indirectly, increase the release of catecholamines by the tumor.
Information from references 329 and 371.

patients with pheochromocytoma.[324,329] Box 43-10 lists perioperative medications that should be avoided to minimize hormone secretion by a pheochromocytoma. A case series of nonpregnant patients suggested that exogenous glucocorticoids can unpredictably trigger a pheochromocytoma crisis,[371] but this observation requires further confirmation. There are two published cases of nonpregnant patients with pheochromocytoma who were incorrectly diagnosed intraoperatively with malignant hyperthermia.[372,373] Manipulation of a pheochromocytoma during resection may result in a small increase in end-tidal carbon dioxide[374]; it is unlikely, however, that the modest magnitude of this effect would be confused with malignant hyperthermia.

In pregnant women with pheochromocytoma, analgesia during labor is not usually a concern because cesarean delivery is preferred. Cesarean delivery, with or without concurrent tumor resection, has been accomplished safely with **general anesthesia**,[313,353,358,360] **epidural anesthesia**,[354,359,375] and **combined epidural-general anesthesia**.[355] There are no prospective randomized studies of the anesthetic management of pregnant women with pheochromocytoma. It seems reasonable to avoid abrupt hemodynamic changes and to avoid the medications listed in Box 43-10. Either neuraxial or general anesthesia for cesarean delivery should be selected on the basis of factors other than the presence or absence of a pheochromocytoma. The care with which anesthesia is administered is probably more important than the specific technique selected.

KEY POINTS

- Pregnancy is characterized by a progressive increase in peripheral insulin resistance.
- Insulin requirements decrease during the first stage of labor, increase during the second stage, and decrease again after delivery.
- Maternal diabetes mellitus is associated with a higher incidence of polyhydramnios, preterm labor, preeclampsia, fetal macrosomia, neonatal hypoglycemia, and cesarean delivery.
- Fetal structural malformations are the leading cause of perinatal mortality in diabetic parturients; strict glycemic control before conception reduces the risk.
- Normal pregnancy is a euthyroid state because serum concentrations of unbound or free thyroid hormones are within the normal nonpregnant range.
- Thyroid storm is a rare but life-threatening disorder during pregnancy. It is best prevented by effective treatment of preexisting hyperthyroidism and adequate preparation of the patient for surgery.
- The required dose of thyroid hormone replacement medication increases during pregnancy; neonatal thyroid function is normal in most cases of maternal hypothyroidism.
- Maternal and fetal safety is enhanced by early diagnosis of pheochromocytoma and effective adrenergic receptor blockade before resection.
- At the time of pheochromocytoma resection, the anesthesiologist should anticipate the potential for (1) episodic hypertension and tachycardia during manipulation of the tumor and (2) severe hypotension after tumor resection.
- For women with an unresected pheochromocytoma, cesarean delivery is preferred.[375]

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CHAPTER 44

Hematologic and Coagulation Disorders

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CHAPTER OUTLINE

ANEMIA

Normal Hemoglobin Morphology

Normal adult hemoglobin consists of four polypeptides (two alpha and two beta chains) and the iron-containing prosthetic group (heme or ferriprotoporphyrin IX). In the early embryo, theta (θ) and zeta (ζ) chains are present instead of the alpha (α) chains, and epsilon (ε) chains are present instead of the beta (β) chains. After early embryogenesis, pairs of alpha chains are linked with pairs of either beta, gamma (γ), or delta (δ) chains to form adult hemoglobin (Hgb A = $\alpha_2\beta_2$), fetal hemoglobin (Hgb F = $\alpha_2\gamma_2$), or hemoglobin A_2 (Hgb A_2 = $\alpha_2\delta_2$). By term gestation, the ratio of hemoglobin F to hemoglobin A is approximately 1:1. By 1 year of age, hemoglobin F typically constitutes less than 1% of total hemoglobin. Although hemoglobin A_2 is present, it constitutes less than 2.5% of total adult hemoglobin.

The sequence of amino acids (141 amino acids for alpha chains and 146 for beta chains) defines the **primary structure**. The three-dimensional shape of each chain defines the **secondary structure**, and the relationship between the four chains and the heme prosthetic group defines the **tertiary structure** of the hemoglobin molecule. The binding of the ligands 2,3-diphosphoglycerate (2,3-DPG) and oxygen defines the **quaternary structure**. The physiology of oxygen transport in the fetus is described in Chapter 5.

Anemia in Pregnancy

During normal pregnancy, plasma volume increases by approximately 50% but red blood cell (RBC) mass increases by only 30%; this differential increase results in the **physiologic anemia of pregnancy** (see Chapter 2). If the hemoglobin concentration decreases below 10.5 g/dL, the physician should consider other causes of anemia.[1,2]

Iron deficiency is the most common cause of anemia in pregnancy. It becomes more prevalent as pregnancy advances; in a population-based sample of women in the United States, the prevalence increased from 7% in the first trimester to 14% in the second trimester and 30% in the third trimester of pregnancy.[3] Iron-deficiency

anemia during the first two trimesters of pregnancy increases the risk for preterm delivery and low birth weight.[4-6] In addition to reduced hematocrit, iron-deficiency anemia is characterized by low mean corpuscular volume (MCV) and low total serum iron, ferritin, and transferrin saturation. In the United States, the risk for iron deficiency is increased by advanced parity, short interpregnancy interval, Mexican-American ethnicity, and African race.[3,7] Daily oral iron treatment in pregnancy reduces the risk for anemia and low birth weight; a 2013 meta-analysis of randomized controlled trials suggests that there is a clear dose-response relationship for up to a total iron dose of 66 mg/day.[8] Doses greater than 60 mg/day increase side effects, including nausea, vomiting, constipation, and abdominal cramps.[9] Observational data suggest that oral iron therapy can reduce the incidence of preterm birth.[10] Although a 2013 meta-analysis of randomized controlled trials of iron supplementation failed to identify an effect on the incidence of preterm birth or small-for-gestational-age infants, the relative risk confidence intervals were wide.[8] Antepartum anemia is a leading risk factor for postpartum blood transfusion[11]; however, no study has evaluated the impact of antepartum iron supplementation on the risk of postpartum maternal blood transfusion.

Parenteral (intramuscular or intravenous) iron enhances hematologic response compared with oral iron, but formulations that contain dextran may increase risk for venous thrombosis and allergic reactions.[9]

An elevated hemoglobin concentration (≥ 14.5 g/dL) may reflect inadequate volume expansion and has been associated with adverse pregnancy outcomes, including preterm delivery, small-for-gestational-age infants, and stillbirth.[6,12]

Thalassemia

The thalassemias are a group of microcytic, hemolytic anemias that result from the reduced synthesis of one or more of the polypeptide globin chains.[13] This reduced synthesis leads to (1) an imbalance in globin chain ratios, (2) defective hemoglobin, and (3) erythrocyte damage resulting from excess globin subunits. In α-thalassemia, alpha-chain production is reduced, and in β-thalassemia, beta-chain production is reduced.

α-Thalassemia

There are two alpha-chain loci on each chromosome 16; therefore, there are four genes that can produce alpha chains.[14] Because deletions or mutations can affect any or all of these genes, four types of α-thalassemia exist: (1) **silent carrier** (three functioning genes), (2) **α-thalassemia trait** (two functioning genes), (3) **hemoglobin H disease** (one functioning gene), and (4) **α^0-thalassemia** or **Bart's hydrops** (no functioning genes). As the number of functioning genes decreases from three to zero, the ratio of alpha to beta chains decreases from 0.8:1 to 0.6:1 to 0.3:1 to 0:1. The mRNA production from the second alpha gene exceeds that of the first alpha gene by a factor of 1.5 to 3.[14,15] Therefore, deletions of the second alpha gene may produce greater clinical effect. As beta (or beta-like) chains accumulate, they can form tetramers *in utero* (hemoglobin Bart's = γ_4) or after delivery (hemoglobin H = β_4) and appear as Heinz bodies on the peripheral blood smear.

In the United States, 25% to 30% of black women are silent carriers and have slightly smaller (78 to 85 fL) mean corpuscular volume (MCV) than women without thalassemia.[16,17] A chromosome lacking one alpha gene is common in Africa, the Mediterranean basin, the Middle East, India, Southeast Asia, Indonesia, and the South Pacific Islands.[18] Silent carriers are not at increased risk for adverse outcome during pregnancy or surgery.

The **α-thalassemia** trait affects 2% to 3% of black women in the United States[16,17] and is almost exclusively due to homozygous α^+-thalassemia, in which one functional α-globin gene is preserved on each chromosome (α–/α–). These women have an MCV of 70 to 75 fL and mild anemia. They typically are asymptomatic and, beyond the effects of mild anemia, experience no additional risk for adverse outcomes during pregnancy or surgery. Heterozygous α^0-thalassemia trait (––/αα) is common among individuals of Southeast Asian descent. It is phenotypically indistinguishable from homozygous α^+-thalassemia trait but introduces the risk for bearing an offspring with hemoglobin H disease or Bart's hydrops.

Patients with **hemoglobin H disease** experience moderately severe microcytic anemia, splenomegaly, fatigue, and generalized discomfort. Hemoglobin H (β_4) constitutes 2% to 15% of the total hemoglobin in these patients. Affected patients generally do not have a decreased life span, and hospitalization for the treatment of their anemia rarely is required. However, disease severity and prognosis vary, depending on the specific mutations present[19]; some patients require lifelong transfusion and chelation therapy.

Hemoglobin Barts, or **α^0-thalassemia**, is generally incompatible with life. The disease is found predominantly in Southeast Asia, China, and the Philippines. Affected individuals die *in utero* or shortly after birth of hydrops fetalis; mothers carrying these fetuses are prone to develop hypertension or peripartum hemorrhage or both.[20] Intact neonatal survival has been reported with intrauterine transfusion therapy and postnatal hematopoietic stem cell transplantation.[21,22] Antenatal screening for the disease is possible (see later discussion).

β-Thalassemias

In β-thalassemia, the production of beta chains is reduced. There are more than 200 genetic causes for ineffective beta-chain production, including gene deletion, transcription mutations, and RNA-processing mutations.[13] Unlike the alpha chains, which have four genes (two on each chromosome 16), beta chains have only one gene on each chromosome 11. Production of mRNA from the second beta-like gene (i.e., delta) is almost completely suppressed. Therefore, there are only two primary forms of β-thalassemia: (1) **β^0-thalassemia**, in which there is no beta-chain formation, and (2) **β^+-thalassemia**, in which some beta-chain production exists. β^0-Thalassemia also is called **β-thalassemia major** or **Cooley's anemia**. Individuals who receive β-thalassemia genes from both

parents but with mutations of different types often develop a milder form of the disease and require fewer or no transfusions. This condition is known as **thalassemia intermedia**. Finally, **β-thalassemia minor** refers to the heterozygous carrier of β-thalassemia.

β-Thalassemia is found most often in persons from the Mediterranean basin, the Middle East, India, Pakistan, and Southeast Asia and less often among persons from Tajikistan, Turkmenistan, Kyrgyzstan, China, and Africa.[13]

Individuals with β-thalassemia have a relative excess of alpha chains. Excess alpha chains precipitate and form inclusion bodies in red blood cell (RBC) precursors, resulting in anemia secondary to ineffective erythropoiesis and splenic hemolysis.[13] In the fetus, the gamma chain is unaffected; therefore, anemia only develops as gamma-chain production ceases during the first year of life.[13] In some patients, gamma-chain production continues to a variable extent.[13] Thus, the ongoing production of hemoglobin F (even in adults) may minimize the effects of decreased beta-chain production.[13]

β-Thalassemia Major. In patients with β-thalassemia major, progressively severe anemia develops beginning in the first few months of extrauterine life.[13] The anemia results in tissue hypoxia, increased intestinal absorption of iron, and increased erythropoietin production. The resulting expansion of marrow cavities causes skeletal abnormalities and pathologic fractures. Splenomegaly leads to thrombocytopenia and leukopenia.

RBC transfusions are required to maintain life, and the resulting iron load leads to iron accumulation, first in Kupffer's cells (noncirculating macrophages found in the liver), then in liver parenchymal cells, and finally in endocrine and myocardial cells. Deposition of iron in endocrine tissues may result in diabetes mellitus, adrenal insufficiency, and infertility.[23] Myocardial accumulation of iron can lead to conduction abnormalities and intractable heart failure, which are exacerbated by anemia-induced tachycardia. Heart failure and infection are the most common causes of death.

Patients with β-thalassemia major who present when younger than 2 years of age often have hepatomegaly and a hemoglobin concentration as low as 2 g/dL. Patients who present later in life (2 to 12 years of age) typically have a hemoglobin concentration between 4 and 10 g/dL, with marked anisopoikilocytosis and numerous target cells, nucleated RBCs, and inclusion bodies. Levels of hemoglobin F range from 10% to 90% of the total hemoglobin, and hemoglobin A_2 constitutes the remainder of the hemoglobin present.

Treatment includes (1) lifelong transfusion of leukocyte-poor RBCs every 2 to 3 weeks to maintain a hemoglobin concentration greater than 10 g/dL, thus preventing endogenous erythropoiesis; (2) splenectomy; and (3) iron chelation therapy to prevent hemosiderosis.[24] Deferoxamine was the first available chelation agent. It has a long record of successful use, but it requires continuous subcutaneous infusion or intermittent intramuscular injection.[25,26] Deferiprone and deferasirox are alternative oral chelation drugs; deferiprone has emerged as a superior agent for reducing cardiac iron levels and preventing cardiac morbidity and mortality.[25,27] Hematopoietic stem cell transplantation may be curative if a human leukocyte antigen (HLA)-matched family donor without β-thalassemia major is found.[24,28] Research exploring the potential of gene therapy is underway.[29]

It is unusual for patients with β-thalassemia major to become pregnant; nonetheless, transfusion and chelation regimens improve fertility, and assisted reproductive technologies facilitate conception in women with hemosiderosis-related infertility.[30] The metabolic demands of pregnancy increase transfusion requirements. Mordel et al.[31] reviewed reports of these patients and suggested that up to 8 L of transfused RBCs may be required to maintain the hemoglobin concentration above 10 g/dL during pregnancy.[31] It is unclear whether iron-chelation therapy should be continued throughout pregnancy; insufficient evidence is available to refute theoretical concerns about teratogenicity and fetal iron depletion.[32,33] Monitoring for maternal cardiac iron deposition and heart failure may be accomplished using modified magnetic resonance imaging and echocardiography, respectively.[25,34] Historically, these patients had an increased incidence of spontaneous abortion, intrauterine fetal death, and fetal growth restriction (also known as intrauterine growth restriction).[31] Recent case series suggest that among women with normal cardiovascular function, careful transfusion therapy and multidisciplinary care may facilitate uneventful pregnancy.[30,35,36]

A trial of labor is appropriate, and operative delivery should be reserved for obstetric indications.[37] Chronic transfusions increase the risk for alloimmunization, which prolongs the time required to identify compatible allogeneic blood products in the event of peripartum hemorrhage. Intraoperative blood salvage has been safely performed during cesarean delivery in a parturient with thalassemia.[38] Postpartum pharmacologic thromboprophylaxis is indicated.[37]

Extramedullary hematopoiesis can result in vertebral cortical weakening, pathologic fractures, and, rarely, paraplegia. However, in the absence of a major pathologic process of the spine, neuraxial anesthesia can be safely administered.[39] Patients with splenomegaly may develop thrombocytopenia; therefore, anesthesia providers should exclude a history of spontaneous hemorrhage and determine the platelet count before initiating a neuraxial procedure.

β-Thalassemia Minor. The clinical course is usually benign in patients with β-thalassemia minor. The anemia is typically mild (hemoglobin concentration of 9 to 11 g/dL) and is characterized by microcytosis and hypochromatosis. Levels of hemoglobin F range from 1% to 3%, and levels of hemoglobin A_2 range from 3.5% to 7%.

Moderate anemia develops only during periods of stress, such as pregnancy and severe infection. Nonetheless, most patients with β-thalassemia minor tolerate pregnancy well, although the incidence of oligohydramnios and fetal growth restriction are greater than in nonthalassemic women.[40] Because of an increased rate of RBC turnover and an increased risk for neural tube defects, high-dose folate supplementation is recommended in the first trimester. Transfusions are

reserved for patients with hemorrhage or a hemoglobin concentration below 8 g/dL. Infection, which can cause bone marrow suppression, must be treated promptly. β-Thalassemia minor typically does not affect anesthetic management during labor or cesarean delivery.

Antenatal Thalassemia Screening

Among populations at risk for α- or β-thalassemia, antenatal screening can identify couples at increased risk for offspring with a serious hemoglobinopathy. Low maternal and paternal MCV (≤ 80 fL) or mean corpuscular hemoglobin (MCH ≤ 27 pg) with normal serum iron and ferritin should prompt peripheral smear analysis for inclusion bodies or hemoglobin electrophoresis or both.[18] The latter test may reveal elevated hemoglobin A_2 or hemoglobin F, suggesting β-thalassemia or another hemoglobinopathy (sickle cell trait [AS], sickle cell anemia [SS], or hemoglobin C trait [SC]). α-Thalassemia requires α-globin gene testing for diagnosis because hemoglobin electrophoresis will not detect it.[18] Counseling for fetal genetic testing should be offered if both parents carry at least one abnormal hemoglobin gene.[18]

Prenatal diagnosis can be accomplished with the use of fetal cells obtained by means of chorionic villus sampling or amniocentesis and subjected to DNA analysis.[18,37] In the future, cell-free fetal DNA obtained from maternal plasma may provide an alternative source of material for fetal genetic analysis.

Sickle Cell Disease

More than 1000 abnormal α-, β-, γ-, and δ-globin chains have been identified.[41] Structural hemoglobinopathies result when these abnormal chains are used to form hemoglobin molecules. The most common abnormal hemoglobins are hemoglobin S, hemoglobin C, hemoglobin D, and hemoglobin E.[41] Patients can be homozygous for an abnormal hemoglobin (e.g., **hemoglobin SS** or **sickle cell anemia**), heterozygous for an abnormal hemoglobin (e.g., **hemoglobin SA** or **sickle cell trait**), or doubly heterozygous for an abnormal hemoglobin (e.g., **hemoglobin SC** or **sickle cell hemoglobin C disease**).[18,41] The heterozygous state for both the thalassemias and the structural hemoglobinopathies appears to protect against malaria, which may explain their geographic distribution and continued presence in the gene pool.[42]

A **sickle cell disorder** refers to a state in which erythrocytes undergo sickling when they are deoxygenated.[42] Normal erythrocytes have a biconcave shape. Sickle cells are elongated and crescent shaped, with two pointed ends. **Sickle cell disease** refers to disorders in which sickling results in clinical signs and symptoms; it includes hemoglobin SS disease, hemoglobin SC disease, hemoglobin SD disease, and sickle cell β-thalassemia.[18,42]

Sickle Cell Anemia

Epidemiology. Table 44-1 lists the prevalence of sickle cell anemia and the other common hemoglobinopathies in the adult black population in the United States. The current number of individuals with sickle cell disease in the United States may approach 90,000, with 10% of Hispanic origin[43]; however, high-quality surveillance data are not available.[44]

TABLE 44-1 Prevalence of Hemoglobinopathies in the United States in Persons of African Descent

Type	Estimated Prevalence
Traits	
Hemoglobin AS	1:12.5
Hemoglobin AC	1:33
β-Thalassemia minor	1:67
Persistent hemoglobin F	1:1000
Sickling Disorders	
Hemoglobin SS	1:625
Hemoglobin SC	1:833
Hemoglobin S–β-thalassemia	1:1667
Hemoglobin S–persistent hemoglobin F	1:25,000
Hemoglobin CC	1:4444
β-Thalassemia major	1:17,778
Hemoglobin C–β-thalassemia	1:4444

Modified from Motulsky AG. Frequency of sickling disorders in U.S. blacks. N Engl J Med 1973; 288:31-3.

BOX 44-1 Factors That Increase Sickling in Women with Sickle Cell Anemia

- Hemoglobin S concentration more than 50% of the total hemoglobin concentration
- Dehydration leading to increased blood viscosity
- Hypotension causing vascular stasis
- Hypothermia
- Acidosis

Pathophysiology. In hemoglobin S molecules, valine is substituted for glutamic acid as the sixth amino acid in the beta chains.[41] This substitution results in a propensity for hemoglobin molecules to aggregate when the hemoglobin is in the deoxygenated state. The hemoglobin molecules stack on top of one another and form microtubules.

Oxygen tension is the most important determinant in sickling; other factors that affect sickling are listed in Box 44-1. Hemoglobin S begins to aggregate at a Po_2 of less than 50 mm Hg, and all of the hemoglobin S is aggregated at a Po_2 of approximately 23 mm Hg. The formation of hemoglobin S aggregates is time dependent[45]; the proportion of sickled hemoglobin increases with decreasing cardiac output and prolonged venous transit time. If an erythrocyte sickles, it can return to its normal shape once the hemoglobin S becomes oxygenated.[41,45] However, repeated sickling cycles produce erythrocyte metabolic abnormalities and membrane damage, eventually leading

to irreversible sickling regardless of oxygen tension.[41,45] Sickled cells are cleared rapidly from the circulation by the reticuloendothelial system; as a result, the erythrocyte life span is reduced to approximately 12 days.[41,45]

Sickled cells can form aggregates and lead to vaso-occlusive crises and end-organ injury. Repeated cycles of sickling, vaso-occlusion, reperfusion injury, and acute inflammation can lead to chronic inflammation and inflammatory vascular disease. Elevated levels of cell-free hemoglobin deplete nitric oxide, activate the endothelium, and further exacerbate inflammation.[41,42] The reduced erythrocyte life span results in anemia, jaundice, cholecystitis, and a hyperdynamic hemodynamic state.

Marked ventricular hypertrophy can occur in pregnant women with sickle cell disease secondary to increased cardiac output. This may lead to a decrease in ventricular compliance and a deterioration in ventricular diastolic function.[46] Anemia also leads to erythroblastic hyperplasia, expansion of medullary spaces, and a loss of cortex in long bones, vertebral bodies, and the skull.[41] Vaso-occlusive events can give rise to **infarctive crises** (which most often occur in the chest, abdomen, back, and long bones), **cerebrovascular accidents**, and rarely **peripheral neuropathy**.[47] Aggregate formation in the spleen can result in microinfarcts.

Functional asplenia and abnormal neutrophil responses both contribute to susceptibility to infection. Consequently, the incidence of pneumonia and pyelonephritis is higher in pregnant patients with sickle cell disease than healthy pregnant patients. **Aplastic crises** can occur from depression of erythropoiesis secondary to infection (especially parvovirus) or from marrow failure secondary to folate deficiency during pregnancy.[41] During an aplastic crisis, the hemoglobin concentration can decrease rapidly, leading to high-output cardiac failure and death. **Sequestration crises** can result from the massive pooling of erythrocytes, especially in the spleen. This event occurs more frequently in patients with hemoglobin SC disease or sickle cell β-thalassemia than in patients with other forms of sickle cell disease. In general, a major sequestration crisis is one in which the hemoglobin concentration is less than 6 g/dL and has decreased more than 3 g/dL from the baseline measurement.[41]

The long-term clinical course of sickle cell disease is highly variable. Higher fetal hemoglobin expression and coincident α-thalassemia were among the first genetic modulators described.[48] Subsequent work has identified a complex network of single nucleotide polymorphisms associated with specific complications of sickle cell disease, most prominently the transforming growth factor-beta (TGF-β) family of membrane-bound receptors. These receptors play a role in fibrosis, cell proliferation, hematopoiesis, osteogenesis, angiogenesis, nephropathy, wound healing, and immune response.[48]

Diagnosis. In the adult, sickle cell anemia is characterized by (1) a hemoglobin concentration of 6 to 8 g/dL, (2) an elevated reticulocyte count, and (3) the presence of sickle cells on a peripheral blood smear. The diagnosis is confirmed by electrophoresis, thin layer isoelectric focusing, or high-pressure liquid chromatography.[41] Because most hemoglobinopathies are inherited as autosomal recessive conditions, prenatal screening for abnormal hemoglobin is recommended in couples at high risk for sickle cell disease.[18] *In utero*, the diagnosis can be made through the use of restriction endonucleases specific for the sickle mutation applied to fetal cells obtained during amniocentesis or chorionic villus sampling.

Interaction with Pregnancy. Pregnancy typically exacerbates the complications of sickle cell anemia. Maternal mortality from sickle cell disease comprises as many as 1% of all maternal deaths in the United States.[49] Thromboembolic complications, infection, cardiomyopathy, and pulmonary hypertension are the most serious maternal medical complications.[49] Patients with sickle cell anemia have an increased incidence of preterm labor, placental abruption, fetal growth restriction, hypertension, and eclampsia.[49] Intensive fetal surveillance may reduce the risk for intrauterine fetal death.[49]

Medical Management. Sickle cell anemia is a chronic anemia; blood transfusions are given only when they are specifically indicated (e.g., acute anemia, aplastic crisis, pneumonia with hypoxemia, before or during surgery).[41] The goals of transfusion are to achieve a hemoglobin concentration greater than 8 g/dL and to ensure that hemoglobin A represents more than 40% of the total hemoglobin present. Prophylactic blood transfusions do not appear to alter fetal or maternal mortality, although the frequency of maternal pain crises may be reduced.[50,51] If the patient's baseline hemoglobin concentration is less than 6 to 7 g/dL, simple transfusions with buffy-coat-poor, hemoglobin S–free, washed RBCs should be adequate to meet treatment goals. Otherwise, partial exchange transfusions may be necessary.

Hemoglobin F does not form aggregates with hemoglobin S. Administration of hydroxyurea may enhance the production of hemoglobin F, which may decrease the morbidity and mortality of sickle cell anemia. It is unclear whether hydroxyurea is safe in pregnancy; the drug is known to be carcinogenic, mutagenic, and teratogenic in animals.[52] However, among a small series of pregnancies conceived at the time of maternal or paternal hydroxyurea administration, there was no evidence of abnormal pregnancy outcomes or teratogenicity among surviving offspring.[52] Bone marrow transplantation is a potentially curative therapy for individuals with complicated sickle cell disease, although HLA-matched donors can be difficult to locate and the procedure is associated with significant morbidity and mortality.[28,53]

Obstetric Management. During prenatal visits, the obstetrician should monitor maternal weight gain, blood pressure, urine protein content, and uterine and fetal growth. Antepartum fetal surveillance begins at the time of extrauterine viability. Blood transfusions are reserved for specific indications. There is no evidence that preoperative blood transfusion to achieve a hemoglobin concentration of 10 g/dL improves perioperative outcomes for nonobstetric sickle cell patients, but no trial has evaluated prophylactic blood transfusion before cesarean delivery.[42,54] Early preparation of cross-matched blood products should be considered because

alloimmunization, and the antigen crossmatching procedures recommended to prevent its development, can prolong crossmatching procedures.[42] Finally, postpartum pharmacologic thromboprophylaxis is indicated.[55]

Anesthetic Management. Preoperative evaluation should focus on recent sickle cell disease exacerbations, the degree of anemia, and chronic end-organ injury.[42] Pulmonary hypertension and high-output heart failure should be excluded with echocardiography.[55] Pain control during labor is essential; continuous neuraxial analgesia is recommended.[42] Although general anesthesia for cesarean delivery has been associated with postoperative sickling complications, either neuraxial or general anesthesia is acceptable, and the choice of anesthetic technique ultimately depends on the time available to induce anesthesia and the patient's preference and physical status.[56] Principles of anesthetic management include (1) use of crystalloid to maintain intravascular volume, (2) transfusion of RBCs to maintain oxygen-carrying capacity, (3) administration of supplemental oxygen, (4) maintenance of normothermia, (5) prevention of peripheral venous stasis, and (6) provision of appropriate venous thromboembolism prophylaxis.[42,55,56]

Sickle Cell Disease Variants

If a patient carries one sickle cell gene and another gene for a hemoglobin that has a propensity to sickle, that patient is considered to have sickle cell disease. Patients with hemoglobin SD disease tend to have the mildest form, and patients with SC disease or sickle cell β-thalassemia tend to have more severe disease.[41,57]

As with the hemoglobin S gene, hemoglobin C is most prevalent among persons of West African descent, whereas hemoglobin D is more often found among persons of African, northern European, and Indian descent, and hemoglobin E is most prevalent among persons of Southeast Asian descent.[41] Patients with hemoglobin SC and hemoglobin SD disease tend to be asymptomatic during childhood with only mild anemia. Typically, these individuals do not develop symptoms until the second half of pregnancy. During late pregnancy they may have severe anemia (secondary to splenic sequestration) and splenomegaly. Patients with hemoglobin SC disease also have a tendency to develop bone marrow necrosis, which predisposes to fat emboli. The other clinical manifestations are similar to those observed in patients with sickle cell anemia.

Blood transfusion is recommended only when the hemoglobin concentration is less than 7 to 8 g/dL. Obstetric and anesthetic management are similar to the management of patients with sickle cell anemia.

Patients who are homozygous for hemoglobin C, D, or E typically have mild anemia. Target cells often are observed and splenomegaly is common. Patients who are heterozygous (i.e., one gene for hemoglobin C, D, or E and one gene for normal hemoglobin) are asymptomatic. The diagnosis is confirmed with electrophoresis, thin-layer isoelectric focusing, or high-pressure liquid chromatography.[41] Pregnancy typically is well tolerated, and no specific change in obstetric or anesthetic management is required.

Sickle Cell Trait

Sickle cell trait is the most benign form of the sickle cell disorders. It occurs in approximately 8% of black women in the United States. The RBCs of patients with sickle cell trait do not sickle until the Po_2 decreases below 15 mm Hg; therefore, RBC life span is normal.[58] A study of 65,000 patients with sickle cell trait found only a slight increase in the incidence of renal (hematuria) and pulmonary (emboli) complications compared with patients without sickle cell trait.[59] Patients with sickle cell trait are not at increased risk for adverse outcome during surgery.

Autoimmune Hemolytic Anemia

Patients with autoimmune hemolytic anemia produce antibodies to their own RBCs, resulting in hemolysis and varying degrees of anemia. The annual incidence of new cases of autoimmune hemolytic anemia is approximately 1 per 80,000 persons, but the prevalence approaches 1 in 5,000.[60] Table 44-2 lists the characteristics of the four main types of autoimmune hemolytic anemia.[61] Warm antibodies react with RBCs at a temperature of 35° to 40° C, whereas cold antibodies react optimally at a temperature lower than 30° C. Table 44-3 lists the various causes of autoimmune hemolytic anemia.[62]

Patients with **warm-reacting antibodies** typically respond to treatment with corticosteroids; splenectomy and the anti-CD20 antibody rituximab are second-line therapies.[60] After splenectomy, relapses and blood transfusions may lead to the continued requirement for intermittent or continuous corticosteroid therapy. The requirement for extended phenotyping may delay matched blood product availability. In acute hemorrhage, the rapid transfusion of body-temperature, ABO-compatible and Rh-negative blood can be lifesaving, with the expectation that the half-life of transfused red blood cells will be shortened; this practice will allow time to procure compatible blood products.[60]

In patients with **cold-reacting antibodies**, the anemia typically is mild and maintenance of normal body and ambient temperatures typically is all that is required to prevent hemolysis.[61]

COAGULATION

Thrombotic and Thrombolytic Pathways

Hemostasis depends on the normal function of vascular tissue, platelets, and coagulation factors. During the initial response to loss of vessel integrity, platelets adhere to exposed collagen, facilitated by the von Willebrand factor (vWF) (primary hemostasis). Platelet activation results in the release of substances that constrict the injured vessels and cause other platelets to adhere and form a hemostatic plug. The platelet plug is not stable, and initiation of the coagulation cascade, followed by deposition and stabilization of fibrin, is necessary for

TABLE 44-2 Characteristics of Autoimmune Hemolytic Anemias

Disease	Immunoglobulin (Ig)	Complement Involved	Site of Red Blood Cell Destruction	Treatment	Transfusion Requirements
Incomplete warm autoantibodies	Typically IgG Rarely IgA Rarely IgM	No No C4b and C3b	Spleen Spleen Liver	Corticosteroids, splenectomy, immune globulin	Rarely needed; if given, combined with corticosteroids
Complete warm autoantibodies					
Type 1	IgM	C4b and C3b	Liver	Corticosteroids, splenectomy	Rarely needed
Type 2	IgM	C1-9	Intracellular	Plasma exchange, corticosteroids	Frequently needed
Cold autoagglutinins and hemolysins	IgM	No	Intracellular	Corticosteroids, keeping patient warm	Very rarely needed
Biphasic hemolysins:					
Acute	IgG	Yes	Intracellular agglutination	Treatment of underlying infection	Occasionally needed
Chronic	IgG	Yes	Intracellular hemolysis	Plasmapheresis, chlorambucil	Frequently needed

IgA, immunoglobulin A; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.
From Gibson J. Autoimmune hemolytic anemia: current concepts. Aust NZ J Med 1988: 18:625-37; and Engelfriet CP, Overbeeke MA, von dem Borne AE. Autoimmune hemolytic anemia. Semin Hematol 1992; 29:3-12.

TABLE 44-3 Etiology of Autoimmune Hemolytic Anemias

Etiology	Approximate Percentage
Primary or idiopathic	43
Secondary:	
Neoplasms	22
Drug-related	15
Infections	8
Connective tissue diseases	5
Other diseases	5
Pregnancy	2

definitive hemostasis (secondary hemostasis). Most coagulation factors circulate in the blood as zymogens, which are converted to active enzymes that in turn convert other zymogens to active enzymes. For example, factor X (a zymogen) is converted to factor Xa (an enzyme), which converts prothrombin (factor II) to thrombin (factor IIa).

In its original conception, the coagulation cascade (Figure 44-1) was believed to propagate within plasma. Subsequent work has located the enzymatic reactions of the **extrinsic system** primarily to the surface of subendothelial cells and those of the **intrinsic system** to the activated platelet surface.[63] Currently, a widely used model divides the coagulation cascade into three phases: (1) an **initiation phase** (classical extrinsic pathway), in which small amounts of active coagulation factors are generated; (2) an **amplification phase**, in which the level of active coagulation factors is boosted; and (3) a **propagation phase**, in which coagulation factors bind to the membrane of activated platelets, leading to the formation of fibrin clots.[63]

In the classical extrinsic pathway, tissue damage activates tissue factor (TF) (also known as factor III or thromboplastin) on the surface of extravascular cells (e.g., fibroblasts, smooth muscle cells), which are exposed to the bloodstream after tissue damage. TF has also been identified on the surfaces of syncytiotrophoblasts,[64] adhered leukocytes, circulating monocytes, and circulating microparticle membrane vesicles released by inflammatory and tumor cells.[63] TF binds factor VII and promotes proteolysis and activation to factor VIIa. On the membrane surface, the TF/VIIa complex converts factor X to Xa and small amounts of factor IX to IXa. Factor Xa amplifies conversion of factor VII to VIIa in the first of many positive feedback loops, and factor Xa forms a complex with factor Va. The membrane-bound prothrombinase complex (i.e., Xa/Va) converts small amounts of soluble prothrombin to thrombin. This thrombin diffuses to the activated platelet surface, where it amplifies the intrinsic coagulation pathway.

In the intrinsic pathway, factor XII binds to a negatively charged substrate (e.g., collagen, platelet phosphatidylserine) and may undergo autolysis to form factor XIIa, or it may be converted to XIIa by trace amounts of XIIa. In addition to activating its own zymogen, factor XIIa converts prekallikrein to kallikrein and factor XI to XIa. High-molecular-weight kininogen can bind factor XI and facilitate its conversion to XIa by XIIa. Kallikrein and high-molecular-weight kininogen also can convert factor XII to XIIa. Factor XIa converts factor IX to IXa, which, with factor VIIIa, converts factor X to Xa. Factor Xa promotes platelet aggregation, and it

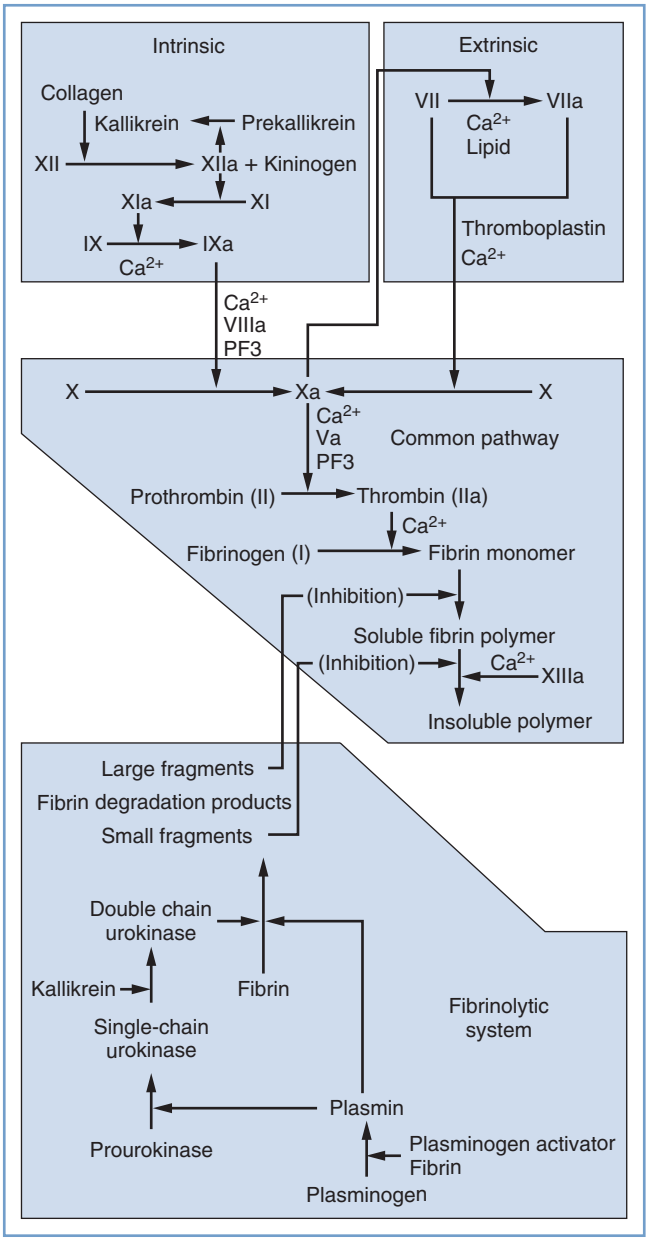

FIGURE 44-1 ■ Components of the extrinsic, intrinsic, and common pathways and the fibrinolytic system. The term *cascade* is a misnomer that stems from the presence of positive and negative feedback loops in both the coagulation and fibrinolytic systems. *PF3,* Platelet factor 3.

converts factors V and VIII to factors Va and VIIIa, respectively. Factor Xa, combined with factor Va, converts factor II (prothrombin) to factor IIa (thrombin), a process termed the *thrombin burst*. Activated platelets provide the primary surface for conversion of factor X to Xa and prothrombin to thrombin. Thrombin converts factors I (fibrinogen), V, VIII, and XIII to factors Ia (fibrin), Va, VIIIa, and XIIIa, respectively. Thrombin also causes platelet activation. Factor XIIIa is required to cross link fibrin strands, which helps form a stable clot.

Clot formation is limited by the natural anticoagulants antithrombin III, proteins C and S, and tissue factor pathway inhibitor (TFPI). Antithrombin III, whose activity is enhanced by heparin, inhibits factor IXa, factor Xa, and thrombin. Protein C is activated by a thrombin-thrombomodulin complex. With protein S as a cofactor, protein C breaks down factors Va and VIIIa. TFPI is produced by endothelial cells and inhibits coagulation by simultaneously binding factor Xa and the TF/factor VIIa complex.

The final component of the coagulation system is the **fibrinolytic system**, in which plasmin breaks down fibrin. Tissue-type plasminogen activator (t-PA) circulates as an active protease; however, its activity increases dramatically when it binds to fibrin, at which time it converts plasminogen to plasmin. Urokinase-like plasminogen activator (u-PA) is secreted as the relatively inactive pro-urokinase; it is converted to the active form (single-chain urokinase) by plasmin. Single-chain urokinase is converted to its most active form (double-chain urokinase) by kallikrein, which is released during activation of the coagulation cascade.

Plasmin-mediated fibrinolysis is confined to the clot by the local availability of fibrin and by plasminogen activator inhibitor-1 (PAI-1), which is secreted by many cells, and by plasminogen activator inhibitor-2 (PAI-2), which is secreted primarily by the placenta. Thrombin-activatable fibrinolysis inhibitor (TAFI) is synthesized in the liver, is activated by the thrombin-thrombomodulin complex, and inhibits fibrinolysis by eliminating the binding sites on fibrin for plasminogen and t-PA. The antifibrinolytic drugs **tranexamic acid** and **epsilon-aminocaproic acid (EACA)** inhibit fibrinolysis by binding to plasminogen and plasmin and preventing their binding to fibrin.

Changes in the concentrations of coagulation factors during pregnancy are outlined in Chapter 2 (see Box 2-2). The levels of most procoagulants increase during pregnancy, while anticoagulant levels remain stable or decrease.[64] Although t-PA levels decrease and antifibrinolytic proteins (i.e., PAI-1, PAI-2, TAFI) increase, plasminogen and fibrin degradation product levels increase, suggesting that fibrinolysis continues unabated during pregnancy.

Placental syncytiotrophoblasts promote coagulation by presenting tissue factor and phospholipids to maternal blood coursing through the intervillous space.[64] The concentrations of the thrombin-antithrombin complex and fibrin degradation products are elevated in blood from the uterine vein compared with peripheral blood, suggesting that many of the hemostatic changes of pregnancy originate in the placental bed.[65]

Deficiencies in procoagulant factors or an increase in fibrinolytic factors cause **hemorrhagic disorders**. Deficiencies in antithrombin III, protein C or S, or the fibrinolytic system cause **thromboembolic disorders**.

Assessment of Coagulation

Routine Hematology

The increase in the concentration of most coagulation factors is associated with a shortening of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) during normal pregnancy. Similarly, fibrinogen

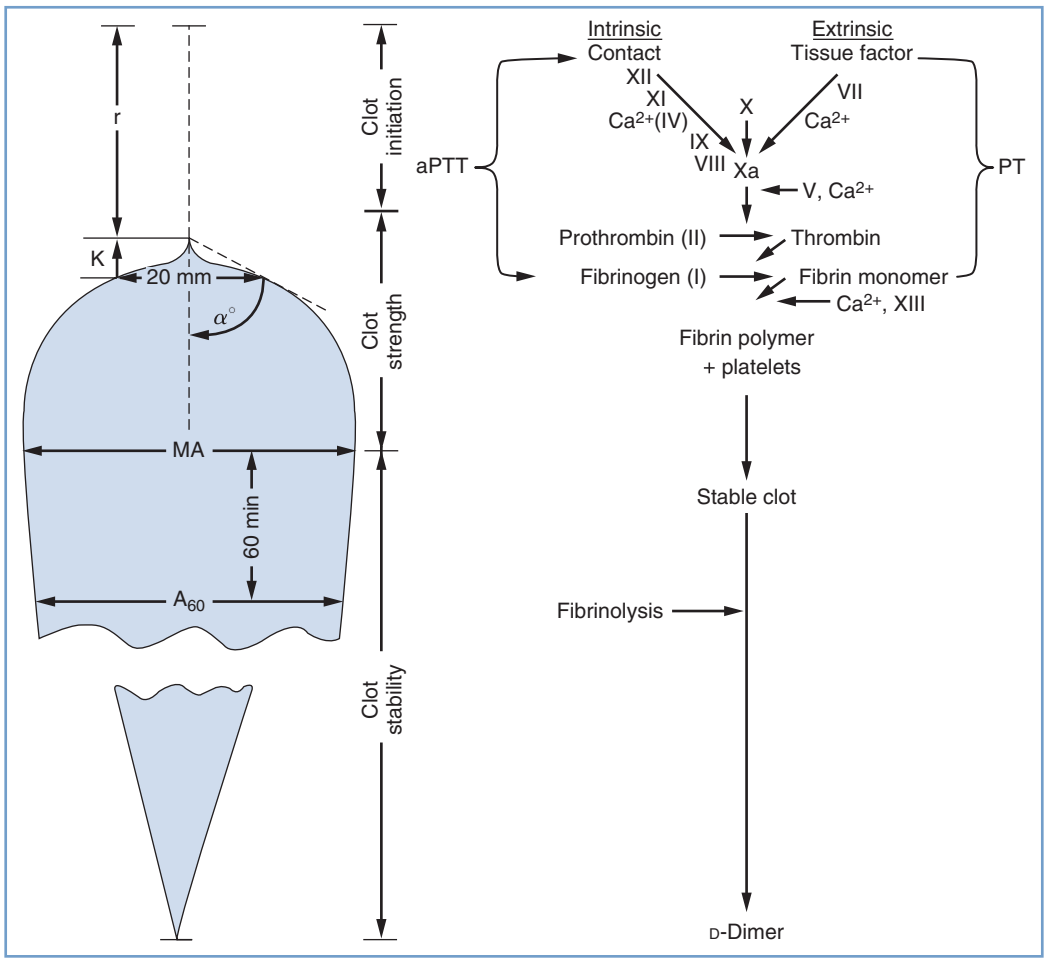

FIGURE 44-2 ■ Simplified side-by-side presentation of thromboelastographic parameters and the routine coagulation profile. *α angle,* clot formation rate; *A60,* amplitude 60 minutes after MA; *aPTT,* activated partial thromboplastin time; *K,* clot formation time; *MA,* maximum amplitude; *PT,* prothrombin time; *r,* reaction time. (Modified from Sharma SK, Vera RL, Stegall WC, Whitten CW. Management of a postpartum coagulopathy using thromboelastography. J Clin Anesth 1997; 9:243-7.)

and fibrin degradation products are increased in normal pregnancy. These changes may mask the early diagnosis of **disseminated intravascular coagulation (DIC)**, so serial laboratory parameters are indicated if the diagnosis is suspected.[64] Thrombocytopenia is a sensitive, but not specific, indicator of DIC. For women with severe preeclampsia, a platelet count is a clinically useful screening test; a result below 100,000/mm^3 suggests the possibility of impaired hemostasis and even DIC.[66,67] In the healthy parturient with no history or clinical signs of bleeding, the routine laboratory assessment of hemostasis parameters, including platelet count, is not indicated.[66] Although used historically, the bleeding time is no longer recommended as a preprocedure screening tool.[68]

Thromboelastography

Thromboelastography (TEG) measures whole blood coagulation and can rapidly provide information about the adequacy of platelet function and other coagulation factors. Thromboelastographic parameters are interrelated and reflect activities of coagulation proteins, platelets, and their interaction (Figure 44-2). TEG has been used to assess coagulation status in normal and high-risk pregnant women,[69] to manage peripartum coagulopathy,[70] and to assess hemostasis before the initiation of neuraxial anesthesia in pregnant patients with thrombocytopenia.[71] In a study of serial coagulation assessment during pregnancy, TEG demonstrated increased coagulability and decreased fibrinolysis during normal pregnancy.[72] However, in another study, TEG was not useful in predicting estimated blood loss during cesarean delivery.[73] Some investigators found a correlation between TEG measurements and low-molecular-weight heparin (LMWH) anticoagulation activity as measured by serum anti–factor Xa (anti-Xa) concentrations. They concluded that TEG might be a useful test to monitor LMWH activity.[74] TEG measurements were also able to detect and quantify the effect of unfractionated heparin on blood coagulation in postcesarean delivery patients.[75]

Thromboelastometry

Thromboelastometry, similar to TEG, is a bedside test that assesses the shear elasticity of whole blood as it clots using a ROTEM® (Pentapharm GmbH, Munich, Germany) monitor. ROTEM thromboelastometry is performed with specific activators, and a real-time graph

provides continuous assessment of the coagulation time, clot formation time, and maximal clot firmness to evaluate the extrinsic and intrinsic coagulation systems, and the fibrinogen and platelet contributions to clotting within 15 to 30 minutes of initiating the test.[76] Further research is needed to establish the clinical value of thromboelastometry in the obstetric population.

Platelet Function Analyzer

The PFA-100® (Siemens Healthcare Diagnostics, Deerfield, IL) measures platelet function *in vitro*, especially platelet activation and aggregation. This simple test evaluates the capacity of a sodium-citrated whole blood sample to form a platelet plug at the aperture situated on a collagen/adenosine phosphate or collagen/epinephrine surface under high-shear conditions. The time required for full occlusion of the aperture by the platelet plug is designated as the *closure time*. Some investigators have found this test equally sensitive to platelet aggregometry and more sensitive than the bleeding time in detecting both congenital and acetylsalicylic acid–induced platelet defects.[77] PFA-100 measurements do not correlate with platelet counts in healthy parturients,[78] but they may demonstrate impairment in platelet function with severe preeclampsia.[79]

THROMBOCYTOPENIC COAGULOPATHIES

Autoimmune Thrombocytopenic Purpura

Several terms have been used to describe autoimmune thrombocytopenic purpura. *Idiopathic thrombocytopenic purpura* was used first, but the name was changed to *immune thrombocytopenic purpura* when it was discovered that immunoglobulin G (IgG) antibodies were responsible for the increased platelet destruction.[80] Currently the preferred term is **autoimmune thrombocytopenic purpura (ATP)**. This disease should not be confused with neonatal alloimmune thrombocytopenia, in which maternal antibodies to a fetal platelet antigen cause fetal and neonatal thrombocytopenia.

The incidence of mild thrombocytopenia during pregnancy is 5% to 8%,[81] but the incidence of ATP is 0.01% to 0.1%.[81,82] Antibodies directed against platelet antigens are produced primarily in the spleen, where phagocytosis by macrophages occurs. Antibody production and phagocytosis also can occur in the liver and bone marrow. The binding of complement to platelets can facilitate their clearance, and antibody binding to megakaryocytes can result in ineffective production of platelets.[83]

Diagnosis

The diagnosis of ATP must be considered if the platelet count is less than 100,000/mm^3 and normal or higher numbers of megakaryocytes are present in the bone marrow. Moreover, the blood smear often reveals the presence of higher platelet volume and greater platelet diameter.[81] Other *nonimmunologic* conditions that must be considered include (1) **gestational or essential thrombocytopenia**, (2) **preeclampsia**, (3) **DIC**, (4) **thrombotic thrombocytopenic purpura**, and (5) **acute fatty liver of pregnancy**.[81,82] Other *immunologic* conditions that must be considered include (1) **drug-induced thrombocytopenia**, (2) **post-transfusion purpura**[84] (in individuals who have received a blood transfusion in the previous 1 to 2 weeks), and (3) **pseudothrombocytopenia**. Pseudothrombocytopenia is a laboratory artifact in which chelation of calcium ion by ethylenediaminetetraacetic acid (EDTA) exposes antigenic sites that react with antibodies, causing clumping that artificially lowers the platelet count.[85] In these cases, the automated platelet count is normal if citrate anticoagulant is used.

Interaction with Pregnancy

Conservative management is typically sufficient if ATP is diagnosed during pregnancy. Corticosteroids are administered if the platelet count is less than 20,000 to 30,000/mm^3 before the onset of labor or less than 50,000/mm^3 at the time of delivery.[82,86] High-dose intravenous immune globulin (IVIG) produces a rapid but transient increase in the platelet count and is administered if there is no response to corticosteroid therapy.[82,86] In some women with preexisting ATP who become pregnant, thrombocytopenia becomes sufficiently severe that administration of high-dose corticosteroids and immune globulin is inadequate. Splenectomy may be necessary and, if so, is best performed in the second trimester.[82,87]

Some obstetricians have observed significant hemorrhage during the immediate postpartum period in as many as 33% of women with a platelet count of less than 100,000/mm^3.[88] In contrast, others have noted no increase in peripartum blood loss in women with a platelet count between 60,000/mm^3 and 100,000/mm^3.[89]

Obstetric Management

Maternal IgG can cross the placenta and cause fetal thrombocytopenia, which increases the risk for neonatal hemorrhage. Although there is a correlation between maternal platelet-associated IgG and fetal thrombocytopenia,[90] it is not possible to predict the degree of fetal thrombocytopenia based on maternal platelet count[91] or serology.[81,82,92] No study has demonstrated a correlation between the fetal platelet count and intrapartum fetal risk. There are no definitive reports of fetal intracranial hemorrhage secondary to ATP. Neonatal intracranial hemorrhage is rare and is not related to the method of delivery.[93] Thus, current guidelines recommend that cesarean delivery should be reserved for obstetric indications.[82,93] Percutaneous umbilical cord blood sampling at 38 weeks' gestation has been suggested.[94] However, it is likely that the risk of the procedure is greater than the risk for intrapartum fetal hemorrhage. Fetal scalp blood sampling during labor can cause significant hemorrhage and can generate misleading results if the sample is exposed to vernix or amniotic fluid. Current guidelines do not recommend attempts to measure the fetal platelet count before delivery.[82]

Because episiotomies and perineal lacerations pose the greatest potential for peripartum bleeding, it is preferable to avoid performing an episiotomy in thrombocytopenic women, if possible. Bleeding occurs less often from the placental implantation site.[90] (Contraction of the uterus represents the primary mechanism for postpartum hemostasis.) After delivery, the platelet count often returns to normal in these patients.[95]

Thrombotic Thrombocytopenic Purpura

The classic pentad that defines the syndrome of thrombotic thrombocytopenic purpura (TTP) includes (1) thrombocytopenia (platelet count as low as 20,000/mm^3), (2) microangiopathic hemolytic anemia, (3) fever, (4) neurologic signs such as photophobia, headache, and seizures, and (5) renal failure. Only the first two elements are essential for diagnosis.[96] Disseminated platelet aggregation is a hallmark of TTP.[96,97] Neurologic and renal changes result from the deposition of platelet emboli and may be of variable intensity in the acute presentation and during recurrences. Diseases that share some of the clinical findings of TTP include DIC, preeclampsia, and hemolytic-uremic syndrome.

TTP is associated with either a congenital or acquired deficiency of enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). ADAMTS13 is responsible for cleaving vWF multimers. These multimers promote systemic platelet aggregates and microemboli.[96] Decreased levels of the large multimeric forms of vWF are seen in the acute phase of TTP[98] but return to normal during remission. In contrast, in hemolytic-uremic syndrome the large multimeric forms of vWF are present in normal amounts.[99] The affinity of vWF for platelet membrane glycoprotein IIb/IIIa is also increased in TTP.[97] The presence of vWF (but not fibrinogen) in platelet aggregates helps to differentiate TTP from DIC.[100] (In patients with DIC, fibrinogen but not vWF is found in platelet aggregates.)

Approximately 40% of patients who achieve remission have at least one recurrence, but relapse is rare in patients without severe ADAMTS13 deficiency.[101] Pregnancy appears to be a precipitating event for both initial and recurrent episodes of TTP, particularly among women with congenital ADAMTS13 deficiency.[101] ADAMTS13 activity declines progressively through normal pregnancy, while vWF levels increase.[102]

Prompt diagnosis and effective treatment for TTP appear to improve both maternal and fetal survival,[86,103] although perinatal loss remains significant if the disease develops in the first and second trimesters.[103] Diagnosis of TTP may be delayed because of a misdiagnosis with the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; concurrent diagnoses have been reported.[103] Clinical signs that suggest TTP include microangiopathic anemia with thrombocytopenia in the first half of pregnancy, concomitant fever or neurologic signs, and a high ratio of lactate dehydrogenase to aspartate aminotransferase.[103]

Plasma exchange is the mainstay of therapy for TTP, with an exchange volume of 1.0 to 1.5 times the predicted plasma volume of the patient.[96,103,104] Corticosteroids are recommended for second-line therapy.[105] Additional treatments include rituximab, intravenous immunoglobin, and prostacyclin.[105-107] Termination of pregnancy may be beneficial if medical treatment is ineffective[108] but has not been shown to improve maternal outcomes. Platelet transfusions are usually avoided but may be safe if administered immediately before or after plasma exchange therapy begins.[105] Because of the coagulopathy present in patients with TTP, neuraxial anesthesia is not recommended. One case report described spinal anesthesia administered for cesarean delivery in a woman with familial ADAMTS13 deficiency treated with fresh frozen plasma.[109]

Inherited Platelet Disorders

Bernard-Soulier syndrome is a rare autosomal recessive disorder characterized by (1) thrombocytopenia, (2) large platelets on the peripheral blood smear, and (3) defects of the platelet membrane glycoprotein Ib-IX-V complex.[110] Laboratory diagnosis includes prolonged bleeding time and prolonged closure time on PFA-100. Treatment during labor and delivery may require tranexamic acid or administration of recombinant factor VIIa (rFVIIa).[110] Other therapies include human leukocyte antigen (HLA)– and platelet antigen–matched platelet transfusion, if available, or unmatched platelet transfusion, if necessary.

Patients with **Glanzmann thrombasthenia** have a deficiency in platelet surface glycoprotein IIb/IIIa receptors, the major receptor for fibrinogen; this deficiency results in abnormal platelet aggregation.[111] These patients have a normal platelet count, but bleeding time and closure time on PFA-100 are prolonged. The treatment of Glanzmann thrombasthenia during labor and delivery is similar to that for Bernard-Soulier syndrome.[111]

Drug-Induced Platelet Disorders

Drugs can accelerate platelet destruction through an immunologic mechanism[112]; however, drugs that are likely to result in this complication are not often used in obstetric patients (e.g., quinidine, quinine, gold salts).[113] Heparin is an exception; it can cause thrombocytopenia via a nonimmunologic or an immunologic mechanism.[114] The risk for heparin-induced thrombocytopenia (HIT) is lower with LMWH than unfractionated heparin.[115]

Drugs that *impair* platelet function are often used in obstetric patients (Table 44-4). Aspirin irreversibly inactivates cyclooxygenase.[116] The bleeding time is prolonged for 1 to 4 days after the ingestion of aspirin,[117] and *in vitro* platelet function tests can remain abnormal for as long as 1 week.[116] However, low-dose aspirin (i.e., 60 to 70 mg) does not significantly prolong the bleeding time in pregnant women.[118] Moreover, a large number of women receiving low-dose aspirin therapy for the prevention or treatment of preeclampsia have received neuraxial analgesia for labor and delivery without complications.[119] Therefore, in the absence of a coadministered anticoagulant (e.g., LMWH) or preexisting hemostatic defect

TABLE 44-4 Drugs That Affect Platelet Function

Category	Drug(s)
Inhibitors of cyclooxygenase	Aspirin, nonsteroidal anti-inflammatory drugs
Stimulators of adenyl cyclase	Prostaglandin E_1, prostacyclin
Inhibitors of phosphodiesterase	Caffeine, theophylline
Antibiotics	Penicillins, cephalosporins
Anticoagulant	Heparin
Volume expanders	Dextran, hydroxyethyl starch

TABLE 44-5 Classification of von Willebrand's Disease

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight VWF multimers
2B	Increased affinity for platelet glycoprotein Ib
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight VWF multimers
2N	Markedly decreased binding affinity for factor VIII
3	Virtually complete deficiency of VWF

VWF, von Willebrand factor.
From Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost 2006; 4:2103-14.

(e.g., von Willebrand's disease, hemophilia A, uremia) in which aspirin's effect is more pronounced,[120,121] recent ingestion of aspirin does not contraindicate the administration of neuraxial anesthesia.[122]

Other nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, indomethacin, naproxen) reversibly inhibit cyclooxygenase.[123] These drugs have only a transient effect on the bleeding time[117,124] and have been given to patients with hemostatic diseases (e.g., hemophilia A) without deleterious effect.[125] Maternal ingestion of these drugs should not affect anesthetic management for delivery.

Drugs that increase platelet cyclic adenosine monophosphate (cAMP) levels decrease platelet responsiveness.[123] This increase in cAMP levels can occur after the administration of prostaglandin E_1 or prostacyclin (which stimulates adenyl cyclase)[126] or after the administration of drugs that decrease the destruction of cAMP (e.g., caffeine, theophylline).

Most penicillins and some cephalosporins impair platelet activity.[123,127] In addition to its effect on the coagulation system, heparin impairs platelet function by reducing the production of thrombin, a potent platelet activator.[123] Dextran, which is absorbed onto platelet membranes, can reduce platelet aggregation, secretion, and procoagulant activity.[123] Because platelet membranes are a substrate for steps in the coagulation system, clot formation may also be impaired by dextran. Hydroxyethyl starch also appears to worsen platelet function.[123] A diet rich in omega-3 fatty acids or fish oil can reduce the platelet concentration of arachidonic acid and prolong bleeding time.[123] Herbal therapies including garlic, gingko, and ginseng can similarly impact hemostasis.[122]

CONGENITAL COAGULOPATHIES

von Willebrand's Disease

The hemostatic disorder, von Willebrand's disease, was named for Erich von Willebrand, who first described it in 1926.[128] vWF is synthesized by endothelial cells and megakaryocytes.[129] The vWF subunit is 260 to 275 kDa. A dimer is formed by a combination of two subunits, and variable numbers of the dimers are combined to form multimers that range from 500 to 200,000 kDa. vWF plays two primary roles in coagulation: (1) it forms a complex with factor VIII, which decreases the excretion of factor VIII; and (2) it mediates platelet adhesion by binding to platelets (a reaction enhanced by ristocetin) and collagen.[129]

von Willebrand's disease can be divided into several subtypes based on quantitative and qualitative defects in vWF (Table 44-5).[129-131] **Type 1 von Willebrand's disease** is the most common congenital bleeding disorder, which typically is inherited as an autosomal dominant trait[132]; its incidence ranges from 1:100 to 1:2500.[129,132,133] In this subtype, vWF functions normally but its levels are reduced. Both vWF and factor VIII increase in normal pregnancy, so antenatal bleeding is rare in women with type 1 disease. **Type 2 von Willebrand's disease** is less common and includes a family of disorders characterized by qualitative dysfunction of vWF, with normal plasma concentrations.[129] Although types 2A and 2M lead to decreased platelet aggregation, type 2B results from a gain-of-function mutation in which vWF increases binding between platelets, leading to accelerated platelet turnover and thrombocytopenia.[129] Finally, **type 3 von Willebrand's disease** is caused by a severe quantitative deficiency in vWF and is inherited in an autosomal recessive pattern; the estimated incidence is between 1:200,000 and 1:2,000,000.[134,135]

Patients with von Willebrand's disease have variable levels of both vWF and factor VIII. Thus, some patients with von Willebrand's disease are asymptomatic. Because vWF aids in platelet binding to sites of vascular damage, symptoms of von Willebrand's disease (e.g., bleeding from skin and mucosae) can mimic those of platelet disorders.[129] vWF slows the clearance of factor VIII; therefore, a deficiency can result in decreased factor VIII levels, and patients with severe disease can present with hemorrhages into muscles and joints similar to those seen in patients with classic hemophilia.[129]

Patients with von Willebrand's disease usually have decreased platelet aggregation in response to ristocetin. Levels of factor VIII and vWF ristocetin cofactor should

be determined during pregnancy, at least during the third trimester. Prophylactic treatment is reserved for patients with a factor VIII level below 50 IU/dL.[129] For patients with von Willebrand's disease type I or IIA, 0.3 μg/kg of desmopressin (l-desamino-8-D-arginine vasopressin [DDAVP]) is administered intravenously as labor begins, and the dose is repeated every 12 to 24 hours.[129] For patients who are unresponsive to desmopressin, commercial preparations of plasma concentrates that contain both vWF and factor VIII are administered.[129] The usual dose is 40 to 60 IU/kg. For acute bleeding, fresh frozen plasma (FFP) or cryoprecipitate (500 to 1500 units of factor VIII activity) may be administered; however, large volumes of FFP are needed for factor replacement.

During labor, factor VIII and vWF ristocetin cofactor levels should be maintained at greater than 50% of normal.[130] When considering anesthetic and analgesic options, the balance between risks and benefits of a neuraxial procedure should be evaluated for each patient.[136] Postpartum hemorrhage rates are increased for up to 1 month after delivery.[130] The factor VIII level should be checked daily during the postpartum period, and treatment should be initiated if the factor VIII level decreases below 50% of normal levels or if significant bleeding occurs.[129,137]

Other Coagulation Factor Deficiencies

In males, the two most common coagulation factor deficiencies are factor VIII (**hemophilia A**) and factor IX (**hemophilia B**). Both occur as X-linked traits. It is possible for a female to have hemophilia if her father is a hemophiliac and her mother is a carrier for hemophilia and passes the abnormal X chromosome to her daughter.[138] A female can also have hemophilia if she is a carrier (i.e., she received one abnormal gene from a carrier mother or an affected father) and she has either a new mutation of the other gene for factor VIII or IX or another X-chromosome abnormality.[138]

In early embryogenesis, half of the X chromosomes are inactivated.[139] Of the gene population, half of the abnormal genes and half of the normal genes are inactivated in females who are heterozygous for hemophilia A or B. On average, these women have half of the normal concentration of factor VIII or IX, which typically is adequate for coagulation. Because the chromosome inactivation is random, more abnormal genes are inactivated in a certain percentage of carriers, and these women have a normal concentration of factor VIII or IX. However, if most of the normal genes are inactivated, the individual can have severely depressed levels of factor VIII or IX. If such a patient becomes pregnant, factor supplementation with pooled human plasma concentrate (antihemophilic factor/vWF concentrate [hemophilia A] or prothrombin complex concentrate [PCC] [hemophilia B]) may be necessary before or during delivery.

On average, half of the male children of heterozygous carriers for hemophilia A or B will have hemophilia. These infants have an increased incidence of excessive bleeding after circumcision, but the incidence of cephalohematoma does not appear to be increased.[140] It is not clear whether the mode of delivery affects the incidence of cephalohematoma. Women who are heterozygous carriers may undergo a trial of labor and vaginal delivery, but the following procedures should be avoided: (1) placement of a fetal scalp electrode, (2) fetal scalp blood pH determination, (3) vacuum extraction, and (4) difficult forceps delivery.[141] One report has described the administration of epidural analgesia during labor in a patient with severe hemophilia A after factor replacement.[142]

Acquired hemophilia is an autoimmune disease resulting from antibodies to factor VIII and is associated with pregnancy and the postpartum period.[143] Both rFVIIa and factor eight inhibitor bypassing activity (FEIBA) have been used to treat bleeding in patients with acquired hemophilia, but both agents are associated with thromboembolism.[143] Immunosuppression is necessary to treat the underlying cause of the disease.

Other congenital factor deficiencies occur as autosomal recessive traits and cause symptoms only in the homozygous state. Table 44-6 lists the plasma concentrations of coagulation factors that are required for hemostasis. The patient whose liver disease or vitamin K deficiency is responsible for the coagulopathy may benefit from intramuscular administration of vitamin K. In an emergency, factors may be rapidly replaced by administration of the appropriate pooled human plasma product or FFP (10 to 20 mL/kg).

TABLE 44-6 Minimum Coagulation Factor Levels

Coagulation Factor	Plasma Concentration Required for Hemostasis (U/dL)
I	10-25
II	40
V	10-15
VII	5-10
VIII	10-40
IX	10-40
X	10-15
XI	20-30
XIII	1-5

ACQUIRED COAGULOPATHIES

Disseminated Intravascular Coagulation

DIC results from an abnormal activation of the coagulation system, which leads to (1) formation of large amounts of thrombin, (2) activation of the fibrinolytic system, (3) depletion of coagulation factors, and (4) hemorrhage. In severe cases, diffuse microvascular thrombosis can lead to end-organ injury.[144] In the obstetric population, the most frequent causes of DIC are preeclampsia, placental abruption, sepsis, retained dead fetus syndrome, postpartum hemorrhage, acute fatty liver of pregnancy, and amniotic fluid embolism.[64]

Laboratory findings consistent with DIC include (1) a decreased platelet count; (2) decreased fibrinogen and

antithrombin III concentrations; (3) variable increases in PT, aPTT, and thrombin and reptilase times; and (4) higher concentrations of D-dimer, fibrin monomer, and fibrin degradation products than are normal during pregnancy.[64]

Therapeutic goals for these patients are to (1) treat or remove the precipitating cause, (2) replace depleted coagulation factors, (3) stop ongoing proteolytic activity (i.e., both the coagulation and fibrinolytic pathways), and (4) provide multisystem support as required.[145] In obstetric patients, evacuation of the uterine contents often results in removal of the precipitating cause.[146] A vaginal delivery can be attempted if the mother is stable and delivery can be achieved in a timely manner. If delivery cannot be achieved quickly, cesarean delivery may be required. Rarely, cesarean delivery may be necessary to deliver a dead fetus.

Considerable controversy exists regarding the medical management of patients with DIC.[144,146] Management may vary according to the etiology of the disorder.[144] In the presence of active bleeding or when an invasive procedure is required, the physician should transfuse FFP (15 to 30 mL/kg) to maintain the PT and aPTT within 1.5 times normal values, cryoprecipitate or fibrinogen concentrate to maintain the fibrinogen concentration above 150 to 200 mg/dL, and platelets to maintain a platelet count above 50,000/mm^3.[64,145]

The use of heparin is controversial. No trials have demonstrated improved clinical outcomes with heparin treatment,[145] but experts suggest that heparin at therapeutic doses may be helpful in cases of DIC complicated by thromboembolism or extensive fibrin deposition.[145,147,148] Both unfractionated heparin and LMWH are effective only in the presence of an adequate concentration of antithrombin III.[147] Patients with DIC may have a depleted concentration of antithrombin III,[147] and administration of FFP, lyophilized antithrombin III, or both may be necessary.[64,149] Several reports have described the use of rFVIIa in massive obstetric hemorrhage with DIC (see Chapter 38).[64]

Patients with DIC often have multiorgan system failure and require mechanical ventilatory support and care in the intensive care unit. DIC almost always mandates administration of general anesthesia in patients who require cesarean delivery. Given the increased risk for venous thromboembolism among patients with DIC, thromboprophylaxis with unfractionated heparin or LMWH, mechanical methods, or a combination of multiple methods is indicated.[145,148]

Therapeutic Anticoagulation

Most pregnant women who require long-term anticoagulation receive LMWH throughout pregnancy.[150] If warfarin is administered during pregnancy, it is typically discontinued in favor of unfractionated heparin or LMWH before the onset of labor. If a patient begins to labor while she is still taking warfarin, the effects can be reversed by oral or intravenous administration of vitamin K and intravenous PCC.[151,152] Although in emergency situations warfarin has traditionally been reversed with the rapid administration of FFP, PCC is increasingly used for this indication.[152] In 2013, a four-factor PCC (Kcentra) was approved by the U.S. Food and Drug Administration (FDA) for warfarin reversal. The dose of PCC depends on the patient's INR.[152]

Unfractionated heparin therapy should be discontinued and normalization of coagulation can be monitored by regular assessment of the aPTT or the activated coagulation time (ACT). If conditions require immediate reversal of anticoagulation, intravenous protamine 12.5 to 50 mg can be administered,[151] with additional doses administered as determined by the aPTT or the ACT. Protamine reversal of heparin therapy to allow administration of neuraxial anesthesia is not recommended. Further, protamine is unpredictable in reversing the anti–factor Xa activity caused by LMWH.[151] Therefore, protamine reversal of LMWH is not recommended.

If the coagulation status is deemed adequate for cesarean delivery, a neuraxial anesthetic technique can be considered. The anesthesia provider should weigh the risks and benefits of neuraxial and general anesthesia for the individual patient. It is preferable not to administer neuraxial anesthesia to a patient with a persistent laboratory coagulation abnormality. However, in selected circumstances, neuraxial anesthesia may be offered to a patient who has an isolated laboratory abnormality and no clinical evidence of coagulopathy. In such patients, frequent neurologic examinations are performed to facilitate the early detection of an epidural hematoma during the postpartum period.

Other Acquired Coagulopathies

Coagulopathies associated with hypertensive disorders of pregnancy and obstetric hemorrhage are discussed in Chapters 36 and 38, respectively.

NEURAXIAL ANESTHESIA IN THE PATIENT WITH ONGOING COAGULOPATHY OR PHARMACOLOGIC ANTICOAGULATION

Concern exists that an epidural hematoma may develop after the administration of neuraxial anesthesia in patients with coagulopathy (see Chapter 32). There are only a few published case reports of epidural or spinal subdural hematoma after the administration of neuraxial anesthesia in pregnant patients.[122] Similarly, multicenter survey studies have not reported this complication in obstetric patients.[153,154] However, in view of the serious consequences of an epidural hematoma, the risks and benefits of performing neuraxial anesthesia should be carefully assessed in a patient with either clinical or laboratory evidence of coagulopathy.

Frank coagulopathy represents an absolute contraindication to the administration of neuraxial anesthesia. The anesthesia provider can use PT/INR, aPTT, and ACT measurements or TEG to assess the extent of anticoagulation and the effectiveness of reversal therapy in patients receiving unfractionated heparin or oral anticoagulation therapy. If use of a neuraxial

anesthetic technique is considered in a patient with a congenital coagulopathy, results of relevant factor assays should be within the normal range before neuraxial needle placement.[130,142,155,156]

Professional societies have developed evidence-based guidelines to improve the safety of neuraxial anesthesia/analgesia in anticoagulated patients. The American Society of Regional Anesthesia and Pain Medicine (ASRA) Third Consensus Conference on Neuraxial Anesthesia and Anticoagulation concluded that *thromboprophylaxis* with twice-daily dosing of **unfractionated heparin** does not contraindicate the use of neuraxial anesthetic techniques as long as the total daily dose is not greater than 10,000 units (see Table 39-4).[122] However, the safety of neuraxial procedures in patients receiving daily heparin doses greater than 10,000 units or more than twice-daily dosing has not been established.[122] The platelet count should be assessed before the administration of neuraxial anesthesia or catheter removal in patients who have received unfractionated heparin therapy for more than 4 days.[122]

LMWH is considered to be more efficacious for thromboprophylaxis than unfractionated heparin.[115,150] However, a significant increase in the incidence of epidural and spinal hematoma after neuraxial anesthesia in *nonobstetric* patients receiving LMWH was recorded by the FDA between 1993 and 1998.[122,157] In December 1997, the FDA issued a warning that called attention to the risk for epidural or spinal hematoma in the setting of LMWH therapy. The apparent increase in the risk for an epidural hematoma after concurrent administration of neuraxial anesthesia and prophylactic LMWH may be related to the use of higher doses of LMWH and the relatively greater bioavailability and longer biologic half-life of LMWH than unfractionated heparin.[157] Recent reports have identified very few cases of epidural hematoma among nonobstetric patients who received care fully compliant with the ASRA guidelines.[153] No case of neuraxial hematoma in an obstetric patient has been attributed to antithrombotic or antiplatelet therapy.[122] Studies suggest that the risk for epidural hematoma is lower in obstetric patients than elderly nonobstetric patients.[153,154]

In patients receiving LMWH for *thromboprophylaxis*, the ASRA guidelines recommend an interval of at least 10 hours after the last LMWH dose before initiation of a neuraxial procedure (see Table 39-4).[122] In patients receiving higher doses of LMWH (e.g., enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, tinzaparin 175 U/kg daily), neuraxial needle placement should not occur until at least 24 hours after the last dose of LMWH.[122] Concomitant administration of medications affecting hemostasis (e.g., administration of both LMWH and an antiplatelet drug) further increases the risk for hemorrhagic complications.[122]

In patients receiving a single daily dose of LMWH thromboprophylaxis, the first postoperative LMWH dose should be administered 6 to 8 hours after surgery.[122] An indwelling epidural catheter may be safely maintained in these patients; however, it should be removed at least 10 to 12 hours after the last dose of LMWH, and the next dose of LMWH should be administered at least 2 hours* *after* catheter removal. In patients receiving higher (e.g., twice-daily) doses of LMWH, the first dose of LMWH should be delayed for 24 hours postoperatively, and an indwelling catheter should be removed at least 2 hours* *before* initiation of LMWH therapy. The anti-Xa level is not predictive of the risk for bleeding during or after administration of neuraxial anesthesia.

Fondaparinux is a newer antithrombotic drug that inhibits factor Xa activity. Its use has been reported in pregnant women who developed HIT.[158] The American College of Chest Physicians (ACCP) recommends limiting the use of fondaparinux to those with severe allergic reactions to heparin (e.g., HIT).[150] The risk for spinal hematoma with fondaparinux is not known.[122]

In patients receiving long-term **warfarin** therapy, the anticoagulation therapy should be stopped at least 4 to 5 days before the planned procedure and the INR should be normalized before needle placement, with catheter removal deferred until the INR is 1.5 or less.[122]

Aspirin or **NSAID** therapy is not a contraindication for neuraxial anesthesia. The use of **herbal medications** such as garlic, ginkgo, or ginseng alone may not increase the risk for spinal hematoma; however, concurrent use of an oral anticoagulant or heparin may increase the risk for bleeding complications in these patients.[122]

The assessment of risk is more problematic in patients with isolated laboratory evidence of thrombocytopenia. **Thrombocytopenia** (defined as a platelet count $< 100{,}000/mm^3$) develops in up to 1 in 20 healthy women by the end of pregnancy, normally with little clinical consequence.[81] However, the combination of both quantitative and qualitative platelet deficits presents a more serious risk for epidural hematoma and may develop in the context of severe preeclampsia (see Chapter 36), ATP, and congenital platelet disorders. A number of groups have reported the safe administration of epidural anesthesia—without any neurologic complications—in healthy pregnant women with thrombocytopenia, preeclamptic women, and women with ATP.[156,159,160] Published studies of neuraxial anesthesia in thrombocytopenic patients are small and retrospective and do not exclude the possibility that modest thrombocytopenia increases the risk for epidural hematoma.[156] However, no published evidence suggests that a specific platelet count predicts the risk for epidural hematoma in obstetric patients.

Although there is no widespread consensus about the minimum platelet count needed to ensure safe neuraxial procedures, several experts have reviewed the available evidence and concluded that a minimum platelet count of $80{,}000/mm^3$ is usually sufficient for the safe initiation of neuraxial analgesia/anesthesia and removal of a neuraxial catheter.[159,160] Under selected circumstances, neuraxial procedures may be appropriate in a

*The U.S. Food and Drug Administration recommends waiting at least 4 hours after removal of a neuraxial catheter before administering a postprocedure dose of LMWH. (U.S. Food and Drug Administration. Low molecular weight heparins: drug safety communication—recommendations to decrease risk of spinal column bleeding and paralysis. November 6, 2013. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm373918.htm. Accessed November 2013.)

well-counseled patient with a platelet count between 50,000 and 80,000/mm^3.[159] When determining whether neuraxial anesthesia is safe in a thrombocytopenic patient, the anesthesia provider should consider the following factors: (1) clinical evidence of bleeding, (2) time interval since the platelet count was measured, (3) any recent change in the platelet count (e.g., downward trending), (4) quality of platelet function, (5) adequacy of coagulation factor level and function, and, perhaps most importantly, (6) the risk versus benefit of performing neuraxial anesthesia. The bleeding time measurement is *not* helpful in determining the risk for epidural hematoma. Although TEG shows some promise, its usefulness in predicting the risk for epidural hematoma is unproven. The use of single-shot spinal anesthesia may be associated with a lower risk for epidural vein trauma than epidural catheter insertion and removal.

Clinical judgment represents the most important means of assessing the risk for epidural hematoma in an individual patient. Clearly, the anesthesia provider would not want to perform neuraxial anesthesia in a patient with clinical evidence of coagulopathy (e.g., bleeding from nasal or oral mucosae or venipuncture sites, presence of petechiae or ecchymoses). In contrast, a patient with severe preeclampsia, severe upper airway edema, a stable platelet count of 95,000/mm^3, and no clinical evidence of coagulopathy may be an appropriate candidate for neuraxial anesthesia. The risk for a failed tracheal intubation is greater than the risk for an epidural hematoma in such a patient. Neuraxial analgesia may be offered to such a patient after a thorough discussion of the risks and benefits. However, some anesthesia providers advocate a more conservative approach in such cases and recommend alternative methods of analgesia during labor, followed by awake laryngoscopy and tracheal intubation if cesarean delivery should become necessary.

Several modifications of the neuraxial technique may decrease the risk for venous injury during the administration of epidural analgesia: (1) administration of epidural analgesia early in labor before the platelet count or platelet function declines, (2) needle and catheter placement with the patient in the lateral rather than sitting position, (3) the use of a wire-embedded polyurethane rather than polyamide epidural catheter, (4) limiting catheter insertion length to 6 cm or less, and (5) administration of saline through the needle to distend the epidural space before insertion of the catheter.[161] The epidural catheter may be sited several hours before the patient requires analgesia. This interval allows the anesthesia provider to observe for symptoms and signs of epidural hematoma formation (e.g., back pain, radicular pain, leg weakness) before the administration of an analgesic or anesthetic solution. This last recommendation is impractical in most circumstances. Furthermore, it is unclear that any of these recommendations reduces the likelihood of epidural hematoma in patients with platelet dysfunction or coagulopathy.

During the administration of epidural analgesia, the anesthesia provider can minimize motor blockade, which might confuse the diagnosis of epidural hematoma, by administering a dilute solution of local anesthetic with an opioid. A neurologic examination should be performed at 1- to 2-hour intervals to look for evidence of an epidural hematoma. In addition, all clinical staff should be aware of the signs and symptoms of epidural hematoma, including (1) severe, unremitting backache; (2) neurologic deficit, including bowel or bladder dysfunction or radiculopathy; (3) tenderness over the spinous or paraspinous area; and (4) unexplained fever.[162] If clinical findings raise concern for epidural hematoma, immediate steps should be taken to obtain appropriate diagnostic imaging and to consult a neurosurgeon (see Chapter 32).

In some cases, severe thrombocytopenia and coagulopathy may develop *after* the placement of an epidural catheter. Epidural hematomas have been reported after epidural catheter removal in obstetric patients with coagulopathy.[122] It is possible that movement or removal of the catheter may dislodge a clot, resulting in fresh bleeding and an epidural hematoma. As such, recommended hemostatic conditions for epidural catheter removal parallel those recommended for neuraxial block administration.[122,159]

HYPERCOAGULABLE STATES

Effective hemostasis is maintained by an appropriate balance of procoagulant and anticoagulant activity. A congenital deficiency in anticoagulant activity occurs in more than 50% of women with pregnancy-related venous thrombosis.[163,164] Factor V Leiden mutation, prothrombin mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency are the most common thrombophilias diagnosed in pregnancy.[164] Venous thromboses are more common than arterial thromboses[165]; the incidence increases with surgery, pregnancy, oral contraceptive use, and immobilization. Although the results of small case-control studies have suggested that patients with thrombophilias may have an increased incidence of fetal growth restriction, intrauterine fetal death, preeclampsia, and placental abruption, these associations have not been replicated in large prospective cohorts.[164,166] There is insufficient evidence that screening for thrombophilias improves birth outcomes for women with a history of pregnancy complications.[150]

Commonly used anticoagulation regimens during pregnancy are listed in Table 39-3. The American College of Obstetricians and Gynecologists (ACOG) and the ACCP has recommended thromboprophylaxis regimens for pregnancies complicated by inherited thrombophilias.[150,164,167] Additionally, the ACCP recommends LMWH during pregnancy for the prevention and treatment of venous thromboembolism, rather than unfractionated heparin or warfarin.[150]

For women receiving long-term thromboprophylaxis with LMWH or vitamin K antagonists during pregnancy, consideration should be given toward transitioning the patient to a shorter-acting agent in anticipation of delivery to facilitate initiation of neuraxial procedures and peripartum hemostasis.[150] Intermediate- and therapeutic-dose LMWH heparin should be discontinued at least 24 hours before the induction of labor or cesarean delivery.[150]

Factor V Leiden Mutation

Factor V Leiden is a genetic disorder attributable to genetic mutation resulting in a single amino acid substitution in the factor V protein. The mutant protein persists longer in the circulation owing to its slower degradation by activated protein C, leading to a hypercoagulable state.[164] The incidence of heterozygous factor V Leiden is 5% to 8%; the risk for thrombosis is increased 4- to 8-fold.[163,168] A homozygous state is found in 1 in 1600 individuals, and these patients have at least a 25-fold higher risk for thrombosis.[163,168]

Prothrombin Gene Mutation

The prothrombin *G20210A* gene mutation results in elevated circulating prothrombin levels.[163] This gene mutation is present in 2% to 3% of the general population and accounts for up to 17% of cases of venous thromboembolism in pregnancy.[163,164] For women who are heterozygous for the prothrombin mutation, a personal or family history of venous thrombosis increases risk for a subsequent venous thromboembolism in pregnancy from less than 0.5% to approximately 10%.[164] Further, the combination of factor V Leiden and prothrombin mutations has synergistic hypercoagulable effects.[164]

Protein C Deficiency

Protein C is produced in the liver and acts by inhibiting activated factors V and VIII. Deficiency is defined by an activity level less than 50%. The incidence of protein C deficiency is approximately 0.3% in the general population; the risk for thrombosis in pregnancy is increased up to fivefold.[163,168] Protein C levels normally increase by 35% during pregnancy, but this increase is attenuated in patients with protein C deficiency.[169] Among women with protein C deficiency, the risk for venous thromboembolism during pregnancy increases from less than 1% among those without previous thrombosis to between 2% and 17% for those with a previous thrombosis.[164]

Protein C is a vitamin K–dependent protein with a short half-life (8 hours). If warfarin is administered without prior heparin anticoagulation, protein C levels decrease before the levels of factors II, VII, IX, and X decrease. Thrombosis with skin necrosis can result.[170]

Protein S Deficiency

Protein S acts as a cofactor for protein C. In contrast to protein C, the plasma levels of protein S normally *decrease* during pregnancy.[169] The prevalence of protein S deficiency is approximately 0.2 % in the general population; the risk of venous thromboembolism during pregnancy is increased up to 2- to 4-fold.[163,168] Protein S is also produced in the liver and depends on vitamin K for its synthesis.[170] Circulating protein S binds to C4b-binding protein (a protein of the complement system), but it is the free fraction of protein S that acts as a cofactor for protein C.[170] Immunologic assays measure total protein S concentration; therefore, a diagnosis of protein S deficiency is made either by using a functional assay (< 50% activity) or by calculating the percent of protein S bound to C4b-binding protein.[170] The risk of antepartum and postpartum venous thromboembolism is low in patients with protein C or protein S deficiency; hence thromboprophylaxis is not indicated unless the patient has a history of venous thromboembolism or additional risk factors are present.[167]

Antithrombin III Deficiency

Antithrombin III is synthesized in the liver and endothelial cells. It inactivates thrombin and factors IXa, Xa, XIa, and XIIa[171]; its activity is potentiated by heparin. Deficiency of antithrombin III occurs in 0.02% to 0.4% of the general population[164,172]; the risk for thrombosis in pregnancy is increased up to fivefold.[163,168,172] The risk for thrombosis during pregnancy increases from 3% to 7% among those with antithrombin III deficiency and no prior thromboembolism to more than 40% among those with a prior venous thromboembolism.[164] Quantitative (type I) and qualitative (type II) deficiencies exist[170]; thus, both immunologic and functional assays are required to detect abnormalities.[173]

Heparin acts by potentiating the activity of antithrombin III. If antithrombin III levels are decreased, heparin may not ensure effective thromboprophylaxis. Antithrombin III replacement, with or without coadministration of heparin, has been proposed for perioperative or peripartum therapy for patients with antithrombin III deficiency and a history of venous thromboembolism.[171] Although long-term antithrombin III replacement is expensive, its use may be indicated for women who experience venous thrombosis despite thromboprophylaxis with LMWH.[174] Warfarin is an alternative option for women in the second or third trimester of pregnancy, remote from delivery.[174]

Lupus Anticoagulant

The term *lupus anticoagulant* is a misnomer. Patients with lupus anticoagulant do *not* have a coagulopathy; rather, they are at risk for thromboembolic events. The hypercoagulable state associated with lupus anticoagulant is discussed in Chapter 41.

KEY POINTS

- Neuraxial anesthetic techniques can be used safely during labor and delivery in patients with a hemoglobinopathy.
- Routine laboratory assessment of the platelet count and coagulation status is not indicated before the initiation of neuraxial procedures in healthy parturients.
- The first goal in the treatment of disseminated intravascular coagulation is to treat or remove the precipitating cause. In pregnant patients, evacuation of the uterine contents often results in removal of the precipitating cause.

- Uncorrected, frank coagulopathy represents an absolute contraindication to the administration of neuraxial anesthesia.
- In a patient with an isolated laboratory abnormality and no clinical evidence of coagulopathy, the anesthesiologist should assess the risks and benefits of performing neuraxial anesthesia.
- Prophylactic and therapeutic anticoagulation regimens exist for patients with venous thromboembolism or those at increased risk for thromboembolism; anesthesia providers should be aware of the safety implications of anticoagulation therapy on the timing of initiation of neuraxial anesthesia and neuraxial catheter removal.

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CHAPTER 50

Obesity

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CHAPTER OUTLINE

Obesity is a worldwide health problem, with the prevalence in the general population growing at an alarming rate and reaching epidemic proportions. Data from the National Center for Health Statistics show that in 2010, 69% of Americans were overweight and 36% were obese; 56% of women of reproductive age (20 to 39 years old) were overweight, and 32% were obese.[1] Although no definition of obesity specific to pregnancy exists, a pregnant woman is generally considered overweight when her body mass index (BMI) is 25.0 to 29.9 kg/m^2, and obese when her BMI is 30 kg/m^2 or greater. The World Health Organization defines three grades of obesity: class I (BMI 30.0 to 34.9 kg/m^2), class II (BMI 35.0 to 39.9 kg/m^2), and class III (BMI 40 kg/m^2 or greater).

Obesity is associated with an increased risk for maternal morbidity and mortality. The care of obese parturients poses significant challenges to the anesthesia provider as a result of common comorbidities, an increased cesarean delivery rate, and technical difficulties associated with both neuraxial and general anesthesia. Understanding the pathophysiologic changes and comorbidities associated with obesity and pregnancy is crucial for the safe conduct of anesthesia in these high-risk patients.

PHYSIOLOGIC CHANGES OF OBESITY

Pulmonary Changes

Obesity increases the demands on the pulmonary system. As energy expenditure increases proportionate to the increase in body mass,[2] oxygen consumption and carbon dioxide (CO_2) production also increase proportionate to the increase in work performed.[3] Minute ventilation is increased owing to the elevated respiratory demand, except in the 5% to 10% of patients with Pickwickian syndrome, who display a reduced sensitivity to CO_2.[4] Obesity affects the body's ability to meet these demands by changing pulmonary mechanics, altering lung volumes, and impairing oxygen consumption. The combined effects of obesity and pregnancy on the respiratory system are summarized in Table 50-1.

Pulmonary Mechanics

Obesity increases the weight of the chest wall; thus, greater energy expenditure is required during ventilation to move this greater mass. Several prospective studies have demonstrated that morbidly obese patients, in comparison with controls, expend a disproportionately high percentage of total oxygen consumption on respiratory work, even during quiet breathing.[5] The weight gain associated with pregnancy further increases the work of breathing in obese patients. In obese individuals, frequent shallow respirations may represent a more efficient breathing pattern than a pattern characterized by large tidal volumes. This pattern of frequent shallow respirations contrasts to the increased tidal volumes that typically accompany pregnancy. Although the $Paco_2$ in most morbidly obese pregnant women is not different from that in nonobese pregnant women, pulmonary reserve is reduced.

Lung Volumes

Greater abdominal weight restricts diaphragm movement, especially in the supine or Trendelenburg position,

TABLE 50-1 Physiologic Changes in the Respiratory System Induced by Pregnancy and Obesity

	Pregnancy	Obesity	Combined Effect
Tidal volume	↑	↓	↑
Respiratory rate	↑	↔ or ↑	↑
Minute volume	↑	↓ or ↔	↑
Expiratory reserve volume	↓	↓↓	↓
Residual volume	↓	↓ or ↔	↓
Functional residual capacity	↓↓	↓↓↓	↓↓
Vital capacity	↔	↔	↓
FEV_1	↔	↓ or ↔	↔
FEV_1/VC	↔	↔	↔
Total lung capacity	↓	↓↓	↓
Compliance	↔	↓↓	↓
Work of breathing	↑	↑↑	↑
$\dot{V}/\dot{Q}$ mismatch	↑	↑	↑↑
Pao_2	↓	↓↓	↓
$Paco_2$	↓	↑	↓

↑, increase; ↓, decrease, ↔, no change; more than one arrow represents the degree of intensity; *FEV*, forced expiratory volume in 1 sec; *VC*, vital capacity; $\dot{V}/\dot{Q}$, ventilation/perfusion.
Modified from Saravanakumar K, Rao SG, Cooper GM. Obesity and obstetric anaesthesia. Anaesthesia 2006; 61:36-48.

TABLE 50-2 Physiologic Changes in the Cardiovascular System Induced by Pregnancy and Obesity

	Pregnancy	Obesity	Combined Effect
Heart rate	↑	↑↑	↑↑
Stroke volume	↑↑	↑	↑
Cardiac output	↑↑	↑	↑↑↑
Blood volume	↑↑	↑	↑
Hematocrit	↓↓	↑	↓
Systemic vascular resistance	↓↓	↑	↔ or ↓
Mean arterial pressure	↓ or ↔	↑↑	↑↑
Systolic function	↔	↔ or ↓	↔ or ↓
Diastolic function	↔	↓	↓
Central venous pressure	↔	↑	↑↑
Pulmonary artery occlusion pressure	↔	↑↑	↑↑

↑, increase; ↓, decrease, ↔, no change; more than one arrow represents the degree of intensity.
Modified from Saravanakumar K, Rao SG, Cooper GM. Obesity and obstetric anaesthesia. Anaesthesia 2006; 61:36-48.

thus encouraging smaller tidal volumes. Functional residual capacity (FRC) decreases at the expense of expiratory reserve volume and may be less than closing capacity. In morbidly obese patients, this difference can result in airway closure during tidal ventilation. Similarly, expiratory reserve volume, vital capacity, inspiratory capacity, total lung capacity, and maximum minute ventilation all decrease in morbidly obese patients. Both chest wall and lung compliance decrease, but airway resistance increases.[6,7]

Pregnancy also alters lung volumes, and these changes may modify some of the normal effects of obesity on respiratory function. In nonobese pregnant women, expiratory reserve volume and FRC both decline 20% to 25% by term. Eng et al.,[8] examining a series of pregnant women whose estimated prepregnancy weights ranged from 50% to 140% above normal, measured lung volumes during the third trimester and again at 2 months postpartum. With the exception of FRC, the lung volume changes resembled those that occur in nonobese pregnant women. However, FRC decreased less in obese pregnant women than in nonobese pregnant women.

Oxygenation

Pulmonary diffusion typically remains normal in most women with morbid obesity. Decreased chest wall compliance and greater abdominal weight promote airway closure in the dependent portion of the lung.[9] Ventilation preferentially occurs in the more compliant, nondependent portion of the lung. In contrast, pulmonary blood flow preferentially occurs in the dependent portion of the lung, resulting in ventilation-perfusion mismatch and hypoxemia.[9]

Consistent with the positional deterioration of lung volumes, oxygenation worsens in obese persons in the supine and Trendelenburg positions. Both term pregnant and obese patients are prone to rapid oxygen desaturation during induction of general anesthesia.[10] Although oxygenation does not necessarily correlate linearly with weight,[11] massive weight loss improves Pao_2 and expiratory reserve volume. Weight loss does not, however, improve forced expiratory volume in 1 second, forced vital capacity, or maximum mid-expiratory flow.[12]

Cardiovascular Changes

Cardiovascular changes associated with pregnancy and obesity are summarized in Table 50-2. Both obesity and pregnancy increase blood volume and cardiac output. The latter increases by 30 to 50 mL/min for every 100 g of fat.[13] This change occurs as a result of increases in both stroke volume and heart rate. In addition to the elevated preload observed in obese parturients, left ventricular afterload is also increased owing to the high peripheral resistance and greater arterial wall stiffness. These changes result in both eccentric and concentric left ventricular hypertrophy. Messerli et al.[14] documented a 30-fold increase in premature ventricular contractions in obese patients with eccentric left ventricular hypertrophy in comparison with lean subjects. The increase in heart rate limits the time available for diastolic filling. Diastolic relaxation is impaired, leading to diastolic dysfunction.[15] In contrast, ventricular systolic function is usually normal in obese individuals.[16]

Pulmonary blood volume increases in proportion to increases in cardiac output and total blood volume. Pulmonary hypertension can occur and may be position

dependent. Paul et al.[17] observed an 11% increase in oxygen consumption and a 44% increase in pulmonary capillary wedge pressure when morbidly obese patients were placed in a supine position. Hypoxemia, if present, increases pulmonary vascular resistance. Airway obstruction may also increase pulmonary artery pressure.

Hypertension occurs more frequently among obese pregnant women than lean women. A BMI of 30 kg/m^2 or more is associated with a threefold higher incidence of hypertension during pregnancy than a BMI less than 30 kg/m^2.[18] BMI and left ventricular mass are directly related, even after controlling for age and blood pressure, especially in patients with a BMI greater than 30 kg/m^2.[19] Among morbidly obese pregnant women, left atrial size, left ventricular thickness, interventricular septal thickness, and left ventricular mass are increased compared with nonobese pregnant women.[13] Fatty infiltration of the heart can occur, especially in the right ventricle and perhaps in the conduction system.[20]

Aortocaval compression of the great vessels in the supine position may be greater in obese parturients, particularly those with a large fat panniculus.[21] Tsueda et al.[22] reported two cases of cardiac arrest in morbidly obese patients who had been placed in the supine position. The authors speculated that the sudden circulatory changes associated with this change in position accounted for the sudden death of these patients.

Gastrointestinal Changes

It is unclear whether obesity in pregnancy is associated with an increase in gastric volume and a decrease in gastric pH. Vaughan et al.[23] observed that 88% of obese nonpregnant patients presenting for surgery had a gastric pH less than 2.5 and 86% had a gastric volume exceeding 25 mL. These findings resemble those in a cohort of healthy pregnant women who presented for elective cesarean delivery.[24] Roberts and Shirley[25] reported that gastric volumes aspirated from obese laboring women undergoing cesarean delivery were significantly higher than those obtained from lean controls.

Other studies, however, did not confirm these findings and reported conflicting evidence regarding gastric volume and pH in obese patients.[26,27] Similarly, studies have reported conflicting data regarding gastric emptying in the obese population; studies have reported delayed, unchanged, or more rapid rates of gastric emptying in obese subjects compared with lean subjects.[28] In a nonobstetric obese population, Maltby et al.[29] reported that drinking 300 mL of clear fluid 2 hours before surgery had no effect on gastric fluid volume and pH compared with fasting after midnight. Similarly, Wong et al.[30] found that gastric emptying in obese, nonlaboring term pregnant volunteers was not delayed after ingestion of 300 mL of water compared with ingestion of 50 mL of water. The gastric volume was similar to baseline 60 minutes after ingestion of water. It should be remembered, however, that obesity is a risk factor for diabetes,[18] which may cause delayed gastric emptying.

Both gastroesophageal reflux and hiatal hernia are more common in obese than in nonobese patients.[31] Obesity is also associated with a higher risk for difficult airway management, which is a known risk factor for aspiration.[32] Therefore, it seems likely that morbidly obese patients are at higher risk for pulmonary aspiration of gastric contents.

Coagulation Changes

Obesity is associated with a higher risk for thromboembolic complications.[33] Venous thromboembolism was the leading cause of direct maternal mortality in the United Kingdom from 1985 to 2005.[34] Although the most recent report of the *Confidential Enquiries into Maternal Deaths in the United Kingdom* covering the triennium 2006 to 2008 showed a reduction in deaths from venous thromboembolism, 12 of the 16 women who died were obese.[34] Obesity is associated with changes in coagulation, venous stasis, and endothelial injury that contribute to the pathogenesis of venous thromboembolism. For instance, adipose tissue secretes the following: (1) adipokines such as plasminogen activator inhibitor-1 (PAI-1), which results in impaired fibrinolysis; (2) leptin, which promotes platelet aggregation; and (3) interleukin-6, which stimulates the liver to produce coagulation factors.[35,36] C-reactive protein levels are also elevated in obese women, leading to platelet activation.[37] Venous stasis is compounded in obese women by increased intra-abdominal pressure, which leads to increased iliofemoral venous pressure.[38] Endothelial injury may also be increased in obese patients; obesity was shown to be associated with endothelial dysfunction in the nonpregnant population.[39] Therefore, all risk factors that contribute to the pathogenesis of thromboembolic complications are likely to be exacerbated by obesity.

Endocrine Changes

Gestational diabetes and diabetes mellitus occur more frequently in obese patients.[18] The pathologic process is attributed to the following: (1) peripheral insulin resistance as a result of augmentation of free fatty acids by visceral obesity,[40] (2) increased proinflammatory cytokine levels,[41] (3) relative gonadotropin resistance, and (4) a low sex hormone–binding globulin concentration, which leads to hyperandrogenism and decreased insulin sensitivity.[42] The concentration of adiponectin, an adipokine with insulin-sensitizing properties, is also decreased in obesity, which leads to decreased insulin sensitivity.[43]

COMORBIDITIES ASSOCIATED WITH OBESITY

Sleep Apnea

Obesity is a significant risk factor for obstructive sleep apnea (OSA), which is characterized by repeated episodes of complete or partial upper airway collapse, leading to hypoxemia and hypercarbia. Those repeated periods of hypoxemia and reoxygenation lead to significant endocrine and metabolic disturbances, which result in an increased risk for hypertension, myocardial infarction, stroke, diabetes, and metabolic syndrome.[44] There is no

consensus on the definition of OSA in pregnancy, and therefore the prevalence is unknown.

The changes of pregnancy may both worsen and protect against OSA. For instance, weight gain[45] and estrogen-induced hyperemia and edema of nasal mucosa[46] might promote OSA, whereas sleeping in the lateral position,[47] reduced rapid eye movement (REM) sleep, and the progesterone-induced increase in minute ventilation might protect against it. Obesity does not seem to be as strongly correlated with OSA in pregnancy as in the nonpregnant population.[45]

The risks for gestational hypertension, preeclampsia, and gestational diabetes are increased with OSA.[48,49] Some studies have examined the potential impact of maternal OSA on poor perinatal outcomes, but most of the studies have been small with conflicting results. For instance, Sahin et al.[50] simultaneously performed polysomnography and a nonstress test to assess the impact of hypoxemia due to OSA on the fetus. OSA was found in 4 of the 35 women evaluated; in 3 of these women fetal heart rate (FHR) decelerations accompanied maternal oxyhemoglobin desaturation. Olivarez et al.[51] performed simultaneous polysomnography and at least 3 hours of continuous FHR monitoring on 100 pregnant women (including 19 with a diagnosis of OSA), and they found no association between FHR abnormalities and OSA parameters. Louis et al.[52] reported an increased risk for preeclampsia (odds ratio [OR], 3.54; 95% confidence interval [CI], 1.26 to 9.92), neonatal intensive care unit admission (OR, 3.39; 95% CI, 1.23 to 9.32), and cesarean delivery (OR, 3.04; 95% CI, 1.14 to 8.1) among obese pregnant women with OSA compared with those with no OSA after adjusting for age, race, and BMI.

Other Comorbidities

Obesity is associated with an increased risk for a number of disease states compared with lean controls (Table 50-3).[31,33,53] These comorbidities complicate the care of obese parturients.

TABLE 50-3 Relative Risk or Odds Ratio of Comorbidities in Obese Women

Comorbidity	Relative Risk	95% CI of Relative Risk
Type 2 diabetes*	12.41	9.03, 17.06
Hypertension*	2.42	1.95, 3.67
Coronary artery disease*	3.10	2.81, 3.43
Congestive heart failure*	1.78	1.07, 2.95
Pulmonary embolism*	3.51	2.61, 4.73
Stroke*	1.49	1.27, 1.74
Asthma*	1.78	1.36, 2.32
Gallbladder disease*	2.32	1.17, 4.57
Osteoarthritis*	1.96	1.88, 2.04
Chronic back pain*	2.81	2.27, 3.48
	Odds Ratio	**95% CI of Odds Ratio**
Depression†	1.55	1.22. 1.98
Gastroesophageal reflux disease‡	1.89	1.70, 2.09

CI, confidence interval.
*Data from Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009; 9:88.
†Data from Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010; 67:220-9.
‡Data from Eslick GD. Gastrointestinal symptoms and obesity: a meta-analysis. Obes Rev 2012; 13:469-79.

IMPACT OF OBESITY ON PREGNANCY

Maternal and Fetal Complications

Obesity results in greater use of health care resources. Chu et al.[54] reported that obese pregnant women receive significantly more prenatal tests, ultrasonographic examinations, medications, and prenatal visits with a physician, and they are at greater risk for having a high-risk pregnancy, cesarean delivery, and prolonged hospitalization than pregnant women of normal weight.

Obesity is associated with a significantly increased incidence of maternal, fetal, and neonatal complications. These include a higher risk for spontaneous abortion (miscarriage), thromboembolic complications, gestational diabetes, hypertensive disorders of pregnancy, dysfunctional labor, shoulder dystocia, operative vaginal delivery, cesarean delivery, postpartum hemorrhage, wound infection, fetal macrosomia, fetal congenital anomalies, stillbirth, and neonatal death.[18,55,56] In a prospective multicenter cohort study of more than 16,000 unselected pregnant women in the United States, Weiss et al.[18] assessed obstetric complications in 1473 obese women (BMI 30.0 to 34.9 kg/m^2), 877 morbidly obese women (BMI ≥ 35 kg/m^2), and 3752 lean controls (BMI < 30.0 kg/m^2). The odds of gestational diabetes, gestational hypertension, preeclampsia, macrosomia, preterm delivery, and operative vaginal and cesarean delivery were all greater in morbidly obese pregnant women compared with lean women (Table 50-4).

Most importantly, obesity increases the risk for death during pregnancy. The latest report of *Confidential Enquiries into Maternal Deaths in the United Kingdom* for the 2006 through 2008 triennium showed that 49% of women who died were overweight or obese.[34] Similarly, in the previous report that covered the 2003-2005 triennium, 52% of the mothers who died were overweight or obese.[57] The impact of obesity on maternal mortality was even greater among women who died of thromboembolism or cardiac disease; of the mothers who died of these two disease entities, 78% and 61%, respectively, were overweight or obese.[34] Because of the high risk for thromboembolism in obese pregnant women and the significant probability of subtherapeutic anticoagulation with fixed-dose low-molecular-weight heparin regimens, the Royal College of Obstetricians and Gynaecologists (RCOG) added weight-based recommendations for thromboprophylaxis to their 2009 guidelines.[58]

Obesity has also been identified as a risk factor for anesthesia-related maternal mortality. Six of the 13 direct

TABLE 50-4 Obstetric Complications in Obese and Morbidly Obese Women

Outcome	Odds Ratio (95% Confidence Interval)	
	OBESE VERSUS CONTROL	MORBIDLY OBESE VERSUS CONTROL
Gestational diabetes	2.6 (2.1, 3.4)	4.0 (3.1, 5.2)
Gestational hypertension	2.5 (2.1, 3.0)	3.2 (2.6, 4.0)
Preeclampsia	1.6 (1.1, 2.3)	3.3 (2.4, 5.5)
Birth weight > 4500 g	2.0 (1.4, 3.0)	2.4 (1.5, 3.8)
Birth weight > 4000 g	1.7 (1.4, 2.0)	1.9 (1.5, 2.3)
Preterm delivery	1.1 (0.9, 1.5)	1.5 (1.1, 2.1)
Operative vaginal delivery	1.0 (0.8, 1.3)	1.7 (1.2, 2.2)
Cesarean delivery*	1.7 (1.4, 2.2)	3.0 (2.2, 4.0)

*Nulliparous women.

Data from Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. Am J Obstet Gynecol 2004; 190:1091-7.

maternal deaths attributed to anesthesia in the last two triennial reports from the United Kingdom occurred in obese parturients.[34,57] In the United States, Mhyre et al.[59] reported that six of eight pregnant women who died of anesthesia-related deaths in Michigan between 1985 and 2003 were obese. Because of the increased risk for complications, in 2010 the United Kingdom Centre for Maternal and Child Enquiries (CMACE) and the RCOG published joint guidelines on the management of women with obesity in pregnancy.[60] Both these guidelines and the American College of Obstetricians and Gynecologists (ACOG) guidelines[61] recommend a multidisciplinary approach to the care and treatment of obese pregnant women, including (1) evaluation of all women for obesity by calculating BMI, (2) offering preconception counseling to obese women, (3) screening for gestational diabetes, (4) providing guidelines for prenatal weight gain, and (5) referring obese women for antepartum consultation with an anesthesiologist.

Progress of Labor and Method of Delivery

The progress of labor appears to be impacted by BMI. A large multicenter study involving 118,978 patients, whose labor management reflected current practice in the United States, reported that labor progressed more slowly with increasing BMI for both nulliparous and parous women.[62] The median time to progress from 4 to 10 cm cervical dilation increased from 5.4 hours to 7.7 hours for lean and morbidly obese *nulliparous* women, respectively, and from 4.6 hours to 5.4 hours for lean and morbidly obese *parous* women, respectively. These findings were independent of gestational age and induction of labor. Entry into the active phase of labor was also delayed in parous women as a function of BMI. Possible explanations include increased fetal size, higher induction rates, and/or decreased responsiveness to oxytocin.[62] Poor uterine contractility has also been demonstrated in obese parturients. Zhang et al.[63] found that myometrium obtained from obese women at cesarean delivery contracted with less force and frequency and had less calcium flux than that from normal-weight women. This observation may be attributable to the inhibitory effect of cholesterol[63] and/or adipokines (e.g., leptin, ghrelin, apelin), which were shown to inhibit human uterine contractility *in vitro*.[64]

Obesity is also associated with a higher risk for failed medical induction of labor. In a secondary analysis of data from a large labor induction trial involving 1273 patients (in which patients were stratified according to BMI), the duration of labor, oxytocin requirements, and cesarean delivery rates were significantly higher in women with a greater BMI.[65] In a large series from Sweden involving 233,887 deliveries, Cedergren[66] found a fourfold increase in the risk for cesarean delivery in parturients with a BMI greater than 40 kg/m^2, primarily because of failed or obstructed labor, despite attempts at augmentation.

Operative vaginal delivery, with its associated maternal and fetal morbidity, is more likely in the obese parturient.[18] One study examining maternal anthropometric parameters associated with shoulder dystocia reported a 2.7-fold increase in risk for shoulder dystocia in obese compared with lean parturients after adjustment for potential confounders such as macrosomia and diabetes.[67] Risk for fetal macrosomia is also higher with obesity, which, in addition to increasing the risk for shoulder dystocia and its associated birth trauma, predisposes to perineal lacerations, newborn infant injury, and postpartum hemorrhage.[18,67,68]

Higher BMI, increased prepregnancy weight, and excessive maternal weight gain increase the risk for both elective and emergency cesarean delivery.[69,70] This risk is further increased by obesity-related pregnancy complications such as macrosomia, fetal growth restriction (also known as intrauterine growth restriction), diabetes mellitus, and hypertensive disorders of pregnancy.[55,71] In a meta-analysis of 33 trials,[56] the unadjusted odds ratios (95% CI) of cesarean delivery were 1.46 (1.34 to 1.60), 2.05 (1.86 to 2.27), and 2.89 (2.28 to 3.79) among overweight, obese, and severely obese women, respectively, compared with normal-weight pregnant women.

ANESTHETIC MANAGEMENT

The high incidence of comorbid conditions among obese pregnant women necessitates early, careful preanesthetic assessment. There are also a number of technical matters that should be considered when caring for an obese parturient.

An appropriate-sized blood pressure cuff must be used for noninvasive blood pressure measurements. Unless the length of the sphygmomanometer cuff exceeds the circumference of the arm by 20%, systolic and diastolic blood pressure measurements may overestimate true maternal blood pressure. Forearm blood pressure measurement is sometimes used if an appropriate-sized blood pressure cuff is not available or if the upper arm cuff continues to slide from its position owing to the shape of the obese patient's upper arm. There is a good correlation

between upper arm and forearm noninvasive measurements, but forearm pressures exceed upper arm pressures by 10 ± 10 mm Hg (mean ± SD).[72] In selected cases, invasive monitoring of blood pressure with an intra-arterial catheter may be desirable.[57]

Intravenous access may be difficult in some obese patients. Ultrasonographic guidance may be useful; however, if peripheral intravenous access remains unsuccessful, central venous cannulation may be necessary.

Appropriately sized labor beds, transportation gurneys, and operating tables, and sufficient personnel to assist with patient transport, are imperative. Although standard operating tables are generally rated for persons weighing up to 500 pounds (227 kg), this rating may be insufficient for morbidly obese patients, especially when the table is articulated. Regardless of the weight rating of the table, it is critical that the obese patient be centered over the operating table pedestal at all times. Special equipment for positioning the patient, and longer spinal/epidural needles, may be needed (see later discussion).

Labor and Vaginal Delivery

Options for analgesia are the same as those for nonobese patients. Using the McGill pain questionnaire, Melzack[73] reported a positive correlation between BMI and the severity of labor pain. A later study, however, did not confirm these findings.[74]

Many of the options for labor analgesia have limitations in the obese parturient. For example, obese parturients with OSA may be more susceptible to the respiratory depressant effect of systemic opioids, leading to episodes of apnea and oxyhemoglobin desaturation. Pudendal nerve block may be more difficult technically in obese patients. Inhalation analgesia is useful in some patients; however, nitrous oxide has limited effectiveness and is not available in many birthing rooms. Further, inhalation analgesia may lead to loss of consciousness, which can be very dangerous in an obese woman with a difficult airway.

Neuraxial analgesia represents the best option for pain relief and is particularly desirable in the obese parturient. Given the greater risks for fetal macrosomia and shoulder dystocia in obese patients, adequate analgesia is often needed to facilitate an atraumatic vaginal delivery. The use of epidural analgesia during labor allows the anesthesia provider to extend epidural analgesia to surgical anesthesia for cesarean delivery and thus avoid the need for general anesthesia with its associated risks. Given the increased likelihood for cesarean delivery and the greater risks of general anesthesia in the obese parturient, the early administration of neuraxial labor analgesia is recommended in the obese parturient.

When performing a neuraxial anesthetic technique in the obese parturient, technical difficulties may include (1) inability to palpate the spinous processes or identify the midline[75]; (2) greater depth of the epidural space,[76] which may exaggerate minor needle directional errors and increase the likelihood of identifying a lateral portion of the epidural space[77]; and (3) the presence of fat pockets as well as hormonal softening of the ligaments, which may result in a false loss of resistance and/or a higher risk for unintentional dural puncture.[78] In the majority of obese parturients, however, the epidural space can be identified with a standard-length epidural needle.[79] Therefore, it seems prudent to use a standard-length needle first, which allows the provider better control, before switching to a longer needle.

Observing the prominence of the seventh cervical vertebra and the gluteal cleft can facilitate identification of the midline. Asking the parturient about the perceived location of the needle during block placement (relative to the midline) can also facilitate identification of the midline. Marroquin et al.[80] reported that 77% of morbidly obese parturients who were questioned about the position of the needle during a difficult labor epidural needle placement provided useful feedback to the anesthesia provider. Probing the subcutaneous tissue with a needle can also help identify the spinous processes and help identify a lumbar interspace.[81] More objectively, ultrasonographic guidance can be used to identify the midline, image the epidural space, and measure the distance from the skin to the epidural space. Grau et al.[82] reported that prepuncture ultrasonographic imaging significantly reduced the number of puncture sites and attempts and facilitated the performance of labor epidural analgesia. Similarly, Vallejo et al.[83] reported that prepuncture ultrasonography (performed to determine the midline, correct needle direction, and distance from the skin to the epidural space) reduced the number of attempts and need for catheter replacements when inexperienced trainees performed the blocks. Balki et al.[84] found a strong correlation between the depth of the epidural space measured by ultrasonography and that measured by the epidural needle in obese parturients. However, ultrasonographic imaging is more difficult in obese individuals; the same group of investigators reported that they were able to identify the midline but not measure the depth of the epidural space in a morbidly obese parturient with a BMI of 70 kg/m^2.[78] Furthermore, not all anesthesia providers are proficient in this technique.

Placing the patient in the sitting position facilitates identification of the midline and is preferred by many anesthesia providers when initiating a neuraxial anesthetic procedure in obese parturients. In the lateral position, gravity may cause lateral fat to sag down and obscure the midline. Bahar et al.[85] reported that the risk for epidural venous cannulation was lower in the lateral head-down position than in the sitting position and that there was no difference between the two positions in the number of attempts required to locate the epidural space. However, the average BMI of subjects in their study was approximately 37 kg/m^2.[85] Further, the distance from the skin to the epidural space is minimized when the patient is in the sitting flexed position.[86,87]

Care is needed to avoid dislodgement of the epidural catheter after insertion. Hamilton et al.[87] demonstrated that patient movement from the sitting-flexed to the lateral decubitus position causes redistribution of the soft tissue of the back. The distance from the skin to the epidural space increases, and an unsecured catheter will appear to be drawn inward by as much as 1.0 to 2.5 cm.[87] An epidural catheter secured with tape to the back of a patient in the sitting flexed position can be

unintentionally dislodged from the epidural space when the patient moves from the sitting to the lateral decubitus position. Movement of the epidural catheter relative to the skin is most striking in obese patients. Therefore, these investigators recommended that the patient assume the lateral position before the epidural catheter is secured to the skin.

Numerous authors have documented technical difficulties with neuraxial techniques in obese parturients. Hood and Dewan[88] reported that 94% of patients who weighed more than 300 lb (136.4 kg) experienced adequate analgesia for delivery, compared with 98% of controls. More attempts were required to identify the epidural space in obese women, there was a significantly higher initial failure rate (42% versus 6%), and placement of a second or third epidural catheter was more often required. Similarly, Dresner et al.[89] reported an increased risk for labor epidural block failure and need for catheter replacement with increasing BMI (2.4% for BMI < 25 kg/m^2 versus 6.6 % for BMI > 40 kg/m^2). Perlow et al.[90] reported that 74.4% of morbidly obese parturients needed more than one attempt and 14% needed more than three attempts for successful epidural catheter placement. In contrast, Bamgdade et al.[91] reported a significantly higher number of attempts to perform neuraxial anesthesia in obese parturients, but they observed no difference in the rate of failure of neuraxial anesthetic techniques for cesarean delivery in obese parturients. Although some investigators have reported a higher incidence of unintentional dural puncture in morbidly obese parturients than in lean parturients,[92] others did not confirm those findings.[74]

It is not known if epidural local anesthetic dose requirements are altered in morbidly obese parturients. In 1980, Hodgkinson and Husain[93] administered 20 mL of 0.75% epidural bupivacaine at the L3 to L4 interspace to women undergoing elective or emergency cesarean delivery over a period of 40 seconds. The patients remained supine for 40 minutes after drug injection. Twenty-seven percent of the patients with a BMI less than 28 kg/m^2 needed supplementation of the block at 30 minutes, whereas none of the patients whose BMI exceeded 28 kg/m^2 required additional local anesthetic to achieve surgical anesthesia. The cephalad extent of neuroblockade was associated with patient BMI and weight but not with height. Similarly, using an up-down sequential allocation study design to estimate the median effective epidural bupivacaine dose (administered in a volume of 20 mL), Panni and Columb[94] found that obese women required significantly less epidural bupivacaine for initiation of labor analgesia than lean parturients.[94] In contrast, Milligan et al.[95] observed that neither patient position nor obesity affected the extent of sensory blockade when 12 mL of 0.25% bupivacaine was administered for epidural analgesia during labor.[95] Duggan et al.[96] found that obesity had only a weak effect in enhancing the spread of epidural local anesthetics; this effect was only observed with the largest volume and concentration used in the study (15 mL of bupivacaine 0.75%), but not with a lower volume (10 mL) and concentration (0.5%) of bupivacaine.

The goals of epidural labor analgesia should be the provision of excellent pain relief with minimal motor block. Epidural administration of a dilute solution of bupivacaine with fentanyl provides analgesia for labor while minimizing adverse effects such as hypotension and motor blockade. The neuroblockade provided to obese parturients in labor should be bilateral and *near perfect*. Otherwise, the epidural catheter should be removed and replaced because an inadequate block with a frequent need for top-up doses may lead to failure of extending the block for cesarean delivery.[97] Regular evaluation of the parturient's neuraxial block is essential. In a study of morbidly obese parturients, the initial administration of local anesthetic through the epidural catheter resulted in failure of analgesia/anesthesia in 42% of the women, a rate that was seven times higher than that in control parturients.[88] However, careful evaluation of the epidural block and early replacement of a malpositioned catheter resulted in a high rate of success, so that only 1 of 55 cesarean deliveries attempted with epidural anesthesia required conversion to general anesthesia because of inadequate anesthesia.

The combined-spinal epidural (CSE) technique provides a rapid onset of excellent pain relief. However, the epidural catheter remains untested until the spinal block has worn off, and therefore it might fail to provide adequate anesthesia if it is malpositioned and a need for emergency cesarean delivery arises. For this reason, some anesthesia providers prefer to use a standard epidural technique when providing labor analgesia in morbidly obese parturients. On the other hand, a number of studies have reported a higher success rate for epidural catheters inserted as part of a CSE technique compared with those inserted as part of a standard epidural technique[98,99]; presumably, obtaining backflow of cerebrospinal fluid (CSF) through the spinal needle indirectly confirms correct epidural needle position.

In cases of unintentional dural puncture, continuous spinal analgesia can be used to provide labor analgesia. In addition to providing reliable labor analgesia, continuous spinal analgesia may be converted to spinal anesthesia for emergency cesarean delivery. It is crucial, however, that the catheter be clearly labeled and all personnel are made aware of its intrathecal location because unintentional administration of an epidural dose of a local anesthetic through the spinal catheter markedly increases the risk for high spinal block and subsequent respiratory arrest. The risk for post–dural puncture headache may be lower in the obese parturient. The higher intra-abdominal pressure that results from a large abdominal panniculus may contribute to reduced CSF leak through the dural puncture site.[92]

Cesarean Delivery

A thorough preanesthetic evaluation is critical to the safe care of the obese parturient. Of particular importance is a thorough airway assessment. Large breasts, the greater anteroposterior diameter of the chest, airway edema, and reduced chin-to-chest distance increase the likelihood of difficult laryngoscopy and failed tracheal intubation in obstetric patients.[100] Obesity exaggerates many of the anatomic changes of pregnancy. Increased fat in the neck and shoulders increases the difficulty of positioning the

patient for laryngoscopy and tracheal intubation. Excess fat deposition may also cause distorted anatomy, such as an enlarged tongue and redundant pharyngeal and palatal soft tissue. Further, the fat pads on the back of the shoulders often restrict the range of motion of the neck, exacerbating the difficulty of mask ventilation, laryngoscopy, and tracheal intubation.

All morbidly obese parturients undergoing cesarean delivery should be placed in a ramped position with left uterine displacement, regardless of the planned anesthetic technique. This position was shown to improve laryngoscopic view in morbidly obese patients undergoing elective bariatric surgery.[101] Folded blankets or a padded ramp designed for this purpose are placed under the chest and head to achieve horizontal alignment between the external auditory meatus and the sternal notch (Figure 50-1).[102] This position aligns the oral, pharyngeal, and tracheal axes to facilitate tracheal intubation and has been shown to improve hemodynamic and respiratory parameters during laparoscopic gastric bypass surgery.[103] Modern surgical tables can also be flexed at a number of angles, and this feature can be used to optimize the patient position for laryngoscopy and tracheal intubation.

It may be difficult to position the obese patient appropriately and safely. The protuberant abdomen may shift markedly with left uterine displacement. The patient must be secured to the operating table before the table is tilted leftward; however, it is important to initiate left uterine displacement as soon as possible. Tsueda et al.[22] described two obese patients who experienced acute cardiovascular collapse after assuming the supine position.

The anesthesia provider should confirm that the patient's weight does not exceed the weight limits of the operating table, consider use of lateral table extenders, and use foam or blankets to ensure that the shoulders and arms are positioned in a horizontal plane. Correct arm position will maximize patient comfort, improve stability, and avoid neurologic injury to the upper extremity.[104]

The anesthesia care team may be asked to participate in cephalad retraction of the large panniculus by tethering retractors to an object such as the ether screen. Both the obstetrician and the anesthesia provider must remain cognizant of the risks of hypotension, difficulty with ventilation, and fetal compromise during cephalad retraction of the panniculus in morbidly obese patients. Hodgkinson and Husain[105] reported an intraoperative fetal death in a morbidly obese patient who had received epidural anesthesia for cesarean delivery. The death was attributed to prolonged hypotension associated with cephalad retraction of a large panniculus. A vertical and cephalad suspension of the panniculus has been suggested to avoid maternal hypotension and hypoxemia.[78]

Pharmacologic aspiration prophylaxis is crucial in this patient population. Oral administration of 30 mL of a 0.3 M solution of sodium citrate effectively increases gastric pH within 5 minutes.[106] Administration of a histamine-2 (H_2)-receptor antagonist and metoclopramide provide additional protection.[107] The anesthesia provider must be aware that the patient remains at risk for aspiration at the end of surgery; the efficacy of sodium citrate wanes 45 to 60 minutes after administration.[24]

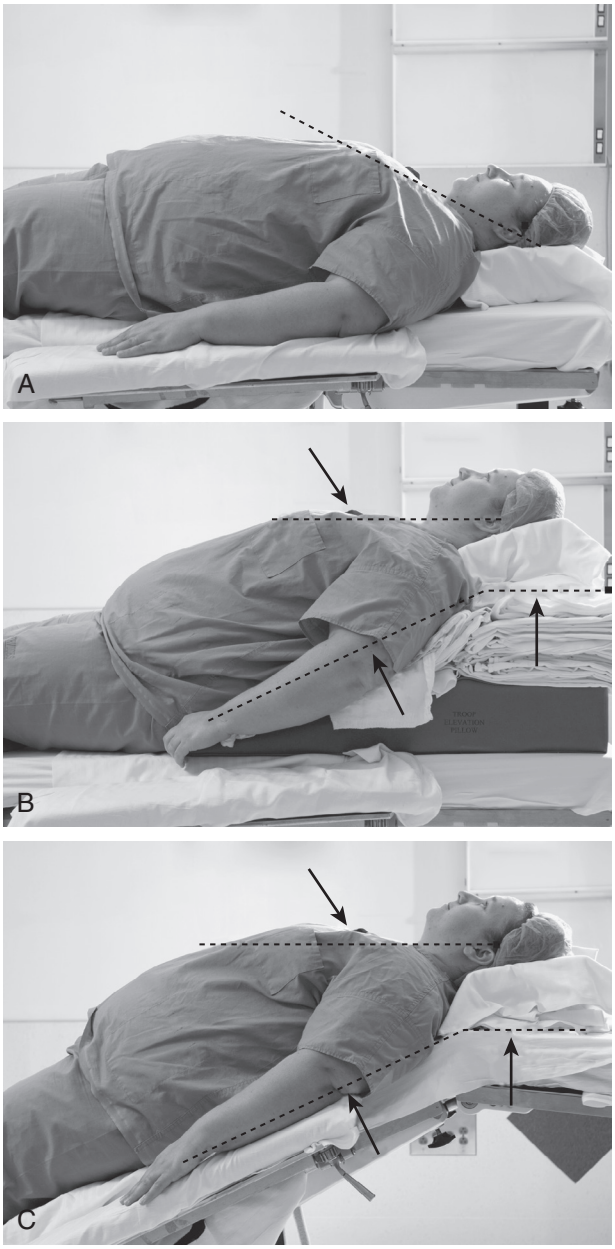

FIGURE 50-1 ■ Positioning the obese patient to facilitate intubation of the trachea. **A,** Patient in the supine position using standard head support. Note that the *dashed line* (compare with **B**) is not parallel to the floor. **B,** Elevating the patient's head with neck and shoulder supports so that an imaginary line drawn through the external auditory meatus and the sternal notch (*upper dashed line*) is parallel to the floor may facilitate tracheal intubation. **C,** Similar positioning achieved by repositioning the operating table. Note the similarity of the *upper* and *lower dashed lines* with use of the second and third positioning techniques.

Neuraxial Techniques

Neuraxial anesthesia is the anesthetic technique of choice in the obese parturient. Single-shot spinal anesthesia provides a reliable, fast onset and dense neuroblockade, and it is a common anesthetic technique in nonobese parturients undergoing planned cesarean delivery. However,

concerns about the use of single-shot spinal anesthesia in obese patients include technical difficulties, appropriate dosing, and insufficient duration of anesthesia.

Spinal anesthesia is technically feasible in morbidly obese pregnant women, although a longer spinal needle may be required. The distribution of adipose tissue varies among obese patients. Spinal needle placement can be uneventful in women who do not have excessive adipose tissue over the midline of the back. However, in others with excessive adipose tissue at the needle placement site, identification of the intrathecal space with a small-gauge spinal needle can be very challenging. Identification of the epidural space with a large-gauge epidural needle is often technically easier, and a needle-through-needle CSE technique may be easier to perform than a single-shot spinal technique in the morbidly obese parturient. Furthermore, the duration of surgery is often prolonged in the obese parturient.[108] Therefore, single-shot spinal anesthesia may not have sufficient duration. Because intraoperative induction of general anesthesia is undesirable and potentially hazardous in morbidly obese pregnant women, a continuous neuraxial technique such as a CSE or epidural technique that allows the maintenance of neuraxial anesthesia with the epidural catheter is preferable to a single-shot spinal technique. Epidural anesthesia is preferred if the patient has a well-functioning epidural catheter *in situ*. Otherwise, a CSE technique may be preferable because it combines the reliability of the spinal block and the flexibility of epidural anesthesia. Anesthesia can be initiated with a low dose of intrathecal local anesthetic combined with an opioid (see Chapter 26). Insufficient extent of cephalad neuroblockade can be treated by administering additional local anesthetic via the epidural catheter. Continuous spinal anesthesia with a spinal catheter is also an option. Some anesthesiologists have suggested that this technique should be considered in the setting of emergency cesarean delivery for obese parturients because it may be technically easier to rapidly identify the spinal space with a large-gauge epidural needle than with a spinal needle.[79]

Local Anesthetic Dosing for Neuraxial Techniques. The choice of local anesthetic dose in morbidly obese parturients in controversial. It has been a long-held belief that neuraxial local anesthetic doses should be reduced in obese patients because of fear of an unpredictable and exaggerated spread of local anesthetic, resulting in a high block. Magnetic resonance imaging (MRI) has confirmed that obese patients have a reduced lumbar CSF volume.[109] Engorgement of the epidural veins secondary to compression of the inferior vena cava by the gravid uterus and abdominal panniculus, as well as inward movement of soft tissue through the intervertebral foramina as a result of increased abdominal pressure, may be responsible for the reduced CSF volume in these patients. A separate study using MRI demonstrated an inverse correlation between the cephalad extent of neuroblockade and lumbar CSF volume[110]; this finding suggests that reduced CSF volume in obese patients increases the risk for a high spinal block. Additionally, Greene[111] has suggested that excess adipose tissue in the buttocks may result in relative Trendelenburg positioning of the vertebral column in the patient in the supine position, which can lead to an exaggerated cephalad spread of anesthesia.

A number of studies, however, do not seem to support the concerns of exaggerated cephalad spread of spinal anesthesia in morbidly obese women undergoing cesarean delivery. Norris[112] and Hartwell et al.[113] administered hyperbaric bupivacaine 12 mg intrathecally and found no correlation between height, weight, BMI, and the extent of spinal anesthesia. However, morbidly obese patients were not specifically studied, so these results may not be applicable to heavier parturients. In an up-down sequential allocation dose-finding study, Lee et al.[114] reported that the estimated ED_{95} (effective dose in 95% of patients) for hyperbaric bupivacaine was similar between obese and nonobese patients; no patient had an excessively high cephalad block with bupivacaine doses up to 12 mg. More recently, Carvalho et al.[115] estimated the ED_{50} (median effective dose) and ED_{95} for hyperbaric spinal bupivacaine for cesarean delivery in 42 morbidly obese parturients who were randomized to receive doses that ranged from 5 to 11 mg as part of a CSE technique. They reported that the ED_{50} and ED_{95} in these morbidly obese parturients were similar to those in nonobese parturients enrolled in a previous study performed by the same authors using similar methodology. Although it was common to obtain a satisfactory initial sensory level even with the lowest doses studied, few of the low-dose blocks were adequate for surgery and many required supplementation via the epidural catheter. Thus, the findings of these studies suggest that reducing the dose of intrathecal bupivacaine is not justified in morbidly obese patients and might increase the risk for inadequate anesthesia.

Results of studies of epidural local anesthetic dosing in morbidly obese parturients are also inconsistent (see earlier discussion). Unlike single-shot spinal anesthesia in which titration of the dose is not possible, careful titration of epidural anesthesia is recommended to achieve the desired dermatomal level of neuroblockade.

General Anesthesia

Difficult mask ventilation and tracheal intubation may be associated with more rapid oxyhemoglobin desaturation during apnea in obese patients than in lean individuals. The association between obesity and a short neck can make tracheal intubation difficult in this population.[116] In a series of patients who received general anesthesia for cesarean delivery, the incidence of difficult tracheal intubation was 33% among women who weighed more than 300 lb (136.4 kg).[88] Lee et al.[117] reported their experience with difficult tracheal intubation in 284 morbidly obese patients who underwent gastric bypass surgery. The incidence of difficult tracheal intubation was 2.4% among patients between 1.5 and 1.75 times the ideal weight and tripled to 7.3% in patients whose weight was 1.75 to 2.0 times the ideal. In a meta-analysis of 35 studies (with 50,760 patients), Shiga et al.[118] reported that obese patients had a threefold higher risk for difficult tracheal intubation than nonobese patients. In an analysis of 91,332 patients undergoing general anesthesia and direct laryngoscopy, a BMI of 35 kg/m^2 or more was associated

with a greater risk for difficult tracheal intubation (OR, 1.34; 95% CI, 1.19 to 1.51).[119]

The potential for failed tracheal intubation and difficult mask ventilation in the obese patient underscores the need for an experienced assistant during induction of general anesthesia. The primary anesthesia provider may fatigue rapidly with attempted mask ventilation of an obese patient. Further, the jaw-thrust maneuver may require the use of both hands, and additional personnel will be required to provide positive-pressure ventilation and cricoid pressure. A short-handled laryngoscope, assorted laryngoscope blades, various sizes of endotracheal tubes and supraglottic airway devices (e.g., laryngeal mask airways), a video laryngoscope, a fiberoptic intubation device, and equipment for percutaneous cricothyrotomy and transtracheal jet ventilation should be readily available.[120] A failed tracheal intubation algorithm should be initiated and help should be called immediately in the event of failed tracheal intubation (see Chapter 30). Supraglottic airway devices may be lifesaving in these situations.

Awake tracheal intubation, via either video laryngoscopy or direct fiberoptic laryngoscopy, is an alternative method of securing the anticipated difficult airway. However, women requiring urgent performance of cesarean delivery may not be ideal candidates for awake tracheal intubation because of the lack of adequate time to optimally prepare the patient's airway.

When preanesthetic assessment suggests that tracheal intubation will not be difficult, a rapid-sequence induction is indicated. The administration of general anesthesia begins with effective pulmonary denitrogenation (so-called *preoxygenation*). During apnea, pregnant women become hypoxemic more rapidly than nonpregnant women.[121] Similarly, during apnea, obese patients become hypoxemic more rapidly than nonobese patients.[122] Therefore, adequate denitrogenation is essential before the administration of general anesthesia in obese pregnant women.

One study demonstrated that four maximal inspirations of 100% oxygen within 30 seconds provide benefit similar to that provided by 3 minutes of tidal-volume breathing of 100% oxygen before rapid-sequence induction of general anesthesia for cesarean delivery.[123] However, another study reported a more rapid onset of hypoxemia in patients who underwent four maximal inspirations of 100% oxygen than in similar patients who underwent 3 minutes of tidal-volume breathing of 100% oxygen.[124] Goldberg et al.[107] evaluated the use of both techniques in morbidly obese nonpregnant patients undergoing gastric bypass surgery. The techniques provided similar increases in Pao_2, but patients who used the 3-minute technique showed evidence of a slight retention of CO_2. The investigators speculated that a blunted ventilatory response to CO_2 contributed to the increase in $Paco_2$. In contrast, other studies have suggested that obese patients have a normal ventilatory response to CO_2.[4] Later data from a study in 20 pregnant volunteers (at 36 to 38 weeks' gestation) compared 3 minutes of tidal-volume breathing with four deep breaths in 30 seconds (4 DB) or eight deep breaths in 1 minute (8 DB) of 100% oxygen by measuring end-tidal fractional oxygen concentration ($FETO_2$) after preoxygenation.[125] An $FETO_2$ value of 90% or greater was achieved in 76% of women after either the 3-minute or the 8-DB method, compared with only 18% of women after the 4-DB method of preoxygenation.[125] The investigators concluded that for emergency cesarean delivery using general anesthesia, the 8-DB method was as effective as the 3-minute tidal volume method of preoxygenation and was more quickly performed.

It is wise to apply a tight-fitting face mask and administer 100% oxygen as soon as the patient is moved onto the operating table; this maneuver helps achieve denitrogenation while other preparations are being made. It then seems reasonable to let circumstances dictate the selected method of denitrogenation. When the 3-minute tidal volume breathing technique is selected, the anesthesia provider should encourage the patient to take several deep breaths. In urgent situations, such as emergency cesarean delivery for maternal hemorrhage, the patient should be instructed to take eight deep breaths (the 8-DB method) to extend the safe interval before oxyhemoglobin desaturation occurs. When time allows, the 8-DB method is preferred over the 4-DB method.

The dose of intravenous induction agents should not be based on total body weight. Rather, the induction dose of propofol or thiopental in the obese parturient should be based on the lean body weight.[126] This practice will avoid excessive doses of drug with subsequent adverse effects. Propofol 2 to 2.8 mg/kg, thiopental 4 to 5 mg/kg, or other induction agents can be used according to the clinical circumstances and the anesthesia provider preference. All these agents will cross the placenta and can affect the neonate.

Succinylcholine remains the muscle relaxant of choice for rapid-sequence induction, and doses of 1.0 to 1.5 mg/kg are commonly used for general anesthesia and tracheal intubation in obese parturients. Lemmens et al.[127] compared the efficacy of succinylcholine in dosing regimens of 1 mg/kg based on ideal body weight, lean body weight, and total body weight in morbidly obese nonpregnant patients. The third regimen (1 mg/kg total body weight) was superior for providing complete neuromuscular paralysis and predictable laryngoscopic conditions in almost every patient, whereas intubating conditions were poor in one third of the patients dosed according to ideal body weight. The investigators also noted that "none of these dosing regimens will provide… a safe (short) duration of apnea."

Rocuronium at a dose of 1 to 1.2 mg/kg provides equivalent intubating conditions to succinylcholine 1 mg/kg. However, this dose range is associated with a significantly prolonged duration of neuromuscular blockade.[128] In obese patients, the dose of rocuronium should be based on ideal body weight.[129] Sugammadex is a cyclodextrin molecule that has been available in Europe since 2008. Sugammadex will effectively reverse high-dose rocuronium (1.2 mg/kg) in 2 minutes when used in a dose of 12 mg/kg in surgical patients.[130] Recent small series in obstetric patients have reported the use of sugammadex after rocuronium doses of 0.6 mg/kg,[131] 1 mg/kg,[132] and 1.2 mg/kg,[133] with no major adverse maternal or neonatal effects. Two studies in nonpregnant obese patients

suggested that sugammadex dosing can be based on ideal body weight plus 40%[134] or on corrected body weight (ideal body weight + 0.4[total body weight – ideal body weight]).[135] However, its use has not been specifically studied in obese parturients and its safety in this patient population remains to be confirmed.

Maintenance of anesthesia is usually achieved with a volatile halogenated agent with or without nitrous oxide. No evidence suggests that obesity alters the minimum alveolar concentration (MAC) of volatile halogenated anesthetic agents in pregnant women. In theory, increased body fat serves as a reservoir for inhalational and intravenous agents. Likewise, the body fat reservoir could increase the threat of biotransformation of volatile halogenated agents, which would increase the risk for organ toxicity. Isoflurane is an appropriate choice for morbidly obese parturients owing to its limited biotransformation.[136] Desflurane and sevoflurane are associated with a shorter time to extubation than isoflurane in obese patients, although the difference may not be clinically relevant.[137,138]

Morbidly obese patients may require administration of a higher inspired oxygen concentration and may not tolerate usual concentrations of nitrous oxide. Moreover, general anesthesia reduces FRC. The supine and Trendelenburg positions further decrease FRC, thus increasing the risk for intraoperative hypoxemia. The following strategies have been recommended to reduce the risk for small airway closure, atelectasis, and hypoxemia in obese patients: (1) use of inspired oxygen concentration of less than 0.8, (2) ventilation with tidal volumes ranging from 6 to 10 mL/kg ideal body weight, (3) increasing the respiratory rate to maintain physiologic $Paco_2$, (4) use of manual or automated periodic lung inflation (i.e., a recruitment maneuver), and (5) application of positive end-expiratory pressure.[139]

Emergence from general anesthesia is a critical period. Indeed, maternal deaths from hypoventilation and airway obstruction have been reported during emergence and recovery from general anesthesia.[59] It is imperative that the patient is fully awake with complete reversal of neuromuscular blockade before tracheal extubation, which preferably should be performed in the semi-upright position to minimize diaphragmatic compression by abdominal viscera. Trained personnel should provide postoperative care before the discharge of the patient to the ward.

POSTOPERATIVE COMPLICATIONS

Obesity increases the risk for postoperative complications such as endometritis, urinary tract infection, wound infection, wound dehiscence, peripheral nerve injury, hemorrhage, deep vein thrombosis, pulmonary thromboembolism, atelectasis, pneumonia, respiratory depression, hypoxemia, tracheal reintubation, sleep apnea, myocardial infarction, cardiac arrest, and maternal death.[79,140]

The combination of obesity, OSA, general anesthesia, and opioid administration may increase the risk for opioid-induced respiratory depression. In a report on maternal mortality in Michigan, Mhyre et al.[59] found that all anesthesia-related maternal deaths from airway obstruction or hypoventilation occurred during emergence and recovery, with obesity being identified as a significant risk factor for these complications. The American Society of Anesthesiologists (ASA) has issued Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea, which include recommendations for the preoperative, intraoperative, and postoperative management of these patients.[141] Although the published literature is often insufficient to establish definite relationships between interventions and outcomes, the Task Force consultants made the recommendations listed in Box 50-1. These recommendations are not intended specifically for pregnant women, but they do provide some guidance for the care of the obese parturient with OSA undergoing cesarean delivery. Morbidly obese patients at risk for OSA who have undergone cesarean delivery should be monitored with continuous pulse oximetry after being discharged from the postanesthesia care unit.

POSTOPERATIVE CARE

Postoperative Analgesia

Adequate postoperative analgesia is crucial to facilitate early mobilization, thereby reducing the risk for thromboembolic and pulmonary complications. However, the ideal analgesic regimen in the obese parturient remains unclear. Neuraxial morphine has been shown to provide superior analgesia to that provided by parenteral and oral opioids after cesarean delivery, at the expense of increased opioid-related side effects such as pruritus and nausea.[142,143] There is a concern, however, that morbidly obese patients might be at higher risk for respiratory depression after neuraxial opioid administration, although there are few data addressing this issue. In a series of 856 patients who received intrathecal morphine 0.2 mg added to hyperbaric bupivacaine for cesarean delivery, Abouleish[144] reported that respiratory depression, defined as an Sao_2 of 85% or less and/or a respiratory rate of 10 breaths per minute or less, occurred in 8 patients, all of whom were obese. In patients who have received general anesthesia, postoperative opioids are best administered using an intravenous patient-controlled analgesia (PCA) system. With all routes of opioid administration, vigilance and appropriate postoperative monitoring are essential in the obese patient who might have undiagnosed OSA and may be at a higher risk for opioid-induced respiratory depression.

A multimodal analgesic regimen including regular administration of a nonsteroidal anti-inflammatory drug and acetaminophen may contribute to opioid sparing and improve postoperative analgesia (see Chapter 27). Local anesthetic techniques including wound infiltration and transversus abdominis plane (TAP) block may also be valuable for postoperative analgesia. A systematic review of randomized controlled trials (including both obstetric and nonobstetric patients) found that continuous infusion of local anesthetic through catheters placed at the incisional site led to an improvement in analgesia and

BOX 50-1 American Society of Anesthesiologists Practice Guidelines for Perioperative Management of Patients with Obstructive Sleep Apnea

Preoperative

- Preoperative initiation of continuous positive airway pressure (CPAP) should be considered, particularly if obstructive sleep apnea (OSA) is severe.
- Patients with known or suspected OSA may have a difficult airway and therefore should be managed according to the ASA Practice Guidelines for Management of the Difficult Airway* or other similar airway management guidelines.

Intraoperative

- The potential for postoperative respiratory compromise should be considered.
- Patients at increased perioperative risk from OSA should be extubated while awake.
- Full reversal of neuromuscular blockade should be verified before extubation.
- When possible, extubation and recovery should be carried out in the lateral, semi-upright position.

Postoperative

- Postoperative analgesia: regional analgesic techniques should be considered to reduce or eliminate the requirement for systemic opioids in patients at increased perioperative risk from OSA.
- If neuraxial analgesia is planned, the anesthesiologist should weigh the benefits (improved analgesia, decreased need for systemic opioids) and risks (respiratory depression from rostral spread) of using an opioid or opioid–local anesthetic mixture as compared with a local anesthetic alone.
- If a patient-controlled systemic opioid analgesic technique is used, a continuous background infusion should be used with extreme caution or avoided entirely.
- Nonsteroidal anti-inflammatory agents and other modalities should be considered if appropriate to reduce opioid requirements.
- Supplemental oxygen should be administered continuously to all patients who are at increased perioperative risk from OSA until they are able to maintain their baseline oxygen saturation while breathing room air.
- Hospitalized patients at increased risk for respiratory compromise from OSA should be monitored with continuous pulse oximetry after discharge from the post–anesthesia care unit.

*American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway. Anesthesiology 2013; 118:251-70.

Selected recommendations from American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea. Anesthesiology 2006;104:1081-93.

patient satisfaction as well as a reduction in opioid use, side effects, and duration of hospital stay, in comparison with administration of systemic opioids alone.[145] However, the value of this technique combined with neuraxial administration of a long-acting opioid is unclear.

Similarly, TAP block was found to produce opioid sparing and reduce pain scores and opioid-related side effects in women who received general anesthesia or did not receive neuraxial morphine as part of their neuraxial anesthetic technique. However, it did not enhance analgesia in patients who received neuraxial morphine and produced analgesia inferior to that produced by neuraxial morphine.[146] Further, performance of TAP block may be technically challenging in the obese parturient with a large abdominal panniculus. Patient-controlled epidural analgesia (PCEA) with ropivacaine provides analgesia comparable to that provided by epidural morphine,[147] but with more motor block, thus delaying patient mobilization.[147] PCEA techniques have not been specifically studied in obese parturients.

Thromboprophylaxis

The American College of Chest Physicians published guidelines for antithrombotic therapy in the parturient.[148] They used major and minor risk factors to identify women at increased risk for venous thromboembolism after cesarean delivery, and they classified obesity (BMI > 30 kg/m^2) as a minor risk factor. Thromboprophylaxis was recommended in the presence of one major risk factor (risk for thromboembolism > 3%) or two minor risk factors (combined risk > 3%) (see Box 39-4). In the setting of emergency cesarean delivery, one minor risk factor results in a risk greater than 3%, and, therefore, mechanical or pharmacologic thromboprophylaxis is recommended. In the United Kingdom, the RCOG guidelines[58] recommend thromboprophylaxis with low-molecular-weight heparin for all obese parturients undergoing either emergency or elective cesarean delivery. Further, the RCOG guidelines[58] recommend thromboprophylaxis after vaginal delivery in all morbidly obese women.

KEY POINTS

- The presence of coexisting disease(s) complicates obstetric and anesthetic management of the morbidly obese pregnant woman.
- The obese pregnant woman is at increased risk for obstetric, anesthetic, neonatal, surgical, and postoperative complications.
- The obese pregnant woman should be referred to an anesthesiologist for preanesthesia consultation.
- Airway complications, which can occur during the postoperative period as well as during the induction and emergence from general anesthesia, constitute the most common cause of anesthesia-related maternal death.
- The anesthesia provider should perform a careful, thorough assessment of the airway in every obese pregnant woman and should consider securing the airway before induction

of general anesthesia when a difficult airway is anticipated.

- Early labor administration of neuraxial analgesia is advised in obese parturients; anesthesia providers should critically evaluate the quality of the epidural block and replace any catheter that does not provide excellent analgesia.
- Continuous spinal anesthesia should be considered in emergency settings involving potentially difficult tracheal intubation and in cases of unintentional dural puncture in morbidly obese patients.
- Morbidly obese parturients may be at significant risk for obstructive sleep apnea; therefore, they should be carefully monitored with continuous pulse oximetry for postoperative hypoxemia resulting from airway obstruction and/or respiratory depression after discharge from the postanesthesia care unit.

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CHAPTER 45

Human Immunodeficiency Virus

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CHAPTER OUTLINE

In 1981, a cluster of cases of an unusual disorder, *Pneumocystis carinii* pneumonia (PCP), in five otherwise healthy men, initiated a search that culminated in the characterization of a new disease, acquired immunodeficiency syndrome (AIDS), and the identification of its causative agent, the human immunodeficiency virus (HIV). Subsequently, there has been an explosion of this disease in the United States. Geographically, a disease that once was limited to two or three urban areas is now found throughout the country. Further, the number of cases of HIV infection has reached epidemic levels. At the end of 2008, an estimated 1,178,000 persons were living with HIV in the United States, including more than 236,000 whose infection was undiagnosed.[1] As of December 2011, more than 1,155,000 cases of AIDS had been reported to the U.S. Centers for Disease Control and Prevention (CDC). Some 636,000 people were reported to have died of AIDS and its complications by December 2010.[2] HIV infection has exploded demographically from its initial isolation among homosexual men to its current endemic status among intravenous drug users, their sexual partners, and children born to women infected with HIV.

The impact of HIV infection in the developing world has been nothing less than catastrophic. As of 2012, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that approximately 34 million people worldwide were infected with HIV (Figures 45-1 and 45-2). More than two thirds of these infections have occurred in sub-Saharan Africa, where nearly 5% of adults are infected with HIV and where 70% of all new infections that occurred worldwide during 2011 originated. It is encouraging that the number of new cases of HIV infection in sub-Saharan Africa has decreased by 25% between 2001 and 2011. Unfortunately, in at least nine countries, the number of new infections has increased by more than 25% in the same period.[3]

In the United States, although the rate of new infection in women appears to be decreasing, 21% of all new diagnoses of HIV infection identified in 2008 through 2011 occurred in women.[2] Minority populations are disproportionately affected; 47% and 20% of all newly diagnosed infections in 2011 were seen in African-American and Hispanic populations, respectively.[2] In 2009, HIV was the third leading cause of death in African-American women aged 35 to 44 years.[4] Clearly, anyone providing anesthesia to pregnant women in the United States in the 21st century will care for patients who are infected with HIV. Neither medicolegal concerns nor fear of infection with HIV should prevent anesthesia providers from providing effective intrapartum analgesia and anesthesia to HIV-infected women.

PATHOPHYSIOLOGY

HIV, previously known as lymphadenopathy-associated virus (LAV) and human T-cell lymphotropic virus type III (HTLV-III), is a member of the lentivirus subfamily of human retroviruses. The lentiviruses typically cause indolent infections in their hosts. These infections are notable for central nervous system (CNS) involvement, long periods of clinical latency, and persistent viremia caused by an impaired humoral immune response.[5] HIV

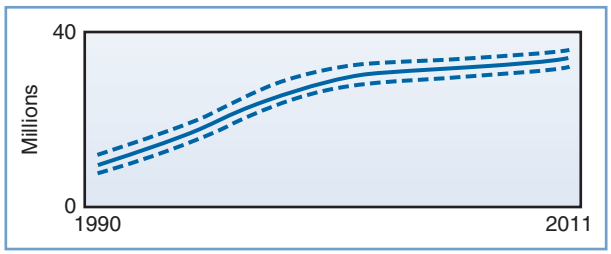

FIGURE 45-1 ■ Estimated number of people living with HIV globally, 1990-2011. The bold line represents the estimate, and the dotted lines represent the high and low estimates. (From Global Report. UNAIDS report on the global AIDS epidemic 2012. Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012. Available at http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf.)

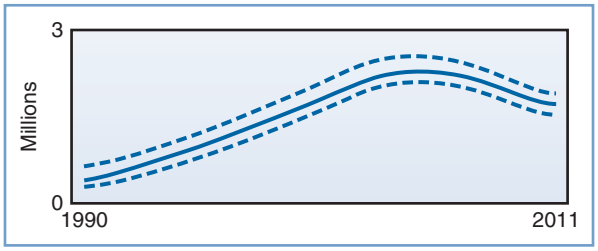

FIGURE 45-2 ■ Adult and child deaths due to AIDS globally, 1990-2011. The bold line represents the estimate, and the dotted lines represent the high and low estimates. (From Global Report. UNAIDS Report on the global AIDS epidemic 2012. Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012. Available at http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf.)

is a retrovirus (i.e., it carries the enzyme reverse transcriptase). This enzyme converts the single-stranded viral RNA into double-stranded DNA, which subsequently can be integrated into the DNA of the infected cell. This process is error prone, leading to rapid mutation of the virus, which significantly complicates drug therapy. HIV displays similarity to human immunodeficiency virus type 2 (HIV-II), a virus that is endemic in western Africa and that produces a similar syndrome. HIV-II is even more closely related to the simian immunodeficiency virus (SIV). It has been suggested that HIV arose in human populations through transmission of SIV via infected "bush meat," the meat of chimpanzees and other primates consumed as food.[6]

For infection of the host cell to occur, HIV must bind to a cell-surface receptor, the $CD4^+$ antigen complex.[7] This protein molecule was first detected on helper T cells, and it subsequently was identified on B cells, macrophages, and monocytes.[8] It also is found on placental cells[9] and may provide a route of vertical transmission to the fetus during early pregnancy. The interaction between HIV and host cells requires an interaction with an additional cell-surface protein; binding with either the CCR5 or CXCR4 co-receptor is required for infection to occur. A number of therapeutic agents target this interaction.[10]

Infection of helper T cells is the key to immune suppression in HIV disease. These cells play a major role in the initial recognition of foreign antigen as well as in the activation of other immune system components.[11] $CD4^+$ monocytes and macrophages are also targeted by HIV. In addition to these T cell–mediated effects, both neutropenia and disturbances of neutrophil function are common in the later stages of HIV infection.[12] Abnormalities of these elements of the immune system render the HIV patient vulnerable to bacterial, viral, fungal, parasitic, and mycobacterial infection. In addition, for reasons that are not entirely clear, patients infected with HIV are susceptible to several malignancies (e.g., Kaposi's sarcoma, B-cell lymphoma, invasive cervical carcinoma). AIDS-associated Kaposi's sarcoma is almost exclusively limited to homosexual men with HIV or to women whose male sexual partners are bisexual; this fact suggests that the malignancy is related to another sexually transmitted disease. In fact, DNA sequences from human herpesvirus-8 have been identified in AIDS-associated Kaposi's sarcoma.[13,14]

DIAGNOSIS

The techniques for diagnosing HIV infection include viral culture, p24 antigen detection tests, nucleic acid amplification tests such as viral polymerase chain reaction (PCR), and immune function tests. Most often, the diagnosis is made on the basis of results of one of two antibody detection tests: enzyme immunoassay (EIA) and the Western blot technique. EIA measures the binding of anti-HIV antibody from the patient's serum to a mixture of antigens that typically have been obtained through recombinant DNA techniques (third-generation tests). The use of third-generation tests has improved the reliability of EIA, but false-positive results (caused by autoimmune disorders, influenza or hepatitis B immunization, and/or high parity) and false-negative results (caused by immunosuppressive therapy and various malignancies) can occur.[11] For these reasons, a Western blot test usually is performed after a positive EIA result is obtained. False-positive Western blot tests can also occur, but they are less common than false-positive EIA tests. The Western blot technique allows the identification of antibodies to nine specific HIV antigens. Different organizations have different criteria for a positive Western blot test, but a positive Western blot test generally requires the presence of antibody to at least three different antigens. If there is no detectable antibody to any of these antigens, the result is negative.[11] Identification of any combination of antibodies that does not meet the criteria for a positive result is considered an indeterminate result and an indication for retesting in 4 to 8 weeks.

Nucleic acid amplification tests can detect extremely low levels of infection. This technique can detect viremia as early as 1 to 2 weeks after exposure, during the period of primary symptomatic infection.[11] Although this technique can be used to diagnose acute HIV infection, it is typically used to monitor the response to ongoing antiretroviral therapy.

Both the EIA and the Western blot tests rely on the detection of antibody to HIV antigens. Unfortunately, there may be an interval of several weeks to months after the initial infection before detectable levels of antibody

BOX 45-1 Acquired Immunodeficiency Syndrome—Indicator Conditions

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, human immunodeficiency virus–related
- Herpes simplex: chronic ulcer(s) (longer than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (longer than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to human immunodeficiency virus
- CD4 T lymphocyte count < 200 cells/μL

Modified from 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992; 41(RR-17):1-19.

are present. A patient infected with HIV who is tested during this "window period" has a negative test result but is fully capable of infecting others. In fact, exceptionally high levels of viremia are present during the initial period of infection, and transmission after needle-stick injury or other occupational exposure is more likely.[15] This is a strong argument for instituting universal precautions. If barrier precautions are instituted only for patients with positive test results, health care workers will be exposed unnecessarily to seronegative but infectious patients.

Patients may be chronically infected with HIV for many years yet appear clinically well or have only minor evidence of immune suppression, such as oral candidiasis or recurrent herpes zoster. The diagnosis of AIDS is made when any one of a number of AIDS-indicator conditions develops (Box 45-1).

CLINICAL MANIFESTATIONS

In the early years of the AIDS epidemic, the predominant symptoms were those of immune suppression (e.g., opportunistic infections, unusual malignancies). Disturbances of gastrointestinal function were also prominent. As improvements in prophylaxis and treatment of opportunistic infections have increased longevity, it has become apparent that HIV eventually affects multiple organ systems. The aggressive use of highly active antiretroviral therapy (HAART) can significantly prolong the symptom-free interval, and it is highly unusual for a pregnant patient to have significant organ system involvement due to HIV.

BOX 45-2 Neurologic Manifestations of Human Immunodeficiency Virus Infection

Early (Initial Infection)

- Headache
- Photophobia
- Meningoencephalitis
- Cognitive and affective changes
- Cranial neuropathy
- Peripheral neuropathy

Latent Phase

- Demyelinating neuropathy
- Cerebrospinal fluid abnormalities, even in asymptomatic patients

Late (Clinical Acquired Immunodeficiency Syndrome)

- Meningitis
- Diffuse encephalopathy
- Focal brain lesions
- Myelopathy (segmental or diffuse)
- Peripheral neuropathy
- Myopathy

Neurologic Abnormalities

Neurologic involvement can occur at any time during HIV infection (Box 45-2). Viral particles can be isolated from the cerebrospinal fluid (CSF) at the time of primary infection.[16] The manifestations of nervous system involvement vary with the stage of the disease.

During **initial systemic HIV infection,** a variety of CNS disorders may occur. Headache, photophobia, and retro-orbital pain are common. Cranial and peripheral neuropathies, demyelinating polyneuropathy, and septic meningoencephalitis have been reported.[17] Cognitive and affective changes (e.g., depression, irritability) may be noted. Most of these disorders are self-limited, but persistent neurologic dysfunction may occur.[17]

A subset of patients remains neurologically asymptomatic during the **latent phase of HIV infection.** Nevertheless, these patients typically have CSF abnormalities, including the local synthesis of HIV antibody and the presence of HIV particles or viral nucleic acid.[18] This is an important consideration when one is determining the risk for introducing virus into the CNS during the performance of neuraxial anesthesia in an asymptomatic patient. It is almost certain that CNS infection has already occurred.

Finally, the **late stages of HIV infection** are marked by significant neurologic deterioration in almost all patients. **Meningitis** is common, and its causes include tuberculosis, infection with *Cryptococcus*, metastatic lymphoma, and direct infection of the meninges by HIV. **Diffuse encephalopathy** can occur; cytomegalovirus (CMV), herpes simplex virus (HSV), and toxoplasmosis typically produce a simultaneous impairment of both cognition and alertness. Diffuse encephalopathy may also be seen as a consequence of systemic disease, such as sepsis or hypoxemia secondary to respiratory disease. Patients with the **AIDS dementia complex** also have a diffuse encephalitic picture; however, unlike other forms of encephalitis in which cognitive function is diminished, the level of alertness remains unimpaired. In addition, the complex is associated with impairment of motor function and behavioral changes (apathy, agitation). **Focal brain disorders** can occur secondary to toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy, an opportunistic viral infection that causes selective destruction of white matter tracts. **Myelopathy** is common; it can manifest in an acute, segmental form, as in the transverse myelitis produced by varicella infection, or as a more progressive and diffuse disorder—vacuolar myelopathy—which is marked by a progressive, painless gait disturbance and spasticity. A distal, predominantly sensory **peripheral neuropathy** is quite common in late HIV infection. The etiology is unknown; it has been suggested to occur as a result of cytokine-mediated neurotoxicity.[19] Sensory and motor dysfunction typically are minimal, but pain can be severe enough to prevent walking. CMV infection can also lead to a polyradiculopathy that usually responds to anti-CMV therapy. **Autonomic neuropathy** can manifest as mild postural hypotension or severe cardiovascular instability during invasive procedures. Autonomic dysfunction also can contribute to the chronic diarrhea that occurs in some patients with AIDS. An inflammatory myopathy resembling dermatomyositis has been reported, although this disorder is less common than the neuropathies.[19] Finally, neurologic side effects of antiretroviral and other therapies also may occur (see later discussion).

Pulmonary Abnormalities

The pulmonary manifestations of HIV disease are caused not by a direct effect of the virus but, rather, by the opportunistic infections associated with the disease. The most prominent of these is *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii)*, a fungal organism that is seen in a wide variety of mammals and appears to be carried asymptomatically by many humans.[20] Despite this evidence of widespread exposure to the organism, symptomatic *Pneumocystis* pneumonia (PCP) is typically seen only in patients with severe immune suppression. The clinical picture is similar to the adult respiratory distress syndrome, consisting of severe hypoxemia and a pattern of diffuse interstitial infiltrates on chest radiography. The mortality rate of patients with PCP who require tracheal intubation may be as high as 75%.[21] Early initiation of corticosteroid therapy decreases the likelihood of progression to respiratory failure.[22] Patients who survive the disease are at risk for the development of pneumatoceles; subsequent rupture leading to pneumothorax is common. Survivors of PCP also are at risk for developing chronic airway disease, including chronic bronchitis and bronchiectasis.[23]

Reactivation of latent **tuberculosis** is common in patients with HIV infection because of the impairment of cellular immunity that ordinarily keeps the disease in a quiescent state; HIV-infected individuals also may be more susceptible to acquiring tuberculosis when they are exposed to an infectious individual.[24] The impairment of humoral immunity is responsible for a higher incidence of bacterial pneumonia caused by encapsulated organisms (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*).[25] Finally, although less common than PCP, pneumonia secondary to other fungal organisms (e.g., *Aspergillus*, *Cryptococcus*, *Coccidioides*) is much more common in patients infected with HIV than in the general population.[25]

Gastrointestinal Abnormalities

Gastrointestinal disturbances occur at some time in almost all patients with HIV infection (Box 45-3). Painful or difficult swallowing is common and is typically caused by herpetic, CMV, or candidal **esophagitis;** the contribution of these disorders to gastroesophageal reflux is unclear.[26] **Severe diarrhea** resulting from infection with CMV, HSV, *Shigella*, *Salmonella*, *Candida*, *Cryptosporidia*, *Giardia*, *Mycobacterium avium* complex (MAC), or HIV itself can lead to significant cachexia and electrolyte abnormalities. Finally, **hepatobiliary disease** is common. Causes of parenchymal liver disease include hepatitis B and C, CMV, mycobacterial infection (both *Mycobacterium tuberculosis* and MAC), and *Cryptococcus*. Kaposi's sarcoma and non-Hodgkin's lymphoma may involve the liver. Biliary tract disease can develop in patients with advanced HIV infection; although several pathogens have been associated with this disorder (cryptosporidium, CMV), treatment of those pathogens is seldom effective.[27] Endoscopic retrograde cholangiopancreatography (ERCP)–guided stenting has been successfully used to treat this disorder.[28]

Hematologic Abnormalities

HIV infection is associated with hematologic abnormalities that affect each of the peripheral cell lines.[12] **Leukopenia** is a hallmark of the disease, especially the depletion

BOX 45-3 Gastrointestinal Manifestations of Human Immunodeficiency Virus (HIV) Infection

- Esophagitis and dysphagia
- Hepatitis (opportunistic organisms, coexisting hepatitis B)
- Biliary disease (acalculous cholecystitis, sclerosing cholangitis)
- Wasting ("slim disease")
- Chronic diarrhea (HIV infection of bowel, superinfection with bacterial or parasitic pathogens)

of $CD4^+$ lymphocytes; qualitative alterations in the functions of neutrophils and macrophages also occur. **Anemia** is quite common. Causes include direct HIV infection of erythroid precursors, suppression of erythropoiesis due to inappropriate release of tumor necrosis factor, infiltration of bone marrow with MAC or malignancy, and occult gastrointestinal blood loss.

Coagulation disturbances are common in patients with HIV. **Immune thrombocytopenia** is common and typically is only mildly symptomatic. Platelet production may be impaired because of direct infection of megakaryocytes with HIV. Thrombocytopenia frequently responds to the initiation of antiretroviral therapy. The response to corticosteroid therapy is variable. Intravenous immune globulin produces a rapid but transient effect, and it may be indicated in patients with life-threatening hemorrhage. The activated partial thromboplastin time may be prolonged because of the presence of the lupus anticoagulant; this finding is linked to a higher incidence of major thromboembolic events in HIV-infected patients. Finally, many of the antiretroviral agents and other drugs used in these patients have hematologic toxicity.

Cardiovascular Abnormalities

When echocardiography and autopsy evidence of lymphocytic infiltration of the myocardium are used as evidence of cardiovascular involvement in patients with HIV, the prevalence of such involvement is as high as 50%.[29] Nevertheless, clinically significant cardiovascular disease is rare in patients with HIV. **Pericarditis** has been reported to be the most prevalent cardiovascular disorder seen in HIV-infected patients. The most common etiology appears to be mycobacterial infection; CMV, HSV, Kaposi's sarcoma, malignant lymphoma, and HIV itself have also been implicated.[30] **Pulmonary hypertension** can develop secondary to repeated episodes of PCP and can also be a consequence of cytokine-mediated endothelial injury.[29] Direct **myocardial involvement**—typically, focal myocarditis—is identified in 15% to 50% of autopsy studies, but clinical myocarditis or cardiomyopathy is rare.[29] **Infective endocarditis** among patients with HIV occurs almost exclusively in intravenous drug users. Finally, the elevations in serum cholesterol and triglyceride concentrations produced by antiretroviral agents appear to increase the risk for coronary artery disease in patients receiving these drugs.[31]

Endocrine Abnormalities

Endocrine dysfunction can result from HIV infection, opportunistic infections, or drug therapy.[32] There is a relatively high incidence of pathologic findings in the adrenal gland at autopsy, yet clinical evidence of glucocorticoid insufficiency is rare. Patients with AIDS frequently have abnormal thyroid function test results, similar to the findings in patients with other chronic illnesses, yet clinical hypothyroidism is unusual. Insulin resistance and diabetes are increasingly recognized as consequences of HIV infection and antiretroviral treatment.[33]

Renal Abnormalities

Patients with HIV are at risk for acute renal failure secondary to sepsis, dehydration, and drug toxicity.[34] A common cause of chronic renal insufficiency is proliferative glomerulonephritis secondary to deposition of immune complexes containing HIV antigen within the glomeruli. Renal failure may also occur because of a specific disorder, **HIV-associated nephropathy.**[35] This entity, seen almost exclusively in African-American patients, is characterized by a focal segmental glomerulosclerosis. Hypertension is uncommon, deterioration of renal function is extremely rapid, and the long-term prognosis is worse than that seen in renal failure from other causes. The underlying cause appears to be direct infection of renal cells by HIV. Antiretroviral therapy appears to modify the course of the disease.[35]

INTERACTION WITH PREGNANCY

In 1991 and in 1995, the nationwide seroprevalence rate of HIV during pregnancy was reported to be 1.5 and 1.7 per 1000 pregnant women, respectively.[36,37] There was considerable geographic variation in these figures; the highest rates of seroprevalence were found in New York (5.8 per 1000), Washington, DC (5.5 per 1000), and New Jersey (4.9 per 1000). In 1991, seropositive women were identified in all but 2 of the 39 reporting areas.[36] In New York City, the prevalence of HIV infection among pregnant women was 6.2 per 1000 in 1999-2000, having declined by 49% over the previous decade. This decrease was markedly greater in white women than in African-American women.[38] According to the CDC, the number of HIV-infected women giving birth in the United States increased from 6000 to 7000 in 2000 to 8700 in 2006, an increase of approximately 30%.[39]

The diagnosis of HIV infection in the offspring of HIV-infected mothers has been hampered by the persistence of passively acquired maternal antibody in the infant for as long as 18 months. Until 18 months of age, an infant's HIV status must be confirmed by viral culture or DNA polymerase chain reaction (PCR). Measurement of circulating p24 antigen has been used for rapid diagnosis of neonatal HIV infection,[40] but this test is no longer recommended because it is less sensitive than PCR and is associated with false-positive results.[41]

There is intense interest in the identification of factors that promote perinatal transmission of HIV from mother to the newborn (i.e., vertical transmission) (Box 45-4).[42] Clinical severity of maternal disease is associated with an increased risk for transmission, as reflected by a higher rate of infection in newborns of women with symptomatic AIDS.[43] Maternal viral burden correlates with transmission. In one study, 13 of 13 women with more than 80,000 viral RNA copies per mL of plasma transmitted the disease, but none of the 63 women with less than 20,000 copies per mL transmitted HIV.[44] Other factors that have been implicated in vertical transmission are the presence of ruptured membranes for more than 4 hours,[45] coexisting sexually transmitted diseases,[46] chorioamnionitis,[47] and invasive procedures such as amniocentesis and

BOX 45-4 Risk Factors for Vertical Transmission of Human Immunodeficiency Virus

- Severity of maternal disease
- Maternal viral burden
- Viral genotype
- Sexually transmitted disease
- Substance abuse
- Lack of maternal antiviral therapy
- Chorioamnionitis
- Prolonged ruptured membranes
- Invasive fetal monitoring
- Vaginal delivery
- Forceps delivery
- Breast-feeding
- Prematurity

cerclage.[46] At least one study has demonstrated that fetal scalp blood sampling and the use of fetal scalp electrodes do not increase vertical transmission[48]; however, the documented presence of HIV in maternal cervical secretions has made some clinicians reluctant to use this monitoring technique.[49] Finally, there is considerable evidence that breast-feeding may double the rate of perinatal transmission in women with established HIV infection.[50] Thus, breast-feeding should be discouraged unless bottle-feeding is not a safe alternative, as is true in many developing countries.

In addition to identifying risk factors for vertical transmission, there is a significant effort to determine which active interventions might decrease the transmission of HIV. The first such intervention that was identified is the administration of zidovudine (ZDV, formerly azidothymidine [AZT]). In a study known as the AIDS Clinical Trial Group (ACTG) Protocol 076, administration of ZDV orally during pregnancy, intravenously during labor, and orally to the infant for the first 6 weeks of life decreased the transmission rate from 25.5% to 8.3%. No significant adverse effects were noted in these infants.[51] Because of the success of HAART in reducing perinatal transmission to 1% to 2%—compared with 10% for ZDV monotherapy[52]—it has been suggested that all HIV-infected pregnant women should receive an aggressive treatment regimen, regardless of viral load.[42]

Because neonatal infection rates are low when the time interval between rupture of membranes and delivery is shortened, it has been suggested that cesarean delivery might decrease vertical transmission. At least four studies have suggested that elective cesarean delivery may decrease the rate of transmission by as much as 80%.[53] The American College of Obstetricians and Gynecologists (ACOG) has recommended that HIV-infected women be offered the option of elective cesarean delivery to decrease the rate of transmission below the rate that would be expected with ZDV therapy alone.[54] Although the ACOG acknowledged that the data were insufficient to demonstrate a benefit for women with viral loads less than 1000 viral copies per milliliter of plasma, there is some evidence that abdominal delivery may be beneficial even in the setting of viral loads below that threshold[55]; thus, it has been suggested that elective cesarean delivery be offered to patients in this group as well.[53]

A number of studies have assessed the effect of HIV infection on pregnancy outcome. Alger et al.[56] followed 97 seronegative and 101 seropositive but asymptomatic women throughout pregnancy. There was no difference between groups in the incidence of low-birth-weight (LBW) (< 2500 g), small-for-gestational-age (SGA) infants, or low 5-minute Apgar scores.[56] However, in a study of 315 seropositive and 311 seronegative women in Kenya, HIV seropositivity was associated with an increased risk for preterm delivery and LBW infants but not with an increased incidence of SGA infants.[57] These different results may reflect the higher incidence of symptomatic HIV disease in the Kenyan patients. Another study noted that the incidence of serious infectious complications (e.g., PCP, CNS toxoplasmosis) is greater than 30% in pregnant women with advanced HIV infection ($CD4^+$ lymphocyte counts < 300 cells/mm^3).[58] The fetal implications of such infections are obvious. Drug therapy *per se* does not seem to affect pregnancy outcome; specifically, evidence suggests that there is no higher incidence of preterm delivery, LBW infants, low Apgar scores, or stillbirth in women receiving therapy than in controls.[59]

There also is concern that pregnancy itself may have an adverse effect on the progression of HIV infection. However, no evidence suggests that pregnancy accelerates clinical deterioration in the HIV-infected patient or that viral RNA load changes significantly during pregnancy.[56,60,61]

DRUG THERAPY

There is an ever-increasing number of medications used to treat HIV infection, administered in innumerable multidrug regimens; in addition to HIV medications, patients may receive a number of other drugs to treat or prevent opportunistic infections. The side effects of the most commonly used antiretroviral agents and medications used for prophylaxis and treatment of opportunistic infections are listed in Tables 45-1 and 45-2, respectively.

Fetal Side Effects

There are few published data regarding the use of HIV medications in pregnant women. Fortunately, clinical experience suggests that fetal risk is minimal. This is best demonstrated by ACTG Protocol 076, which showed a significant reduction of vertical transmission of HIV with maternal ZDV therapy.[51] There was no difference between the ZDV and placebo groups in the number and type of birth defects. The only apparent difference in neonatal outcome was a mild transient anemia (which required no treatment) in the ZDV group. Ongoing observation of these infants is planned, but no difference in growth or neurodevelopmental status has been identified in the ZDV group. As of July 2012, the Antiretroviral Pregnancy Registry[62] had collected records of more than 14,000 women who had received these agents during pregnancy in the United States; the data indicate no

TABLE 45-1 Side Effects of Antiretroviral Agents

Drug	Side Effects
Zidovudine (ZDV, AZT, Retrovir)	Headache, N&V, bone marrow suppression
Didanosine (ddI, Videx)	N&V, peripheral neuropathy, pancreatitis, lactic acidosis
Zalcitabine (ddC, HIVID)	Peripheral neuropathy, pancreatitis
Stavudine (d4T, Sterit)	Peripheral neuropathy, pancreatitis, lactic acidosis
Lamivudine (3TC, Epivir)	N&V, headache, pancreatitis (children)
Emtricitabine (FTC, Emtriva)	Headache, N&V
Abacavir (ABC, Ziagen)	Systemic hypersensitivity reaction, headache, N&V
Delavirdine (Rescriptor)	Rash, elevated liver function test results
Nevirapine (NVP, Viramune)	Rash, hepatotoxicity
Efavirenz (EFV, Sustiva)	Dizziness, lightheadedness, vivid dreams, rash
Saquinavir (SQV, Invirase)	N&V, diarrhea, abdominal pain, hyperglycemia, increased triglycerides, fat redistribution
Ritonavir (RTV, Norvir)	N&V, diarrhea, abdominal pain, hyperglycemia, increased triglycerides, fat redistribution
Indinavir (IDV, Crixivan)	Nephrolithiasis, gastrointestinal intolerance, hyperglycemia, increased triglycerides, fat redistribution
Nelfinavir (NFV, Viracept)	N&V, diarrhea, hyperglycemia, increased triglycerides, fat redistribution
Amprenavir (APV, Agenerase)	Headache, N&V, hyperglycemia, increased triglycerides, fat redistribution
Lopinavir/ritonavir (LPV/RTV, Kaletra)	N&V, diarrhea, hyperglycemia, increased triglycerides, fat redistribution
Atazanavir (ATV, Reyataz)	N&V, headache, smaller increase in triglycerides than with other protease inhibitors
Tenofovir (TDF, Viread)	N&V, headache
Enfuvirtide (T20, Fuzeon)	Injection site reaction

N&V, Nausea and vomiting.
Modified from Pau AK, Robertson S. AIDS-related medications. In Dolin R, Masur H, Saag MS, editors. AIDS Therapy. 3rd edition. St. Louis, Churchill Livingstone, 2008:1407-40.

TABLE 45-2 Side Effects of Agents Used for Prophylaxis/Treatment of Opportunistic Infections

Opportunistic Infection	Drug	Side Effects
Pneumocystis jiroveci	Trimethoprim-sulfamethoxazole	Nausea, vomiting, anorexia, rash
	Dapsone	Fever, rash, hepatitis
	Pentamidine	*Intravenous:* nephrotoxicity, leukopenia, hypoglycemia, hyperglycemia *Inhaled:* cough, dyspnea, dizziness
Cytomegalovirus	Ganciclovir	Neutropenia, thrombocytopenia, central nervous system disturbances
	Foscarnet	Nephrotoxicity, electrolyte disturbances
Mycobacterium avium complex	Clarithromycin	Nausea, vomiting, diarrhea
Fungal infections: cryptococcosis, histoplasmosis, coccidiomycosis	Amphotericin	Nephrotoxicity, fever, hypotension
	Fluconazole	Nausea, headache, rash
Herpes simplex virus	Acyclovir	Nephrotoxicity, neurotoxicity

From Pau AK, Robertson S. AIDS-related medications. In Dolin R, Masur H, Saag MS, editors. AIDS Therapy. 3rd edition. St. Louis, Churchill Livingstone, 2008:1407-40.

increase in overall risk for birth defects or risk for specific defects for the overall population exposed to antiretroviral drugs. However, exposure to didanosine or nelfinavir was associated with a modest but statistically significant increase in overall rates of birth defects. The clinical relevance of this finding is unclear, and no pattern of birth defects has been observed with either drug.[62]

Historically, physicians have been concerned that the use of trimethoprim-sulfamethoxazole during the third trimester might increase the risk for neonatal kernicterus. This complication has not been reported, and trimethoprim-sulfamethoxazole should be continued until delivery in women who tolerate the drug.[63]

None of the antiretroviral agents or drugs used to treat opportunistic infections during pregnancy are listed in U.S. Food and Drug Administration pregnancy category A, which signifies a lack of fetal effect in controlled human trials.[42] Despite the reassuring findings of the Antiretroviral Pregnancy Registry, the use of these drugs requires a full discussion of the risks and benefits with the mother.[64] Minkoff and DeHovitz [63] concluded, "The guiding principle in the use of medications by HIV-infected women who become pregnant is to adhere strictly to standards promulgated for nonpregnant women, unless there are documented and compelling fetal concerns that would justify a modification of those standards."

ANESTHETIC MANAGEMENT

Coexisting Diseases

Many pregnant women infected with HIV have health problems that are related to the behaviors that led to their infection with HIV. The most significant of these is substance abuse. A significant proportion of women with HIV contract the disease through intravenous drug use. It can be expected that many of these patients also abuse alcohol and crack cocaine.

The HIV-positive parturient is at high risk for harboring other sexually transmitted diseases. From the anesthesia provider's perspective, the most significant of these diseases is syphilis, because of its neurologic effects in later stages. If neuraxial anesthesia is performed, a careful neurologic examination should be completed and documented. Hepatitis B also is a sexually transmitted disease, and it should be investigated in HIV-positive parturients. Severe hepatic impairment affects anesthetic management. Of equal importance are the infectivity of hepatitis B and the high likelihood of its transmission after needlestick injury. For this reason, it is unacceptable for health care workers to remain unvaccinated against hepatitis B.

Choice of Anesthetic Technique

There are concerns with the use of either general or neuraxial anesthesia. Overall, both techniques are safe, keeping in mind the precautions outlined in this chapter.[65]

Neuraxial Anesthesia

Whether HIV-infected pregnant women are more prone to the occurrence of infection after administration of neuraxial anesthesia is an important concern. Hughes et al.[66] performed a study of 30 HIV-positive parturients, of whom 18 received neuraxial anesthesia and 12 did not; there was no evidence of accelerated disease progression in either group, and there were no neurologic or infectious complications in either group immediately after delivery and at 4 to 6 months postpartum.[66] A later study demonstrated no postoperative changes in viral load or $CD4^+/CD8^+$ lymphocyte ratio and no increased hemodynamic instability or blood loss in HIV-infected patients undergoing elective cesarean delivery with spinal anesthesia.[67] The prevention of infectious complications of neuraxial anesthesia depends on the maintenance of strict aseptic technique, which should include careful hand washing and wearing a face mask (see Chapter 12). Although the American Society of Anesthesiologists (ASA) practice advisory[68] does not specifically recommend that anesthesia providers wear a sterile gown during initiation of neuraxial anesthesia, the U.S. CDC has recommended that a gown should be worn to prevent the transmission of HIV to the health care worker "during invasive procedures likely to result in the splashing of blood or other bodily fluids."[69]

Some physicians may question whether it is prudent to administer neuraxial anesthesia to a patient who almost certainly will develop neurologic deficits at some time in the future and whether these deficits might be ascribed to the neuraxial anesthetic technique. Because such deficits are unlikely to be temporally related to the anesthesia, this does not seem to be a significant concern. Further, it seems cruel to deny the most effective intrapartum analgesic techniques to HIV-positive women simply because of fear of future litigation.

Another question is whether an anesthesia provider can ethically or legally refuse to provide care to an HIV-positive patient. Specifically, can an anesthesia provider refuse to provide epidural analgesia during labor? The American Medical Association has taken the position that physicians have an ethical duty to treat HIV-positive patients. Refusing to treat a patient with HIV also places the physician at legal risk, because numerous federal, state, and local statutes prohibit discrimination against patients with HIV disease. Any physician who refuses to provide care for patients with HIV must participate in a referral system ensuring that such patients receive prompt medical care.[70]

Despite the use of small-gauge, pencil-point spinal needles, and despite careful technique during administration of epidural anesthesia, post–dural puncture headache (PDPH) remains a problem in pregnant patients (see Chapter 31). Clearly, the onset of headache and photophobia in an immunosuppressed patient who has recently received a major neuraxial anesthetic can be worrisome, but the typical postural nature of a PDPH should allay fears of bacterial meningitis. Once the diagnosis of PDPH is made, an initial course of conservative therapy is indicated. It typically consists of bed rest, analgesics, and oral hydration. Although dehydration can worsen PDPH, there is no evidence that forced oral or intravenous overhydration has any beneficial effect.

Should conservative therapy for PDPH fail, a number of additional pharmacologic interventions have been proposed, including intravenous or oral caffeine, adrenocorticotropic hormone, and the $5\text{-}HT_3$ receptor agonist sumatriptan; all have varying degrees of success. However, the "gold standard" for treatment of PDPH is an autologous epidural blood patch. Such treatment can be expected to produce permanent and complete pain relief in the great majority of patients; a second epidural blood patch typically produces relief in most patients for whom the initial procedure fails.

Some physicians have expressed concern that the introduction of HIV-infected blood into the neuraxis might lead to the introduction of HIV into a previously uninfected CNS.[71] Demonstration of subarachnoid extension of an epidural blood patch on magnetic resonance imaging heightens these concerns.[72] However, it is likely that CNS infection occurs quite early in the course of HIV disease, even in asymptomatic patients. Nevertheless, it seems prudent to acknowledge the possibility that an epidural blood patch could accelerate the CNS manifestations of the disease. This question was addressed in a study of six seropositive patients who experienced PDPH after diagnostic lumbar puncture and who subsequently received an epidural blood patch.[73] These patients subsequently underwent serial neuropsychological testing for as long as 2 years. The investigators stated that "none of these six subjects had a decline in neurocognitive performance or other adverse neurologic or infectious

sequelae" during the period of the study. Although these numbers are small and this study has never been repeated, it provides the best evidence to date of the safety of epidural blood patch in an HIV-infected patient.

An alternative to autologous epidural blood patch is the epidural infusion of normal saline or colloidal solutions such as hetastarch. Unfortunately, the relief obtained from this technique is often transient, lasting only as long as the infusion continues. Further, the safety of epidural colloid infusion has not been established. Another proposed alternative is an epidural blood patch with fresh allogeneic whole blood; however, there are no published data on this technique.

General Anesthesia

As with neuraxial anesthesia, it is appropriate to ask whether patients with HIV might be more susceptible to the infectious (e.g., pulmonary) complications of general anesthesia. No published study has addressed this question. However, it seems appropriate to handle the endotracheal tube in as sterile a manner as possible and to minimize the duration of postoperative ventilation.

Another question involves the effect of general anesthesia on immune function. Several published studies suggest that general anesthesia can transiently depress immune function, but this depression appears to be clinically insignificant in healthy patients.[74] It is appropriate to ask whether this effect might be exaggerated to the point of clinical significance in patients with HIV disease. Studies on this issue are lacking. At present, it would be inappropriate to recommend one anesthetic technique over another on the basis of their effects on immune function.[75]

STRATEGIES TO MINIMIZE TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS

To the Uninfected Patient

Any survey of HIV and anesthesia must include a discussion of those measures that can decrease the risk for HIV transmission to the uninfected patient. The most common iatrogenic cause of such transmission is the transfusion of infected blood. The use of nucleic acid amplification techniques to test donor blood should reduce the risk for transfusing HIV-infected blood. Nonetheless, the most significant impact that anesthesia providers can have on disease transmission is to minimize the transfusion of allogeneic blood.

In healthy patients, oxygen delivery is satisfactorily maintained at hemoglobin levels much lower than the historical transfusion threshold of 10 g/dL. The Consensus Development Conference on Perioperative Red Blood Cell Transfusion concluded that healthy patients tolerate a hemoglobin concentration as low as 7 g/dL.[76] Patients with chronic anemia have a higher concentration of 2,3-diphosphoglycerate, which allows effective oxygen delivery at low hemoglobin concentrations. ASA guidelines[77] state the following:

> *The information needed to precisely define when a blood transfusion should be given is not available….Red blood cells should usually be administered when the hemoglobin concentration is low (e.g., less than 6 g/dL in a young, healthy patient), especially when the anemia is acute. Red blood cells are usually unnecessary when the hemoglobin concentration is more than 10 g/dL….The determination of whether intermediate hemoglobin concentrations (i.e., 6 to 10 g/dL) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.*

It is not clear how these guidelines should be applied to pregnant women. An association between preterm delivery and hemoglobin concentrations of less than 10 g/dL has been reported,[78] as has a similar association between LBW infants and hemoglobin concentrations lower than 9 g/dL.[79] However, whether this is a causal relationship or whether anemia serves as a marker of poor nutrition or lower socioeconomic status that may independently lead to perinatal morbidity is unknown. Although it is impossible to designate a minimum acceptable hemoglobin level during pregnancy, anemia is clearly undesirable. Once a cause is determined, appropriate therapy should be initiated, including transfusion if the anemia is life threatening for the mother or fetus.

Patients often want to use blood specifically donated by friends or relatives for their use (**directed donation**). There are disadvantages of directed donation. First, a directed unit is unavailable to another patient who may need it more urgently. Second, directed donation may discourage the routine voluntary donation of blood. Third, the directed donor sacrifices anonymity and legal protection. More pertinent to the issue of HIV transmission, there is no evidence that blood from designated donors is safer than anonymously donated bank blood[80]; this finding may be related to the slightly higher rate of HIV seropositivity among first-time donors.[81] Further, fatal graft-versus-host disease has been reported in patients receiving blood from first-degree relatives.[82]

Another approach is the use of **autologous blood donation** during pregnancy in patients at high risk for peripartum hemorrhage, such as those with placenta previa or suspected placenta accreta. Several studies have demonstrated the safety of autologous donation in pregnant women with a hematocrit of at least 34%.[83,84] However, it may be impossible to identify the patients who are more likely to require transfusion. In one study, only 4 (1.6%) of 251 high-risk patients eventually required transfusion. Further, only 2 of 13 patients who did receive blood during the peripartum period had identifiable risk factors. These results cast doubt on the benefits and cost-effectiveness of autologous blood donation during pregnancy.[85]

In patients at risk for hemorrhage during cesarean delivery, the use of **acute normovolemic hemodilution** may reduce the need for transfusion. This approach involves the collection of blood immediately before

surgery with the simultaneous infusion of an appropriate volume of crystalloid or colloid to maintain normovolemia. In one study of 38 patients at risk for hemorrhage, 750 to 1000 mL of blood was removed with the simultaneous infusion of an equal volume of pentastarch. The hemoglobin concentration dropped from 10.9 to 8.3 g/dL; fetal monitoring revealed no change in the fetal heart rate pattern. The blood was reinfused during surgery. Neonatal outcome was satisfactory, and only one patient required allogeneic blood.[86] In contrast, a meta-analysis in nonpregnant patients did not support the use of normovolemic hemodilution as an effective strategy for avoiding allogeneic transfusion.[87]

A final option for minimizing allogeneic transfusion is **intraoperative blood salvage** through the use of a cell salvage device (see Chapter 38). In the past, the use of intraoperative blood salvage in obstetric patients has been limited, in part by concern that transfusion of salvaged blood might precipitate amniotic fluid embolism. Waters[88] and others have argued that this rare but devastating complication is not an embolic disease but rather an anaphylactoid reaction that would occur with or without transfusion of cell-salvaged blood, given that amniotic fluid is routinely entrained into the maternal circulation at the time of delivery.

Published experience with intraoperative blood salvage suggests that it is safe in obstetric patients.[89,90] Allam et al.[89] reviewed the use of intraoperative blood salvage in obstetric patients; at the time of their review in 2008, approximately 400 published cases had been reported. (In most published cases, the total volume of transfused salvaged blood was small.) These investigators concluded that "no single serious complication leading to poor maternal outcome has been directly attributed to its use." They suggested that large prospective studies are needed to evaluate the efficacy and safety of cell salvage in obstetric patients.[89] Arguments against use of intraoperative blood salvage in obstetric patients include (1) because of the low use of blood salvage procedures in obstetrics, ongoing operator (user) competency may be problematic and the risk for error may be increased; and (2) the number of patients studied to date is not sufficient to detect rare adverse events.[91] Uncertainty remains about the cause of the syndrome of amniotic fluid embolism (including uncertainty as to which agent[s] trigger[s] the syndrome and which patients are at risk). Also, the blood salvage procedure does not eliminate fetal red blood cells, so the Rh-negative mother is at risk for isoimmunization from transfusion of salvaged blood.

The revised ASA Practice Guidelines for Obstetric Anesthesia[92] recommend that "in cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell salvage should be considered if available." And a 2012 ACOG committee opinion[93] concluded that "autologous blood salvage devices have proved safe and the use of these devices may be a valuable adjunct during…surgery [for placenta accreta]." At best, however, intraoperative blood salvage will reduce or eliminate exposure to allogeneic blood in a minority of parturients who require transfusion[94] (see Chapter 38 for a more complete discussion of intraoperative blood salvage).

Standards for Equipment Disinfection

The ASA Subcommittee on Infection Control Policy[95] has made specific recommendations about the disinfection of reusable anesthesia equipment that comes in contact with mucous membranes. In practice, this equipment consists of laryngoscope blades, endoscopes, and face masks. The ASA Subcommittee recommends that such items be washed as soon as possible to remove gross contamination, followed by either high-level disinfection or sterilization. Functionally, each of these procedures kills fungi, viruses, and vegetative bacteria (including mycobacteria). In addition, sterilization kills larger numbers of endospores.[95]

In many institutions, disposable carbon dioxide absorbers and unidirectional valves are used for the anesthetizing of HIV-infected patients. However, no evidence suggests that HIV is transmitted in respiratory aerosols.[96] This practice is unnecessary and is not recommended by the ASA subcommittee. An exception involves the HIV patient with active pulmonary tuberculosis; if a disposable absorber is not used for such a patient, the entire assembly distal to the fresh gas source must be disassembled and sterilized.

The rate of nosocomial transmission of HIV is negligible, and the only documented cases of such transmission apparently occurred in a setting in which disinfection procedures were notably lax.[96] Commonsense measures should effectively reduce the rate of nosocomial transmission to zero.

To the Health Care Worker

The primary means of preventing the transmission of HIV to health care workers is the mandatory use of universal blood and body fluid barrier precautions. This policy has three crucial components. First, it must be universal. Establishing a higher level of concern for dealing with known HIV-positive patients implies a lower level of concern in the care of patients not known to be HIV positive. Unfortunately, a patient who is infected with HIV may be living within the window between the acquisition of infection and seroconversion. Further, all care providers should be equally concerned with the transmission of other bloodborne infections of higher infectivity and sometimes equal deadliness, such as hepatitis B and C.

Second, this policy must be followed whenever contact with infectious material is anticipated. Blood obviously is the primary source of exposure, but other potentially infectious body fluids include amniotic fluid, CSF, synovial fluid, pleural fluid, and pericardial fluid. Saliva is not believed to be infectious, but manipulations of the oral mucosa (e.g., laryngoscopy, tracheal intubation) probably lead to the contamination of saliva with blood.

Third, barrier precautions must be effective. Barriers include gloves, mask, and eye shields. The use of gloves prevents 98% of an anesthesia provider's contact with patient blood.[97] When gross contamination is likely (e.g., during neonatal resuscitation), full-length gowns are indicated.

An additional component of universal precautions is the avoidance of needle-stick injuries. The recapping of

needles is the most common cause of needle-stick injuries. Contaminated needles, including needles that have been injected into intravenous tubing, should not be recapped by hand. If recapping is necessary, a mechanical protective device should be used. The use of needleless systems can be expected to significantly decrease the risk for injury, and the use of such systems should be encouraged.[98]

Postexposure Prophylaxis for Health Care Workers

Occupational exposure to HIV is perhaps the most frightening work-related injury that an anesthesia provider can sustain. The risk for seroconversion after percutaneous exposure to HIV-infected blood is approximately 0.3%,[99] but this statistic provides little reassurance to the exposed health care worker in view of the presumed 100% fatality rate of HIV infection. As of June 2000, the CDC had received voluntary reports of 56 U.S. health care providers with documented HIV seroconversion temporally related to occupational exposure, and an additional 138 reports of seroconversion that were considered possibly a result of occupational exposure.[100] There have been no confirmed cases of occupational transmission since 1999.[101]

Certain measures should be taken after any parenteral exposure to potentially infectious body fluids, even those of the HIV-negative patient (Box 45-5). Although it is of unclear efficacy in preventing HIV seroconversion, local wound care with an antiseptic solution is indicated.[102] In view of the exceedingly high transmission rate of hepatitis B infection, it is mandatory to determine the health care worker's antibody status after parenteral exposure to body fluids from a patient known to have or to be at high risk for hepatitis B. A previously vaccinated health care worker with absence or insufficiency of antibodies to hepatitis B should receive a booster dose of vaccine and hepatitis B immune globulin to provide protection until an adequate antibody response develops. A health care worker with no history of vaccination and an absence of antibodies should undergo primary immunization and should receive hepatitis B immune globulin.[99]

Several primate studies have demonstrated that the administration of antiretroviral drugs shortly after inoculation with SIV or HIV-2 can prevent seroconversion.[103,104] Further, although prospective data are lacking, a retrospective case-control study demonstrated an 81% reduction in transmission of HIV to exposed health care workers who received ZDV prophylaxis.[105] Finally, the reduction of vertical transmission by ZDV therapy demonstrated by ACTG Protocol 076 was only partly a result of the reduction of maternal viral load; inhibition of viral replication clearly played some role.[99] Altogether, these results suggest that postexposure prophylaxis may play a significant role in preventing seroconversion.

The U.S. Public Health Service has issued postexposure prophylaxis guidelines for health care workers who have experienced either percutaneous or permucosal exposure to HIV.[99] These recommendations attempt to determine the relative risk of transmission on the basis of (1) the nature of the material to which the worker was exposed, (2) the size of the inoculum, (3) the route of exposure, and (4) the presumed viral titer in the inoculum. Although encouraging results have been obtained, the primary strategy for the prevention of occupational transmission should focus on the prevention of exposure, especially the prevention of needle-stick injuries.

BOX 45-5 Treatment of Occupational Exposure to Human Immunodeficiency Virus

- Local wound care
- Administration of tetanus toxoid
- Determination of worker's hepatitis B antibody titers
- Risk stratification
- Chemoprophylaxis as indicated

KEY POINTS

- Over two thirds of all new cases of HIV infection in the United States occur in minority populations.
- More than 20% of all new HIV infections in the United States occur in women.
- HIV infection eventually can be expected to involve every organ system. Central nervous system involvement occurs as early as the period of initial infection and seroconversion.
- Highly active antiretroviral therapy during pregnancy can reduce the rate of vertical transmission of HIV infection to the fetus to 1% to 2%.
- Elective cesarean delivery can provide further protection in women with more than 1000 copies of viral RNA per mL of plasma and may benefit women with lower viral loads.
- HIV-infected patients often are treated with multiple medications, each of which has side effects that are relevant to anesthetic management.
- Neuraxial anesthesia is safe in the HIV-infected parturient.
- Autologous epidural blood patch is safe in the HIV-infected patient.
- Our greatest contribution to minimizing the spread of HIV to uninfected patients is the minimization of homologous blood transfusion.
- The most effective method of minimizing HIV transmission to health care workers is strict adherence to universal blood and body fluid barrier precautions.
- Postexposure prophylaxis is indicated for all health care workers who experience high-risk exposures to potentially infectious materials.

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CHAPTER 46

Liver Disease

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CHAPTER OUTLINE

LIVER DISEASES

Liver diseases can be either incidental or unique to pregnancy and complicate as many as 3% of all pregnancies. The more common conditions are addressed in this chapter, and the hepatic aspects of preeclampsia/eclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome are discussed in Chapter 36.

Liver Diseases Incidental to Pregnancy

Viral Hepatitis

The presentation of viral hepatitides ranges from mild, nonclinical illness to fulminant hepatic necrosis. Viral hepatitis is the most common cause of jaundice and most frequent reason for gastroenterology consultation during pregnancy.[1] Six types—hepatitis A, B, C, D, E, and G—have been identified and are associated with specific viruses. Types A, B, and C are the most common. Infrequently, hepatitis can also be caused by herpes simplex virus (HSV), yellow fever virus, rubella virus, Epstein-Barr virus (EBV), or cytomegalovirus (CMV).

Hepatitis A (**HAV**) and **hepatitis E** (**HEV**) are viral infections of hepatocytes that typically spread by oral ingestion of food or water contaminated with feces from infected individuals. Although endemic in other countries, the current all-time low incidence of 1.3 per 100,000 in the United States is attributed to good sanitation.[2] The incidence of HAV infection has been reduced by vaccination for preexposure prophylaxis; immune globulin is available for postexposure prophylaxis to prevent or attenuate infection. Clinically, a preicteric phase typically occurs with nonspecific viral symptoms, followed by an icteric phase with jaundice and acholic stools. Acute treatment is supportive. Chronic HAV infection does not occur, but a prolonged or relapsing course occurs in up to 20% of patients and an acute fulminant course occurs in less than 1% of patients.[3] Vertical transmission to the fetus has been reported rarely.[4]

HEV infection may be largely asymptomatic. In symptomatic patients, the disease is usually self-limited. Pregnant women and patients already infected with another hepatitis virus, however, are more likely to develop fulminant hepatic failure. Chronic HEV infection may occur in immunosuppressed patients, and vertical transmission can occur.[5] Pegylated interferon and/or ribavirin treatment for chronic HEV infection has shown moderate success, and HEV vaccines are under development.[6]

Hepatitis B (**HBV**) and **hepatitis D** (**HDV**) are usually transmitted via percutaneous or permucosal exposure to infected body fluids. In high-prevalence areas, HBV infection is most commonly acquired perinatally or in early childhood. In low-prevalence areas, infection is primarily acquired in adulthood through sexual contact or intravenous drug abuse. The incidence is decreasing after widespread vaccination and safety precautions in health care settings. Postexposure prophylaxis with HBV vaccination alone or a combination of vaccination with HBV immunoglobulin is highly effective in preventing HBV transmission in adults as well as in infants of HBV-infected mothers and may prevent perinatal transmission in 90% of cases. The majority of acute infections are asymptomatic, with only 30% of adults developing typical symptoms of hepatitis, and less than 0.5% developing fulminant hepatitis. Most cases can be managed with supportive treatment, although nucleoside analogue therapy may improve prognosis in severe cases. Chronic

HBV develops in less than 5% of adults but in more than 20% of children, and exacerbations of chronic HBV may occur in the postpartum period. The 5-year cumulative incidence of cirrhosis in those with chronic HBV may be as high as 20%, and once cirrhosis has developed the annual risk for hepatocellular carcinoma may be as high as 5%. Treatment of chronic HBV, therefore, is aimed at clearance of virus to prevent the development of cirrhosis and cancer. Vertical transmission to the fetus from hepatitis Be antigen (HBeAg)-positive mothers can be as high as 90% without attempts to prevent transmission.[7] Nucleoside analogue antiviral therapy with lamivudine has a favorable side-effect and safety profile and may be used during pregnancy to reduce vertical transmission, but there is significant risk for viral resistance.[8] In contrast, interferon therapy has a finite course of treatment and an increased chance of viral clearance and significantly reduces the risk for cirrhosis and liver cancer; however, it has more side effects and is contraindicated during pregnancy.[9] Current recommendations are to administer HBV vaccination to *all* neonates, and to administer hepatitis B immune globulin (HBIG) to all offspring of infected mothers.[10]

HDV is dependent on HBV co-infection to replicate. Acute co-infection with both viruses can be more severe than acute HBV infection alone and may result in acute liver failure. HDV superinfection in the setting of chronic HBV results in chronic HDV infection in most patients, and these patients have more rapid progression to cirrhosis.[11]

Hepatitis C (HCV) transmission most commonly occurs from transfusion of infected blood products or injection of contaminated drugs (both illicit and iatrogenic). Maternal-fetal and sexual transmission are less common routes of transmission. Initial infection is generally asymptomatic, but up to 30% of patients develop acute hepatitis. In patients with acute HCV infection that has not cleared spontaneously within 12 weeks, treatment with pegylated interferon may be used to prevent chronic infection, with treatment success in up to 98% of patients. In most asymptomatic and untreated cases, infection persists for over 6 months and leads to chronic infection with progression to cirrhosis in up to 30% of patients within 30 years. Thus, HCV is the leading cause of chronic hepatitis, cirrhosis, and liver cancer (which develops in up to 3% of patients per year) and a primary indication for liver transplantation in the developed world. Depending on the severity of liver fibrosis, therapy may be warranted to prevent these complications. Combination treatment with pegylated interferon, ribavirin, and a protease inhibitor can result in a sustained virologic response in up to 80% of patients, but is contraindicated during pregnancy.[12,13]

Hepatitis G (HGV) is transmitted parenterally, sexually, or vertically. In the United States, nearly 20% of all blood preparations are infected with HGV. Although there have been reports of acute, fulminant, and chronic hepatitis and hepatic fibrosis, HGV replicates predominantly in the hematopoietic system rather than in hepatocytes. Clinical significance is mostly for those co-infected with HCV or human immunodeficiency virus (HIV) or for individuals with hematologic cancers.[14]

Cholecystitis

Pregnancy may promote gallstone formation. Cholelithiasis is present in up to 3% of pregnant women, although acute cholecystitis occurs in only 0.1% of pregnancies.[15] Patients may have right upper quadrant pain, fever, and leukocytosis, and diagnosis is generally made by ultrasonography. Serious complications include **cholangitis, pancreatitis, gangrenous cholecystitis,** and **perforation.** To avoid surgery, conservative treatment may be considered in mild cases and includes intravenous hydration, antibiotics, opioid analgesia, bowel rest, and possibly percutaneous cholecystostomy. There is some evidence, however, that there is greater risk for fetal demise among patients treated conservatively.[16] When surgical intervention is required, both laparoscopic and open cholecystectomy have been safely used during pregnancy.[15]

Liver Abscess

Liver abscess can develop from infection by a range of organisms with various sites of entry. Organisms with a predilection for the liver include parasites such as ***Entamoeba***, ***Echinococcus***, ***Clonorchis***, and ***Ascaris***. Direct inoculation during medical instrumentation or hematogenous spread from intravenous drug abuse or endocarditis can occur. Appendicitis, diverticulitis, or other intra-abdominal infections may spread to the liver. **Fungal infections** are also possible in immunocompromised patients. Management of liver abscess includes antimicrobial agents, percutaneous or open drainage, and possibly surgical resection.[17] The condition is rare during pregnancy, but treatment modalities are similar to those described for the nonpregnant woman.[18]

Autoimmune Diseases

Autoimmune hepatitis, primary biliary cirrhosis, and **primary sclerosing cholangitis** are conditions that may overlap and may also be associated with other extrahepatic autoimmune disorders.[19,20] All may lead to end-stage liver disease, and treatment with corticosteroids, other immunosuppressants, and/or ursodeoxycholic acid is aimed at preventing this progression. For advanced and intractable disease, liver transplantation may be necessary. Pregnancy is associated with a 33% incidence of disease flares (mostly in the postpartum period), and an 11% incidence of serious maternal adverse events associated with hepatic decompensation, as well as increased neonatal intensive care requirement. Immunosuppressive therapy during pregnancy is reportedly safe and effective in reducing disease flares.

Vascular Syndromes

Budd-Chiari syndrome involves thrombosis of the hepatic vein or suprahepatic inferior vena cava and may be associated with pregnancy or other hypercoagulable states.[21] Hepatic venous congestion can also result from right-sided heart failure or other cardiopulmonary diseases that increase central venous pressure or from

mechanical compression or compartment syndrome that impedes hepatic venous outflow. This congestive hepatopathy can ultimately lead to fibrosis, portal hypertension, and liver failure. **Portal vein thrombosis** may also occur and cause portal hypertension without cirrhosis. Initial therapy is anticoagulation, and liver transplantation may ultimately be required in chronic cases. Disruption of hepatic arterial and/or portal venous inflow can result in acute ischemic/hypoxic hepatitis, especially in the setting of other coexisting liver disease. This "shock liver" syndrome can occur in the setting of perioperative hypotension, critical illness with septic shock or cardiac arrest, pulmonary embolus, heart failure, or heatstroke.[22,23]

Metabolic Diseases

Wilson's disease is a condition of reduced copper excretion. Gradual copper accumulation in the liver can lead to cirrhosis, while rapid accumulation may result in acute liver failure. Patients may also develop neurologic, ophthalmologic, and renal dysfunction. Fertility is generally reduced in women, but treatment with copper-chelating agents during pregnancy can result in positive outcomes for both the mother and fetus.[24] **Hemochromatosis** is a condition of iron accumulation that results in arthropathy, skin pigmentation, diabetes, hypopituitarism, hypogonadism, heart failure, and liver cirrhosis. Phlebotomy (with or without a chelating agent) to deplete iron stores markedly improves survival and prevents most of the complications.[25] **α_1-Antitrypsin deficiency** results in uncontrolled tissue degradation, with effects predominantly in the lungs and liver. This leads to emphysematous changes in the lung as well as liver cirrhosis.[26] Pregnancy can be complicated by fetal growth restriction (also known as intrauterine growth restriction), preterm labor, and pneumothorax or other respiratory decompensation.[27]

Hepatotoxicity

Hepatotoxicity can result from a variety of exposures. **Acetaminophen (paracetamol),** involved in 20% of drug overdoses during pregnancy, is metabolized by the liver into highly reactive oxides. If their formation exceeds the binding capacity of glutathione, maternal and fetal hepatic injury occurs. Treatment with *N*-acetylcysteine within 16 hours of acetaminophen ingestion may bind toxic metabolites in both the mother and the fetus and improve outcomes.[28] **Alcoholic hepatitis** can result from the acute ingestion of large amounts of alcohol, and chronic alcohol ingestion may lead to cirrhosis.[29] Other agents that have potential to cause hepatotoxicity during pregnancy are **antiretroviral drugs** for HIV infection, **propylthiouracil** for hyperthyroidism, **alpha-methyldopa** for hypertension, **isoniazid** for tuberculosis, **statins** for antiphospholipid syndrome or hyperlipidemia, **mushrooms** and **herbal supplements**, and **industrial agents**.[30-32] In one report, liver transplantation was successfully accomplished during pregnancy to treat acquired propylthiouracil-induced hepatotoxicity.[33]

Liver Diseases Specific to Pregnancy

Liver diseases specific to pregnancy are summarized in Table 46-1.

Hyperemesis Gravidarum

Hyperemesis gravidarum occurs in 0.3% of pregnancies and is characterized by a severe and persistent form of nausea and vomiting that can lead to dehydration and electrolyte imbalances, as well as elevated liver transaminases, mild jaundice, and transient hyperthyroidism (see Chapter 16).[34] The possible etiologies include hormonal, infectious (e.g., *Helicobacter pylori*), mechanical (e.g., gastroesophageal reflux), genetic, and psychogenic causes. Treatment with vitamin supplementation and antiemetics (e.g., doxylamine, metoclopramide, ondansetron) may be indicated, and severe cases may require enteral or parenteral nutrition and rehydration. Adverse pregnancy outcomes are rare but may occur in women who fail to gain adequate weight during pregnancy.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy occurs in less than 0.3% of pregnancies overall in the United States but in up to 6% in some (e.g., Hispanic) subpopulations. It is more common in nulliparous women with multiple gestation.[35] Proposed causes include genetic mutations that alter phospholipid or bile salt transport across hepatocyte membranes, as well as abnormal steroid hormone profiles, resulting in pruritus and elevated serum bile acid levels during the second or third trimester. Pruritus is primarily on the palms and soles, is more severe at night, and may lead to excoriations resulting from scratching. Jaundice may also be present.

Intrahepatic cholestasis of pregnancy has minimal impact on maternal health during gestation. However, failure to correct vitamin K malabsorption may lead to clinical coagulopathy. Fisk et al.[36] reported an 11% incidence of postpartum hemorrhage among women with intrahepatic cholestasis of pregnancy. Although maternal outcome is generally good, the fetus is at increased risk. A study of 693 women with a diagnosis of intrahepatic cholestasis of pregnancy showed an increased risk for preterm delivery (4.3%), asphyxia events (7.1%), and meconium staining.[37] Fetal complications were increased when bile acid levels were greater than 40 μmol/L.

Ursodeoxycholic acid is currently the treatment of choice until fetal lung maturity allows for early delivery.[38] Antihistamines may also be used to relieve pruritus. Delivery at 37 weeks' gestation is recommended because most fetal demise occurs with longer gestations; even earlier delivery may be warranted in cases of intolerable pruritus or previous fetal demise. Recurrence of the disease is common in subsequent pregnancies.[39-41]

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP), or reversible peripartum liver failure, occurs in up to 1 per 7,000 pregnancies and is more common in twin gestations. Maternal

TABLE 46-1 **Liver Diseases Specific to Pregnancy**

	Hyperemesis Gravidarum	Intrahepatic Cholestasis of Pregnancy	Preeclampsia/ Eclampsia	HELLP Syndrome	AFLP
Incidence	< 0.3%	0.3%-6%	2%-8%	0.1%-0.6%	<0.01%
Presentation	1st trimester	2nd or 3rd trimester	2nd or 3rd trimester, or after delivery	2nd or 3rd trimester, or after delivery	3rd trimester
Symptoms, Signs, and Complications	Nausea/vomiting Ketosis	Pruritus Jaundice	Hypertension Proteinuria Edema Seizures Renal failure Pulmonary edema Hepatic hematoma/ rupture	Abdominal pain Renal dysfunction Hypertension Hepatic hematoma/ rupture Liver infarction	Nausea/vomiting Abdominal pain Jaundice Hepatic failure
Laboratory Findings	Elevated aminotransferase levels	Increased serum bile acid levels Hyperbilirubinemia Mild abnormalities of liver function tests	Low platelet count Proteinuria Increased uric acid level Mildly elevated aminotransferase levels	Low platelet count Hemolysis Markedly elevated aminotransferase levels	Low platelet count Hypoglycemia Mildly/moderately elevated aminotransferase levels
Treatment	Supportive management	Delivery at fetal maturity Ursodeoxycholic acid	Blood pressure control Seizure control Delivery	Prompt delivery	Prompt delivery
Outcome	Benign for mother and fetus	No increase in maternal death rate Increased risk for preterm delivery and fetal loss May recur with subsequent pregnancies Increased risk for subsequent liver and biliary tract disease	Increased risk for maternal morbidity and mortality Increased risk for perinatal morbidity	Maternal death rate 1%-4% Fetal death rate 1%-30%	Maternal death rate < 12% Fetal death rate < 66%

AFLP, acute fatty liver of pregnancy; *HELLP,* hemolysis, elevated liver enzymes, and low platelet count.
Adapted from Schutt VA, Minuk GY. Liver diseases unique to pregnancy. Best Pract Res Clin Gastroenterol 2007; 21:771-92.

mortality up to 12% and fetal mortality up to 66% have been reported, but with prompt and aggressive care the mortality rates can be significantly decreased.[42] The disease is characterized by microvesicular fatty infiltration of the liver (and possibly kidney) believed to be due to defective beta oxidation of fat, usually in the third trimester. To date, AFLP has been documented in 30% to 80% of pregnancies in which the fetus was found to have a long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency. It remains unclear why only some mothers who give birth to a child with fatty acid oxidation defects develop AFLP. Multiple gestation may further stress the fatty acid oxidation capacity in susceptible pregnant women. Davidson et al.[43] reported three cases of AFLP in parturients with triplet gestation.

Early symptoms are nonspecific and include anorexia, nausea, emesis, malaise, fatigue, and headache. Jaundice, edema, hypertension, hypoglycemia, diabetes insipidus, and encephalopathy may develop. Progression to fulminant hepatic and renal failure can be rapid. AFLP is commonly misdiagnosed as preeclampsia or HELLP syndrome because of a similar constellation of presenting symptoms. Similarities between AFLP and preeclampsia or eclampsia are intriguing. Both disorders primarily occur near term and are associated with nulliparity and multiple gestation.

AFLP is a medical emergency that demands rapid evaluation and treatment. Hepatic failure and fetal death may occur within days. Management includes control of hypertension, seizure prophylaxis, and immediate delivery of the fetus or termination of the pregnancy. Mode of delivery is not as critical as is doing so expeditiously.[44] Liver transplantation may be indicated in severe cases. The anesthesiologist should anticipate postpartum hemorrhage, establish adequate intravenous access, and ensure that crossmatched blood is immediately available for any parturient with AFLP.[45] There is often a worsening of liver function, renal function, and coagulopathy for 48 hours after delivery, followed by improvement during the subsequent weeks.[39,40,44] Survivors experience no

hepatic residua, and subsequent liver biopsy specimens show no evidence of fibrosis.[42] Episiotomy is avoided if possible, and abdominal delivery may be complicated by wound dehiscence related to coagulopathy; delayed wound closure may be indicated.[44]

Spontaneous Hepatic Rupture of Pregnancy

In 2003, 150 cases of hepatic rupture in pregnancy had been published.[46] Hepatic rupture may also complicate preeclampsia, eclampsia, HELLP syndrome, and AFLP. By definition, spontaneous hepatic rupture of pregnancy occurs in the absence of antecedent trauma. Instead, rupture is preceded by an intraparenchymal hepatic hematoma. The strong association with preeclampsia suggests that periportal hemorrhagic necrosis, hypertension, and coagulopathy may lead to hematoma formation. With expansion of the hematoma, the hepatic capsule is progressively distended and dissected from the parenchyma, leading to rupture.[47] **Primary hepatic pregnancy** with embryonic implantation on the liver is another rare condition that can result in liver hemorrhage and shock. In the early postpartum period, growth of hepatic hemangiomas, adenomas, or other potentially hemorrhagic masses may occur.

The mortality rate from hepatic rupture in pregnancy is greater than 60% but may be reduced by greater awareness and improved diagnostic modalities.[48] Ultrasonography, computed tomography, magnetic resonance imaging, angiography, technetium scintigraphy, and exploratory laparotomy may demonstrate the expanding hematoma before rupture.[49] Hematomas that are contained within the liver may be conservatively managed with intravenous fluids and blood products. More aggressive treatment options include open laparotomy, hepatic artery ligation or embolization, and compression of bleeding points with hepatic packing. Recombinant factor VIIa may be considered in the presence of intractable hemorrhage,[50] and liver transplantation can be considered as a last resort.[51]

LIVER FUNCTION AND DYSFUNCTION

Regardless of the disease state and whether it is incidental or unique to pregnancy, the signs and symptoms of acute and chronic liver diseases are similar.

Markers of Liver Dysfunction

The liver performs a variety of physiologic functions, derangements of which are characteristic of liver diseases (Box 46-1). Amino acid metabolism in the liver uses enzymes that include alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Levels of these enzymes are generally normal in pregnancy, but hepatocyte injury leads to their release (commonly called "transaminitis") into the blood where abnormal serum levels can be detected. The liver also removes bilirubin produced from heme metabolism in the blood. Thus, liver dysfunction can lead to accumulation of bilirubin that becomes symptomatic as jaundice. Gluconeogenesis can be impaired by liver dysfunction leading to hypoglycemia and accumulation of lactate. Synthetic functions of the liver include production of albumin and coagulation factors. Although albumin concentration normally decreases during pregnancy secondary to increased maternal plasma volume, prothrombin time (PT) is unchanged during normal pregnancy; therefore, an increase in PT is an indicator of possible liver disease. Decreased thrombopoietin production in the liver, along with hypersplenism from portal hypertension, may lead to thrombocytopenia. Alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) are found in biliary tract cells. ALP is normally increased during pregnancy because of fetal and placental production, but an elevated level of GGT is suggestive of biliary disease. Detoxification functions of the liver are responsible for clearance of many toxic metabolites and drugs. Failure of conversion of ammonia to urea in the liver results in accumulation of ammonia and consequent encephalopathy. Decreased clearance of estrogen and progesterone with liver disease may cause hyperventilation, and other signs of a hyperestrogenic state such as telangiectases and palmar erythema, although this may occur even in normal pregnancies because of increased production by the placenta. Various antigens and antibodies also show characteristic patterns of abnormalities in autoimmune and infectious forms of hepatitis and can be used for diagnosis and treatment monitoring.[22,52]

BOX 46-1 Signs and Symptoms of Liver Disease

Laboratory Findings

- Increased
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Gamma glutamyl transferase (GGT)
  - Bilirubin
  - Lactate
  - Prothrombin time/international normalized ratio (PT/INR)
  - Ammonia
- Thrombocytopenia
- Hypoglycemia
- Hypoalbuminemia
- Metabolic acidosis
- Respiratory alkalosis
- Immune dysfunction
- Renal dysfunction
- Decreased systemic vascular resistance
- Portal hypertension and varices
- Pulmonary hypertension

Symptoms and Physical Findings

- Jaundice
- Pruritus
- Abdominal pain
- Decreased appetite
- Telangiectases
- Palmar erythema
- Easy bruising
- Gastrointestinal bleeding
- Ascites
- Encephalopathy

Acute Liver Failure

Acute (or fulminant) liver failure is an extreme complication of liver disease specific or incidental to pregnancy. Because the liver is responsible for many physiologic processes, liver failure manifests in profound ways that may be life threatening. A patient's condition can deteriorate in an unpredictable and rapid manner, and the patient may require management in a critical care setting. Treatment is mostly supportive, except in cases with specific anecdotal or proven therapies (e.g., immediate delivery for pregnancy-related causes,[53] *N*-acetylcysteine therapy for acetaminophen toxicity, lamivudine for acute HBV infection, penicillin therapy in *Amanita phalloides* intoxication, chelating agents in Wilson's disease, and steroid therapy for autoimmune hepatitis). Advances in critical care medicine and management strategies have improved 1-year survival to approximately 25% without a liver transplant and to 60% to 80% with a liver transplant.[54]

Encephalopathy results from reduced hepatic ammonia metabolism that leads to astrocytic glutamine accumulation and cerebral edema. Subtle mental status changes are followed by somnolence and disorientation, then by incoherence, and finally by coma. Use of invasive intracranial pressure (ICP) monitoring to determine cerebral perfusion pressure (CPP) is controversial because of questionable usefulness and concerns about intracranial bleeding from the procedure. If monitored, ICP should be maintained below 25 mm Hg and CPP should be maintained above 50 mm Hg. Jugular bulb oxygen saturation can provide information about cerebral oxygen use, with levels below 55% indicative of cerebral hypoperfusion and levels above 85% suggestive of cerebral hyperemia or inadequate neuronal metabolism.[55]

Patients should be kept in a quiet room with the head of the bed elevated more than 30 degrees. Mannitol or hypertonic saline infusion may be used to manage intracranial hypertension. Tracheal intubation should be considered once encephalopathy progresses, to prevent pulmonary aspiration, allow for sedation, prevent agitation that can contribute to increased ICP, and facilitate hyperventilation to treat refractory intracranial hypertension. High levels of positive end-expiratory pressure, hypercarbia, and frequent suctioning should be avoided. Other options to consider include thiopental or pentobarbital coma, mild hypothermia (35°C to 36°C [95°F to 96.8°F]), or moderate hypothermia (with a paralytic agent to prevent reflex shivering) to reduce brain oxygen requirement. Phenytoin or propofol can effectively decrease the risk for seizure activity. For patients whose ICP and CPP have been refractory to therapy, a technetium-99m albumin scan can document the absence of cerebral blood flow so that these patients can be removed from the liver transplant waiting list.

Immune dysfunction is related to loss of Kupffer and other immune cell function, and complications of bacterial or fungal infections are a leading cause of mortality. Prophylactic treatment with intravenous antibiotics and antifungal agents significantly reduces the risk for sepsis, decreases the risk for progression to high-grade encephalopathy, and increases the potential for successful transplantation.

Coagulopathy results from impaired synthesis of coagulation factors, most of which are produced in the liver, and from thrombocytopenia, which may be caused by reduced hepatic thrombopoietin production, acute portal hypertension with splenic sequestration, and reduced marrow production. Disseminated intravascular coagulation may also develop. Mucocutaneous, gastrointestinal, and iatrogenic bleeding can all occur in this setting. Cholestasis leads to malabsorption of vitamin K, an important cofactor required for the synthesis of factors II, VII, IX, and X. A therapeutic trial of vitamin K may be attempted if malabsorption is the primary defect, but women with impaired hepatic synthesis do not respond. Routine use of fresh frozen plasma or platelet transfusion is not recommended except when there is evidence of active bleeding or an invasive procedure is planned. Proton-pump inhibitors may help prevent gastric stress ulcers and bleeding. Although liver failure is generally thought to be a hypocoagulable state, it can also be a hypercoagulable state, with clinical manifestations that are difficult to predict and cannot be effectively prevented by prophylactic treatment with blood product transfusions.[56]

Circulatory dysfunction is common because of low systemic vascular resistance, and subclinical myocardial injury is common. Fluid resuscitation is the initial treatment for hypotension, but fluid overload can increase the risk for cerebral edema and acute lung injury. Dopamine or norepinephrine may be used to maintain CPP. Vasopressin and epinephrine are not first-line agents because they may have deleterious effects on splanchnic blood flow, acid-base status, and ICP. Corticosteroids may be considered for patients unresponsive to vasopressors.

Increased production and reduced hepatic uptake of lactate results in metabolic acidosis. In addition, renal function is impaired in up to 40% of patients. Renal failure, acidemia, electrolyte disturbances, or volume overload necessitate renal replacement therapy with continuous venovenous hemofiltration with dialysis. Decreased gluconeogenesis can lead to hypoglycemia, whereas hyperglycemia may worsen neurologic outcome. Enteral feeding is preferred to parenteral nutrition, although parenteral nutrition with hypocaloric, low-glutamine, and normal protein formula appears to be safe.

For patients who are not expected to recover liver function necessary for survival, liver transplantation may be planned. In patients with toxicity from massive liver necrosis, total hepatectomy and temporary portocaval shunting can be done in the interim, while awaiting a donor organ. Auxiliary partial orthotopic liver transplantation has also been performed where only half the native liver is resected and transplanted, allowing the native liver time to recover/regenerate and eventually allowing the donor liver to be rejected, avoiding lifelong immunosuppression. Artificial and bioartificial liver-support devices are also under development.[28,53,54,57,58]

Cirrhosis and Chronic Liver Failure

Any chronic liver disease can progress to cirrhosis, which is characterized by diffuse hepatic fibrosis. Cirrhosis may be asymptomatic until up to 90% of the hepatic parenchyma is destroyed or until a comorbidity causes

decompensation. Many manifestations are similar to those of acute liver failure, although gradual in onset and of lesser severity, whereas others are unique to cirrhosis. Pregnancy is rare in patients with cirrhosis because cirrhosis is uncommon in women of reproductive age and because hormonal changes can cause anovulation and infertility in those who are cirrhotic during childbearing age. Spontaneous abortion rates, risk for prematurity, and perinatal death rates are all greater than those for noncirrhotic parturients.[59]

Hepatic fibrosis causes increased resistance to portal blood flow, resulting in portal hypertension that promotes blood flow through portosystemic anastomoses such as esophageal, hemorrhoidal, and other intra-abdominal veins. Congestion and dilation of these collateral vessels increases the risk for spontaneous or iatrogenic bleeding. In addition, coagulopathy of cirrhosis resulting from decreased clotting factor production and thrombocytopenia can exacerbate bleeding from many causes. **Esophageal variceal bleeding** has been reported in up to 32% of pregnant women with cirrhosis, 50% of those with known portal hypertension, and 78% of those with preexisting varices, with a mortality rate up to 50%. It most commonly occurs later in pregnancy when maternal blood volume is expanded and fetal growth causes compression of collateral vessels. Risk increases during labor because of the repetitive intra-abdominal pressure increases, especially from pushing during the second stage. Elective cesarean delivery or forceps delivery to shorten the second stage of labor and avoid the need for the Valsalva maneuver may decrease this risk.[60] Prophylaxis against variceal bleeding may be considered but is of unproven benefit during pregnancy. Nonselective beta-adrenergeic receptor antagonists can decrease the risk for variceal bleeding by reducing portal pressure through reduction of cardiac output and splanchnic vasoconstriction, but they may cause fetal complications. Prophylactic endoscopic band ligation or surgical portocaval shunting may also be considered in high-risk parturients. For acute esophageal variceal hemorrhage, endoscopic band ligation (after tracheal intubation for airway protection) is the first-line management. Octreotide infusion may also be considered, although its safety has not been proven in pregnant patients. Transjugular intrahepatic portosystemic shunting may be considered for refractory variceal bleeding (see later discussion).[61] Surgical shunt procedures may also be considered in extreme cases.

Splenic artery aneurysms may also develop in cirrhotic parturients, and rupture in late pregnancy carries high maternal and fetal mortality rates. Management options include splenectomy, transcatheter embolization, and stent-graft placement. Postpartum uterine hemorrhage is another potential source of maternal morbidity and mortality, occurring in up to 10% of pregnancies in patients with cirrhosis. In patients with portal hypertension, cesarean delivery can also lead to additional bleeding from intra-abdominal collateral vessels.

Encephalopathy secondary to ammonia accumulation may occur in cirrhotic patients and may be precipitated or exacerbated by sedative medications, infection, hypoglycemia, gastrointestinal hemorrhage, hypotension, or hypoxemia. Management includes correction of precipitating factors and reducing the nitrogenous load from gastrointestinal tract with oral, nonabsorbed antimicrobial agents such as lactulose and neomycin. Flumazenil may also improve mental status transiently, and bromocriptine may improve extrapyramidal symptoms, although these have not been studied extensively in cirrhotic parturients.

Massive **ascites** appears to be uncommon in pregnancy, possibly because the increased intra-abdominal pressure from the gravid uterus opposes extravasation of fluid from splanchnic vessels and organs. If therapy is required, sodium restriction and diuretics can be used. Symptomatic ascites refractory to medical treatment may require paracentesis for drainage, although this could potentially increase the risk for bacterial peritonitis and pregnancy complications.

Cardiovascular manifestations of cirrhosis include systemic vasodilation due to reduced hepatic clearance of endogenous substances regulating vascular tone. Cardiac output is thereby increased, assuming cardiomyopathy is not present as may occur in the settings of alcoholic cirrhosis or hemochromatosis. **Portopulmonary hypertension,** a progressive disease characterized by increased pulmonary vascular resistance due to arteriolar medial hyperplasia, thrombosis, or fibrosis, and eventually right-sided heart failure, has been reported as a complication during pregnancy resulting in postpartum maternal death.[62] **Hepatorenal syndrome,** renal dysfunction secondary to splanchnic and systemic vasodilation of cirrhosis, does not appear to be a common complication in cirrhotic parturients. Similarly, **hepatopulmonary syndrome** due to intrapulmonary vasodilation and shunting resulting in hypoxemia appears to be rare during pregnancy.[62-68]

LIVER SURGERY

Liver Transplantation during Pregnancy

Liver transplantation during pregnancy and successful maternal and fetal outcomes have been reported.[69] Severe fulminant hepatic failure of any cause during pregnancy may necessitate liver transplantation, if a suitable living or deceased donor can be found. For second-trimester transplants, maternal outcomes are excellent but fetal outcomes are poor as a result of elective abortions due to concerns over teratogenicity of therapy, spontaneous abortions, fetal demise, and neonatal death. The literature is inadequate to recommend choice of surgical technique, use of venovenous bypass, or other therapies during the transplantation surgery. In patients for whom a matching organ cannot be found, artificial support systems have been used temporarily while awaiting an organ or spontaneous recovery of liver function.[70-72]

Pregnancy after Liver Transplantation

In 1978, the first pregnancy in a liver transplant recipient was reported.[73] Subsequently, hundreds of such pregnancies have been reported worldwide. Hormonal changes of chronic liver disease can disrupt menstruation, but

liver transplantation restores menstrual function in most female recipients of childbearing age. Despite transplantation and immunosuppression, pregnancy in these patients results in a live birth rate comparable to that in nontransplanted parturients. Successful pregnancy outcome has even been achieved after triple organ transplantation (small intestine, liver, and pancreas).[74] A systematic review and meta-analysis of articles that reported pregnancy outcomes in liver transplant recipients between 2000 and 2011 reported data on 450 pregnancies in 306 recipients.[75] Overall, the pregnancy outcomes of liver transplant recipients appear to be favorable, but pregnancy complications are more common in transplant recipients, with hypertension being the greatest risk to the mother and preterm delivery the greatest risk to the infant. Data from one study suggest that use of the immunosuppressant drug tacrolimus in pregnant women is associated with a lower incidence of new-onset hypertension and preeclampsia than the use of cyclosporine.[76] Based on data from kidney transplants, it is recommended that transplant recipients wait 1 to 2 years before becoming pregnant to allow for stabilization of graft function and immunosuppression and ensure the best maternal and fetal outcomes.[77]

Liver Resection

Benign and malignant liver tumors may occur during pregnancy in patients with or without chronic underlying liver disease. Surgical resection, where feasible, is the definitive treatment.[78] Partial hepatectomy has been reported during pregnancy with good maternal outcomes. Management of the pregnancy has ranged from termination,[79] to simultaneous cesarean delivery,[80] to later spontaneous vaginal delivery.[81] There are inadequate data to make specific recommendations about the intraoperative management of liver resection during pregnancy, including the role of vascular clamping and maintenance of low central venous pressure to reduce blood loss.[82]

Transjugular Intrahepatic Portosystemic Shunt

Indications for a transjugular intrahepatic portosystemic shunt include variceal bleeding and massive ascites refractory to other therapies. Contraindications include right-sided heart failure, polycystic liver disease, severe hepatic failure, systemic infection, hepatic encephalopathy, hepatic tumors, and portal vein thrombosis. The procedure involves accessing a jugular vein, fluoroscopically guiding an endovascular needle into a hepatic vein, and then perforating the liver parenchyma until the needle tip reaches an intrahepatic portal vein. An endovascular stent is then placed across the liver parenchyma to maintain the shunt. The communication created between the portal and systemic venous systems decompresses the portal system, thereby decreasing the pressure that was causing bleeding and formation of ascites.[83] This procedure has been successfully performed during pregnancy and can be done with radiation-limiting techniques that minimize exposure to the fetus and allow the pregnancy to continue.[61,84]

ANESTHETIC CONSIDERATIONS

Anesthetic management is influenced by the extent of hepatic impairment. If hepatic synthetic and metabolic functions are intact, the patient may be managed in the same manner as healthy parturients. In contrast, the parturient with evidence of severe hepatic impairment presents the anesthesiologist with many challenges (Box 46-2).

For patients with underlying liver disease, ischemic or other hepatic insults have the potential to exacerbate liver dysfunction. Many retrospective analyses of various types of hepatic and nonhepatic surgery and anesthesia have focused on perioperative outcomes in patients with liver disease, although not specifically during pregnancy. Most studies have shown an association between preoperative liver disease (and its severity) and postoperative morbidity and mortality, suggesting that abdominal surgery should be avoided or deferred, if possible, until full evaluation and optimal treatment has been completed.[85-93] Other studies, however, found no such association.[94-96] The timing of delivery should be based on maternal and fetal considerations. If possible, it is best to fully evaluate the liver disease before delivery, although sometimes this may not be practical. Early delivery should be considered if the liver disease is exacerbated by the pregnancy (e.g., acute fatty liver of pregnancy or cholestasis of pregnancy) or if the pregnancy is limiting the ability to perform a full liver evaluation. Neuraxial techniques have been used safely in asymptomatic chronic hepatitis patients, as well as after liver transplantation, although data specifically on pregnant patients are lacking.[27,96-99]

Hepatic Effects of Anesthesia

Various studies have examined the effects of anesthetics on hepatic blood flow, although these investigations were not in the setting of pregnancy. Volatile anesthetics appear to decrease hepatic blood flow, with **enflurane**

BOX 46-2 Anesthetic Guidelines for the Parturient with Liver Disease

- Evaluate the extent of hepatic impairment.
- Recognize and evaluate underlying systemic abnormalities, including coagulation and volume status.
- Assist the obstetric team with stabilization of maternal condition before delivery.
- Plan preferentially for neuraxial analgesia/anesthesia for labor, delivery, and cesarean delivery in the absence of contraindications.
- Exclude coagulopathy before administration of neuraxial anesthesia.
- Prevent further hepatic injury by optimizing hepatic blood flow and oxygenation.
- Recognize altered pharmacokinetics and pharmacodynamics.
- Prevent transmission of viral hepatitis to the health care team.
- Monitor the patient for evidence of postoperative hepatic dysfunction.

and **halothane** causing significantly more reduction (> 20%) than **isoflurane**, **sevoflurane**, or **desflurane** (< 20%). Additionally, halothane is thought to cause two distinct forms of drug-induced hepatitis. **Nitrous oxide** may further decrease hepatic blood flow, whereas propofol or ketamine anesthesia may maintain hepatic blood flow better than inhalational anesthesia.[100-107] **Neuraxial anesthesia** also may reduce hepatic blood flow via the effects of systemic arterial hypotension secondary to sympathetic blockade.[108-110] In one study,[110] this reduction persisted during lumbar epidural anesthesia despite maintenance of normotension by infusion of colloid, but the decrease in hepatic blood flow was reversed by dopamine infusion. These findings suggest that reduced cardiac output, secondary to sympathetic blockade, may be responsible for the observed decrease in hepatic blood flow rather than hypotension. Nevertheless, judicious hydration and avoidance of systemic hypotension should minimize the chances of a clinically significant reduction in hepatic blood flow.

Pharmacokinetic Effects of Liver Failure

The liver's numerous metabolic functions include clearance of drugs as well as synthesis of plasma proteins that bind drugs. Liver disease, therefore, can alter the normal pharmacokinetics of anesthetics and other drugs. Drug clearance may be decreased by hepatocyte dysfunction or reductions in liver blood flow. Impaired hepatic synthesis of plasma proteins can lead to decreased drug binding and increased free fraction of drugs. This makes more drug available for clearance by the liver, but at the same time increases tissue availability and effective volume of distribution, which can alter drug effects and clearance. Overall, severe liver disease can decrease clearance of various agents, and repeated or continuous administration can lead to drug accumulation and adverse effects. Additionally, compared with their effects in healthy individuals, anesthetic agents at any concentration may cause increased sedation or decompensation in patients already compromised by hepatic encephalopathy.

Clearance of some opioids, including **morphine**, **meperidine**, and **alfentanil** may be decreased in patients with advanced liver disease. Other opioids, including **fentanyl** and **sufentanil**, do not appear to have significantly impaired clearance, although repeated or continuous dosing may be problematic. **Remifentanil** undergoes breakdown by plasma and tissue esterases, and so its pharmacokinetics are not significantly changed. **Methadone** also appears to have nearly normal disposition. **Codeine**, which requires hepatic conversion to morphine for analgesia and clearance, may not be safe or effective, and similar uncertainty exists regarding tramadol.[111-114] Prolonged effects can also be seen with **etomidate** and benzodiazepines including **midazolam** and **diazepam**, whereas **propofol**, **methohexital**, and **thiopental** clearances are unchanged after anesthesia induction doses.[115-119] Neuromuscular blocking agents normally cleared by the liver (**vecuronium**, **rocuronium**) or by liver-synthesized enzymes (**succinylcholine**), or that may be present in a larger volume of distribution (**pancuronium**), may have longer durations of action, whereas agents not dependent on liver function (**atracurium**, **cisatracurium**) should have normal durations of action.[120-124] The half-lives of amide local anesthetics (**lidocaine**, **bupivacaine**, **ropivacaine**) may be prolonged and potential for toxicity increased because of decreased liver clearance, whereas ester local anesthetics (**2-chloroprocaine**) have potentially prolonged half-lives because of decreased hepatic pseudocholinesterase synthesis.[125-127] **Acetaminophen** can be safely administered in routine doses for acute pain in patients with cirrhosis, but chronic administration can provoke hepatic injury. Although **ketorolac** metabolism may be normal, **nonsteroidal anti-inflammatory drugs** (**NSAIDs**) can precipitate renal dysfunction and should be avoided.[67,128]

Neuraxial Anesthesia

Neuraxial analgesia/anesthesia is the preferred technique for labor, vaginal delivery, and cesarean delivery and can be offered to patients with liver disease in the absence of significant intravascular volume depletion and a coagulopathy. Prior to administration of a neuraxial technique, a full coagulation profile and platelet count should be obtained and intravascular volume assessed. Epidural techniques in particular may have added risk in patients with portal hypertension because the epidural venous plexus is engorged even beyond that of normal pregnancy and could predispose to intravascular needle/catheter placement or epidural hematoma.[129] The potential for impaired clearance of local anesthetics and opioids described earlier should also be considered, especially when repeated boluses or continuous infusions are used. There are no data indicating that one local anesthetic is clearly superior to another for epidural analgesia, and we use our standard epidural infusion of bupivacaine with fentanyl for labor analgesia. Single-shot spinal techniques with small-gauge needles may minimize the issues of drug metabolism and bleeding, although with possibly increased risk for acute hypotension and reduced liver blood flow.

General Anesthesia

Coagulopathy, obstetric hemorrhage, altered mental status, and severe fetal compromise may necessitate the use of general anesthesia for cesarean delivery. Intravascular volume should be evaluated before induction. Invasive blood pressure monitoring and pulmonary artery catheterization may be useful in the patient with cardiovascular compromise or portopulmonary hypertension. Large-bore intravenous access should be established and blood products should be available. Gastric acid neutralization should precede rapid-sequence induction and tracheal intubation. All standard induction agents are safe, and the dose should not be altered. Liver disease and reduced pseudocholinesterase concentrations may delay the metabolism of succinylcholine, but the delay is of negligible clinical importance. Succinylcholine thus remains the muscle relaxant of choice during rapid-sequence induction of general anesthesia, and it should be administered in the same dose as for healthy parturients. Careful gastric tube placement may be considered even in the presence of esophageal varices.[130] For maintenance of

anesthesia, agents that do not undergo significant hepatic metabolism (e.g., isoflurane, desflurane, atracurium, cisatracurium, remifentanil, and nitrous oxide) may be preferable to other inhalational agents that further reduce liver blood flow or intravenous agents that may accumulate before clearance. Reversal of neuromuscular blockade must be ensured before tracheal extubation.

Postoperative Care

Although clearance is delayed in patients with severe liver disease, intravenous opioids may be administered judiciously to provide postoperative analgesia. Neuraxial opioids, especially a single dose of morphine, may obviate any accumulation issues. Advanced liver disease can lead to hepatic encephalopathy. Neurologic deterioration in the postoperative period may result from the residual effects of anesthetic agents, acute liver decompensation, or an intracranial process. Neurologic observation and liver function monitoring is essential to the proper postoperative management of pregnant women with advanced liver disease.

KEY POINTS

- Liver disease can be either incidental or unique to pregnancy and complicates as many as 3% of all pregnancies.
- Viral hepatitides are the most common cause of jaundice during pregnancy.
- All pregnant women should be screened for hepatitis B virus, and all neonates should be vaccinated against it.
- Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy that demands rapid evaluation and prompt delivery.
- AFLP is commonly misdiagnosed as preeclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome because of a similar constellation of presenting symptoms.
- Hepatic rupture may complicate preeclampsia/eclampsia, HELLP syndrome, or AFLP; and the mortality rate can be greater than 60%.
- Encephalopathy may result from reduced hepatic ammonia metabolism.
- Coagulopathy may result from impaired liver synthesis of coagulation factors and from thrombocytopenia.
- Renal failure and cardiovascular, renal, pulmonary, and immune dysfunction may accompany liver failure.
- Women with portal hypertension may develop esophageal varices that are prone to bleed during the third trimester of pregnancy, and this risk increases during labor.
- Successful pregnancy is common after liver transplantation, and pregnancy does not affect the long-term survival of hepatic allografts.
- Pregnancy complications are more common; hypertension is the greatest risk to the mother, and preterm delivery is the greatest risk to the infant.
- Liver disease can alter the normal pharmacokinetics of anesthetics and other drugs.
- Both neuraxial and general anesthesia can be administered safely to the parturient with liver disease, with close attention to hemodynamics to preserve hepatic blood flow.
- Neuraxial analgesia/anesthesia is the preferred technique for labor, vaginal delivery, and cesarean delivery and can be offered to patients with liver disease provided significant intravascular volume depletion and coagulopathy have been excluded.
- Neurologic observation and liver function monitoring should continue into the postoperative period.

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CHAPTER 51

Psychiatric Disorders

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CHAPTER OUTLINE

Psychiatric disorders occur commonly during pregnancy, but their prevalence is often underestimated and underappreciated. Women have higher rates than men of many psychiatric disorders, such as anxiety, feeding and eating disorders, and depression; the reproductive years coincide with the greatest period of risk.[1] Management can be difficult and may be complicated by variable presentation of symptoms, social stigmas, confusion with normal symptoms of pregnancy, and inconsistent published treatment recommendations. Further, pregnant women with psychiatric disorders may resist drug treatment because of their desire to avoid fetal harm. Psychiatric disorders during pregnancy may be associated with other aspects of poor maternal health and deficient prenatal care, which may have an impact on anesthesia care.[2] Women with a history of previous psychiatric hospitalization or an identified mental illness are at increased risk for cesarean delivery.[3]

CLASSIFICATION

Internationally, psychiatric disorders are most commonly classified according to the *International Statistical Classification of Diseases and Related Health Problems (ICD)*, produced by the World Health Organization; the current version is *ICD-10* and is available on the Internet.* In the United States, a clinical modification of *ICD* is used; the latest version, *ICD-10-CM*, is due for implementation on October 1, 2014, and is also available on the Internet.† Although in the United States *ICD* is the official diagnostic system for mental disorders, the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, published by the American Psychiatric Association (APA), is widely used; the current version is *DSM-5*.[4] These classification systems provide standardized language and criteria for diagnosis and classification of mental disorders, but it should be noted that definitions may not have precise boundaries and may not cover all situations, and there may be considerable overlap between "mental" and "physical" disorders.[4]

EPIDEMIOLOGY

Estimates of the prevalence of psychiatric disease in pregnancy vary. It has been estimated that more than 500,000 pregnancies each year in the United States involve women who have a psychiatric illness that either predates or emerges during pregnancy[1] and that 14% to 23% of pregnant women will experience a depressive disorder during pregnancy.[5] Importantly, data from the *Confidential Enquiries into Maternal Deaths in the United Kingdom*[6]

*http://apps.who.int/classifications/icd10/browse/2010/en#/V

†http://www.cdc.gov/nchs/icd/icd10cm.htm#icd2014

have consistently highlighted suicide as a major indirect cause of maternal death.

Pregnancy is widely considered a time of increased vulnerability to psychiatric disorders. However, a large national epidemiologic survey in the United States found that although the prevalence of disorders was high among pregnant women, pregnancy itself was not associated with an increased risk; the results were thought to reflect a general increase in risk for psychiatric disorders in women during the childbearing years.[2] A conspicuous exception was the risk for major depressive disorder, which appears to be increased during the postpartum period. Identified risk factors for developing psychiatric disorders during pregnancy include younger age, unmarried status, exposure to traumatic or stressful life events, pregnancy complications, and poor overall health. The survey also noted that treatment rates among pregnant women with psychiatric disorders were very low.

MOOD DISORDERS

Mood disorders include depressive disorders and bipolar disorders ("manic-depressive disorders").[4]

Major Depressive Disorder

Box 51-1 includes diagnostic criteria for major depressive disorder. Although depression is recognized as being relatively common during pregnancy, many of its symptoms (e.g., weight gain, appetite changes, sleep disturbances, fatigue) must be differentiated from symptoms that may occur during normal pregnancy. Risk factors for depression during pregnancy include a history of depression or bipolar disorder, childhood mistreatment, being a single mother or having more than three children, marital problems, unwanted pregnancy, smoking, low income, age younger than 20 years, poor social support, and domestic violence.[7,8] The risk for major depressive illness is increased in women who have a miscarriage (i.e., spontaneous abortion); this most frequently occurs in the first month after miscarriage and is more likely to occur in women who are childless or who have a prior history of major depressive disorder.[9] Depression during pregnancy is associated with an increased risk for poor obstetric outcomes such as miscarriage, preterm birth, and low birth weight.[10]

Bipolar (Manic-Depressive) Disorder

Patients with bipolar disorder (BPD) have episodes of major depression with other distinct periods of mania or hypomania. A strong familial association exists. Diagnostic criteria for mania are summarized in Box 51-2. BPD in pregnancy is particularly important because there is a strong link between discontinuation of medication and relapse of BPD and a relatively high suicide rate among patients. Treatment of BPD typically consists of mood stabilizer and antipsychotic medication, with psychotherapy as an adjunct.[11] Electroconvulsive therapy (ECT) is very effective for patients with BPD and severe depression.

BOX 51-1 Diagnostic Criteria for Major Depressive Episode

- Five or more of the following symptoms present in the same 2-week period, representing a change from previous functioning, and including at least either number 1 or 2:
  1. Depressed mood most of the day, nearly every day
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
  3. Significant weight loss when not dieting, or weight gain, or a decrease or increase in appetite nearly every day
  4. Insomnia or hypersomnia nearly every day
  5. Psychomotor agitation or retardation nearly every day
  6. Fatigue or loss of energy nearly every day
  7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
  9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- In addition, symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and should not be a result of the physiologic effects of a substance. The episode should not be better explained by schizoaffective disorder, schizophrenia, or schizophrenia-related or other psychotic disorders, and there should never have been a manic or hypomanic episode.

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Postpartum Depression

Postpartum depression describes a major depressive episode that occurs in the first 4 to 6 weeks after birth. Symptoms do not differ from those of depression occurring at other times. There may be accompanying psychotic features, which are thought to be more common in nulliparous women,[4,12] and there is a high risk for recurrence in subsequent pregnancies. It is important to differentiate postpartum depression from the "baby blues," which affects up to 70% of women in the first 10 days after delivery and is transient without functional impairment. It is also important to differentiate postpartum depression from delirium that arises from physical causes.[4] In a systematic review, Robertson et al.[13] showed that the strongest predictors of postpartum depression were (1) depression, anxiety, or stressful life events occurring during pregnancy or the early puerperium; (2) low levels of social support; and (3) previous history of depression. Biologic effects such as hormonal changes and psychologic and social role changes that occur with childbirth may increase the risk for postpartum depression.[14]

BOX 51-2 Diagnostic Criteria for Manic Episode

- A distinct period when there is abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy, that lasts at least 1 week and is present most of nearly every day, or requires hospitalization
- Concurrent occurrence of three or more of the following symptoms:
  1. Inflated self-esteem or grandiosity
  2. Decreased need for sleep
  3. More talkative than usual (pressured speech)
  4. Flight of ideas or racing thoughts
  5. Distractibility
  6. Increased goal-directed activity or psychomotor agitation
  7. Excessive involvement in pleasurable activities with a high potential for painful or negative consequences
- Symptoms should be severe enough to cause marked impairment in occupational functioning, social activities, and interpersonal relationships and necessitate hospitalization or have psychotic features. Symptoms should not meet criteria for mixed episode and should not be caused by substance abuse or general medical conditions (e.g., hyperthyroidism).

From American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Postpartum Psychosis

Postpartum psychosis occurs within 2 weeks of approximately 1 to 2 per 1000 live births; a relatively high risk continues for the first 3 months postpartum.[15] The risk is higher in patients with a history of BPD or a history of previous postpartum psychosis,[16] as well as in women with major depression and schizophrenia. Typical features include prominence of cognitive symptoms such as disorganization, confusion, impaired sensorium, disorientation, and distractibility.[15] Infanticide may be associated with command hallucinations to kill the infant or delusions that the infant is possessed.[12]

ANXIETY DISORDERS

Anxiety disorders affect women twice as often as men and are the most common psychiatric disorders during pregnancy and the postpartum period.[17] There is a wide range of anxiety disorders, including **panic disorder**, **separation anxiety disorder**, **selective mutism**, **specific phobia**, **social anxiety disorder**, **agoraphobia**, **generalized anxiety disorder**, **substance /medication-induced anxiety disorder**, **anxiety disorder due to another medical condition**, **other specified anxiety disorder**, and **unspecified anxiety disorder**. Closely related to anxiety disorders are **trauma- and stressor-related disorders**, which includes **post-traumatic stress disorder**, and **obsessive-compulsive disorder**.[4] Clinical features of anxiety disorders in pregnant women are similar to those in nonpregnant women, but concern about the pregnancy and the fetus may be the predominant feature.[18]

Panic Disorder

Panic disorder is characterized by the occurrence of recurrent, unexpected panic attacks. Affected women experience discrete episodes of intense fear or discomfort in the absence of a true danger; these episodes are accompanied by somatic or cognitive symptoms such as palpitations, sweating, shaking, dyspnea, choking, chest pain, nausea, paresthesias, chills, and/or flushes. Typically there is a rapid onset and peak of symptoms that may be accompanied by an urge to escape.[4] It is important to be aware of the possibility that panic attacks may occur during preparation of a patient for cesarean delivery. Panic attacks with hyperventilation may mimic systemic local anesthetic toxicity.[19] A possible role of lactated Ringer's solution as a trigger has been refuted.[20] Patients with panic disorder often have co-morbid major depression.[17]

Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) occurs after the experience of a traumatic event that evokes intense fear or helplessness.[1] Pregnancy and childbirth may exacerbate symptoms of PTSD. Symptoms of PTSD are more common after emergency cesarean delivery than after other modes of delivery,[21] and PTSD has resulted from (1) awareness during general anesthesia,[22] (2) inadequate regional anesthesia for cesarean delivery,[23] and (3) inadequate pain control during vaginal delivery.[23] The risk for PTSD may be increased if the pregnancy has resulted from rape or if memories of sexual trauma are triggered. It has been suggested that the childbirth experience itself can precipitate PTSD with a resulting fear of pregnancy termed *tocophobia*.[1] Fear of vaginal delivery may be a factor that contributes to maternal request for cesarean delivery.[21]

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions (intrusive thoughts or images) and compulsions (repetitive or ritualistic behaviors or thought patterns).[17] Pregnancy is a potential trigger of the onset of symptoms.[1] Classically, pregnant women with OCD may focus on protection of the fetus, which may manifest as cleaning and checking compulsions.[18] Care should be taken to identify infanticidal ideation.[17]

FEEDING AND EATING DISORDERS

There are conflicting data on the effect of pregnancy in patients with feeding and eating disorders, which include **anorexia nervosa** and **bulimia nervosa** as well as **pica**, **rumination disorder**, **avoidant/restrictive food intake disorder**, **binge-eating disorder**, **other specified feeding or eating disorder**, and **unspecified**

feeding or eating disorder.[4] Improvement in symptoms during pregnancy has been described, but conversely, pregnancy may result in body image preoccupations and unfavorable eating habits that may develop into a frank eating disorder.[15] Although fertility is reduced in patients with anorexia nervosa, patients may still conceive. Patients with eating disorders have a higher risk for psychiatric comorbidity, including anxiety and postpartum depression,[1] and are at greater risk for cesarean delivery.[15]

SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDERS

These disorders include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. Defining features include abnormalities in one or more of the following areas: hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms.[4] In **schizophrenia**, the disorder lasts for at least six months, with at least one month of active symptoms.[4]

Limited data are available on the course of psychotic disorders in pregnancy; both deterioration and improvement have been reported. The postpartum period is thought to be a high-risk period for relapse.[15] Compared with women without psychotic disorders, pregnant women who have psychotic disorders often receive less prenatal care; have poorer nutrition; exhibit greater use of tobacco, alcohol, and illicit drugs; and have higher rates of obstetric interventions and obstetric complications.[1,15] Fear of loss of child custody may result in underreporting of symptoms.[15]

OTHER DISORDERS

Personality Disorders

Personality disorders have high prevalence rates of approximately 10% in the general population and up to 40% among psychiatric patients.[24] The *DSM 5* lists 10 specific personality disorders that are grouped into three clusters based on descriptive similarities. Patients in cluster A **(paranoid, schizoid, schizotypal)** appear odd or eccentric; patients in cluster B **(antisocial, borderline, histrionic, narcissistic)** appear dramatic, emotional, or erratic; and patients in cluster C **(avoidant, dependent, obsessive-compulsive)** appear anxious and fearful.[4] There is also one further category, **personality disorder not otherwise specified**. The *DSM-5* also provides an alternative dimensional model for personality disorders based on both personality functioning and pathologic personality traits that takes the perspective that personality disorders represent maladaptive variants of personality traits that merge into normality and into one another.[4] This accounts for the observation that patients who meet criteria for a specific personality disorder frequently also meet criteria for other personality disorders.[4]

Pseudocyesis

Pseudocyesis is a clinical syndrome in which a woman firmly believes that she is pregnant in the absence of a true gestation. Patients may develop convincing signs and symptoms suggestive of pregnancy, including abdominal enlargement and menstrual disturbance.[25] Diagnosis can be made using a pregnancy test and ultrasonography. Physical diagnoses should be excluded. For example, tumors such as bronchogenic carcinoma may produce hormones (e.g., human chorionic gonadotrophin [hCG]) that can cause secondary amenorrhea, which may be confused with pregnancy.[26]

Denial of Pregnancy

In contrast to pseudocyesis, denial of pregnancy is more common, with an estimated incidence of 1 in 400 to 516 pregnancies.[27] It may be associated with adverse outcomes, including psychological stress, unassisted delivery, and infanticide. Patients who are identified should be referred for psychiatric assessment.[27]

Substance Abuse

Substance abuse during pregnancy is covered in Chapter 54.

MANAGEMENT OF PSYCHIATRIC DISORDERS IN PREGNANCY

General Considerations

Treatment options for different psychiatric disorders overlap. Data are limited on pregnancy-specific efficacy, but, in general, response in pregnant patients is thought to be similar to that in nonpregnant patients.[1] There is often concern about potential harmful effects of psychotropic drugs given during pregnancy and lactation, particularly the potential for teratogenicity, perinatal syndromes, neonatal toxicity, and abnormal postnatal behavioral development.[12] Because of the difficulties of performing experimental studies in this area, inadequate data are available from randomized controlled trials, and much of the available information is based on observational studies, which provide a less-than-optimal level of evidence. Because many patients with psychiatric disorders also smoke or abuse illicit substances, it can be difficult to separate the effects of psychiatric drugs on the fetus from the effects of these other substances and other behavioral factors.[8] Further, because women who take medication for their psychiatric disorders are likely to have more severe disease than women who do not, some of the risks associated with psychiatric drugs may be attributable to factors associated with the more severe disease (i.e., confounding by indication).[7] These considerations are important because the risks of withholding psychiatric drugs in pregnancy must always be balanced against the risks and potential harm of exacerbation of psychiatric disorders that can result from cessation or withholding of treatment.

General recommendations for the management of women with psychiatric disorders include the following[6]: (1) a psychiatric history should be identified prenatally, and even if affected patients are well, they should be frequently monitored and supported during pregnancy and the first few weeks postpartum; (2) psychiatric services should have priority-care pathways for pregnant and postpartum women; and (3) care by multiple psychiatric teams should be avoided. Conversely, care should be taken to avoid misattribution of physical symptoms to psychological causes in patients with no psychiatric history and other concurrent disease. Consensus guidelines for the treatment of depression during pregnancy are available from the APA and the American College of Obstetricians and Gynecologists (ACOG).[14] The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has also published guidelines for antenatal and postnatal mental health.[28] All patients with psychiatric disorders, particularly those with acute or postpartum psychosis, should be carefully screened for thoughts of harm to themselves and/or their infants.

A multidisciplinary approach is essential in the management of pregnant patients with psychiatric disorders, especially because many anesthesia providers may not be familiar with management of these patients. Patients who are noncooperative or violent may be challenging and require patience, compassion, and emotional support. Flexibility in management is important. For example, general anesthesia may sometimes be required if neuraxial anesthesia is considered not practical or unsafe. Consent and medicolegal issues are covered in Chapter 33.

Psychotherapy and Light Therapy

These nonpharmacologic options are effective particularly for treatment of anxiety disorders and depression but are underinvestigated.[1] They have the advantage of nonexposure to potentially teratogenic drugs. Psychotherapy techniques include cognitive-behavioral therapy and interpersonal psychotherapy. A randomized controlled trial demonstrated that light therapy (fluorescent white light for 1 hour per morning for 5 weeks) improved antenatal depression compared with placebo.[29]

Psychotropic Drugs

Box 51-3 includes principles related to the use of psychiatric medications during pregnancy. The use of nonanesthetic drugs during pregnancy and lactation is discussed in Chapter 14.

Selective serotonin uptake inhibitors (SSRIs), which include **sertraline** (Zoloft), **paroxetine** (Paxil), **fluoxetine** (Prozac), and **citalopram** (Celexa) are a mainstay therapy for depression and anxiety. Some concerns have been raised about a possible association between their use in pregnancy and an increased risk for birth defects, although data are conflicting. In a large multicenter evaluation, Louik et al.[30] found no overall association between first-trimester maternal use of SSRIs and birth defects; however, analysis of individual drugs showed small but significant associations between the use of sertraline and omphalocele and cardiac septal defects and between the use of paroxetine and right ventricular outflow tract obstruction. Other studies have also found associations between use of SSRIs and these and other birth defects, including craniosynostosis, anencephaly, and persistent pulmonary hypertension of the newborn.[7] Exposure to SSRIs in the third trimester has been associated with an increased risk for perinatal complications, including preterm delivery, admission to the special care nursery, poor neonatal adaptation, and lower birth weight and length.[31] Of note, the absolute risk of exposure to SSRIs during pregnancy is considered to be small, and overall these drugs are not considered major teratogens.[12] However, the ACOG[12] has recommended that paroxetine should be avoided by pregnant women and women planning pregnancy, if possible, and fetal echocardiography should be considered for women who are exposed to paroxetine in early pregnancy. Serotonin syndrome (i.e., agitation, restlessness, hallucinations, increased body temperature, vomiting) may occur with an overdose or a combination of serotonergic drugs.[32]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of drugs related to SSRIs that are also considered relatively safe in pregnancy, although fewer reassuring data are available for this class of drug than for SSRIs.[7]

Tricyclic antidepressants have a long history of use and have generally been considered safe to use in pregnancy. However, a large review of data from the Swedish Medical Birth Registry reported that these drugs were associated with a greater risk for congenital malformations compared with other antidepressants.[33] Tricyclic antidepressants may have anticholinergic side effects,

BOX 51-3 General Principles Related to the Use of Psychiatric Drugs in Pregnancy

- All psychotropic drugs cross the placenta and pass into breast milk.
- The major time of risk for teratogenesis occurs during embryogenesis (i.e., 3 to 8 weeks' gestation).
- Use of a single medication at a higher dose (monotherapy) is preferred to use of multiple medications.
- Medications with fewer metabolites, higher protein binding, and fewer drug interactions are preferred.
- Discontinuing medication exchanges the fetal and neonatal risks of drug exposure for the risks of untreated maternal illness.
- Changing medication increases fetal drug exposure.
- Major concerns about use of psychotropic drugs in pregnancy include risks for morphologic teratogenicity, behavioral teratogenicity, and perinatal syndromes.
- Drug doses may need adjustment during pregnancy because of alteration in pharmacokinetics.

Modified from American College of Obstetrics and Gynecologists. Use of psychiatric medications during pregnancy and lactation. ACOG Practice Bulletin No. 92. Washington, DC, April 2008. (Obstet Gynecol 2008; 111:1001-20); and Levey L, Ragan K, Hower-Hartley A, et al. Psychiatric disorders in pregnancy. Neurol Clin 2004; 22:863-93.

especially after overdose; clinical features include dilated pupils, agitation, seizures, delirium, hyperthermia, and arrhythmias. The fatality risk after overdose is greater with most tricyclic antidepressants than with SSRIs. Tricyclic antidepressants have been largely replaced by SSRIs and SNRIs as first-line therapy for depression.

Routine prescription of **benzodiazepines** for pregnant women is typically avoided, except for short-term treatment of extreme anxiety and agitation, because of concern for risks including oral clefts, floppy baby syndrome, and neonatal withdrawal syndrome.[12,28] The risk for oral clefts is a matter of dispute.[12] If benzodiazepine use is discontinued during pregnancy, this should not be done abruptly.[12]

Lithium is a foundation therapy for management of BPD. Early studies reported that use of lithium in early pregnancy was associated with an increased risk for congenital malformations, with particular concern for cardiac abnormalities, especially Ebstein's anomaly. Although the risk now appears to be less than initially thought, it has been recommended that women who are exposed to lithium in the first trimester undergo fetal echocardiography. Exposure in later gestation has been associated with fetal and neonatal diabetes insipidus, polyhydramnios (thought to occur from fetal diabetes insipidus), thyroid dysfunction, cardiac arrhythmias, hypoglycemia, preterm delivery, and floppy baby syndrome.[12] Renal clearance of lithium is increased in pregnancy, and a reduced serum lithium concentration may result in a relapse of symptoms; therefore, serum levels should be closely monitored in pregnant women who are taking lithium. Discontinuation of lithium is associated with a high risk for recurrent illness, particularly in the postpartum period.

Anticonvulsant drugs are often used as mood stabilizers in patients with BPD. **Valproate** use in pregnancy is associated with an increased risk for many congenital anomalies (e.g., craniofacial, limb, cardiovascular abnormalities) and a variable risk for cognitive impairment.[1] A meta-analysis showed that the risk for neural tube defects in infants of mothers taking valproate was 3.8% and that the risk for major congenital malformations was dose-related, with the risk particularly high when the daily dose exceeded 1000 mg.[34] **Fetal valproate syndrome**, which includes fetal growth restriction (also known as intrauterine growth restriction), facial dysmorphology, and limb and heart defects, has been described.[12] **Carbamazepine** has also been associated with congenital abnormalities, although with less frequency or severity compared with valproate.[1] **Fetal carbamazepine syndrome**, which includes facial dysmorphism and fingernail hypoplasia, has been described.[12] **Lamotrigine** appears to be associated with less fetal risk than occurs with valproate and carbamazepine.[1,12] Folate supplementation is sometimes offered to patients taking anticonvulsants to reduce the risk for neural tube defects.

Typical antipsychotic drugs (e.g., **haloperidol, thioridazine, fluphenazine, perphenazine, chlorpromazine, trifluoperazine**) have a long history of use in pregnant patients and generally have minimal teratogenic effects.[12] The phenothiazines are also used for their antiemetic effects. Fetal and neonatal toxicity after maternal exposure can include dyskinesia, extrapyramidal side effects, neonatal jaundice, and postnatal intestinal obstruction. The **neuroleptic malignant syndrome** is of particular interest to anesthesia providers because of its similarity to malignant hyperthermia. Features include hyperthermia, rigidity, mental status alteration, creatine kinase elevation, sympathetic nervous system lability, tachycardia, and tachypnea.[35] Treatment is largely supportive and includes discontinuation of triggering agents, antipyretics, cooling, rehydration, and management of autonomic instability. Use of dantrolene, bromocriptine, and amantadine has been described.[32]

Atypical antipsychotic drugs (e.g., **clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole**) are now commonly used for schizophrenia and also for BPD, OCD, and resistant depression. Although these drugs are well tolerated, fewer data about reproductive safety are available, when compared with older drugs.

Drug Interactions

A number of drug interactions involving psychiatric drugs are relevant to anesthesia providers. The most important of these involve monoamine oxidase inhibitors (MAOIs), which include older irreversible drugs (e.g., phenelzine, tranylcypromine) and newer reversible drugs (e.g., selegiline, moclobemide). Potential interactions include (1) hypertension after administration of an indirect-acting vasopressor (e.g., ephedrine, metaraminol), which results from increased norepinephrine concentration in sympathetic nerve endings, and (2) excitatory interactions associated with serotonin toxicity. The latter are characterized by clonus, hyperreflexia, hyperthermia, and agitation and may be precipitated by co-administration of an MAOI and a serotonin uptake inhibitor. Of note, phenylpiperidine opioids, especially meperidine (pethidine), but also tramadol, methadone, and dextromethorphan, are weak serotonin uptake inhibitors and have been implicated in toxic reactions associated with MAOIs, including hyperpyrexic coma. Irreversible MAOIs should be stopped 2 weeks before administration of anesthesia to allow regeneration of MAO and restoration of normal monoamine metabolism, and reversible MAOIs should be stopped for 24 hours before administration of anesthesia.[36]

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is considered an important treatment option in the pregnant patient with psychiatric disease, especially when balancing the risk for morbidity from psychiatric illness and the potential adverse effects of psychiatric drugs. The APA has endorsed the use of ECT in all three trimesters of pregnancy.[37] Indications include major unipolar or bipolar depressive episodes, mania, and certain acute schizophrenia exacerbations. Acute suicide risk, poor response to medications, and patient preference may also affect the decision to use ECT.[38] Contraindications include anticipated intolerance of associated physiologic

BOX 51-4 Suggested Guidelines for Electroconvulsive Therapy during Pregnancy

- Obtain preoperative obstetric consultation.
- Monitor fetal heart rate and check for uterine contractions before and after the procedure.
- Ensure adequate hydration.
- Maintain left uterine displacement after 18 to 20 weeks' gestation.
- Consider pharmacologic aspiration prophylaxis and tracheal intubation in patients with symptoms of gastroesophageal reflux.
- Observe for vaginal bleeding after the procedure.

Modified from Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry 1994; 45:444-50.

changes that result from autonomic activation during ECT (e.g., increased intracranial pressure). Relative contraindications include hypertensive disease and impaired uteroplacental perfusion.

There is a paucity of controlled data evaluating the use of ECT in pregnancy, with most information coming from case series. In a series of 300 published cases of ECT in pregnancy between 1942 and 1991, Miller[39] reported complications in 28 (9.3%) cases, which included self-limited fetal heart rate abnormalities (five cases), vaginal bleeding, uterine contractions, abdominal pain, spontaneous abortion, preterm labor, stillbirth, and neonatal death. The overall incidence of spontaneous abortion was 1.6%—a rate much lower than that in the general population—suggesting that ECT is not a significant risk factor for spontaneous abortion. There were five cases of congenital anomalies, but neither the pattern nor the number of anomalies suggested that ECT was a determining factor. The author concluded that ECT was effective and that the risks to both mother and fetus are low. However, Pinette et al.[40] reported a case of deep cerebral interhemispheric infarcts in a neonate whose mother had received ECT during pregnancy. After a review of fetal and neonatal risks, the authors recommended that ECT in pregnancy should be performed specifically according to APA guidelines and only after medical therapy has failed.

ECT for pregnant patients should be administered in a facility that can handle fetal emergencies. Anesthetic agents commonly used during ECT include barbiturates, succinylcholine, and anticholinergics (e.g., glycopyrrolate); these agents have a long history of use during pregnancy. Suggested guidelines for ECT during pregnancy are summarized in Box 51-4. These guidelines include left uterine displacement and both fetal heart rate and uterine monitoring. Pharmacologic aspiration prophylaxis and tracheal intubation should be considered in patients with symptoms of gastroesophageal reflux. Some anesthesia providers contend that tracheal intubation should be performed after 20 weeks' gestation, when the enlarging uterus has arisen out of the pelvis.

KEY POINTS

- Psychiatric disorders occur commonly during pregnancy, but their prevalence is often underestimated and underappreciated.
- The risk for major depressive disorder is increased during the postpartum period.
- Anxiety disorders are the most common psychiatric disorders in pregnant women.
- When managing pregnant patients with psychiatric disorders, the risks of withholding psychiatric drugs because of concerns for teratogenic or other harmful effects on the fetus must be balanced against the risks and potential harm for exacerbation of psychiatric disorders.
- Patients with a previous psychiatric history should be identified prenatally and frequently monitored and supported during pregnancy and the first few weeks postpartum. Psychiatric services should have priority-care pathways for pregnant and postpartum women, and care by multiple psychiatric teams should be avoided.
- A multidisciplinary approach is essential in the management of pregnant patients with psychiatric disorders.
- Awareness during general anesthesia for cesarean delivery, inadequate neuraxial anesthesia for cesarean delivery, and poor pain control during vaginal delivery may result in post-traumatic stress disorder in susceptible patients.
- Anesthesiologists should be aware of potential drug interactions with psychotropic drugs.
- The use of electroconvulsive therapy has been endorsed for selected psychiatric conditions in all three trimesters of pregnancy.

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CHAPTER 47

Malignant Hyperthermia

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CHAPTER OUTLINE

Malignant hyperthermia (MH) is an inherited disorder of skeletal muscle. On exposure to triggering agents (e.g., succinylcholine, volatile halogenated anesthetic agents), affected individuals demonstrate a hypermetabolic syndrome characterized by hypercapnia, acidosis, muscle rigidity, arrhythmias, and hyperthermia. MH was first described in 1960 by Denborough and Lovell,[1] but may have been responsible for some of the earlier deaths attributed to ether and chloroform anesthesia.[2]

EPIDEMIOLOGY

Ørding,[3] reviewing the incidence of MH in Denmark, noted that the incidence of the fulminant syndrome (e.g., muscle rigidity, acidosis, hyperkalemia, arrhythmias, hyperthermia, increased creatine kinase [CK] levels, myoglobinuria) was 1 in 220,000 patients who received general anesthesia and 1 in 62,000 patients in whom succinylcholine was combined with a volatile halogenated agent. MH (either mild or fulminant) was suspected in 1 in 16,000 patients who received anesthesia of any type. The male-to-female ratio was 1.4:1.[3] There is some geographic variation in the incidence of MH.[4]

There are few reports of development of MH during pregnancy and parturition.[5-12] The infrequent occurrence during pregnancy probably reflects both the low frequency of this disorder in the general population and the widespread use of local and neuraxial anesthetic techniques in obstetric patients.

PATHOPHYSIOLOGY

MH is the result of a disorder in the regulation of intracellular calcium in skeletal muscle. The precise mechanism by which volatile anesthetics and depolarizing muscle relaxants cause an MH crisis is still unknown.[13] In muscle the sarcoplasmic reticulum is responsible for controlling calcium release and reuptake during muscle contraction.[14] During skeletal muscle excitation-contraction coupling, calcium is released from the terminal sarcoplasmic reticulum via the **ryanodine receptor** (RYR1). Dihydropyridine receptors in the T-tubule membrane also participate in the excitation-contraction coupling. In humans, mutations in both the dihydropyridine receptor and the ryanodine receptor can result in clinical MH. Dantrolene inhibits excitation-contraction coupling, and succinylcholine, caffeine, and volatile halogenated agents increase it.

GENETICS

MH is a heterogeneous disorder, meaning that more than one gene defect is responsible for expression of the clinical syndrome.[15] It is inherited in an autosomal dominant fashion with variable penetrance, although this pattern has been questioned in some families.[16] Porcine MH is transmitted as a recessive gene. The defective gene in MH-susceptible pigs has been localized to a single point

BOX 47-1 Triggers for Malignant Hyperthermia

- Volatile anesthetic agents
  - Sevoflurane
  - Desflurane
  - Isoflurane
  - Halothane
  - Enflurane
- Succinylcholine

BOX 47-2 Signs and Symptoms of Malignant Hyperthermia

- Tachycardia
- Tachypnea
- Masseter spasm
- Generalized rigidity
- Elevated end-tidal CO_2 concentration
- Cyanosis
- Arrhythmias
- Acidosis
- Hyperkalemia
- Hyperpyrexia
- Myoglobinuria
- Increased creatine kinase level

mutation in the ryanodine receptor gene (*RYR1*) responsible for the calcium release channel.[17]

Investigators have found the corresponding point mutation on the human ryanodine receptor gene (*RYR1*) in some families with MH (chromosome 19q12.1-13.2; locus MHS-1), and other mutations in *RYR1* have been linked to MH susceptibility.[18] Other point mutations in *RYR1* are found in patients with central core disease, a myopathy associated with MH.[19] As of 2011, more than 200 *RYR1* mutations associated with MH had been identified.[15] Mutations responsible for MH in some families are located on chromosomes 5p, 17, 7q, 3q, and 1q.[20] Other myopathies may be characterized by a hyperthermic state with muscle damage and metabolic derangements similar to those seen in MH, but their chromosomal abnormality has not been mapped to the same area.[15]

TRIGGERS

Known triggers of MH include the depolarizing muscle relaxants (e.g., succinylcholine) and all the volatile halogenated anesthetic agents (i.e., sevoflurane, desflurane, isoflurane, halothane, enflurane) (Box 47-1). The dose and duration of exposure to the triggering agent may influence the onset and severity of a reaction. Previous uneventful administration of general anesthesia with triggering anesthetic agents does not rule out the diagnosis of MH.[21]

In contrast to the porcine model, reports of stress-induced MH in humans are rare.[22-28] In one report two cases of fatal, stress-induced MH occurred in unrelated families[26]; both children had a known *RYR1* mutation and one had a second mutation, possibly suggesting an additive effect.[29] The sympathetic nervous system is active during an episode of acute MH, but there is insufficient evidence to implicate increased sympathetic activity as a cause in humans. Although muscle biopsy testing may help distinguish MH from exercise-induced myolysis, exertional heat stroke, and other myopathies, there is some evidence of a link between some cases of heat stroke and exercise-induced rhabdomyolysis and MH susceptibility.[30]

Investigators have explored other possible triggers of MH both in the porcine model and in humans. No evidence suggests that exogenous calcium, digoxin, hypercarbia, potassium,[31] or norepinephrine[32] triggers MH. Exercise[33] and environmental temperature[34-36] may intensify an existing reaction or modify a developing reaction. Sodium thiopental and pancuronium delay the onset in pigs and may modify the reaction in humans.[37] Duke et al.[38] postulated that hypomagnesemia may increase the probability and severity of an MH event in MH-susceptible humans.

There are case reports of the occurrence of MH during regional anesthesia and during general anesthesia with nontriggering agents.[39-43] The cases that occurred during regional anesthesia appeared mild and responded readily to treatment. In some cases, however, the diagnosis was not confirmed with muscle biopsy or appropriate laboratory investigation at the time of the event.

CLINICAL PRESENTATION

Individuals who are MH-susceptible may demonstrate the fulminant syndrome when anesthetized with a triggering agent. During an acute episode, the diagnosis is based on the finding of an elevated end-tidal CO_2 concentration, muscle rigidity (generalized and/or masseter), respiratory and metabolic acidosis, rhabdomyolysis, hyperkalemia, elevated CK concentration, and myoglobinuria (Box 47-2). Hypoxemia, unstable blood pressure, and evidence of sympathetic hyperactivity (e.g., tachycardia, hypertension, arrhythmias) are other signs. Hyperthermia may occur early, but often it is a late sign. Perioperative rhabdomyolysis, without any of the previously mentioned clinical signs, also may indicate MH susceptibility.[44,45]

With the advent of routine end-tidal CO_2 monitoring, MH may be detected early, often before the development of rhabdomyolysis and hyperthermia.[46] This situation may lead to uncertainty about the clinical diagnosis of MH, given that many of the confirmatory signs and laboratory abnormalities may be absent during the early phase of MH. Thus, early treatment of possible MH could present a dilemma as to whether the patient should undergo diagnostic muscle biopsy or should be assumed to be MH susceptible.

Masseter Muscle Rigidity

Masseter muscle rigidity is one of the early signs of MH.[46] The masseter muscles are sensitive to the action of succinylcholine and respond with increased tension in normal individuals.[47,48] Often this tension is imperceptible, but in some patients it is impossible to open the mouth for laryngoscopy and intubation. The duration of rigidity parallels the duration of action of succinylcholine. Typically there is no difficulty with mask ventilation. Masseter muscle rigidity rarely occurs after the use of nondepolarizing muscle relaxants such as rocuronium and vecuronium.[49] Patients with myopathies and other neuromuscular disorders also may have masseter muscle rigidity after the administration of succinylcholine.[50]

If masseter muscle rigidity is accompanied by generalized rigidity, anesthesia should be discontinued, dantrolene should be administered, and the patient should be monitored closely.[51] However, there is controversy regarding the management of isolated masseter muscle rigidity.[52] Options include (1) discontinuation of the anesthetic agents and administration of dantrolene; (2) continuation of anesthesia with nontriggering, "safe" agents and close attention to the end-tidal CO_2 concentration; and (3) continuation of anesthesia with triggering agents and careful monitoring. In my judgment, the anesthesia provider should either discontinue anesthesia altogether or continue anesthesia with nontriggering agents. If the anesthesia is continued, the minute ventilation, end-tidal CO_2 concentration, electrocardiogram (ECG), temperature, and arterial blood gas measurements should be monitored. The anesthesia provider also should look for evidence of rhabdomyolysis by monitoring CK levels and looking for myoglobinuria, and should recommend that the patient undergo muscle biopsy and caffeine-halothane contracture test (see later discussion).[53]

DIAGNOSIS

Investigators have correlated clinical presentation (i.e., evidence of metabolic and muscle derangements) with abnormal contracture on the caffeine-halothane contracture test.[54-56] The greater the number of clinical signs or abnormal laboratory findings, the greater the risk for MH (Table 47-1).[54] An early assessment of the risk for MH allows the anesthesia provider to initiate appropriate treatment. The mortality rate for MH is as high as 80% without dantrolene therapy.[56] Early administration of dantrolene lowers the mortality rate to 4%.[57]

An international group of experts has developed a clinical grading scale to predict MH susceptibility.[58] This scale consists of six processes (rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, family history) and their clinical indicators. Points are assigned for each indicator present in a patient, and the total represents a raw score. A rank is subsequently assigned to this score, which indicates the likelihood of development of MH in the patient.

TABLE 47-1 Risk for Malignant Hyperthermia (MH) with Associated Signs and Symptoms

Type	Symptoms/Signs	Risk
Fulminant/classic	Metabolic acidosis Muscle rigidity Hyperthermia (> 38.5° C) Arrhythmias Hyperkalemia Myoglobinuria Increased creatine kinase level	0.96
Moderate	Inconclusive signs of MH involving metabolic and muscle abnormalities, with MH the probable diagnosis	0.88
Mild	Signs of metabolic derangement (pH > 7.3, body core temperature < 38.5° C)	0.14
Masseter spasm with rhabdomyolysis	Creatine kinase level > 1500 U/L, myoglobinuria	0.76
Masseter spasm with signs of metabolic disturbance	Arrhythmias, rising core temperature	0.57
Masseter spasm only		0.28
Unexplained perioperative death or cardiac arrest		0.66
Other	Postoperative pyrexia or rhabdomyolysis	0.07

Data from Ellis FR, Halsall PJ, Christian AS. Clinical presentation of suspected malignant hyperthermia during anaesthesia in 402 probands. Anaesthesia 1990; 45:838-41.

TESTING

Susceptibility to MH is determined by a positive caffeine-halothane contracture test result. During this test, fresh muscle is exposed to halothane and caffeine, and the extent of contraction is measured. The caffeine-halothane contracture test has been standardized in MH testing centers throughout North America (the North American protocol)[59] and Europe (the European protocol is called the *in vitro* contracture test).[60] This test is the "gold standard" for the diagnosis of MH. The sensitivity and specificity of the North American protocol are 97% and 78%, respectively.[61] Some false-positive results may occur.[62] Patients with a negative caffeine-halothane contracture test result subsequently have received anesthesia with triggering agents without incident.[63-66]

Testing for the known genetic mutations associated with MH is now available. However, because all the genetic mutations responsible for MH have yet to be identified, genetic testing is still not sensitive enough to use for routine screening.[67] In the future, MH may be detected in most MH-susceptible patients without the need for an invasive muscle biopsy.[67] In the absence of muscle biopsy results, a parturient with a positive family history should be treated as if she were MH susceptible.

PREGNANCY AND MALIGNANT HYPERTHERMIA

In 1972, Crawford[68] wondered "whether or not there was a record of a pregnant or newly born patient or animal having developed hyperpyrexia and … whether hyperpyrexia has been encountered in a patient undergoing an operation under regional block anesthesia." Subsequently there have been few reports of MH during parturition and fewer reports of maternal mortality attributable to MH. Wadhwa[5] reported the death of a woman with a known family history of MH in whom muscle rigidity developed during twilight sleep for parturition. Douglas et al.[6] reported one fatal case of MH in a parturient undergoing general anesthesia for cesarean delivery.

There are three published reports[7-9] of nonfatal MH during cesarean delivery and one report of MH after cesarean hysterectomy performed because of postpartum hemorrhage.[12] The triggering agents were succinylcholine and halothane,[7] succinylcholine and isoflurane,[12] cyclopropane,[8] and succinylcholine alone (without a volatile halogenated agent).[9] There are several reports of the successful administration of epidural and spinal anesthesia during labor and cesarean delivery in MH-susceptible parturients.[5,12,69-76]

Although it is unclear whether pregnancy alters susceptibility to MH, the rarity of MH events during pregnancy suggests that pregnancy protects against the occurrence of MH. However, it also may reflect the widespread use of neuraxial anesthesia for labor, vaginal delivery, and cesarean delivery.

Maternal Physiology

Basal metabolic rate, oxygen consumption, and minute ventilation increase during pregnancy (see Chapter 2). Serum bicarbonate, buffer base, and base excess decrease to maintain normal pH. Thus, the pregnant patient typically has a compensated respiratory alkalosis. The reduced buffering capacity could adversely affect the pregnant woman during an episode of MH.

Oxygen consumption and minute ventilation increase further during labor. Maternal lactate and pyruvate concentrations increase steadily during labor, indicating an increase in both aerobic and anaerobic metabolism. Hyperventilation during contractions may result in periods of hypoventilation between contractions, which may adversely affect the Pao_2 of both the mother and the fetus. These metabolic and physiologic responses to pain are similar to the metabolic and physiologic changes that are observed during acute MH. Effective epidural analgesia decreases oxygen consumption and minute ventilation. If tachycardia and hyperventilation occur despite effective analgesia, they are more likely to signal an episode of MH.

Aortocaval compression from the pregnant uterus results in decreased cardiac output, hypotension, and reduced uteroplacental perfusion. Thus, aortocaval compression may accelerate the occurrence of acidosis during an episode of MH. Aortocaval compression hinders resuscitative efforts during cardiac arrest, and evacuation of the uterus (i.e., delivery of the fetus) facilitates maternal resuscitation.[77] The obstetrician may need to deliver the fetus to facilitate maternal resuscitation during a fulminant case of MH.

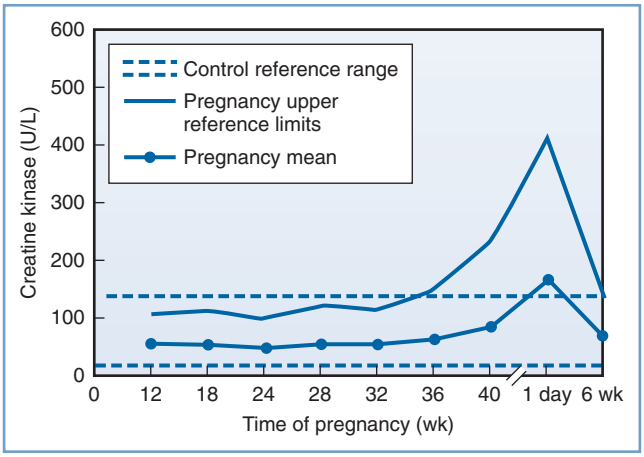

FIGURE 47-1 ■ Changes in creatine kinase activity during and after pregnancy. (Modified from Lockitch G, editor. Handbook of Diagnostic Biochemistry and Hematology in Normal Pregnancy. Boca Raton, FL, CRC Press, 1993:59.)

CK concentrations are not diagnostic of MH. During pregnancy, there is a slight decrease in CK levels during the first trimester. CK levels remain stable until term, when they increase by approximately 50%. At delivery, there is an abrupt rise in the CK concentration, followed by a return to normal by 6 weeks postpartum (Figure 47-1).[78] The increased CK concentration results from increases in both the CK-M fraction (skeletal muscle) and the CK-B fraction (myometrium, placenta, and fetal blood). Postpartum CK levels are higher in nulliparous women regardless of differences in duration of labor.[79] Mean plasma CK activity is approximately 50% higher in African-Americans than in Caucasians or Asians.[78]

Acute cocaine toxicity may mimic MH. Although cocaine does not induce contractures in MH-susceptible muscle,[80] elevated CK concentrations and myoglobinemia can occur secondary to rhabdomyolysis and renal failure from cocaine intoxication.[81] Umbilical cord blood CK and myoglobin levels are elevated when cocaine metabolites are present in maternal urine.[82]

Effects on the Fetus and Newborn

MH often is inherited as an autosomal dominant gene. In these cases there is a 50% chance that the infant of an MH-susceptible parent will also be MH susceptible. All anesthetic agents cross the placenta. Small quantities of succinylcholine also cross the placenta. This knowledge should prompt the anesthesia provider to question the choice of anesthetic agents for an MH-negative mother whose fetus has an MH-susceptible father. In this situation, the anesthesia provider should avoid the use of triggering agents until after delivery.[83]

There is only one published report of suspected MH in a newborn.[84] The condition is rare in infancy, and some

TABLE 47-2 **Common Anesthetic Drugs and Their Safety in Malignant Hyperthermia–Susceptible (MHS) Women**

Drug	Route	Use	Safe in MHS Women
Local Anesthetic Agents			
Bupivacaine	Neuraxial	Analgesia/anesthesia	Yes
Lidocaine	Neuraxial	Analgesia/anesthesia	Yes
	Intravenous	Arrhythmia	Yes
Ropivacaine	Neuraxial	Analgesia/anesthesia	Yes
2-Chloroprocaine	Neuraxial	Analgesia/anesthesia	Yes
Opioids			
Fentanyl	Neuraxial, intravenous	Analgesia	Yes
Sufentanil	Neuraxial, intravenous	Analgesia	Yes
Meperidine	Neuraxial, intravenous	Analgesia	Yes
Morphine	Neuraxial, intravenous	Analgesia	Yes
Sedative-Hypnotics			
Propofol	Intravenous	Induction of anesthesia	Yes
Sodium thiopental	Intravenous	Induction of anesthesia	Yes
Etomidate	Intravenous	Induction of anesthesia	Yes
Ketamine	Intravenous	Induction of anesthesia, analgesia	Yes
Benzodiazepines	Intravenous	Amnesia, anxiolysis	Yes
Neuromuscular Blocking Agents			
Succinylcholine	Intravenous	Muscle relaxation	No
Rocuronium	Intravenous	Muscle relaxation	Yes
Cis-atracurium	Intravenous	Muscle relaxation	Yes
Vecuronium	Intravenous	Muscle relaxation	Yes
General Anesthetic Agents			
Sevoflurane, desflurane, isoflurane, halothane, enflurane	Inhalation	Anesthesia, uterine relaxation	No
Nitrous oxide	Inhalation	Analgesia/anesthesia	Yes

reports of infant MH may represent undiagnosed myopathy.[50,85,86]

MANAGEMENT OF THE MALIGNANT HYPERTHERMIA–SUSCEPTIBLE PARTURIENT

Ideally, an anesthesiologist will evaluate every MH-susceptible pregnant patient before she is hospitalized for labor and delivery. Clearly, the obstetrician should consult an anesthesia provider immediately after the admission of each MH-susceptible patient. All hospitals and birthing facilities should be prepared to provide care for MH-susceptible patients. Adequate supplies of dantrolene (at least 36 vials), sterile water, and sodium bicarbonate should be immediately available.

Analgesia for Labor

Soon after admission, a large-gauge intravenous catheter should be placed in each MH-susceptible patient. Maternal temperature, heart rate, and blood pressure should be monitored throughout labor. During early labor, it may be acceptable to monitor temperature and heart rate intermittently to facilitate maternal ambulation, if desired. Once active labor is established, frequent monitoring of the maternal heart rate and temperature should be initiated. Continuous ECG and axillary temperature monitoring are ideal once the parturient is confined to bed. (Measurement of axillary temperature allows placement of a temperature probe in close proximity to large muscle groups.) Of course, aortocaval compression should be avoided throughout labor and delivery.

Most agents used for intrapartum analgesia are considered safe in the MH-susceptible parturient (Table 47-2). Both the obstetrician and the anesthesia provider should encourage the early administration of neuraxial analgesia. Relief of pain reduces maternal stress (as reflected by decreased catecholamine,[87] cortisol,[88] and adrenocorticotropic hormone [ACTH] concentrations), and decreases maternal metabolism and oxygen consumption.[89] Although experts continue to debate the role of stress in human MH,[90,91] it is best to diminish stress when possible. Further, the anesthesia provider may extend epidural analgesia for vaginal or cesarean delivery if necessary, thus avoiding administration of general anesthesia.

All local anesthetic agents appear safe for MH-susceptible patients. Epinephrine can be safely added to the local anesthetic agent to improve the quality and duration of analgesia, if clinically appropriate.

Anesthesia for Cesarean Delivery

General anesthesia should be avoided for operative delivery if possible. Spinal or epidural anesthesia using either

amide or ester local anesthetic agents can be given safely. Epidural anesthesia may be preferred because slow induction of anesthesia may decrease the risk for hypotension. Phenylephrine is probably the preferred agent for the treatment of hypotension. Ephedrine may exacerbate the catecholamine response during an acute episode of MH. In doses greater than those used clinically, ephedrine exacerbates halothane-induced muscle contractures *in vitro*.[92]

Rarely, the mother may refuse neuraxial anesthesia. In other cases, neuraxial anesthesia may be contraindicated (e.g., maternal hemorrhage, coagulopathy, prolonged fetal bradycardia). When the anesthesia provider encounters an MH-susceptible parturient, the anesthesia machine and delivery circuit should be flushed of volatile agents. Preparation consists of replacing the carbon dioxide absorbent and the delivery tubing, disabling the vaporizers, and purging the machine of residual anesthetic agent with a 10 L/min flow of oxygen through the circuit (including the ventilator).[93] The time required to purge the anesthesia machine is dependent on the specific machine.[93] Activated charcoal filters appear to be an effective alternative to the prolonged flushing required to reduce the volatile anesthetic concentration in new-model anesthesia machines.[94]

In cases of general anesthesia, the anesthesia provider should administer a nonparticulate antacid and perform adequate denitrogenation. Nontriggering agents should be administered for induction and maintenance of general anesthesia (Box 47-3, see also Table 47-2). Unless a difficult intubation is expected, rapid-sequence induction should be performed with a sedative-hypnotic drug and a nondepolarizing neuromuscular blocking agent. All commonly used induction agents (e.g., propofol, thiopental, ketamine, etomidate) are safe in MH-susceptible patients. Succinylcholine and the volatile halogenated agents (sevoflurane, desflurane, isoflurane, halothane, enflurane) are contraindicated. For intubation, rapid onset (approximately 60 to 90 seconds) of muscle relaxation can be achieved with rocuronium (0.6 to 0.9 mg/kg, which is two to three times the effective dose in 95% of patients [ED_{95}])[95] or vecuronium[96] (0.25 mg/kg). Nitrous oxide (delivered via a prepared anesthesia machine), opioids, and propofol are safe agents for the maintenance of anesthesia. Midazolam administered after delivery provides amnesia. It is safe to reverse neuromuscular blockade with glycopyrrolate and neostigmine or edrophonium. Atropine may cause an increase in temperature, which could cause a diagnostic dilemma.

At delivery, determination of maternal and umbilical cord blood gas and pH measurements may provide information about an impending reaction in either the mother or the neonate. As well, if the MH-susceptible mother has a known genetic mutation, umbilical cord blood may be used to assess MH susceptibility in the neonate.[97] If uterine relaxation (tocolysis) is required to assist with delivery of the baby or to facilitate the removal of a retained placenta, I prefer to give 100-μg bolus doses of nitroglycerin intravenously[98]; the action of this agent is brief and easily reversed with oxytocin. Clearly, a volatile halogenated agent should *never* be given to effect uterine relaxation in an MH-susceptible patient.

Concern has been raised about administering triggering agents to a non–MH-susceptible mother who is carrying a fetus whose father is MH susceptible.[99] In this situation the Malignant Hyperthermia Association of the United States recommends that the mother be treated as if she were MH susceptible to avoid a possible MH reaction in the neonate.[83]

BOX 47-3 General Anesthesia for Cesarean Delivery in the Malignant Hyperthermia–Susceptible Patient

Monitoring
- End-tidal CO_2
- Pulse oximeter
- Electrocardiogram
- Automatic blood pressure monitoring
- Peripheral nerve stimulator
- Temperature (central)

Induction of Anesthesia
- Denitrogenation
- Rapid-sequence induction (propofol 2.0 to 2.8 mg/kg, thiopental 4 mg/kg, ketamine 1 mg/kg)

Muscle Relaxant
- Intubation: rocuronium 0.6 to 0.9 mg/kg
- Maintenance: rocuronium

Maintenance of Anesthesia
- Nitrous oxide/oxygen, propofol, opioid

Amnestic Agent
- Midazolam

Reversal of Neuromuscular Blockade
- Glycopyrrolate and neostigmine

Obstetric Drugs in Malignant Hyperthermia–Susceptible Parturients

Information on use of obstetric drugs in MH-susceptible patients is scant (Table 47-3). The beta-sympathomimetic tocolytic agents (e.g., terbutaline) produce anxiety and tachycardia in normal parturients. Such side effects may be confused with MH, although these agents most likely are safe in the MH-susceptible parturient.

Magnesium sulfate attenuates but does not prevent MH in MH-susceptible swine.[100] There is one report of a fatal adverse interaction between dantrolene and the calcium entry–blocking agent diltiazem,[101] and hyperkalemia has been described after the co-administration of dantrolene and verapamil.[102] Administration of calcium entry–blocking agents should be avoided during an episode of MH. These agents do not prevent the development of MH.[103]

Oxytocin is safe. Some of the commercial preparations of oxytocin contain a preservative (chlorbutol) that has been shown to reverse the development of MH in susceptible pigs *in vitro*.[104] The ergot alkaloids cause

TABLE 47-3 Drugs Commonly Used for Labor and Delivery and Their Safety in Malignant Hyperthermia–Susceptible (MHS) Women

Drug	Route	Use	Safe in MHS Women
Tocolytics			
Nitroglycerin	Intravenous, sublingual	Tocolysis, antihypertensive	Yes
Terbutaline	Intravenous, subcutaneous	Tocolysis	Yes
Calcium entry–blocking agents	Oral	Tocolysis, antihypertensive	Yes*
NSAIDs	Oral	Tocolysis	Yes
Oxytocics			
Oxytocin	Intravenous, intramuscular	Induction/augmentation of labor, uterine atony	Yes
Prostaglandin $F_{2\alpha}$	Intramuscular, intramyometrial	Uterine atony	Inadequate information available
Misoprostol	Vaginal, rectal	Uterine atony	Inadequate information available
Ergot alkaloids	Intramuscular	Uterine atony	Inadequate information available
Cardiovascular Drugs			
Phenylephrine	Intravenous	Vasopressor	Yes
Ephedrine	Intravenous	Vasopressor	Yes†
Epinephrine	Intravenous, neuraxial	Vasopressor, epidural test dose, neuraxial local anesthesia adjunct	Yes
Beta-adrenergic receptor antagonists	Intravenous, oral	Antihypertensive	Yes
Antiemetics			
Metoclopramide	Intravenous	Prophylaxis, therapeutic	Yes
Ondansetron	Intravenous	Prophylaxis, therapeutic	Yes
Other			
Magnesium	Intravenous	Seizure prophylaxis, cerebral palsy prophylaxis	Yes
H_2-blocking agents	Intravenous, oral	Aspiration prophylaxis	Yes

NSAIDs, nonsteroidal anti-inflammatory drugs.
*Do not use during an MH crisis (see text).
†May exacerbate the catecholamine response during an MH crisis (see text).

vasoconstriction, which may lead to decreased muscle perfusion and a greater tendency toward lactic acidosis. The prostaglandins may be associated with changes in blood pressure and maternal oxygen desaturation.[105] Prostaglandin E_2 and misoprostol may cause pyrexia, which may lead to confusion in the diagnosis of an MH episode.[106] The routine postpartum administration of ergot alkaloids, prostaglandins, or misoprostol probably should not be performed in MH-susceptible patients. However, persistent uterine atony and postpartum hemorrhage may warrant the administration of these agents.

ASSESSMENT OF HYPERTHERMIA AND TACHYCARDIA

The hallmark signs of MH may be present during normal labor (Boxes 47-4 and 47-5). Other causes of fever and tachycardia in the MH-susceptible parturient should be excluded. Tachycardia and tachypnea are normal responses to pain, anxiety, and fever. Fever may be a sign of dehydration and infection. Pain and infection (e.g., chorioamnionitis, urinary tract infection) are much more common during parturition than MH. Some healthy parturients may have a gradual increase in

BOX 47-4 Differential Diagnosis of Fever during Parturition

- Infection: chorioamnionitis, urinary tract infection, other infections (e.g., influenza, viral illness)
- Environmental temperature
- Labor epidural analgesia
- Dehydration/labor
- Malignant hyperthermia
- Drug reactions: cocaine, atropine, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, neuroleptic malignant syndrome, prostaglandins (misoprostol)

BOX 47-5 Differential Diagnosis of Tachycardia during Parturition

- Pain
- Fever
- Anxiety
- Blood loss
- Hypotension
- Drug reactions: cocaine, atropine, beta-adrenergic tocolytic agents
- Malignant hyperthermia

temperature during epidural analgesia.[107] The fever may be accompanied by corresponding increases in maternal and fetal heart rates.

The butyrophenones, phenothiazines, thioxanthenes, and other miscellaneous antipsychotic agents may produce tachycardia, fever, and rigidity (i.e., neuroleptic malignant syndrome).[108] There is one published report of neuroleptic malignant syndrome in a pregnant woman.[109] Drugs capable of increasing serotonin in the central nervous system (i.e., serotonin reuptake inhibitors) also can produce a hypermetabolic reaction. Cocaine intoxication causes severe vasoconstriction, fever, and rhabdomyolysis.[110]

TREATMENT

Box 47-6 summarizes the treatment of MH; a more detailed protocol for the management of an MH episode is available online from the Malignant Hyperthermia Association of the United States (http://www.mhaus.org). The anesthesia provider should call for help, obtain dantrolene, and notify the surgeon. All triggering agents must be stopped immediately, and the patient should be hyperventilated with 100% oxygen at 10 L or more per minute. The level of volatile agent decreases rapidly with flushing of the machine with 100% oxygen. Therefore, substitution with a vapor-free machine is not an immediate priority. Insertion of an activated charcoal filter into the breathing circuit, if available, may also be helpful, but administration of dantrolene is the first priority.[111]

The anesthesia provider should give dantrolene intravenously in a dose of 2.5 mg/kg, until the signs and symptoms (e.g., tachycardia, hypercarbia, rigidity, fever) have subsided.[112] Although the maximum dantrolene dose is often listed as 10 mg/kg, there are case reports in which higher doses of dantrolene were required to control an MH reaction. Oxygen saturation, end-tidal CO_2, ECG, blood pressure, arterial and venous blood gas measurements, core temperature, potassium levels, lactate concentration, CK levels, coagulation profile, urine output, and urine myoglobin should be monitored.

The anesthesia provider must initiate treatment of acidosis, hyperkalemia, arrhythmias, and hyperthermia. Metabolic acidosis is treated by giving sodium bicarbonate in 1- to 2-mEq/kg increments as guided by blood gas and pH measurements. Hyperkalemia is treated by administration of bicarbonate, glucose, and insulin. Calcium administration may also be indicated.

Early administration of dantrolene often prevents or successfully treats arrhythmias. If arrhythmias persist, one should follow standard advanced cardiac life support (ACLS) protocols. Amiodarone, lidocaine, procainamide, and adenosine may be used safely. Calcium entry–blocking agents should be avoided because simultaneous administration of dantrolene and a calcium entry–blocking agent may precipitate cardiovascular collapse.[102]

The operating room care team should actively cool the patient. Options for doing so include (1) intravenous administration of cold saline; (2) surface cooling with ice and/or a hypothermia blanket; and (3) lavage of stomach, bladder, rectal, peritoneal, and thoracic cavities with iced saline.

Myoglobin is excreted in the urine. Thus, diuresis should be maintained by giving adequate volumes of crystalloid and furosemide 1 mg/kg and/or mannitol 0.25 g/kg. Mannitol is present in dantrolene, and separate administration of a diuretic agent may not be necessary. Sedation should be administered as necessary.

After an acute episode of MH, postoperative administration of dantrolene (1 mg/kg or more intravenously every 4 to 6 hours for 24 to 48 hours) is recommended. In addition, the patient should be monitored closely in an intensive care unit for at least 24 to 48 hours. In a retrospective analysis of data from the North American Malignant Hyperthermia Registry, 20% of patients had recrudescence of MH after the initial MH episode.[113] Recrudescence was associated with increased muscle mass and a longer interval between anesthesia induction and intraoperative reaction. Counseling and diagnostic muscle biopsy should be performed after recovery from the acute episode. The Malignant Hyperthermia Association of the United States provides a registry and an informative newsletter for MH-susceptible patients. An MH hotline (800-MH-HYPER [800-644-9737] or, outside the United States, +1-209-417-3722) is available 24 hours a day to assist physicians with questions on treatment, diagnosis, and follow-up.

BOX 47-6 Management of Malignant Hyperthermia Crisis

1. Call for help and obtain dantrolene.
2. Notify the surgeon.
3. Discontinue all triggering agents.
4. Hyperventilate with 100% oxygen at high gas flows (≥10 L/min).
5. Administer dantrolene 2.5 mg/kg intravenously. Repeat until signs and symptoms resolve.
6. Perform serial blood gas measurements. Treat acidosis with sodium bicarbonate 1 to 2 mEq/kg.
7. Treat hyperkalemia with sodium bicarbonate, glucose, insulin, and calcium.
8. Treat arrhythmias with amiodarone or lidocaine.
9. Cool patient (external cooling blanket, ice packs, cold intravenous solutions, lavage of body cavities with cold solutions).
10. Maintain urine output with fluids, mannitol, and/or furosemide.
11. Call the Malignant Hyperthermia Hotline for assistance (1-800-MH-HYPER).
12. Postoperatively, monitor patient in intensive care unit for 24 to 48 hours. Administer maintenance dantrolene.
13. Counsel patient and family, and refer for caffeine-halothane contracture test.

Modified from Malignant Hyperthermia Association of the United States. Emergency Therapy of Malignant Hyperthermia. September 2011. Available at http://www.mhaus.org/healthcare-professionals/#.T6rV3VI2cTY. Accessed December, 2012.

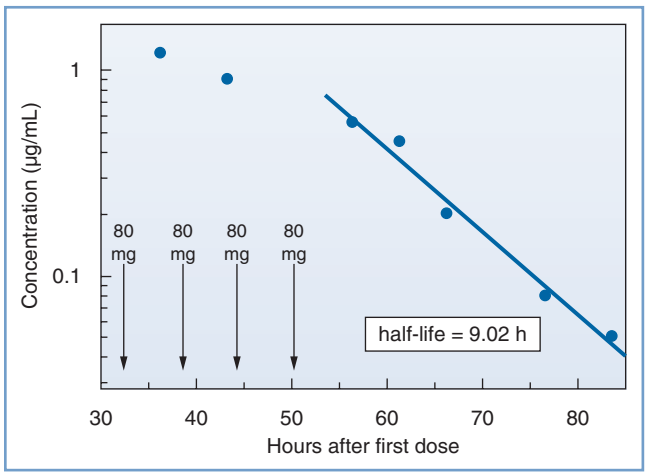

FIGURE 47-2 ■ Estimation of the half-life of dantrolene in breast milk by log-linear fitting of the terminal elimination phase (dantrolene measured in breast milk by high-pressure liquid chromatography, reverse-phase high-pressure liquid chromatographic column, by in-line ultraviolet absorption spectrometer; detection limit, 0.02 µg/mL). (From Fricker RM, Hoerauf KH, Drewe J, Kress HG. Secretion of dantrolene into breast milk after acute therapy of a suspected malignant hyperthermia crisis during cesarean section. Anesthesiology 1998; 89:1023-5.)

DANTROLENE IN PREGNANCY

Dantrolene is the drug of choice for the treatment of an MH crisis. Dantrolene works by blocking the release of calcium from the sarcoplasmic reticulum of skeletal muscle cells.[114] It crosses the placenta and can be detected in the fetus after maternal administration.[115] Clinical doses do not adversely affect maternal or fetal cardiovascular and acid-base measurements in gravid ewes. Morison[74] reported a fetal-to-maternal serum dantrolene concentration ratio of approximately 0.4 after prophylactic oral administration of dantrolene. Theoretically, dantrolene may cause neonatal hypotonia if it is administered before delivery.

There is one published report of postpartum uterine atony after the administration of dantrolene.[10] Laboratory testing of the effects of dantrolene sodium on pregnant uterine muscle suggests that the relaxant effect is secondary to the mannitol.[116]

There is no benefit to dantrolene prophylaxis in the MH-susceptible patient when all triggering agents are avoided.[114] However, the anesthesia provider should give dantrolene promptly when an MH crisis is suspected.

Fricker et al.[117] reported serial measurements of dantrolene concentrations in breast milk after administration of dantrolene in a patient with suspected MH during cesarean delivery (Figure 47-2). They estimated that the half-life of dantrolene in breast milk is approximately 9 hours. They concluded that "breast-feeding can be expected to be safe for the newborn 2 days after discontinuation of intravenous dantrolene administration in the mother."[117]

KEY POINTS

- Malignant hyperthermia is a heterogeneous disorder of skeletal muscle with variable clinical penetrance.
- Affected individuals develop a hypermetabolic syndrome on exposure to triggering agents (succinylcholine, volatile halogenated agents).
- The current diagnostic test is the caffeine-halothane contracture test.
- Current genetic testing has low sensitivity.
- It is unclear whether pregnancy alters susceptibility to MH.
- Both the obstetrician and the anesthesia provider should encourage early administration of neuraxial analgesia during labor in MH-susceptible patients.
- The anesthesia provider may convert epidural *analgesia* to epidural *anesthesia* for emergency cesarean delivery and thus avoid administration of general anesthesia.
- All local anesthetic agents are safe in MH-susceptible patients.
- Intravenous administration of dantrolene is life-saving treatment for an MH crisis.
- Dantrolene crosses the placenta and may result in neonatal hypotonia.
- Dantrolene may cause uterine atony.
- The anesthesia provider need not administer dantrolene prophylactically to MH-susceptible parturients.

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CHAPTER 48

Musculoskeletal Disorders

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CHAPTER OUTLINE

Pregnancy commonly results in musculoskeletal complaints. Although they typically are benign and self-limited, symptoms may be disabling in some women. In addition, preexisting musculoskeletal disorders interact with pregnancy to a variable extent. These interactions range from an ameliorating effect of pregnancy on the course of the disease (e.g., rheumatoid arthritis) to the potential for a significant and possibly life-threatening deterioration in maternal condition (e.g., uncorrected severe thoracic scoliosis). The purpose of this chapter is to discuss the most common musculoskeletal disorders encountered in pregnant women and their implications for obstetric and anesthesia providers.

LUMBOPELVIC PAIN OF PREGNANCY

Lumbopelvic pain is the most common musculoskeletal complaint during pregnancy; it comprises two distinct areas of discomfort: (1) the lumbar spine area (low back pain) and (2) the posterior pelvic girdle area (from the sacroiliac joints radiating down into the posterior thighs), which has been termed *pelvic girdle pain*.[1-3] Lumbopelvic pain of pregnancy occurs at some time during gestation in more than 50% of pregnant women and impairs at least one normal activity of daily life, including sleep. Although originally it seemed to be a more significant problem in Scandinavian countries than elsewhere, it is now recognized as a universal issue, with the prevalence ranging from 25% to 70%. It is the most common reason for sick leave during pregnancy.[2] Women with mainly pelvic girdle pain report more disability during pregnancy than those with lumbar pain alone.[3,4] Differentiation between pelvic girdle pain and low back pain is important because the management differs and the disability of pelvic girdle pain is more likely to extend into the postpartum period for up to 1 to 2 years.[2] Risk factors for lumbopelvic pain of pregnancy include a history of low back pain, young age, hypermobile joints, low socioeconomic class, multiparity, and spondylolisthesis; however, the strongest factors are prior history of lumbopelvic pain of pregnancy, previous non–pregnancy-related low back pain, and strenuous work.[3-7] Unfortunately, women who suffer from lumbopelvic pain in one pregnancy have a very high risk for experiencing it during subsequent pregnancies.

The etiology includes hormonal and mechanical factors. The corpus luteum synthesizes and releases relaxin, and maternal blood concentrations of this peptide hormone increase 10-fold during gestation. Relaxin induces ligamentous softening and peripheral and pelvic joint laxity, which cause instability of the symphysis pubis and sacroiliac joints; the extent of instability and disability may be related to the maternal concentration of

relaxin. There is a correlation between mean serum levels of relaxin and the occurrence of back pain during pregnancy, and women with incapacitating symptoms have the greatest serum concentrations of relaxin.[8]

Mechanical changes have a later onset than hormonal changes. Women with pelvic girdle pain have increased pelvic joint motion, which increases sheer forces across the joints and likely results in pain.[2] In all pregnant women uterine enlargement results in a forward rotation of the sacrum and an increase in the lumbar lordotic curve, which tends to close the lumbar interlaminar space (Figure 48-1). This change exaggerates the mechanical load borne by both the facet joints and the posterior aspect of the intervertebral discs. These mechanical changes also may compromise nerve root foramina. Sciatica occurs in 1% of pregnant women, and most cases occur late in pregnancy.[9] Sciatica is distinguished from pelvic girdle pain by its extension to the ankle or involvement of the foot, and it may be associated with neurologic changes.[9] Disc herniation is rare in pregnancy but does occur.[10] Incapacitating pain that radiates below the knee, typically accompanied by progressive neurologic deficits or bowel and bladder dysfunction, distinguishes disc herniation from the more common and benign lumbopelvic pain of pregnancy.[3,10]

In summary, hormonal changes cause sacroiliac joint dysfunction, which is responsible for the lumbopelvic pain that occurs early in pregnancy. Mechanical changes are primarily responsible for the pain that manifests during late gestation, although symphysis pubis and sacroiliac joint instability may also continue to cause pain.

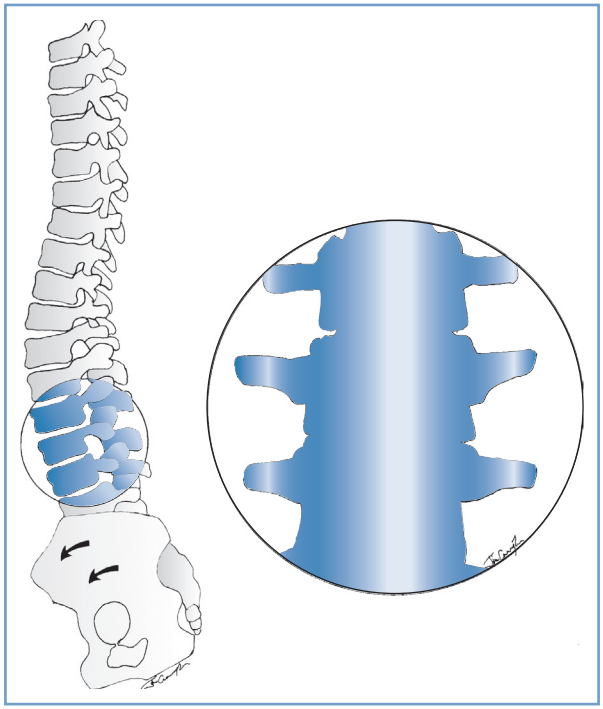

FIGURE 48-1 ■ Musculoskeletal changes of pregnancy. Forward rotation of the pelvis and greater lumbar lordosis increase the load borne by the posterior vertebral elements and tend to close the lumbar interlaminar spaces. *Inset,* Lumbar vertebrae L2 to L4.

Disc herniation is uncommon and is characterized by the presence of neurologic findings.

Obstetric Management

Treatment is conservative in the absence of neurologic compromise. Structured exercise programs, acetaminophen, transcutaneous electrical nerve stimulation (TENS), and acupuncture have been shown to be beneficial for women suffering from lumbopelvic pain during pregnancy.[11,12] Bed rest is reserved for patients with neurologic symptoms or disability secondary to pelvic instability. Patients with severe neurologic signs or symptoms of disc herniation should be assessed by a consultant neurosurgeon who can provide recommendations for intrapartum and postpartum care. Surgical intervention may be required in women with incapacitating pain or progressive neurologic deficits.[13] In a woman with severe symptoms, the obstetrician may choose to perform elective instrumental vaginal delivery to decrease maternal work and back stress during the second stage of labor. Because the disability associated with lumbopelvic pain of pregnancy, especially pelvic girdle pain, can impair the woman's ability to function postpartum, it is important to diagnose lumbopelvic pain of pregnancy and treat it appropriately.[2]

Anesthetic Management

No evidence suggests that epidural or spinal anesthesia is contraindicated in patients with lumbopelvic pain. The anesthesia provider may administer neuraxial anesthesia, even to patients with sciatica. However, neurologic signs and symptoms should be first identified, delineated, and recorded. It seems prudent to administer a dilute solution of local anesthetic, with or without an opioid, to minimize motor block associated with epidural analgesia during labor to reduce any further stress on relaxed sacroiliac joints. Women with lumbopelvic pain of pregnancy may be reluctant to have neuraxial anesthesia because of concern that it may aggravate symptoms. The literature does not support this fear, and reassurance may be required.

All members of the obstetric care team must pay careful attention to the positioning of the patient with back complaints. The patient must not be placed in a position that she could not tolerate before the administration of neuraxial anesthesia. The lithotomy position puts significant stress on the lower back and should be avoided whenever possible. If it is used, care must be taken to raise and lower both legs simultaneously to prevent injury to the lumbar spine and to avoid extremes when positioning the legs. Finally, caregivers should avoid rotational movements of the spine during transfer of the patient between the bed and the operating table.[2]

CHRONIC LOW BACK PAIN

Approximately 50% of pregnant women with a previous history of back pain or those with chronic low back pain experience a recurrence or exacerbation of their

symptoms during pregnancy.[6] Neuraxial anesthesia is more likely to fail in patients with chronic low back pain and in those who have had back surgery.[14-16] Benzon et al.[14] reported a delayed onset of epidural anesthesia in patients with back pain or sciatica; the affected roots were blocked 10 to 70 minutes later than the contralateral roots at the same level. The delay in block onset most likely results from the inability of the local anesthetic agent to diffuse into the area of the injured root. Luyendijk and van Voorthuisen[17] evaluated 600 epidurograms and confirmed that contrast material failed to reach the nerve root in 33% of patients with uncomplicated disc prolapse and did not move beyond the affected disc space in 5% of cases. This may be due to epidural scarring and adhesions that may develop during healing after disc injury. During epidurography, they noted that contrast material did not diffuse past the level of an injured disc and exited through the foramina below the abnormal disc. Prolapse of an intervertebral disc may result in relative or total obstruction of the flow of local anesthetic agent within the epidural space. The unblocked area includes the affected segment but also may include all segments (either ipsilateral or bilateral) distal to the affected level.

Sharrock et al.[15] reported a high rate (91%) of successful epidural anesthesia in patients with a history of limited spinal surgery. However, the success rate was lower than that achieved by the same group of anesthesiologists in a population with no history of back surgery (98.7%). They attributed the greater rate of failure to the distortion of surface anatomy and the tethering of the dura to the ligamentum flavum by scar formation, which rendered the epidural space discontinuous or obliterated it entirely. Support for this hypothesis is provided by LaRocca and MacNab's[18] description of the post-laminectomy membrane. They noted the post-laminectomy formation of organized fibrous tissue surrounding the dura and, at times, binding of the nerves to the posterior aspect of the disc and adjacent vertebral body. The fibrous response was proportional to the extent of surgical trauma and was more marked with greater operative exposures. Consequently, a local anesthetic agent injected into the epidural space may not diffuse beyond the area of scarring and an inadequate or unexpectedly high block may result.[16] Post-laminectomy spinal stenosis also may lead to attenuation or obliteration of the epidural space, and the most common site of obstructive stenosis is immediately above the fusion mass.[19]

Obstetric Management

It is not uncommon for obstetricians to offer pregnant women who have had persistent chronic low back pain the option of cesarean delivery to decrease the potential for further back injury during labor. There are no data to either encourage or discourage this option.

Anesthetic Management

The anesthesia provider may offer epidural or spinal anesthesia to patients with previous lumbar spine pathology or surgery after an appropriate history and screening examination to identify any neurologic deficits.[10] A decreased incidence of successful epidural anesthesia may be expected, especially in patients who have had extensive surgery. Nonetheless, the experienced anesthesia provider will likely administer epidural anesthesia successfully in the majority of patients. Sharrock et al.[15] recommended administration of epidural anesthesia one or two interspaces above the operated segment to improve the likelihood of a successful block. Subarachnoid anesthesia is likely to be more reliable than epidural anesthesia in this patient population.

POSTPARTUM BACKACHE

Postpartum backache is a common complaint worldwide, occurring in at least 25% of women, with 5% to 7% of women seeking medical help.[3] MacArthur et al.,[20,21] citing data obtained from a postal survey of 11,701 women who had delivered 1 to 9 years previously, reported that postpartum backache, starting within 3 months of delivery and persisting for 6 weeks or longer, occurred in 23% of women. Approximately 25% of these women had experienced backache before delivery, but 14% reported new-onset backache. In many women, the pain was persistent; 70% had experienced it for more than 2 years, and 65% had pain at the time of questioning 1 to 9 years later. Back pain was more common in women who delivered vaginally with epidural analgesia than in those who did not have epidural analgesia (18.9% versus 10.5%, respectively). Women who had epidural analgesia also were more likely to have had induced labor, an abnormal fetal position, a multiple pregnancy, a prolonged first or second stage of labor, forceps delivery, episiotomy, cesarean delivery, postpartum hemorrhage, or a large infant.

MacLeod et al.[22] also performed a postal survey of 2065 patients 1 year postpartum and reported a 26.2% incidence of postpartum backache in women who had received epidural analgesia, compared with a 1.7% incidence in those who had not; the latter incidence of postpartum backache (1.7%) is the lowest, by far, reported by any investigator in a postpartum population in the first year after delivery. Orlikowski et al.,[23] who examined data from 992 women as a secondary analysis of a prospective randomized study on epidural analgesia versus continuous midwifery support, found no relationship between back pain at 6 months postpartum and the use of epidural analgesia. Mogren[24] sent a questionnaire to 639 women who had completed an earlier postpartum survey in which they indicated that they had suffered from lumbopelvic pain during pregnancy. Mogren explored the relationship between persistent lumbopelvic pain at 6 months postpartum, mode of delivery, and the use of epidural or spinal anesthesia. She concluded that use of epidural or spinal anesthesia was not associated with persistent lumbopelvic pain.

A number of investigators have carried out prospective evaluations to eliminate the potential for reporting bias that may confound retrospective surveys. Breen et al.[25] assessed 1042 women at 6 months postpartum. Although 44% of women experienced postpartum backache, there was no difference between those who had received

epidural analgesia and those who had not. The most significant predictor of postpartum backache was antenatal back pain. Weight gain was greater in patients with postpartum and new-onset back pain.

Macarthur et al.[26] also prospectively studied the association between epidural analgesia and early, new-onset postpartum backache in 329 women. In patients who labored without epidural analgesia, the incidence of postpartum backache was 43% at 1 day, 23% at 7 days, and 7% at 6 weeks. The incidence of symptoms in patients who had received epidural analgesia was greater on the first postpartum day (53%), but this increase was not persistent. At 1 year postpartum, 12% of the patients had back pain (9.9% in the epidural group and 13.8% in the control group). Howell et al.[27] performed a randomized controlled trial comparing epidural with nonepidural analgesia during labor in 369 nulliparous women. There was no difference in the incidence or characteristics of postpartum backache at 3 and 12 months postpartum. In a follow-up study, there was no difference between the two groups in the incidence of back pain, disability, or movement restriction more than 2 years after delivery.[28]

The type of epidural analgesia provided has also been reviewed to determine whether alteration of the technique affects postpartum backache. Wilson et al.[29] reported the incidence of postpartum backache in 1054 nulliparous women enrolled in the Comparative Obstetric Mobile Epidural Trial (COMET). The women had received either high-dose labor epidural analgesia (bupivacaine 0.25% administered with intermittent bolus injections) or low-dose mobile analgesia (either combined spinal-epidural [CSE] analgesia followed by intermittent epidural bolus injections of 0.1% bupivacaine with fentanyl or a low-dose epidural infusion of 0.1% bupivacaine with fentanyl). The incidence of backache that started within 3 months and lasted for at least 6 weeks did not differ between the three groups: 46.9% (high dose), 41.7% (CSE), and 45.8% (low-dose infusion). These findings are similar to results of previous studies of this issue.

Both transient and more persistent postpartum backaches are common, but there is little evidence that they are related to the provision of epidural analgesia during labor. Similarly, no evidence suggests that denying a parturient epidural analgesia results in a lower incidence of back problems during the postpartum period. Factors associated with more persistent postpartum backache include the presence of back pain before pregnancy, the presence of lumbopelvic pain of pregnancy, cesarean delivery, and performance of physically demanding work.[3,24]

SCOLIOSIS

Scoliosis is a lateral deviation in the vertical axis of the spine. The severity of scoliosis is determined by measurement of the angle of the spinal curve, the Cobb angle, which is expressed in degrees (Figure 48-2). The incidence of minor curves is 4 per 1000 in the North American population; larger curves occur less frequently, predominantly in females. Severe scoliosis is relatively rare in pregnant women, occurring in 0.03% of pregnancies.[30] Although women with moderate to severe scoliosis constitute a small population of obstetric patients, pregnancy within this population is common.[31] Most cases of scoliosis are idiopathic, although some are associated with other conditions, most commonly neuromuscular disorders (Box 48-1).

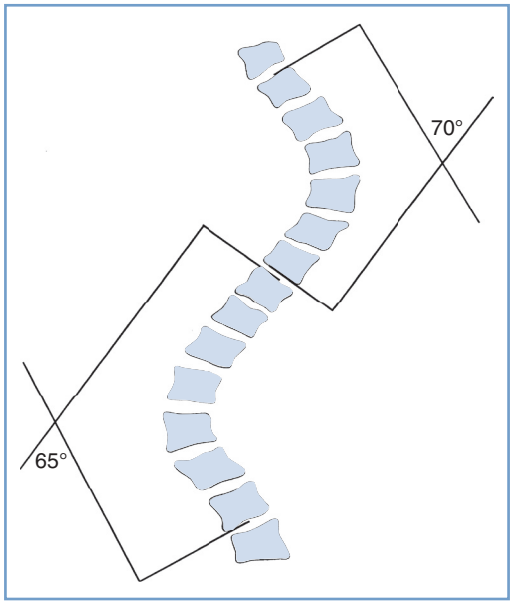

FIGURE 48-2 ■ Schematic representation of the Cobb angle. A line is drawn parallel to the superior cortical plate of the proximal end vertebrae and another line parallel to the inferior cortical plate of the distal end vertebrae. A perpendicular line is drawn to each of these lines. The angle of intersection is the Cobb angle of the curve.

BOX 48-1 Conditions Associated with Scoliosis

Congenital (Vertebral) Anomalies
- Hemivertebra
- Spina bifida

Neurologic Disorders
- Cerebral palsy
- Polio
- Neurofibromatosis

Myopathic Disorders
- Myotonic dystrophy
- Muscular dystrophy

Connective Tissue Disorders
- Marfan syndrome
- Rheumatoid disease

Osteochondrodystrophies
- Achondroplasia/hypochondroplasia
- Osteogenesis imperfecta

Infection
- Tuberculosis

Previous Trauma

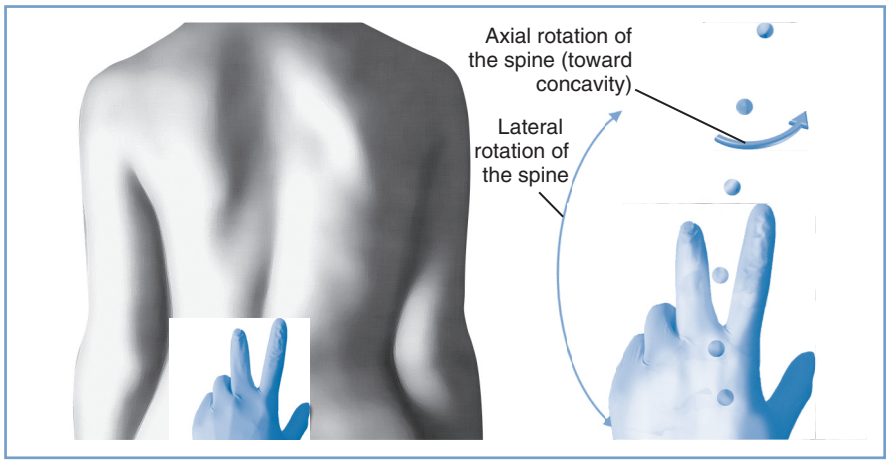

FIGURE 48-3 ■ Spinal rotation with scoliosis. *Left,* View of the lumbar spine in a patient with a scoliotic curve to the left demonstrating surface landmark palpation. *Right,* Skeletal anatomy at the same level in the same patient. There is a reduction in the dimensions of the interlaminar space on the concave side of the curve (to the right) and an expansion on the convex side. These changes are enhanced with greater severity of the curve. As the curve increases, the spinous processes rotate into the concavity of the curve, further altering the local anatomy. Surface landmark palpation from the view at left superimposed on the skeleton reveals how the palpated midline (*indicated by the white X*) is to the right of the true midline. (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Scoliotic curves can be divided into structural and nonstructural varieties. **Nonstructural curves** are those seen with postural scoliosis, sciatica, and leg-length discrepancies. They do not affect the mobility of the spine and are nonprogressive. **Structural curves** are seen in patients with idiopathic scoliosis and with scoliosis resulting from the conditions listed in Box 48-1. Structural curves lead to reduced spinal mobility, and affected patients typically have a fixed prominence (rib hump) on the convex side of the curve. There is also a rotatory component associated with the structural scoliotic curve. The axial rotation of the vertebral body is such that the spinous processes rotate away from the convexity of the curve and back toward the midline of the patient (Figures 48-3 and 48-4).[32] Deformation of the vertebral bodies results in shorter, thinner pedicles and laminae and a more narrow vertebral canal on the concave side. Vertebral deformation is unusual in patients with a Cobb angle less than 40 degrees.

Scoliosis interferes with the formation, growth, and development of the lungs; the occurrence of scoliosis before lung maturity may reduce the number of alveoli that ultimately form. The pulmonary vasculature develops in parallel with the alveoli; early-onset scoliosis and severe scoliosis may result in greater pulmonary vascular resistance and eventually lead to pulmonary hypertension. Musculoskeletal deformities also affect the mechanical function of the lungs; anatomic findings in scoliosis that are most commonly associated with respiratory compromise include the presence of a thoracic curve, thoracic lordosis, and a rib cage deformity. The most common pulmonary function abnormality is a restrictive pattern with decreases in vital capacity, total lung capacity, and lung compliance. This pattern occurs in all patients with a thoracic curve greater than 65 degrees. The functional residual capacity (FRC) is reduced, and airways may close during normal tidal breathing. If the FRC is reduced to the extent that it falls below the closing capacity, atelectasis may occur in basal alveoli. The most common blood gas abnormality is an increased alveolar-to-arterial oxygen gradient, with reduced Pao_2 and a normal $Paco_2$. It results from both venoarterial shunting and altered regional perfusion. Venous admixture may lead to arterial hypoxemia.

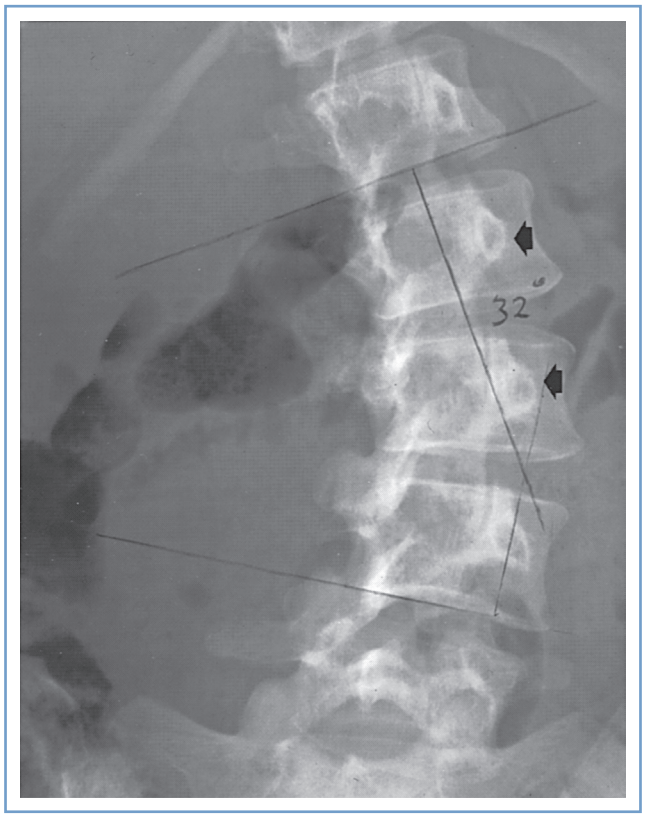

FIGURE 48-4 ■ Radiographic study of the lumbar spine in a 26-year-old woman with idiopathic scoliosis. The spinous processes and pedicles (*arrows*) are rotated away from the convexity and into the concavity of the curve. (The epidural space was entered easily with direction of the needle approximately 15 degrees off the perpendicular at the skin level toward the convexity of the curve.)

The natural history of severe, progressive scoliosis includes early death from cardiopulmonary failure.[33]

Permanent changes of the pulmonary vasculature are common in patients with a curve greater than 65 degrees. Pulmonary hypertension (a resting mean pulmonary artery pressure exceeding 25 mm Hg) occurs in many patients with severe deformity long before the onset of

right-sided heart failure and is largely attributable to increases in vascular resistance resulting from chronic alveolar hypoxia, hypoxic pulmonary vasoconstriction, and anatomic changes in the vascular bed. Fixed pulmonary hypertension carries a grave prognosis in pregnancy and may prompt a recommendation to avoid or terminate pregnancy.[34]

Scoliosis Associated with Neuromuscular Disease

When scoliosis develops secondary to a neurologic or myopathic disorder, abnormal respiratory function results not only from the skeletal deformity but also from abnormalities in the central control of respiration and the supraspinal innervation of the respiratory muscles, as well as from the loss of muscle function caused by the underlying disorder. Respiratory function may be further compromised by (1) impairment of the defense mechanisms of the airways due to loss of control of the pharynx and the larynx, (2) an ineffective cough mechanism, and (3) infrequent or reduced large breaths. Recurrent aspiration pneumonitis may result from compromised protective airway reflexes. In general, the prognosis of scoliosis due to neuromuscular disease is worse than that of idiopathic scoliosis and is determined predominantly by progression of the primary disorder. Affected patients typically develop irreversible respiratory failure at a younger age, and pulmonary hypertension is common; pregnancy is uncommon in this population.

Interaction with Pregnancy

Pregnancy may exacerbate both the severity of the spinal curvature and cardiopulmonary abnormalities in women with uncorrected scoliosis. Progression of a curve, defined as an increase in the Cobb angle of 5 degrees or more over subsequent assessments, most likely occurs during periods of rapid growth and in patients with larger curves at the time of diagnosis. Curves that are less than 25 degrees or curves that have been stable before pregnancy typically do not progress during pregnancy.[35,36] In contrast, more severe curves and those that have not stabilized may worsen. Some investigators have described a correlation between the severity of the curve and maternal morbidity and mortality. However, it is likely that the severity of functional cardiopulmonary impairment before pregnancy is a better predictor of maternal outcome than the severity of the curve.[37] Patients with a severe curve (i.e., Cobb angle > 60 degrees) but good cardiopulmonary function tolerate pregnancy well, whereas in those with significant cardiopulmonary compromise, and especially in those with pulmonary hypertension, maternal mortality is high.[38,39]

The physiologic changes of pregnancy include decreases in both functional residual and closing capacities and increases in minute ventilation and oxygen demand. The thoracic cage normally increases in circumference during pregnancy as a result of increases in both anteroposterior and transverse diameters. If the chest cage is relatively fixed by scoliosis, the diaphragm is responsible for all increments in minute ventilation. As the enlarging uterus causes elevation of the diaphragm, diaphragmatic activity is restricted and further decreases in residual and closing capacities may occur, which may result in both greater ventilation-perfusion mismatch and decreased arterial oxygen content. The antepartum onset of new symptoms of respiratory compromise or the exacerbation of preexisting symptomatology is associated with higher maternal morbidity and a greater likelihood that assisted ventilation will be required after cesarean delivery.[37]

Minute ventilation typically increases by 45% during pregnancy. In normal pregnancy, the increase is primarily a result of increased tidal volume. In the scoliotic patient with restrictive lung disease, a larger tidal volume may not be possible, and the increased minute ventilation is achieved by means of a higher respiratory rate and increased work of breathing. Peak increases in pulmonary activity are reached by the middle of the third trimester, but the uterus continues to grow until term, and it may further encroach on the noncompliant thorax, causing late gestational deterioration despite stabilization of respiratory demand.

Dyspnea on exertion is uncommon in patients with scoliosis who have curves less than 70 degrees, but it becomes more common as the deformity exceeds 100 degrees. In younger patients with a curve less than 70 degrees, exercise capacity is more likely to be impaired because of the lack of regular aerobic exercise and subsequent deconditioning rather than intrinsic ventilatory impairment.[40] Dyspnea is common in many pregnant women, typically begins in the first or second trimester, and is most prevalent at term. Two features help distinguish physiologic from pathologic dyspnea.[41] **Physiologic dyspnea** tends to occur earlier in pregnancy and often plateaus or even improves as term approaches. The **pathologic dyspnea** of cardiopulmonary decompensation more often begins in the second half of pregnancy and is progressive, often becoming most severe as gestation advances and the physiologic loading is maximal. Second, physiologic dyspnea is rarely extreme, and patients can maintain most daily activities. Dyspnea that is extreme or has a limiting effect on normal activity may signal maternal cardiorespiratory decompensation. Dyspnea at rest is also rare in the absence of cardiopulmonary dysfunction, as is dyspnea that is acute in onset or progressive and intractable.

Minute ventilation of the unmedicated parturient increases by a further 75% to 150% in the first stage of labor and by 150% to 300% in the second stage. Oxygen consumption increases above prelabor values by 40% in the first stage and 75% in the second stage. These levels may be unattainable by the scoliotic parturient with restrictive lung disease, and respiratory failure and hypoxemia may result during labor.

Pregnant women with pulmonary hypertension have a limited ability to increase cardiac output. During normal pregnancy, cardiac output increases 40% to 50% above nonpregnant measurements; during labor and delivery, even greater increases are observed. These increases are achieved with both larger stroke volume and a higher heart rate. These demands may put an excessive burden on the cardiovascular system in parturients who

had marginal cardiac reserve before pregnancy. If the right ventricle fails in the presence of pulmonary hypertension, left ventricular filling will decrease and low-output failure and sudden death may occur.[34]

Surgical Management

During spinal fusion and instrumentation, the spinal musculature is reflected off the vertebrae over the course of the curve and the spinous processes and interspinous ligaments are removed. The spine is subsequently extended, correcting the curve. The vertebrae are decorticated throughout the extent of the planned fusion, instrumentation is placed, and bone graft material from the ileum is placed over the decorticated vertebrae. A number of techniques for fusion have been described, but all involve both spinal instrumentation and extensive bone grafting in the axial spine (Figure 48-5).

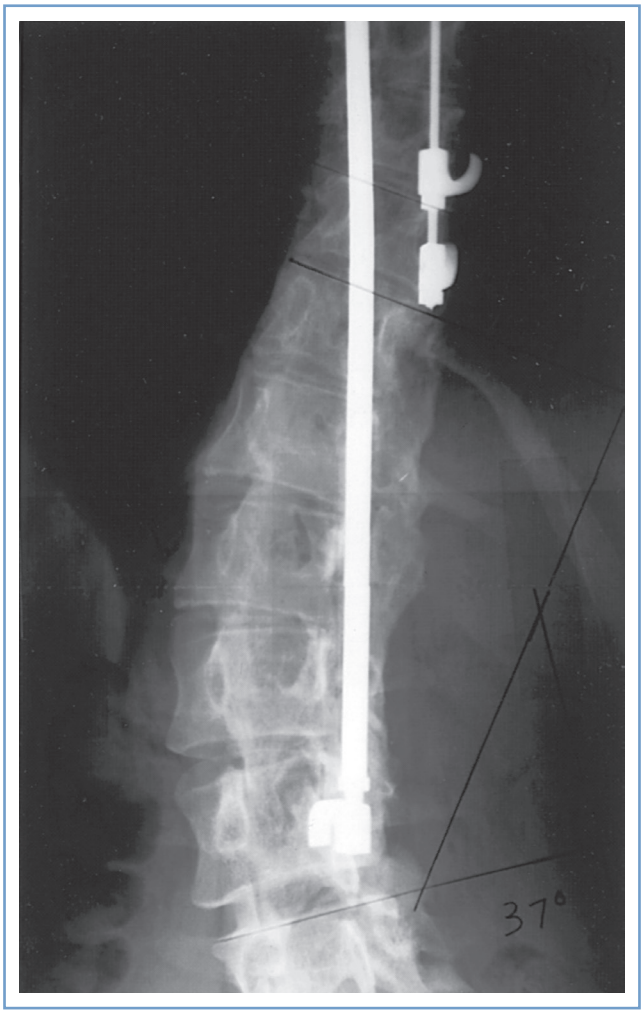

FIGURE 48-5 ■ Harrington rod instrumentation. Radiographic study of the lumbar spine in a 31-year-old woman with thoracolumbar scoliosis corrected with spinal instrumentation. There is rotation of the vertebrae into the curve (toward the rod), and extensive bone grafting is evident adjacent to the rod. Two lumbar interspaces (L4 to L5 and L5 to S1) are not involved in the fusion.

Obstetric Management

Pregnant women with corrected scoliosis tolerate pregnancy, labor, and delivery well. In the absence of major lumbosacral deformity, there is little alteration of the pelvic cavity and malpresentation is not more common than in women without scoliosis. Uterine function is normal, and labor is not prolonged. Spontaneous vaginal delivery is anticipated, and cesarean delivery should be reserved for obstetric indications.

One uncontrolled study suggested no difference in the requirement for cesarean delivery in patients with previous Harrington rod instrumentation for correction of idiopathic scoliosis[31]; a second and similar study reported a higher incidence of operative delivery.[42] The difference in outcomes may be influenced by the severity and etiology of the scoliosis in the populations reviewed and/or differences in the local practice patterns for managing atypical patients. Pelvic abnormalities are more common when scoliosis is associated with neuromuscular disorders and in patients with a severe, uncorrected curve.[43] In addition, abdominal and pelvic muscle weakness predisposes parturients to problems with expulsion of the infant during the second stage of labor and may necessitate instrumental vaginal delivery. The need for instrumental or cesarean delivery seems to be related to the severity of skeletal deformity, the resulting maternal compromise, and cephalopelvic disproportion.

In the second stage of labor, the diaphragm has a nonrespiratory function. With expulsive efforts, maximal isometric contractions may be sustained for 20 seconds or more, and diaphragmatic fatigue has been demonstrated even in normal, laboring women. In parturients whose diaphragmatic function is compromised by neuromuscular disease or severe scoliosis, the potential for fatigue and failure is greater; expulsive forces are decreased, the second stage may be prolonged, and a trial of labor may fail, necessitating instrumental or cesarean delivery. In addition, women with severe cardiopulmonary disease (especially those with gestational decompensation) may require urgent or emergency cesarean delivery because of maternal compromise or nonreassuring fetal status.

Anesthetic Management

Pregnant women who have thoracolumbar scoliosis with a Cobb angle greater than 30 degrees or who have undergone spinal instrumentation and fusion for scoliosis should be referred to an anesthesiologist for antepartum consultation. The anesthesiologist should (1) determine the etiology of the scoliosis, as well as the severity and stability of the curve; (2) obtain a history of maternal musculoskeletal and cardiopulmonary symptoms; and (3) review prior obstetric and anesthetic experiences. For patients with scoliosis secondary to neuromuscular disorders, the anesthesiologist should also become familiar with anesthetic considerations specific to those underlying disorders.

Women with suspected or evident pulmonary compromise should undergo evaluation by a pulmonologist, and pulmonary function studies and arterial blood gas measurements should be obtained. These patients must

be reevaluated periodically to ensure that they are tolerating the increasing physiologic demands of pregnancy. Echocardiography is useful to assess right-sided heart function in patients with one or more of the following: (1) a curve of 60 degrees or more, (2) hypoxemia on arterial blood gas measurement, (3) moderate or greater reductions in predicted lung volumes or flows, and/or (4) pulmonary hypertension. Radiographic studies performed before pregnancy and operative notes describing spinal surgical procedures should be reviewed before neuraxial anesthesia is given to any patient with significant scoliosis or previous spinal surgery. The anesthesiologist should also examine the spine and note the surface landmarks and interspaces that are least affected by the deformity. Modes of analgesia and anesthesia for labor and delivery can be discussed during antepartum consultation.

Invasive hemodynamic monitoring is rarely indicated during labor and delivery. Pulmonary function studies that suggest significant respiratory compromise or clinical evidence of impending respiratory failure warrant placement of an arterial catheter and serial assessment of blood gas measurements. Echocardiographic demonstration of significant right-sided heart dysfunction may warrant central venous pressure monitoring. The use of echocardiography may allow for detailed anatomic and physiologic assessment in severely ill mothers with advanced and decompensated cardiopulmonary disease.

The anesthesiologist may offer epidural analgesia for labor and delivery to patients with severe thoracolumbar scoliosis. Identification of the epidural space is more difficult in such patients, and the anesthesiologist should anticipate a greater incidence of complications. It is useful to remember the presence of the vertebral rotation during the performance of neuraxial anesthesia in a patient with a significant lumbar curve, which results in the spinous processes (which often may be structurally deformed) rotating into the concavity of the curve. Therefore, the midline of the epidural space is deviated toward the convexity of the curve relative to the spinous process palpable at the skin level (see Figures 48-3 and 48-4). The extent of lateral deviation is determined largely by the severity of the deformity.[44] One method of placing an epidural or spinal needle is to direct the needle from a palpated spinous process toward the convexity of the curve, often at a significant angle. The experienced anesthesiologist can track the resistance of both the interspinous ligament and the ligamentum flavum to maintain the correct course into the epidural space. The extent of the local anatomic distortion is the limiting factor, and the selection of spaces that are least involved with the curve is advised (Figure 48-6). More recently, Huang[45] suggested a modified paramedian approach based on Boon's[46] work in cadavers, in which the needle is placed lateral to the spinous process on the convex side of the curve (taking advantage of the wider interlaminar spaces on that side) and then aimed directly perpendicular to the skin. The intent is to find lamina with the needle tip and then "walk up or down" the lamina to enter the epidural space (Figure 48-7).

In patients with scoliosis resulting from myopathic or neurologic disease, distortion of spinal anatomy may be

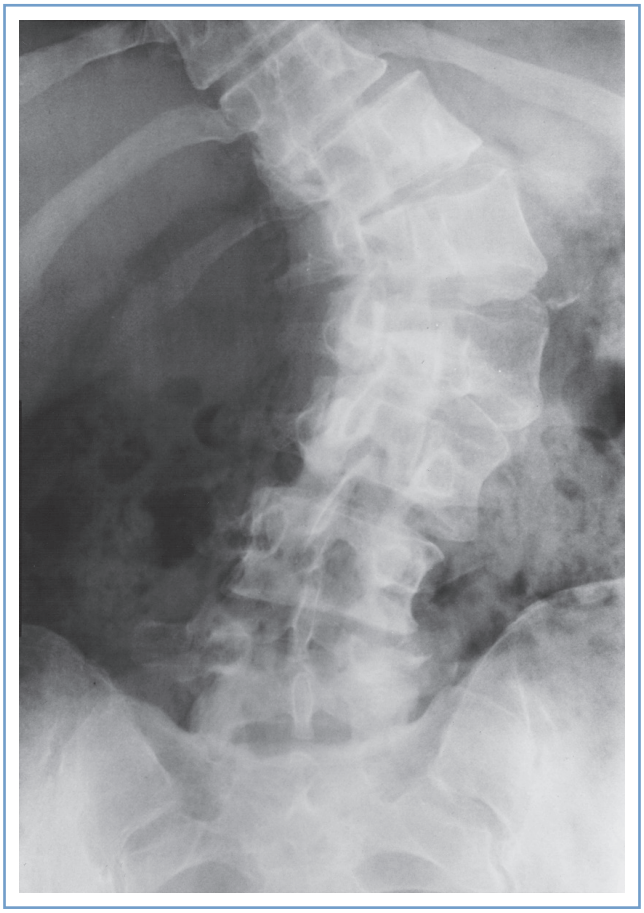

FIGURE 48-6 ■ Radiograph of the lower thoracolumbar spine in a young woman with scoliosis predominantly affecting the lumbar spine and markedly distorting her local anatomy. She received lumbar epidural analgesia for labor during her first pregnancy, after a catheter was placed with some difficulty. She received patient-controlled intravenous nalbuphine for labor analgesia during her second pregnancy after persistent, unsuccessful attempts to insert an epidural catheter. For her third pregnancy, this radiograph directed the practitioner toward the lower lumbar spaces, where anatomic distortion is less pronounced.

significant enough to prohibit the administration of neuraxial anesthesia. Ultrasonography is becoming a useful technique to facilitate administration of neuraxial anesthesia in parturients with challenging spinal anatomy, including those with scoliosis.[47,48] Asymmetry of the spine is not difficult to appreciate; learning how to use the information and determine the optimal space and needle direction requires more experience.[49] The paramedian view may provide the best information with respect to the widest interlaminar space in a woman with lumbar scoliosis.[46] There is limited published experience with use of *real-time* ultrasonography during neuraxial needle placement. One report described its use in two patients; one patient had scoliosis, for whom standard preprocedural ultrasonographic imaging did not provide adequate information.[50]

Local anesthetic dose requirements for epidural and spinal anesthesia in the patient with scoliosis are variable. Moreover, during administration of spinal anesthesia in a patient with a severe scoliotic curve, hyperbaric local

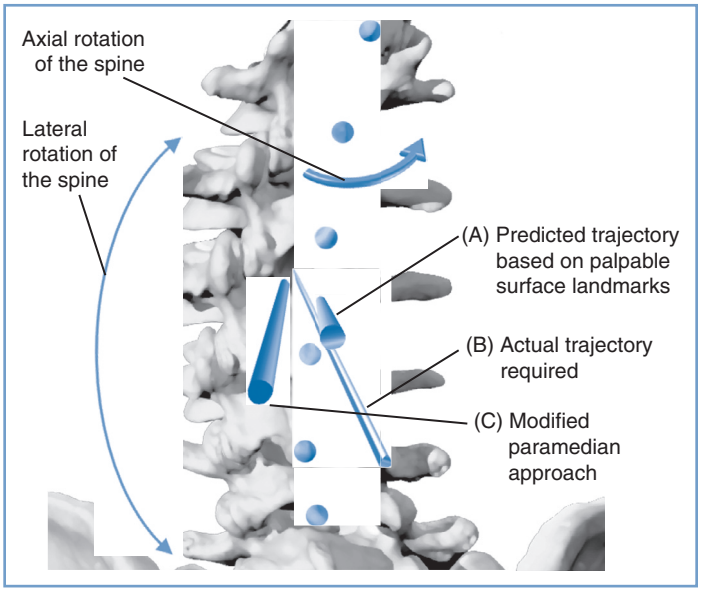

FIGURE 48-7 ■ Image of the lumbosacral vertebrae affected by a scoliotic curve to the left. Note the axial and lateral rotation of the vertebral bodies, and the rotation of the affected spinous processes (*blue dots*) into the concavity of the curve; these spinous processes are frequently anatomically abnormal. The apparent midline (*trajectory A*) suggested by palpated surface landmarks is to the right (toward the concavity of the curve) of the true midline. The figure demonstrates two approaches to enter the epidural/subarachnoid space: one where the needle is directed along the line of a spinous process toward the convexity of the curve (*trajectory B*), and the other a modified paramedian approach where needle entry starts on the convex side of the curve and is directed perpendicular to the skin (*trajectory C*). (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

anesthetic solution may pool in dependent portions of the spine, resulting in an inadequate block.[51] Thus, it may be preferable to use a continuous technique in those women with severe scoliosis so that the dose of local anesthetic agent can be titrated to the desired segmental level of anesthesia.

When offering neuraxial anesthesia to patients with a history of corrective surgery, the anesthesiologist must consider the following potential problems:

- Persistent back pain occurs in many patients with corrected scoliosis and correlates with both the extent of fusion and the time since surgery.[52,53]
- Degenerative changes occur in the spine below the area of fusion, and there is a higher incidence of both retrolisthesis and spondylolisthesis.[53]
- Twenty percent of patients undergo fusion to the lowest lumbar levels, limiting the potential for neuraxial anesthesia.[42,54]
- Insertion of an epidural needle in the fused area may not be possible because of the presence of instrumentation, scar tissue, and bone graft material.
- Intraoperative trauma to the ligamentum flavum may result in adhesions in or obliteration of the epidural space, and these changes may interfere with the spread of injected local anesthetic.[18]
- Obliteration of the epidural space may increase the incidence of unintentional dural puncture.
- These patients often manifest a high level of anxiety about their backs and may be reluctant to have neuraxial anesthesia.

A recent qualitative literature review by Ko and Leffert[55] on neuraxial anesthesia in the parturient with scoliosis provides insight into the challenges of neuraxial anesthesia administration in these women. There were 117 attempted neuraxial procedures, the majority (93) in surgically corrected patients. Overall, 71% had a successful neuraxial block; however, the corrected patients proved to be more challenging, with a 69% success rate versus 79% for the uncorrected group. The challenges in corrected patients included (1) inability to place the needle (22%), (2) multiple attempts (13%), (3) patchy analgesia (10%), (4) excessive local anesthetic dose requirements (9%), (5) unintentional dural puncture (4%), and (6) inadequate analgesia (4%). In the uncorrected group, the issues included (1) patchy, asymmetric, or unilateral blocks (8% of each) and (2) multiple attempts or failed placement (4% of each). There were also two cases of persistent low back pain of unknown etiology. Complications seem to occur more frequently in patients with fusion that extends to the lower lumbar and lumbosacral interspaces than in those with fusion that ends in the upper lumbar spine.

Both the anesthesiologist and the patient should anticipate the possibility that blind attempts to identify the epidural space may fail, and consideration should be given to the use of ultrasonography to guide the performance of a neuraxial block.[47] Although there is limited published experience to date with this specific population, Costello and Balki[56] reported the use of ultrasonography to facilitate the successful administration of neuraxial anesthesia in a patient with Harrington rod instrumentation. Alternative modes of intrapartum analgesia include administration of intraspinal opioids, caudal anesthesia, patient-controlled intravenous opioid analgesia, and inhalation analgesia.[55] Continuous spinal analgesia or anesthesia is a reasonable alternative to epidural analgesia or anesthesia for labor or cesarean delivery in parturients who have undergone major spinal surgery with instrumentation. Even making a dural puncture with a small-gauge spinal needle to confirm needle location and enhance spread of epidural local anesthetic is not unreasonable in this patient population.[55] It is possible to make an intentional dural puncture with a small-gauge needle either through or adjacent to a fusion mass in some patients in whom epidural space identification was previously unsuccessful and then consider performing repeat subarachnoid injections as needed for labor analgesia.

CHRONIC INFLAMMATORY ARTHRITIDES

This group of diseases includes rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and undifferentiated arthritis. Of these, rheumatoid arthritis is most affected by pregnancy and has been studied most extensively with respect to the immunologic relationship between mother and fetus. The most common arthritides seen in pregnancy are rheumatoid arthritis and ankylosing spondylitis and are discussed here in more detail.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic systemic disorder characterized by synovial proliferation that leads to joint destruction and subsequent deformity. It is becoming increasingly a disease of older people. Since 1985, the overall prevalence in the United States has fallen from 1.07% to 0.6%; the greatest decline in prevalence has occurred among people younger than age 55 years.[57] The disease occurs approximately two times more frequently in women than in men.[57]

The lumbosacral spine is affected in only 5% of patients with rheumatoid arthritis. In contrast, the cervical spine is commonly involved, and atlantoaxial subluxation occurs in 30% to 45% of patients with rheumatoid arthritis.[58,59] Although atlantoaxial subluxation may occur early in the course of the disease, it most often occurs in patients with a history of 5 years or more of highly active and erosive disease.[60] Atlantoaxial subluxation occurs as a result of an attenuation or disruption of the transverse ligament, which allows anterior movement of C1 on C2 during neck flexion. Radiographically, atlantoaxial subluxation is marked by an increase in the atlas-dens interval, which is best demonstrated on the lateral cervical spine radiograph with the neck flexed (Figure 48-8).

Vertical subluxation of the odontoid process occurs primarily in older patients with severe and long-standing disease. A scoliotic deformity of the trachea and larynx has been reported in patients with vertical subluxation.[61] The deformity is complex, involving both rotation and deviation of the larynx from the midline, and it may make laryngoscopy and tracheal intubation difficult. However, vertical subluxations occur primarily in older patients with severe, long-standing disease and are unlikely to be seen in women of childbearing age. Other airway issues such as cricoarytenoiditis and temporomandibular joint (TMJ) dysfunction may occur earlier in the disease and complicate airway management of the parturient.[62]

Extra-articular features are common in patients with rheumatoid arthritis. Anesthesiologists have a special interest in abnormalities that affect the airway and the cardiovascular and respiratory systems (Box 48-2). Although these complications occur more typically in patients with long-standing disease, it is prudent to inquire about those with more significant anesthetic implications. Cardiovascular mortality is especially high in patients with rheumatoid arthritis, similar to that of patients with type 2 diabetes, and often presents atypically.[62]

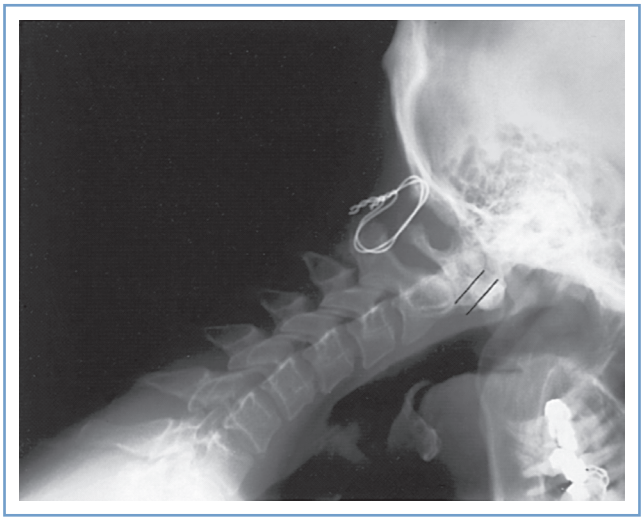

FIGURE 48-8 ■ Lateral radiographic study of the cervical spine (in flexion) in a 32-year-old woman with rheumatoid arthritis. There is isolated atlantoaxial subluxation (6 mm) in the absence of other radiologic changes of rheumatoid arthritis. She presented with neck pain, and a wire was placed between the occiput and the spinous process of C2 to limit the subluxation.

BOX 48-2 Extra-articular Features of Rheumatoid Arthritis

Cardiovascular
- Pericarditis
- Pericardial effusions
- Endocardial vegetations
- Myocardial nodules—conduction disturbance
- Arteritis/vasculitis

Airway
- Mandibular hypoplasia
- Cricoarytenoiditis
- Temporomandibular joint dysfunction
- Laryngeal deviation and rotation

Pulmonary
- Pleural effusion
- Pulmonary fibrosis
- Pulmonary nodules

Chest Wall
- Costochondritis

Neurologic
- Peripheral nerve compression
- Cervical nerve root compression

Hematologic
- Anemia
- Felty's syndrome

Ophthalmic
- Keratoconjunctivitis

Interaction with Pregnancy

Rheumatoid arthritis is associated with a slightly higher incidence of preterm birth, small for gestational age infants, and elective cesarean delivery, as compared with a reference population of women as shown in large databases from Norway and the United States.[63,64] In the absence of vasculitis, fetal outcome is good, although as a group the chronic inflammatory arthritides are associated with a higher perinatal mortality rate.[63] Since the 1930s, evidence has consistently shown that pregnancy has a beneficial, ameliorating effect on the activity of rheumatoid arthritis.[65] Approximately 75% of women note improvement in symptoms during pregnancy, which is typically evident by the end of the first trimester, with a gradual resolution of pain, swelling, and stiffness. The clinical improvement usually continues throughout pregnancy and recurs in future pregnancies. This remission often occurs despite the discontinuation of effective but teratogenic disease-modifying antirheumatic drugs and a substantial reduction in the dosage of safe drugs (e.g., corticosteroids). Relapse occurs postpartum in approximately 60% to 90% of women,[66] beginning as early as the second week after delivery. It appears that most women return to a disease status comparable to their prepregnant state.

Medical Management

Drug therapy for rheumatoid arthritis is divided into (1) symptom-modifying drugs, (2) disease-modifying antirheumatic drugs, and (3) biologic drugs.

Symptom-modifying therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, and corticosteroids. **NSAIDs** and **corticosteroids** have been the mainstay of therapy in rheumatoid arthritis during pregnancy for many years.[67] No evidence suggests that these drugs are teratogenic. However, there is limited experience with COX-2 inhibitors; hence, they are best avoided in pregnancy.[66] NSAIDs are classified as U.S. Food and Drug Administration (FDA) Category B medications in the first part of pregnancy, even though they are associated with an increased incidence of early pregnancy loss.[68] When used later in pregnancy, NSAIDs are associated with premature closure of the ductus arteriosus and increased risk for neonatal bleeding and are therefore classified as FDA Category C medications after 30 to 32 weeks' gestation. All NSAIDs except low-dose aspirin should be discontinued at 32 weeks' gestation.[67]

Corticosteroids are considered safe in doses up to 15 mg/day of prednisone equivalent. Larger doses increase risk for maternal infection and neonatal prematurity.[66]

Disease-modifying antirheumatic drugs reduce flares, prevent joint erosions, and have proven efficacy in decreasing morbidity and mortality from rheumatoid arthritis. This category of drugs for anti–rheumatoid arthritis treatment includes sulfasalazine, azathioprine, methotrexate, leflunomide, gold salts, and antimalarial agents. **Methotrexate** is considered a first-line treatment for rheumatoid arthritis and is typically started at diagnosis, but unfortunately it and **leflunomide** are highly teratogenic and must be stopped several months before conception.[66] **Sulfasalazine** inhibits folate synthesis, and therefore additional folate supplementation is required during pregnancy. **Azathioprine** is an FDA Category D drug, and although it may be used during pregnancy at doses less than 2 mg/kg/day, other options are preferable.

The **biologic drugs**, which are proving as effective as methotrexate in preventing erosions and reducing long-term disability, include the **anti–tumor necrosis factor-alpha (TNF-α) therapies** (e.g., etanercept), which are classified as FDA Category B in pregnancy and lactation. The other biologic drugs (e.g., abatacept, rituximab, tocilizumab) are Category C drugs, and there is very limited experience with their use in pregnancy; thus, the recommendation is to discontinue them 10 weeks before conception.[66]

An attempt is made to reduce the dose of all antirheumatic agents during pregnancy and resume antepartum therapy after delivery before disease activity flares.

Obstetric Management

Vaginal delivery is preferred for parturients with rheumatoid arthritis, and cesarean delivery should be reserved for obstetric indications. A major concern is maternal positioning during labor. Rheumatoid joints are unstable because of ligament loosening associated with chronic swelling and because of the destruction of ligaments and cartilage. It is important to determine the permissible range of motion and activity for affected joints. Special emphasis should be given to the hips, knees, and neck. Physicians and nurses should be aware of the potential risks of forcing motion beyond the disease-imposed limits.

Anesthetic Management

The preanesthetic evaluation should include a careful evaluation of the airway. Patients with rheumatoid arthritis may have a small mandible, TMJ dysfunction, cricoarytenoid arthritis, and laryngeal deviation, all of which may complicate direct laryngoscopy.[62] In particular, these findings may be present in parturients with juvenile rheumatoid arthritis. Cervical spine involvement is not common in young patients but may occur in patients with disease of long duration and in those with severe, deforming disease—typically, patients with juvenile rheumatoid arthritis. Although there is no guideline or consensus on the need to obtain cervical spine radiographs in patients with rheumatoid arthritis, it would be reasonable even in the pregnant woman if her rheumatoid arthritis includes severe erosive disease, neck symptoms, or a history of disease of 10 or more years' duration.[62] The cardiac and pulmonary features of rheumatoid arthritis are not common in young patients, but signs and symptoms of pleural and pericardial effusions and pulmonary parenchymal involvement should be sought.

No evidence contraindicates the administration of spinal or epidural anesthesia in patients with rheumatoid arthritis. However, recent evidence in the nonpregnant population has indicated that spinal blocks rise higher

than expected in patients with rheumatoid arthritis, independent of body mass index.[69,70] Care should be taken to avoid excessive manipulation of the neck during administration of general anesthesia. Finally, joints should be padded and protected appropriately during anesthesia.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthropathy characterized by infiltration of granulation tissue into the bony insertions of ligaments and joint capsules, with subsequent fibrosis, ossification, and ankylosis. Ankylosing spondylitis is a major subtype of an interrelated group of rheumatic disease called the spondylarthritides, which are linked by the major histocompatibility complex (MHC) Class 1 tissue antigen HLA B27.[71] Ankylosing spondylitis primarily affects the sacroiliac, facet, and costovertebral joints; sacroiliitis is pathognomonic. There is progressive flexion and fusion of the spine and fixation of the rib cage; however, the clinical spectrum is wide, and only a small proportion of patients progress to total spinal ankylosis.

The prevalence of ankylosing spondylitis is 0.1% to 1.4%.[71] Onset is common during the second and third decades of life, a period of peak childbearing potential. The disease is milder in women than in men, but women are more likely to have peripheral arthritis and involvement of the cervical spine and symphysis pubis.[72] Although clinically significant lesions of the cervical spine may occur early in the course of the disease, they are far more common in patients with long-standing ankylosing spondylitis (Figure 48-9).[61,73] Ultimately, 21% of patients with ankylosing spondylitis develop clinically significant atlantoaxial subluxation. TMJ involvement causes limited mouth opening in 10% of patients early in the disease, increasing to 30% to 40%.[72] A slower development of radiologic changes of the dorsolumbar spine occurs in women, and spinal rigidity or deformity and extra-articular manifestations are rare in young patients (Box 48-3).[62,71,74]

The mainstays of therapy for ankylosing spondylitis are NSAIDs and exercise programs. Disease-modifying antirheumatic drugs have not been proven beneficial, but for those patients not controlled on NSAIDs, anti–TNF-α therapies have proven quite effective.[71]

Interaction with Pregnancy

In contrast to rheumatoid arthritis, pregnancy does not seem to reduce the symptoms or slow the progression of disease in patients with ankylosing spondylitis, and many patients experience an aggravation of morning stiffness and back pain.[75] However, a recent retrospective review of 35 case-control matched pregnancies revealed improvement in pain and stiffness in 51% of women in early pregnancy, although unfortunately there was some return of pain as pregnancy progressed.[76] Pregnancy may ameliorate the extra-articular features of this disease (e.g., psoriasis, inflammatory bowel disease, small joint arthritis), but it appears that women with ankylosing spondylitis are more likely than women with rheumatoid arthritis to enter pregnancy with active disease and, hence, to have higher levels of pain at the beginning of pregnancy.[75] Ankylosing spondylitis does not adversely affect pregnancy, labor, or delivery; in the absence of pelvic joint ankylosis and/or hip joint involvement, an uncomplicated vaginal delivery at term should be anticipated in most patients. As in rheumatoid arthritis, NSAID therapy should be withdrawn by 32 weeks' gestation.

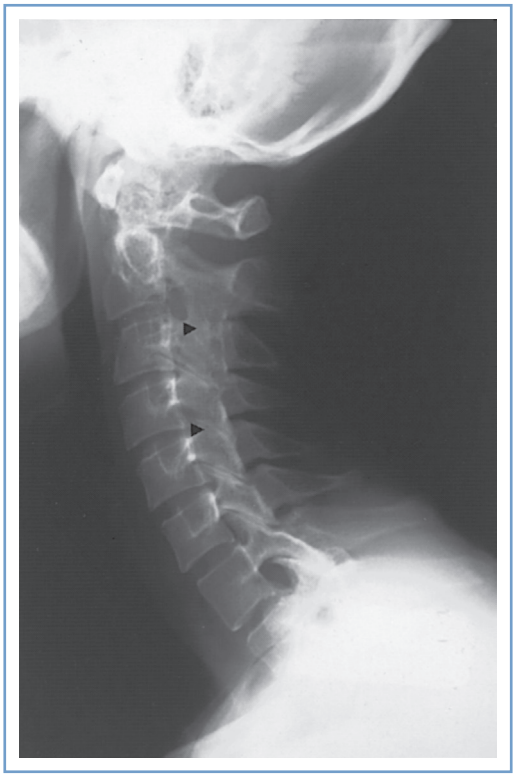

FIGURE 48-9 ■ Lateral radiographic study of the cervical spine in a 31-year-old woman with ankylosing spondylitis. There is evidence of facet joint ankylosis (*arrowheads*), although the lordotic curve remains well preserved. The ligaments of the thoracic spine are undergoing calcification with the spine in flexion, and there is a compensatory increase in the lumbar lordosis to maintain erect posture. (Flexion of the lumbar spine proved difficult, and a paramedian approach was used to enter the epidural space.)

Anesthetic Management

An anesthesiologist should review the patient's history with respect to the duration of the disease, the presence of extra-articular features, and the recent use of analgesics. Temporomandibular joint disorders, cervical spine involvement, and cardiopulmonary complications are rare early in the disease course; however, difficult tracheal intubation has been reported in parturients.[77] Severity of back symptoms is often out of proportion to the radiographic appearance of the spine, and calcification of the spinal ligaments is typically not advanced in young patients. Neuraxial anesthesia is acceptable in parturients with ankylosing spondylitis; however, even in young patients it may be technically challenging. Calcification of the interspinous ligaments and osteophyte formation

BOX 48-3 Extra-articular Features of Ankylosing Spondylitis

Systemic
- Fever
- Weight loss
- Fatigue

Cardiovascular
- Aortitis
- Aortic insufficiency
- Conduction disorders—heart block

Pulmonary
- Restrictive lung disease
- Pulmonary fibrosis

Neurologic
- Cauda equina syndrome
- Vertebrobasilar insufficiency
- Peripheral nerve lesions

Hematologic
- Anemia

Urologic
- Prostatitis

Ophthalmic
- Uveitis

may limit the parturient's ability to flex forward, making midline needle placement difficult.[72] A paramedian approach can be considered in this instance.[78] Additionally, the epidural space becomes narrowed in patients with ankylosing spondylitis, and there have been reports of unexpectedly high blocks,[79] as well as failed blocks despite confidence that the catheter was in the epidural space. After multiple failed attempts to provide epidural analgesia in a parturient with advanced ankylosing spondylitis, Hoffman et al.[80] suggested that a highly calcified posterior longitudinal ligament may limit rostral spread of local anesthetic in the epidural space. Preprocedural ultrasonography may be helpful, either to identify the best interlaminar space, or to indicate that administration of neuraxial anesthesia may be impossible.[81]

SPINA BIFIDA

Spina bifida results from the failure of the developing spine to completely enclose the neural elements in a bony canal. There is a wide spectrum with respect to the severity of the deformity and its implications. **Spina bifida occulta** is defined as failed fusion of the neural arch without herniation of the meninges or neural elements. A defect limited to a single vertebra, typically L5 or S1, is so common (occurring in 5% to 36% of the population) that it can be considered a normal variant.[82] Superficial signs of spina bifida occulta include a tuft of hair, cutaneous angioma, lipoma, or a skin dimple, but such signs are not common in patients with isolated vertebral arch anomalies and an underlying normal cord. Patients with spina bifida occulta rarely have symptoms related to this anomaly, although they may have a higher incidence of posterior disc herniation.[82]

Spina bifida cystica is defined as failed closure of the neural arch with herniation of the meninges (i.e., meningocele) or the meninges and neural elements (i.e., myelomeningocele) through the vertebral defect. These conditions are relatively uncommon, occurring in 1 to 3 per 1000 births.[83] Neurologic deficits involving the lower extremities and sphincters occur in almost all patients, and these deficits vary primarily in severity. Hydrocephalus is present in many patients, and shunting of the ventricular system is common, with revisions often required during childhood. By puberty as many as 50% of patients who have received shunts have little or no requirement for them.[84] Early and aggressive surgical treatment of spina bifida cystica has improved survival from 45% in the early 1970s to 70% to 90% by the mid-1980s. Obstetric and anesthesia providers can expect to encounter a growing number of pregnant women with spina bifida cystica.[85] Unfortunately, many surviving patients have significant residual neurologic impairment and ongoing orthopedic and genitourinary complications. Myelomeningocele is a progressive neurologic disease that eventually produces orthopedic, neurologic, and genitourinary complications. Kyphoscoliosis, which is common in patients with a thoracic lesion, occurs in 20% of patients with a lumbosacral defect.[86] Paralytic scoliosis is the most common type and results from an imbalance of paravertebral muscle tone.

Occult spinal dysraphism is an intermediate group of conditions in which the bony defect is associated with one or more anomalies of the spinal cord, including intraspinal lipomas (the most common), dermal sinus tracts, dermoid cysts, fibrous bands, and diastematomyelia (split cord). These lesions are differentiated from the more benign occulta lesions described previously.[87,88] Affected patients may have no neurologic symptoms or may have minor sensory, motor, and functional deficits of the lower limbs, bowel, and bladder[89]; they also may have orthopedic issues, such as scoliosis, limb pain, and lower extremity abnormalities.[90] Patients with cord abnormalities have cutaneous stigmata in 50% of cases, and 70% have a tethered spinal cord, which has implications for neuraxial anesthesia.[91]

Tethered Cord and Arnold-Chiari Malformation

Tethered cord syndrome (TCS) is characterized by neurologic deterioration secondary to traction on the conus medullaris, which typically, but not invariably, is low lying (L2 to L3).[87,91] Congenital abnormalities of the spinal cord such as lipoma, tight filum terminale, dermal sinus, meningocele manqué, and diastematomyelia are found in more than 50% of patients with adult-onset TCS.

A new classification of TCS in adults has been proposed to differentiate tethered cord occurring secondary to spina bifida cystica from the adult-onset neurologic

syndrome associated with spinal dysraphism.[92] Magnetic resonance imaging studies suggest that tethering is present in virtually all patients with spina bifida cystica and myelomeningocele, and it is also common in patients with occult spinal dysraphism.[88] Although many of the latter patients do not have obvious neurologic impairment secondary to the tethering, adults with TCS often have a long history of minor neurologic or orthopedic issues.[87,92] Others present with acute symptoms after a precipitating event that stretched the spinal cord, such as heavy lifting or placement in the lithotomy position.[93] Of note, more than 50% of adults with TCS present only with a history of low back and leg pain before a precipitating event that leads to the diagnosis.[87,88]

Low-lying spinal cords and the possibility of undiagnosed TCS have come to the attention of obstetric anesthesiologists with the publication of several case reports of neurologic injury after spinal or epidural anesthesia for delivery in women subsequently diagnosed with occult spinal dysraphism.[89,90] An important feature of adult TCS is that the low-lying cord is located more posteriorly than a normal cord, increasing the likelihood of direct needle trauma during administration of spinal or epidural anesthesia (Figure 48-10).[94] As noted previously, the isolated finding of a defective laminar arch (spina bifida occulta) is not associated with a low-lying or tethered cord.[87]

More severe forms of spina bifida may also be associated with **Arnold-Chiari malformation,** which is characterized by cerebellar herniation through the foramen magnum and descent of the pons and medulla. Tethered cord from a tight filum terminale has also been deemed causal in the development of syringomyelia and subsequent Arnold-Chiari syndrome.[95] Symptoms are more common if the cerebellar herniation exceeds 12 mm or if syringomyelia is present.[96,97]

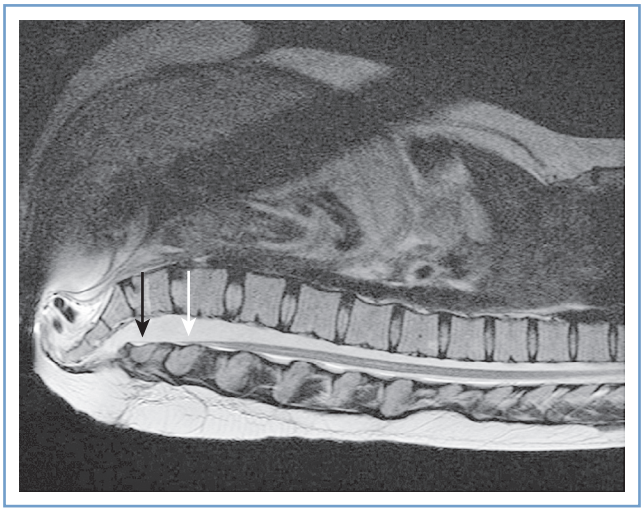

FIGURE 48-10 ■ Magnetic resonance image of the spine in a 27-year-old woman with history of a lumbar myelomeningocele excised as a neonate, with residual bladder dysfunction. A tethered spinal cord is present with a typical posterior low-lying position. The *white arrow* indicates the termination of the conus medullaris at L4 to L5, and the *black arrow* indicates the filum terminale located at L5 to S1. (This patient had a vaginal delivery at term, requiring only nitrous oxide for analgesia.)

Obstetric Management

Pregnancy is not complicated by the presence of a spina bifida occulta lesion. However, women with known TCS should avoid both the squatting position and a prolonged lithotomy position for delivery. Recurrent urinary tract infection is the most common antenatal complication in patients with spina bifida cystica and is associated with preterm labor.[85] Intestinal and urinary tract obstruction, as well as problems related to ileal conduits and stomas, are common during pregnancy, as are pressure sores resulting from greater immobility.[85] Uterine enlargement may compromise pulmonary function, especially in patients with kyphoscoliosis. Vaginal delivery is more common in women who are independently mobile and is less common in wheelchair-dependent patients.[85] Pelvic and lower limb anomalies and contractures may obstruct the pelvic outlet and warrant cesarean delivery. The obstetrician should evaluate the adequacy of the pelvis to determine whether a trial of labor is appropriate. Cesarean delivery is reserved for obstetric indications, and its incidence is increased and proportionate to the severity of the underlying defect and its consequences. Cesarean delivery is complicated by the presence of stomas and conduits; postoperative complications and prolonged hospital stays are common.[85]

Anesthetic Management

The epidural space may be incomplete or discontinuous across the level of **spina bifida occulta** lesions because of absence of the lamina and variable formation of the ligamentum flavum at this site. An attempt to identify the epidural space at the site of this lesion will likely result in unintentional dural puncture, although successful epidural analgesia has been reported with the catheter placed within the zone of the lesion. Fortunately, for two reasons, spina bifida occulta rarely causes issues for administration of neuraxial anesthesia. First, the lesion typically occurs at the L5 to S1 segments, below the level at which most epidural and spinal anesthetics are administered. Second, the most common anomaly is a simple midline split in the lamina, and this defect rarely seems to interfere with either the performance or the development of spinal or epidural anesthesia.

Occult spinal dysraphism is of more concern because of the potential for a low-lying, posteriorly located, and tethered spinal cord. A neurologic history should be taken and a screening neurologic examination should be performed in all women with a known defective laminar arch, preferably antenatally, to determine whether magnetic resonance imaging for spinal dysraphism is necessary.[90,98] The presence of skin dimpling or hair tufts should raise suspicion that an underlying cord abnormality exists. In my judgment, in women with a known low-lying cord, epidural anesthesia performed by an experienced anesthesiologist is safer than spinal anesthesia. If spinal dysraphism is suspected but no imaging studies are available, it would be prudent to avoid neuraxial anesthesia. Women with TCS may prefer to avoid neuraxial anesthesia because of the greater potential for direct neural trauma.

In the patient with a **spina bifida cystica** lesion, the anesthesiologist should determine the level of the lesion and whether the patient has residual spinal cord function below it. Patients with a complete lesion at or above T11 are likely to experience painless labor. However, the risk for autonomic hyperreflexia should be evaluated in patients with thoracic lesions, and prophylaxis should be provided if the patient is deemed to be at risk; this issue is especially important if the lesion is between T5 and T8. If the patient has undergone ventricular shunt placement, the current status of the shunt should be determined. Neurosurgical consultation should be obtained if questions remain about the requirement for—or function of—the shunt. Pulmonary function should be assessed, especially in patients with scoliosis. Baseline renal function also should be determined.

There are published reports of the use of epidural and spinal anesthesia in patients with spina bifida cystica.[83,98-100] Unfortunately the experience is limited, and most published series of pregnant women with spina bifida cystica report neither the type of anesthesia provided nor the complications experienced. Tidmarsh and May[99] reported management of intrapartum analgesia in 16 patients with spina bifida, 8 of whom had spina bifida cystica (with meningomyelocele). Five of the eight patients with spina bifida cystica received epidural analgesia for labor and/or delivery. Three patients had a "normal" block, one patient had a somewhat high block (sensory block level of T3 after administration of 10 mL of 0.25% bupivacaine), and one patient had poor sacral analgesia. In the U.K. Registry of High-Risk Obstetric Anesthesia, the period from 1997 through 2002 included 23 cases of parturients with spina bifida among 102 cases of neurologic conditions.[101] Of those, the extent of spina bifida was defined further in only 10 cases, and 8 had spina bifida occulta. Neuraxial anesthesia was provided in 8 cases, although 17 patients had planned to receive neuraxial anesthesia if needed. Only epidural anesthesia was used owing to concern about a low-lying or tethered cord; only 5 patients had magnetic resonance imaging performed before delivery.

Limited data exist on the obstetric anesthesia experience in parturients with Arnold-Chiari malformations. The largest series is that of Chantigian et al.,[96] who described their experience with 12 parturients who delivered a total of 30 infants. Nine deliveries were accomplished with neuraxial anesthesia, including six vaginal deliveries with epidural analgesia, two cesarean deliveries performed with single-shot spinal anesthesia, and one cesarean delivery performed with a spinal catheter. No patient experienced postprocedural neurologic sequelae related to the use of neuraxial anesthesia.

Administration of epidural or spinal anesthesia may be considered in women with various forms of spina bifida and stable neurologic function. Patients should be informed that there is limited published information on the administration of neuraxial anesthesia (and the risk for neurologic injury) in patients with neural tube defects, and these patients should be actively involved in decision-making. In patients with either surgically corrected spina bifida cystica or occult spinal dysraphism, the anesthesiologist should be aware that the terminal portion of the spinal cord typically lies at a vertebral level lower than normal. Imaging studies provide valuable information on neural anatomy and facilitate anesthetic management. In women with spinal dysraphism, a neurologic examination, as well as a full discussion of the risks and benefits of neuraxial anesthesia, should be performed and documented before administration of neuraxial anesthesia. A recent report by Asakura demonstrated that ultrasonography can be used to detect spina bifida occulta[102]; however, ultrasonographic imaging of the terminal portion of the cord would be much more difficult, although it has been shown to be feasible in children.[103] Spinal anesthesia should be performed below the known level of the conus or avoided in favor of epidural anesthesia. In women with spina bifida or occult spinal dysraphism, the epidural space is often abnormal, which increases the likelihood of inadequate epidural anesthesia. In our judgment, spinal anesthesia is not contraindicated in women with negligible function of the lower extremities and sphincters, given that the concern for direct neural trauma to a low-lying spinal cord is not clinically relevant.

ACHONDROPLASIA

Achondroplasia, an inherited disorder of bone metabolism, is the most common cause of disproportionate dwarfism, with a prevalence of 1 in 26,000 live births. Although it is inherited in an autosomal dominant mode, most cases arise from spontaneous mutation.[104] The range of cervical motion may be decreased, lumbar lordosis and thoracic kyphosis are increased, and thoracic kyphoscoliosis occurs.[105] The vertebral pedicles are short, and reduced length of the neural arch leads to shortened anteroposterior and transverse diameters of the vertebral canal, resulting in foramen magnum and spinal stenosis.[106,107] Although it may occur earlier, symptomatic spinal stenosis often does not present until the fourth or fifth decade, when kyphosis, scoliosis, osteophytes, and herniated discs typically cause further narrowing of the spinal canal. There is considerable interindividual variation in the clinical and radiographic characteristics, and skeletal abnormalities often show more variation than consistency.[106,108]

Obstetric Management

The uterus is an abdominal organ in the achondroplastic patient.[109] With advancing pregnancy it may encroach on the small thoracic cage and lead to decreases in the functional residual and closing capacities; severe dyspnea may occur with advancing gestational age. Back discomfort is common during pregnancy, and the reported incidence of sciatica is greater than in normal pregnant women,[110] most likely owing to the underlying spinal abnormalities. Typically, an inadequate maternal pelvis combined with a normal-sized (nonachondroplastic) fetus results in cephalopelvic disproportion. Imaging techniques may be used to confirm this situation, and the obstetrician should anticipate the need to deliver most patients with achondroplasia by cesarean delivery.[105,106]

Anesthetic Management

The short, obese limbs of the patient with achondroplasia may make it difficult to obtain measurements of blood pressure with a noninvasive cuff, and an intra-arterial catheter may be necessary. Prominent paraspinal muscles and marked lumbar lordosis may complicate attempts to palpate landmarks during the administration of spinal or epidural anesthesia; the use of ultrasonography may help identify landmarks.[105] Scoliosis of the spine also may cause technical difficulties with neuraxial anesthesia attempts. The small stature and spinal stenosis reduce the dose of local anesthetic required for major neuraxial anesthesia.[105,108,109,111] It is difficult to estimate the appropriate dose of local anesthetic for single-shot spinal anesthesia. Continuous epidural anesthesia or CSE anesthesia is preferable because it allows the anesthesia provider to titrate the dose of local anesthetic to the desired level of anesthesia. Local anesthetic dose requirements are typically smaller than those in parturients of normal stature[112]; this is not always the case, however, supporting the use of a neuraxial anesthetic technique that may be titrated to the desired effect.[110,113,114]

Difficult tracheal intubation has been reported in achondroplastic patients and should be anticipated. A case report noted that use of a video laryngoscope did not allow visualization of the vocal cords, and flexible fiberoptic bronchoscopy was required to intubate the trachea in an achondroplastic dwarf undergoing cesarean delivery.[115]

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is an inherited condition that occurs with an incidence between 1 in 21,000 and 1 in 60,000.[116,117] The genetic defect is within the genome that encodes for type I collagen, the major collagen in tissues that require structural strength. The disease is a generalized connective tissue disorder, and expression ranges from mild osteoporosis to the classical clinical stigmata characterized by multiple bone fractures and skeletal deformities, blue sclera, and middle ear deafness (otosclerosis). Four types may be distinguished clinically, and a system of classification (types I through IV) has been proposed.[118] Type I is the prototype disease. It is inherited as an autosomal dominant trait and is the most common and mildest form of this disease. It typically manifests in childhood as multiple fractures after minor trauma.[118] Types II and III are inherited as autosomal recessive traits and are characterized by extreme bone fragility. Type II is uniformly lethal, and stillbirth or early neonatal death is common; death *in utero* is caused by skeletal collapse, and early neonatal death typically results from chest wall failure and respiratory insufficiency. Infants with type III disease may have fractures at birth and may have progressive skeletal deformities during the first two decades of life. Type IV, also autosomal dominant, is much less common and is variable in expressivity.

The majority of pregnant women with osteogenesis imperfecta have type I disease, although pregnancy has been reported in more severe forms of the disease.[117,119]

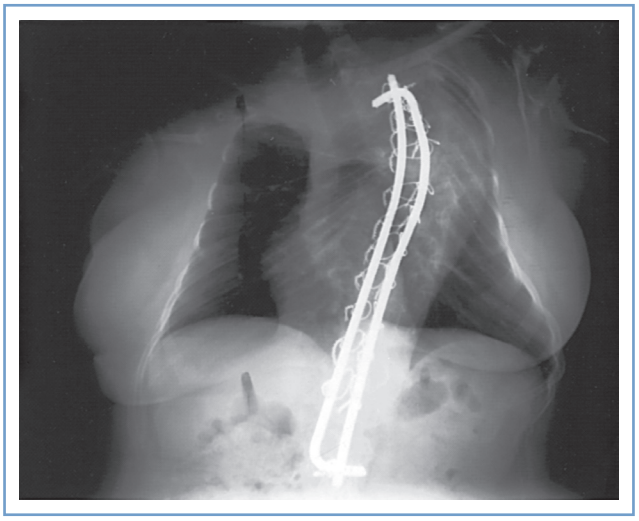

FIGURE 48-11 ■ A chest radiograph of a 30-year-old woman with osteogenesis imperfecta type I. Generalized osteoporosis, corrected thoracic kyphoscoliosis, a restricted thoracic cage, and multiple old fractures are demonstrated. (General anesthesia was provided for cesarean delivery and tubal ligation.)

There is considerable variability among affected patients as to the age at onset and frequency of fractures. Dwarfism is typical, and kyphoscoliosis is common, as are other chest wall abnormalities. These chest and spinal abnormalities result in restrictive lung disorders (Figure 48-11). Other abnormalities include a decrease in the range of motion of the shortened cervical spine, micrognathia, and malformed, brittle teeth.[119] Poor platelet adhesion may cause platelet dysfunction and a modest bleeding tendency. Hyperthyroidism occurs in 40% of patients with osteogenesis imperfecta; an elevated concentration of thyroxine leads to increases in both oxygen consumption and heat production.[118,119] Association with malignant hyperthermia is very weak; there is only one published case of a patient with osteogenesis imperfecta who developed malignant hyperthermia.[120] Intraoperative hyperthermia has often been reported; however, a recent retrospective cohort study of 49 patients with osteogenesis imperfecta undergoing noncardiac surgery revealed no difference in intraoperative temperature changes as compared with matched controls.[121] This recent information should allay ongoing concerns about risk for developing malignant hyperthermia.

Obstetric Management

Pregnancy results in transfer of calcium from the mother to the fetus, which in the patient with osteogenesis imperfecta can lead to increased fracture risk. In one published case, quantitative ultrasonometry of the phalanges was used to follow a woman with type I osteogenesis imperfecta who had increasing joint arthralgias to assess her fracture risk.[122] By 33 weeks' gestation, the ultrasonometry data and increased pain level guided the decision for early elective cesarean delivery. Platelet dysfunction in osteogenesis imperfecta may result in a higher incidence of intrapartum and postpartum hemorrhage,

although this finding is uncommon. Labor and vaginal delivery is associated with an increased risk for uterine rupture and pelvic fracture[123]; maternal pelvic fracture during pregnancy is an indication for cesarean delivery. These complications are also uncommon and most likely are influenced primarily by the severity of the underlying disease. Cephalopelvic disproportion typically mandates cesarean delivery in severely affected parturients.

Anesthetic Management

The anesthesiologist must be aware of the fragility of the bones, the potential for difficult tracheal intubation, and the presence and severity of restrictive lung disease. Transfers, positioning, and any invasive intervention must be accomplished with extreme care. Blood pressure cuffs and tourniquets to facilitate placement of intravenous catheters should be applied gently to prevent fractures. Difficult tracheal intubation may occur because of a short neck with limited range of motion and should be anticipated.[119] The anesthesiologist should take care not to hyperextend the neck, and laryngoscopy should be gentle to avoid fractures. Alternatives to direct laryngoscopy may be considered to reduce the applied forces necessary. If succinylcholine is used, a defasciculating dose of a nondepolarizing muscle relaxant should be employed in an attempt to prevent fasciculations.[124] An alternative to succinylcholine (e.g., rocuronium) may also be administered to prevent fasciculations.

Before administration of neuraxial anesthesia, the anesthesiologist should consider the technical difficulties inherent in performing neuraxial anesthesia in patients with spinal deformities. The anesthesiologist also should be aware of the platelet dysfunction in these patients. This risk is best evaluated by obtaining a thorough history before the administration of neuraxial anesthesia. In the setting of a reassuring history, neuraxial anesthesia need not be withheld. A hematology consult to better assess platelet function can be requested, if there is any doubt. Small stature and spinal abnormalities reduce the local anesthetic dose requirements and increase the risk for both misplaced injection and local anesthetic toxicity. It may be difficult to estimate the appropriate dose for single-shot spinal anesthesia in these patients. Thus, continuous epidural, continuous spinal, or CSE anesthesia is the neuraxial anesthetic technique of choice, barring other contraindications.[125] Yeo and Paech[126] reported the successful use of both epidural and subarachnoid blocks for cesarean delivery on five occasions over 9 years in a single patient with type I osteogenesis imperfecta. The use of ultrasonography may facilitate the administration of neuraxial anesthesia.

SPONDYLOLISTHESIS

Isthmic spondylolisthesis is a condition in which a defect in the pars interarticularis of a vertebra allows anterior slippage of the subjacent portion of the spine. As the body slips forward, it does not carry the neural arch with it; thus, there is little tendency toward spinal canal stenosis. Isthmic spondylolisthesis typically occurs at the lumbosacral junction, although it is not uncommon in the lumbar spine. Approximately 38% of cases occur in women.[127] The onset is common in the second and third decades, a period of peak childbearing potential.

Back pain is the presenting feature. Strenuous physical activity often precipitates the onset of pain. Pregnancy increases back symptoms in approximately half of patients with isthmic spondylolisthesis, but obstetric complications are unusual.[127,128] This disorder is not affected by pregnancy.[129]

Degenerative spondylolisthesis occurs when there is a forward slip of one vertebra on the subjacent level with no break in the neural arch.[130] It is four times more common in women than in men and occurs most frequently at the L4 to L5 level. It is not usually diagnosed before the onset of the fourth decade of life and seems to be twice as common in parous women. It is suggested that rotational and sheer stresses on the L4 to L5 joint during gestation may be responsible for the higher incidence of degenerative spondylolisthesis in women who have borne children.

There is no published case of neuraxial anesthesia during labor in a parturient with severe spondylolisthesis (e.g., lumbosacral subluxation). Ideally, an anesthesiologist will see the patient during pregnancy to assess her symptoms and lumbar spinal anatomy. In the absence of evidence of a neurologic deficit, it seems appropriate to administer either epidural or spinal anesthesia. There is one note of caution: Horduna and Legaye[131] have shown that the presence of spondylolisthesis affects the relative position of the palpated intercristine line. As a result, in patients with high-grade spondylolisthesis, the actual lumbar interspace is one to three segments higher than is normally expected when using the palpated intercristine line as a guide for neuraxial anesthesia needle placement. It would be reasonable to use preprocedural ultrasonography to identify the appropriate lumbar interspace before needle insertion in parturients with known spondylolisthesis.

KEY POINTS

- Lumbopelvic pain is the most common musculoskeletal complaint during pregnancy. It results from both hormonal and mechanical factors.
- Low back pain does not contraindicate the administration of spinal or epidural anesthesia.
- Corrected idiopathic thoracolumbar scoliosis is the most common major musculoskeletal disorder seen in pregnant women. Prepregnancy pulmonary function is a better predictor of maternal outcome than the severity of the curve.
- Neuraxial anesthesia is technically challenging in patients with scoliosis, and the anesthesiologist should anticipate a greater incidence of complications and inadequate anesthesia.

- Maternal rheumatoid arthritis is associated with prematurity and low birth weight, but ankylosing spondylitis does not adversely affect the outcome of pregnancy.
- Pregnancy often ameliorates the symptoms of rheumatoid arthritis.
- Spina bifida occulta is a common incidental finding and does not contraindicate the administration of spinal or epidural anesthesia.
- Spina bifida cystica and occult spinal dysraphism are associated with a high incidence of tethered cord, which may complicate the administration of subarachnoid (spinal) anesthesia.
- Cephalopelvic disproportion often mandates cesarean delivery in parturients with achondroplasia or osteogenesis imperfecta.
- Ultrasonography is rapidly becoming a useful tool to facilitate administration of neuraxial anesthesia in patients with challenging spinal anatomy.

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CHAPTER 52

Renal Disease

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CHAPTER OUTLINE

"Children of women with renal disease used to be born dangerously or not at all—not at all if their doctors had their way."[1] This statement describes early experiences with maternal renal disease and pregnancy outcome. It remains true that renal disease, either preexisting or occurring during gestation, may impair maternal and fetal health. Experience and investigations during the past three decades have significantly improved the outcome for pregnant women with renal disease.[2]

PHYSIOLOGIC CHANGES IN PREGNANCY

A review of the renal physiologic changes that occur during normal pregnancy is helpful to understand and evaluate coexisting renal disorders (see Chapter 2). Early in gestation, increased intravascular volume leads to renal enlargement. Hormonal changes result in dilation of the renal pelvis and ureters; dilation often is accompanied by decreased ureteral peristalsis. Dilated uterine and ovarian veins, and the gravid uterus, may obstruct ureter drainage at the pelvic brim. Together, these changes predispose pregnant women to vesicoureteric reflux and ascending infection. Alterations in glomerular hemodynamics and tubular function also occur. Increased cardiac output and decreased intrarenal vascular resistance cause an 80% increase in renal blood flow and a 50% increase in glomerular filtration rate (GFR) during pregnancy. These changes are somewhat less pronounced near term. Because of the increased GFR, a serum creatinine concentration greater than 0.6 to 0.8 mg/dL and a blood urea nitrogen (BUN) concentration greater than 8 to 9 mg/dL (upper limit of normal for the pregnant patient) suggest renal insufficiency in the pregnant woman. Tubular sodium reabsorption and osmoregulation are reset, allowing a "physiologic hypervolemia" during gestation. Modest proteinuria, up to 300 mg in 24 hours, also occurs during pregnancy.[3]

Urinary tract infections (see Chapter 37) and renal dysfunction associated with hypertensive disorders of pregnancy (see Chapter 36) are discussed elsewhere in this text.

RENAL PARENCHYMAL DISEASE

Definition and Pathophysiology

Renal parenchymal disease consists of two general groups of disorders, **glomerulopathies** and **tubulointerstitial**

disease. Glomerulopathies are further subdivided into disorders that involve inflammatory or necrotizing lesions—the **nephritic syndromes**—and disorders that involve abnormal permeability to protein and other macromolecules—the **nephrotic syndromes**. More than 20 specific glomerulopathies exist. The nomenclature for these glomerulopathies is complex, and specific diseases are not discussed in detail here.

Tubulointerstitial diseases are disorders characterized by abnormal tubular function. They result in abnormal urine composition and concentration but are not characterized by decreased GFR until late in the disease course. The disorders in this category include interstitial nephritis, renal cystic disease, renal neoplasia, and functional tubular defects.

Patients with renal parenchymal disorders may remain asymptomatic for years, and they may exhibit only proteinuria and microscopic hematuria, with little if any evidence of reduced renal function. Spontaneous recovery or improvement with treatment occurs with many glomerulopathies. However, other patients exhibit progressive nephropathy, hypertension, and renal insufficiency. The incidence of kidney disease in pregnancy is approximately 0.12%.[4] In two thirds of these patients, the disorder results from glomerulopathy, and in one third, from tubulointerstitial disease.[5]

Diagnosis

Women with preexisting disease may choose to become pregnant without the counsel of their nephrologist. When such patients become pregnant, the obstetrician and nephrologist seek to define the extent of renal involvement. Serial blood pressure measurements are obtained to define the severity of hypertension and the efficacy of current antihypertensive therapy. Creatinine clearance and the level of proteinuria should be determined. Urinalysis yields information about the presence of renal casts and bacteriuria. The determination of serum creatinine and BUN concentrations defines the extent of renal insufficiency. A serum creatinine concentration greater than 0.8 mg/dL, which may be normal in the nonpregnant woman, may represent significant renal insufficiency during pregnancy. Alternatively, the obstetrician may first detect renal dysfunction through routine prenatal screening tests. If proteinuria, hematuria, or azotemia is detected, a complete biochemical evaluation should be performed.

Both preeclampsia and renal disease may manifest as hypertension, proteinuria, and edema. The distinction between the two disorders is often unclear, especially after 20 weeks' gestation. Fisher et al.[6] evaluated 176 renal biopsy specimens obtained from hypertensive women immediately postpartum, most of whom had a clinical diagnosis of preeclampsia. The clinicopathologic correlation was poor. Histologic evidence of preeclampsia (e.g., glomerular endotheliosis without hypercellularity) was present in only 65% of these hypertensive women. Primary renal disease was present in 20%, and hypertensive nephrosclerosis occurred in 11%. Nulliparous women (84%) were more likely to have a correct diagnosis of preeclampsia than parous women (38%).

Renal tissue biopsy is often used to establish a diagnosis in nonpregnant patients. Chen et al.[7] reported a series of 15 percutaneous renal biopsies performed in 15 pregnant women with onset of renal dysfunction of unknown cause during pregnancy. All patients underwent biopsy before 30 weeks' gestation. A biopsy-related complication occurred in only one patient who experienced gross hematuria. The authors judged that histologic results provided useful clinical guidance that facilitated successful fetal outcome in 14 of the pregnancies. More recently, Day et al.[8] performed renal biopsy in 20 pregnant women; the biopsy results led to altered management in 9 of 20. One patient had minor hematuria that resolved spontaneously. In contrast, Kuller et al.[9] reviewed 18 renal biopsies performed during pregnancy (n = 15) or in the immediate postpartum period (n = 3) in 15 women with elevated blood pressure. After the biopsy, renal hematoma was identified in 7 (39%) women, and 2 (11%) women required blood transfusion. Four intrauterine fetal deaths occurred, although none was a direct result of the biopsy. It is possible that women with elevated blood pressure are at a greater risk for postbiopsy complications. Because renal biopsy exposes the pregnant woman to potential complications, many perinatologists recommend biopsy only when sudden deterioration in renal function or symptomatic nephrotic syndrome occurs before 28 weeks' gestation, at which time definitive diagnosis may guide appropriate treatment. For problems beyond 28 weeks' gestation, the recommendation is to delay biopsy until the postpartum period.[8,9]

Effect of Pregnancy on Preexisting Kidney Disease

The extent to which pregnancy affects preexisting renal disease depends on the level of renal insufficiency before pregnancy. Among women with mild antenatal renal insufficiency, pregnancy does not substantially alter the natural course of renal disease.[10,11] Jungers et al.[10] evaluated the effect of pregnancy on renal function among 360 women with primary glomerulonephritis. During the study period, 171 (48%) women became pregnant. All study subjects had normal renal function at the time of entry into this study, and all of the patients who became pregnant had normal renal function at conception. In this case-controlled study, pregnancy was not identified as a risk factor for progression to end-stage renal failure. Limardo et al.[11] evaluated 223 women with biopsy-documented IgA nephropathy who had a serum creatinine level greater than 1.2 mg/dL, 136 of whom became pregnant. Women were observed for a minimum of 5 years (median, 10 years), and pregnancy did not seem to affect long-term outcome of kidney disease or the onset of proteinuria or hypertension.

In contrast, Jones and Hayslett[12] analyzed the outcome of 82 pregnancies in 67 women with preexisting moderate or severe renal insufficiency (i.e., serum creatinine level > 1.4 mg/dL before pregnancy or at the first antepartum visit). The mean ± SD serum creatinine concentration increased from 1.9 ± 0.8 mg/dL in early pregnancy to 2.5 ± 1.3 mg/dL in the third trimester. The prevalence of hypertension rose from 28% at baseline to 48%

during late pregnancy. Pregnancy-related deterioration of maternal renal function occurred in 43% of cases. Purdy et al.[13] also found that greater than 40% of women with moderate to severe kidney disease had deterioration in renal function due to pregnancy. Women with a serum creatinine concentration greater than 2.0 mg/dL who became pregnant had a one-in-three chance of developing dialysis-dependent end-stage renal disease during or shortly after pregnancy.[14]

The pathophysiology by which pregnancy exacerbates renal disease is unknown. One hypothesis is that increased glomerular perfusion, which normally accompanies pregnancy, paradoxically causes further injury to the kidneys in patients with preexisting impairment of function. However, this hypothesis is unsupported by published data, which demonstrate no evidence of hyperfiltration (i.e., an initial decline in serum creatinine concentration) during early pregnancy in patients with renal disease.[15] An alternative hypothesis is that preexisting renal disease may induce a cascade of platelet aggregation, microvascular fibrin thrombus formation, and endothelial dysfunction that leads to microvascular injury in the already tenuous kidneys.[14]

Effect on the Mother and Fetus

Pregnant women with chronic kidney disease are at an increased risk for maternal and fetal complications. Nevis et al.[16] systematically reviewed all published observational studies of women with chronic kidney disease that included a control group for comparison, excluding retrospective studies. They identified 13 studies that included at least five women between 1966 and 2010. Maternal complications included gestational hypertension, preeclampsia/eclampsia, and maternal mortality. Adverse fetal outcomes included preterm births, fetal growth restriction (also known as intrauterine growth restriction), small-for-gestational-age infants, neonatal mortality, stillbirths, and low birth weight. Adverse maternal outcomes were found in 12 studies, and the incidence was five times greater than in women without kidney disease. Adverse fetal outcomes were identified in nine studies, and the incidence was two times greater than in the normal healthy women.

The incidence of obstetric complications is proportional to the extent of preexisting maternal renal disease and preexisting hypertension.[17] Bar et al.[18] evaluated maternal and neonatal outcomes in 38 women (46 pregnancies) with primary renal disease. They observed an increase in complications compared with healthy women (Figure 52-1). In a logistic regression model, only preexisting hypertension and a high preconception serum uric acid level predicted worse outcome. Other factors (e.g., degree of preexisting renal impairment) were not significant predictors, but, of note, 90% of the cohort had mild disease. In a study of women with moderate to severe renal disease, Jones and Hayslett found the complication rate was much greater.[12] The incidence of preterm birth was 59%, the incidence of fetal growth restriction was 37%, and the cesarean delivery rate was 59%. Ramin et al.[19] reviewed the literature for studies of renal disease and maternal and fetal outcome. Overall, fetal survival ranged from 64% to 98% depending on the extent of renal insufficiency and the presence or absence of hypertension.

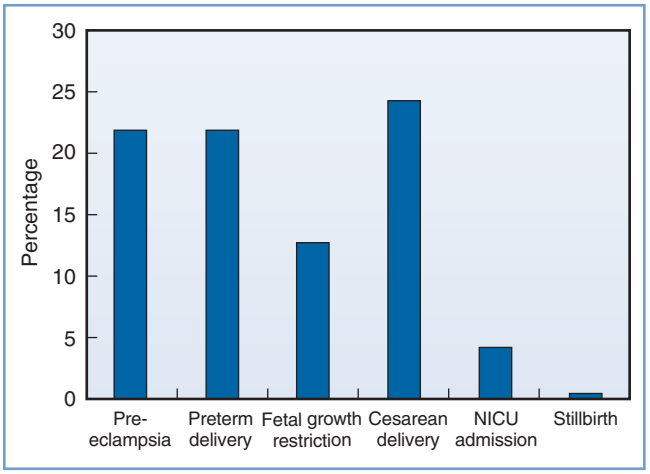

FIGURE 52-1 ■ Rate of short-term pregnancy outcome in women with primary renal disease. *NICU,* neonatal intensive care unit. (From Bar J, Orvieto R, Shalev Y, et al. Pregnancy outcome in women with primary renal disease. Isr Med Assoc J 2000; 2:178-81.)

Medical and Obstetric Management

During pregnancy, the nephrologist and the obstetrician monitor maternal renal function, blood pressure, and fetal development at frequent intervals. Monthly determination of serum creatinine concentration, creatinine clearance, and proteinuria allows the recognition of renal deterioration. An antepartum consultation with the anesthesiologist should also be considered.

Some glomerulopathies respond to corticosteroids, and corticosteroid therapy should be continued during pregnancy. Rapid deterioration of renal function that occurs before 28 weeks' gestation may require renal biopsy to exclude rapidly progressive glomerulopathies that require treatment. Antihypertensive therapy should be instituted as needed (see Chapter 36). Recombinant human erythropoietin improves maternal anemia during pregnancy.[20] Protein restriction places the fetus at risk for growth restriction and is not used. Deterioration of maternal renal function, the onset of preeclampsia, or evidence of fetal compromise may necessitate preterm delivery.

Hemodialysis and Long-Term Ambulatory Peritoneal Dialysis

When renal disease has progressed to end-stage renal failure (i.e., GFR < 5 mL/min), fertility is suppressed and conception and pregnancy are rare. Less than 10% of premenopausal patients undergoing dialysis have regular menses. Luteinizing hormone and follicle-stimulating hormone concentrations assume an anovulatory pattern, which causes 40% of affected women to be amenorrheic. Half of all female patients undergoing dialysis exhibit hyperprolactinemia because of reduced clearance and

hypothalamic disturbances.[21] Toma et al.[22] surveyed 2504 dialysis units in Japan and reported only 172 pregnancies among 38,889 women who were undergoing dialysis.

There are two modalities of dialysis: extracorporeal hemodialysis and intracorporeal peritoneal dialysis. **Hemodialysis** necessitates vascular access and the need for anticoagulation of the extracorporeal circuit and may be complicated by cardiovascular instability, large fluid and electrolyte shifts, and the risk for hepatitis. Hypotension may compromise uteroplacental perfusion and cause fetal compromise. Even when hypotension and major fluid shifts are avoided, Doppler ultrasonographic examination of uterine and umbilical artery flow during hemodialysis suggests the occurrence of a redistribution of arterial flow away from the uteroplacental vascular bed.[23] Fetal heart rate monitoring is recommended during dialysis.[24] Rapid removal of maternal solutes and reduced oncotic pressure with attendant free-water diffusion into the amniotic cavity may lead to polyhydramnios. Hemodynamic consequences are minimized by more frequent but shorter dialysis runs. Long-term ambulatory **peritoneal dialysis** allows less hemodynamic trespass, a more stable fetal environment, and the freedom to undergo dialysis at home. However, peritoneal dialysis may not be associated with greater fetal survival. Complications of this modality include peritonitis and catheter difficulties.[25]

Published reports have noted a wide range of successful pregnancies in dialysis-dependent pregnant women, regardless of the modality of dialysis. Toma et al.[22] reported that 90 (52%) of 172 pregnancies in women undergoing long-term hemodialysis were successful. More recently, because of improvement in maternal-fetal care, the success rate appears to be improving. Chou et al.[26] pooled data from 10 published case series and 12 case reports and found that 71% of women undergoing hemodialysis and 64% of women undergoing peritoneal dialysis had a successful delivery. Similarly, Piccoli et al.[27] pooled data from 10 studies that included 90 conceptions in 78 women and reported successful delivery can be achieved 75% of the time.

Maternal complications include malnutrition, anemia, and hypertension. Fetal complications include fetal growth restriction, fetal death, and preterm labor. BUN levels should be kept below 50 mg/dL before dialysis and below 30 mg/dL after dialysis.[25] At birth, azotemia in the newborn is similar to that in the mother, but this quickly corrects because the newborn has normal kidney function. The long-term effects of intrauterine azotemia on newborn cognitive development are unknown.[28]

Patients undergoing hemodialysis have a high prevalence of viral hepatitis, a greater frequency of active tuberculosis, and a higher rate of infection with vancomycin-resistant enterococci, human immunodeficiency virus (HIV), and methicillin-resistant *Staphylococcus aureus*. The risk for hepatitis C virus (HCV) infection is particularly of concern, with reported rates as high as 36%. However, with improvement in aseptic technique and more attention to hand washing, the decline in the reuse of dialysis equipment, and the use of dedicated isolated dialysis machines for HCV-seropositive patients, the rates of infection and seroconversion can be markedly reduced.[29,30]

Anesthetic Management

Anesthetic management is influenced by the extent of renal dysfunction and hypertension. The parturient with stable renal disease, mild to moderate renal insufficiency, well-controlled hypertension, and euvolemia requires minimal special consideration. In contrast, the dialysis patient with end-stage renal failure presents many anesthetic challenges because renal disease may affect almost every organ system (Box 52-1). Poorly controlled hypertension leads to left ventricular hypertrophy and dysfunction. Symptoms of cardiovascular compromise should prompt echocardiography to evaluate ventricular

BOX 52-1 Chronic Renal Failure: Abnormalities That May Affect Anesthetic Management

Cardiovascular
- Hypertension
- Fluid overload
- Ventricular hypertrophy
- Accelerated atherosclerosis
- Uremic pericarditis
- Uremic cardiomyopathy

Pulmonary
- Increased risk of difficult airway
- Recurrent pulmonary infections
- Pleural effusion

Metabolic and Endocrine
- Hyperkalemia
- Metabolic acidosis
- Hyponatremia
- Hypocalcemia
- Hypermagnesemia
- Decreased protein binding of drugs
- Hypoglycemia

Hematologic
- Anemia
- Platelet dysfunction
- Decreased coagulation factors
- Leukocyte dysfunction

Neurologic
- Autonomic neuropathy
- Mental status changes
- Peripheral neuropathy
- Restless legs syndrome
- Seizure disorder

Gastrointestinal
- Delayed gastric emptying
- Increased gastric acidity
- Hepatic venous congestion
- Hepatitis (viral or drug-induced)
- Malnutrition

Neurologic
- Autonomic neuropathy
- Peripheral neuropathy
- Cerebrovascular insufficiency

function. An intra-arterial catheter also may aid the management of the parturient with poorly controlled hypertension. Uremic pericarditis, cardiomyopathy, and accelerated atherosclerosis are rarely seen until advanced uremia has been present for several years.

Normochromic, normocytic anemia secondary to impaired erythropoietin production, chronic gastrointestinal bleeding, and vitamin deficiency are common findings. Typically, the anemia is well tolerated and does not require transfusion, unless excessive surgical bleeding occurs. Uremic toxins may cause functional platelet defects; these abnormalities are reversed by dialysis. Thrombocytopenia may also occur as a result of increased peripheral destruction of platelets. Generalized coagulopathy may result from the anticoagulation used during the dialysis process.[31] A full coagulation profile and careful bleeding history should be performed, especially before the initiation of neuraxial anesthesia. Hemodialysis fistulas should be padded carefully to prevent thrombosis. Blood pressure cuffs should not be placed on these extremities.

Neuraxial Anesthesia

Neuraxial anesthesia is the preferred technique for both labor analgesia and cesarean delivery, but there are some unique considerations in the parturient with renal disease. Uremic patients may be hypervolemic or hypovolemic, depending on the time elapsed since their last dialysis session. Hypovolemia and autonomic neuropathy may lead to profound hypotension during the initiation of sympathetic blockade. Intravascular volume should be assessed before induction of anesthesia. Assessment of clinical signs (e.g., skin turgor, mucous membranes, tachycardia) is generally sufficient. Central venous pressure monitoring or transthoracic echocardiography may be useful when the volume status remains unclear. Although there are no studies in the renal transplant patient, a role for intravenous prehydration to prevent hypotension is unlikely because this modality is not efficacious in the healthy parturient.[32] There is insufficient evidence to recommend spinal versus epidural techniques for the patient with renal disease. Frequent monitoring of blood pressure and immediate treatment of hypotension is suggested.[33] Preexisting peripheral neuropathy should be documented before the administration of neuraxial anesthesia.

Local anesthetic systemic toxicity (LAST) after bupivacaine brachial plexus blockade has been reported in patients with chronic renal failure.[34] Whether LAST is related to toxic levels of local anesthetic unique to the renal failure patient is unclear. Rice et al.[35] found no significant difference in the pharmacokinetic profile of bupivacaine after brachial plexus blockade in a group of uremic patients and in patients with normal renal function. There are no published data on the pharmacokinetics of epidurally administered local anesthetic agents in patients with chronic renal failure.

Orko et al.[36] administered spinal anesthesia with plain bupivacaine 22.5 mg to 20 nonpregnant patients with chronic renal failure and 20 control patients. Maximal segmental anesthesia occurred more rapidly in the patients with renal disease (21 versus 35 minutes), but the duration was reduced. Further, the extent of sensory blockade was two segments higher in the patients with renal disease. There were no untoward effects in any of the patients.

General Anesthesia

Patients with chronic uremia exhibit delayed gastric emptying and hyperacidity, which may increase the risk for aspiration pneumonitis. In addition to sodium citrate, when time allows, the anesthesia provider also should consider administering a histamine-2 (H_2)-receptor antagonist and metoclopramide. Recommended single doses for patients with renal failure are ranitidine 50 mg and metoclopramide 10 mg given intravenously. Weir and Chung[37] suggested that patients with chronic renal failure present greater difficulties with tracheal intubation than otherwise healthy patients; however, an objective analysis of airway difficulty has not been performed in this population.

All the standard induction agents are safe in patients with renal failure. Etomidate may have an advantage because it supports the circulation better than other induction agents. Propofol exhibits normal volume of distribution and elimination in patients with renal failure and is also commonly used. Protein binding of propofol is unaffected by renal failure.[38] Uremia increases blood-brain barrier permeability to many drugs.[39] These changes may warrant a small reduction in the dose of propofol or thiopental for induction. The serum potassium concentration should be determined before induction of anesthesia. If the potassium concentration is greater than 5.5 mEq/L, dialysis should be performed before an elective procedure. Succinylcholine will cause a 0.5 to 0.7 mEq/L increase in potassium concentration, which is similar to the increment that occurs in patients without renal disease.[40] If the patient is already hyperkalemic, this mild elevation may be sufficient to precipitate cardiac dysrhythmias. Plasma cholinesterase concentrations are normal, even after dialysis, and the duration of action of succinylcholine is not prolonged.[41]

Neuromuscular blockade should be maintained with an agent that does not rely on renal elimination. Cisatracurium undergoes Hofmann degradation, and therefore the duration of action is not prolonged in patients with renal failure. Hypermagnesemia, commonly found in patients with kidney disease, may potentiate neuromuscular blockade.[42] Although anticholinesterase agents undergo renal elimination and have a prolonged duration in patients with renal insufficiency, the volume of distribution remains the same and standard doses are used for the reversal of neuromuscular blockade.

Postoperative Analgesia

The principles of postoperative analgesia for the woman with renal disease are the same as for healthy woman, with some important considerations because drug clearance can be altered for opioids and their metabolites (see Chapters 27 and 28). Morphine is generally safe as a single dose, but with longer-term use its metabolite, morphine-6-glucuronide, may accumulate. Meperidine is

of particular concern because its active metabolite, normeperidine, is neurotoxic and is renally excreted. Hydromorphone and oxycodone, and their metabolites hydromorphone-3-glucuronide and α- and β-oxycodol, respectively, are also renally excreted and may accumulate with prolonged use. Methadone does not accumulate in patients with renal disease and may be a useful long-term analgesic. Fentanyl and sufentanil are only minimally excreted in the urine, and because they are short-acting drugs they may be particularly useful. Remifentanil is metabolized by blood and tissue esterases and is not dependent on the kidney for excretion, making it safe as well for use in patients with renal failure.[43] The safest approach may be to use neuraxial opioids because small doses are administered. Alternative techniques that avoid opioids such as transversus abdominis plane (TAP) block may also be considered, but the efficacy of TAP block for analgesia after cesarean delivery has been questioned (see Chapter 27).[44]

ACUTE RENAL FAILURE

Definition and Epidemiology

Acute renal failure (ARF) is an uncommon but serious complication of pregnancy. Rapid deterioration of renal function leads to an accumulation of fluid and nitrogenous waste products with impaired electrolyte regulation. In the mid-20th century, nearly a fourth of all cases of ARF were obstetric. Fortunately, during the past five decades, the incidence of ARF in developed countries has decreased significantly.[45,46] Stratta et al.[45] reported a steady decline in the incidence of ARF from 1 in 3000 to 1 in 18,000 pregnancies from 1958 to 1994. With respect to all ARF cases, the proportion related to pregnancy decreased from 43% to 0.5%. This progress has resulted from improved obstetric care and fewer septic abortions.

Pathophysiology and Diagnosis

ARF is suggested by a sharp increase in the plasma creatinine (> 0.8 mg/dL) and BUN (> 13 mg/dL) concentrations. In complete renal failure, the serum creatinine concentration increases at the rate of 0.5 to 1.0 mg/dL/day. Urine output typically decreases to less than 400 mL/day (oliguria), but some patients may be nonoliguric. ARF is subdivided according to underlying cause (i.e., prerenal, postrenal, and intrarenal) (Box 52-2). The inciting disorders vary throughout the world. In developing countries septic abortion is the leading cause of pregnancy-related ARF.[47,48] In developed countries, severe preeclampsia/eclampsia, acute pyelonephritis of pregnancy, and bilateral renal cortical necrosis are the most common underlying disorders.[45,46]

Prerenal Causes

The most common prerenal causes of ARF—hyperemesis gravidarum and obstetric hemorrhage—lead to hypovolemia and inadequate renal perfusion.[49,50] Urinary indices show urinary osmolality greater than 500 mOsm/kg water, urine sodium less than 20 mEq/L, fractional sodium excretion less than 1%, and a urinary-to-plasma creatinine ratio greater than 40.[51] Concealed uterine hemorrhage from placental abruption may remain unrecognized until hypotension and renal failure ensue.[52] Women with preeclampsia may be more likely to develop ARF after hemorrhage because of preexisting intravascular contraction and widespread maternal endothelial dysfunction.[53] Women who developed preeclampsia during pregnancy, with or without renal failure, are more likely to develop renal failure later in life.[54]

BOX 52-2 Causes of Acute Renal Failure during Pregnancy

PRERENAL
- Hyperemesis gravidarum
- Uterine hemorrhage
- Heart failure

INTRARENAL
- Acute tubular necrosis
- Septic abortion
- Amniotic fluid embolism
- Drug-induced acute interstitial nephritis
- Acute glomerulonephritis
- Bilateral renal cortical necrosis
- Acute pyelonephritis
- Preeclampsia/eclampsia
- Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
- Acute fatty liver of pregnancy
- Idiopathic postpartum renal failure

POSTRENAL
- Urolithiasis
- Ureteral obstruction by the gravid uterus

Intrarenal Causes

An intrarenal cause is diagnosed once prerenal and postrenal causes of ARF have been excluded. In general, oliguric intrarenal ARF is not easily reversed and must run its course. Causes include acute tubular necrosis, interstitial nephritis, and acute glomerulonephritis as well as a few causes unique to pregnancy. These include renal cortical necrosis, acute pyelonephritis, severe preeclampsia/eclampsia, acute fatty liver of pregnancy, and idiopathic postpartum renal failure. A thorough history, review of medications, and urinalysis typically help determine the specific initiating factor.[55]

Acute tubular necrosis results from nephrotoxic drugs, amniotic fluid embolism, rhabdomyolysis, intrauterine fetal death, and prolonged renal ischemia secondary to hemorrhage or septic shock. Urinalysis demonstrates dirty brown epithelial cell casts and coarse granular casts. Urinary indices show urine osmolality less than 350 mOsm/kg water, urine sodium concentration greater than 40 mEq/L, fractional sodium excretion greater than 1%, and a urinary-to-plasma creatinine ratio less than 20.[55]

Acute interstitial nephritis is caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and various

antibiotics. Patients typically have fever, rash, eosinophilia, and urine eosinophils.

Acute glomerulonephritis is rare during pregnancy. It is suggested by hematuria, red cell casts, and proteinuria. Urinary indices of acute glomerulonephritis are similar to those of prerenal ARF.

Bilateral renal cortical necrosis, which is rarely observed in the nonobstetric patient, is responsible for 10% to 38% of cases of obstetric ARF.[47,56-58] It may occur during early or late pregnancy. Hemorrhage is the most common precipitating event. The pathogenesis of this disorder is unclear but may involve renal hypoperfusion or endothelial damage by endotoxins imposed on the normal hypercoagulable state of pregnancy.[59] A single dose of endotoxin may precipitate bilateral renal cortical necrosis in pregnant animals and has led some investigators to view this disorder as a clinical analogue of the experimental Sanarelli-Shwartzman reaction.[60] Extensive microthrombi are found within the glomeruli and renal arterioles. Diagnosis is made by selective renal arteriography, which reveals absence or patchiness of blood flow in the cortex. Renal biopsy may also be performed in the absence of active coagulopathy.[9]

Acute pyelonephritis is one of the most common infectious complications of pregnancy (see Chapter 37). Although acute pyelonephritis rarely leads to ARF in the nongravid patient, it accounts for 5% of cases of ARF among pregnant women.[53] The reason for this greater susceptibility is unclear. Whalley et al.[61] noted that acute pyelonephritis causes a marked reduction of GFR in pregnant women. In contrast, pyelonephritis causes little reduction in GFR in nonpregnant patients. The kidney may be more sensitive to bacterial endotoxins during pregnancy.

Severe preeclampsia/eclampsia may be responsible for 20% of cases of obstetric ARF in developed countries[53] and as much as 35% of cases in developing countries.[62] Renal failure is generally associated with severe preeclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets); in these patients the incidence may be as high as 36%.[63] However, many cases of renal dysfunction and failure may only mimic preeclampsia and may actually result from other factors.[6] Other causes of ARF should be considered before preeclampsia is considered to be the basis of renal failure.

Sibai and Ramadan[64] reported 32 cases of ARF associated with HELLP syndrome. The majority of patients had derangement of multiple organ systems and other obstetric complications (e.g., placental abruption, intrauterine fetal death, disseminated intravascular coagulation, postpartum hemorrhage, sepsis). Renal histology in a woman with HELLP syndrome and renal failure demonstrated thrombotic microangiopathy and acute tubular necrosis, suggesting a possible pathogenesis of acute renal failure associated with HELLP syndrome.[65] In the Sibai and Ramadan[64] report, 4 (13%) parturients died, and 10 (31%) required dialysis. The perinatal mortality rate was 34%, with 72% of deliveries occurring preterm. Of interest, Flynn et al.[66] reported the successful use of cadaveric kidneys procured from a parturient who died after HELLP syndrome and ARF. Both recipients had acceptable graft function 2 years after transplantation.

Acute fatty liver of pregnancy, a rare but life-threatening disorder of pregnancy, is associated with a 60% to 100% incidence of ARF. Specific clinical features of acute fatty liver of pregnancy are discussed in Chapter 46.

The syndrome of **idiopathic postpartum renal failure** was initially described in 1968 by Robson et al.[67] Subsequently, approximately 200 cases have been reported. This syndrome is characterized by ARF, microangiopathic hemolytic anemia, and thrombocytopenia occurring 2 days to 10 weeks after an uncomplicated delivery. It appears closely related to the hemolytic-uremic syndrome. Idiopathic postpartum renal failure is typically preceded by a viral upper respiratory tract or gastrointestinal syndrome that rapidly progresses to ARF. The use of ethinyl estradiol as a contraceptive may also be causally related to this syndrome.[68] Spontaneous bleeding, congestive heart failure, hypertension, and seizures have been reported with this syndrome.[69] Some investigators believe that this syndrome represents a clinical analogue to the generalized Shwartzman reaction, a condition induced in laboratory animals by two successive injections of endotoxin, which results in factor XII activation, thrombin generation, and fibrin deposition.[60] Others consider the platelet deposition to be the primary event that leads to microvascular thrombi.[69]

Management involves plasma exchange transfusion, dialysis, and antiplatelet therapy. The role of heparin therapy in idiopathic postpartum renal failure is controversial. The morbidity and mortality among affected patients vary by study. Reports from 1979 and 1988 suggested a mortality rate of approximately 50%.[70,71] Although survival has improved with prompt diagnosis and aggressive treatment, morbidity is still high. Shrivastava et al.[72] reported three patients who had postpartum hemolytic-uremic syndrome and had initial recovery with immediate exchange transfusion; long-term follow-up was not reported. Dashe et al.[73] reported 10 patients with peripartum or postpartum hemolytic-uremic syndrome and followed their course for a mean of 9 years. Although all 10 initially survived, 1 subsequently died and all had major morbidity, including recurrence of renal failure, hypertension and seizures.

Postrenal Causes

The postrenal causes of ARF include nephrolithiasis and ureteral obstruction by the gravid uterus.[74] The latter complication is more likely in pregnant women with polyhydramnios or multiple gestation.[75] Preexisting ureteral dilation and impaired peristalsis increase the risk for obstructive uropathy during pregnancy. Flank pain and decreased urine output during late gestation should alert the clinician to this possibility. Courban et al.[76] reported an unusual case of obstructive uropathy leading to ARF in a pregnant woman with multiple uterine leiomyomas.

Effect on the Mother and Fetus

Maternal mortality from ARF has decreased significantly in the past 40 years. Stratta et al.[45] reviewed their

experience with ARF in pregnancy from 1958 to 1995. In the early period from 1956 to 1957 the maternal mortality rate was 31% but decreased to zero from 1988 to 1994. They hypothesized that this was probably due to improvement in medical and obstetric care, especially of women with preeclampsia. Although maternal prognosis has improved significantly in developed countries, mortality ranges between 20% and 30% in developing countries.[48,62] The prognosis for the fetus is worse than for the mother. Reported fetal mortality is as high as 40% to 50%,[77,78] although outcomes may be improving. Two groups reported much lower mortality rates (0% to 13%) with the use of aggressive hemodialysis (six times per week with the goal of maintaining the blood urea nitrogen level < 50 mg/dL).[79,80]

Medical and Obstetric Management

Management is directed toward rapid recognition of the underlying abnormality. Reversible disorders such as hypovolemia, concealed uterine hemorrhage, urinary tract infection, ureteral obstruction, and drug-induced ARF must be excluded. The urine-to-plasma osmolality ratio is a useful laboratory test to identify reversible prerenal causes. Intravascular volume should be optimized. Electrolyte and acid-base status should be monitored carefully. Hypertension and preeclampsia must be managed aggressively. Many obstetric causes of ARF also may cause disseminated intravascular coagulation; therefore, coagulation abnormalities should be excluded in pregnant women with ARF.[45]

Because urea and other metabolic products cross the placenta, hemodialysis or peritoneal dialysis should be directed toward maintaining the postdialysis BUN concentration at or below 30 mg/dL. Fluid shifts during hemodialysis should be minimized by short but frequent periods of dialysis. If the fetus is mature, delivery should be accomplished when the maternal condition is stabilized. The pediatrician must be alerted to the presence of high fetal BUN levels, which may lead to an osmotic diuresis and neonatal dehydration. Ertürk et al.[81] reported the first known delivery of a healthy infant during a hemodialysis session.

Anesthetic Management

A multidisciplinary approach involving anesthesiologists, obstetricians, and nephrologists should be employed to optimize the maternal condition before the induction of labor or performance of cesarean delivery in a woman with ARF. The level of azotemia, electrolyte balance, and hematologic status should be assessed. If the BUN level is greater than 80 mg/dL or the serum potassium concentration greater than 5.5 mEq/L, dialysis should be performed before elective vaginal or cesarean delivery. Neuraxial anesthesia may be administered in the absence of coagulopathy, thrombocytopenia, and severe hypovolemia. Volume status is difficult to assess. In the past, it was common to place a central line or pulmonary artery catheter to assess volume status, but this is now rarely done. Intravenous fluid without potassium (e.g., 0.9% saline) should be administered. Occult uterine hemorrhage should be excluded, and hypertension, if present, controlled. Both spinal and epidural analgesia/anesthesia are safe and preferred to general anesthesia. As the sympathetic blockade dissipates, the mother should be monitored for evidence of volume overload and pulmonary edema. General anesthesia may be required for urgent cesarean delivery or in patients with coagulopathy or hemorrhage.

RENAL TRANSPLANTATION

Although pregnancy is uncommon in women undergoing long-term dialysis,[22] fertility is improved within months of transplantation. The first recorded live birth to a woman with a kidney transplant was reported in 1958.[82] In a review of female renal transplant patients in the United States, a pregnancy rate of 20 per 1000 was estimated in transplanted patients in the year 2000 compared with 100 per 1000 in the general population.[83]

Although a successful obstetric outcome can be anticipated in more than 95% of kidney transplant recipients, they are at greater risk for both maternal and fetal complications than healthy women. In a systematic review of articles published between the years 2000 and 2010, Deshpande et al.[84] reported pregnancy-related outcome data in kidney transplant recipients. Fifty studies representing 4706 pregnancies in 3570 recipients met inclusion criteria. The incidences of preeclampsia (27%), gestational diabetes (8%), cesarean delivery (56.9%), and preterm delivery (45.6%) were greater than in the general population.

Effect of Pregnancy on the Renal Allograft

When a kidney is removed from a donor and transplanted into an anephric recipient, it undergoes a process of hyperfiltration. This is a maladaptive response that, in the short term, attempts to bring the GFR toward the rate of a bi-nephric system. In the long term, this hyperfiltration may lead to glomerular sclerosis and loss of renal function if it is associated with increased glomerular or capillary pressure.[85] In normal pregnancy, the GFR increases by 30% to 50% during the first and second trimesters and subsequently decreases somewhat during the third trimester. Theoretically, this additional hyperfiltration of pregnancy predisposes the patient to a loss of renal function.

Baylis et al.[86] allayed many of these concerns by demonstrating that gestational hyperfiltration is not associated with increased glomerular pressure because of matching afferent and efferent arteriolar vasodilation. They produced hyperfiltration in rodent kidneys by performing uninephrectomy, maintaining the animals on a high-protein diet, and subjecting them to five consecutive pregnancies. The investigators observed no functional impairment or renal histologic changes in this animal model. In addition, they demonstrated that glomerular pressure is lower in female rats than in male rats 10 months after uninephrectomy.[87] Similar sex advantage has been seen in humans after uninephrectomy.[88]

There have been a number of studies assessing graft function after pregnancy. Most studies suggest that there is no adverse effect provided renal function is normal before conception and there is no evidence of hypertension.[89-93] Levidiotis et al.[90] analyzed 40 years of outcome data from the Australian and New Zealand Dialysis and Transplant Registry and did not find any impact of pregnancy on 20-year graft or patient survival.

Rahamimov et al.[91] compared long-term graft survival, kidney function, and patient survival between women who became pregnant after renal transplantation (n = 39; 55 births) with those who did not (n = 117). Each pregnant woman was matched with three nonpregnant women for 12 factors that may affect graft survival. Graft (61.6%) and patient survival (84.8%) in the pregnant women did not differ from the matched nonpregnant group (68.7% graft and 78.8% patient survival) during the 15-year follow-up study.

Sturgiss and Davison[92] performed a case-control study of 36 renal transplant recipients, of whom 18 became pregnant and 18 did not. Groups were matched according to age, early rejection episodes, primary renal function, interval since transplantation, and extent of histocompatibility. The investigators noted no significant difference between the two groups in plasma creatinine concentration, GFR, mean arterial blood pressure, or the number who suffered graft loss or chronic rejection over a mean follow-up period of 12 years (Table 52-1).

Kashanizadeh et al.[93] also compared graft survival, allograft function, and patient survival between transplant recipients who conceived (n = 86) and those who did not (n = 125). They, too, did not find a difference in 5-year graft or patient survival between groups. Interestingly, they noted a smaller increase in creatinine levels in women who had conceived, suggesting that pregnancy might exert a protective effect, but this finding has not been confirmed by others.[94]

Effect on the Fetus

Although pregnancy seems to have minimal effect on maternal health or allograft survival in renal transplant recipients, fetal outcome is less favorable. The Toronto Renal Transplant Program reviewed 44 consecutive pregnancies in 26 women who had undergone renal transplantation.[95] Of these, 12 (27%) pregnancies ended with abortion (two elective, four spontaneous) or intrauterine death, and 32 (73%) pregnancies resulted in live-born infants. The mean birth weight in this group was 2540 g, versus 3590 g in a control group. In Singapore, Tan et al.[96] reported abortion or stillbirth among 13 (31%) of 42 pregnancies after renal transplantation. The remaining successful pregnancies were complicated by preterm delivery (45%) and fetal growth restriction (86%). Toma et al.[22] surveyed 194 pregnancies in renal transplant recipients. Spontaneous or elective abortion occurred in 28 (14%) of these gestations, and successful delivery of surviving infants occurred in 159 (82%). Deshpande et al.,[84] in their large systematic review, found a 73.5% live birth rate in renal transplant patients, which is similar to that found in the individual studies.[22,95,96]

Most post-transplantation protocols consist of a primary immunosuppressant (cyclosporine or tacrolimus) and one or two adjunctive agents (azathioprine, mycophenolate mofetil, sirolimus, and/or corticosteroids).[97] Despite transplacental exposure to immunosuppressant drugs, congenital anomalies and other adverse effects are not greater than in the general population, but none of the studies included patients who were receiving mycophenolate mofetil.[96,98] There have been reports of congenital defects with mycophenolate mofetil, including cleft lip and palate, microtia, absence of auditory canals, brachydactyly of the fifth finger, and hypoplastic toenails; therefore, its use has to be weighed against the risk for allograft rejection.[99]

Intrauterine exposure to cyclosporine impairs development and function of T, B, and NK lymphocytes in neonates. This effect, as well as depressed levels of serum immunoglobulin, persists during the first year of life.[100] These factors place the infant at risk for a suboptimal immunologic response after administration of classic vaccines and for adverse effects after administration of live, attenuated vaccines.

Transplant recipients may become infected with cytomegalovirus (CMV) at the time of transplantation, or they may experience reactivation secondary to immunosuppression. Active CMV infection during pregnancy is associated with congenital anomalies (e.g., cerebral cysts, microcephaly, mental retardation). In addition, active neonatal CMV infection may lead to serious illness or death.

After renal transplantation, residual impairment of renal function may lead to false-positive results of biochemical screening for trisomy 21. Karidas et al.[101] demonstrated a significant correlation between free β-subunit human chorionic gonadotropin and serum urea and creatinine concentrations. Similar alterations in alpha-fetoprotein levels were not observed. In this setting, the double-marker biochemical test may be interpreted inaccurately. In patients with altered serum urea and creatinine concentrations, first-trimester nuchal translucency measurement—in combination with second-trimester ultrasonography—may be a more useful screening regimen (see Chapter 6).

TABLE 52-1 Effect of Pregnancy on Long-Term Function of Renal Allografts*

Parameter	Pregnant Group (n = 18)	Nonpregnant Control Group (n = 18)
Plasma creatinine (mg/dL)	1.26 ± 0.83 (19% increase)	1.44 ± 0.59 (8% increase)
Glomerular filtration rate (mL/min)	58 ± 29 (18% decrease)	56 ± 32 (7% decrease)
Mean arterial pressure (mm Hg)	96 ± 12 (1% decrease)	101 ± 9 (5% increase)
Graft loss or chronic rejection	2 (11%)	2 (11%)

*Percentage increase or decrease represents change from initial assessment to end of follow-up. No statistically significant differences were noted.

From Sturgiss SN, Davison JM. Effect of pregnancy on long-term function of renal allografts. Am J Kidney Dis 1992; 19:167-72.

Medical and Obstetric Management

Discontinuation of immunosuppressant therapy, even years after transplantation, may lead to acute rejection. Thus, the renal transplant recipient's immunosuppressant regimen must be continued during pregnancy unless toxicity results, although some practitioners discontinue mycophenolate mofetil. Cyclosporine requirements increase during pregnancy, most likely because of enhanced metabolism.[102] The pregnant patient must be intensively monitored for any evidence of acute or chronic allograft rejection, infection, ureteral and renal artery obstruction, impaired renal function, hypertension, fluid volume disturbances, anemia, or any combination of these symptoms. Recombinant human erythropoietin (darbepoetin) has been successfully used to treat anemia during pregnancy.[103]

Initial laboratory studies in pregnant renal transplant patients include (1) complete blood cell count, (2) renal function tests, (3) serum electrolyte and glucose concentrations, and (4) viral serologic testing for CMV, hepatitis B virus, HCV, and HIV. Serial ultrasonographic assessments allow the recognition of fetal anomalies and the evaluation of fetal growth.

Cultures of the lower genital tract should be obtained in women with lesions suggestive of herpes simplex virus infection. A patient who presents in labor and with evidence of active genital herpes simplex virus infection should undergo cesarean delivery (see Chapter 37).

Vaginal examinations are minimized and always performed in a strict aseptic manner. The renal allograft is typically implanted in the extraperitoneal iliac fossa and does not impair vaginal delivery. Prophylactic antibiotics and stress-dose corticosteroids are indicated in patients who undergo cesarean delivery.

Anesthetic Management

In the absence of renal dysfunction and hypertension, anesthetic management of the parturient with a renal transplant is similar to that of the healthy parturient. Strict aseptic technique is maintained during the placement of intravascular catheters and the performance of neuraxial anesthetic techniques. Sowter et al.[104] reported an epidural abscess that occurred 23 days after epidural anesthesia in a nonpregnant patient receiving corticosteroid therapy for rheumatoid arthritis. Fortunately, this complication is exceedingly rare. In the absence of systemic infection, immunosuppression itself should not be considered a contraindication to administration of epidural or spinal anesthesia.

UROLITHIASIS

Definition and Epidemiology

Urolithiasis is characterized by the abnormal formation of calculi within the renal calyces or pelvis. Calculi may lodge within the ureters or bladder. Most stones are calcium oxalate (70%) or calcium phosphate (10%). The disorder affects 1% to 5% of the general U.S. population, but it is more common in the southeastern "stone belt" and mountainous regions. Symptomatic urolithiasis occurs during 1 in 240 to 1 in 3300 pregnancies and is more common among whites than African-Americans.[105] This incidence approximates that observed among nonpregnant young women, suggesting that pregnancy does not affect the rate of urolithiasis.

Pathophysiology

The presence of urolithiasis presumes an underlying physiologic abnormality that leads to persistent supersaturation of the particular minerals involved. During pregnancy, an elevated plasma 1,25-dihydroxyvitamin D level causes greater intestinal absorption of calcium, net mobilization of calcium from bone, and a state of absorptive hypercalciuria.[106] Ultimately, these changes provide calcium for the fetal skeleton. Because pregnant women do not develop urolithiasis at a rate greater than that in the general population, it would appear that the occurrence of other physiologic changes during pregnancy offsets this stone-forming factor. Calcium stone inhibitors such as citrate, magnesium, and glycoprotein are excreted in the urine to a greater extent during pregnancy.[107]

Diagnosis

Urolithiasis most commonly manifests during the second or third trimester. Only 20% of affected pregnant women recount a prior history of renal calculi. More than 80% of cases of gestational urolithiasis are diagnosed in parous women, possibly reflecting the higher incidence of this disease with advanced age.[108] Similar to that seen in the nonpregnant woman, stones occur with equal frequency on the right and left sides.[109] The signs and symptoms of urolithiasis during pregnancy must be differentiated from that of ectopic pregnancy, preterm labor, appendicitis, pyelonephritis, and benign hematuria of pregnancy. A history of previous urolithiasis, recurrent urinary tract infections, or urologic surgery is suggestive. Symptoms include flank and abdominal pain, urgency, dysuria, nausea, and fever. Examination reveals costovertebral tenderness, abdominal tenderness, pyuria, and hematuria. Urolithiasis must be considered in patients with pyelonephritis who remain febrile or have continued bacteriuria despite 48 hours of parenteral antibiotics.

The initial imaging modality for the evaluation of urolithiasis during pregnancy is transabdominal ultrasonography. Transabdominal ultrasonography is diagnostic in about 60% of cases and does not expose the mother or fetus to radiation.[110] Color Doppler ultrasonography allows the identification of ureteral jets; the asymmetry or absence of these jets indicates the presence of urinary calculi. Transvaginal ultrasonography may augment suboptimal transabdominal ultrasonographic images.[111] Combining ultrasound evaluation with assessment of the intrarenal artery resistive index increases the accuracy of ultrasonography to greater than 70%.[112]

If urinary calculi are not successfully visualized with ultrasonography and clinical suspicion for urolithiasis remains high, magnetic resonance (MR) urography

should be considered because it does not use ionizing radiation or iodinated contrast media (see Chapter 17).[113] If the diagnosis is still unclear and the patient has persistent flank pain after both these tests, some experts recommend low-dose computed tomography[114] whereas others recommend intravenous pyelography.[108]

Effect of Pregnancy on Urolithiasis

In an effort to determine any effect of pregnancy on the natural history of urolithiasis, Coe et al.[115] reviewed the records of 58 pregnancies in women with the preexisting diagnosis of urolithiasis. The stone recurrence rate in this group was 0.49 stone per patient-year, which was not significantly different from the rate of 0.44 stone per patient-year in the general population. The authors concluded that pregnancy does not alter the activity or severity of stone disease.

Effect on the Mother and Fetus

In a retrospective cohort study, Swartz et al.[116] compared pregnant women with nephrolithiasis (n = 2339) with randomly selected women without nephrolithiasis (n = 6729). The investigators found that women with nephrolithiasis had an almost twofold higher rate of preterm delivery. However, these women were not at increased risk for other adverse pregnancy outcomes, including premature rupture of the membranes, low birth weight, and infant death. The etiology of preterm labor and perhaps delivery is unclear but may be related to urinary tract infections that occur with a greater frequency in those with urolithiasis.[117] Honoré[118] suggested that there is a higher incidence of renal stones among women who have a spontaneous abortion. He hypothesized that abnormalities of calcium hemostasis may lead to myometrial hyperirritability or abnormal hormonal secretion by the corpus luteum, the placenta, or both. Rare cases of ureteral rupture[119] and obstructed labor caused by a bladder calculus[120] have been reported.

Urologic and Obstetric Management

Women with a history of urolithiasis should increase their intake of fluids. Calcium supplementation through prenatal vitamins should be avoided in women with recurrent urolithiasis. During pregnancy, 70% of calculi pass spontaneously with conservative management (e.g., hydration, antibiotics if the patient is febrile, bed rest, analgesia). More aggressive therapy will be required if conservative management is not successful. The decision to move beyond conservative therapy should be taken on a case-by-case basis. Infected hydronephrosis, especially with impaired renal function or urosepsis, is an indication for more aggressive therapy.[121]

Medical management, commonly used for treatment of urolithiasis,[122] is limited during pregnancy by fetal concerns. Medical expulsive therapy with alpha-adrenergic receptor blocking agents has been used successfully to increase the rate of stone passage and decrease pain associated with expulsion by relaxing ureteral smooth muscle.[123] However, there are no published reports of its use during pregnancy. Other medical treatments that are used to treat urolithiasis, including thiazide diuretics, xanthine oxidase inhibitors, and D-penicillamine, are contraindicated during pregnancy owing to possible effects on the fetus.[124,125]

Urologic intervention is indicated in the patient with persistent pyelonephritis, deterioration of renal function, massive hydronephrosis, persistent pain, or sepsis. Ureteral stent placement with ureteroscopy and ultrasonographic guidance, or percutaneous nephrostomy, should be considered because either can be performed without the need for anesthesia or radiation exposure.[105] Holmium:yttrium-aluminum-garnet (YAG) laser lithotripsy, using state-of-the-art ureteroscopes, is an emerging technique for stone management in pregnancy.[126] Extracorporeal lithotripsy should be avoided during pregnancy because the shockwaves may be harmful to the fetus.[127]

The following conditions may raise suspicion of the presence of **primary hyperparathyroidism** in a pregnant woman: (1) urolithiasis with or without pancreatitis, (2) hyperemesis beyond the first trimester, (3) a history of recurrent spontaneous abortion or intrauterine fetal death, (4) neonatal hypocalcemia or tetany, and (5) a total serum calcium concentration greater than 10.1 mg/dL during the second trimester or greater than 8.8 mg/dL during the third trimester.[128]

Anesthetic Management

Anesthesiologists are occasionally asked to provide analgesia for patients with renal or ureteral stones. The ureters receive sensory innervation through the renal, ovarian, and hypogastric plexuses (T11 to L1 spinal segments). During conservative management of urolithiasis, epidural analgesia provides the patient with significant pain relief and facilitates the passage of the calculus, possibly through decreased ureteral spasm.[129,130] Ready and Johnson[129] reported the use of epidural analgesia in a patient with severe renal colic at 23 weeks' gestation. Analgesia that was maintained for 16 hours allowed the passage of the stone. Neuraxial analgesia avoids the use of systemic opioids, which impair normal peristalsis in ureteric smooth muscle. Improved maternal pain control may also decrease endogenous catecholamine release and improve uteroplacental blood flow.

KEY POINTS

- Pregnant women with moderate or severe renal insufficiency are at increased risk for deterioration of renal function, exacerbation of hypertension, and other obstetric complications, including fetal growth restriction and preterm delivery.
- Patients requiring renal dialysis have decreased fertility, and pregnancy is rare.
- Pregnancy does not affect the long-term survival of a renal allograft.

- Both preeclampsia and renal disease may manifest as hypertension, proteinuria, and edema; the distinction between the two disorders is often unclear, especially after 20 weeks' gestation.
- Renal disease affects almost every organ system, so a thorough history before initiation of anesthesia, with emphasis on the cardiac and respiratory system, is critical.
- Anesthetic management is influenced by the extent of renal dysfunction and hypertension.
- Neuraxial anesthetic techniques are safe and are the preferred methods for labor analgesia and cesarean delivery anesthesia.
- Immunosuppressive therapy must be continued during pregnancy in renal transplant patients. The anesthesia provider should maintain strict aseptic technique during the placement of intravascular catheters and the performance of neuraxial anesthetic techniques.
- Epidural analgesia may facilitate the spontaneous passage of renal calculi.

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CHAPTER 53

Respiratory Disease

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CHAPTER OUTLINE

ASTHMA

Definition

Asthma is defined by the presence of the following three characteristic findings: (1) reversible airway obstruction, (2) airway inflammation, and (3) airway hyperresponsiveness. **Airway obstruction** produces the clinical manifestations of wheezing, cough, and dyspnea. **Airway inflammation** modulates the course of asthma by independently producing airway obstruction and enhancing airway hyperresponsiveness. **Airway hyperresponsiveness** is marked by exaggerated responses to a wide variety of bronchoconstrictor stimuli, including histamine, methacholine, prostaglandin $F_{2\alpha}$, hypo-osmotic solutions, and cold air.

Epidemiology

Asthma is an increasingly common problem among young, otherwise healthy women of childbearing age. Morbidity and mortality rates from this disease increased during the 1980s and 1990s. From 2001 to 2010, the prevalence of asthma in the United States increased from 7.3% to 8.4%.[1]

The prevalence of asthma in women of childbearing age also continues to rise. The rate was approximately 3% in the 1990s and has increased to approximately 8.8% in the early 2000s.[2]

Pathophysiology

Asthma is believed to occur under a variety of environmental influences in the presence of genetic susceptibility.[3] The underlying defect that produces the clinical syndrome of asthma is unknown. The most important potential mechanisms are (1) an enhancement of contractility or an impairment of relaxation of airway smooth muscle, (2) a neural imbalance, (3) airway inflammation, and (4) changes in the function of the airway epithelium.

Airway Smooth Muscle

Contraction of airway smooth muscle is believed to be the most important factor in producing acute airway obstruction. For many years, an enhancement of airway smooth muscle responsiveness to contractile agonists was assumed to be a major mechanism of asthma. To test this hypothesis, investigators attempted to correlate

airway responsiveness *in vivo* and *in vitro* in humans[4-8] and in the basenji-greyhound dog model of asthma.[9] These studies did not demonstrate a significant correlation between the airway response to histamine or cholinergic agonists *in vivo* and airway smooth muscle contraction *in vitro*. Some studies actually demonstrated a negative correlation between the *in vivo* and *in vitro* responses,[8,9] suggesting that diminished responsiveness may represent a chronic adaptive response of airway smooth muscle.

Instead of an enhancement in responsiveness to contractile stimuli, a reduction in responsiveness to relaxant stimuli may contribute to airway obstruction. One study demonstrated impaired relaxant responses to isoproterenol in airway smooth muscle from human asthmatic subjects in comparison with the responsiveness of airway smooth muscle from controls.[10] Other evidence substantiates the presence of impaired airway relaxation in asthmatic subjects *in vivo*.[11] Although the mechanism for this effect is poorly understood, a reduction in airway sensitivity to beta-adrenergic agonists could contribute to airway hyperresponsiveness by altering the balance between constricting and dilating influences.

Neural Components

A balance between constricting and dilating influences also exists with respect to the autonomic nervous system. A shift in this balance, with an increase in constricting influences, may be a mechanism of asthma.

The parasympathetic nervous system provides the dominant constrictor input to the airways (Figure 53-1). Efferent cholinergic fibers travel in the vagus nerve to synapse in ganglia within the airway wall.[12] Postganglionic fibers release acetylcholine to activate muscarinic receptors and stimulate airway smooth muscle contraction. A negative feedback system limits release of acetylcholine from nerve terminals. Muscarinic autoreceptors, or receptors on the nerve ending,[13] also are activated by acetylcholine and inhibit further release of acetylcholine from the nerve terminal.

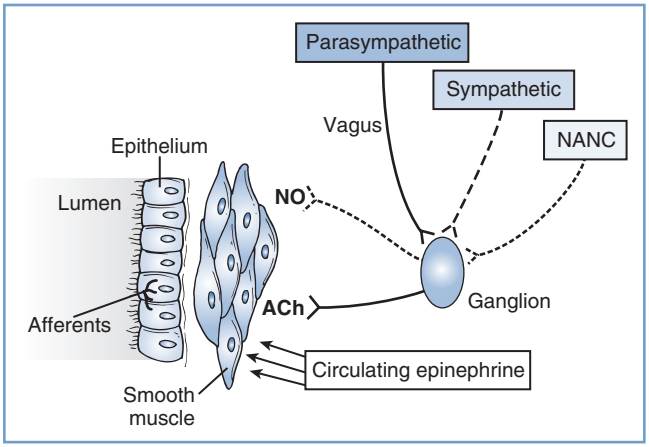

FIGURE 53-1 ■ Neural control of the airway. Parasympathetic, sympathetic, and nonadrenergic noncholinergic (NANC) efferents innervate ganglia within the airway wall. Postganglionic cholinergic efferents release acetylcholine (ACh) to constrict airway smooth muscle. Postganglionic NANC efferents release nitric oxide (NO) to relax airway smooth muscle. Circulating epinephrine relaxes the airway. Afferents from the airway originate in the epithelium and are activated by airway irritation, as occurs with tracheal intubation.

The importance of exaggerated cholinergic efferent activity in the pathogenesis of airway hyperreactivity has been debated extensively. The relatively limited efficacy of anticholinergic agents in relieving clinical bronchospasm, as well as growing evidence supporting other mechanisms, suggests that this pathway has a limited role in the pathophysiology of asthma. However, this mechanism appears to be very important in the perioperative management of asthmatic subjects. Reflex stimulation of airway smooth muscle by placement of a tracheal tube represents one of the most important causes of bronchospasm in the perioperative period.

An alternative mechanism by which the parasympathetic nervous system may contribute to airway hyperresponsiveness is through dysfunction of the muscarinic autoreceptors. Dysfunction of these receptors allows increased postganglionic release of acetylcholine after reflex stimulation.[14] This mechanism is well established in a guinea pig model of viral infection[15] and may explain the airway hyperresponsiveness that occurs for several weeks after an upper respiratory tract infection, although additional autoreceptor-independent mechanisms may also be present.[16] The role of this mechanism in the pathophysiology of clinical asthma is unclear.

The sympathetic nervous system primarily acts to decrease airway tone. In contrast to the parasympathetic nervous system, sympathetic innervation of airway smooth muscle in human subjects is either sparse or absent.[17] Circulating catecholamines activate beta-adrenergic receptors in airway smooth muscle and provide the primary sympathetic efferent input to human airways. Because airways of normal human subjects do not become hyperresponsive after beta-adrenergic blockade,[18] it is unlikely that impaired catecholamine secretion contributes significantly to the pathogenesis of asthma.

The alpha-adrenergic system is thought to play a relatively minor role in determining the state of airway responsiveness. Although alpha-adrenergic receptors are present in human airways,[19] the protective effects of alpha-adrenergic antagonists have been disappointing and can be attributed to other properties, such as antihistamine activity.

In addition to cholinergic and adrenergic input, a third neural system, the nonadrenergic noncholinergic (NANC) system, provides efferent nerves to the airways. Both constricting and dilating pathways have been identified.[20] Nitric oxide serves as the inhibitory NANC neurotransmitter in human airways.[21] Potentially, a relative increase in constricting influences or a decrease in dilating influences in the NANC system could contribute to asthma. However, asthmatic subjects demonstrated no deficit in NANC inhibitory pathways,[22] and inhibition of NANC excitatory neurotransmission did not improve airway hyperresponsiveness.[23] Thus, current evidence does not support imbalance of the NANC system as a major mechanism of asthma.

Airway Inflammation

Airway inflammation appears to serve primarily as a modulating influence in asthma. Inflammation is certainly present in some but not all asthmatic subjects.[24] The process of inflammation involves the occurrence of airway wall edema and infiltration of the mucosa by a variety of inflammatory cells, including neutrophils, mast cells, helper T lymphocytes, macrophages, and eosinophils.[25] These cells produce and release mediators of inflammation, such as histamine, leukotrienes, platelet-activating factor, prostaglandins, thromboxanes, cytokines, serotonin, and nitric oxide.[25] Mediators can modulate airway responsiveness by stimulating airway smooth muscle contraction,[26] directing migration of inflammatory cells,[27] modifying neural control of the airways,[28] increasing mucosal permeability,[29] or disrupting airway epithelium.[30] In addition, airway inflammation can reduce airway diameter. Airway hyperresponsiveness is correlated with increased baseline airway tone.[31] The overall importance of inflammation in asthma has been debated. Although inflammation appears to modulate the course of asthma, other factors certainly contribute to the pathogenesis.

Airway Epithelium

The epithelium provides a barrier to protect the subepithelial layers against stimuli that could provoke bronchospasm. Airways of asthmatic subjects demonstrate areas of epithelial destruction,[32] and the clinical significance of this finding has been demonstrated.[33]

The epithelium not only serves as a barrier but also plays an active role in the maintenance of airway tone. The epithelium produces constricting and dilating factors.[34,35] An alteration in the balance between these factors could alter airway responsiveness. The relative importance of alterations in epithelial function in the pathogenesis of asthma is unknown.

Diagnosis

Medical History

The classic symptoms of asthma include wheezing, cough, dyspnea, and chest tightness. A patient's medical history also should include information about the pattern and severity of the symptoms, precipitating and aggravating factors, and the duration and course of these symptoms.

Physical Examination

Physical examination is directed to the respiratory tract. Auscultation of the chest may reveal wheezing and a prolonged phase of expiration.

Laboratory Studies

Laboratory studies that aid in the diagnosis of asthma depend on findings from the medical history and physical examination. In general, pulmonary function tests are useful to document the severity and establish the reversibility of obstruction (Box 53-1). In the absence of additional findings, other tests are not as useful in establishing the diagnosis of asthma. Bronchoprovocation tests (with agents such as methacholine or histamine) are used when the history and physical examination strongly suggest the presence of asthma but spirometry does not show airway obstruction.

BOX 53-1 Pulmonary Function Tests in Patients with Asthma

Forced Vital Capacity (FVC)

- The volume of gas exhaled after maximal inspiration
- May be reduced in asthma

Forced Expiratory Volume in 1 Second (FEV_1)

- The volume exhaled in the first second after maximal inspiration
- May be reduced in asthma

$FEV_1/FVC < 0.75$ in Asthma

Interaction with Pregnancy

Effects of Pregnancy on Asthma

The overall course of asthma has been reported to improve, worsen, or remain the same during pregnancy.[36] Earlier evidence suggested that patients with more severe asthma are more likely to experience deterioration during pregnancy,[36] but a recent study demonstrated that asthma severity during pregnancy is similar to severity during the year before pregnancy, provided that patients continue to use their prescribed medication during pregnancy. The investigators concluded that even mild asthma is likely to become significantly more severe if women discontinue their prescribed medication during pregnancy.[37] A likely reason for the variation in the results of published studies is the difference in methods of assessing the severity of asthma. Most studies have used either clinical symptoms or requirements for pharmacologic therapy as indicators of the course of the disease. These measures do not correlate with objective measures of airway obstruction.[38] Juniper et al.[39] measured methacholine sensitivity before, during, and after pregnancy. Measurements of sensitivity to methacholine made during the second and third trimesters were lower than preconception or postpartum measurements (Figure 53-2). Although these findings suggest a reduction in airway hyperresponsiveness during pregnancy, the limited study population (16 subjects) makes extrapolation of the data to the general population unclear. Exacerbations of asthma during labor and delivery occur in as many as 20% of subjects[37] and occur more frequently after cesarean delivery than after vaginal delivery (41% and 4%, respectively).[40]

A number of mechanisms may be responsible for the changes in the clinical course of asthma during pregnancy (Box 53-2). An increase in the progesterone level is thought to be one mechanism that improves asthma during pregnancy. Progesterone relaxes uterine and gastrointestinal smooth muscle and may or may not have

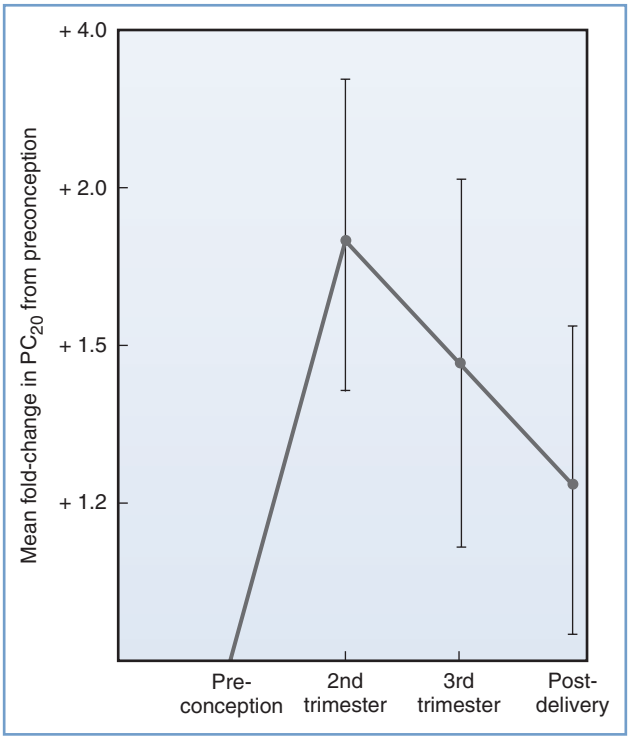

FIGURE 53-2 ■ Airway responsiveness before, during, and after pregnancy expressed as fold change in PC_{20}—dose of methacholine needed to reduce FEV_1 (forced expiratory volume in 1 second) by 20%—compared with values before conception (n = 16; $P = .033$ for the effect of pregnancy on airway responsiveness). (From Juniper EF, Daniel EE, Roberts RS, et al. Improvement in airway responsiveness and asthma severity during pregnancy. Am Rev Respir Dis 1989; 140:924-31.)

BOX 53-2 Factors That May Improve or Worsen Asthma during Pregnancy

Factors That May Improve Asthma

- Progesterone-induced relaxation of airway smooth muscle
- Increased production of bronchodilating prostaglandins
- Higher circulating cortisol level

Factors That May Worsen Asthma

- Decreased sensitivity to beta-adrenergic agonists
- Increased production of bronchoconstricting prostaglandins
- Reduced sensitivity to circulating cortisol because of binding of steroid hormones (e.g., progesterone) to cortisol receptors

similar effects on airway smooth muscle. However, Juniper et al.[39] did not demonstrate a strong association between methacholine responsiveness and progesterone levels during pregnancy, suggesting that progesterone does not play a central role in attenuating airway hyperresponsiveness. In contrast, progesterone may actually worsen asthma by enhancing inflammation.[41] Thus, effects of pregnancy on asthma appear to involve a number of factors other than direct effects of hormones on airway smooth muscle.

Effects of Asthma on the Parturient and Fetus

Many investigators have questioned whether maternal asthma adversely affects perinatal outcome. Differences in study design (e.g., retrospective, prospective) and differences in severity and treatment of asthma may account for different study results. Some studies have reported an increased incidence of preeclampsia,[42,43] cesarean delivery,[44-46] low-birth-weight (LBW) infants,[47] preterm labor,[45,48] antepartum and postpartum hemorrhage,[49] and perinatal mortality.[50] Diabetes mellitus appears to be more common among asthmatic patients treated with corticosteroids.[51] Severe or poorly controlled asthma is a predictor of adverse outcome.[40] Although asthma in pregnancy is associated with an increased risk for adverse perinatal outcomes, a meta-analysis of cohort studies suggested that active asthma management, which is intended to reduce the exacerbation rate, may reduce the risk for perinatal complications, particularly preterm delivery.[52] No controlled studies have documented better perinatal outcome with aggressive asthma treatment. Potential mechanisms of increased perinatal morbidity and mortality in patients with uncontrolled asthma include hypoxemia and hypocapnia, inflammation, and altered placental function from asthma-associated mediator release.[53] Siddiqui et al.[54] have documented an association between preeclampsia and airway hyperresponsiveness and have proposed that the mechanism involves an interaction between mast cells and smooth muscle. A large prospective study is needed to confirm this association.

Medical Management

Pharmacologic therapy for asthma during pregnancy is directed toward avoiding acute exacerbations and episodes of status asthmaticus. Ideally, management should begin before conception. Although general principles typically dictate that unnecessary medication should be avoided during pregnancy, studies investigating the effects of asthma on perinatal outcome suggest that the risks for uncontrolled asthma are significantly higher than medication-associated risks.[55] Medications that are currently used to treat asthma fall into two general categories: bronchodilators and anti-inflammatory agents. These agents generally are safe for the fetus. The prophylactic use of antibiotics is unnecessary.

Bronchodilators

Beta-adrenergic agonists exert beneficial effects in asthmatic patients by activation of β_2-adrenergic receptors, which mediate a number of processes (Box 53-3). Short-acting beta-adrenergic agonists represent the most effective therapy for acute exacerbations of asthma.[56] Daily use of long-acting beta-adrenergic agonists is controversial. Long-acting beta-adrenergic agonist therapy is associated with a significant increase in the risk for death,[57] but controlled studies have not confirmed a cause-and-effect relationship.[58] Certain genetic polymorphisms affect responses to short-acting but not long-acting beta-adrenergic agonists,[59] leading to hopes that a

BOX 53-3 Mechanisms of Beneficial Effects of Beta-Adrenergic Agonists in Asthma

- Direct airway smooth muscle relaxation
- Enhanced mucociliary transport
- Decreased airway edema
- Inhibition of cholinergic neurotransmission

personalized approach to therapy would improve clinical efficacy. Although regular use of beta-adrenergic agonists in asthma may be beneficial in conjunction with other forms of therapy, these agents do not appear to provide optimal control when used alone. Conversely, no compelling evidence requires that beta-adrenergic agonists be discontinued after conception or that their use be reserved for treatment of an acute exacerbation.

These agents may be administered as aerosols, orally, or parenterally. The aerosol route is generally preferred during pregnancy because high concentrations of the medication can be delivered directly to the site of activity in the airways, with relatively less drug delivered to the uteroplacental circulation.

The limited number of human studies investigating the fetal safety of long-term administration of a beta-adrenergic agonist have not shown significant adverse neonatal outcomes.[60,61] In addition, the long history of use of these agents without reports of teratogenicity suggests that their use should not be restricted because of fetal concerns. Optimal control of maternal symptoms of asthma appears to be more important for the fetus than potential detrimental effects of beta-adrenergic agonists.

On the basis of the potential risks of long-term single-agent therapy with a beta-adrenergic agonist, a paradoxical approach to the treatment of asthma may involve long-term administration of a beta-adrenergic antagonist.[62] This approach is analogous to the paradigm based in the cardiovascular system, in which long-term administration of a beta-adrenergic antagonist is beneficial in patients with congestive heart failure. Studies in asthmatic patients are ongoing.

Methylxanthines (e.g., **theophylline**, **aminophylline**) were used for many years in the long-term treatment of asthma. Although their mechanism of action is controversial, relaxation of airway smooth muscle is the most prominent effect. The ability of the agents to inhibit intracellular phosphodiesterase and increase concentrations of cyclic adenosine monophosphate (cAMP) is not the mechanism of bronchodilation, because these effects do not occur at clinically relevant concentrations *in vivo*.[63] Furthermore, in the patient taking anti-inflammatory agents and beta-adrenergic agonists, methylxanthines add little to optimal asthmatic control.[64] Although their use is now limited to patients whose asthma responds poorly to other forms of therapy, methylxanthines do not appear to cause significant adverse fetal outcomes.[61] Serum concentrations of theophylline should be monitored carefully, especially in the third trimester, when theophylline clearance decreases.[65]

Bronchodilation with **anticholinergic agents** occurs through the blockade of muscarinic receptors on airway smooth muscle. Overall, anticholinergic agents alone are not as effective as beta-adrenergic agonists, but some patients show better response to anticholinergic agents.[66] The effects of adding anticholinergic agents to beta-adrenergic agonists for acute[67] and chronic[68] asthma were evaluated in meta-analyses of randomized trials. Anticholinergic agents improved lung function in acute asthma[67] but had little benefit in chronic asthma.[68] The **quaternary anticholinergic agent ipratropium bromide** can be delivered as an aerosol, allowing higher concentrations in the lung with reduced systemic absorption and potential effects on the fetus. Human data on the safety of anticholinergic agents and on potential teratogenicity are lacking, but ipratropium bromide is not associated with teratogenicity in animal studies.[69]

Magnesium sulfate relaxes airway smooth muscle, most likely via its antagonism of calcium entry into airway smooth muscle cells.[70] Its use is limited primarily to acute bronchospasm.[71]

Anti-Inflammatory Agents

Proposed mechanisms of action for corticosteroids are (1) decreases in cellular infiltration and mediator release, (2) reductions in airway permeability, and (3) up-regulation of the beta-adrenergic system.[72] Unlike bronchodilators, corticosteroids not only reduce airway sensitivity to a constrictor stimulus[73] but also decrease the maximal extent of airway narrowing, a feature that may predict severity of an acute asthmatic episode.[74]

The use of **inhaled corticosteroids** has gained popularity. This route of administration is effective and may limit fetal side effects. Studies have assessed the effects of systemic and inhaled corticosteroids on the fetus. Neither systemic nor inhaled corticosteroids have been proven to increase the risk for congenital malformations in humans. Inhaled corticosteroids do not affect glucocorticoid-regulated pathways in the fetus and therefore are unlikely to cause adverse effects on fetal growth and development.[75] Although oral corticosteroid use is associated with an increased incidence of LBW infants,[76] inhaled corticosteroids do not appear to increase perinatal risk.[77] Further, a meta-analysis did not show an association between inhaled corticosteroid use and any adverse perinatal outcome.[78] Of interest, use of inhaled corticosteroids during pregnancy can be guided by measurements of exhaled nitric oxide, which, in a randomized trial, were shown to significantly reduce exacerbations when compared with use of a clinical algorithm based on symptoms alone.[79]

Corticosteroids may increase perinatal morbidity by exacerbating maternal glucose intolerance, especially in women who also receive treatment with a beta-adrenergic agonist. Thus, careful monitoring of maternal glucose concentration is indicated in asthmatic women who require treatment with a corticosteroid during pregnancy. However, because of the efficacy of corticosteroids in controlling severe asthma during pregnancy, these agents should not be withheld from the medical regimen.

Some authorities have recommended that corticosteroid-dependent asthmatic women receive large doses of parenteral corticosteroids during labor to prevent complications related to adrenal suppression.[55,80,81] The scientific basis for this recommendation is questionable. Although physiologic glucocorticoid replacement reduced hemodynamic instability and mortality in adrenalectomized primates that underwent surgery, supraphysiologic doses provided no additional benefit.[82] Furthermore, inhaled corticosteroids in moderate doses do not produce adrenocortical suppression.[83] There is little information about the benefit of corticosteroid replacement therapy during labor. The potential for adrenal insufficiency in infants of asthmatic mothers taking inhaled or oral corticosteroids appears to be very low,[81] most likely owing to the widespread use of either prednisone or prednisolone. In the mother, prednisone is converted rapidly to prednisolone, which crosses the placental barrier to a very limited extent.

Cromolyn sodium and **nedocromil sodium** belong to a class of drugs that are thought to reduce inflammation and mediator release primarily by stabilizing mast cells and perhaps other inflammatory cells. Nedocromil also inhibits cellular chloride ion flux, a feature that may explain its ability to affect a range of airway cells, including nerve cells.[84]

Cromolyn and nedocromil are administered as aerosols. Limited studies suggest that cromolyn is safe during pregnancy,[85] and clinical experience is greater with cromolyn than with nedocromil. Thus, use of cromolyn is preferred.

On the basis of the observation that leukotrienes are released into the airways by immune cells and contribute to the inflammatory process, other forms of anti-inflammatory therapy are **leukotriene receptor antagonists** and **leukotriene synthesis inhibitors**. Safety data for the use of these agents in pregnancy are scarce. Bracken et al.[47] did not observe adverse neonatal outcomes in nine women exposed to these agents. A later prospective study of 96 women showed that use of leukotriene receptor antagonists was not associated with a specific pattern of congenital abnormalities, but the investigators cautioned that extrapolation of the data to a large population would require additional studies because of the limited sample size of the study.[85]

Obstetric Management

The following aspects of obstetric management of the asthmatic parturient may differ from that of the nonasthmatic patient: (1) induction of labor, (2) management of postpartum hemorrhage, and (3) treatment of hypertension.

For induction of labor, prostaglandins should be administered cautiously in women with asthma. Prostaglandin $F_{2\alpha}$ constricts airways *in vivo*[86] and *in vitro*.[87] Airways of asthmatic subjects demonstrate greater sensitivity to prostaglandin $F_{2\alpha}$, and its use to induce labor is associated with bronchospasm.[88] Prostaglandin E_2 can have either dilating or constricting effects on the airways, perhaps because of its ability to activate a variety of different types of prostaglandin receptors.[89] Because of the known risk for bronchospasm after exposure to prostaglandin $F_{2\alpha}$ and the possible risk after exposure to prostaglandin E_2, alternative methods of induction of labor are preferred in asthmatic women.

Likewise, asthma represents a relative contraindication to the administration of 15-methyl prostaglandin $F_{2\alpha}$ (carboprost, Hemabate) for the treatment of postpartum hemorrhage. The use of ergot alkaloids to treat postpartum hemorrhage in asthmatic women has also been questioned. Although controlled studies have not been performed, ergot alkaloids have been associated with episodes of acute bronchospasm,[90,91] on the basis of either their tryptaminergic actions or their ability to activate α_1-adrenergic receptors on airway smooth muscle cells. Oxytocin, which does not significantly affect airway tone, is the preferred ecbolic agent in asthmatic patients.

Beta-adrenergic receptor antagonists are used to treat hypertension in some pregnant women. In asthmatic women, these agents may provoke bronchospasm when used acutely.[92] Other antihypertensive agents, such as hydralazine and sodium nitroprusside, do not seem to enhance airway responsiveness.

Anesthetic Management

Preoperative Assessment

During the preoperative evaluation, the anesthesia provider should assess the severity of the disease and whether an acute asthmatic episode is present. The medical history should include information about symptoms of wheezing, dyspnea, and cough. Further information should be sought about the frequency and severity of symptoms, the course of these symptoms during pregnancy, and the date of the most recent exacerbation. Patients who have frequent, severe attacks are at increased risk for morbidity in the peripartum period.

Physical examination should focus on the pulmonary system. Chest auscultation may demonstrate wheezing with or without a prolonged expiratory phase. However, wheezing may not be audible if air movement is markedly reduced. Additional signs of an acute exacerbation of asthma include tachypnea, an exaggerated (> 20 mm Hg) pulsus paradoxus, and the use of accessory respiratory muscles.

In a pregnant woman with stable asthma, laboratory tests add little to anesthetic management. However, if an acute exacerbation is suspected, chest radiographic examination, arterial blood gas measurements, and pulmonary function tests may assist with diagnosis and therapy. **Chest radiographic examination** helps diagnose precipitating or complicating conditions such as pneumonia, pneumothorax, and heart failure. During an episode of acute asthma, **arterial blood gas measurements** often show hypoxemia and respiratory alkalosis. After a prolonged, severe episode, arterial carbon dioxide tension increases as a result of fatigue. **Spirometry** measures the volume of gas exhaled over time (see Box 53-1). The most convenient indirect measurement for assessing airway obstruction during labor is the **peak expiratory flow rate,** which can be measured at the bedside with a Wright peak flowmeter.[93]

Management during Labor and Vaginal Delivery

The goals of analgesia for labor and delivery in asthmatic women include (1) provision of pain relief, (2) reduction in the stimulus to hyperpnea, and (3) prevention or relief of maternal stress. The goal of adequate pain relief does not differ for asthmatic women. It is important to prevent hyperpnea and stress in women who describe asthmatic episodes triggered by exercise or stress. These goals should be accomplished with minimal sedation, minimal paralysis of the muscles of respiration, and minimal depression of the fetus. Possible analgesic regimens include systemic opioids, paracervical block, pudendal nerve block, lumbar sympathetic block, and epidural or spinal analgesia using local anesthetic agents, opioids, or both.

Systemic opioids may provide reasonable pain relief and reduce the stimulus to hyperpnea, especially during the early part of the first stage of labor. In theory, opioids reduce the risk for bronchospasm in asthmatic subjects. Opiate receptors are believed to be present in the respiratory tract[94] and to inhibit release of excitatory neuropeptides. The clinical relevance of these findings is unknown, because moderate doses of inhaled morphine do not significantly alter airway tone.[95] Conversely, high doses of some opioids (e.g., morphine) may increase the risk for bronchospasm by releasing histamine. The risk of using moderate doses of morphine does not seem excessive, because airway tone does not change in subjects with moderate to severe asthma after inhalation of morphine.[95] An opioid that does not release histamine (e.g., fentanyl, remifentanil) may be a better choice for the asthmatic parturient. High doses of opioids are not desirable in subjects with active wheezing because of the risks for maternal and neonatal respiratory depression (see Chapter 22).

Paracervical block and **pudendal nerve block** performed by an obstetrician are acceptable choices for analgesia during the first and second stages of labor, respectively. These techniques provide analgesia without sedation or paralysis of the respiratory muscles. The problems with these techniques in asthmatic women are similar to those in nonasthmatic parturients (see Chapter 24).

Lumbar sympathetic block also provides pain relief without sedation or motor block during the first stage of labor. This technique has the same limitations as for women without asthma (see Chapter 24).

Intrathecal and **epidural opioid** techniques are useful during the first stage of labor and do not produce motor block (see Chapter 23). The advantage of the absence of motor block should be weighed against the risk for respiratory depression in asthmatic subjects.

Advantages of the use of local anesthetic agents for **lumbar epidural analgesia** in asthmatic patients include continuous pain relief and a reduction in the stimulus to hyperventilation. These goals typically are achieved without maternal sedation or neonatal depression. Unlike other analgesic techniques, continuous lumbar epidural analgesia adds a margin of safety by providing the opportunity to extend the sensory block for cesarean delivery. The possibility of extension allows the anesthesia provider to avoid some of the risks of general anesthesia. The most significant disadvantage of epidural local anesthetics in an asthmatic subject is the risk for a high thoracic motor block and respiratory insufficiency. Use of an appropriate epidural catheter test dose and maintenance of a sensory level at the 10th thoracic dermatome minimize this risk. In addition, the use of a dilute concentration of local anesthetic combined with a modest dose of an opioid produces satisfactory analgesia with less motor block than local anesthetic alone.[96]

Management during Cesarean Delivery

The choice between neuraxial anesthesia and general anesthesia for cesarean delivery depends on obstetric considerations and the respiratory status of the parturient. In general, avoidance of airway instrumentation is desirable, because tracheal intubation markedly increases airway tone in asthmatic subjects.[97]

The most significant advantage of neuraxial anesthesia in the asthmatic patient is that this technique obviates the necessity for tracheal intubation. Neuraxial anesthesia is associated with a lower incidence of bronchospasm than general anesthesia in asthmatic subjects.[98] Stable asthmatic patients can undergo either spinal anesthesia or epidural anesthesia. In unstable asthmatic patients who require the use of accessory muscles of respiration, neuraxial anesthesia may be hazardous because of impaired ventilatory capacity in the presence of a high thoracic motor block. Intrathecal administration of either ropivacaine or levobupivacaine, which may produce less motor block than bupivacaine, does not confer any advantage with respect to pulmonary function in women receiving spinal anesthesia for cesarean delivery.[99]

The adrenal medulla receives innervation from preganglionic sympathetic fibers arising from the sixth thoracic to the second lumbar spinal segment.[100] Some authors have postulated that neuraxial anesthesia and the ensuing sympathectomy could precipitate or potentiate bronchospasm during cesarean delivery in asthmatic subjects by reducing adrenal output of epinephrine. This possibility seems remote. First, although epinephrine infusion can reduce airway reactivity in asthmatic subjects,[101] epinephrine concentrations do not decrease during nonobstetric surgery performed with neuraxial anesthesia that achieves high thoracic sensory levels.[102,103] Second, the idea that neuraxial anesthesia may prevent increases in circulating epinephrine that are required to compensate for stress-induced bronchospasm does not appear to be valid. Bronchoconstriction does not stimulate epinephrine secretion in human asthmatic subjects.[104] Thus, neuraxial anesthesia is appropriate for cesarean delivery in stable asthmatic subjects.

General anesthesia for asthmatic women undergoing cesarean delivery requires a balance between the competing considerations of pulmonary aspiration and intraoperative bronchospasm. Although airway instrumentation provides a great stimulus for bronchospasm, the high risk for aspiration mandates tracheal intubation during administration of general anesthesia in parturients.

Most commonly, options for tracheal intubation include awake intubation and rapid-sequence induction,

although mask induction of general anesthesia with sevoflurane has been described in a parturient with status asthmaticus.[105] Indications for awake intubation in asthmatic subjects are similar to those for nonasthmatic patients, and pretreatment with a local anesthetic and a beta-adrenergic agonist can attenuate reflex-induced bronchoconstriction after awake intubation.[97] The benefits of topical local anesthetics and airway nerve blocks for awake intubation should be weighed against a possible increase in the risk for aspiration from the loss of protective airway reflexes. Rapid-sequence induction for cesarean delivery in asthmatic patients is most often accomplished using either **propofol** or **ketamine**. A sympathomimetic agent, ketamine has long been considered the intravenous induction agent of choice for asthmatic subjects. Ketamine relaxes airway smooth muscle and inhibits neural reflexes.[106] Propofol provides better protection than thiopental against bronchospasm associated with tracheal intubation in asthmatic patients,[107] but it has not been compared directly with ketamine in humans. Beneficial airway effects of propofol, like those of ketamine, also appear to occur via inhibition of airway reflexes.[106] Intravenous **lidocaine,** which also inhibits airway reflexes, attenuates irritant-induced bronchoconstriction,[108] including tracheal intubation, and produces an additional protective effect above that of beta-adrenergic agonist pretreatment alone.[109]

In patients *without* asthma, maintenance of general anesthesia typically includes administration of a low concentration of a volatile halogenated anesthetic agent, with or without nitrous oxide, before delivery of the infant. After delivery, maintenance of anesthesia typically consists of nitrous oxide and an intravenous opioid, with or without a low concentration of a volatile halogenated agent. In *asthmatic* parturients, the **volatile halogenated anesthetic agents** are considered the agents of choice for the maintenance of anesthesia. These agents attenuate airway responsiveness through direct effects on airway smooth muscle,[110-112] inhibition of airway reflexes,[113] and effects on the epithelium.[114]

A high concentration of a volatile halogenated anesthetic agent has salutary effects on the airways but also increases the risk for hemorrhage during cesarean delivery by causing dose-dependent uterine relaxation.[115] Alternatively, nitrous oxide, an intravenous opioid, and a low concentration of a volatile halogenated agent may be given. Although halothane and isoflurane are approximately equipotent bronchodilators at high concentrations, halothane produces greater bronchodilation at lower concentrations[116] and therefore may be preferable for anesthesia for cesarean delivery. Sevoflurane acts as a bronchodilator in large and small airways[117] and reverses airway constriction associated with tracheal intubation.[118] Effects of desflurane are controversial. Desflurane protects against a direct stimulus to the airways[119] but may be less effective against reflex stimuli, such as tracheal intubation.[120]

A bronchodilator can be added if bronchospasm occurs. The potential disadvantage of this technique is that the most effective bronchodilators (i.e., the beta-adrenergic agonists) also relax uterine smooth muscle. The administration of a beta-adrenergic agonist by aerosol delivers a relatively greater dose of drug to the airways and minimizes uterine relaxation.

Emergence from general anesthesia, as with induction, requires a balance between reducing the risk for aspiration and lowering the risk for bronchospasm. Extubation of the trachea when the patient is awake minimizes the risk for aspiration, but the tracheal tube may stimulate reflexes and precipitate bronchospasm as the depth of anesthesia is reduced. If bronchospasm occurs during emergence, bronchodilators can be administered. For refractory bronchospasm, continued mechanical ventilation in an intensive care unit may be required.

CIGARETTE SMOKING

Epidemiology

Cigarette smoking is a significant, preventable cause of maternal morbidity and perinatal morbidity and mortality.[121] The prevalence of smoking among pregnant women in the United States declined from 18.1% in 1991 to 16% in 2010.[122] Approximately 46% of women who smoke quit smoking during pregnancy.[123]

Pathophysiology

Cigarette smoke contains a large number of separate components that have a variety of biologic effects. Nonrespiratory effects of cigarette smoking are described in Chapter 54.

The primary respiratory effects of cigarette smoking include alterations in small airway function, increased mucus secretion, and impairment of ciliary transport.[124] The precise mechanisms for these effects are unknown. Smoking also is associated with an increase in nonspecific airway reactivity, possibly through epithelial damage, altered airway geometry due to increased mucus secretion, or up-regulation of endothelin receptors.[125] These changes lead to a marked increase in the incidence of postoperative pulmonary complications.[124]

Interaction with Pregnancy

Few studies have documented the respiratory effects of cigarette smoking during pregnancy. In one study, reductions in forced expiratory flow rates suggested that pregnant women who smoke cigarettes have greater small airway resistance than those who do not smoke.[126] These and other abnormalities were similar to the changes in airway function observed in nonpregnant smokers. Although further studies are warranted, other respiratory effects of cigarette smoking in pregnant women are likely to be similar to those effects in nonpregnant women.

Cigarette smoking adversely affects pregnancy in a number of ways. The association between smoking and LBW has a genetic influence, such that the specific variation of the nicotinic acetylcholine receptor gene cluster is associated with lower newborn birth weight in smokers but not in nonsmokers.[127] Although observational, this study suggests a causal relationship between smoking during pregnancy and lower offspring birth weight.

Further details regarding adverse maternal and fetal effects of smoking are described in Chapter 54.

Medical Management

Cessation of smoking is the preferred form of medical management. Smoking cessation programs are effective in pregnant women.[128] Nonpharmacologic methods are preferred to pharmacologic methods (e.g., nicotine patches) because of insufficient safety information for the latter.[123] Das et al.[129] demonstrated that smoking cessation before or early in pregnancy results in prompt improvement in maternal airway function. Smoking cessation reduces perioperative complications in the nonpregnant patient undergoing surgery,[130] but no controlled studies have evaluated effects of smoking cessation on peripartum outcome.

Anesthetic Management

Tracheal intubation is associated with bronchospasm in smokers.[131] For vaginal delivery, any of the analgesic techniques described earlier for asthmatic parturients are acceptable. For cesarean delivery, neuraxial anesthesia achieves the goal of avoiding airway instrumentation and is therefore preferable to general anesthesia, although no controlled studies have documented differences in peripartum morbidity. If general anesthesia is required, the methods for reducing the risk for intraoperative bronchospasm described previously may be considered. During induction of general anesthesia in smokers, the formulation of propofol containing sulfite results in greater respiratory resistance after tracheal intubation than the formulation containing ethylenediaminetetraacetic acid (EDTA).[132] The clinical significance of this finding is unknown. One study noted that respiratory resistance did not decrease after tracheal intubation in smokers anesthetized with desflurane,[120] suggesting that other volatile halogenated anesthetic agents might be preferable.

CYSTIC FIBROSIS

Epidemiology

Cystic fibrosis, a lethal genetic disorder that is transmitted as an autosomal recessive trait, affects approximately 1 in 3200 white neonates in the United States.[133] Because of improvements in diagnosis and therapy, a growing number of women with cystic fibrosis survive to reproductive age. The number of pregnancies reported to a national cystic fibrosis registry increased from fewer than 100 in the 1980s[134] to approximately 240 in 2010.[135]

Pathophysiology

Clinical features of cystic fibrosis result from abnormalities of epithelial tissues, especially in the respiratory, digestive, and reproductive tracts. The underlying mechanism is a defect in cAMP-mediated activation of chloride (Cl^-) conductance in the epithelium.[136,137] Normal epithelial cells secrete Cl^- in response to an increase in intracellular cAMP. In cystic fibrosis, a genetic mutation makes epithelial cells unable to alter Cl^- permeability in response to changes in cAMP. The gene responsible for cystic fibrosis is located on chromosome 7 and encodes a protein known as the *cystic fibrosis transmembrane regulator* (CFTR).[138,139] The CFTR acts as a Cl^- channel but also has a number of other actions.[140] Cystic fibrosis is characterized by obstruction of exocrine glands with mucus, but the precise molecular mechanism is not well understood. In sweat glands, however, patients with cystic fibrosis show abnormalities that can be readily explained by impairment of the CFTR, which limits reabsorption of Cl^- and therefore of salt. In the airways, two opposing hypotheses, one in which the airway epithelium behaves similarly to the sweat duct epithelium and one in which the airway epithelium "behaves in a fashion essentially opposite to that of the sweat duct," have been proposed to explain alterations in fluid and electrolyte composition of airway secretions in patients with cystic fibrosis.[140]

In the lungs, abnormalities of electrolyte transport alter the composition of airway secretions. Inflammation, with infiltration of polymorphonuclear leukocytes, also contributes to changes in airway secretions.[141] Large numbers of disintegrating neutrophils release DNA in quantities sufficient to overwhelm the ability of deoxyribonuclease I (DNAse I), an endogenously released enzyme, to digest extracellular DNA. Undigested DNA increases the viscosity of airway secretions, which causes obstruction of small airways and reduced lung volumes. The ensuing ventilation-perfusion inequalities produce arterial hypoxemia. Some patients have hyperreactive airways. Spontaneous pneumothorax often occurs. Chronic airway obstruction and impaired mucus clearance increase the frequency of pulmonary infection. Most patients become colonized or infected with *Pseudomonas aeruginosa*. Eventually, tissue damage leads to bronchiectasis and pulmonary insufficiency. Chronic hypoxemia and lung destruction may produce pulmonary hypertension and cor pulmonale. Nonrespiratory manifestations of cystic fibrosis include pancreatic exocrine insufficiency, intestinal obstruction, and infertility.

Diagnosis

Clinical criteria for the diagnosis of cystic fibrosis include (1) the presence of chronic obstructive lung disease and colonization with *Pseudomonas aeruginosa* before age 20 years, (2) exocrine pancreatic insufficiency, and (3) a family history of cystic fibrosis. Laboratory findings include (1) sweat Cl^- concentrations greater than 60 mEq/L, (2) CFTR genotype with two known cystic fibrosis mutations, and (3) detection of CFTR dysfunction by nasal potential difference test.[142] Chest radiographic examination often demonstrates hyperinflation, and arterial blood gas measurements may show hypoxemia. Pulmonary function tests, which can reveal obstructive or restrictive lung patterns, are useful to assess the severity of the disease. With serial measurements, clinicians should look for evidence of an increased residual volume and a reduced FEV_1 (forced expiratory volume in 1 second).[143]

Interaction with Pregnancy

Effect of Pregnancy on Cystic Fibrosis

The following factors may contribute to the deterioration of pulmonary function during pregnancy: (1) increased airway responsiveness and obstruction (as can occur in patients with asthma), (2) increased work of breathing, and (3) cardiovascular changes such as congestive heart failure and pulmonary hypertension associated with the increased blood volume of pregnancy.

In spite of potential negative effects of pregnancy on the course of cystic fibrosis, long-term survival does not appear to be affected.[144] However, enthusiasm for these results should be tempered by the knowledge that pregnant women with cystic fibrosis require more intensive medical care than healthy pregnant women.[145,146]

Effect of Cystic Fibrosis on Pregnancy

Cystic fibrosis has been associated with an increased risk for LBW infants and preterm delivery,[146] but recent evidence suggests that improved care of these patients can mitigate these problems.[147] Potential mechanisms for these complications include chronic hypoxemia and poor maternal nutrition. Low prepregnancy FEV_1 and BMI are associated with an increased risk for adverse fetal outcome.[148]

Medical Management

Respiratory management of cystic fibrosis is primarily symptomatic. Patients with large volumes of mucus production undergo mechanical airway clearance. Some patients inhale recombinant human deoxyribonuclease I to reduce viscosity of lung secretions caused by accumulating DNA.[133] Hypertonic saline inhalation aids clearance of airway mucus.[149] Bronchodilators may help those patients who manifest a reversible component of airway obstruction. Continuous oxygen therapy may benefit patients with hypoxemia and cor pulmonale.

Long-term antibiotic therapy with inhaled tobramycin reduces both the incidence of recurrent pulmonary infection and the frequency of exacerbations in patients with cystic fibrosis.[150] Long-term administration of oral azithromycin also decreases exacerbations from cystic fibrosis[151] through either its antibiotic or its anti-inflammatory properties. Effects of long-term antibiotic therapy on the fetus are unknown.

Other forms of therapy include gene therapy and lung transplantation. Gene therapy uses viral (recombinant adeno-associated) or nonviral (liposome) vectors to transfer the normal CFTR to airway epithelium of patients with cystic fibrosis. A meta-analysis of randomized trials provided no evidence that topical CFTR gene replacement therapy improved clinical outcome, but further studies are needed owing to a limited number of study subjects.[152] Significant pulmonary deterioration sometimes leads to double-lung transplantation, although it is unclear whether transplantation alters survival.[153]

Obstetric Management

Because of the influence of pregravid maternal health on pregnancy outcome, the primary obstetric issue centers on the advisability of pregnancy in patients with cystic fibrosis. Criteria for the termination of pregnancy are not clearly defined. Genetic counseling regarding the risks of cystic fibrosis in the offspring is another important component of obstetric management.

Anesthetic Management

Considerations for anesthetic management focus primarily on the pulmonary system. Because of the high incidence of hypoxemia in patients with cystic fibrosis, continuous monitoring of oxygen saturation and appropriate oxygen therapy are advisable.

The goals of pain relief during labor are to provide adequate analgesia and to prevent maternal hyperventilation while avoiding high thoracic motor block and respiratory depression. High thoracic motor block may impair the parturient's ability to cough and eliminate thick secretions. Hyperventilation increases the work of breathing and may cause decompensation in patients with severe pulmonary dysfunction. For pain relief during labor, parenteral opioid analgesia may worsen pulmonary function by depressing respiratory drive and inhibiting cough. Intrathecal opioids have been used successfully,[154] but patients should be monitored carefully for respiratory depression. An ideal way to deliver a short-acting intrathecal opioid might be through a microcatheter, which would provide a margin of safety by allowing repeated administration of small doses of the opioid.[155] Alternatively, continuous lumbar epidural analgesia, with a sensory nerve block maintained at the level of the 10th thoracic dermatome, can provide excellent pain relief and reduce the stimulus for hyperventilation, with minimal motor block of the thorax. A dilute solution of bupivacaine, with or without an opioid, provides sensory analgesia with minimal motor block and is therefore nearly ideal in this setting.[156] In healthy parturients, this technique actually improves respiratory function slightly.[157]

Cesarean delivery necessitates the choice between general anesthesia and neuraxial anesthesia. Among patients with cystic fibrosis, no studies have documented differences in outcome between general anesthesia and neuraxial anesthesia. Neuraxial anesthesia offers the advantage of avoiding tracheal intubation, which may be associated with bronchospasm or obstruction of the tracheal tube with secretions. Neuraxial anesthesia also avoids positive-pressure ventilation, which may enlarge a preexisting pneumothorax. The primary consideration for neuraxial anesthesia during cesarean delivery is to avoid a high thoracic motor block, which may impair ventilation and the ability to cough. Effective spinal anesthesia for cesarean delivery slightly decreases vital capacity.[158] Methods for reducing the risk for excessively high motor block include the use of a continuous catheter technique, which allows titration of the local anesthetic agent to achieve the desired sensory level, and the use of the lowest concentration of local anesthetic (with or without an opioid) that provides surgical anesthesia. Both epidural

anesthesia[159] and combined spinal-epidural anesthesia[160,161] have been used in parturients with cystic fibrosis.

For general anesthesia, techniques to reduce the risk for bronchospasm, as described for patients with asthma (see earlier discussion), may be warranted. Additional considerations include (1) humidification of gases to prevent inspissation of mucus, (2) frequent suctioning to remove excess secretions, and (3) use of ventilator settings that allow an appropriately long expiratory phase to prevent air trapping and pneumothorax. It may also be prudent to avoid nitrous oxide in the parturient with cystic fibrosis, because of the risk for pneumothorax. Patients with cystic fibrosis should be allowed to awaken fully before extubation of the trachea. Chest physiotherapy may be required in the immediate postoperative period.

RESPIRATORY FAILURE

Epidemiology

The prevalence of respiratory failure during pregnancy is unknown. A significant subset of patients with respiratory failure suffers from **acute respiratory distress syndrome** (ARDS). The prevalence of ARDS in pregnancy has been estimated at approximately 1 in 6000 to 7000 deliveries.[162,163] Mortality from respiratory failure during pregnancy is high.[164]

BOX 53-4 Etiology of Respiratory Failure during Pregnancy

Adult Respiratory Distress Syndrome (ARDS)

- Infection
  - Bacterial or viral pneumonia
  - Endometritis
  - Pyelonephritis
  - Sepsis
  - Preeclampsia
- Hemorrhage
  - Multiple transfusions
  - Disseminated intravascular coagulation
- Aspiration of gastric contents
- Embolism
- Drugs
  - Salicylates
  - Opioids

Pulmonary Embolism

- Thromboembolism
- Amniotic fluid embolism
- Venous air embolism

Cystic Fibrosis

Pulmonary Edema

- Beta-adrenergic receptor agonists (e.g., ritodrine, terbutaline)
- Cardiogenic

Pathophysiology

The pathophysiology of respiratory failure depends on the underlying disorder. ARDS results from a group of predisposing conditions, but a common final pathway leads to similar manifestations.[165] Damage to the alveolar and capillary membranes initiates a cascade of events leading to fluid transudation that often is accompanied by pulmonary venoconstriction. Direct injury to the alveolar and capillary membranes can result from pulmonary aspiration of gastric contents and perhaps oxygen toxicity. Indirect toxicity can result from humoral and cellular mechanisms caused by triggers such as sepsis and amniotic fluid embolism. Transudation of fluid leads to atelectasis, airway obstruction, reduced lung compliance, and altered ventilation-perfusion relationships. Both physiologic dead space and shunt fractions are increased.

Diagnosis

A variety of disorders can cause acute respiratory failure during pregnancy (Box 53-4). Specific diagnostic criteria depend on the disorder.

The diagnosis of ARDS requires the exclusion of other disorders. Prominent characteristics of ARDS include arterial hypoxemia, radiographic evidence of pulmonary infiltrates, and reduced lung compliance in the setting of a recognized predisposing condition.[166]

Interaction with Pregnancy

Pregnancy is not known to alter the overall course of respiratory failure. However, differences in outcome between pregnant and nonpregnant patients have been observed in subsets of patients with respiratory failure. In a series of patients with **severe acute respiratory syndrome** (SARS), pregnant patients had greater morbidity.[167] Mortality rates are similar in pregnant and nonpregnant subjects.[164]

The most significant effect of respiratory failure on pregnancy is a reduction in oxygen delivery to the fetus. This reduction results most commonly from maternal arterial hypoxemia or maternal hypotension, which often accompanies respiratory failure. Hypotension may result from associated underlying conditions or from elevated mean airway pressures during mechanical ventilation. High rates of prenatal complications with or without preterm delivery have been reported.[162,163]

Medical Management

Therapeutic strategies for managing respiratory failure during pregnancy do not differ qualitatively from those in nonpregnant patients. The primary goals of medical management are to (1) eliminate predisposing conditions, (2) limit fluid transudation, and (3) maintain maternal oxygen delivery. Fluid restriction and diuretics help limit fluid transudation, although this therapy must be used cautiously when the underlying cause of respiratory failure is associated with intravascular fluid depletion. The goals for maintenance of oxygen delivery may differ quantitatively during pregnancy. Oxygen delivery to the fetus worsens significantly when Pao_2 decreases below 70 mm Hg or oxygen saturation (Sao_2) falls below

95%.[162,168] Standard methods of maintaining oxygen delivery include (1) administration of a higher inspired concentration of oxygen, (2) administration of bronchodilators in the presence of reversible airway obstruction, (3) administration of pharmacologic agents to support the circulation as needed, and (4) mechanical ventilation. A higher inspired oxygen concentration, delivered by face mask, is safe during pregnancy and may obviate the necessity of tracheal intubation and its risks for aspiration and difficult airway management. Bronchodilator therapy can also be used for respiratory failure, as described earlier for asthma. Pharmacologic agents for circulatory support include agents with both alpha- and beta-adrenergic receptor activity.

Indications for tracheal intubation and mechanical ventilation are similar for pregnant and nonpregnant patients with respiratory failure.[167,169] Maternal and fetal effects of current approaches to mechanical ventilation, including use of low tidal volumes and permissive hypercapnia, have not been studied in pregnant patients. Positive end-expiratory pressure may be used if cardiac output is maintained to allow sufficient blood flow to the uterus.

Some pregnant patients with respiratory failure do not show adequate response to conventional methods of treatment. For these patients, treatment options include extracorporeal membrane oxygenation (ECMO),[170] high-frequency oscillatory ventilation,[171] and inhaled **nitric oxide**.[172,173] Nitric oxide relaxes vascular smooth muscle. Rapid inactivation of nitric oxide by binding to hemoglobin in the circulation allows inhaled nitric oxide to produce pulmonary vasodilation without systemic vascular effect. Selective pulmonary vasodilation in well-ventilated areas of the lung presumably would improve oxygen delivery. The safety of these alternative forms of treatment in pregnancy is unknown because reports of their use are anecdotal.

Obstetric Management

Because the beneficial effects of delivery on the course of respiratory failure have not been proved, indications for induction of labor or cesarean delivery in this setting are not well defined. Small observational studies have not clearly shown an association between delivery and improved respiratory status in pregnant women with respiratory failure.[163,174,175] Further, data to support decisions regarding mode of delivery are limited. Vaginal delivery is possible during mechanical ventilation[176,177] and may avoid complications of major intra-abdominal surgery in a critically ill woman.

Anesthetic Management

The anesthetic management of patients with respiratory failure requires appropriate medical management. During labor, analgesia for mechanically ventilated patients can be achieved with intravenous opioids, which are often used for sedation during mechanical ventilation. Lumbar epidural analgesia provides pain relief without the neonatal respiratory depression associated with high doses of opioids. Labor epidural analgesia also reduces oxygen consumption,[178] which may be beneficial in hypoxemic patients. The use of labor epidural analgesia in patients with respiratory failure depends on underlying conditions and ongoing therapy. Close attention should be paid to intravascular volume, adequacy of coagulation, and presence or absence of infection.

In mechanically ventilated patients, general endotracheal anesthesia is often the most convenient choice for cesarean delivery. Aside from the issues of medical management (as discussed earlier), the techniques and pharmacologic agents do not differ substantially from those used in patients without respiratory failure.

KEY POINTS

- Patients with asthma, infection, respiratory failure, or cystic fibrosis and patients who smoke cigarettes may have reversible airway obstruction.
- In patients with airway hyperresponsiveness, tracheal intubation provides one of the most significant stimuli for bronchospasm during the perioperative period.
- Inhaled β_2-adrenergic agonists are the most effective therapy for perioperative bronchospasm.
- Most bronchodilators also produce uterine relaxation. However, their administration by aerosol should minimize their effects on uterine tone.
- Neuraxial anesthesia is often the anesthetic technique of choice in patients with respiratory disease because it does not require tracheal intubation.
- Techniques of neuraxial anesthesia should be modified to reduce the likelihood of a high thoracic motor block in patients with significant respiratory disease.

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CHAPTER 54

Substance Abuse

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CHAPTER OUTLINE

Abuse of licit and illicit substances by pregnant women can pose a significant risk to maternal and fetal health. Estimates of the prevalence of substance abuse in pregnant women vary depending on the particular licit or illicit substance, the maternal age group, and the data source.[1-3] The rate of illicit drug use during pregnancy as reported in the National Survey on Drug Use and Health from 2009 to 2010 was 16.2% among pregnant women aged 15 to 17 years, 7.4% among pregnant women aged 18 to 25 years, and 1.9% among pregnant women aged 26 to 44 years. During the same time period, among pregnant women aged 15 to 44 years, 4.4% were current illicit drug users. This 4.4% rate was lower than the rate among nonpregnant women (10.9%).[1]

Depending on the particular substance ingested, pregnant women may experience little to no acute and chronic adverse effects, or alternatively, manifest one or more of the following: (1) cardiovascular, pulmonary, and neurologic complications; (2) obstetric complications (e.g., decreased intrauterine fetal growth, preterm labor, placental abruption, fetal death); and (3) heightened sensitivity to pain.[4-12] Anesthesia providers often care for these patients during the provision of analgesia for labor and anesthesia for cesarean delivery as well as during other obstetric procedures before and after delivery. Patients with substance abuse may have altered pain sensitivity, and anesthesia providers are often consulted for help with management of acute postoperative pain.

DRUG DETECTION

Optimal care requires developing a therapeutic bond with these patients and identifying what substances have been ingested.[13] The anesthesia provider should ask questions in a respectful and nonjudgmental manner. It is vital to respect patient confidentiality, and it may be necessary to speak to the patient without family or friends present. Self-reporting typically underrepresents the true incidence of substance abuse.[14-16] Therefore, health care providers should be familiar with the characteristic signs and symptoms associated with acute and chronic intoxication. The myriad of methods available to test pregnant patients and their infants for the presence of illicit drugs include analysis of urine, blood, saliva, hair, meconium, and umbilical cord tissue. Amniotic fluid and neonatal gastric aspirate have also been analyzed (Tables 54-1 and 54-2).[14-19] It is vital to understand which compounds a particular drug test identifies before interpreting the results. Caregivers should be aware that the immunoassays most commonly used in drug testing can have false-positive or false-negative results in the presence of structurally related drugs or additives. Gas chromatography with mass spectrometry ideally should be used to provide confirmation of positive results.[16]

LICIT DRUGS

Alcohol

Epidemiology

Alcohol (ethanol) abuse represents a significant problem for pregnant women and their developing fetus. Since 1981, official advisories have warned against the use of alcohol by pregnant women or women considering pregnancy.[20] Yet the 2010 National Survey on Drug Use and Health noted that 10.8% of pregnant women 15 to 44 years old reported current alcohol use, 3.7% reported binge drinking, and 1.0% reported heavy drinking. These rates are significantly lower than those of nonpregnant women in the same age brackets (54.7%, 24.6%, and 5.4%, respectively). Survey data indicate that among heavy drinkers, approximately 1.8% also use illicit drugs.[1]

TABLE 54-1 Drug Detection: Overview

Specimen	Advantages	Limitations
Urine	Detection of diverse group of illicit substances (except volatile alcohols) Specimen and test readily available Short turnaround time (30 minutes at point of care; 2 hours for laboratory specimens) More sensitive test (compared with meconium and hair) for cannabis	Underrepresents most illicit drug use Significant false-positive rate for phencyclidine (PCP) Narrow detection window compared with that for meconium and hair Specimen can more easily be adulterated
Blood	Most commonly used for volatile alcohols (can detect other illicit substances) Specimen and test readily available	Invasive Narrow detection window compared with that for urine, meconium, and hair
Meconium	Highly sensitive (compared with urine testing) for cocaine and opioids Wide detection window No false-positive results for cocaine	Report may be delayed (days) Low sensitivity and specificity for detecting cannabinoids and amphetamines via immunoassay
Hair	Highly sensitive test for detecting cocaine (three times that of urine) and opioids Wide detection window (reflects chronic cumulative use) Samples can be stored at room temperature Samples can be analyzed remote from collection	Multiple hairs required; harvested close to scalp Environmental contamination may cause false-positive result Low sensitivity for detecting tetrahydrocannabinol
Umbilical cord blood	Comparable to meconium with more rapid results May reflect a wide window of detection	Specimen not available before delivery
Oral fluid	Highly sensitive for methamphetamine and other basic drugs Easy, noninvasive Primarily detects parent compound	If mouth is dry, salivary stimulation may be associated with a decreased drug concentration in oral fluid

Data from references 3, 14, 15, 17, and 165.

TABLE 54-2 Drug Detection Window in Urine*

Drug†	Analyte	Detection Window
Tobacco	Cotinine Nicotine	19 h (urine $T_{1/2}$) 2 h (urine $T_{1/2}$)
Cocaine	Cocaine Benzoylecgonine	3-6 h IV use: 1-2 days Intranasal use: 2-3 days
Amphetamines	Amphetamine Methamphetamine	1-3 days Smoked: 60 h
Methylenedioxymethamphetamine (MDMA, ecstasy)	MDMA	1-3 days
Marijuana (cannabis)	Tetrahydrocannabinol (THC) THCCOOH	Smoked: 10 h Up to 25 days
Lysergic acid diethylamide (LSD)	LSD 2-Oxo-3-OH-LSD	24 h 96 h
Heroin	6-Acetyl morphine Morphine	IV use: 2-4.5 h 19-54 h
Benzodiazepines	Flunitrazepam: 7-aminoflunitrazepam	< 72 h Chronic use: 4-6 wk
γ-Hydroxybutyric acid (GHB)	Rapidly metabolized to CO_2 and H_2O	< 12 h

IV, intravenously; $T_{1/2}$, half-life.
*Average values based on recent use; precise values may vary according to method of ingestion, assay employed, and duration of use.
†Detection of methadone, buprenorphine, oxycodone, and oxymorphone typically requires an additional screening test.
Data from references 5, 19, 74, 120, and 166.

Pharmacology

Alcohol, usually ingested orally, is absorbed through the gastrointestinal tract, primarily within the small intestine. Ingested alcohol is metabolized by alcohol and acetaldehyde dehydrogenases. This process leads to the production of acetaldehyde and the reduction of nicotinamide adenine dinucleotide (NAD) to its reduced form NADH. The excess reduced form relative to NAD results in metabolic derangements. A small residual amount (2% to 8%) of alcohol is excreted via the lungs, urine, and sweat.[21-23]

Systemic Effects

According to legal statutes, the definition of "intoxication" requires a blood alcohol level of at least 80 to 100 mg/dL, although behavioral, cognitive, and psychomotor changes can occur at levels of 20 to 30 mg/dL (e.g., after one to two drinks) (Table 54-3).[21-23]

Alcohol has complex effects on the central nervous system (CNS); it acts as both a depressant and a stimulant through a variety of neurotransmitter pathways.[23] When alcohol is consumed in conjunction with barbiturates or benzodiazepines, these effects can be compounded. Endogenous opioids interact with alcohol to "reinforce" further alcohol use; this effect is blunted by opioid antagonists.[23]

Alcohol and its metabolites (e.g., acetaldehyde) can be directly toxic to brain tissue.[21,22] Chronic alcoholism is associated with brain atrophy that results in impairment of memory, abstract problem-solving, verbal learning, and visual-spatial processing.[21,22] Additional adverse neurologic effects result from vitamin (e.g., thiamine, vitamin B_{12}) deficiencies.[21,22]

Heavy alcohol consumption also damages other organs. Over time, hepatic cirrhosis can develop, which, in turn, can lead to encephalopathy, coagulopathy, and esophageal varices (Table 54-4). Gastrointestinal mucosa injury, pancreatitis, and cardiomyopathy may also occur.[9,10,22,24]

Women who abuse alcohol are at increased risk for depression, suicide, and accidents.[7] Symptoms of acute alcohol withdrawal (e.g., nausea, vomiting, tachycardia, hypertension, arrhythmias, tremor, hallucinations, agitation, seizures) usually occur within 6 to 48 hours after cessation of alcohol consumption (Table 54-5).[9,10,25] Pharmacologic therapy to minimize the signs and symptoms of alcohol withdrawal includes the use of benzodiazepines and α_2-adrenergic agonists (e.g., clonidine).[9] The most severe form of withdrawal symptoms, **delirium tremens**, manifests as agitation, disorientation, hallucinations, and fever combined with autonomic instability. Delirium tremens occurs rarely in pregnant women, but it can lead to maternal and fetal death if untreated.[6, 26]

Effects on Pregnancy and the Fetus

Intrauterine alcohol exposure is the leading cause of preventable birth defects in the United States.[27,28] No safe level of alcohol consumption by pregnant women has been identified.[26,27] In contrast to other investigations of high-risk populations, a 2010 population-based cohort study found no association between low or moderate prenatal alcohol exposure before or during pregnancy and the occurrence of birth defects.[29] However, the authors recognized that the incidence of birth defects is low and the sample size may not be sufficient to draw definitive conclusions. **Fetal alcohol syndrome** is defined as the presence of particular neonatal facial features (e.g., small palpebral fissures, flat midface with a short upturned nose, thin upper lip) and significant impairment in neurodevelopment and physical growth.[9,10,27,30] **Fetal alcohol spectrum disorders** refer to the wide range of possible adverse effects of fetal exposure to alcohol.[27] The extent to which an individual fetus is affected is related to the characteristics of the exposure, genetic variables, and the intrauterine environment.[31]

Alcohol exposure is also associated with pregnancy loss. Harlap and Shiono[32] reported an increased risk for second-trimester fetal loss in pregnant women who consumed alcohol early in pregnancy (relative risk, 1.98 for those consuming one to two drinks daily and 3.53 for those consuming more than three drinks daily, compared with nondrinkers). Identification of mothers at risk can facilitate treatment and perhaps improve pregnancy outcomes.[27]

Anesthetic Management

Alcohol-intoxicated parturients are at increased risk for behavioral problems, electrolyte abnormalities, greater gastric acid secretion, and co-intoxication with other substances.[9,10,26] Determining whether the patient can protect her airway is of paramount importance because acute intoxication increases the risk for pulmonary aspiration of gastric contents. In addition, these patients may have intravascular volume depletion secondary to vomiting, inadequate oral intake, diuresis, and hypoalbuminemia. Significant alcohol ingestion in the setting of poor oral intake may also manifest as severe hypoglycemia.[22,24,33]

Neuraxial analgesia or anesthesia can be safely administered for labor or cesarean delivery provided that (1) the patient is cooperative, (2) there is no evidence of coagulopathy (as a result of liver disease), (3) the patient is volume replete, and (4) baseline neurologic deficits (e.g., peripheral neuropathy, cognitive deficits) are assessed and documented.[9]

If emergency delivery is required and the patient is either uncooperative or too sedated to protect her airway, general anesthesia will be necessary. The patient should receive pharmacologic aspiration prophylaxis (e.g., nonparticulate antacid, histamine-2 (H_2)-receptor antagonist, metoclopramide) and should undergo a rapid-sequence induction of general anesthesia.[34]

Evidence from published reports is inconclusive about predictable differences in anesthetic requirements in patients with acute and chronic alcohol use.[35] Acute alcohol intoxication is believed to decrease a patient's anesthetic requirements, in part because of the additive effect of alcohol and other CNS depressants. The notion that chronic alcoholics require more anesthesia than their non–alcohol-using counterparts is based primarily on data from an abstract published by Han in 1969,[36] who demonstrated that the mean minimum alveolar concentration (MAC) for halothane in six chronic alcoholic patients who had been heavy drinkers for more than 10 years was significantly greater than that for six healthy adults. Subsequently, Swerdlow et al.[37] assessed the response to thiopental in 11 nonpregnant, chronic alcohol users. After eliminating potential confounders such as acute intoxication, withdrawal, polysubstance abuse, and end-organ dysfunction, they found that chronic alcohol intake did not alter thiopental dose requirements, pharmacokinetics, or pharmacodynamics. No large population studies have assessed dose requirements for volatile anesthetic agents or hypnotic agents in patients who chronically abuse alcohol.

TABLE 54-3 **Acute Intoxication and Organ Dysfunction**

Substance	Neurologic	Cardiovascular	Pulmonary	Gastrointestinal	Hematologic	Other
Alcohol	↓ Cognition	—	↑ risk for aspiration	—	—	↑ Cortisol ↓ Glucose
Tobacco	—	↑HR, BP, myocardial work	↓ Tissue oxygenation secondary to ↑ carboxyhemoglobin ↓ Mucociliary clearance ↑ Airway irritability	—	—	Impaired wound healing
Caffeine	—	Mild ↑ BP in low doses	—	—	—	Diuresis
Marijuana (cannabis)	↓ Cognitive and motor performance	Biphasic autonomic effect ST-segment and T-wave changes on ECG	↑ HR **If smoked:** effects similar to those of tobacco	Appetite stimulation	—	Conjunctival vasodilation and reddening
Cocaine	Subarachnoid or intracranial hemorrhage Cerebral infarct Seizures	Hemodynamic instability, arrhythmias Acute myocardial infarction Aortic dissection	**If free based:** pulmonary edema and pulmonary hemorrhage **If smoked:** see "Tobacco" **If snorted:** nasal septal injury and epistaxis	↑ AST and ALT	↓ Platelets (?)	Infection ↑ Temperature ↑ Cortisol ↑ Glucose
Amphetamines	Seizures Stroke Paranoia Hallucinations	Similar to effects associated with cocaine	—	—	—	Proteinuria ↑ Temperature
Hallucinogens	Hallucinations Paranoia Intracerebral hemorrhage (rare) Seizures (rare)	Supraventricular tachycardia (rare) Acute myocardial infarction (rare)	—	—	—	—
Opioids	—	↓ HR ↓ BP	Respiratory depression	—	—	—
Solvents	Encephalopathy Seizures	Arrhythmias Acute myocardial infarction	Hypoxemia Bronchospasm Acute respiratory distress syndrome	Mucosal injury		Ethylene glycol ingestion: Metabolic acidosis Renal failure

ALT, alanine aminotransferase; *AST,* aspartate aminotransferase; *BP,* blood pressure; *ECG,* electrocardiogram; *HR,* heart rate; ↑, increase in; ↓, decrease in; ?, questionable.

TABLE 54-4 **Effects of Chronic Substance Abuse**

Substance	Neurologic	Cardiac	Pulmonary	Gastrointestinal	Hematologic	Other
Alcohol	Peripheral neuropathy Brain atrophy Encephalopathy	Cardiomyopathy	—	Hepatitis Cirrhosis Gastric mucosal injury Pancreatitis	Anemia (± leukopenia, thrombocytopenia) Coagulopathy	↑ Cortisol
Tobacco	—	Atherosclerosis	Diffusion capacity abnormalities ↓ Pulmonary immune function ↑ Incidence of bronchitis, COPD ↑ Airway irritability ↑ Risk for lung cancer	—	—	—
Caffeine	Cessation may produce withdrawal headache	Does *not* negatively affect cardiac health at moderate dose	—	—	—	↑ Risk for bladder dysfunction with high dose
Marijuana (cannabis)	↓ Attention, memory ↓ Ability to process complex information	—	**If smoked:** effects similar to those associated with tobacco	↑ Rare forms of oropharyngeal cancer	—	—
Cocaine	Brain atrophy	Cardiomyopathy Myocarditis Blood vessel occlusion	**If smoked:** effects similar to those associated with tobacco **If snorted:** mucosal and nasal septal injury	Gastrointestinal ischemia/ulceration ↑ AST and ALT	↓ Platelets (?)	Renal failure
Amphetamines	Paranoid psychosis Impaired memory	—	—	—	—	↑ Tooth decay ("meth mouth")
Hallucinogens (episodic use)	Delayed hallucinations	—	—	—	—	—
Opioids	Abnormal pain sensitivity	Infective endocarditis	—	—	—	Hepatitis or HIV infection with exposure to contaminated needles
Solvents	Visual loss Cranial neuropathy Peripheral neuropathy Autonomic dysfunction Ataxia Brain atrophy Encephalopathy	Cardiomyopathy Acute myocardial infarction	—	Nonviral hepatitis Hepatocellular carcinoma	Aplastic anemia	"Glue-sniffer's" rash Renal failure

ALT, alanine aminotransferase; *AST,* aspartate aminotransferase; *COPD,* chronic obstructive pulmonary disease; *HIV,* human immunodeficiency virus; ↑, increase in; ↓, decrease in; ?, questionable.

TABLE 54-5 Symptoms of and Treatment for Substance Abuse Withdrawal

Substance	Symptoms	Therapy
Alcohol (ethanol)	Nausea Vomiting Tachycardia Hypertension Tremor Hallucinations Agitation	Benzodiazepines and α_2-adrenergic agonist (e.g., clonidine)
	Delirium tremens: • Autonomic instability/arrhythmias • Seizures • Severe tremors • Disorientation • Fever	Benzodiazepines and α_2-adrenergic agonist (e.g., clonidine) Antiarrhythmics Anticonvulsants (e.g., phenytoin)
Tobacco	Cravings Irritability Headache Cough Insomnia	Nicotine replacement therapies, including patch, gum, and inhalers
Caffeine	Headache Anxiety Depressed mood Fatigue	Supportive care Caffeine ingestion
Cannabis	Mild abstinence syndrome Headache Restlessness Tremor Anxiety Autonomic effects	Supportive care
Cocaine	Prolonged sleep phase Hunger Anxiety Weakness Headaches Tremors and seizures	Supportive care Reintroduction of drug, if necessary, with slow taper
Amphetamines	Fatigue Depression Hunger Intense cravings	Tricyclic antidepressants, dopaminergic agents (e.g., bromocriptine), and amino acid therapy (no therapy has proved to be successful)
Hallucinogens (e.g., phencyclidine [PCP], lysergic acid diethylamide [LSD])	No clearly associated withdrawal symptoms, although psychological dependence can occur	Not applicable
Opioids (e.g., heroin)	Flulike symptoms, such as fatigue, weakness, restlessness, rhinorrhea, perspiration, fever, diarrhea	Supportive therapy α_2-Adrenergic agonist (e.g., clonidine) Doxepin Reintroduction of drug, if necessary, with slow taper
Solvents (e.g., ethylene glycol, toluene, glue)	Not applicable	Not applicable

Short-term consumption of alcohol inhibits the metabolism of drugs by the liver (through competition for cytochrome P450), which results in higher plasma concentrations of drugs metabolized by the liver. *Long-term* consumption of alcohol increases the levels of cytochrome P450, resulting in decreased levels of medications such as diazepam and labetalol, and increased levels of toxic metabolites that occur from hepatic degradation of illicit drugs such as cocaine.[22] Both pregnancy and liver disease can lead to decreased plasma concentrations of pseudocholinesterase; however, this decrease does not seem to have a clinically significant effect on the degradation of succinylcholine and ester local anesthetics.[35]

Parturients who regularly consume large amounts of alcohol and undergo general anesthesia for cesarean delivery may be at high risk for awareness under anesthesia.[38] The high doses of volatile anesthetics often recommended in nonpregnant, chronic alcohol-using patients can lead to significant uterine atony and potential increased blood loss. Therefore, a balanced anesthetic technique that combines induction with generous doses of the hypnotic agent with succinylcholine (if not otherwise contraindicated), followed by maintenance with a volatile anesthetic agent (limited to 0.5 to 0.8 MAC after delivery to prevent uterine atony), nitrous oxide (up to 67%), and an opioid and a benzodiazepine (for analgesia and amnesia), should be employed. Withholding

additional muscle relaxation after induction and adding a brain function monitor if time and circumstance permits[39] may help to identify patients who could benefit from additional anesthesia.

Tobacco

Epidemiology

Cigarette smoking is the most common form of substance abuse during pregnancy. As public awareness has grown regarding the hazards of smoking during pregnancy, the prevalence of cigarette smoking during pregnancy has declined over the past 40 years. An estimated 18% of pregnant women reported smoking (in the past month) in 2003,[40] compared with 16% in 2010.[1] Although the overall smoking rate in pregnant women is lower than in nonpregnant women, the rate among pregnant teens aged 15 to 17 years is actually higher than that among nonpregnant teens (22.7% versus 13.4%).[1] Among the approximately 40% of patients who stop smoking when they discover that they are pregnant, 60% to 80% return to smoking by 6 months postpartum.[41]

Pharmacology

More than 4000 chemicals are found in tobacco, including nicotine, carbon monoxide, and cyanides.[23,42] Tobacco is most often smoked, but it can also be chewed or sniffed. Nicotine, the principal drug of abuse in tobacco, acts at peripheral and central nicotinic (acetylcholine) receptors throughout the body to affect the release of catecholamines. Nicotine's effects begin immediately on exposure; it is then rapidly metabolized in the liver and the lungs and excreted by the kidneys. The half-life is typically a few hours. The duration of the acute effects of nicotine is shorter in heavy smokers than in light smokers.[23]

Carbon monoxide, another constituent of cigarette smoke, interferes with oxygen delivery to the cells by competitively binding to hemoglobin, thereby decreasing the oxygen-binding capacity and shifting the oxyhemoglobin dissociation curve to the left.[43] Depending on the extent of smoke inhalation, carbon monoxide may occupy 3% to 15% (or more) of the oxygen-carrying capacity of the blood.[44]

Systemic Effects

Smoking alters maternal physiology through both the acute pharmacologic actions of tobacco's chemical constituents and their contribution to comorbid disease. Peripherally, nicotine increases sympathetic tone, thereby increasing maternal heart rate, blood pressure, and cardiac work (see Table 54-3).[45] Nicotine affects neurotransmitter release in different areas of the brain, producing feelings of alertness, euphoria, and, ultimately, dependence.[23,45]

Increased production of carboxyhemoglobin is thought to be a major factor in the impaired wound healing observed in smokers.[43] Smoking also promotes atherosclerosis. The effects of tobacco smoking on the lungs include changes in the volume and composition of mucus, impaired mucociliary clearance, and an increased incidence of bronchitis and chronic obstructive pulmonary disease (see Table 54-4).[45]

Tobacco is addictive, and cessation of its use produces withdrawal symptoms, including cravings, irritability, headache, cough, and insomnia (see Table 54-5). Smoking cessation interventions include counseling and therapy, hypnosis, acupuncture, and pharmacologic therapy. The use of nicotine replacement therapy (e.g., nicotine gum, patch, inhaler) has not undergone sufficient evaluation of safety during pregnancy; thus, the American College of Obstetricians and Gynecologists (ACOG) has recommended that nicotine replacement therapy be used only when nonpharmacologic interventions have failed.[40] The physiologic benefits of smoking cessation are progressive. Even brief smoke-free intervals can result in a reduction in the carboxyhemoglobin concentration, improved ciliary function, and decreased small airway obstruction.[46]

Effects on Pregnancy and the Fetus

Nicotine has a low molecular weight and readily crosses the placenta.[4] Smoking may result in decreased fetal oxygenation as a result of increased concentrations of carboxyhemoglobin and reduced uteroplacental perfusion. It also leads to decreased uptake of nourishing amino acids by the placenta.[42] Smoking is associated with a higher incidence of ectopic pregnancy, spontaneous fetal loss, placental abruption, and sudden infant death syndrome (SIDS).[32,40,47] Smoking may protect against the occurrence of preeclampsia (see Chapter 36).[48]

Smoking adversely affects fetal growth.[42,49,50] Low birth weight (LBW) is associated with increased neonatal and infant mortality.[42,50] Salihu et al.[50] documented that infant mortality was 40% higher in the offspring of women who smoked than in the offspring of nonsmoking women; this risk increased in a dose-dependent fashion for the infants who were small for gestational age (SGA). Smoking cessation before the third trimester ameliorates the smoking-associated reduction in birth weight.[40]

Intrauterine exposure to smoking (tobacco and/or marijuana) may also have long-term effects. Fried et al.[51] examined the cognitive performance in 145 adolescents (13 to 16 years of age) from a low-risk, middle-class population. After controlling data for socioeconomic status and polysubstance abuse, they found that measures of overall intelligence and auditory memory were negatively related to prenatal maternal smoking in a dose-related fashion.

Anesthetic Management

Smoking is a risk factor for several perioperative complications, including respiratory sequelae and impaired wound healing.[43,45] Smoking results in increased airway secretions, decreased ciliary motility, and impaired gas exchange.[45] Smoking is also associated with an increase in nonspecific airway reactivity, and tracheal intubation may provoke bronchospasm. Wilkes et al.[52] observed that coughing after exposure to desflurane was more pronounced in smokers. By contrast, Kim and Bishop[53]

observed that although most patients coughed as they awakened from general anesthesia maintained with isoflurane, smokers were not more likely to cough than nonsmokers.

Six months of abstinence may be required before the function of alveolar macrophages and pulmonary cytokines during and after general anesthesia in former smokers is similar to that of nonsmokers.[46] Administration of neuraxial anesthesia avoids airway manipulation and is typically preferred in parturients who smoke.

Caffeine

Epidemiology

On a daily basis, 80% to 98% of women drink caffeine-containing beverages.[9,54] The prevalence of consumption of caffeine-containing beverages during pregnancy is unknown.

Pharmacology

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring alkaloid found in coffee, tea, cocoa, and some soft drinks and medicines.[9,54,55] The primary sources of caffeine in the adult diet are coffee (56 to 100 mg/100 mL if brewed) and tea (20 to 73 mg/100 mL). Caffeine is readily absorbed through the gastrointestinal tract, and maximum blood concentrations of caffeine are attained 1 to 1.5 hours after ingestion. Caffeine undergoes hepatic metabolism and is then excreted in the urine.[54,55] The elimination half-life of caffeine is 3 to 7 hours. In pregnancy, the half-life increases from 4 hours in the first trimester to 18 hours by the third trimester. Caffeine crosses the placenta and can also be found in breast milk.[54,56] Habitual use of caffeine at levels greater than 500 to 600 mg/day is defined as abuse.[54,56]

The half-life of caffeine in the neonate is prolonged in comparison with that in children and nonpregnant women.[54]

Systemic Effects

Caffeine acts as an antagonist at the adenosine receptor. In the absence of the inhibitory effects of adenosine, the neurotransmitters norepinephrine, dopamine, and serotonin are released in increased concentrations.[54,56] Systemic effects of caffeine include CNS stimulation, changes in blood pressure and metabolic rate, and diuresis (see Table 54-3).[55] The side effects commonly attributed to caffeine vary among individuals, in part related to the doses ingested and the degree of chronic use. Studies of the effects of caffeine on alertness, vigilance, mood, and memory have produced inconsistent results.[54]

Moderate caffeine intake (≤ 400 mg/day or ≤ 4 cups of coffee/day) does not seem to negatively affect cardiovascular health in most people. Although some people who ingest caffeine report tachycardia and palpitations, doses lower than 450 mg/day do not appear to increase significant cardiac arrhythmias in either healthy patients or in those with ischemia or ventricular ectopy. Caffeine doses as low as 250 mg have been reported to have a hypertensive effect after acute ingestion (an increase in systolic blood pressure of 5 to 15 mm Hg and an increase in diastolic blood pressure of 5 to 10 mm Hg), particularly in caffeine-naive individuals; however, epidemiologic studies have produced inconsistent results. In general, people who ingest caffeine on a long-term and frequent basis are less likely than occasional users to have difficulty sleeping.[54]

Caffeine appears to affect bladder function in women. Moderate caffeine intake may exacerbate preexisting bladder symptoms, and excessive intake (> 400 mg/day) increases the risk for bladder dysfunction.[54]

Evidence suggests that caffeine is not a human carcinogen.[55] The lethal dose of caffeine in humans has been estimated to be 10 g; however, only a few such cases have been reported.[54]

Caffeine withdrawal is associated with headache, anxiety, depressed mood, and fatigue (see Table 54-5). Typically, symptoms begin 12 to 24 hours after cessation of use, peak at 20 to 48 hours, and last up to 7 days. The severity and likelihood of symptoms are not predictable.[54]

Effects on Pregnancy and the Fetus

Caffeine readily crosses the placenta. Whereas animal studies have shown that very high doses can have a teratogenic effect, moderate doses do not appear to result in teratogenesis in humans.[54,57,58] There is some evidence that caffeine at doses greater than 300 mg/day may result in fetal growth restriction (also known as intrauterine growth restriction) and decreased birth weight, particularly in women who also smoke or drink significant amounts of alcohol.[54] Although previous studies[56] have not shown an association between low or moderate caffeine intake (< 300 mg/day) and greater risk for spontaneous abortion or preterm delivery, Weng et al.[59] found that caffeine consumption greater than 200 mg/day was associated with an increased risk for miscarriage, particularly among pregnant women who did not have a previous history of miscarriage. Moderate intake of caffeine in lactating women does not adversely affect postnatal development.[54,55]

Two studies have suggested that moderate caffeine intake during pregnancy may actually have beneficial effects on the mother and the fetus. Adeney et al.[60] found that women who consumed caffeinated coffee before conception had a significantly lower risk for development of gestational diabetes mellitus than women who did not consume coffee. No reduction in risk was associated with ingestion of tea or soda. Back et al.[61] showed that neonatal mice exposed to caffeine and subsequently subjected to hypoxia seemed to have less neurologic injury (i.e., less ventriculomegaly, less disruption in myelination) than non–caffeine-exposed mice.

Anesthetic Management

Caffeine may enhance the side effects of beta-adrenergic receptor agonists such as epinephrine and albuterol. Caffeine may also increase the risk for a hypertensive crisis in patients taking monoamine oxidase (MAO) inhibitors. Caffeine slows the elimination of theophylline and

acetaminophen, resulting in higher drug concentrations in the blood. In contrast, serum concentrations of lithium may be decreased secondary to caffeine-enhanced elimination.[55]

Perhaps of greatest significance to the anesthesia provider is the potential for **caffeine withdrawal headache** in parturients who abruptly decrease their usual caffeine intake during labor and delivery. Caffeine withdrawal should be considered in a postpartum patient who has a nonspecific, nonpositional headache without associated lateralizing neurologic findings (see Chapter 31). Evidence for the efficacy of caffeine in the treatment of post–dural puncture headache is scant (see Chapter 31).[62] Resumption of caffeine ingestion should be considered for treatment of caffeine withdrawal headache.

ILLICIT DRUGS

Marijuana (Cannabis)

Use of marijuana for medical and recreational purposes can be traced back thousands of years.[63] In 2010, approximately 2.4 million people in the United States used marijuana for the first time.[1] Marijuana was the illicit drug with the largest number of new users aged 12 or older. Estimates of marijuana use in the pregnant population vary from 6% to 7%.[17,64]

Pharmacology

Marijuana contains more than 400 compounds, including 60 cannabinoids. Most of the psychotropic effects are caused by 9-tetrahydrocannabinol (THC).[63,65] Noncannabinoid constituents of marijuana are similar to those in tobacco without the nicotine. Inhaled THC is absorbed through the lungs and reaches the brain within minutes. Oral ingestion of marijuana results in blood THC concentrations that are 25% to 30% of those obtained by smoking, but with a delayed onset of up to 2 hours. Cannabinoids are highly lipid-soluble compounds that are sequestered in fatty tissues and are gradually released into other tissues. Thus, a single ingestion can have an elimination half-life of up to 7 days; complete elimination of the inactive metabolite 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) takes as long as 25 to 30 days. Metabolism occurs in the liver, with excretion in the urine. Measured concentrations of THC and other cannabinoid metabolites in the blood and urine correlate poorly with the degree of intoxication.[65]

Systemic Effects

Cannabis interacts with specific cannabinoid receptors in the brain and peripheral nerves. Psychoactive effects include anxiolysis, analgesia, appetite stimulation, euphoria, and, sometimes, dysphoria (see Table 54-3).[65] Marijuana intoxication impairs cognitive and psychomotor function. Impairment of memory, attention, and the ability to process complex information can occur with long-time heavy use (see Table 54-4). It is unclear whether these effects are reversible.[66]

Acute intoxication with marijuana appears to have a biphasic effect on the autonomic nervous system; low doses cause tachycardia and higher cardiac output due to increased sympathetic and decreased parasympathetic tone. In contrast, high doses produce sympathetic inhibition and parasympathetic stimulation, resulting in bradycardia and hypotension.[5,63] Although ventricular ectopy can occur, life-threatening arrhythmias in patients without preexisting cardiac disease are rare and autonomic disturbances are generally well tolerated. Reversible ST-segment and T-wave abnormalities may occur, perhaps as a result of the higher heart rate associated with marijuana use.[5]

As with tobacco, the respiratory consequences of smoking marijuana include mucociliary dysfunction, increased susceptibility to bronchitis, and chronic obstructive pulmonary disease (see Table 54-4). Acute intoxication may cause conjunctival vasodilation and visible reddening of the eyes. Although high doses of marijuana can cause hallucinations and psychosis, fatal overdose has not been documented.[6,65]

Withdrawal from long-time marijuana use may produce a mild abstinence syndrome that includes headache, restlessness, tremor, anxiety, and autonomic effects, similar to those of withdrawal from benzodiazepines and hypnotic drugs (see Table 54-5).[5,66]

Effects on Pregnancy and the Fetus

It is difficult to ascertain specific effects of marijuana on pregnancy, because women who use marijuana often engage in polysubstance abuse. In a prospective study of more than 3800 pregnancies, Hatch and Bracken[66] showed that regular marijuana use by white women was associated with an increased risk for delivering an LBW and/or SGA infant, but occasional use was not. The risk for these adverse outcomes in nonwhite marijuana-using women was not elevated above their baseline level of increased risk. In a prospective multicenter study of more than 7000 multiethnic pregnant women, marijuana use was not associated with increased risk for LBW, preterm delivery, or placental abruption.[67]

Intrauterine exposure to marijuana has not been proven to be teratogenic, but some research suggests that it is associated with subtle postnatal neurologic derangements. Fried et al.[51] did not find an association between maternal marijuana use and overall intelligence quotient (IQ) and verbal memory in exposed offspring; however, certain aspects of cognition, such as memory at 4 years of age, attention at 6 years, attention and visually related cognition at 9 to 12 years, and stability of attention at 13 to 16 years, were negatively associated with prenatal marijuana exposure.

Anesthetic Management

Neuraxial analgesia is typically preferred during labor and delivery and can be safely performed in patients who use marijuana, in the absence of other contraindications. Drug-related changes in heart rate and blood pressure are usually well tolerated in otherwise healthy patients who are acutely intoxicated. However, the administration

of atropine, pancuronium, and ketamine can exacerbate existing tachycardia.[63]

Long-time marijuana smokers are at risk for many of the same respiratory complications during and after general anesthesia as are tobacco cigarette smokers; these patients may have increased airway secretions, impaired mucociliary clearance, and potentially increased airway reactivity.[45,65] Persistent postextubation laryngospasm in a patient with a history of heavy marijuana smoking has been reported.[68]

Acute intoxication with marijuana can have additive effects with those of sedative agents and volatile anesthetic agents, including myocardial depression[24,63]; careful titration to clinical effect is recommended.

The effect of marijuana on pain perception has been explored. Wallace et al.[69] presented a model of human experimental pain in which smoked marijuana had a differential effect on pain scores; a low dose had no effect, a medium dose reduced pain, and a high dose significantly increased pain. The clinical implications of these findings are unclear.

Cocaine

The use of cocaine, extracted from the leaf of the South American *Erythroxylum coca* bush, can be dated as far back as 600 AD.[70] Cocaine was introduced into clinical practice as a local anesthetic in the 1880s. During this period, Sigmund Freud also experimented with cocaine's ability to combat hunger and fatigue and opiate addiction.[70,71] Cocaine has both vasoconstrictive and local anesthetic properties as a result of its ability to block sodium channels during depolarization.

Epidemiology

The prevalence of cocaine use during pregnancy is difficult to estimate. Studies using a variety of detection techniques have reported rates that range from 1.8% to greater than 10% depending on the method and the population studied.[70] Survey data demonstrate that cocaine abuse in pregnancy is distributed broadly across ethnic and socioeconomic groups. In addition, an estimated 60% to 90% of pregnant cocaine users engage in polysubstance abuse, including the use of tobacco.[72,73] As with other illicit substances, the self-reporting of cocaine use results in identification of fewer drug users than urine testing and use of other biologic markers.[3] There is an association between cocaine use and an increased risk for sexually transmitted diseases, preterm labor, and failure to obtain prenatal care.[3]

Pharmacology

Cocaine (benzoylmethylecgonine) is an ester of benzoic acid and the base ecgonine, which is the parent compound of atropine and scopolamine.[71,74] Cocaine is consumed in a variety of forms. When dissolved in hydrochloric acid to form a water-soluble powder (cocaine hydrochloride), it can be chewed, administered intravenously ("mainlined"), or taken intranasally ("snorted"). Intrarectal and intravaginal use has also been reported.[75] When cocaine is processed with either sodium bicarbonate ("crack") or ammonia and ether ("free base"), the resulting cocaine alkaloid can be smoked.[71,74,76] The amount (dose) and duration of exposure are more important determinants of the effects of cocaine than is the chemical formulation. Smoked cocaine ("crack" or "free base") is rapidly absorbed through the lungs and reaches the brain in 6 to 8 seconds, intravenous cocaine reaches the brain in 12 to 16 seconds, and snorted cocaine reaches the brain in 3 to 5 minutes.[77] The typical half-life of cocaine is 30 to 90 minutes, although its effects can last as long as 6 hours.[71]

Cocaine is metabolized to ecgonine esters and benzoylecgonine (biologically inactive) by plasma and hepatic cholinesterases and to norcocaine (biologically active) by nonenzymatic hydrolysis. Only small amounts of cocaine are excreted unchanged in the urine. In the presence of alcohol, cocaine is transesterified to cocaethylene, which has a longer half-life and greater physiologic effects than cocaine.[76,77]

Systemic Effects

Cocaine has complex actions on the central and peripheral nervous systems and on nerve conduction. The powerful sympathomimetic effects of cocaine are due to the drug's inhibition of the reuptake of norepinephrine, dopamine, and serotonin, which allows these neurotransmitters to accumulate at the synaptic clefts and produce sustained stimulation.[70,76-78] This process can result in as much as a fivefold increase in circulating concentrations of catecholamines,[5] which, in turn, may lead to feelings of euphoria, increased energy, and decreased fear.[70,77] Repetitive use of cocaine eventually leads to depletion of neurotransmitter stores, up-regulation of receptors, and a higher dose requirement to achieve the desired euphoric effects.[71]

The peripheral nervous system effects of cocaine and its derivatives result from binding to tissue receptors involved in monoamine reuptake, which results in hypertension and/or labile blood pressure and tachycardia. Cocaine produces widespread small and large vessel occlusion through vasospasm, thrombosis, and endothelial injury, which may result in significant end-organ damage.[71]

Cocaine has profound effects on the **cardiovascular** system, and pregnancy appears to enhance them. Acute administration of cocaine increases peripheral vascular resistance, cardiac contractility, and myocardial oxygen demand (see Table 54-3).[71,79] Coronary vasoconstriction also occurs; a greater effect occurs in diseased vessel segments than in nondiseased segments.[76] Studies *in vitro* have indicated that cocaine can have a procoagulant effect in small and large vessels.[5] This may lead to thrombus formation and coronary plaque rupture in the setting of cocaine-induced hypertension.[71,80]

Cocaine-induced chest pain is a common complaint among young people presenting to the emergency department.[81] Mittleman et al.[80] found that cocaine use was associated with a significant, abrupt, and transient increase in the risk for acute myocardial infarction in patients who were otherwise at low risk.[82] The occurrence of cocaine-induced electrocardiographic changes is fairly common

and is not necessarily associated with true ischemia.[76,83] If true ischemia is suspected, treatment with supplemental oxygen, aspirin, vasodilators, with or without reperfusion therapy,[81] as well as measurement of troponin I levels,[82] is indicated. Although cocaine abusers who suffer a myocardial infarction have fewer postinfarction sequelae than the general population, the incidence of major cardiovascular complications is not trivial; 5% to 7% have congestive heart failure, 4% to 17% have ventricular arrhythmias, and up to 2% die.[76]

Prompt recognition of acute cocaine-induced cardiovascular toxicity facilitates management. However, not all cocaine-induced hypertension in pregnant women requires intervention. If pharmacotherapy is used, it is important to understand the potential undesired consequences. Beta-adrenergic receptor blockade may result in unopposed alpha-adrenergic receptor–mediated vasoconstriction that can lead to coronary artery vasoconstriction and myocardial failure. Labetalol, which is both an alpha- and a beta-adrenergic receptor antagonist, may be preferred, although it does not ameliorate cocaine-induced coronary artery vasoconstriction. Direct vasodilators (e.g., nitrates, hydralazine) can be used but may cause further tachycardia.[5,76] Hydralazine treated the hypertension in cocaine-intoxicated pregnant ewes but did not restore uterine blood flow.[84] Calcium entry–blocking agents can potentiate the toxic effects of cocaine.[5] Sedatives (e.g., benzodiazepines) or magnesium sulfate may ameliorate cocaine's cardiovascular effects.[5,76]

Other acute cardiovascular effects of cocaine include QT prolongation, bradycardia, and arrhythmias, including supraventricular or ventricular tachycardia and ventricular fibrillation.[71] Severe bradycardia can be treated with atropine or electrical pacing. If supraventricular tachycardia (SVT) occurs and is well tolerated, close observation, vagal maneuvers, and/or the use of adenosine are warranted. In the unstable patient with SVT, direct current (DC) cardioversion may be required.[85,86]

The use of lidocaine as an antiarrhythmic agent appears to be acceptable in patients who have used cocaine. In a retrospective multicenter study, Shih et al.[87] found that the use of lidocaine in nonpregnant patients with cocaine-induced myocardial infarction was not associated with significant cardiovascular or CNS toxicity. Although amiodarone therapy for maternal and fetal arrhythmias has been described as having only minor adverse effects in some patients, there are also reports of associated fetal hypothyroidism and fetal growth restriction.[85,88,89] Thus, the use of amiodarone in pregnant women is reserved for malignant arrhythmias that are refractory to other therapies.

Long-time cocaine abuse can cause left ventricular hypertrophy and dilated cardiomyopathy with accompanying systolic dysfunction (see Table 54-4).[71,76] Aortic dissection has also been reported.[76] Intravenous use of cocaine and other injectable drugs increases the risk for development of infective endocarditis. Noncardiogenic pulmonary edema, pulmonary hypertension, and right-sided heart failure can also occur in the setting of cocaine abuse.[5,71]

The **neurologic** complications of cocaine may be transient or permanent. Morbidity and mortality may result from subarachnoid hemorrhage, intracerebral hemorrhage, cerebral vasculitis, and/or transient ischemic attacks.[8,90,91] Many cocaine-abusing patients in whom cerebral infarct(s) and hemorrhage developed had additional risk factors for stroke, including hypertension, alcohol abuse, and smoking. Cocaine-induced seizures, if self-limited, are typically treated with supportive care and benzodiazepines.[90]

Respiratory complications occur in 25% of cocaine users. As with tobacco, smoking cocaine can have profound respiratory effects, which include bronchospasm, chronic cough, and diffusion capacity abnormalities.[75,77] Cocaine-abusing parturients are at increased risk for peripartum wheezing.[8] Inhaled cocaine vapor can produce thermal airway burns. "Snorting" cocaine can lead to epistaxis, oral ulcers, and nasal septal injury. The intense pulmonary and bronchial arterial vasoconstriction produced by cocaine can cause interstitial and alveolar hemorrhage. Pneumothorax, pneumomediastinum, and pneumopericardium have also been reported.[71]

Cocaine ingestion can result in serious **gastrointestinal** complications, such as ischemia, ulceration, and perforation.[77] In addition, cocaine's anticholinergic effects include delayed gastric emptying and an increased risk for aspiration.[71] Although some cocaine users have abnormal liver enzyme levels, cocaine is not clearly hepatotoxic.[77]

Hematologic consequences of cocaine exposure during pregnancy may include thrombocytopenia.[63,92,93] Cocaine-induced thrombocytopenia has a clinical course similar to that of idiopathic thrombocytopenic purpura, with platelet counts normalizing after termination of drug exposure, therapy with corticosteroids, and, in one published case, splenectomy.[93] Kain et al.[92] examined the prevalence of cocaine-associated thrombocytopenia in an inner-city obstetric hospital; the rate of thrombocytopenia was higher in the cocaine group than in the drug-free group (6.7% versus 1.5%, respectively), even when human immunodeficiency virus (HIV)–positive patients were excluded. However, Gershon et al.[94] compared platelet counts in a group of more than 7000 pregnant patients, 671 of whom tested positive for cocaine; only 2.5% of the cocaine-positive women had a platelet count lower than 140,000/mm^3, compared with 4.7% in the cocaine-negative group.

Renal failure can result from cocaine abuse on the basis of rhabdomyolysis, renal infarction, and impaired immunologic functions.[71] Cocaine-abusing patients have a higher prevalence of syphilis, HIV infection, and other **infectious diseases** compared with non–cocaine-using patients, even after controlling for intravenous drug abuse.[77,95] Studies of the **endocrine system** in gravid ewes have shown that cocaine exposure results in increases in maternal adrenocorticotropic hormone and cortisol as well as maternal and fetal plasma glucose and lactate.[96,97]

Cocaine also impairs cutaneous vasodilation and sweating. The lethal effects of cocaine are related, in part, to the drug's tendency to produce **hyperthermia**, particularly in hot weather.[98]

Cocaine use has been associated with **sudden death** from a variety of the above mentioned factors, including cardiac arrhythmias, respiratory arrest, status epilepticus, and impaired thermoregulation.

Cocaine withdrawal can be difficult to recognize because its signs and symptoms are nonspecific; they consist of a prolonged sleep phase followed by hunger, anxiety, weakness, headaches, tremors, and seizures (see Table 54-5). Recommended therapy involves supportive care and reintroduction of the drug, if necessary, followed by a slow taper of the dose over days to weeks.[24]

Effects on Pregnancy and the Fetus

Pregnant women metabolize cocaine to norcocaine to a greater extent than their nonpregnant counterparts, exposing both mother and fetus to this more potent metabolite.[70,74] Cocaine has a low molecular weight and high lipophilicity, and it is mostly un-ionized at physiologic pH; thus, it readily crosses the placenta.[8,70]

Woods et al.[99] demonstrated that cocaine increases both heart rate and myocardial oxygen consumption and decreases cardiac output to a greater extent in gravid ewes than in nonpregnant ewes. Cocaine also increases maternal blood pressure and decreases uterine blood flow in gravid ewes.[100]

In a 2011 meta-analysis, Gouin et al.[101] found that cocaine use during pregnancy was associated with significantly higher risk of preterm birth (odds ratio [OR], 3.38), SGA infants (OR, 3.23), and LBW infants (OR, 3.66). Obstetric complications associated with maternal cocaine use include a higher incidence of placental abruption and preterm labor; the latter occurs in 17% to 29% of women who use cocaine.[102] Acute cocaine toxicity can mimic preeclampsia or eclampsia when pregnant women present with hypertension, headache, blurred vision, and/or seizures. In one case series, cocaine-induced changes were distinguished through a positive urine test result for cocaine, the presence of normal laboratory measurements, and rapid resolution of symptoms without delivery.[103]

The impact of maternal use of cocaine (particularly "crack") on the fetus has been the subject of intense legal, political, and scientific debate since the 1980s.[104] Initial animal data and retrospective human studies have suggested an increased risk for major congenital anomalies such as genitourinary and abdominal wall defects in fetuses exposed to cocaine. However, these reports are confounded by concurrent use of other drugs and low statistical power.[105] Subsequent studies found no significant difference in type or number of congenital anomalies between infants who had and those who had not been exposed to cocaine *in utero*, after accounting for confounding variables.[106,107]

Frank et al.[108] reviewed studies published between 1984 and 2000 to assess the possible relationships between maternal cocaine use during pregnancy and childhood outcome. After controlling for possible confounding factors, they found no consistent negative association between intrauterine cocaine exposure and physical growth, developmental test scores within the first 6 years of life, or the presence of expressive or receptive language skills. They observed less optimal motor performance up to 7 months of age, but after this age, these effects did not appear to persist. They also indicated that there were insufficient data to comment on cocaine's effects on developmental scores in infants born preterm.

Subsequently, Mayes et al.[109] examined the trajectories of motor and mental development between the ages of 3 and 36 months in an impoverished high-risk population. These investigators found (1) a general decline (compared with age-adjusted equivalents) in motor performance for these high-risk children and a trend toward a greater decrease in performance in cocaine-exposed children; (2) a decline in performance on mental tasks until 24 months, with a similar trajectory of decline for the cocaine-exposed and non–cocaine-exposed cohorts; and (3) evidence of lower mental performance in cocaine-exposed children compared with non–cocaine-exposed children at all assessment ages.

Bauer et al.[106] found that infectious complications, such as hepatitis, syphilis, and, to a lesser extent, HIV infection, were more common in infants of cocaine-abusing mothers. Bae and Zhang[110] used a rat model to test prenatal cocaine exposure. Their results showed abnormal apoptosis and myocyte hypertrophy in the postnatal heart, which they speculated might result in greater susceptibility to myocardial ischemia and reperfusion injury.

Anesthetic Management

Cocaine-abusing patients are at risk for acute and chronic multiorgan system dysfunction[95] and the need for urgent cesarean delivery. During labor, early administration of neuraxial anesthesia should be encouraged provided that the patient is cooperative and has a platelet count above the threshold of concern for the anesthesia provider.[73] The use of neuraxial anesthesia can reduce levels of circulating catecholamines and thereby may mitigate the systemic effects of cocaine.[8] Existing epidural analgesia facilitates the extension to anesthesia for emergency cesarean delivery.

In one study, cocaine users had a greater incidence of hypotension during administration of epidural anesthesia for cesarean delivery; however, there was no difference between cocaine users and nonusers in the incidence of hypotension during spinal anesthesia.[8] When it occurs, treatment of hypotension should include volume resuscitation, and, if needed, careful titration of vasopressors. Depending on the level of circulating catecholamines, cocaine-intoxicated patients can be either more or less responsive to ephedrine; thus, phenylephrine may be a better choice for treatment of hypotension.[11,63,73]

When an ester local anesthetic or succinylcholine is administered to a patient who has ingested cocaine, the medication might compete with cocaine for available plasma cholinesterase.[8,74] Kain et al.[8] described a prolonged response to succinylcholine in a parturient who had abused cocaine chronically and had a normal dibucaine number but a low level of pseudocholinesterase.

Changes in μ- and κ-opioid receptors and altered baseline endorphin levels may result in an increased perception of pain in cocaine-abusing patients despite the presence of an apparently satisfactory level of neuraxial anesthesia.[63] Ross et al.[111] observed a reduction in duration of intrathecal sufentanil analgesia during labor in cocaine-abusing women, although the quality of analgesia was not diminished.

Cocaine-abusing patients who receive general anesthesia are at greater risk for hypertension and tachycardia during and after laryngoscopy and tracheal intubation.[8,9] If general anesthesia is required, premedication with a benzodiazepine or an opioid may help attenuate the acute physiologic effects of cocaine.

The anticholinergic effects of cocaine can delay gastric emptying and may also increase the risk for aspiration; pharmacologic prophylaxis and a rapid-sequence induction of general anesthesia are indicated. Ketamine and etomidate should be avoided because ketamine may stimulate the CNS and etomidate may precipitate myoclonus or hyperreflexia.[63] Induction of general anesthesia with propofol is commonly used in clinical practice. Dexmedetomidine, an α_2-adrenoreceptor agonist, has been shown in animal studies to delay the onset of cocaine-induced seizures and may be useful in selected patients.[112] Despite the theoretical risk for altered metabolism of succinylcholine, a standard intubating dose should be administered.[73] Early studies in dogs demonstrated that acute cocaine intoxication was associated with a dose-dependent increase in halothane dose requirements.[113] Whether this extends to other volatile agents has not been studied.

Cocaine can cause hyperthermia in both laboratory animals and humans[71,98]; core temperature should be monitored in cocaine-abusing patients. However, given the propensity for nasal septal defects in such patients, temperature probes (and other tubes and monitors) should *not* be inserted intranasally. Measures that provide active warming should be used only if needed.

Amphetamines and "Club" Drugs

Because of their high potential for abuse, amphetamines have been categorized by the U.S. Drug Enforcement Agency (DEA) as Schedule II stimulants since 1971.[64] Amphetamines have historically been prescribed as components of nasal decongestants, bronchodilators, weight loss drugs, and therapies for narcolepsy and attention deficit hyperactivity disorder.[114]

Methamphetamine ("ice") has become the most common illicit substance requiring medical treatment during pregnancy.[115] The availability of this compound is facilitated by its production in low-cost, home laboratories within and outside the United States.[114] It and MDMA (3,4-methylenedioxymethamphetamine) ("ecstasy") are thought to be the most widely abused amphetamines.[64]

Epidemiology

The number of new users of methamphetamine among persons aged 12 years or older was 105,000 in 2010, similar to the 2009 estimate (154,000) but lower than the 2002 to 2007 estimates (ranging from 157,000 to 318,000).[1] In a 2010 sample population between 12 and 49 years of age, the average age of new methamphetamine users was 18.8 years, which was not significantly different from corresponding 2002 to 2009 estimates.[1]

Arria et al.[64] observed that 5.2% of high-risk pregnant women had used methamphetamine at some time during pregnancy. Polydrug use in women who use methamphetamine and MDMA appears to be common.[64,116] According to analysis of national administrative data, the hospitalization ratio for amphetamine abuse has doubled, whereas that for cocaine abuse has decreased 44%.[117]

Pharmacology

Amphetamines (and related compounds) are amines that exist as either salts of various acids or free bases. Used illicitly, they can be ingested orally, inhaled, or, less commonly, injected, resulting in significant CNS penetration.[23] The plasma half-life ranges from 5 to 30 hours. Metabolism is variable; up to 30% of the parent compound can be found in the urine. Detection of these compounds and their metabolites in the urine is possible up to several days after ingestion.[5]

Methamphetamine ("speed" or "crystal meth") is a congener of amphetamine that contains a methyl radical.[64] This white, odorless, bitter-tasting powder can be smoked, snorted, ingested orally, or administered rectally.[116] Methamphetamine is more potent than amphetamine and has a longer half-life; 50% of the drug is cleared in 12 hours. When it is smoked or injected intravenously, the "flash" from this drug is intense and of short duration. Snorting produces euphoria within 5 minutes, and oral ingestion does so within 20 minutes.[114]

The amphetamine analogue, MDMA, or ecstasy, has been steadily growing in popularity, particularly in young women.[118] The methylenedioxy group that is attached to the aromatic ring of the amphetamine molecule confers some of the pharmacologic hallucinogenic effects.[119] The effects of MDMA typically begin approximately 20 minutes after ingestion and last approximately 6 hours; large doses have effects for up to 2 days. MDMA is metabolized by the liver and excreted by the kidneys.[5]

The "club" drug, **γ-hydroxybutyric acid** (GHB), derived from gamma-aminobutyric acid (GABA), readily enters the brain when ingested, producing anxiolytic, euphoric, and sedative effects.[120] Severe cardiorespiratory depression, coma, and seizures can occur at high doses. Overdose is common, owing in part to the variable individual responses to the drug.[120,121] Chronic use may be associated with a down-regulation of GABA receptors, and withdrawal manifests as insomnia, tachycardia, hypertension, and nausea/vomiting.[120]

The newest designer drug of the phenethylamine class is 3,4-methylenedioxypyrovalerone (MDPV), also known as "bath salts." Typically sold in crystal or powder form that can be snorted, smoked, or injected, these substances act as norepinephrine and dopamine reuptake inhibitors.[122] Until recently, "bath salts" could be purchased legally over the Internet, at some convenience stores, or in "head shops," but its active ingredients were banned by the DEA after several deaths were reported.[123]

Systemic Effects

Acute amphetamine ingestion leads to indirect sympathetic activation through the release of norepinephrine, dopamine, and serotonin from adrenergic nerve terminals (see Table 54-3).[5,124] The physiologic effects of amphetamines are similar to those of cocaine and other stimulants, with two important differences:

(1) amphetamines and their derivatives lack local anesthetic properties, and (2) amphetamine can inhibit monoamine oxidase activity, leading to decreased degradation of catecholamines.[5] Amphetamine-induced seizures can masquerade as eclampsia in parturients who have ingested the drug in the peripartum period.[125]

Long-term use of high doses of amphetamines can have a number of adverse maternal effects, including damage to the cardiovascular and neurologic systems, and behavioral changes such as hostility, violence, hallucinations, and paranoid psychosis (see Table 54-4).[116]

The **cardiovascular** effects of amphetamines and their derivatives are similar to those of cocaine.[5] Methamphetamine has a much longer duration of action than cocaine, because a smaller fraction of the former drug is metabolized.[114] Drug-induced effects include vasoconstriction, tachycardia, and labile blood pressure.[24] Patients are typically hypertensive, although catecholamine depletion over time can result in hypotension. Arrhythmias, myocardial ischemia, endothelial damage, and acceleration of atherosclerosis can also occur. Recommendations for the management of cardiovascular complications are similar to those for cocaine toxicity.[5]

The pleasurable effects of methamphetamine and the deleterious **neurologic** sequelae are believed to be the result of high levels of dopamine in the brain. In addition to positive feelings, patients who have taken methamphetamine may experience anxiety, mood disturbances, paranoia, and hallucinations. Severe intracranial hypertension[6] and hemorrhagic stroke[91] has been reported in the setting of acute use. Long-time use has been associated with impairment of motor function and verbal learning as well as with significant changes in the areas of the brain associated with memory and emotion (see Table 54-4).[114] Volkow et al.[126] observed that prolonged abstinence (12 to 17 months) resulted in significant recovery of brain dopamine transporters, although performance on neuropsychological tests did not improve to the same extent. In addition, psychotic features of long-time amphetamine use may be precipitated by stress in former users after months or even years of abstinence.[114] Ecstasy users are prone to drink excessive amounts of water, predisposing them to hyponatremia and the resulting CNS effects.[63]

Psychostimulant withdrawal causes fatigue, depression, hunger, and intense cravings (see Table 54-5). Pharmacologic therapy for stimulant withdrawal (e.g., tricyclic antidepressants, dopaminergic agents [e.g., bromocriptine], amino acid replacement therapy) has not been particularly successful.[127] In the setting of methamphetamine overdose, the ensuing seizures, severe hypertension, and hyperthermia can be fatal. Treatment goals include provision of a calm environment (with or without a benzodiazepine) and airway protection. Active cooling, antihypertensives, and anticonvulsants should be used as needed.[119,127]

Effects on Pregnancy and the Fetus

Ingestion of amphetamines results in high levels of circulating catecholamines, which may lead to vasoconstriction and decreased uteroplacental blood flow. Animal studies have suggested that intrauterine exposure to methamphetamine is associated with an increased incidence of retinal defects, cleft palate, and rib malformations and a decreased overall rate of growth and motor development.[116,128] Results from a meta-analysis revealed that exposure to amphetamines in pregnancy had a negative impact on birth outcomes, specifically, increasing the risk for preterm birth, LBW, and SGA infants.[129] Cernerud et al.[130] conducted long-term follow-up of 65 Swedish children with intrauterine exposure to amphetamines and found that a higher percentage of these children were in a grade lower than their chronologic age and that their performance in mathematics, language, and sports was significantly below that of their peers.

Specific pregnancy and fetal effects of ecstasy and bath salts are not known.

Anesthetic Management

Amphetamines cause (indirect) sympathetic activation. Intoxicated patients are at risk for dangerous cardiovascular events, including hemodynamic instability and cardiac arrest. Recommendations for anesthetic management are similar to those for patients with cocaine toxicity (as discussed earlier).[5]

A cooperative patient may be a candidate for neuraxial analgesia/anesthesia, although refractory hypotension has been reported in a case of a long-time amphetamine user undergoing neuraxial anesthesia with intravenous propofol sedation.[131] The authors attributed the response to down-regulation of beta-adrenergic receptors and catecholamine depletion. As with cocaine, phenylephrine may be a better choice than ephedrine for the treatment of hypotension in amphetamine-intoxicated patients.

Parturients who are amphetamine abusers may be at increased risk for urgent cesarean delivery requiring general anesthesia. Evidence from animal studies suggests that acute ingestion of amphetamines increases the MAC for volatile halogenated anesthetic agents, whereas chronic ingestion of amphetamines decreases the MAC of volatile agents.[132,133] There is a well-recognized association between methamphetamine abuse and severe tooth decay (i.e., "meth mouth") which can present a significant hazard during laryngoscopy. The airway assessment should include attention to the presence of fragile or loose teeth that might be dislodged during laryngoscopy as well as to the possible presence of burns throughout the airway. High doses of MDMA can cause rhabdomyolysis, and dantrolene has been used successfully in these cases.[119]

Hallucinogens

LSD (lysergic acid diethylamide), PCP (phencyclidine), psilocybin, and mescaline are drugs of abuse that are hallucinogens.[127] 3,4-Methylenedioxymethamphetamine (MDMA) also has hallucinogenic effects.

Epidemiology

Hallucinogen use is usually episodic.[9,134] In 2006, 1.1 million Americans 12 years or older used hallucinogens

for the first time; more than 75% of these encounters involved the hallucinogen MDMA.[135] The prevalence of hallucinogen use during pregnancy is unknown.

Pharmacology

The hallucinogens are a diverse group of drugs notable for their complex mechanism of actions, which include agonist, partial agonist, and antagonist effects at serotonergic, dopaminergic, and adrenergic receptors. Overall, the adrenergic effects of these drugs are mild compared with those of cocaine and amphetamine.[5]

Both **psilocybin**, the hallucinogen in some wild mushrooms, and **LSD**, manufactured synthetically,[127] are indole derivatives that chemically resemble serotonin.[5] When ingested, they evoke auditory, visual, and tactile hallucinations. Clinical effects usually develop over 15 to 60 minutes and last for 6 to 12 hours.[9,127] LSD is 100 times more potent than psilocybin and can be detected in urine or plasma for up to 3 days. LSD is metabolized by the liver and has a plasma half-life of 100 minutes.[5] The potency of individual samples of psilocybin varies, and the physiologic effects typically occur at doses of 20 to 60 mg. Animal studies indicate that 65% of psilocybin is excreted in urine and 15% to 20% is excreted in bile or feces. Most of the drug is excreted in the first 8 hours, although small amounts are excreted for up to a week.[127]

Phencyclidine, initially developed as a general anesthetic agent, was removed from the legal market in 1978. **Ketamine**, a related compound, is a clinically used anesthetic agent that is also a drug of abuse. In powder form these drugs can be ingested orally, intranasally, intravenously, or rectally and can be smoked. The psychological effects of PCP typically last 12 to 48 hours. Ketamine has a shorter duration of action.[127]

The phenethylamines include MDMA, GHB (see earlier discussion), and mescaline. **Mescaline**, the active ingredient in peyote cactus buttons, is typically eaten or drunk as a tea. The effects of mescaline, which last approximately 12 hours, include visual hallucinations, nausea, and vomiting.[127]

Systemic Effects

Ingestion of hallucinogens causes activation of the **sympathetic nervous system**, which results in hypertension, tachycardia, dilated pupils, and increased core body temperature (see Table 54-3).[9] The cardiovascular effects of these drugs are rarely serious, although some instances of supraventricular tachycardia and acute myocardial infarction have been reported. Myocardial infarction may result from vasospasm and increased platelet aggregation.[5]

Carotid artery occlusion has been reported after the use of LSD. PCP use has been associated with seizures, delayed hypertensive crisis, and intracerebral hemorrhage.[6] Overdose with PCP can be associated with confusion and combativeness, which may progress to seizures and catatonia.

Some users of LSD experience a "bad trip," which is likely to be a manifestation of an acute anxiety reaction. Other users report "flashbacks" or systemic effects of these drugs that occur months or even years after ingestion. Some of these episodes are likely due to delayed release of small amounts of drug from fatty tissues. The use of LSD may unmask an underlying psychiatric disorder in vulnerable patients.[127]

The psychological effects of psilocybin ("magic mushrooms") include giddiness, visual hallucinations, and gastrointestinal dysfunction. Morbidity is associated primarily with inadvertent ingestion of toxic species of mushrooms.[127] Although psychological dependence on these drugs has been observed, no clearly associated withdrawal symptoms occur with abstinence (see Table 54-5).[9]

A direct causal relationship between abuse of these drugs and death has not been documented; however, hallucinogens can cause feelings of paranoia and panic that can lead to accidents or fatalities.[6,9]

Effects on Pregnancy and the Fetus

There is conflicting evidence as to whether intrauterine PCP exposure has deleterious fetal effects. Mvula et al.[136] found that PCP-positive women had smaller and more preterm infants compared with non–PCP-positive women. The PCP-positive women were also more likely to have syphilis and diabetes and to use tobacco, alcohol, and marijuana. Early reports of chromosomal damage secondary to LSD were not confirmed by later studies.[6]

Anesthetic Management

Management of a hallucinogen-intoxicated patient is primarily supportive and noninterventional.[5] Stressful situations can provoke panic attacks, which in turn can intensify the physiologic effects of these drugs. Specific recommendations include provision of a quiet, supportive environment and administration of a benzodiazepine if needed. Neuroleptic medications are relatively contraindicated in such a patient, because they can intensify toxic reactions.[5, 9]

Hemodynamic perturbations are usually relatively mild and well tolerated.[63] Occasionally, patients experience supraventricular tachycardia, hypertension, and myocardial ischemia.[5] The acutely intoxicated patient may have an exaggerated response to ephedrine[9]; phenylephrine may be preferable and should be titrated to effect. LSD may have some intrinsic anticholinesterase activity, but the clinical significance is unclear. Hallucinogens may also prolong opioid-induced analgesia and respiratory depression.[63]

Either neuraxial or general anesthesia can be administered for vaginal or cesarean delivery as the clinical situation warrants.

Opioids

Opioids refer to the class of naturally occurring and synthetic drugs that are structurally and functionally related to morphine. The term *opiate* specifically describes any of the narcotic alkaloids found in the juice of poppy plants, including morphine and codeine.[23]

Epidemiology

The estimated prevalence of opioid use during pregnancy varies from 1.6% to 7.2%, depending on the methodology of the survey and the studied population.[137] The National Survey on Drug Use and Health estimated that more than 359,000 Americans 12 years of age and older used heroin in 2010, including approximately 140,000 who used it for the first time that year.[1] Among youths and young adults, nonmedical use of prescription drugs, particularly pain relievers, was the second most common form of drug abuse.[1]

Pharmacology

The naturally occurring opioids are metabolized first to morphine, which has a plasma half-life of 2 to 3 hours. Morphine then undergoes rapid metabolism in the liver and is excreted in the urine, where both active and inactive metabolites can be detected for up to 2 days in occasional users, and longer in chronic users.[5,23]

Heroin (diacetylmorphine or diamorphine) is a commonly abused and highly addictive semisynthetic analogue of morphine. It can be smoked, snorted, or injected intravenously or intramuscularly. Most fatal overdoses occur in users of intravenous heroin. The speed of onset varies from less than 1 minute to 15 minutes, depending on the delivery method; the elimination half-life is typically 1 to 2 hours. Heroin is metabolized by the liver and excreted in the urine.[5,23,24,138] The formulation of street heroin has become increasingly pure. In 1990, a typical 100-mg bag of powder had up to 8 mg of heroin mixed with inert, often toxic additives; subsequently the drug has become available with a purity as high as 45% to 90%. Heroin is more lipid soluble than other opioids; thus, it rapidly crosses the blood-brain barrier and has significant and toxic CNS effects.[138]

Rapidly acting semisynthetic opioids such as **oxycodone** and **hydrocodone** are prescribed legitimately and distributed illicitly. The oral bioavailability of oxycodone is higher than that of morphine, and its potency with oral ingestion is greater.[23]

Methadone is a synthetic compound that is structurally unrelated to the other opioids but has similar effects.[23,139] It is formulated as a racemic mixture of two enantiomers: R-methadone, which is a potent μ- and δ-opioid receptor agonist, and S-methadone, which is a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist that prevents the reuptake of 5-hydroxytryptamine and norepinephrine.[140] Typically available in powder form, methadone can be reconstituted for oral, rectal, or intravenous use.[141] Oral bioavailability of methadone is typically three times that of morphine.[140,141] There is significant inter-individual variability in its clinical effect and duration of action. The peak effect occurs approximately 3 hours after oral ingestion, and its half-life varies from 15 to 40 hours.[23,24,140-142] Life-threatening complications may result from the cumulative effects of successive doses.[140]

Unlike morphine, methadone undergoes biotransformation (rather than conjugation) in the liver and is excreted primarily by the fecal route. Methadone has been used since the 1960s for stabilization and maintenance therapy for patients suffering from opioid-addictive disorders and since the 1970s for the same reason in pregnant patients. It is also used for analgesia in patients with chronic pain.[140,142] Pregnancy is associated with greater methadone metabolism and reduced methadone bioavailability because of greater maternal blood volume and changes in hepatic enzymatic activity and glomerular filtration rate.[23,142,143]

Buprenorphine is a semisynthetic opioid that acts as a partial μ-receptor agonist (with low intrinsic opioid activity) and *k*-receptor antagonist and therefore can also be used as part of maintenance therapy for patients suffering from opioid-addictive disorders.[61,144,145] The two sublingual formulations of this drug (**Subutex** and **Suboxone)** contain naloxone, which becomes active only if the user attempts to snort, inject, or cook the drug.[144] Buprenorphine binds up to 1000 times more tightly to the μ- and *k*-receptors than morphine, and it has a slow dissociation half-life of approximately 166 minutes.[144] Primary metabolism of buprenorphine occurs in the liver with excretion in the bile.[146] Buprenorphine has a ceiling effect at 24 to 32 mg, which makes respiratory depression less likely and contributes to the opioid tolerance of treated patients.[144,147]

Two additional formulations for intravenous and transdermal administration of buprenorphine are used for analgesia and are *not* approved for opiate addiction therapy.[147]

When used as part of a maintenance therapy for patients with addiction to opioids, methadone must be prescribed and dispensed on a daily basis by a registered substance abuse treatment program; buprenorphine, however, can only be prescribed by physicians who have been specially trained and credentialed for distribution in an office-based setting.[148] All dose adjustments needed in the course of pregnancy or the postpartum period must be done in close consultation with the addiction treatment program (for methadone) or the providers responsible for prescribing and managing the patient's buprenorphine therapy.[148]

Systemic Effects

Opioids mimic the activity of endogenous peptides and exert their effects through binding to μ-, δ-, and κ-opioid receptors. Morphine and heroin exert their euphoric, analgesic, and reinforcing effects primarily through stimulation of the μ-opioid receptors. Long-time opioid use causes neuroadaptations in the brain that may explain the manifestations of withdrawal.[23,138]

Opioids act in the CNS to reduce sympathetic activity and increase parasympathetic activity; they also promote histamine release from mast cells. The resulting cardiovascular effects include bradycardia, hypotension, and, in some cases, potentially lethal tachyarrhythmias and bradyarrhythmias (see Table 54-3). Noncardiogenic pulmonary edema has been observed in some cases of overdose and is believed to be caused by hypoxia, intense pulmonary vasoconstriction, and, perhaps, the use of reversal agents (e.g., naloxone).[5]

Opioid-induced respiratory depression occurs through a direct effect on the brainstem that reduces the

ventilatory response to hypercarbia.[138] Opioid overdose can progress from miosis and respiratory depression to obtundation and death.[6,10] Treatment of overdose includes maintenance of a patent airway, provision of hemodynamic support, and, if necessary, administration of an opioid antagonist (e.g., naloxone).[5]

Women who abuse opioids or other drugs intravenously are at risk for infective endocarditis (usually affecting right-sided valves), HIV infection, viral hepatitis, septic emboli, and pulmonary abscess formation.[5,24] In addition, hilar adenopathy may develop as a result of ingestion of additives such as quinine and starch. Opioid-dependent patients may have additional end-organ damage and may exhibit opioid tolerance, physical dependence, and withdrawal.[139]

Animal studies have found an association between opioid administration and abnormal pain sensitivity, including hyperalgesia and allodynia (see Table 54-4).[149] Opioid tolerance develops with chronic use and is related to amount and duration of drug exposure; tolerance results from changes in drug distribution and metabolism (pharmacokinetics) and in receptor density and activity (pharmacodynamics).[139] Patients receiving methadone maintenance therapy often have diminished pain tolerance.[150]

Acute opioid withdrawal results from sympathetic hyperactivity, resulting in flulike signs and symptoms such as fatigue, weakness, restlessness, rhinorrhea, perspiration, fever, and diarrhea (see Table 54-5).[6,24] These can persist for several days if not treated. The onset and duration of withdrawal symptoms vary according to the opioid ingested; morphine or heroin withdrawal symptoms typically begin within 6 to 18 hours after the last dose, reach their peak intensity by 3 days, and last for 7 to 10 days. Methadone withdrawal symptoms are delayed—with an onset within 24 to 48 hours, a peak intensity within 3 to 21 days, and a duration of up to 6 to 7 weeks.[139] Clonidine, an α_2-adrenergic agonist, can modulate these effects, although postural hypotension may result.[24] Doxepin, a tricyclic antidepressant that inhibits the reuptake of serotonin and norepinephrine, has also been administered in this setting. Acute withdrawal can also be treated by administration of a short-acting opioid and initiation of a gradual dose taper.[9]

Substitution pharmacology (e.g., **methadone maintenance** or **buprenorphine therapy**) has been recommended for the treatment of opioid dependency if abstinence is not attainable and withdrawal is not feasible. Typically, long-acting μ-agonists (e.g., methadone) or partial agonists (e.g., buprenorphine) are substituted for the opioid of abuse in combination with behavioral modification therapy. Drug maintenance therapy decreases withdrawal symptoms and attenuates both craving and the positive rewards associated with subsequent opioid use (see later discussion on effects on the neonate).[142]

The U.S. Food and Drug Administration (FDA) guidelines for methadone administration in pregnancy were developed in 1970.[4,142] Several studies have shown that methadone maintenance therapy in heroin-addicted pregnant women is beneficial for both the mother and the infant. Specific benefits include better medical and prenatal care,[151] a lower incidence of unplanned pregnancy,[152] decreased neonatal abstinence symptoms and days of hospitalization, and less maternal illicit drug use at delivery.[141,143]

Effects on Pregnancy and the Fetus

In general, published reports have not shown an increased risk for birth defects after prenatal exposure to oxycodone, meperidine or propoxyphene, but they have shown an association between congenital heart defects and early use of codeine.[148] A retrospective population-based study (data from 1997 to 2005) identified an association between maternal therapeutic use of opioid medications early in pregnancy and atrial and ventricular septal cardiac defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis.[153] Data were obtained retrospectively via maternal interviews and did not control for dose, therapeutic indication (including if the drug was administered within the context of a surgical procedure), duration, or frequency of opioid exposure.

Heroin use during pregnancy is associated with first-trimester spontaneous abortion, preterm delivery, and fetal growth restriction, in part as a result of poor maternal nutrition.[4,141,151,154] Maternal and neonatal infection and neonatal abstinence syndrome have also been described. **Neonatal abstinence syndrome (NAS)**, which occurs in neonates repeatedly exposed to opioids *in utero*, is characterized by irritability, poor feeding, abnormal sleep patterns, diarrhea, fever, and seizures. Affected neonates may also have autonomic symptoms such as yawning and mottling. If prolonged and untreated, NAS can result in death.[4,154] Children born to women using heroin have been found to have normal development at the time of entry into school.[4] However, *in utero* heroin exposure appears to be associated with a high rate of attention deficit hyperactivity disorder.[155]

In 2010, Jones et al.[145] performed a multicenter, randomized controlled trial comparing the neonatal effects of methadone and buprenorphine therapy on NAS when used as part of an opioid dependence program during pregnancy. They found the length of hospitalization and amount of morphine therapy needed for NAS was significantly less in the infants of buprenorphine-treated mothers, although the percentage of neonates requiring treatment for NAS did not differ between groups.

When obstetric complications were compared in methadone- and buprenorphine-treated pregnant women, maternal weight gain, cesarean delivery rates, birth weights, and Apgar scores were similar.[147] However, medical complications and overdoses were less frequent in buprenorphine-treated women.[147] Based on these data the ACOG issued a 2012 committee statement suggesting that buprenorphine be considered "a potential first-line medication for pregnant opioid-dependent women who are new to treatment."[148]

Anesthetic Management

Preanesthesia Assessment and Communication. Establishing trust and effective communication is critical in the care of opioid-tolerant, methadone- or buprenorphine-maintained or opioid-addicted patients

and may improve the ability to elicit a more complete drug history. Ideally, before the patient presents for delivery, a thorough anesthesia consultation and development of a mutually agreeable strategy for pain management with appropriate goals for pain intensity scores should be conducted.

Providers, family, and patients may express concern that exposing a previously addicted patient to opioids or other sedatives will prompt cravings or a frank relapse. However, withholding appropriate analgesic and anxiolytic medications from such a patient cannot be justified. Patient monitoring (e.g., drug screens, pill counts) may be necessary.[139]

Opioid Maintenance Requirements. Opioids used on a regular basis for chronic pain or methadone or buprenorphine maintenance therapy should be continued during the hospitalization,[108,139-141] with additional therapies added for acute pain management. The precise dose of methadone must be confirmed with the dispenser, because improper dosing can result in inadequate analgesia, withdrawal phenomena, or life-threatening overdose.[140] Any methadone or buprenorphine dose adjustments needed in the course of pregnancy or the postpartum period must be done in close consultation with the prescribing physicians and addiction treatment program.[148] Although some providers advocate trying to substitute a pure opioid agonist for buprenorphine in advance of elective induction of labor or elective cesarean delivery to maximize the effect of peripartum opioid analgesics, there are several potential pitfalls to this approach. First, most admissions for delivery are unplanned. Second, it can be extremely challenging to effectively manage predelivery transition from buprenorphine to opioid-agonist therapy in the outpatient setting. Third, reintroduction of buprenorphine therapy in the postpartum period may induce acute withdrawal symptoms.[156]

An alternative approach to switching to pure opioid agonist therapy is to continue the buprenorphine through the peripartum period. Kronfeld and Manfredi[156] described five nonpregnant patients who continued their buprenorphine through the operative period; postoperative pain was successfully controlled using full doses of agonist opioids. A third approach is to continue the buprenorphine through the operative period but to divide the usual dose into three or four partial doses that maximize the analgesic properties of the medication.[144,148] Importantly, the patient must receive the correct total methadone or buprenorphine dose; therefore, dividing the dose should only be attempted if administration of the correct total dose can be ensured.

Alterations of Drug Levels. Sedative medications can increase the depressant effects of chronically ingested opioids. Methadone has a long half-life and is metabolized by cytochrome P450; thus, women receiving methadone are particularly vulnerable to changes in metabolism that result from administration of other medications. Anticonvulsants (e.g., phenobarbital, phenytoin) increase methadone clearance, and selective serotonin reuptake inhibitors decrease it. Methadone dose requirements are typically established by titrating to effect; thus, the discontinuation of these other medications can have unintended consequences.[139]

Anesthetic Technique and Dose Requirements. Neuraxial analgesia or anesthesia is the technique of choice for chronic opioid-abusing parturients or those receiving methadone or buprenorphine maintenance therapy undergoing vaginal or cesarean delivery, assuming that the patient is cooperative and has no evidence of coagulopathy or other contraindication to a neuraxial technique.[148]

Providers should not assume that the cause of inadequate neuraxial labor analgesia is solely a result of the patient's addiction. Opioid-addicted patients can have objectively inadequate (failed) neuraxial analgesia and anesthesia just like their nonaddicted counterparts.

In a review of publications on opioid-dependent parturients, Cassidy and Cyna[157] catalogued the needs of these patients across a broad range of anesthetic techniques and modes of delivery. The proportion of opioid-dependent women who required general anesthesia for cesarean delivery, or the number who requested epidural labor analgesia, did not differ compared with the proportions in non–opioid-dependent women. However, a significant incidence of pain management challenges were observed, particularly after cesarean delivery; 26% of the patients required consultation for inpatient pain management in addition to usual labor analgesia, and 74% of the patients had difficulties with postcesarean analgesia. These patients also had significant vascular access problems and generated more emergency calls for fainting and collapse. Meyer et al.[152] noted that pregnant women on methadone maintenance therapy had similar pain scores and analgesia requirements during labor compared with matched control women, but the methadone-maintained patients required 70% more opioid analgesia after cesarean delivery.[152]

Although mixed opioid agonists/antagonists (e.g., nalbuphine) are commonly employed for labor analgesia or treatment of neuraxial opioid-induced pruritus in parturients, these agents should be *avoided* in patients with a history of opioid abuse because they can precipitate withdrawal.

If neuraxial techniques are contraindicated for labor, intravenous patient-controlled analgesia can be used. Patients who use either physician-prescribed or illicit opioids over the long term demonstrate a relative insensitivity to opioids. Their opioid dose requirements for intraoperative and postoperative analgesia may be 30% to 100% higher than those of opioid-naive patients.[139,158]

During administration of general anesthesia for cesarean delivery, the anesthesia provider should consider the potential for decreased MAC in a patient with acute opioid intoxication as well as the potential for cross-tolerance with CNS depressants in a patient with a history of long-time opioid use.[9]

Postpartum Analgesia. Postoperative pain management can be challenging in patients with a history of chronic opioid use. In one study, methadone-maintained women had higher pain scores but did not receive greater

doses of opioids after vaginal delivery. However, methadone-maintained women had higher pain scores and received greater doses of opioids after cesarean delivery.[152] Multimodal therapy, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, should be used after vaginal delivery.[139] For cesarean delivery, multimodal analgesia with neuraxial morphine and systemic NSAID therapy is recommended. Epidural analgesia, transversus abdominis plane (TAP) block, and intravenous patient-controlled opioid analgesia can also be considered, similar to that in women who are not chronic opioid users (see Chapters 27 and 28).

Solvents

Solvents are a chemically diverse group of readily available substances (e.g., toluene, ethylene glycol) that can be sniffed, aerosolized, or ingested to produce feelings of euphoria, excitement, and invulnerability.[5,159,160]

Epidemiology

In 2010, more than 700,000 individuals in the United States used an inhalant for the first time.[1] Of the 3 million persons aged 12 years or older who used illicit drugs for the first time within that year, 9% reported that their first drugs were inhalants. The prevalence of solvent abuse in pregnant patients is not known.

Pharmacology

Inhalants are quickly absorbed through the lungs and typically are rapidly metabolized in the liver. The precise mechanism of action of inhalants is variable and is not completely understood.

Detection, although difficult, can be suspected by the presence of the "glue sniffer's" facial rash[24] or the odor of the abused inhalant.[160] Laboratory assays can detect many solvents in the blood within 10 hours of exposure. Urine assays are available only for certain volatile substances (e.g., toluene, chlorinated solvents) but may provide a longer window of detection.[5]

Ethylene glycol, a bittersweet-tasting component of antifreeze, brake fluids, and industrial solvents, is sometimes ingested by substance-abusing adults as an inexpensive substitute for alcohol. Readily absorbed via the gastrointestinal tract with ingestion, this solvent reaches maximal blood concentrations within 1 to 4 hours. It is metabolized by the hepatic enzyme alcohol dehydrogenase to four toxic organic acids. The primary screening test findings for ethylene glycol intoxication include serum anion-gap metabolic acidosis, high urine osmolality with an osmol gap, and the presence of calcium oxalate crystals in the urine.[161,162]

Toluene, a primary component of household paint and cleaning agents, is also sniffed or ingested orally for its transient euphoric effects.[63]

Systemic Effects

Typically, the user of inhalants feels an initial sense of euphoria followed by a brief period of disinhibition and impulsivity. Intoxication can be prolonged through repeated inhalation of the solvent. As the dose increases, dizziness, diplopia, and disorientation manifest, followed by headache, nausea, vomiting, drowsiness, and sleep.[160]

Mucous membrane irritation can result in rhinorrhea, epistaxis, excessive salivation, and conjunctival redness. Nausea, vomiting, and diarrhea can also occur.[160] Ingestion of volatile substances can lead to potentially lethal tachyarrhythmias, likely secondary to sympathetic stimulation, or bradyarrhythmias from decreased sinoatrial node automaticity or direct vagal stimulation and myocardial depression (see Table 54-3).[5] Hypoxemia may occur as a result of formation of carboxyhemoglobinemia, methemoglobinemia, or suffocation.[5,160,163]

Chronic inhalant abuse can cause multiorgan system disease, with **cardiac** (e.g., cardiomyopathy, arrhythmias, myocardial infarction), **pulmonary** (e.g., wheezing, acute respiratory distress syndrome, pulmonary hypertension), **central and peripheral nervous system** (e.g., cognitive impairment, ataxia, muscle weakness, peripheral neuropathy), and **autonomic dysfunction** (see Table 54-4).[5,6] Renal toxicity, aplastic anemia, and hepatocellular carcinoma have also been reported.[127,160] Imaging studies have demonstrated loss of brain mass, white matter degeneration, and subcortical abnormalities in long-term users. Significant methemoglobinemia with attendant cyanosis can also occur from exposure to some compounds.[5,160,163]

Cessation of chronic use can lead to reversal of many of the pathophysiologic changes, although the CNS effects may persist. Death from inhalant use typically occurs from suffocation, aspiration, or accidental injury. **Sudden sniffing death syndrome**, likely secondary to a fatal arrhythmia in the setting of a sensitized myocardium, electrolyte abnormalities, and hypoxemia, has been reported in both new and long-term users.[160]

Ingestion of ethylene glycol has inebriating effects similar to those of alcohol with more devastating consequences. Accumulation of the toxic metabolite glycolic acid occurs, resulting in CNS depression and seizure activity. Cardiopulmonary manifestations are often delayed (12 to 24 hours after ingestion) and may be fatal. If the patient survives, she will likely experience **renal failure** 24 to 72 hours after ingestion. The estimated lethal dose of undiluted ethylene glycol is 1.4 mL/kg. Treatment of ethylene glycol ingestion may require the induction of emesis with ipecac in the alert and awake patient or the use of gastric lavage. The conversion of ethylene glycol to its toxic metabolites can be prevented with the use of the antidote **fomepizole** or **ethanol.** Hemodialysis may be warranted.[162]

Ingestion of toluene can similarly cause cardiac arrhythmias, acute respiratory distress syndrome, hepatic failure, cerebral edema, and death.[63]

Effects on Pregnancy and the Fetus

Solvent abuse has been associated with fetal growth restriction, preterm delivery, and perinatal mortality.[9] Infants born of inhalant-abusing women exhibit NAS symptoms, including excessive and high-pitched crying, sleep disorders, CNS irritability, and poor feeding.

Phenobarbital can be somewhat effective in ameliorating these manifestations.[164]

Ethylene glycol intoxication has been misdiagnosed as eclampsia in a patient who presented at 26 weeks' gestation with hypertension and seizures followed by coma. Her postoperative course was complicated by hemodynamic instability, severe metabolic acidosis, and acute renal failure, which prompted suspicion of substance intoxication. Toxicology investigation confirmed ethylene glycol poisoning. Subsequently, the patient was successfully treated with hemodialysis and intravenous ethanol; her neonate was treated with diuresis and replacement transfusion.[161]

Anesthetic Management

Identification of solvent abuse in the parturient is critical to safe anesthetic care.[163] The parturient's skin and clothing should be decontaminated if inhalation abuse is suspected.[160] A careful physical examination, including documentation of preexisting sensory and motor deficits, should be undertaken, and electrolyte abnormalities should be identified and corrected.[9]

If the patient is cooperative and able to protect her airway, neuraxial labor analgesia can be administered. It may be prudent to avoid administration of an epinephrine-containing local anesthetic solution, given the significant risk for arrhythmias in these patients. The treatment of hypotension should include the use of intravenous fluids. Phenylephrine may be preferable to ephedrine because the latter may predispose to arrhythmias. Atropine should be readily available but used with caution. In a stable patient with sustained tachyarrhythmias, beta-adrenergic receptor antagonists should be the first line of therapy.[5]

In intoxicated or otherwise uncooperative patients, rapid-sequence induction of general anesthesia for cesarean delivery may be indicated.[9]

KEY POINTS

- Substance abuse by pregnant women results in significant risks for maternal and fetal morbidity and mortality.
- Anesthesia providers often care for substance-abusing patients during labor or cesarean delivery.
- Maternal self-reporting underestimates the true incidence of substance abuse. Drug testing (e.g., urine, blood, oral fluid, hair, meconium) should be employed if substance abuse is suspected.
- Optimal care of these patients requires developing a therapeutic bond and an explicit pain management plan. Anesthesia providers should ask patients questions about substance abuse in a respectful and nonjudgmental manner.
- Neuraxial anesthetic techniques are the preferred methods for labor analgesia and cesarean delivery anesthesia for most patients with a history of substance abuse, provided that the patient is cooperative, is able to protect her airway, and does not have a coagulopathy or a platelet count below the threshold of concern for the anesthesia provider.
- Although patients with substance abuse may have abnormal pain sensitivity, providers should not assume that the etiology of inadequate neuraxial labor analgesia is solely a result of the patient's addiction. Opioid-addicted patients can have inadequate (failed) neuraxial analgesia and anesthesia just like their nonaddicted counterparts.
- Intrauterine alcohol exposure is the leading cause of preventable birth defects in the United States.
- Smoking during pregnancy negatively affects fetal growth. Pregnant women who smoke are more likely to suffer respiratory complications and impaired wound healing.
- Moderate maternal caffeine intake (< 300 mg/day) does not appear to have adverse maternal or fetal effects.
- Marijuana is thought to be the most common illicit substance used by pregnant women. Smoking marijuana increases maternal respiratory comorbidities. The long-term effects on exposed offspring are unclear.
- Cocaine use has been associated with sudden death from a variety of factors, including cardiac arrhythmias, respiratory arrest, status epilepticus, and impaired thermoregulation. Maternal cocaine use increases the likelihood of placental abruption and urgent cesarean delivery.
- Acute cocaine intoxication can mimic preeclampsia, eclampsia, or malignant hyperthermia.
- Evidence is conflicting as to whether intrauterine hallucinogen exposure has deleterious effects on the fetus.
- Inhalant abuse can lead to severe maternal hypoxemia and potentially lethal arrhythmias.
- Ingestion of amphetamines results in high levels of circulating catecholamines, leading to hemodynamic instability and, in some cases, cardiac arrest.
- Care of the opioid-dependent patient should involve maintenance of long-term opioid requirements, multimodal management of acute pain, and avoidance of opioid antagonists and mixed-agonists/antagonists (unless the patient shows signs of overdose or is undergoing medically supervised detoxification).
- Buprenorphine is increasingly becoming the opioid maintenance treatment of choice in patients who are addicted to heroin or other opioids. Goals of care in these and methadone-maintained patients include continuing their methadone or buprenorphine treatment, adding multimodal acute pain therapy, and avoiding opioid antagonists and mixed agonists/antagonists.

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CHAPTER 55

Trauma and Critical Care

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CHAPTER OUTLINE

The management of critically ill obstetric patients most commonly involves treatment of disease processes that occur as a direct consequence of pregnancy. Although sometimes life threatening, these conditions are usually reversible. Delivery of the infant often attenuates or ablates the disease process, and the mother typically recovers with supportive and resuscitative measures. Primary obstetric disorders account for 50% to 80% of intensive care unit (ICU) admissions for pregnant patients; approximately 80% of these admissions result from preeclampsia, sepsis, and/or hemorrhage (Box 55-1).[1,2] The estimated ICU admission rate for obstetric patients is 0.5% to 1% in the United States; the mortality rate in this population is 12% to 20%.[3]

Trauma accounts for 45% to 50% of all maternal deaths in the United States, and it is the most common nonobstetric cause of maternal death.[4] Other common nonobstetric causes of ICU admission are respiratory failure, endocrine disorders, preexisting autoimmune disease, and thromboembolic disorders.[5] Ethnic minorities and women with low socioeconomic status have the highest rates of morbidity and mortality. Modern medicine has allowed women with complex medical problems such as congenital heart disease and cystic fibrosis to survive into childbearing age, and these patients are at increased risk for complications during pregnancy and have a higher incidence of ICU admission. Among critically ill obstetric patients admitted to an ICU, the most common cause of death is acute respiratory distress syndrome (ARDS), which can complicate both obstetric and nonobstetric disease processes.[6]

Critical maternal illness places the fetus at significant risk for morbidity and mortality. Important fetal risk factors include maternal shock, transfusion of blood products, and early gestational age at the time of critical maternal illness.[7]

TRAUMA DURING PREGNANCY

Epidemiology

Trauma affects 5% to 7% of pregnancies in the United States and is the leading nonobstetric cause of maternal death; as many as 20% of affected women require emergency surgery.[8,9] Motor vehicle accidents are the most common cause of injury-related maternal death (49% to 70%), followed by domestic violence (11% to 25%) and falls (9% to 23%).[10-12] Not using a seat belt is a major risk factor for maternal and fetal injury in motor vehicle trauma.[13] Penetrating trauma and burns are far less common than blunt mechanisms of injury. The rate of maternal trauma admission to an ICU increases with each trimester: 8% occur in the first trimester, 40% in the second trimester, and 52% in the third trimester.[14] Most women are able to continue their pregnancy at home, but up to 38% are hospitalized until delivery.

Risk factors for maternal trauma include age younger than 25 years, low socioeconomic status, minority race, use of illicit drugs or alcohol, and domestic violence.[14,15] It is important to remember that any female patient

BOX 55-1 Causes of Critical Illness in Pregnancy

Obstetric Causes

- Acute fatty liver of pregnancy
- Amniotic fluid embolism
- Cardiomyopathy
- Chorioamnionitis
- HELLP syndrome
- Hemorrhage
- Pelvic septic thrombophlebitis
- Placental abruption
- Preeclampsia/eclampsia
- Puerperal sepsis

Nonobstetric Causes

- Acute renal failure
- Autoimmune disorders
- Chronic respiratory disease
- Diabetic ketoacidosis
- Drug abuse
- Pneumonia
- Pulmonary thromboembolism
- Trauma
- Urinary tract infection

HELLP, hemolysis, elevated liver enzymes, low platelet count.

of reproductive age who is a victim of trauma could be pregnant at the time of injury.

Complications and Outcomes

As in the general population, hemorrhagic shock and brain injury are the most common mechanisms of death in pregnant trauma victims.[16] Pelvic and acetabular fractures also pose a significant risk. Injuries and complications that are unique to pregnant trauma victims include uterine rupture, placental abruption, preterm labor, and direct fetal injury. Although rare (0.6% of injuries), uterine rupture is a major threat to the life of both the mother (10% mortality) and the fetus (near 100% mortality).[17] Placental abruption complicates 1% to 5% of minor injuries and 20% to 60% of major trauma and usually occurs from 16 weeks' gestation onward.[18] Placental abruption can cause major overt and occult hemorrhage and coagulopathy and should be considered as a possible source of bleeding in the unstable pregnant trauma patient. Preterm labor is a common (25%) complication of trauma and can be precipitated even in cases of apparently minor injury.[19]

Premature rupture of membranes (PROM) increases the risk for both preterm labor and infection. Amniotic fluid embolism is a rare complication of maternal trauma, but it should be considered as part of the differential diagnosis in patients who are refractory to resuscitation.

Fetal-maternal (transplacental) hemorrhage can occur after trauma and result in maternal isoimmunization with the D antigen of the fetal red blood cell Rhesus protein complex (Rh_0[D]) in the Rh-negative mother (see Chapter 6). The Kleihauer-Betke test is used to identify fetal blood in the maternal circulation after maternal injury. When fetal-maternal hemorrhage is present, treatment

BOX 55-2 Factors Associated with Fetal Demise after Trauma

- Ejection from vehicle
- Maternal pelvic fracture
- High maternal Injury Severity Score (> 15)
- Maternal death
- Maternal hypotension
- Uterine rupture
- Uterine tenderness
- Placental abruption
- Vaginal bleeding
- Abnormal fetal heart rate pattern
- Amniotic fluid on pelvic examination
- Maternal history of alcohol use
- Maternal smoking history

with Rh_0(D) immune globulin (RhoGAM) is generally indicated. In a study performed at the R. Adams Cowley Shock Trauma Center of the University of Maryland, more than 50% of evaluated pregnant trauma victims were positive for fetal-maternal hemorrhage as determined by a positive Kleihauer-Betke test.[20] Essentially all patients with a positive test had uterine contractions, whereas patients with a negative Kleihauer-Betke test did not have contractions. The investigators concluded that the Kleihauer-Betke test was a sensitive and specific predictor of preterm labor in pregnant trauma patients and should be performed in all victims regardless of blood Rh phenotype.

Fetal Trauma and Outcome

The fetal mortality rate after maternal blunt trauma has been reported to range from 3.4% to 38.0%; placental abruption, uterine rupture, maternal shock, and maternal death are the most frequent factors associated with fetal demise (Box 55-2).[15,21] The risk for direct fetal trauma increases with gestational age because the bony pelvis protects the uterus and fetus prior to 13 weeks' gestation. Pregnant women who sustain blunt trauma have a lower risk for bowel injury than nonpregnant patients because the uterus acts as a shield and pushes the abdominal contents into the upper abdomen.[22,23] Maternal pelvic fractures are associated with uteroplacental injury and fetal skull fractures. Skull fracture is the most common direct fetal injury and has a reported fetal mortality rate of 42%.[24]

The relationship between the Injury Severity Score (ISS) (see later discussion) and fetal outcome is controversial. Some studies have shown a direct relationship between the ISS and the incidence of fetal demise, whereas others have not. Analysis of outcomes from 1195 pregnant trauma victims showed that an ISS of greater than 15 was associated with increased risk for fetal demise.[25,26] Evidence suggests that decreased serum bicarbonate, an indicator of systemic hypoperfusion, is associated with fetal demise after maternal trauma. Altered maternal mental status and the presence of head trauma have also been linked to adverse fetal outcomes.

It is crucial to preserve maternal cardiac output, blood pressure, and oxygen delivery to optimize maternal recovery and protect fetal well-being. However, fetal loss

can occur even if the mother has not incurred serious injuries. Thus, all pregnant women should be evaluated in a medical setting after trauma, regardless of the apparent severity of injury. The fetus remains at risk for delayed complications after maternal discharge from the hospital. Delayed complications include a twofold increase in the risk for preterm delivery and a ninefold increase in the risk for fetal death.[27] Late complications of trauma, such as cerebral palsy, have also been reported in children born to mothers who experienced trauma during pregnancy.[28,29]

Initial Assessment and Resuscitation

The initial assessment and resuscitation should focus on the mother; it is axiomatic that maternal resuscitation typically facilitates fetal resuscitation. A systematic approach to initial resuscitation and stabilization should be used (Figure 55-1).[4] Immediate interventions are initiated to identify and treat life-threatening conditions based on the principles of Advanced Trauma Life Support (ATLS).[30] Initial focus should be placed on ensuring adequate airway protection, ventilation (breathing),

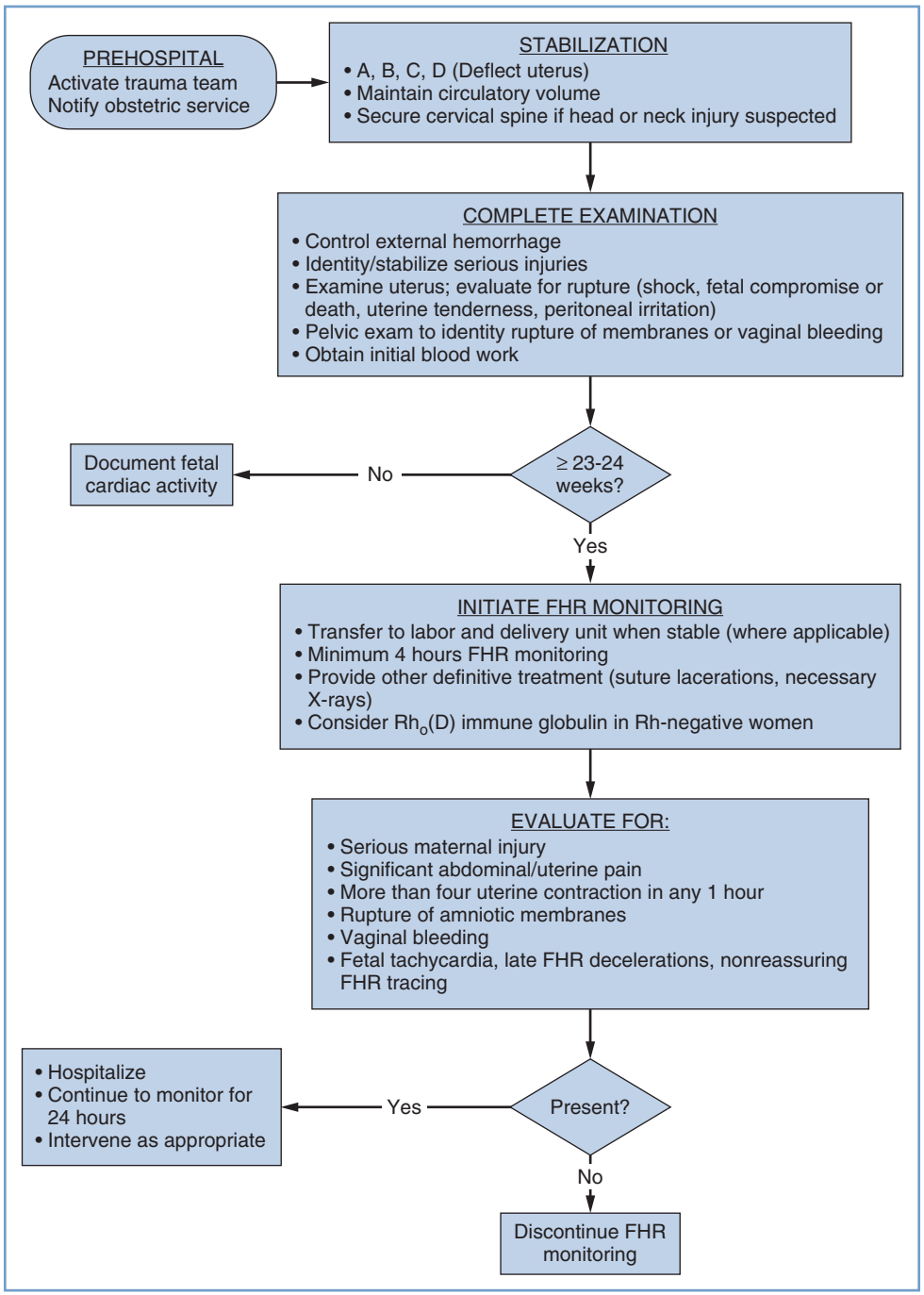


FIGURE 55-1 ■ Algorithm for management of the pregnant woman after trauma. *FHR,* fetal heart rate. (Modified from Chames MC, Pearlman MD. Trauma during pregnancy: outcomes and clinical management. Clin Obstet Gynecol 2008; 51:398-408.)

TABLE 55-1 Physiologic Changes of Pregnancy That May Affect Trauma Management

Parameter	Effect of Pregnancy	Implications
Airway		
Functional residual capacity	Decreased by 20%	More rapid oxyhemoglobin desaturation during periods of apnea
Oxygen consumption	Increased by 15%-20%	
Airway edema	May be present	Tracheal intubation more difficult
Lower esophageal sphincter tone	Decreased	Increased risk for aspiration
Gastric emptying	Decreased during labor	
Breathing		
Diaphragm	Displaced cephalad	Place chest tubes at higher intercostal space
Respiratory rate	No change	
Tidal volume	Increased 35%-45%	
pH	7.42-7.46, partially compensated respiratory alkalosis	
$PaCO_2$	28-32 mm Hg	Reflects normal hyperventilation
HCO_3^-	19-22 mEq/L	Reduced buffering capacity
Base deficit	2-3 mEq/L	
PaO_2	100-107 mm Hg	
Circulation		
Blood volume	Increased by 40%-50%	Significant blood loss may occur before onset of symptoms and hypotension
Cardiac output	Increased by 40%-50%	
Heart rate	Increased by 15%-25%	Early diagnosis of hypovolemia more difficult
Systolic blood pressure	Decreased by 5-15 mm Hg (more pronounced during mid pregnancy)	
Diastolic blood pressure	Decreased by 5-15 mm Hg (more pronounced during mid pregnancy)	
Hemoglobin	10-12 g/dL	Physiologic anemia
Gravid uterus	Aortocaval compression	Decreased cardiac output in the supine position; left uterine displacement required
Other		
Coagulation factors	Increased	Hypercoagulable state
BUN, creatinine	Decreased	Abnormal measurements often overlooked*
Symphysis pubis/sacroiliac joints	Widened	May alter radiographic interpretations

BUN, blood urea nitrogen.
*The reported measurements may fall within the normal range for the hospital laboratory, but the measurements may actually be abnormally high for a pregnant patient.

and circulation (the "ABCs" of resuscitation). Pregnant women experience significant changes in cardiopulmonary and metabolic function that must be considered during resuscitation (Table 55-1).

Airway

Airway patency, stabilization, and protection should be ensured as quickly as possible in all critically injured patients, including those who are pregnant. The status of the patient's airway can be quickly assessed by eliciting a verbal response. The inability to speak is an indication of severely impaired mental status or the inability to move adequate air to mediate phonation, either of which should prompt interventions to secure and protect the airway. Additional means of assessing airway patency include auscultation of the chest, assessment of chest movement, and assessment of air movement at the oral/nasal openings. Immediate interventions to establish airway patency include head tilt and jaw thrust maneuvers, as well as placement of an oral or nasopharyngeal airway to facilitate bag-mask ventilation and oxygenation.

It is essential to consider the possibility of cervical spine injury, facial fractures, and skull base injuries. Excessive head tilt maneuvers can worsen injury if a cervical spine fracture is present.[31] Patients who have sustained severe trauma should be suspected of having a cervical spine injury until proven otherwise. Cervical spine injury must be ruled out by radiographic and physical examination criteria.[32,33] The cervical spine should be stabilized with a hard collar and in-line stabilization until the severity of injury has been established. In cases of documented cervical spine injury, great care must be taken not to worsen spinal cord injury. A nasopharyngeal

airway should not be placed in patients with suspected facial or skull base fractures to avoid further trauma and worsening of preexisting conditions.

Most patients who require interventions to open or support the airway, as just described, will ultimately require tracheal intubation. Indications for tracheal intubation include impaired mental status, airway obstruction, inability to clear secretions or blood from the airway, inadequate spontaneous ventilation, and hypoxemia that is refractory to supplemental oxygen administration.[34] Tracheal intubation of pregnant patients is complicated by changes in respiratory system structure and function (see Table 55-1) (see Chapter 30).[18] Among the most prominent alterations are airway (including vocal cord) edema, decreased functional residual capacity, and increased oxygen consumption. Airway edema impairs vocal cord visualization, thus complicating laryngoscopy and tracheal intubation. Decreased functional residual capacity and increased oxygen consumption result in more rapid oxyhemoglobin desaturation during periods of apnea. These factors increase the risk for failed tracheal intubation and hypoxemia.

Gastric emptying is normal in pregnant women before the onset of labor. However, lower esophageal sphincter tone is commonly decreased in pregnant women (see Table 55-1). Thus, pregnant women are at increased risk for regurgitation and pulmonary aspiration of gastric contents, although all trauma victims are considered to have a full stomach on arrival in the emergency department or operating room. Therefore, in most cases, rapid-sequence induction of general anesthesia is performed to facilitate tracheal intubation. However, the specific tracheal intubation technique will depend on the practitioner's skills and resources, as well as on the location of the patient's injuries. Alternative approaches to rapid-sequence induction include awake tracheal intubation and tracheostomy.

Several factors can complicate tracheal intubation in the trauma patient. The patient may be combative, which complicates awake tracheal intubation strategies. Blood in the airway can also limit the use of a fiberoptic bronchoscope and impair visualization of the glottis when using a standard or video laryngoscope. The presence of facial fractures, direct airway injuries, trauma-induced airway edema, and tracheal deviation can limit access to the airway.

Finally, airway management, including tracheal intubation, is more challenging in the presence of cervical spine injury. If cervical spine injury is present or suspected, it is crucial to avoid flexion, extension, or lateral movement of the neck. The spine is protected using in-line stabilization and/or a hard cervical collar. Airway management devices such as a gum elastic bougie, a video laryngoscope, a lighted intubating stylette, and/or an intubating laryngeal mask airway (LMA), among others, should be available for use if standard laryngoscopy is difficult or impossible. A supraglottic airway device such as an LMA can be used to temporarily provide ventilation in cases in which mask ventilation and tracheal intubation have failed, but an LMA will not provide protection from aspiration and should be replaced by a secure airway device as soon as possible. In some cases, cricothyroidotomy or tracheostomy may be necessary to provide a secure airway.

Breathing

Adequate ventilation and oxygenation should be ensured for the benefit of both the mother and the fetus. Supplemental oxygen should be administered immediately, even if the patient is breathing spontaneously. Mechanical ventilation is often necessary after tracheal intubation in patients with respiratory failure and/or hypoxemia. Ventilation can be compromised by trauma-associated factors such as pneumothorax, hemothorax, lung contusion, mediastinal compression, and chest wall injuries. These problems must be identified during the primary survey and treated to optimize ventilation and oxygenation. In women with advanced pregnancy, it may be necessary to place chest tubes more cephalad than normal owing to the cephalad displacement of the diaphragm and intra-abdominal structures by the gravid uterus. Pregnant trauma patients should be ventilated to maintain $Paco_2$ at a level that is normal for pregnancy (28 to 32 mm Hg) (see Table 55-1). Positive end-expiratory pressure (PEEP) may be added to improve oxygenation, if indicated; however, PEEP should be titrated carefully in the hypovolemic patient because it may impair venous return and worsen cardiac output and organ perfusion.

Circulation

Once respiratory stabilization has been achieved, it is essential to assess cardiovascular function and to determine whether the patient is in shock. Two large-bore peripheral intravenous catheters should be placed in the upper extremities to facilitate resuscitation. Central venous access facilitates rapid resuscitation but may be difficult to obtain. Intraosseous cannulation should be considered if it is difficult or impossible to obtain peripheral or central venous access.

Fluid resuscitation should be initiated using crystalloid solution, but blood transfusion should be considered if significant blood loss is apparent or suspected. Left uterine displacement should be initiated immediately to prevent or minimize aortocaval compression by the gravid uterus. The adverse effects of aortocaval compression may be exacerbated during periods of trauma-associated hypovolemia. The use of the pneumatic antishock garment to stabilize fractures or control hemorrhage is relatively contraindicated in pregnant women owing to its adverse effects on venous return.

The hallmark clinical signs of shock are listed in Box 55-3. The presence of these signs indicates a need for timely and appropriate fluid resuscitation. A rapid assessment of sources of blood loss should be performed. In trauma victims, the most common locations of exsanguinating blood loss are the chest, abdomen, retroperitoneum, long bones, and external sites. In the pregnant trauma patient, placental abruption and uterine rupture are also potential sources of hemorrhage. A brief physical examination will identify fractures of the long bones and external sites of bleeding. Thoracic blood loss and pelvic fractures can be identified by chest and pelvic radiographs, respectively. Focused abdominal sonography in trauma (FAST) or diagnostic peritoneal lavage can be used to identify intra-abdominal bleeding. However,

BOX 55-3 Clinical Signs of Shock in the Trauma Patient

- Agitation
- Confusion
- Poor capillary refill
- Mottled appearance
- Cool extremities
- Diaphoresis
- Tachypnea
- Tachycardia
- Weak distal pulses
- Hypotension
- Decreased pulse pressure
- Decreased urine output
- Lactic acidosis

diagnostic peritoneal lavage may be difficult to perform safely in advanced pregnancy. FAST can be rapidly performed to assess the hepatorenal, splenorenal, and pelvic spaces, which are the most common sites of major hemorrhage in trauma patients. FAST can also be used to assess uteroplacental integrity and the presence of intrauterine bleeding. Finally, ultrasonography facilitates assessment of cardiac filling and recognition of cardiac tamponade in patients with thoracic trauma.

It is important to recognize that pregnant trauma patients may lose a significant amount of blood before the development of hypotension. Pregnant patients have a 40% to 50% increase in blood volume by the third trimester. Classic signs of hypovolemia such as tachycardia, hypotension, and poor capillary refill may not be evident until blood loss approaches 1.5 to 2 liters. Therefore, it is likely that a pregnant trauma victim will have lost significantly more blood volume and oxygen-carrying capacity than a comparable nonpregnant patient when signs of cardiovascular deterioration become evident. Resuscitation should be guided by apparent blood loss to maintain adequate maternal cardiac output and uteroplacental perfusion. Because of the physiologic anemia of pregnancy, oxygen-carrying capacity may be significantly impaired at the time that hypovolemia becomes evident. In addition, maternal perfusion of vital organs is often sustained at the expense of uteroplacental perfusion. Uterine blood flow may decrease by as much as 30% before the mother shows signs of hypovolemia. Therefore, a nonreassuring fetal heart rate (FHR) pattern may be the first sign of significant intravascular volume loss. Fluids should be warmed to minimize the risk for hypothermia, which can contribute to coagulopathy, arrhythmias, and altered drug responses.

Fluid Resuscitation. Current practice supports the use of **crystalloid solutions** to resuscitate the hypovolemic trauma victim. However, the crystalloid versus colloid debate remains to be fully resolved. The Saline versus Albumin Fluid Evaluation (SAFE)[35] did not show any difference in survival in nonpregnant trauma patients randomized to receive resuscitation with either colloid or crystalloid, with the exception of patients with head trauma, who had worse outcomes when resuscitated with albumin. However, colloid solutions are anecdotally preferred in some trauma centers. The current ATLS guidelines advocate the use of lactated Ringer's solution for initial fluid resuscitation.[30] Lactated Ringer's solution has significant buffering properties and is less likely to cause hyperchloremic metabolic acidosis during high-volume resuscitation than normal saline solution. Other buffered salt solutions such as Plasma-Lyte, Ringer's ethyl pyruvate, and Ringer's hydroxybutyrate also may have value. Currently, no evidence supports the use of one buffered isotonic crystalloid solution over another.

The use of **hypertonic crystalloid solutions** such as 3% sodium chloride is controversial; currently no evidence supports their use in pregnant trauma victims. Hypernatremia is a risk in patients resuscitated with hypertonic saline, and some studies have shown increased mortality in patients resuscitated with hypertonic crystalloid solutions.[36]

Some practitioners have advocated **hypovolemic resuscitation** in patients with major hemorrhage after trauma.[37] This technique employs **permissive hypotension** (systolic blood pressure of 80 to 90 mm Hg) until hemorrhage can be controlled in the operative setting. The underlying premise of hypovolemic (hypotensive) resuscitation is that over-resuscitation worsens ongoing blood loss as a result of higher perfusion pressure and dilution of clotting factors. Small boluses of fluids are administered to maintain perfusion in patients without evidence of closed head injury. The use of hypotensive resuscitation is likely to be detrimental in patients with closed head injury because it is crucial to maintain adequate cerebral perfusion pressure (CPP) in patients with elevated intracranial pressure (ICP).[38] (CPP is the difference between mean arterial pressure [MAP] and ICP.) No definitive published data support the use of hypotensive resuscitation in pregnant trauma patients. Current guidelines do not support this approach because it may compromise uteroplacental perfusion.

Damage Control Principles and Resuscitation. The traditional approach to treatment of traumatic life-threatening injuries has been definitive operative repair. However, some patients experience progressive physiologic decline during long surgical procedures and develop severe derangements such as hypothermia, metabolic acidosis, and coagulopathy, a combination that has become known as the *deadly triad*.[39] These pathologic alterations require rapid and effective treatment to prevent severe morbidity and death. More recently, some practitioners have advocated the use of a more targeted approach, termed *damage control*, which is initiated to control hemorrhage without providing early definitive repair of injuries.[40] Major surgical bleeding is controlled, and the thoracic and abdominal cavities are packed to provide hemostasis. Gastrointestinal diversion is performed, and body cavities are temporarily closed, often using vacuum-type closure systems. Active volume resuscitation is performed to achieve metabolic homeostasis. On achievement of stable hemodynamic and acid-base status, coagulation function, and temperature, the patient is taken back to the operating room for definitive repair of injuries.

Blood Products. All trauma centers should have rapid access to **type O**, **Rh-negative blood** for emergency use before type-specific or crossmatched blood is available. Recently, some trauma specialists have advocated damage-control resuscitation using packed red blood cells and fresh frozen plasma mixed in equal proportions (1 : 1) (see Chapter 38). Several investigators have reported the value of this approach in military practice, and they have specifically observed that this approach results in more effective resuscitation, less coagulopathy, and improved survival than more traditional approaches.[41] It remains unclear whether this approach will be advantageous in civilian practice, but many centers are investigating its use.

In the setting of uncontrolled hemorrhage, recombinant activated factor VII (rFVIIa) has been shown to be effective in treating severe coagulopathy in a small number of observational studies. Case reports and case series have described the efficacy of rFVIIa during massive hemorrhage in trauma and obstetric patients (see Chapter 38).[37] A multidisciplinary group in Israel reported that rFVIIa was effective in decreasing severe bleeding in 36 trauma patients.[42] European consensus guidelines also advocate the use of rFVIIa in trauma patients with massive uncontrolled hemorrhage that is refractory to conventional transfusion of blood products.[43] However, further research is needed before rFVIIa can be endorsed for treatment of massive hemorrhage, owing to its high cost and an incomplete risk-benefit analysis. A major concern is the potential increased risk for thromboembolism in patients treated with rFVIIa.

Secondary Survey

As in all trauma cases, it is crucial to evaluate the mother for significant abdominal, thoracic, orthopedic, and neurologic injuries. A head-to-toe examination should be performed to determine the presence of injuries and the need for intervention. A more detailed evaluation of neurologic function, as well as examination of the head and neck, should be performed. This survey includes examination of posterior structures that may be obscured by the supine position and the presence of a cervical collar. The torso should be examined to identify thoracic and abdominal injuries. The thoracic examination should include chest auscultation, inspection, and palpation. Palpation of the abdomen should be performed to evaluate abdominal tenderness, and a rectal examination should be performed to identify evidence of intraluminal bleeding. The extremities must be examined to identify deformities, and each joint should be manipulated. Distal perfusion of the extremities must be continuously monitored, especially in limbs that show signs of significant injury. This is accomplished by evaluation of distal pulses and capillary refill. In cases of penetrating injury, the sites of entry and exit should be identified. It is especially important to examine carefully the areas that are difficult to access such as the oral cavity, perineum, axilla, scalp, and back. Once the secondary survey has been performed, more targeted assessments of suspected injuries can be performed using radiologic imaging.

Fetal Survey. After initial stabilization of the mother, information about the pregnancy should be gathered through a focused history and physical examination. The history should include the date of the last menstrual period, expected date of delivery, and status of the pregnancy. In cases in which there is uncertainty regarding fetal age, an approximate determination can be made by measuring fundal height. The fetal age is estimated to be 1 week for each centimeter of fundal height above the symphysis pubis. In addition to the assessment of fundal height, the abdominal examination should include an assessment of uterine tenderness and consistency, the presence or absence of uterine contractions, and fetal position and movement.

A pelvic examination should be performed to evaluate cervical dilation and effacement, fetal station, and the presence of amniotic fluid and blood. The FHR is assessed by Doppler auscultation or ultrasonography. If maternal stability permits, ultrasonography facilitates estimation of fetal age and assessment of uteroplacental injury.

If no fetal cardiac activity is identified, fetal resuscitation should not be attempted (see Figure 55-1). In a series of 441 pregnant trauma patients, the absence of a detectable FHR was associated with fetal death in all cases.[9] When a FHR is detected, an assessment of fetal viability should be performed. An estimated gestational age of 24 to 25 weeks and an estimated fetal weight of 500 g are common thresholds for extrauterine fetal viability. The FHR should be monitored in cases in which the fetus is determined to be viable. In cases in which a nonviable fetus is present, the importance of FHR monitoring is unclear. However, alterations in FHR and FHR variability may signal maternal deterioration and serve as a good monitor of the effectiveness of maternal resuscitation.

FHR monitoring is generally performed with external Doppler auscultation, and a tocodynamometer is used to assess uterine contractions. Adverse fetal outcomes are unlikely in cases with a reassuring FHR tracing and no early warning signs of uteroplacental injury (bleeding, abdominal pain).[44] In contrast, an abnormal FHR tracing or evidence of uteroplacental injury (vaginal bleeding, uterine contractions, uterine tenderness, presence of amniotic fluid on vaginal examination) predicts poor fetal outcome in approximately 50% of cases.[45]

Fetal Monitoring

Continuous electronic FHR monitoring is the current standard of care for pregnant trauma victims with a viable fetus.[9,14] FHR monitoring should be initiated as soon as maternal stabilization is complete, because placental abruption can occur early during the course of resuscitation. Continuous electronic FHR monitoring is more sensitive for placental abruption than ultrasonography, physical examination, or Kleihauer-Betke testing. Occasional uterine contractions are common after trauma and are usually not associated with poor fetal outcome.[11,45,46] Random uterine contractions usually resolve within a few hours of the accident. However, regular and prolonged uterine contractions (eight contractions per hour for more than 4 hours) are associated with placental abruption, which has a high fetal mortality rate.[46]

The diagnosis of placental abruption should trigger immediate cesarean delivery; a large percentage of viable fetuses can be rescued if expedited delivery is performed. The presence of fetal bradycardia and frequent late FHR decelerations should also prompt delivery if the mother is stable and adequately resuscitated.

The ideal duration of FHR monitoring has not been determined. However, a common practice, based on a prospective study of 60 pregnant trauma patients at more than 20 weeks' gestation, is to monitor the FHR for 4 hours.[47] If maternal-fetal abnormalities are not detected within 4 hours, it is generally considered safe to discontinue FHR monitoring because a normal FHR tracing has a negative predictive value of 100% when combined with a normal maternal physical examination. However, the presence of abnormalities such as vaginal bleeding, spontaneous rupture of membranes, category II and III FHR patterns, persistent uterine contractions, uterine tenderness, abdominal pain, and/or need for maternal analgesia should prompt further FHR monitoring. The sensitivity of ultrasonography for placental abruption ranges from 50% to 80%, but ultrasonography is a safe and effective means of assessing fetal viability, FHR, placental location, gestational age, and amniotic fluid volume. It is particularly valuable in the presence of maternal tachycardia, when it can be difficult to differentiate maternal and fetal heart rates using Doppler auscultation.

Laboratory Studies

Laboratory evaluation in pregnant trauma patients does not differ from the evaluation for nonpregnant patients, with a few exceptions. As for all trauma patients, the laboratory evaluation will be driven by the type and severity of injury. For most patients with significant injury, standard analysis includes a complete blood cell count with a platelet count, coagulation studies, serum electrolyte measurements, blood glucose and lactate levels, liver function tests, arterial blood gas analysis, urinalysis, and toxicology screening, as well as sending a blood sample for typing and crossmatching for compatible blood products (Box 55-4).

The presence of disseminated intravascular coagulation (DIC) and low blood bicarbonate levels is associated with poor fetal outcome.[10,25] Both abnormalities reflect severe maternal injury and should prompt aggressive maternal resuscitation. Of special consideration in pregnant trauma patients is maternal-fetal hemorrhage. The Kleihauer-Betke acid elution assay is used to detect the entry of fetal blood into the maternal circulation.[20] It is typically performed in Rh_0(D) antigen–negative mothers to detect transplacental hemorrhage and the potential for developing Rh_0(D) sensitization, which can be prevented in 99% of cases by early treatment with Rh_0(D) immune globulin (RhoGAM). However, this test may help predict adverse fetal outcomes in all pregnant trauma patients (see earlier discussion).

BOX 55-4 Initial Laboratory Analysis for the Pregnant Trauma Patient

- Blood type and crossmatch
- Complete blood cell count with platelet count
- Prothrombin (INR) and partial thromboplastin times
- Fibrinogen
- Serum electrolytes, BUN, creatinine, glucose
- Liver function tests
- Serum amylase level
- Blood lactate
- Arterial blood gas measurement
- Toxicology screen
- Kleihauer-Betke assay
- Urinalysis

BUN, blood urea nitrogen; *INR*, international normalized ratio.

Imaging

The pregnant trauma patient often requires imaging to evaluate orthopedic, head, thoracic, and abdominal injuries. Although many patients and physicians are concerned about the fetal effects of ionizing radiation, the risks for teratogenesis, malignancy, and gene mutation are small with a radiation exposure less than 5 to 10 rads (see Chapter 17).[48] Less than 1% of trauma patients receive more than 3 rads of radiation exposure. When possible, the fetus should be shielded with lead. Intravenous pyelography subjects the fetus to as much as 1.4 rads of exposure, but the test can be invaluable in diagnosing injuries to the kidneys, ureters, and bladder. Computed tomography (CT) is associated with greater radiation exposure than plain radiography, but exposure levels are generally below that considered to be dangerous to the fetus. Modern multidetector (multislice) CT results in higher fetal radiation exposure, but it has significant advantages in speed and image resolution. Overall, the small risk for fetal radiation exposure is outweighed by the benefits to the injured mother and, by extension, the fetus.

Injury Scoring

Several injury scoring scales have been developed over the past 40 years. The scoring systems provide a framework for standardizing clinical management, benchmarking outcomes, and planning research. Presently, no reliable scoring tool exists for predicting maternal or fetal outcome after trauma. Currently used scoring systems include (1) anatomic injury scales that rely on physical examination and diagnostic procedures, (2) physiologic injury scales that rely on assessment of physiologic responses and function, and (3) combination injury scales.

One of the first anatomy-based injury scales was the **Abbreviated Injury Scale** (AIS) developed by the Association for the Advancement of Automotive Medicine.[49] Each of nine body regions is given an injury severity score that ranges from 1 (minor) to 6 (maximal [currently untreatable]). Although the AIS effectively describes the severity of injuries at specific locations, it provides a limited assessment of the overall pathophysiologic impact of all injuries. The **Injury Severity Score** (ISS), which was developed to address this issue, is obtained by summing the square of the three highest severity scores from the AIS. The ISS ranges from 1 to 75. Minor injuries are classified as an ISS of less than 9; moderate, from

9 to 15; serious, from 16 to 25; and severe, greater than 25. The ISS correlates with the risk for preterm delivery after trauma, but its value in predicting fetal death, placental abruption, and other adverse outcomes is controversial.[15] The American Association for the Surgery of Trauma developed the **Organ Injury Scale** (OIS)[50]; this is an organ-based severity scale designed to facilitate clinical investigation and outcomes research. The value of the OIS in predicting adverse maternal and fetal outcomes remains to be established.

Anatomic scoring systems have value in describing the extent and severity of injuries to specific organ systems. However, physiologic scoring systems may add prognostic value. The **Glasgow Coma Scale**, which is among the most widely used physiologic scoring systems, evaluates the neurologic status of the trauma patient. The Glasgow Coma Scale evaluates eye opening, verbal response, and motor activity; scores range from 3 to 15, with 3 indicating the absence of neurologic activity and 15 representing intact neurologic function. A Glasgow Coma Scale score of less than 9 reflects severe impairment, whereas as a score of 9 to 12 reflects moderate disability. However, concerns have been raised about inter-rater reliability and lack of prognostic utility for the Glasgow Coma Scale. Some researchers have proposed that a simplified motor score would be more reliable. Evidence suggests that the Glasgow Coma Scale has a poor correlation with fetal outcome.[15]

Traumatic Brain Injury

Brain injury is the most common severe injury in patients who suffer from motor vehicle accident, and it is a major cause of mortality among pregnant trauma victims.[51] It is important to perform a thorough neurologic examination with particular attention to level of consciousness. Altered mental status may be an indicator of evolving intracranial pathology, intoxication, hypoperfusion, and/or metabolic disturbances. Mental status should be reevaluated frequently because intracranial pathologic processes may not be apparent on initial evaluation and may evolve during the course of resuscitation.

Elevated ICP is a common finding in patients with traumatic brain injury and may be a significant threat to life. Head CT is the imaging study of choice for identifying the site and severity of intracranial pathologic processes in trauma patients, and it should be performed within 1 hour of arrival in the emergency department.

Crystalloid fluid resuscitation should be used for resuscitation in patients with traumatic brain injury; resuscitation with albumin is deleterious in patients with traumatic brain injury (see earlier discussion).[35] Hypotensive resuscitation is contraindicated in patients with traumatic brain injury and elevated ICP. It is crucial to maintain CPP to minimize the risk for brain ischemia and permanent brain injury. The extent of brain injury will worsen if CPP is not maintained. It is also important to maintain cerebral oxygen delivery by optimizing maternal cardiac output and blood oxygen-carrying capacity.

It may be necessary to intubate the trachea of patients with deteriorating mental status for airway protection and provision of ventilatory support. Hypoventilation should be avoided because it increases ICP. Hyperventilation to a $Paco_2$ between 25 and 30 mm Hg will provide a transient decrease in ICP and may be useful until definitive treatment can be initiated. However, hyperventilation can be disadvantageous for the fetus because it can decrease uteroplacental blood flow by decreasing maternal cardiac output and blood pressure, and perhaps by causing uteroplacental vasoconstriction. Therefore, it is prudent to maintain $Paco_2$ at levels that are normal in pregnant females (28 to 32 mm Hg). Additional maneuvers to decrease ICP include treatment with a diuretic such as mannitol or furosemide and elevation of the head 30 to 45 degrees.

Corticosteroids are no longer recommended for patients with traumatic brain injury because their administration in this setting is associated with increased mortality. Barbiturates decrease cerebral oxygen use and blood flow and may provide cerebral protection in patients with severe impairment. Both mannitol and furosemide cross the placenta and could cause alterations in fetal plasma osmolality and decrease fetal intravascular volume. However, concern regarding adverse fetal effects should be overridden by the needs of the mother in cases of traumatic brain injury.

Cardiopulmonary Resuscitation

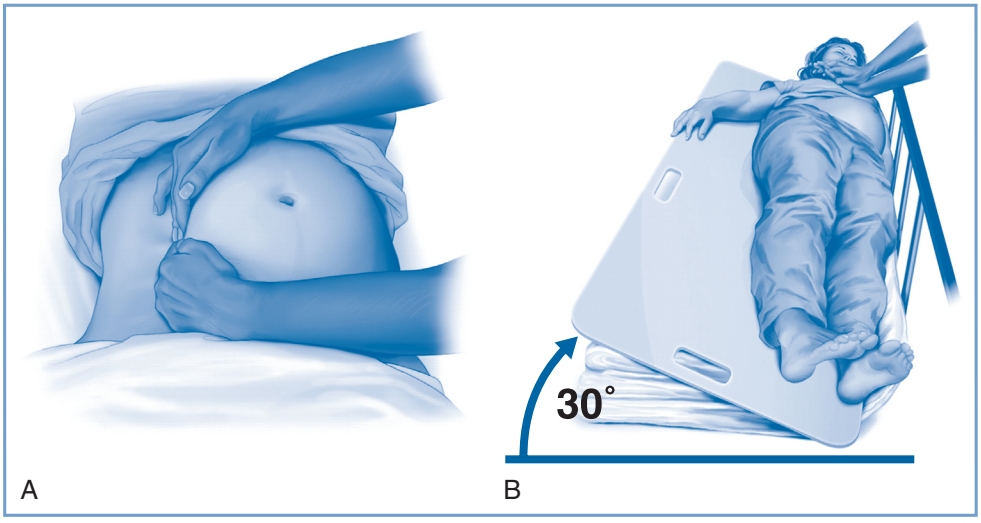
The incidence of cardiac arrest in pregnancy is reported to be 1:20,000 to 1:30,000 patients in industrialized countries.[52] The most frequent causes are trauma, peripartum hemorrhage, embolic phenomena, stroke, preeclampsia/eclampsia, sepsis, status asthmaticus, and anesthesia-related complications.[53] Cardiopulmonary resuscitation should be initiated immediately (see Chapters 17 and 42). The 2010 American Heart Association (AHA) guidelines highlight the importance of initiating high-quality chest compressions to facilitate circulation.[52,54] The hands should be placed slightly above the center of the sternum because the diaphragm and abdominal contents are displaced cephalad during the third trimester of pregnancy (Box 55-5). In the hospital setting, the airway should be secured and the mother ventilated with 100% oxygen. Intravenous or intraosseous access should be secured to facilitate resuscitation. Advanced Cardiac Life Support (ACLS) guidelines should be followed to identify and treat causes of cardiopulmonary arrest.[52]

Cardiac arrest in the pregnant patient is complicated by the physiologic changes of pregnancy, particularly the effect of the gravid uterus on aortocaval blood flow. Well-performed chest compressions in the nonpregnant patient typically result in cardiac output that is approximately 30% of normal. In pregnant patients, aortocaval compression reduces the cardiac output that results from chest compressions. Although it is typically advised to tilt the patient 15 to 30 degrees to facilitate left uterine displacement and optimize venous return and cardiac output, such a maneuver may impede the effectiveness of chest compressions. Therefore, the AHA guidelines advocate manual left uterine displacement rather than the usual whole-body tilt (Figure 55-2).[52] If this technique is not successful, a firm wedge may be placed under a resuscitation board to tilt the patient approximately 30 degrees.

BOX 55-5 Modification of Cardiopulmonary Resuscitation during Pregnancy

- Chest compressions: place the hands slightly higher on the sternum.
- Perform manual left uterine displacement, or place a firm wedge under the resuscitation board to tilt patient approximately 30 degrees.
- Obtain intravenous access above the diaphragm.
- Anticipate difficult airway management.
- Discontinue magnesium sulfate (if applicable) and administer calcium chloride or calcium gluconate.
- Defibrillation: remove both internal and external fetal monitors.
- If spontaneous circulation does not return within 4 minutes of cardiac arrest, immediate hysterotomy or cesarean delivery should be performed if gestational age is 20 weeks or greater, aiming for delivery within 5 minutes of cardiac arrest.
- Continue all resuscitation efforts during and after cesarean delivery.
- Search for possible contributing factors (BEAU-CHOPS):
  - **B**leeding/disseminated intravascular coagulation
  - **E**mbolism: coronary/pulmonary/amniotic fluid embolism
  - **A**nesthetic complications
  - **U**terine atony
  - **C**ardiac disease (myocardial infarction/ischemia/cardiomyopathy)
  - **H**ypertension/preeclampsia/eclampsia
  - **O**ther: differential diagnosis included in standard ACLS algorithms
  - **P**lacenta abruption/previa
  - **S**epsis

ACLS, Advanced Cardiac Life Support.
Modified from Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: Cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122:S829-61.



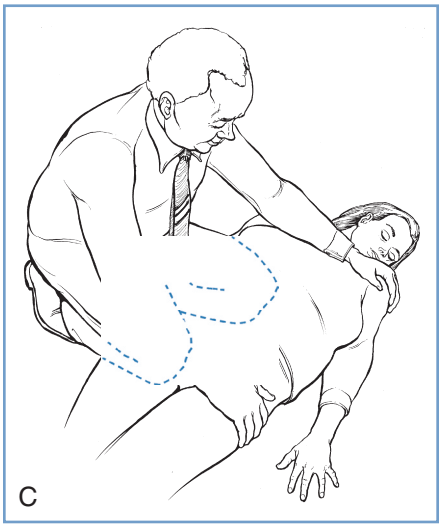


FIGURE 55-2 ■ Methods to relieve aortocaval compression during cardiopulmonary resuscitation in maternal cardiac arrest. **A,** Manual left lateral displacement with two-handed technique. **B,** Patient in a 30-degree left-lateral tilt using a firm wedge to support the pelvic and thorax. **C,** The human wedge position. (**A** and **B** from Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: Cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122:S829-61; **C,** modified from Harnett M, Tsen LC. Cardiovascular disease. In Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia. 4th edition. Philadelphia, Mosby, 2009.)

In the field, the responder may use his or her knees to tilt the patient.

Chest impedance is unchanged during pregnancy. Therefore, the usual voltage levels for defibrillation should be used in pregnant patients.[52] Electric cardioversion during pregnancy appears to be safe for the fetus (see Chapter 42). If spontaneous circulation does not return within 4 minutes of cardiac arrest, immediate hysterotomy or cesarean delivery should be performed if gestational age is 20 weeks or greater, aiming for delivery within 5 minutes of cardiac arrest. Timely delivery facilitates successful resuscitation of both the mother and the infant.[52,54] Furthermore, early hysterotomy and uterine evacuation optimizes maternal resuscitation, even if the fetus has already died. Extrauterine fetal survival is unlikely before 24 to 25 weeks' gestation.

Management of the Brain-Dead Patient

Brain death in the pregnant patient is a rare occurrence. Esmaeilzadeh et al.[55] summarized 30 cases published between 1982 and 2010. Nontraumatic brain injury, primarily intracranial hemorrhage, was the cause of death in 26 of 30 cases. The mean gestational ages at times of injury and delivery were 22 and 29.5 weeks, respectively. Twelve viable infants survived beyond the neonatal period.

In cases of maternal brain death, care providers should focus on saving the life of the fetus; maternal organ preservation for harvest and donation is a secondary consideration. Maintenance of vital functions in mothers with catastrophic brain injury is justified to meet these two goals, but in many cases ethical and legal concerns must be addressed. Consideration must be given to gestational age and the chance for fetal survival. Before 24 weeks' gestation, the chance for extrauterine fetal survival is small. In general, management should follow current guidelines for organ preservation therapy.

The question of whether to preserve maternal circulation and organ function to facilitate fetal development is an ethical dilemma. A fundamental issue relates to the support of the brain-dead mother as an incubator for the unborn fetus. Some professionals argue such an approach is unethical, whereas others view prolonged somatic support as a case of organ donation with the fetus as the recipient. In many cases, the mother's wishes are not known. If the mother indicated a wish to donate organs, prolonged somatic maternal support may be appropriate. Currently, there is no generally accepted lower limit of gestational age for maintenance of maternal support. Each case must be addressed on an individual basis, with close communication among the family, a cohort of care providers, and the hospital ethics committee.

CRITICAL CARE DURING PREGNANCY

Stroke

Ischemic Stroke

Pregnant women are at increased risk for ischemic stroke compared with their nonpregnant counterparts.[56] Pregnancy is a hypercoagulable state characterized by decreased fibrinolysis, increased levels of clotting factors, and decreased levels of certain natural anticoagulants (e.g., protein S). Clinical manifestations of ischemic stroke are similar to those seen in the nonpregnant population and include focal neurologic symptoms, seizures, decreased level of consciousness, and abnormal cranial nerve function. Once the diagnosis is suspected, and initial evaluation and therapy—including airway protection—have been addressed, non–contrast-enhanced CT should follow immediately. The fetal radiation exposure from this test is less than 1 rad.[57] If CT shows no evidence of hemorrhagic stroke, the patient is assumed to have an ischemic stroke. Consideration of thrombolytic therapy should follow, including evaluation of contraindications for thrombolytic therapy (Box 55-6). Thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) has been reported during pregnancy and appears to be safe for the fetus; transplacental passage of r-tPA is minimal. However, retroplacental bleeding with pregnancy loss has been reported.[58-60] Consultation with an experienced neurologist is recommended.

The r-tPA is administered intravenously at a dose of 0.9 mg/kg (maximum, 90 mg) over 1 hour (10% of the dose is commonly administered as an initial bolus over the first minute). The therapeutic window (i.e., time from onset of symptoms to administration of the agent) is 4.5 hours.[61] Patients who are candidates for this therapy should be watched closely in an ICU environment that includes fetal surveillance by a maternal-fetal medicine specialist. Blood pressure should be maintained below

BOX 55-6 Major Contraindications for Thrombolysis in Ischemic Stroke Patients

- History of a previous intracranial hemorrhage
- Genitourinary or gastrointestinal bleeding in the previous 3 weeks
- Closed head trauma in the previous 3 months
- Major surgery in the previous 2 weeks
- Blood pressure above 185/110 mm Hg despite antihypertensive therapy
- Acute active bleeding
- Evidence that symptoms are clearing spontaneously
- Hemorrhagic transformation on initial imaging
- Massive ischemic stroke (hypodensity affecting more than one third of the cerebral hemisphere)
- Platelet count < 100,000/mm^3
- Concurrent heparin or warfarin therapy with a prolonged PT or aPTT
- Blood glucose < 50 mg/dL (symptoms may be due to hypoglycemia)
- Evidence of a seizure with postictal residual neurologic impairment

PT, prothrombin time; *aPTT*, activated partial thromboplastin time.
Modified from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 2007; 115:e478-534.

180/105 mm Hg during r-tPA therapy. Neurologic deterioration during thrombolytic infusion should raise suspicion of **hemorrhagic transformation;** the infusion should be stopped immediately, and the head CT should be repeated. Transfusion of platelets (e.g., 10 units of pooled random donor platelet concentrate or 1 to 2 units of apheresis platelet concentrate) and 10 units of cryoprecipitate is recommended if hemorrhagic transformation of the stroke is documented.[62] Other potential therapies include fresh frozen plasma, activated rFVIIa, and antifibrinolytic therapy.[62]

Patients with ischemic stroke who are not candidates for r-tPA therapy should receive aspirin (162 to 325 mg/day) for 2 weeks; subsequently, the dose may be decreased to 100 mg/day.[61] Deep vein thrombosis prophylaxis with unfractionated heparin should also be started on admission unless contraindicated. Outcome data related to blood pressure management in patients with acute ischemic stroke are inconsistent; however, in 2007, the AHA and the American Stroke Association recommended that, in patients receiving thrombolytic therapy, emergency antihypertensive medication should be withheld unless the blood pressure is above 220/120 mm Hg.[63] If the patient has received thrombolytic therapy, aspirin and prophylactic doses of heparin should be withheld for 24 hours after completion of the infusion. Fever should be aggressively treated to achieve normothermia. Blood glucose measurements higher than 140 to 180 mg/dL should be treated with insulin. Seizure prophylaxis in ischemic stroke patients is not recommended.[63]

Cerebral sinus and vein thrombosis may occur during pregnancy and the puerperium, but most cases occur postpartum. The clinician should suspect cerebral sinus thrombosis in the presence of severe headache, focal neurologic symptoms, and/or papilledema. The diagnostic test of choice is magnetic resonance venography (MRV). Most cases involve the transverse sinuses. Initial imaging reveals concomitant areas of hemorrhage in as many as 40% of these cases. However, treatment involves immediate therapeutic anticoagulation with unfractionated heparin or low-molecular-weight heparin unless massive hemorrhage is present.[61,64]

Ischemic strokes that involve more than 50% of the territory of the middle cerebral artery are known as "malignant strokes." They occur more commonly in young people. In the vast majority of cases, these patients require early decompression hemicraniectomy because the stroke is usually associated with massive cerebral edema that frequently is not responsive to medical therapy.[65]

Hemorrhagic Stroke

Pregnancy typically is accompanied by a 40% to 50% increase in both cardiac output and effective blood volume. These changes, coupled with hormone-induced changes in the vessel wall structure, may render pregnant patients more susceptible to hemorrhagic strokes resulting from intracerebral and subarachnoid hemorrhage.[66]

Intracerebral Hemorrhage. Intracerebral hemorrhage is usually a secondary complication of hypertensive emergencies (e.g., preeclampsia, hypertensive encephalopathy). Clinical presentation is similar to that in nonpregnant individuals. The diagnosis is confirmed with non–contrast-enhanced CT.

As in any other stroke victim, initial management involves securing the airway and facilitating oxygenation and ventilation. Intracranial pressure monitoring should be considered in patients with a Glasgow Coma Scale score less than 8, clinical evidence of transtentorial herniation, and evidence of significant intraventricular hemorrhage or hydrocephalus.[67]

Blood pressure control in this setting is controversial. Current guidelines recommend antihypertensive therapy when the blood pressure exceeds 180/110 mm Hg or when MAP exceeds 130 mm Hg.[67,68] Some experts argue that hypertension leads to hematoma expansion and may worsen cerebral edema. Recent evidence suggests that it is safe to use antihypertensive agents to achieve a systolic blood pressure less than 140 mm Hg. Maintenance of systolic blood pressure below 140 mm Hg leads to decreased hematoma expansion, but the effect on outcomes is unknown.[68] In cases of intracerebral hemorrhage associated with preeclampsia, some practitioners recommend maintenance of systolic and diastolic blood pressures between 140 to 160 mm Hg and 90 to 110 mm Hg, respectively, to maintain uteroplacental perfusion pressure. Blood pressure should be monitored invasively and treated with a titratable intravenous agent such as labetalol or nicardipine.

In the setting of intracerebral hemorrhage secondary to the use of warfarin, rapid reversal of the anticoagulation effect is of paramount importance. Vitamin K (10 mg intravenously over a minimum of 20 minutes) should be administered.[69] Recent guidelines from the American College of Chest Physicians suggest that **prothrombin complex concentrate,** which contains the vitamin K–dependent clotting factors II, VII, IX, and X, should be first-line therapy.[69] Advantages of prothrombin complex concentrate over fresh frozen plasma include no requirement for blood typing and crossmatching, a lower risk for bloodborne infection, and little risk for volume overload. Prothrombin complex concentrate can be infused over 15 to 30 minutes.[69] The role of rFVIIa in this setting is limited, and its use cannot be recommended at this time.

The risk for seizures after intracerebral hemorrhage is higher in cases of lobar hemorrhage; the risk is small if hemorrhage is localized to the basal ganglia, and even less if limited to the posterior fossa. Unless clinical seizures are observed or nonconvulsive activity is noted on the electroencephalogram (EEG), routine seizure prophylaxis in patients with intracerebral hemorrhage is not recommended. Therapy may be associated with worse long-term functional outcome.[67] As with most brain injuries, glucose control is paramount in the management of intracerebral hemorrhage. Blood glucose should be maintained between 140 and 180 mg/dL in critically ill patients who require insulin therapy.[67,70] Once bleeding cessation is documented by repeat imaging, deep vein thrombosis prophylaxis with unfractionated heparin or low-molecular-weight heparin should be initiated (usually 1 to 4 days after the intracerebral hemorrhage).

Subarachnoid Hemorrhage. A subarachnoid hemorrhage may be traumatic or nontraumatic. This discussion is limited to nontraumatic forms of subarachnoid hemorrhage. The most common cause of nontraumatic subarachnoid hemorrhage is rupture of a berry **aneurysm.** The clinical presentation varies from the complaint of the "worst headache in my life" to profound coma. The diagnosis is made by CT followed by cerebral angiography to locate the source of the bleeding. Abdominal shielding is essential during all radiographic procedures to limit fetal radiation exposure. Once the aneurysm is located, two management options exist. Craniotomy with clipping of the aneurysm has been the traditional treatment. More recently, coiling of the aneurysm has emerged as a less invasive option. Controversy exists regarding which option results in the best outcome (see Chapter 49). The largest randomized study comparing both treatment modalities found that endovascular coiling resulted in a lower risk for death at 5 years[71]; however, the risk for rebleeding was higher in the endovascular coiling group. The 2009 AHA guidelines suggested that "endovascular coiling can be beneficial." [72] Endovascular coiling has not been specifically studied in the pregnant population, although several cases of successful endovascular treatment of ruptured intracranial aneurysms in pregnant women have been reported.

Regardless of the treatment modality, it is crucial to secure the aneurysm as early as possible. Before the aneurysm is secured, blood pressure control should target a systolic blood pressure below 160 mm Hg.[73]

Delayed vasospasm is one of the most serious complications of subarachnoid hemorrhage. The onset is usually 4 to 10 days after the hemorrhage and manifests as worsening of the neurologic examination (either new focal symptoms or decreased level of consciousness). If a change in the neurologic status is noted, immediate CT should be performed to rule out rebleeding or hydrocephalus; if absent, vasospasm is likely. Vasospasm is confirmed with cerebral angiography. All patients should be treated with nimodipine (60 mg orally every 4 hours for 21 days) as prophylaxis against delayed-onset ischemia secondary to cerebral vasospasm. Other potential treatments to prevent delayed vasospasm include magnesium sulfate and statins.[74] However, a 2012 meta-analysis does not lend support to the efficacy of magnesium sulfate,[74] and statins should be avoided during pregnancy because of the potential risk for teratogenicity.

Once surgical or endovascular treatment is completed, blood pressure control may be less rigorous because hypertension may be a compensatory mechanism to maintain cerebral perfusion pressure in the setting of vasospasm. During pregnancy, extremely high blood pressure may lead to placental abruption and should be avoided.

Historically, patients presenting with symptomatic delayed cerebral vasospasm have been treated with "triple H therapy." Triple H therapy consists of inducing *hypervolemia* (through administration of crystalloids or colloids), leading to *hemodilution*, accompanied by induced *hypertension* (by using vasopressors) in an attempt to increase cerebral perfusion. Evidence of the efficacy of triple H therapy is extremely limited.[74] The use of hypervolemia and subsequent hemodilution may even be detrimental as a result of a decrease in arterial oxygen content.[75] Instead, many practitioners recommend induced hypertension with intravenous infusion of norepinephrine, phenylephrine, or dopamine and titration of systolic blood pressure to measurements higher than 180 mm Hg (MAP > 120 mm Hg). However, during pregnancy, the use of high-dose vasopressors to induce hypertension may lead to uteroplacental vasoconstriction and hypoperfusion and subsequent fetal demise. Additionally, the hypertension may increase the risk for placental abruption. Pregnant patients requiring induced hypertension for delayed vasospasm present a significant clinical dilemma. If the fetus is sufficiently mature (e.g., more than 32 weeks' gestation), it may be advisable to deliver the fetus before initiation of induced hypertension. If delivery is not an option, balloon angioplasty of the constricted vessels by an interventional radiologist may be considered.

Subarachnoid hemorrhage may also lead to extracerebral manifestations, the most common of which are hyponatremia, cardiac dysfunction, and neurogenic pulmonary edema. Hyponatremia occurs secondary to increased secretion of atrial and ventricular natriuretic peptides (cerebral salt wasting syndrome).[73] Treatment should focus on isotonic sodium replacement (0.9% saline) and diuresis. The massive liberation of catecholamines that accompanies subarachnoid hemorrhage is believed to cause subendocardial ischemia, leading to "cardiac stunning" with concomitant arrhythmias and decreased cardiac output. Patients may require inotropic support and antiarrhythmic therapy. Neurogenic pulmonary edema has both a hydrostatic component (from cardiac stunning and pulmonary venous constriction as a result of increased catecholamine secretion) and a noncardiogenic component (from endothelial injury owing to activation of the inflammatory cascade). Treatment of neurogenic pulmonary edema is supportive and requires low tidal volume ventilation strategies and the use of PEEP to improve oxygenation.

Subarachnoid hemorrhage may also occur secondary to rupture of brain **arteriovenous malformations**.[76] General intensive care provided to these patients is similar to that used in aneurysmal subarachnoid hemorrhage, with a few exceptions. The risk for vasospasm after subarachnoid hemorrhage from arteriovenous malformations is lower and rarely warrants therapy. Once removed (surgically), adjacent brain tissue will be exposed to increased cerebral blood flow leading to cerebral edema. Localized cerebral edema may be prevented by avoidance of severe hypertension. The decision to surgically treat a ruptured arteriovenous malformation is controversial and depends on the location and type of venous drainage (superficial or deep).[76] The risk for rebleeding during pregnancy is increased, and treatment (e.g., surgical resection, embolization) is commonly recommended.[77]

As with intracerebral hemorrhage in general, pregnant patients with subarachnoid hemorrhage should be normothermic and the maximum blood glucose level should be maintained between 140 and 180 mg/dL. Seizure prophylaxis in the setting of subarachnoid hemorrhage is controversial. Prolonged use of phenytoin has been associated with poor neurologic outcomes and should be

avoided.[78] A systematic review suggested that 3 days of seizure prophylaxis therapy provides similar seizure prevention with better outcomes compared with longer-term treatment.[78]

Status Epilepticus

Status epilepticus is defined as a continuous, generalized convulsive seizure lasting more than 5 minutes or two or more seizures with no return to baseline consciousness between the seizures.[79] Status epilepticus may be caused by noncompliance with antiepileptic medications, stroke, brain tumor, central nervous system infection, head trauma, metabolic derangements (e.g., uremia, hepatic encephalopathy, electrolyte abnormalities), cerebral hypoxia, and hypoglycemia/hyperglycemia. Rarely, eclamptic seizures may progress to status epilepticus.

Initial management should include protecting the airway and arresting the epileptic convulsions. Intravenous access should be obtained and hypoglycemia ruled out promptly. If in doubt, a 50-mL bolus of intravenous 50% dextrose with 100 mg of thiamine should be administered. Adequate hydration is of paramount importance because seizure-induced muscle breakdown may lead to myoglobin-induced kidney injury.[79] Initial pharmacologic therapy includes an intravenous benzodiazepine (e.g., lorazepam 0.1 mg/kg) followed by a standard intravenous antiepileptic agent (e.g., phenytoin). If intravenous access is difficult, intramuscular drug administration is an option. A recent study showed that intramuscular midazolam (10 mg) was at least as effective as intravenous lorazepam in the prehospital management of status epilepticus.[80] If seizure control is not achieved, a continuous infusion of propofol, midazolam, or a barbiturate may be required.[81] There is no agreement on the recommended EEG titration goal (burst suppression versus seizure control).[81] Many practitioners recommend 24 to 48 hours of seizure control documented by EEG before slowly weaning the infusion.

Acute Respiratory Distress Syndrome and Acute Lung Injury

Acute respiratory distress syndrome (ARDS) is a severe form of noncardiogenic pulmonary edema; it is a common cause of mortality in the critically ill obstetric patient. Traditionally, it has been defined as (1) pulmonary edema manifested on chest radiograph as bilateral acute infiltrates, (2) normal left ventricular function (pulmonary artery occlusion pressure [PAOP] below 18 mm Hg or normal heart function as determined by transthoracic echocardiography), and (3) a Pao_2/Fio_2 ratio below 200.[82] If the same conditions are present but the Pao_2/Fio_2 ratio is between 200 and 300, then the term *acute lung injury* (ALI) is used. The mortality rate from ARDS is approximately 40%.[83]

ALI/ARDS may occur secondary to a pulmonary or extrapulmonary pathologic process. The common denominator is activation of the inflammatory cascade, leading to inflammation-induced endothelial/epithelial injury in the lung with subsequent leaking of protein-rich fluid into the alveoli. Direct (pulmonary) insults that may lead to ALI/ARDS include pneumonia, aspiration pneumonitis, pulmonary contusion, and smoke inhalation during burns. Indirect (extrapulmonary) causes include sepsis, pancreatitis, trauma, and massive transfusion. Similar to the nonobstetric population, the most common cause of ARDS/ALI in pregnant women is sepsis.[84] Certain obstetric conditions (e.g., placental abruption, amniotic fluid embolism, preeclampsia) may also cause ALI/ARDS because these conditions are associated with inflammation and subsequent diffuse endothelial injury. Also, patients with severe placental abruption or amniotic fluid embolism complicated by DIC are at increased risk for massive transfusion of blood products.

Initial treatment for the patient with acute hypoxemic respiratory failure of noncardiac origin falls into ventilatory and nonventilatory strategies (Box 55-7).

BOX 55-7 Management Strategies in Patients with Acute Lung Injury/Acute Respiratory Distress Syndrome during Pregnancy

Ventilatory Strategies

- Lung-protective mechanical ventilation
  - Limit tidal volume to 6 to 8 mL/kg (lean body weight*). If possible, maintain $Paco_2 < 60$ mm Hg. Limit plateau pressures to 30 to 35 cm H_2O.
- Oxygenation goals
  - Maintain $Pao_2 \geq 55$ mm Hg and $Spo_2 \geq 88\%$ as long as the electronic FHR tracing is reassuring. A higher Pao_2 may be required in patients with nonreassuring fetal status.
- Provide adequate PEEP
  - Titrate according to oxygen requirements.
- Rescue therapies
  - Prone ventilation, extracorporeal membrane oxygenation, high-frequency oscillatory ventilation. airway pressure release ventilation, recruitment maneuvers.

Nonventilatory Strategies

- Limit fluid administration
  - Avoid excessive fluids, especially after the initial phase of resuscitation.
- Neuromuscular blockade
  - May consider early use of cisatracurium for 48 hours. Avoid coadministration of corticosteroids and aminoglycosides.
- Corticosteroids
  - Methylprednisolone 1 mg/kg bolus over 30 minutes followed by a continuous infusion of 1 mg/kg/day for 14 days. The dose is then decreased by half for 1 week, then decreased by half again for 4 days, and finally decreased by half one last time for 3 days.
- Inhaled prostacyclin/nitric oxide
  - Despite improvements in oxygenation, data on survival benefit are lacking. Avoid intravenous vasodilators (e.g., epoprostenol) because these drugs may worsen oxygenation by increasing the shunt fraction.

PEEP, positive end-expiratory pressure.
*Lean body weight in kilograms (females) = 45.5 + 0.91 (height in centimeters − 152.4).

Of vital importance, the underlying cause of the ARDS must be addressed simultaneously with institution of supportive measures (e.g., broad-spectrum antibiotics and surgical drainage if indicated in cases of sepsis-related ARDS; immediate delivery in patients with chorioamnionitis).

Ventilatory Strategies

The only intervention that has convincingly decreased mortality in ARDS is **lung-protective mechanical ventilation**.[85] ALI/ARDS is a heterogeneous disease in which some areas of the lung are affected (consolidated with edema) and others are not. During tidal volume delivery, gas flow is predominantly distributed to unaffected portions of the lung. If large tidal volumes are used, these "normal" areas of the lung are exposed to excessive volumes and pressures that lead to **volutrauma** and **barotrauma**, respectively. Overdistention of the lung provokes a local inflammatory response that further injures the lung parenchyma; locally produced inflammatory mediators (i.e., cytokines) may translocate to the systemic circulation and provoke worsening multiorgan failure (**biotrauma**).[86] If large tidal volumes are used with low PEEP, the constant opening and closing of the recruited alveoli (**atelectrauma**) will also worsen lung inflammation. These four insults (volutrauma, barotrauma, biotrauma, and atelectrauma) constitute what is known as **ventilator-induced lung injury**.[87]

In a randomized clinical trial involving 861 patients with ALI/ARDS, those randomized to receive mechanical ventilation with a small tidal volume (6 mL/kg lean body weight) and a limitation of plateau pressure to less than 30 cm H_2O had a mortality of 31% compared with 40% in the group randomized to receive a larger tidal volume (12 mL/kg lean body weight).[85] Since the publication of this trial in 2000, most intensivists have adopted strategies that limit tidal volumes to decrease ventilator-induced lung injury and improve outcomes in patients with ARDS. By limiting tidal volumes, minute ventilation is invariably decreased, leading to hypercarbia and respiratory acidemia. To improve minute ventilation, the operator may increase the respiratory rate up to 35 breaths per minute to maintain, ideally, an arterial pH above 7.3.[87]

Significant maternal hypercarbia may result in decreased removal of carbon dioxide from the fetus, leading to fetal acidemia. Tidal volumes from 6 to 8 mL/kg (lean body weight) can be used to ventilate pregnant women with ARDS; attempts should be made to maintain maternal $Paco_2$ below 60 mm Hg. Because of decreased compliance of the chest wall during pregnancy, plateau pressures of up to 35 cm H_2O may be tolerated. Continuous electronic FHR monitoring is recommended because abnormal FHR patterns may occur during periods of fetal acidemia.

The use of low tidal volumes to limit ventilator-induced lung injury must be accompanied by the use of adequate levels of PEEP to recruit alveolar units. A discussion of optimization of PEEP is beyond the scope of this chapter, but the reader may access FIO_2-PEEP tables that titrate PEEP according to oxygen requirements.[88] The oxygenation goal is to achieve a Pao_2 of at least 55 mm Hg or higher with an Sao_2 (as measured by pulse oximetry) of at least 88% or higher.[88] The use of high PEEP (levels up to 15 cm H_2O or higher) has been associated with decreased mortality in the subset of patients with the most severe forms of ARDS.[89]

Other ventilatory strategies that may be used in ARDS, but have not been associated with reduced mortality, include the use of recruitment maneuvers, airway pressure release ventilation, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation (ECMO), and prone ventilation.[88,90,91] When patients with ARDS are turned from the supine to the prone position, oxygenation often greatly improves, likely secondarily to anterior displacement of the heart with resultant recruitment of the posterior lung segments and improved ventilation-perfusion matching.[92] However, improved survival has not been documented.[93] A survival benefit may be gained in the subgroup of patients with the most severe forms of ARDS and if the periods of prone ventilation are extended to 12 to 20 hours per day.[94,95] Use of prone ventilation during the second half of pregnancy is obviously technically demanding (and may not be possible) because of the enlarged gravid uterus.

Nonventilatory Strategies

Nonventilatory strategies play an important role in the management of patients who suffer ALI/ARDS (see Box 55-7). The early use of neuromuscular blockade has recently been shown to improve survival in patients with ARDS.[96] A possible advantage of cisatracurium is its significant anti-inflammatory activity; the infusion should be limited to the first 48 hours of mechanical ventilation.[96] Pregnancy is not a contraindication to application of this treatment, if required.

Because ALI/ARDS occurs secondary to inflammation-mediated lung injury, interest has risen regarding the possible benefits of corticosteroid therapy. Theoretically, low-dose corticosteroids could be immunomodulatory (not immunosuppressive), leading to downregulation of excessive inflammation, and thus limiting acute lung injury.[97] Overall, published evidence indicates that low-dose corticosteroids reduce systemic inflammation, improve oxygenation, reduce multiorgan dysfunction, and decrease the duration of mechanical ventilation and ICU stay in patients with ALI/ARDS.[97] If used, low-dose corticosteroids (see Box 55-7) should be initiated before day 14 of the disease; after day 14, corticosteroid therapy is not recommended. The effect on survival is controversial, although some evidence suggests that corticosteroids decrease mortality in patients with ALI/ARDS.[98] Interestingly, the use of these low doses has not been associated with an increased risk for gastrointestinal hemorrhage, hyperglycemia, nosocomial infection, or myopathy.[97] If corticosteroids are used, the use of muscle relaxants should be avoided to prevent critical illness polyneuromyopathy. During pregnancy, the physician should consider the possible risk for fetal cleft lip (with and without cleft palate) associated with corticosteroid administration during the first trimester of pregnancy.[99]

Fluid Management. Management of fluid balance is fundamental in the care of patients with ALI/ARDS. A randomized trial found that conservative fluid management (mean fluid balance in the first 7 days, −136 mL) was associated with a shorter duration of mechanical ventilation and a shorter length of stay in the ICU than liberal fluid management (mean fluid balance, +6992 mL).[100] At the time of enrollment most patients had been fluid resuscitated and were hemodynamically stable. The incidence of adverse effects (e.g., shock, need for renal dialysis) did not differ between groups.

Fluid restriction in patients with ALI/ARDS is usually initiated on day 2 to 3 of the disease process; the first several days are commonly associated with hypotension and shock that invariably requires fluid resuscitation. Provided shock has resolved and vasopressors are not required to support blood pressure, fluids should be restricted to the amount required to maintain hemodynamic stability. Enteral feeding should be the main source of fluids in lieu of "maintenance fluids." If a diuretic is used to achieve a negative fluid balance, judicious use is recommended. Continuous electronic FHR monitoring is recommended to assess the adequacy of uteroplacental perfusion.

Right ventricular failure is a common occurrence in patients with ALI/ARDS. Alveolar "flooding" limits oxygenation with resultant hypoxic pulmonary vasoconstriction. The increase in pulmonary vascular resistances may lead to acute cor pulmonale and right ventricular failure, accompanied by a severe decrease in cardiac output (from both right-sided failure and left ventricular diastolic dysfunction). The administration of an inhaled pulmonary vasodilator such as nitric oxide or prostacyclin often leads to improved oxygenation and right ventricular function. However, there is no evidence that these interventions improve survival.[101] Pregnancy is not a contraindication for pulmonary vasodilator therapy. Pharmaconutritional therapy for ALI/ARDS (e.g., omega-3 fatty acids, linolenic acid, antioxidants) has not been shown to be beneficial and is not recommended.[102]

Nutrition and Glucose Control

Critically ill patients require nutrition to heal. Early aggressive enteral nutrition is of paramount importance and should be implemented within 24 to 48 hours of admission to the ICU.[103] Enteral nutrition (either through a nasogastric tube or a Dobhoff tube with the tip placed in the duodenum) helps maintain gut barrier integrity, thus preventing bacterial and cytokine translocation from the intestine. Enteral nutrition is generally preferred over parenteral nutrition because it is associated with less infectious morbidity and mortality. Enteral nutrition should be discontinued in patients requiring high doses of vasopressors because of a possible increase in the risk for bowel ischemia.[103]

The total amount of calories needed during critical illness is unknown.[104] More than 200 formulas exist to calculate daily energy requirements while in the ICU; many of these formulas coincide with a simple calculation of 25 Kcal/kg/day (ideal body weight).[103] An extra 300 Kcal/day should be added during pregnancy (500 Kcal/day in patients with multiple gestation). Overfeeding should be avoided because it may lead to fatty liver, volume overload, excessive carbon dioxide production, hyperglycemia, infection, and immunosuppression. Protein delivery should not be restricted, and critically ill patients should receive 1.2 to 2.0 g/kg/day of protein.[103] Most available enteral feeding formulas do not contain sufficient protein; it may be necessary to add additional protein to standard formulas.

Stress hyperglycemia refers to the elevation in blood glucose concentration associated with critical illness. Stress hyperglycemia is caused by multiple factors, including massive catecholamine release and systemic inflammation. Hyperglycemia is commonly worsened with initiation of nutritional support. Hyperglycemia worsens oxidative injury and potentiates inflammation and clotting. In 2001, a landmark paper suggested that tight glycemic control during critical illness (intravenous use of an insulin infusion to maintain blood glucose level between 80 and 110 mg/dL) was associated with (1) decreased mortality; (2) a lower incidence of sepsis, critical illness polyneuropathy, and liver injury; (3) reduced transfusion requirements; (4) fewer days of mechanical ventilation; and (5) a decreased need for renal replacement therapy.[105] These findings were not replicated in later studies; the largest available randomized controlled trial actually found that tight glucose control led to a 2.6% increase in mortality compared with less stringent glucose control. Maintaining blood glucose between 80 and 110 mg/dL commonly leads to episodes of iatrogenic hypoglycemia, which may worsen outcome. Current guidelines recommend a target blood glucose level between 140 and 180 mg/dL in ICU patients who are receiving insulin therapy.[70]

Transfusion Triggers

Most packed red blood cell (PRBC) transfusions in the ICU are used to treat anemia in hemodynamically stable patients who are not actively bleeding.[106] The efficacy of such an approach has not been demonstrated. Anemia in the critically ill patient commonly results from inflammation-induced inhibition of erythropoiesis and excessive phlebotomy.[106] Administration of PRBCs theoretically leads to an increase in arterial blood oxygen content, oxygen delivery, and, ultimately, oxygen consumption. Unfortunately, no clear evidence indicates that PRBC transfusions improve oxygen consumption.[107,108] During storage in the blood bank, red blood cells undergo a series of changes that include anomalies in the cytoskeleton, which hinders the red blood cells' capacity for deformability. As a result, transfusion of these rigid red blood cells may cause occlusion of the microvasculature and distal ischemia. These cells do not effectively release oxygen in the tissues because of a deficit in 2,3-diphosphoglycerate (2,3-DPG). Thus, oxygen-carrying capacity often is not improved by PRBC transfusion. In reality, significant risks are associated with transfusion of blood products in the ICU (Table 55-2).[109]

The largest published trial to date evaluating the role of PRBC transfusion in hemodynamically stable ICU patients found no difference in outcome between patients

TABLE 55-2 Potential Complications Associated with Transfusion of Blood Products

Transfusion-related acute lung injury (TRALI)	Noncardiogenic pulmonary edema that occurs within 6 hours of transfusion Risk higher after platelet and fresh frozen plasma transfusions Supportive treatment
Transfusion-related circulatory overload (TACO)	Hydrostatic pulmonary edema secondary to volume overload
Transfusion-related immunomodulation (TRIM)	After transfusion, decreased immunity with increased risk for nosocomial infections
Infectious complications	Viral (hepatitis B and C, HIV, cytomegalovirus, parvovirus B19, West Nile virus, human T-lymphotropic virus) or bacterial (*Staphylococcus* species, *E. coli, Pseudomonas* species, *Yersinia*) Bacterial infections more common
Febrile reactions	Secondary to leukocytes and cytokines accumulated during storage
Allergic nonhemolytic reactions	Urticaria and pruritus, secondary to soluble antigens in the donor plasma
Hemolytic reactions	Secondary to preexisting recipient alloantibodies against donor erythrocytes Sudden onset of fever and chills, pain, hypotension, dyspnea, renal injury, and DIC
Post-transfusion purpura	Purpura and bleeding manifestations after transfusion of blood products Usually seen in patients with antibodies that react against the human platelet antigen-1 from donor platelets Treat with intravenous immunoglobulin
Increased risk for multiorgan system failure	Likely secondary to cytokines contained in stored blood products
Graft-versus-host reaction	Lymphocytes transfused to patient not recognized as foreign but may react against host tissues, leading to pancytopenia, rashes, hepatitis, and diarrhea Mainly seen in patients with profound immunosuppression or in patients receiving blood products from close relatives who share human leukocyte antigens May be prevented with leukoreduction and gamma radiation of blood products.

DIC, disseminated intravascular coagulopathy; *HIV,* human immunodeficiency virus.
Modified from Gilliss BM, Looney MR, Gropper MA. Reducing noninfectious risks of blood transfusion. Anesthesiology 2011; 115:635-49.

randomized to a liberal transfusion strategy (transfuse to maintain hemoglobin above 10 g/dL) or a restrictive strategy (transfuse to maintain a hemoglobin > 7 g/dL).[110] A subgroup analysis revealed that mortality was *increased* with the liberal transfusion strategy in the subgroup of patients younger than 50 years old and with less severe disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score < 20). Based on these findings, most intensivists do not transfuse hemodynamically stable patients in the ICU until the hemoglobin level is less than 7 g/dL. (In patients with acute coronary syndrome, the threshold may be higher at 8 g/dL.[106]) Although each case should be individualized, it seems reasonable to apply these guidelines to critically ill pregnant patients. Fresh frozen plasma, cryoprecipitate, and platelets should not be transfused for the sole purpose of correcting laboratory measurements in patients who are not actively bleeding and are not undergoing an invasive procedure.

Sepsis

Sepsis occurs as the result of a maladaptive systemic inflammatory response to an infectious insult. It is the leading cause of mortality in ICUs in developed countries, and the incidence is increasing worldwide.[111] Sepsis is also one of the leading causes of maternal mortality.[112] The incidence of death from severe sepsis in obstetric patients is lower than that of nonobstetric patients. This likely reflects the fact that pregnant women are younger and have fewer coexisting medical pathologic processes.

Pregnancy affects both humoral and cell-mediated immunologic functions. The white blood cell count rises as pregnancy progresses, and some authors have described neutrophils in pregnant patients as "activated," thus favoring severe inflammatory reactions to infectious stimuli.[113] Cellular immunity is altered as a consequence of a decline in T-helper type 1 cell and natural killer cell function. The impaired cellular immunity may predispose pregnant women to infections from viruses and parasites. In contrast, antibody-mediated immunity is enhanced in pregnancy despite depressed levels of immunoglobulins (likely from hemodilution). Pregnancy is not a state of generalized immunosuppression; rather, it is a state of *immunomodulation* with compromised cellular and enhanced humoral immunity. Unfortunately, published information regarding the management of sepsis in pregnant women is limited; pregnant women typically have been excluded from large trials that have guided the evolution of the management of sepsis over the past several decades.

Definitions

Traditionally, *sepsis* has been defined as the presence of a **systemic inflammatory response syndrome** (SIRS) in

a patient with a defined or suspected infection. The concept of SIRS was introduced by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1992.[114] A patient is considered to have SIRS if two or more of the following criteria are present:

- Temperature greater than 38° C (100.4° F) or less than 36° C (96.8° F)
- Heart rate greater than 90 beats per minute
- Respiratory rate greater than 20 breaths per minute or a $Paco_2$ less than 32 mm Hg
- White blood cell count greater than 12,000/mm^3 or less than 4000/mm^3 or bandemia greater than 10%

Severe sepsis is defined as sepsis with signs of dysfunction of at least one organ (e.g., confusion, respiratory failure, acute kidney injury, thrombocytopenia, prolonged clotting times, elevated liver enzymes, hypotension). *Septic shock* is defined as severe sepsis with hypotension despite adequate fluid resuscitation, accompanied by a requirement for vasopressor therapy.

This definition of sepsis has been criticized for being too sensitive and nonspecific because most ICU patients will meet SIRS criteria.[115] Defining sepsis in pregnant patients is complicated by the fact that normal physiologic changes of pregnancy may include a heart rate above 90 beats per minute, a $Paco_2$ below 32 mm Hg, and a white blood cell count above 12,000/mm^3.

In 2001, extended criteria were developed to improve the diagnosis of sepsis by expanding the list of signs and symptoms of sepsis to reflect bedside clinical experience (Box 55-8).[115] These signs and symptoms serve as clinical guidelines; not every patient with sepsis will manifest these alterations, and some alterations may be present in nonseptic patients.

Pathophysiology

The pathophysiology of sepsis is complicated and not fully understood. After exposure to a microorganism (bacteria, virus, parasite, fungus), the inflammatory cascade is activated. Massive production and release of inflammatory (interleukin-1 beta [IL-1β], tumor necrosis factor-alpha [TNF-α], IL-6, IL-8) and anti-inflammatory (IL-4, IL-10) cytokines, endothelial factors (nitric oxide), and other mediators (prostaglandins, leukotrienes, complement) results in loss of vasomotor tone, profound vasodilation, and increased vascular permeability (secondary to cytokine-induced endothelial injury). Fluids subsequently move out of the vascular space, resulting in so-called third spacing.[111]

The profound decrease in systemic vascular resistance and accompanying tachycardia results in the so-called hyperdynamic state seen in septic patients. However, myocardial function is profoundly altered by the actions of nitric oxide, IL-1, oxygen-derived free radicals, and TNF-α. Up to 60% of patients with sepsis have an ejection fraction less than 45%. Both systolic and diastolic dysfunction may occur. Not infrequently, myocyte injury from proinflammatory cytokines may lead to leakage of troponins. Typically, patients with systolic dysfunction tend to present with biventricular dilation. This dilation appears to be an adaptive response that allows for increased intracavitary filling, leading to an increased stroke volume despite a decrease in ejection fraction (preload recruitment). These cardiac changes tend to resolve spontaneously among survivors of sepsis.

Almost all patients with severe sepsis have clotting abnormalities, ranging from asymptomatic changes to severe DIC.[116] Activation of the clotting cascade results from tissue factor production by macrocytes, neutrophils, and the endothelium as part of the inflammatory response. Tissue factor expressed in the surface of these cells binds factor VII, thus activating the clotting cascade. Excessive activation of the clotting cascade may lead to consumptive coagulopathy and the development of DIC. Development of DIC contributes to organ hypoperfusion (secondary to microvascular occlusion) and multiorgan system failure.

Natural anticoagulant proteins are often consumed in patients with severe sepsis[111]; alterations in protein C, antithrombin III, and plasminogen activator inhibitor have been described. Consumption of activated protein C has been associated with poor outcome in septic patients. Activated protein C is generated by thrombin-thrombomodulin–mediated protein C cleavage. Activated protein C, which inhibits clotting factors V and VIII, promotes fibrinolysis and has anti-inflammatory properties. Cytokines decrease the activity of thrombomodulin, leading to a lack of protein C activity during sepsis. Thus, the decline in activated protein C observed in severe sepsis results in amplified inflammation and a disruption in the normal balance between procoagulant and anticoagulant activity.

Mitochondrial dysfunction is also common in severe sepsis.[116] Even in the presence of adequate oxygen delivery, oxygen consumption cannot be guaranteed if the mitochondria are dysfunctional and cannot extract oxygen and use it in oxidative respiration. This pathologic process explains why patients with sepsis may have normal or above normal oxyhemoglobin saturation in the central or pulmonary circulation despite poor tissue oxygen utilization.

BOX 55-8 Signs and Symptoms Associated with Severe Sepsis

- Altered mental status
- Decreased capillary refill and skin mottling
- Fever or hypothermia
- Tachycardia
- Tachypnea
- Arterial hypotension
- Hypoxemia
- Significant edema or positive fluid balance
- Oliguria or elevated creatinine concentration
- Ileus and feeding intolerance
- Hyperglycemia
- Leukocytosis, leukopenia, or bandemia
- Elevated C-reactive protein or procalcitonin
- Thrombocytopenia and coagulation abnormalities
- Elevated liver enzyme levels
- Elevated blood lactate concentration

Management

Of pivotal importance in the management of sepsis is achieving early infection source control and instituting adequate antibiotic therapy and resuscitation. Infected fluid collections or tissues should be drained/excised if clinically indicated.[117] Broad-spectrum antibiotics should be initiated quickly (ideally after cultures have been obtained); narrow-spectrum antibiotic administration should follow once culture results are available.

Fluid Management. The cornerstone of resuscitation in sepsis is early **goal-directed fluid administration**. Classically, hemodynamic resuscitation in severe sepsis has been directed to achieve a MAP of 65 mm Hg. The placenta should be regarded as the maternal end organ that is most sensitive to hypoperfusion. For this reason, FHR decelerations are often the first sign of maternal hypoperfusion.

Early goal-directed fluid resuscitation improves tissue perfusion by increasing driving pressure and modulating early inflammation by decreasing concentrations of pro-inflammatory cytokines. The Surviving Sepsis Campaign guidelines recommend the use of either crystalloid or colloid for the early resuscitation of sepsis.[35,117] Crystalloids (normal saline, Ringer's lactate, Plasma-Lyte) have an intravascular half-life of 30 to 60 minutes compared with 16 hours for colloids such as albumin. Theoretically, the use of colloid leads to a more efficient resuscitation. The largest published trial comparing the use of crystalloids and colloids in critically ill patients found no difference in outcomes between groups.[35] However, a subgroup analysis suggested that patients with sepsis might benefit from albumin administration.[35] A 2011 systematic review and meta-analysis[118] found a small reduction in mortality in septic patients randomized to receive albumin rather than crystalloid for resuscitation (pooled estimate of the odds ratio, 0.82; 95% confidence interval, 0.62 to 1.0; $P = .047$). The authors suggested that additional study is required before a definitive conclusion can be made.[118]

Randomized trials (and a meta-analysis) that compared hydroxyethyl starch (e.g., 6% hetastarch solution) with crystalloid therapy in patients with severe sepsis found an increased incidence of 90-day mortality and an increased need for renal replacement therapy in the hydroxyethyl starch group.[119,120] Therefore, carbohydrate-based colloid solutions may not be the optimal choice for resuscitation of the septic patient.

One of the most challenging clinical decisions in daily critical care practice is the precise identification of adequate fluid resuscitation. Goal-directed fluid therapy (defined as "adjustments in cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand"[121]) is fundamental in the initial management of sepsis, but one must consider the endpoints of resuscitation. Premature initiation of vasopressors may be harmful because it will worsen tissue ischemia. On the other hand, excessive fluid resuscitation and a positive fluid balance have consistently been associated with increased mortality in critically ill patients. It appears that early in sepsis (the first 6 hours), patients benefit from goal-directed fluid therapy.[121] Later, a conservative fluid strategy may be beneficial. In a randomized trial, Rivers et al.[121] compared early goal-directed fluid therapy with standard care in patients with severe sepsis or septic shock. Goal-directed therapy consisted of early aggressive fluid resuscitation (central venous pressure [CVP] goal of 8 to 12 mm Hg), coupled with the use of vasopressors, inotropes, and blood transfusions to achieve a central venous oxygen saturation of greater than 70%. The in-hospital mortality was 30.5% in the goal-directed therapy group compared with 46.5% in the standard therapy group.[121]

A subsequent trial in patients with ALI or ARDS showed that *after* the initial phase of resuscitation, patients who were randomized to receive a conservative fluid regimen had improved lung function and a shorter duration of mechanical ventilation and ICU stay compared with patients who received a liberal fluid regimen.[100] The study did not have sufficient power to identify a difference in 60-day mortality.

Traditionally, clinicians have titrated fluid therapy to *static* measurements such as CVP or the PAOP. The Surviving Sepsis Campaign still recommends fluid therapy that targets a CVP between 8 to 12 mm Hg (12 to 15 mm Hg in the setting of mechanical ventilation).[117] This recommendation also likely applies to pregnant patients because neither CVP nor PAOP change during gestation. Unfortunately, static measurements of preload are less than ideal for predicting response to fluid administration. Echocardiographic-derived measurements provide further data on the adequacy of fluid resuscitation but suffer from the same limitations.

Current evidence supports the titration of fluid resuscitation to *dynamic* rather that static measurements of preload.[122] For example, an increase in stroke volume as assessed by transthoracic echocardiography during passive leg raising is an accurate predictor of response to fluid administration.[122] The validity of dynamic measures of preload during pregnancy requires investigation.

Vasopressors and Inotropes. When fluid therapy alone is unable to achieve a MAP above 60 to 65 mm Hg, vasopressors are commonly used. The vasopressors of choice in septic shock are **dopamine** and **norepinephrine**.[123] Norepinephrine increases blood pressure primarily by increasing systemic vascular resistance; dopamine's main effect is to increase stroke volume. Although most studies have not found one vasopressor to be clearly superior to others, a 2008 meta-analysis of randomized controlled and observational trials found that dopamine was associated with greater mortality and a higher incidence of arrhythmic events than norepinephrine.[124] Currently, it appears appropriate for the clinician to use the agent with which he or she is most familiar.

Obstetricians have traditionally expressed concern regarding the potential adverse effects of vasopressors on uteroplacental perfusion. However, in the setting of septic shock, restoration of maternal organ perfusion pressure is essential for fetal survival. Multiple case reports have described improved fetal status with the use of vasopressors to increase MAP.

Vasopressin is a peptide hormone synthesized in the hypothalamus and stored in the pituitary gland. A relative deficiency of vasopressin has been described during

septic shock. Vasopressin causes direct vascular smooth muscle constriction via stimulation of V_1 receptors. It also increases the response to catecholamines, likely by increasing cortisol secretion through its action on V_3 receptors in the pituitary gland. Additionally, vasopressin achieves vasoconstriction by closing ATP-dependent potassium channels. Observational studies have shown that the addition of low-dose vasopressin (0.04 U/min) to traditional vasopressor therapy can raise blood pressure in vasopressor-refractory septic shock. A large randomized clinical trial reported no difference in mortality in patients with vasopressor-dependent septic shock who were randomized to receive either vasopressin or norepinephrine in addition to open-label vasopressor therapy.[124] However, the trial did not address the use of vasopressin as rescue therapy for septic shock that is resistant to conventional vasopressors.

No good data exist regarding the use of vasopressin during septic shock in pregnant women. Theoretically, it may activate uterine V1a receptors, leading to uterine contractions. Extreme caution is recommended if this agent is used during pregnancy.

Contrary to popular belief, myocardial contractility is compromised in septic shock because TNF-α, IL-1, and nitric oxide lead to myocardial depression. Patients may develop both systolic and diastolic dysfunction, commonly involving both ventricles. In the subgroup of patients with mainly systolic dysfunction, the ventricles dilate to accommodate increased preload. This adaptive mechanism allows a transient increase in stroke volume and has been associated with improved outcomes. Patients with predominantly diastolic dysfunction do not usually develop this compensatory chamber dilation.

Septic cardiomyopathy may be "unmasked" when vasopressors are used to increase systemic vascular resistance. Assessment of cardiac output (e.g., bedside transthoracic echocardiography) is beneficial when vasopressors (primarily norepinephrine and vasopressin) are used without concomitant inotropic support. If worsening cardiac output is noted after initiating vasoconstrictor therapy, inotropic support (dobutamine or dopamine) may be beneficial.

Anecdotal data suggest that catecholamines may not be effective in patients with severe acidemia. However, data do not support the use of sodium bicarbonate therapy during resuscitation. In septic patients, bicarbonate therapy is not indicated if the pH is above 7.15.[117] If the pH is less than 7.15, the use of sodium bicarbonate should be individualized. Particular care should be taken if the clinician chooses to use bicarbonate during pregnancy because bicarbonate does not cross the placenta, but the carbon dioxide generated from its administration crosses the placenta to the fetal compartment, leading to potential fetal acidemia.

Corticosteroids. Approximately 50% to 75% of patients with severe sepsis/septic shock have **critical illness–related corticosteroid insufficiency**. Cytokines lead to a dysfunctional hypothalamic-pituitary-adrenal axis with a consequent decrease in cortisol secretion. Cortisol plays a pivotal role in the up-regulation of catecholamine receptors at the vascular level (leading to an increased response to endogenous and exogenous catecholamines).

The use of corticosteroid therapy in patients with septic shock has long been controversial. In the past, large doses of corticosteroids were used; however, evidence suggested that the use of high-dose corticosteroids in patients with sepsis/septic shock may be harmful. Studies performed in the past decade suggest that low-dose corticosteroids (hydrocortisone ≤ 300 mg/day) may be beneficial.[125] Currently, physiologic doses of corticosteroids are recommended in patients who fail to respond to catecholamine therapy.[125] Patients who receive vasopressors and are unable to maintain a systolic blood pressure above 90 mm Hg are candidates for corticosteroid therapy.[125] The agent of choice is hydrocortisone (50 mg bolus intravenously every 6 hours or a continuous intravenous infusion at 10 mg/h). This low dose of glucocorticoid is believed to be immunomodulatory; the excessive immune response that leads to shock is down-regulated without causing immunosuppression. Once begun, treatment should be maintained for at least 4 to 7 days, and the dose should be tapered over 1 week to avoid rebound inflammation and shock. The adrenocorticotropic hormone (ACTH) stimulation test should not be used to identify patients with septic shock who should receive glucocorticoids. The same guidelines are applied during pregnancy to decide who might benefit from corticosteroid therapy. The clinician should be cognizant of the possible association between corticosteroid use during the first trimester of pregnancy and the development of fetal cleft lip and palate.[99]

Monitoring Resuscitation. Traditionally, the main goal of resuscitation efforts in sepsis has been to achieve "normal" vital signs (MAP greater than 65 mm Hg, urine output greater than 0.5 mL/kg/h, normal heart rate).[117] Unfortunately, clinical signs and symptoms lack sensitivity for detection of tissue hypoperfusion. Patients may have normal vital signs and still have organ hypoperfusion and anaerobic metabolism. Different strategies have been proposed to detect these patients with "occult shock." Resuscitation may be guided by blood lactate levels. Patients with persistent lactic acidosis, despite apparently normal vital signs, may require further resuscitation to increase tissue oxygen delivery.

Another option is to optimize hemodynamic support using central ($Sc\bar{v}O_2$) and mixed venous ($S\bar{v}O_2$) oxyhemoglobin saturation monitoring. $S\bar{v}O_2$ is the saturation of hemoglobin obtained from blood sampled from the pulmonary artery. It requires placement of a pulmonary artery catheter; a normal value is greater than 65%. Pregnancy *per se* does not alter the $S\bar{v}O_2$.[126]

$Sc\bar{v}O_2$ is the oxyhemoglobin saturation of a blood sample obtained from the junction of the superior vena cava and the right atrium. This measurement is readily achieved by obtaining a blood sample from a central venous catheter. The normal value is greater than 70%. To our knowledge, normal values for $Sc\bar{v}O_2$ during pregnancy have not been described. Patients with tissue hypoperfusion will extract more oxygen in an attempt to increase aerobic metabolism. The increased extraction will lead to a decrease in the oxygen saturation of

hemoglobin returning to the central circulation. Low values of either $S\bar{v}O_2$ or $Sc\bar{v}O_2$ may warrant an attempt to increase oxygen delivery by volume expansion, blood transfusion, or the use of an inotrope.

The Fetus during Critical Maternal Illness

In the vast majority of cases, therapeutic interventions in the critically ill pregnant patient should not be withheld because of fetal concerns. When the alternative is death or severe injury, very few drugs or diagnostic or therapeutic maneuvers are contraindicated. Most medications (sedatives, neuromuscular blocking agents, corticosteroids, vasopressors, inotropes, antibiotics) may be used safely (or with minimal risks that are commonly outweighed by the benefits) during pregnancy. Some of the common agents used in the ICU setting, and the associated fetal risks, are listed in Table 55-3.

Imaging studies should be performed as needed with the use of abdominal shielding to limit fetal radiation exposure. When possible, ultrasonography and magnetic resonance imaging (MRI) are preferred because no ionizing radiation is used. Radiation exposure from common studies, such as a chest or abdominal radiography or CT of the head or chest, are all below the upper limit of safety (5 rads) recommended by the American College of Obstetricians and Gynecologists (ACOG).[57] Similarly, the use of radiopaque (iodide containing) or paramagnetic contrast media during pregnancy is acceptable, provided the study is considered fundamental to the care of the patient.[57]

Critically ill pregnant patients should receive continuous electronic FHR monitoring after 24 weeks' gestation (lower age limit of viability) to continuously evaluate fetal well-being. The presence of fetal bradycardia, tachycardia, or persistent FHR decelerations may signal uterine hypoperfusion that requires improved resuscitation

TABLE 55-3 **Common Medications Used during Critical Illness**

Medication	FDA Pregnancy Category*	Comments
Norepinephrine	C	Uterine vessels are very sensitive to vasoconstriction because they are rich in alpha-adrenergic receptors. As with any vasopressor, this agent may be used after adequate volume resuscitation and with continuous electronic FHR monitoring. Recent evidence suggests that norepinephrine may be the vasopressor of choice during sepsis.
Dopamine	C	Many clinicians are more familiar with the use of dopamine as a vasopressor in sepsis during pregnancy. Dopamine is associated with more tachyarrhythmias than norepinephrine. As with norepinephrine, it should be used after adequate fluid resuscitation and with continuous electronic FHR monitoring.
Vasopressin	C	Low doses used for the treatment of diabetes insipidus have not been associated with fetal harm. No data exist on its use as a continuous infusion for septic shock in pregnancy. Potentially, vasopressin may lead to activation of V1a receptors and uterine contractions; thus, extreme caution is recommended if used during pregnancy. Continuous electronic FHR monitoring is highly desirable.
Dobutamine	B	
Milrinone	C	
Phenylephrine	C	
Epinephrine	C	
Hydrocortisone	C	Some data suggest an association between corticosteroid use during the first trimester and fetal cleft lip/palate. However, if required to improve maternal outcomes, use should not be deferred.
Midazolam	D	No clear correlation between the use of midazolam and fetal anomalies has been described. Use of any sedative close to the time of delivery is associated with neonatal depression.
Lorazepam	D	Limited data have associated prolonged use with fetal anomalies. It is unlikely that its use during a few days of critical illness outside the first trimester is teratogenic.
Propofol	B	
Dexmedetomidine	C	This agent crosses the placenta, but no published studies link dexmedetomidine to fetal malformations.
Cisatracurium	B	May have anti-inflammatory properties
Vecuronium	C	
Morphine	C	
Fentanyl	C	
Hydromorphone	C	
Haloperidol	C	

FHR, fetal heart rate.
*U.S. Food and Drug Administration (FDA) pregnancy category (see Box 14-1).

efforts. Each case should be evaluated individually with the aid of a maternal-fetal medicine specialist. Pregnant women beyond 20 weeks' gestation should be positioned either in the left or right decubitus position to avoid uterine compression of the inferior vena cava, which results in a decrease in cardiac preload.

KEY POINTS

- Trauma is the most common nonobstetric cause of maternal death.
- Head injury and hemorrhagic shock are the most common causes of death in the pregnant trauma victim.
- Even minor trauma increases the risk for placental abruption and preterm labor.
- Resuscitation of the critically ill or injured obstetric patient should be based on the premise that optimized maternal resuscitation will be most beneficial to the fetus.
- Care of the pregnant trauma patient should be based on Advanced Trauma Life Support principles. Additional attention should be given to complications that are specific to pregnancy, such as uterine rupture and placental abruption.
- In addition to standard Advanced Cardiac Life Support guidelines, considerations for resuscitation of the pregnant patient include maintenance of left uterine displacement and evacuation of the uterus. If spontaneous circulation does not return within 4 minutes of cardiac arrest, immediate hysterotomy or cesarean delivery should be performed if the gestational age is 20 weeks or greater, aiming for delivery within 5 minutes of cardiac arrest.
- Neurologic emergencies during pregnancy require prompt intensive care to avoid secondary brain injury due to hypoxia, hypercarbia, seizures, hyponatremia, hyperglycemia, and rebleeding episodes.
- Patients with acute lung injury should receive lung-protective mechanical ventilation. When possible, excessive fluid administration should be avoided.
- Early enteral nutrition and glucose control are basic tenants of contemporary critical care.
- Transfusion of blood products in critically ill patients should follow a restrictive strategy.
- Prompt diagnosis, infection source control, adequate antibiotic therapy, and goal-directed fluid resuscitation are fundamental principles of the early management of sepsis.
- Fetal heart rate monitoring is indicated in pregnant trauma victims and critically ill obstetric patients beginning at 24 weeks' gestation; altered fetal heart rate patterns can serve as a valuable indicator of inadequate resuscitation.

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APPENDIX A

American Society of Anesthesiologists Guidelines for Neuraxial Anesthesia in Obstetrics*

COMMITTEE OF ORIGIN: OBSTETRICAL ANESTHESIA

These guidelines apply to the use of neuraxial anesthesia and labor anesthesia or analgesia in which local anesthetics are administered to the parturient during labor and delivery. They are intended to encourage quality patient care but cannot guarantee any specific patient outcome. Because the availability of anesthesia resources may vary, members are responsible for interpreting and establishing the guidelines for their own institutions and practices. These guidelines are subject to revision from time to time as warranted by the evolution of technology and practice.

GUIDELINE I
NEURAXIAL ANESTHESIA SHOULD BE INITIATED AND MAINTAINED ONLY IN LOCATIONS IN WHICH APPROPRIATE RESUSCITATION EQUIPMENT AND DRUGS ARE IMMEDIATELY AVAILABLE TO MANAGE PROCEDURALLY RELATED PROBLEMS.

Resuscitation equipment should include, but is not limited to: sources of oxygen and suction, equipment to maintain an airway and perform endotracheal intubation, a means to provide positive pressure ventilation, and drugs and equipment for cardiopulmonary resuscitation.

GUIDELINE II
NEURAXIAL ANESTHESIA SHOULD BE INITIATED BY A PHYSICIAN WITH APPROPRIATE PRIVILEGES AND MAINTAINED BY OR UNDER THE MEDICAL DIRECTION[1] OF SUCH AN INDIVIDUAL.

Physicians should be approved through the institutional credentialing process to initiate and direct the maintenance of obstetric anesthesia and to manage procedurally related complications.

GUIDELINE III
NEURAXIAL ANESTHESIA SHOULD NOT BE ADMINISTERED UNTIL: 1) THE PATIENT HAS BEEN EXAMINED BY A QUALIFIED INDIVIDUAL[2]; AND 2) A PHYSICIAN WITH OBSTETRICAL PRIVILEGES TO PERFORM OPERATIVE VAGINAL OR CESAREAN DELIVERY, WHO HAS KNOWLEDGE OF THE MATERNAL AND FETAL STATUS AND THE PROGRESS OF LABOR AND WHO APPROVED THE INITIATION OF LABOR ANESTHESIA, IS READILY AVAILABLE TO SUPERVISE THE LABOR AND MANAGE ANY OBSTETRIC COMPLICATIONS THAT MAY ARISE.

Under circumstanced defined by department protocol, qualified personnel may perform the initial pelvic examination. The physician responsible for the patient's obstetrical care should be informed of her status so that a decision can be made regarding present risk and further management.[2]

GUIDELINE IV
AN INTRAVENOUS INFUSION SHOULD BE ESTABLISHED BEFORE THE INITIATION OF NEURAXIAL ANESTHESIA AND MAINTAINED THROUGHOUT THE DURATION OF THE NEURAXIAL ANESTHETIC.

GUIDELINE V
NEURAXIAL ANESTHESIA FOR LABOR AND/OR VAGINAL DELIVERY REQUIRES THAT THE

*Approved by the ASA House of Delegates on October 12, 1988, and last amended on October 12, 2010.

[1]The Anesthesia Care Team (Approved by ASA House of Delegates 10/26/82 and last amended 10/18/2006).

[2]American Academy of Pediatrics and American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care, 5th Edition. Elk Grove Village, IL: AAP; Washington, DC: ACOG, 2002.

PARTURIENT'S VITAL SIGNS AND THE FETAL HEART RATE BE MONITORED AND DOCUMENTED BY A QUALIFIED INDIVIDUAL. ADDITIONAL MONITORING APPROPRIATE TO THE CLINICAL CONDITION OF THE PARTURIENT AND THE FETUS SHOULD BE EMPLOYED WHEN INDICATED. WHEN EXTENSIVE NEURAXIAL BLOCKADE IS ADMINISTERED FOR COMPLICATED VAGINAL DELIVERY, THE STANDARDS FOR BASIC ANESTHETIC MONITORING[3] *SHOULD BE APPLIED.*

GUIDELINE VI

NEURAXIAL ANESTHESIA FOR CESAREAN DELIVERY REQUIRES THAT THE STANDARDS FOR BASIC ANESTHETIC MONITORING[3] *BE APPLIED AND THAT A PHYSICIAN WITH PRIVILEGES IN OBSTETRICS BE IMMEDIATELY AVAILABLE.*

GUIDELINE VII

QUALIFIED PERSONNEL, OTHER THAN THE ANESTHESIOLOGIST ATTENDING THE MOTHER, SHOULD BE IMMEDIATELY AVAILABLE TO ASSUME THE RESPONSIBILITY FOR RESUSCITATION OF THE NEWBORN.[3]

The primary responsibility of the anaesthesiologist is to provide care to the mother. If the anesthesiologist is also requested to provide brief assistance in the care of the newborn, the benefit to the child must be compared to the risk to the mother.

GUIDELINE VIII

A PHYSICIAN WITH APPROPRIATE PRIVILEGES SHOULD REMAIN READILY AVAILABLE DURING THE NEURACIAL ANESTHETIC TO MANAGE ANESTHETIC COMPLICATIONS UNTIL THE PATIENT'S POSTANESTHESIA CONDITION IS SATISFACTORY AND STABLE.

GUIDELINE IX

ALL PATIENTS RECOVERING FROM NEURAXIAL ANESTHESIA SHOULD RECEIVE APPROPRIATE POSTANESTHESIA CARE. FOLLOWING CESAREAN DELIVERY AND/OR EXTENSIVE NEURAXIAL BLOCKADE, THE STANDARDS FOR POST-ANESTHESIA CARE[4] *SHOULD BE APPLIED.*

GUIDELINE X

THERE SHOULD BE A POLICY TO ASSURE THE AVAILABILITY IN THE FACILITY OF A PHYSICIAN TO MANAGE COMPLICATIONS AND TO PROVIDE CARDIOPULMONARY RESUSCITATION FOR PATIENTS RECEIVING POSTANESTHESIA CARE.

[3]Standards for Basic Anesthetic Monitoring (Approved by ASA House of Delegates 10/21/86 and last amended 10/25/2005).

[4]Standards for Postanesthesia Care (Approved by ASA House of Delegates 10/12/88 and last amended 10/27/04).

Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia*

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints and are not intended to replace local institutional policies. In addition, practice guidelines are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome. Practice guidelines are subject to revision as warranted by the evolution of medical knowledge, technology, and practice. They provide basic recommendations that are supported by a synthesis and analysis of the current literature, expert opinion, open forum commentary, and clinical feasibility data.

This update includes data published since the "Practice Guidelines for Obstetrical Anesthesia" were adopted by the American Society of Anesthesiologists in 1998; it also includes data and recommendations for a wider range of techniques than was previously addressed.

*Excerpted from Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology 2007; 106:843-63. A copy of the full text can be obtained from American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068-2573.

Developed by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia: Joy L. Hawkins, MD (Chair), Denver, Colorado; James F. Arens, MD, Houston, Texas; Brenda A. Bucklin, MD, Denver, Colorado; Richard T. Connis, PhD, Woodinville, Washington; Patricia A. Dailey, MD, Hillsborough, California; David R. Gambling, MBBS, San Diego, California; David G. Nickinovich, PhD, Bellevue, Washington; Linda S. Polley, MD, Ann Arbor, Michigan; Lawrence C. Tsen, MD, Boston, Massachusetts; David J. Wlody, MD, Brooklyn, New York; and Kathryn J. Zuspan, MD, Stillwater, Minnesota.

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Methodology

A. Definition of Perioperative Obstetric Anesthesia

For the purposes of these Guidelines, *obstetric anesthesia* refers to peripartum anesthetic and analgesic activities performed during labor and vaginal delivery, cesarean delivery, removal of retained placenta, and postpartum tubal ligation.

B. Purposes of the Guidelines

The purposes of these Guidelines are to enhance the quality of anesthetic care for obstetric patients, improve patient safety by reducing the incidence and severity of anesthesia-related complications, and increase patient satisfaction.

C. Focus

These Guidelines focus on the anesthetic management of pregnant patients during labor, nonoperative delivery, operative delivery, and selected aspects of postpartum care and analgesia (*i.e.*, neuraxial opioids for postpartum analgesia after neuraxial anesthesia for cesarean delivery). The intended patient population includes, but is not limited to, intrapartum and postpartum patients with uncomplicated pregnancies or with common obstetric problems. The Guidelines do not apply to patients undergoing surgery during pregnancy, gynecologic patients, or parturients with chronic medical disease (*e.g.*, severe cardiac, renal, or neurologic disease). In addition, these Guidelines do not address (1) postpartum analgesia for vaginal delivery, (2) analgesia after tubal ligation, or (3) postoperative analgesia after general anesthesia (GA) for cesarean delivery.

D. Application

These Guidelines are intended for use by anesthesiologists. They also may serve as a resource for other

anesthesia providers and healthcare professionals who advise or care for patients who will receive anesthetic care during labor, delivery, and the immediate postpartum period.

E. Task Force Members and Consultants

The American Society of Anesthesiologists (ASA) appointed a Task Force of 11 members to (1) review the published evidence, (2) obtain the opinion of a panel of consultants including anesthesiologists and nonanesthesiologist physicians concerned with obstetric anesthesia and analgesia, and (3) obtain opinions from practitioners likely to be affected by the Guidelines. The Task Force included anesthesiologists in both private and academic practices from various geographic areas of the United States and two consulting methodologists from the ASA Committee on Standards and Practice Parameters.

The Task Force developed the Guidelines by means of a seven-step process. First, they reached consensus on the criteria for evidence. Second, original published research studies from peer-reviewed journals relevant to obstetric anesthesia were reviewed. Third, the panel of expert consultants was asked to (1) participate in opinion surveys on the effectiveness of various peripartum management strategies and (2) review and comment on a draft of the Guidelines developed by the Task Force. Fourth, opinions about the Guideline recommendations were solicited from active members of the ASA who provide obstetric anesthesia. Fifth, the Task Force held open forums at two major national meetings[†] to solicit input on its draft recommendations. Sixth, the consultants were surveyed to assess their opinions on the feasibility of implementing the Guidelines. Seventh, all available information was used to build consensus within the Task Force to finalize the Guidelines (Appendix 1).

F. Availability and Strength of Evidence

Preparation of these Guidelines followed a rigorous methodologic process. To convey the findings in a concise and easy-to-understand fashion, these Guidelines use several descriptive terms. When sufficient numbers of studies are available for evaluation, the following terms describe the strength of the findings.

Support: Meta-analysis of a sufficient number of randomized controlled trials[‡] indicates a statistically significant relationship ($P < .01$) between a clinical intervention and a clinical outcome.

Suggest: Information from case reports and observational studies permits inference of a relationship between an intervention and an outcome. A meta-analytic assessment of this type of qualitative or descriptive information is not conducted.

Equivocal: Either a meta-analysis has not found significant differences among groups or conditions, or there is insufficient quantitative information to conduct a meta-analysis and information collected from case reports and observational studies does not permit inference of a relationship between an intervention and an outcome.

The *lack* of scientific evidence in the literature is described by the following terms.

Silent: No identified studies address the specified relationship between an intervention and outcome.

Insufficient: There are too few published studies to investigate a relationship between an intervention and outcome.

Inadequate: The available studies cannot be used to assess the relationship between an intervention and an outcome. These studies either do not meet the criteria for content as defined in the Focus section of these Guidelines, or do not permit a clear causal interpretation of findings due to methodologic concerns.

Formal survey information is collected from consultants and members of the ASA. The following terms describe survey responses for any specified issue. Responses are solicited on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree), with a score of 3 being equivocal. Survey responses are summarized based on median values as follows:

Strongly Agree: Median score of 5 (at least 50% of the responses are 5).

Agree: Median score of 4 (at least 50% of the responses are 4 or 4 and 5).

Equivocal: Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contain at least 50% of the responses).

Disagree: Median score of 2 (at least 50% of the responses are 2 or 1 and 2).

Strongly Disagree: Median score of 1 (at least 50% of the responses are 1).

Guidelines

I. Perianesthetic Evaluation

History and Physical Examination. Although comparative studies are insufficient to evaluate the peripartum impact of conducting a focused history (*e.g.*, reviewing medical records) or a physical examination, the literature reports certain patient or clinical characteristics that may be associated with obstetric complications. These characteristics include, but are not limited to, preeclampsia, pregnancy-related hypertensive disorders, HELLP syndrome, obesity, and diabetes.

The consultants and ASA members both strongly agree that a directed history and physical examination, as well as communication between anesthetic and obstetric providers, reduces maternal, fetal, and neonatal complications.

Recommendations. The anesthesiologist should conduct a focused history and physical examination before

[†]International Anesthesia Research Society, 80th Clinical and Scientific Congress, San Francisco, California, March 25, 2006; and Society of Obstetric Anesthesia and Perinatology 38th Annual Meeting, Hollywood, Florida, April 29, 2006

[‡]A prospective nonrandomized controlled trial may be included in a metaanalysis under certain circumstances if specific statistical criteria are met.

providing anesthesia care. This should include, but is not limited to, a maternal health and anesthetic history, a relevant obstetric history, a baseline blood pressure measurement, and an airway, heart, and lung examination, consistent with the ASA "Practice Advisory for Preanesthesia Evaluation."[§] When a neuraxial anesthetic is planned or placed, the patient's back should be examined.

Recognition of significant anesthetic or obstetric risk factors should encourage consultation between the obstetrician and the anesthesiologist. A communication system should be in place to encourage early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team.

Intrapartum Platelet Count. The literature is insufficient to assess whether a routine platelet count can predict anesthesia-related complications in uncomplicated parturients. The literature suggests that a platelet count is clinically useful for parturients with suspected pregnancy-related hypertensive disorders, such as preeclampsia or HELLP syndrome, and for other disorders associated with coagulopathy.

The ASA members are equivocal, but the consultants agree that obtaining a routine intrapartum platelet count does *not* reduce maternal anesthetic complications. Both the consultants and ASA members agree that, for patients with suspected preeclampsia, a platelet count reduces maternal anesthetic complications. The consultants strongly agree and the ASA members agree that a platelet count reduces maternal anesthetic complications for patients with suspected coagulopathy.

Recommendations. A specific platelet count predictive of neuraxial anesthetic complications has not been determined. The anesthesiologist's decision to order or require a platelet count should be individualized and based on a patient's history, physical examination, and clinical signs. A routine platelet count is not necessary in the healthy parturient.

Blood Type and Screen. The literature is insufficient to determine whether obtaining a blood type and screen is associated with fewer maternal anesthetic complications. In addition, the literature is insufficient to determine whether a blood cross-match is necessary for healthy and uncomplicated parturients. The consultants and ASA members agree that an intrapartum blood sample should be sent to the blood bank for all parturients.

Recommendations. A routine blood cross-match is not necessary for healthy and uncomplicated parturients for vaginal or operative delivery. The decision whether to order or require a blood type and screen, or cross-match, should be based on maternal history, anticipated hemorrhagic complications (*e.g.*, placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies.

Perianesthetic Recording of the Fetal Heart Rate. The literature suggests that anesthetic and analgesic agents may influence the fetal heart rate pattern. There is insufficient literature to demonstrate that perianesthetic recording of the fetal heart rate prevents fetal or neonatal complications. Both the consultants and ASA members agree, however, that perianesthetic recording of the fetal heart rate reduces fetal and neonatal complications.

Recommendations. The fetal heart rate should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor. The Task Force recognizes that *continuous* electronic recording of the fetal heart rate may not be necessary in every clinical setting and may not be possible during initiation of neuraxial anesthesia.

II. Aspiration Prevention

Clear Liquids. There is insufficient published evidence to draw conclusions about the relationship between fasting times for clear liquids and the risk of emesis/reflux or pulmonary aspiration during labor. The consultants and ASA members both agree that oral intake of clear liquids during labor improves maternal comfort and satisfaction. Although the ASA members are equivocal, the consultants agree that oral intake of clear liquids during labor *does not* increase maternal complications.

Recommendations. The oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients. The uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sports drinks. The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested. However, patients with additional risk factors for aspiration (*e.g.*, morbid obesity, diabetes, difficult airway) or patients at increased risk for operative delivery (*e.g.*, nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

Solids. A specific fasting time for solids that is predictive of maternal anesthetic complications has not been determined. There is insufficient published evidence to address the safety of *any* particular fasting period for solids in obstetric patients. The consultants and ASA members both agree that the oral intake of solids during labor increases maternal complications. They both strongly agree that patients undergoing either elective cesarean delivery or postpartum tubal ligation should undergo a fasting period of 6-8 h depending on the type of food ingested (*e.g.*, fat content).[‖] The Task Force recognizes that in laboring patients the timing of delivery is uncertain; therefore, compliance with a predetermined fasting period before nonelective surgical procedures is not always possible.

[§]American Society of Anesthesiologists Task Force on Preanesthesia Evaluation: Practice advisory for preanesthesia evaluation. Anesthesiology 2002; 96:485–96.

[‖]American Society of Anesthesiologists Task Force on Preoperative Fasting: Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration. Anesthesiology 1999; 90:896–905.

Recommendations. Solid foods should be avoided in laboring patients. The patient undergoing elective surgery (*e.g.*, scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6-8 h depending on the type of food ingested (*e.g.*, fat content).[ll]

Antacids, H_2 Receptor Antagonists, and Metoclopramide. The literature does not sufficiently examine the relationship between reduced gastric acidity and the frequency of emesis, pulmonary aspiration, morbidity, or mortality in obstetric patients who have aspirated gastric contents. Published evidence supports the efficacy of preoperative nonparticulate antacids (*e.g.*, sodium citrate, sodium bicarbonate) in decreasing gastric acidity during the peripartum period. However, the literature is insufficient to examine the impact of nonparticulate antacids on gastric volume. The literature suggests that H_2 receptor antagonists are effective in decreasing gastric acidity in obstetric patients and supports the efficacy of metoclopramide in reducing peripartum nausea and vomiting. The consultants and ASA members agree that the administration of a nonparticulate antacid before operative procedures reduces maternal complications.

Recommendations. Before surgical procedures (*i.e.*, cesarean delivery, postpartum tubal ligation), practitioners should consider the timely administration of nonparticulate antacids, H_2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis.

III. Anesthetic Care for Labor and Vaginal Delivery

Overview. Not all women require anesthetic care during labor or delivery. For women who request pain relief for labor and/or delivery, there are many effective analgesic techniques available. Maternal request represents sufficient justification for pain relief. In addition, maternal medical and obstetric conditions may warrant the provision of neuraxial techniques to improve maternal and neonatal outcome.

The choice of analgesic technique depends on the medical status of the patient, progress of labor, and resources at the facility. When sufficient resources (*e.g.*, anesthesia and nursing staff) are available, neuraxial catheter techniques should be one of the analgesic options offered. The choice of a specific neuraxial block should be individualized and based on anesthetic risk factors, obstetric risk factors, patient preferences, progress of labor, and resources at the facility.

When neuraxial catheter techniques are used for analgesia during labor or vaginal delivery, the primary goal is to provide adequate maternal analgesia with minimal motor block (*e.g.*, achieved with the administration of local anesthetics at low concentrations with or without opioids).

When a neuraxial technique is chosen, appropriate resources for the treatment of complications (*e.g.*, hypotension, systemic toxicity, high spinal anesthesia) should be available. If an opioid is added, treatments for related complications (*e.g.*, pruritus, nausea, respiratory depression) should be available. An intravenous infusion should be established before the initiation of neuraxial analgesia or anesthesia and maintained throughout the duration of the neuraxial analgesic or anesthetic. However, administration of a fixed volume of intravenous fluid is not required before neuraxial analgesia is initiated.

Timing of Neuraxial Analgesia and Outcome of Labor. Meta-analysis of the literature determined that the timing of neuraxial analgesia does not affect the frequency of cesarean delivery. The literature also suggests that other delivery outcomes (*i.e.*, spontaneous or instrumented) are also unaffected. The consultants strongly agree and the ASA members agree that early initiation of epidural analgesia (*i.e.*, at cervical dilations of less than 5 cm vs. equal to or greater than 5 cm) improves analgesia. They both *disagree* that motor block or maternal, fetal, or neonatal side effects are increased by early administration.

Recommendations. Patients in early labor (*i.e.*, < 5 cm dilation) should be given the option of neuraxial analgesia when this service is available. Neuraxial analgesia should not be withheld on the basis of achieving an arbitrary cervical dilation, and should be offered on an individualized basis. Patients may be reassured that the use of neuraxial analgesia does not increase the incidence of cesarean delivery.

Neuraxial Analgesia and Trial of Labor after Previous Cesarean Delivery. Nonrandomized comparative studies suggest that epidural analgesia may be used in a trial of labor for previous cesarean delivery patients without adversely affecting the incidence of vaginal delivery. Randomized comparisons of epidural *versus* other anesthetic techniques were not found. The consultants and ASA members agree that neuraxial techniques improve the likelihood of vaginal delivery for patients attempting vaginal birth after cesarean delivery.

Recommendations. Neuraxial techniques should be offered to patients attempting vaginal birth after previous cesarean delivery. For these patients, it is also appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia, or for anesthesia in the event of operative delivery.

Early Insertion of a Spinal or Epidural Catheter for Complicated Parturients. The literature is insufficient to assess whether, when caring for the complicated parturient, the early insertion of a spinal or epidural catheter, with later administration of analgesia, improves maternal or neonatal outcomes. The consultants and ASA members agree that early insertion of a spinal or epidural catheter for complicated parturients reduces maternal complications.

Recommendations. Early insertion of a spinal or epidural catheter for obstetric (*e.g.*, twin gestation or preeclampsia) or anesthetic indications (*e.g.*, anticipated difficult airway or obesity) should be considered to reduce the need for GA if an emergent procedure becomes necessary. In these cases, the insertion of a spinal or epidural catheter may precede the onset of labor or a patient's request for labor analgesia.

Continuous Infusion Epidural Analgesia

CIE Compared with Parenteral Opioids. The literature suggests that the use of continuous infusion epidural (CIE) local anesthetics with or without opioids provides greater quality of analgesia compared with parenteral (*i.e.*, intravenous or intramuscular) opioids. The consultants and ASA members strongly agree that CIE local anesthetics with or without opioids provide improved analgesia compared with parenteral opioids.

Meta-analysis of the literature indicates that there is a longer duration of labor, with an average duration of 24 min for the second stage, and a lower frequency of spontaneous vaginal delivery when continuous epidural local anesthetics are administered compared with *intravenous* opioids. Meta-analysis of the literature determined that there are no differences in the frequency of cesarean delivery. Neither the consultants nor ASA members agree that CIE local anesthetics compared with parenteral opioids significantly (1) increase the duration of labor, (2) decrease the chance of spontaneous delivery, (3) increase maternal side effects, or (4) increase fetal and neonatal side effects.

CIE Compared with Single-injection Spinal. There is insufficient literature to assess the analgesic efficacy of CIE local anesthetics with or without opioids compared to *single-injection spinal opioids* with or without local anesthetics. The consultants are equivocal, but the ASA members agree that CIE local anesthetics improve analgesia compared with single-injection spinal opioids; both the consultants and ASA members are equivocal regarding the frequency of motor block. The consultants are equivocal, but the ASA members disagree that the use of CIE compared with single-injection spinal opioids increases the duration of labor. They both *disagree* that CIE local anesthetics with or without opioids compared to single-injection spinal opioids with or without local anesthetics decreases the likelihood of spontaneous delivery or increases maternal, fetal, or neonatal side effects.

CIE with and without Opioids. The literature supports the *induction* of analgesia using epidural local anesthetics combined *with opioids* compared with equal concentrations of epidural local anesthetics *without opioids* for improved quality and longer duration of analgesia. The consultants strongly agree and the ASA members agree that the addition of opioids to epidural local anesthetics improves analgesia; they both disagree that fetal or neonatal side effects are increased. The consultants disagree, but the ASA members are equivocal regarding whether the addition of opioids increases maternal side effects.

The literature is insufficient to determine whether induction of analgesia using local anesthetics with opioids compared with *higher concentrations* of epidural local anesthetics without opioids provides improved quality or duration of analgesia. The consultants and ASA members are equivocal regarding improved analgesia, and they both disagree that maternal, fetal, or neonatal side effects are increased using lower concentrations of epidural local anesthetics with opioids.

For *maintenance of analgesia*, the literature suggests that there are no differences in the analgesic efficacy of *low concentrations* of epidural local anesthetics with opioids compared with *higher concentrations* of epidural local anesthetics without opioids. The Task Force notes that the addition of an opioid to a local anesthetic infusion allows an even lower concentration of local anesthetic for providing equally effective analgesia. However, the literature is insufficient to examine whether a bupivacaine infusion concentration of *less than or equal to 0.125%* with an opioid provides comparable or improved analgesia compared with a bupivacaine concentration *greater than 0.125%* without an opioid.[#] Meta-analysis of the literature determined that low concentrations of epidural local anesthetics with opioids compared with higher concentrations of epidural local anesthetics without opioids are associated with reduced motor block. No differences in the duration of labor, mode of delivery, or neonatal outcomes are found when epidural local anesthetics with opioids are compared with epidural local anesthetics without opioids. The literature is insufficient to determine the effects of epidural local anesthetics with opioids on other maternal outcomes (*e.g.*, hypotension, nausea, pruritus, respiratory depression, urinary retention).

The consultants and ASA members both agree that maintenance of epidural analgesia using *low* concentrations of local anesthetics with opioids provides improved analgesia compared with *higher* concentrations of local anesthetics without opioids. The consultants agree, but the ASA members are equivocal regarding the improved likelihood of spontaneous delivery when lower concentrations of local anesthetics with opioids are used. The consultants strongly agree and the ASA members agree that motor block is reduced. They agree that maternal side effects are reduced with this drug combination. They are both equivocal regarding a reduction in fetal and neonatal side effects.

Recommendations. The selected analgesic/anesthetic technique should reflect patient needs and preferences, practitioner preferences or skills, and available resources. The continuous epidural infusion technique may be used for effective analgesia for labor and delivery. When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the concentration of local anesthetic, improve the quality of analgesia, and minimize motor block.

Adequate analgesia for uncomplicated labor and delivery should be administered with the secondary goal of producing as little motor block as possible by using dilute concentrations of local anesthetics with opioids. The lowest concentration of local anesthetic infusion that provides adequate maternal analgesia and satisfaction should be administered. For example, an infusion concentration greater than 0.125% bupivacaine is unnecessary for labor analgesia in most patients.

Single-injection Spinal Opioids with or without Local Anesthetics. The literature suggests that spinal opioids with or without local anesthetics provide effective

[#]References to bupivacaine are included for illustrative purposes only, and because bupivacaine is the most extensively studied local anesthetic for continuous infusion epidural analgesia. The Task Force recognizes that other local anesthetics are appropriate for continuous infusion epidural analgesia.

analgesia during labor without altering the incidence of neonatal complications. There is insufficient literature to compare spinal opioids with parenteral opioids. There is also insufficient literature to compare single-injection spinal opioids *with* local anesthetics *versus* single-injection spinal opioids *without* local anesthetics.

The consultants strongly agree and the ASA members agree that spinal opioids provide improved analgesia compared with parenteral opioids. They both disagree that, compared with parenteral opioids, spinal opioids increase the duration of labor, decrease the chance of spontaneous delivery, or increase fetal and neonatal side effects. The consultants are equivocal, but the ASA members disagree that maternal side effects are increased with spinal opioids.

Compared with spinal opioids *without* local anesthetics, the consultants and ASA members both agree that spinal opioids *with* local anesthetics provide improved analgesia. They both disagree that the chance of spontaneous delivery is decreased and that fetal and neonatal side effects are increased. They are both equivocal regarding an increase in maternal side effects. However, they both agree that motor block is increased when local anesthetics are added to spinal opioids. Finally, the consultants disagree, but the ASA members are equivocal regarding an increase in the duration of labor.

Recommendations. Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated. If labor is expected to last longer than the analgesic effects of the spinal drugs chosen or if there is a good possibility of operative delivery, a catheter technique instead of a single injection technique should be considered. A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia. The Task Force notes that the rapid onset of analgesia provided by single-injection spinal techniques may be advantageous for selected patients (*e.g.*, those in advanced labor).

Pencil-point Spinal Needles. The literature supports the use of pencil-point spinal needles compared with cutting-bevel spinal needles to reduce the frequency of post–dural puncture headache. The consultants and ASA members both strongly agree that the use of pencil-point spinal needles reduces maternal complications.

Recommendations. Pencil-point spinal needles should be used instead of cutting-bevel spinal needles to minimize the risk of post–dural puncture headache.

Combined Spinal-Epidural Analgesia. The literature supports a faster onset time and equivalent analgesia with combined spinal-epidural (CSE) local anesthetics with opioids *versus* epidural local anesthetics with opioids. The literature is equivocal regarding the impact of CSE versus epidural local anesthetics with opioids on maternal satisfaction with analgesia, mode of delivery, hypotension, motor block, nausea, fetal heart rate changes, and Apgar scores. Meta-analysis of the literature indicates that the frequency of pruritus is increased with CSE.

The consultants and ASA members both agree that CSE local anesthetics with opioids provide improved early analgesia compared with epidural local anesthetics with opioids. They are equivocal regarding the impact of CSE with opioids on overall analgesic efficacy, duration of labor, and motor block. The consultants and ASA members both disagree that CSE increases the risk of fetal or neonatal side effects. The consultants disagree, but the ASA members are equivocal regarding whether CSE increases the incidence of maternal side effects.

Recommendations. Combined spinal-epidural techniques may be used to provide effective and rapid onset of analgesia for labor.

Patient-controlled Epidural Analgesia. The literature supports the efficacy of patient-controlled epidural analgesia (PCEA) *versus* CIE in providing equivalent analgesia with reduced drug consumption. Meta-analysis of the literature indicates that the duration of labor is longer with PCEA compared with CIE for the first stage (*e.g.*, an average of 36 min) but not the second stage of labor. Meta-analysis of the literature also determined that mode of delivery, frequency of motor block, and Apgar scores are equivalent when PCEA administration is compared with CIE. The literature supports greater analgesic efficacy for PCEA with a background infusion compared with PCEA without a background infusion; meta-analysis of the literature also indicates no differences in the mode of delivery or frequency of motor block. The consultants and ASA members agree that PCEA compared with CIE improves analgesia and reduces the need for anesthetic interventions; they also agree that PCEA improves maternal satisfaction. The consultants and ASA members are equivocal regarding a reduction in motor block, an increased likelihood of spontaneous delivery, or a decrease in maternal side effects with PCEA compared with CIE. They both agree that PCEA with a background infusion improves analgesia, improves maternal satisfaction, and reduces the need for anesthetic intervention. The ASA members are equivocal, but the consultants disagree that a background infusion decreases the chance of spontaneous delivery or increases maternal side effects. The consultants and ASA members are equivocal regarding the effect of a background infusion on the incidence of motor block.

Recommendations. Patient-controlled epidural analgesia may be used to provide an effective and flexible approach for the maintenance of labor analgesia. The Task Force notes that the use of PCEA may be preferable to fixed-rate CIE for providing fewer anesthetic interventions and reduced dosages of local anesthetics. PCEA may be used with or without a background infusion.

IV. Removal of Retained Placenta

Anesthetic Techniques. The literature is insufficient to assess whether a particular type of anesthetic is more effective than another for removal of retained placenta. The consultants strongly agree and the ASA members agree that, if a functioning epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is the preferred technique for the removal of retained placenta. The consultants and ASA members both agree that, in cases involving major maternal hemorrhage, GA is preferred over neuraxial anesthesia.

Recommendations. The Task Force notes that, in general, there is no preferred anesthetic technique for removal of retained placenta. However, if an epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is preferable. Hemodynamic status should be assessed before administering neuraxial anesthesia. Aspiration prophylaxis should be considered. Sedation/analgesia should be titrated carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period. In cases involving major maternal hemorrhage, GA with an endotracheal tube may be preferable to neuraxial anesthesia.

Uterine Relaxation. The literature suggests that nitroglycerin is effective for uterine relaxation during the removal of retained placenta. The consultants and ASA members both agree that the administration of nitroglycerin for uterine relaxation improves success in removing a retained placenta.

Recommendations. Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue. Initiating treatment with incremental doses of intravenous or sublingual (*i.e*., metered dose spray) nitroglycerin may relax the uterus sufficiently while minimizing potential complications (*e.g*., hypotension).

V. Anesthetic Choices for Cesarean Delivery

Equipment, Facilities, and Support Personnel. The literature is insufficient to evaluate the benefit of providing equipment, facilities and support personnel in the labor and delivery operating suite comparable to that available in the main operating suite. The consultants and ASA members strongly agree that the available equipment, facilities, and support personnel should be comparable.

Recommendations. Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite. Resources for the treatment of potential complications (*e.g*., failed intubation, inadequate analgesia, hypotension, respiratory depression, pruritus, vomiting) should also be available in the labor and delivery operating suite. Appropriate equipment and personnel should be available to care for obstetric patients recovering from major neuraxial anesthesia or GA.

General, Epidural, Spinal, or Combined Spinal-Epidural Anesthesia. The literature suggests that induction-to-delivery times for GA are lower compared with epidural or spinal anesthesia and that a higher frequency of maternal hypotension may be associated with epidural or spinal techniques. Meta-analysis of the literature found that Apgar scores at 1 and 5 min are lower for GA compared with epidural anesthesia and suggests that Apgar scores are lower for GA *versus* spinal anesthesia. The literature is equivocal regarding differences in umbilical artery pH values when GA is compared with epidural or spinal anesthesia.

The consultants and ASA members agree that GA reduces the time to skin incision when compared with either epidural or spinal anesthesia; they also agree that GA increases maternal complications. The consultants are equivocal and the ASA members agree that GA increases fetal and neonatal complications. The consultants and ASA members both agree that epidural anesthesia increases the time to skin incision and decreases the quality of anesthesia compared with spinal anesthesia. They both disagree that epidural anesthesia increases maternal complications.

When spinal anesthesia is compared with epidural anesthesia, meta-analysis of the literature found that induction-to-delivery times are shorter for spinal anesthesia. The literature is equivocal regarding hypotension, umbilical pH values, and Apgar scores. The consultants and ASA members agree that epidural anesthesia increases time to skin incision and reduces the quality of anesthesia when compared with spinal anesthesia. They both disagree that epidural anesthesia increases maternal complications.

When CSE is compared with epidural anesthesia, meta-analysis of the literature found no differences in the frequency of hypotension or in 1-min Apgar scores; the literature is insufficient to evaluate outcomes associated with the use of CSE compared with spinal anesthesia. The consultants and ASA members agree that CSE anesthesia improves anesthesia and reduces time to skin incision when compared with *epidural* anesthesia. The ASA members are equivocal, but the consultants disagree that maternal side effects are reduced. The consultants and ASA members both disagree that CSE improves anesthesia compared with *spinal* anesthesia. The ASA members are equivocal, but the consultants disagree that maternal side effects are reduced. The consultants strongly agree and the ASA members agree that CSE compared with spinal anesthesia increases flexibility of prolonged procedures, and they both agree that the time to skin incision is increased.

Recommendations. The decision to use a particular anesthetic technique for cesarean delivery should be individualized, based on several factors. These include anesthetic, obstetric, or fetal risk factors (*e.g*., elective vs. emergency), the preferences of the patient, and the judgment of the anesthesiologist. Neuraxial techniques are preferred to GA for most cesarean deliveries. An indwelling epidural catheter may provide equivalent onset of anesthesia compared with initiation of spinal anesthesia for urgent cesarean delivery. If spinal anesthesia is chosen, pencil-point spinal needles should be used instead of cutting-bevel spinal needles. However, GA may be the most appropriate choice in some circumstances (*e.g*., profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption). Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used.

Intravenous Fluid Preloading. The literature supports and the consultants and ASA members agree that intravenous fluid preloading for spinal anesthesia reduces the frequency of maternal hypotension when compared with no fluid preloading.

Recommendations. Intravenous fluid preloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery. Although fluid preloading reduces the frequency of maternal hypotension, initiation of spinal anesthesia should not be delayed to administer a fixed volume of intravenous fluid.

Ephedrine or Phenylephrine. The literature supports the administration of ephedrine and suggests that phenylephrine is effective in reducing maternal hypotension during neuraxial anesthesia for cesarean delivery. The literature is equivocal regarding the relative frequency of patients with breakthrough hypotension when infusions of ephedrine are compared with phenylephrine; however, lower umbilical cord pH values are reported after ephedrine administration. The consultants agree and the ASA members strongly agree that ephedrine is acceptable for treating hypotension during neuraxial anesthesia. The consultants strongly agree and the ASA members agree that phenylephrine is an acceptable agent for the treatment of hypotension.

Recommendations. Intravenous ephedrine and phenylephrine are both acceptable drugs for treating hypotension during neuraxial anesthesia. In the absence of maternal bradycardia, phenylephrine may be preferable because of improved fetal acid-base status in uncomplicated pregnancies.

Neuraxial Opioids for Postoperative Analgesia. For improved postoperative analgesia after cesarean delivery during epidural anesthesia, the literature supports the use of epidural opioids compared with intermittent injections of intravenous or intramuscular opioids. However, a higher frequency of pruritus was found with epidural opioids. The literature is insufficient to evaluate the impact of epidural opioids compared with intravenous PCA. In addition, the literature is insufficient to evaluate spinal opioids compared with parenteral opioids. The consultants strongly agree and the ASA members agree that neuraxial opioids for postoperative analgesia improve analgesia and maternal satisfaction.

Recommendations. For postoperative analgesia after neuraxial anesthesia for cesarean delivery, neuraxial opioids are preferred over intermittent injections of parenteral opioids.

VI. Postpartum Tubal Ligation

There is insufficient literature to evaluate the benefits of neuraxial anesthesia compared with GA for postpartum tubal ligation. In addition, the literature is insufficient to evaluate the impact of the timing of a postpartum tubal ligation on maternal outcome. The consultants and ASA members both agree that neuraxial anesthesia for postpartum tubal ligation reduces complications compared with GA. The ASA members are equivocal but the consultants agree that a postpartum tubal ligation within 8 h of delivery *does not* increase maternal complications.

Recommendations. For postpartum tubal ligation, the patient should have no oral intake of solid foods within 6–8 h of the surgery, depending on the type of food ingested (*e.g.*, fat content). Aspiration prophylaxis should be considered. Both the timing of the procedure and the decision to use a particular anesthetic technique (*i.e.*, neuraxial vs. general) should be individualized, based on anesthetic risk factors, obstetric risk factors (*e.g.*, blood loss), and patient preferences. However, neuraxial techniques are preferred to GA for most postpartum tubal ligations. The anesthesiologist should be aware that gastric emptying will be delayed in patients who have received opioids during labor, and that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals. If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care on the labor and delivery unit.

TABLE 1 Suggested Resources for Obstetric Hemorrhagic Emergencies

- Large-bore intravenous catheters
- Fluid warmer
- Forced-air body warmer
- Availability of blood bank resources
- Equipment for infusing intravenous fluids and blood products rapidly. Examples include, but are not limited to, hand-squeezed fluid chambers, hand-inflated pressure bags, and automatic infusion devices

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

VII. Management of Obstetric and Anesthetic Emergencies

Resources for Management of Hemorrhagic Emergencies. Observational studies and case reports suggest that the availability of resources for hemorrhagic emergencies may be associated with reduced maternal complications. The consultants and ASA members both strongly agree that the availability of resources for managing hemorrhagic emergencies reduces maternal complications.

Recommendations. Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies (table 1). In an emergency, the use of type-specific or O negative blood is acceptable. In cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell-salvage should be considered if available.

Central Invasive Hemodynamic Monitoring. There is insufficient literature to examine whether pulmonary artery catheterization is associated with improved maternal, fetal, or neonatal outcomes in patients with pregnancy-related hypertensive disorders. The literature is silent regarding the management of obstetric patients with central venous catheterization alone. The consultants and ASA members agree that the routine use of central venous or pulmonary artery catheterization does not reduce maternal complications in severely preeclamptic patients.

TABLE 2 Suggested Resources for Airway Management during Initial Provision of Neuraxial Anesthesia

- Laryngoscope and assorted blades
- Endotracheal tubes, with stylets
- Oxygen source
- Suction source with tubing and catheters
- Self-inflating bag and mask for positive-pressure ventilation
- Medications for blood pressure support, muscle relaxation, and hypnosis
- Qualitative carbon dioxide detector
- Pulse oximeter

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

TABLE 3 Suggested Contents of a Portable Storage Unit for Difficult Airway Management for Cesarean Delivery Rooms

- Rigid laryngoscope blades of alternate design and size from those routinely used
- Laryngeal mask airway
- Endotracheal tubes of assorted size
- Endotracheal tube guides. Examples include, but are not limited to, semirigid stylets with or without a hollow core for jet ventilation, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube.
- Retrograde intubation equipment
- At least one device suitable for emergency nonsurgical airway ventilation. Examples include, but are not limited to, a hollow jet ventilation stylet with a transtracheal jet ventilator, and a supraglottic airway device (*e.g.*, Combitube®, Intubating LMA [*Fastrach*™])
- Fiberoptic intubation equipment
- Equipment suitable for emergency surgical airway access (*e.g.*, cricothyrotomy)
- An exhaled carbon dioxide detector
- Topical anesthetics and vasoconstrictors

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

Adapted from Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003; 98:1269–77.

Recommendations. The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient's medical history and cardiovascular risk factors. The Task Force recognizes that not all practitioners have access to resources for use of central venous or pulmonary artery catheters in obstetric units.

Equipment for Management of Airway Emergencies. Case reports suggest that the availability of equipment for the management of airway emergencies may be associated with reduced maternal, fetal, and neonatal complications. The consultants and ASA members both strongly agree that the immediate availability of equipment for the management of airway emergencies reduces maternal, fetal, and neonatal complications.

Recommendations. Labor and delivery units should have personnel and equipment readily available to manage airway emergencies, to include a pulse oximeter and qualitative carbon dioxide detector, consistent with the ASA Practice Guidelines for Management of the Difficult Airway.** Basic airway management equipment should be immediately available during the provision of neuraxial analgesia (table 2). In addition, portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units (table 3). The anesthesiologist should have a preformulated strategy for intubation of the difficult airway. When tracheal intubation has failed, ventilation with mask and cricoid pressure, or with a laryngeal mask airway or supraglottic airway device (*e.g.*, Combitube®, Intubating LMA [*Fastrach*™]) should be considered for maintaining an airway and ventilating the lungs. If it is not possible to ventilate or awaken the patient, an airway should be created surgically.

Cardiopulmonary Resuscitation. The literature is insufficient to evaluate the efficacy of cardiopulmonary resuscitation in the obstetric patient during labor and delivery. In cases of cardiac arrest, the American Heart Association has stated that 4–5 min is the maximum time rescuers will have to determine whether the arrest can be reversed by Basic Life Support and Advanced Cardiac Life Support interventions.†† Delivery of the fetus may improve cardiopulmonary resuscitation of the mother by relieving aortocaval compression. The American Heart Association further notes that "the best survival rate for infants > 24 to 25 weeks in gestation occurs when the delivery of the infant occurs no more than 5 min after the mother's heart stops beating. This typically requires that the provider begin the hysterotomy about 4 min after cardiac arrest."†† The consultants and ASA members both strongly agree that the immediate availability of basic and advanced life-support equipment in the labor and delivery suite reduces maternal, fetal, and neonatal complications.

Recommendations. Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units. If cardiac arrest occurs during labor and delivery, standard resuscitative measures should be initiated. In addition, uterine displacement (usually left displacement) should be maintained. If maternal circulation is not restored within

**American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway: An updated report. Anesthesiology 2003; 98:1269–77.

††2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2005; 112(suppl):IV1–203.

4 min, cesarean delivery should be performed by the obstetrics team.

Appendix 1: Summary of Recommendations

I. Perianesthetic Evaluation

- Conduct a focused history and physical examination before providing anesthesia care
  - Maternal health and anesthetic history
  - Relevant obstetric history
  - Airway and heart and lung examination
  - Baseline blood pressure measurement
  - Back examination when neuraxial anesthesia is planned or placed
- A communication system should be in place to encourage early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team
- Order or require a platelet count based on a patient's history, physical examination, and clinical signs; a routine intrapartum platelet count is not necessary in the healthy parturient
- Order or require an intrapartum blood type and screen or cross-match based on maternal history, anticipated hemorrhagic complications (*e.g.*, placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies; a routine blood cross-match is not necessary for *healthy and uncomplicated* parturients
- The fetal heart rate should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor; *continuous* electronic recording of the fetal heart rate may not be necessary in every clinical setting and may not be possible during initiation of neuraxial anesthesia

II. Aspiration Prophylaxis

- Oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients
- The uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia
- The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested
- Patients with additional risk factors for aspiration (*e.g.*, morbid obesity, diabetes, difficult airway) or patients at increased risk for operative delivery (*e.g.*, nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis
- Solid foods should be avoided in laboring patients
- Patients undergoing elective surgery (*e.g.*, scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6–8 h depending on the type of food ingested (*e.g.*, fat content)
- Before surgical procedures (*i.e.*, cesarean delivery, postpartum tubal ligation), practitioners should consider timely administration of non-particulate antacids, H_2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis

III. Anesthetic Care for Labor and Delivery

Neuraxial Techniques: Availability of Resources.

- When neuraxial techniques that include local anesthetics are chosen, appropriate resources for the treatment of complications (*e.g.*, hypotension, systemic toxicity, high spinal anesthesia) should be available
- If an opioid is added, treatments for related complications (*e.g.*, pruritus, nausea, respiratory depression) should be available
- An intravenous infusion should be established before the initiation of neuraxial analgesia or anesthesia and maintained throughout the duration of the neuraxial analgesic or anesthetic
- Administration of a fixed volume of intravenous fluid is not required before neuraxial analgesia is initiated

Timing of Neuraxial Analgesia and Outcome of Labor.

- Neuraxial analgesia should not be withheld on the basis of achieving an arbitrary cervical dilation, and should be offered on an individualized basis when this service is available
- Patients may be reassured that the use of neuraxial analgesia does not increase the incidence of cesarean delivery

Neuraxial Analgesia and Trial of Labor after Previous Cesarean Delivery.

- Neuraxial techniques should be offered to patients attempting vaginal birth after previous cesarean delivery
- For these patients, it is also appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia or for anesthesia in the event of operative delivery

Early Insertion of Spinal or Epidural Catheter for Complicated Parturients.

- Early insertion of a spinal or epidural catheter for obstetric (*e.g.*, twin gestation or preeclampsia) or anesthetic indications (*e.g.*, anticipated difficult airway or obesity) should be considered to reduce the need for general anesthesia if an emergent procedure becomes necessary
  - In these cases, the insertion of a spinal or epidural catheter may precede the onset of labor or a patient's request for labor analgesia

Continuous Infusion Epidural (CIE) Analgesia.

- The selected analgesic/anesthetic technique should reflect patient needs and preferences, practitioner preferences or skills, and available resources
- CIE may be used for effective analgesia for labor and delivery

- When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the concentration of local anesthetic, improve the quality of analgesia, and minimize motor block
- Adequate analgesia for uncomplicated labor and delivery should be administered with the secondary goal of producing as little motor block as possible by using dilute concentrations of local anesthetics with opioids
- The lowest concentration of local anesthetic infusion that provides adequate maternal analgesia and satisfaction should be administered

Single-injection Spinal Opioids with or without Local Anesthetics.

- Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated
- If labor is expected to last longer than the analgesic effects of the spinal drugs chosen or if there is a good possibility of operative delivery, a catheter technique instead of a single injection technique should be considered
- A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia

Pencil-point Spinal Needles.

- Pencil-point spinal needles should be used instead of cutting-bevel spinal needles to minimize the risk of post–dural puncture headache

Combined Spinal–Epidural (CSE) Anesthetics.

- CSE techniques may be used to provide effective and rapid analgesia for labor

Patient-controlled Epidural Analgesia (PCEA).

- PCEA may be used to provide an effective and flexible approach for the maintenance of labor analgesia
- PCEA may be preferable to CIE for providing fewer anesthetic interventions, reduced dosages of local anesthetics, and less motor blockade than fixed-rate continuous epidural infusions
- PCEA may be used with or without a background infusion

IV. Removal of Retained Placenta

- In general, there is no preferred anesthetic technique for removal of retained placenta
  - If an epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is preferable
- Hemodynamic status should be assessed before administering neuraxial anesthesia
- Aspiration prophylaxis should be considered
- Sedation/analgesia should be titrated carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period
- In cases involving major maternal hemorrhage, general anesthesia with an endotracheal tube may be preferable to neuraxial anesthesia
- Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue
  - Initiating treatment with incremental doses of intravenous or sublingual (*i.e.*, metered dose spray) nitroglycerin may relax the uterus sufficiently while minimizing potential complications (*e.g.*, hypotension)

V. Anesthetic Choices for Cesarean Delivery

- Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite
  - Resources for the treatment of potential complications (*e.g.*, failed intubation, inadequate analgesia, hypotension, respiratory depression, pruritus, vomiting) should be available in the labor and delivery operating suite
  - Appropriate equipment and personnel should be available to care for obstetric patients recovering from major neuraxial or general anesthesia
- The decision to use a particular anesthetic technique should be individualized based on anesthetic, obstetric, or fetal risk factors (*e.g.*, elective vs. emergency), the preferences of the patient, and the judgment of the anesthesiologist
  - Neuraxial techniques are preferred to general anesthesia for most cesarean deliveries
- An indwelling epidural catheter may provide equivalent onset of anesthesia compared with initiation of spinal anesthesia for urgent cesarean delivery
- If spinal anesthesia is chosen, pencil-point spinal needles should be used instead of cutting-bevel spinal needles
- General anesthesia may be the most appropriate choice in some circumstances (*e.g.*, profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption)
- Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used
- Intravenous fluid preloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery
- Initiation of spinal anesthesia should not be delayed to administer a fixed volume of intravenous fluid
- Intravenous ephedrine and phenylephrine are both acceptable drugs for treating hypotension during neuraxial anesthesia
  - In the absence of maternal bradycardia, phenylephrine may be preferable because of improved fetal acid-base status in uncomplicated pregnancies
- For postoperative analgesia after neuraxial anesthesia for cesarean delivery, neuraxial opioids

are preferred over intermittent injections of parenteral opioids

VI. Postpartum Tubal Ligation

- For postpartum tubal ligation, the patient should have no oral intake of solid foods within 6-8 h of the surgery, depending on the type of food ingested (*e.g.*, fat content)
- Aspiration prophylaxis should be considered
- Both the timing of the procedure and the decision to use a particular anesthetic technique (*i.e.*, neuraxial *vs.* general) should be individualized, based on anesthetic risk factors, obstetric risk factors (*e.g.*, blood loss), and patient preferences
- Neuraxial techniques are preferred to general anesthesia for most postpartum tubal ligations
  - Be aware that gastric emptying will be delayed in patients who have received opioids during labor and that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals
- If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care on the labor and delivery unit

VII. Management of Obstetric and Anesthetic Emergencies

- Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies
  - In an emergency, the use of type-specific or O negative blood is acceptable
  - In cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell-salvage should be considered if available
  - The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient's medical history and cardiovascular risk factors
- Labor and delivery units should have personnel and equipment readily available to manage airway emergencies, to include a pulse oximeter and qualitative carbon dioxide detector, consistent with the ASA Practice Guidelines for Management of the Difficult Airway
  - Basic airway management equipment should be immediately available during the provision of neuraxial analgesia
  - Portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units
  - The anesthesiologist should have a preformulated strategy for intubation of the difficult airway
  - When tracheal intubation has failed, ventilation with mask and cricoid pressure, or with a laryngeal mask airway or supraglottic airway device (*e.g.*, Combitube®, Intubating LMA [*Fastrach*™]) should be considered for maintaining an airway and ventilating the lungs
  - If it is not possible to ventilate or awaken the patient, an airway should be created surgically
- Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units
- If cardiac arrest occurs during labor and delivery, standard resuscitative measures should be initiated
  - Uterine displacement (usually left displacement) should be maintained
  - If maternal circulation is not restored within 4 min, cesarean delivery should be performed by the obstetrics team

APPENDIX C

Optimal Goals for Anesthesia Care in Obstetrics*

COMMITTEE OF ORIGIN: OBSTETRICAL ANESTHESIA

This joint statement from the American Society of Anesthesiologists (ASA) and the American College of Obstetricians and Gynecologists (ACOG) has been designed to address issues of concern to both specialties. Good obstetric care requires the availability of qualified personnel and equipment to administer general or neuraxial anesthesia both electively and emergently. The extent and degree to which anesthesia services are available varies widely among hospitals. However, for any hospital providing obstetric care, certain optimal anesthesia goals should be sought. These include:

1. Availability of a licensed practitioner who is credentialed to administer an appropriate anesthetic whenever necessary. For many women, neuraxial anesthesia (epidural, spinal, or combined spinal epidural) will be the most appropriate anesthetic.
2. Availability of a licensed practitioner who is credentialed to maintain support of vital functions in any obstetric emergency.
3. Availability of anesthesia and surgical personnel to permit the start of a cesarean delivery within 30 minutes of deciding to perform the procedure.
4. Because the risks associated with trial of labor after cesarean delivery (TOLAC) and uterine rupture may be unpredictable, the immediate availability of appropriate facilities and personnel (including obstetric anesthesia, nursing personnel, and a physician capable of monitoring labor and performing cesarean delivery, including an emergency cesarean delivery) is optimal. When resources for immediate cesarean delivery are not available, patients considering TOLAC should discuss the hospital's resources and availability of obstetric, anesthetic, pediatric and nursing staff with their obstetric provider[1]; patients should be clearly informed of the potential increase in risk and the management alternatives. The definition of immediately available personnel and facilities remains a local decision based on each institution's available resources and geographic location.
5. Appointment of qualified anesthesiologist to be responsible for all anesthetics administered. There are many obstetric units where obstetricians or obstetrician-supervised nurse anesthetists administer labor anesthetics. The administration of general or neuraxial anesthesia requires both medical judgment and technical skills. Thus, a physician with privileges in anesthesiology should be readily available.

Persons administering or supervising obstetric anesthesia should be qualified to manage the infrequent but occasionally life-threatening complications of neuraxial anesthesia such as respiratory and cardiovascular failure, toxic local anesthetic convulsions, or vomiting and aspiration. Mastering and retaining the skills and knowledge necessary to manage these complications require adequate training and frequent application.

To ensure the safest and most effective anesthesia for obstetric patients, the Director of Anesthesia Services, with the approval of the medical staff, should develop and enforce written policies regarding provision of obstetric anesthesia. These include:

1. A qualified physician with obstetric privileges to perform operative vaginal or cesarean delivery should be readily available during administration of anesthesia. Readily available should be defined by each institution within the context of its resources and geographic location. Neuraxial and/or general anesthesia should not be administered until the patient has been examined and the fetal status and progress of labor evaluated by a qualified individual. A physician with obstetric privileges who concurs with the patient's management and has knowledge of the maternal and fetal status and the progress of labor should be responsible for midwifery back up in hospital settings that utilize certified nurse midwives/ certified midwives as obstetric providers.
2. Availability of equipment, facilities, and support personnel equal to that provided in the surgical suite. This should include the availability of a properly equipped and staffed recovery room capable of receiving and caring for all patients recovering from neuraxial or general anesthesia. Birthing facilities, when used for labor services or surgical anesthesia, must be appropriately equipped to provide

*Approved by the ASA House of Delegates on October 17, 2007 and last amended on October 20, 2010.

safe anesthetic care during labor and delivery or postanesthesia recovery care.

3. Personnel, other than the surgical team, should be immediately available to assume responsibility for the depressed newborn. The surgeon and anesthesiologist are responsible for the mother and may not be able to leave her to care for the newborn, even when a neuraxial anesthetic functioning adequately. Individuals qualified to perform neonatal resuscitation should demonstrate:
   - 3.1 Proficiency in rapid and accurate evaluation of the newborn condition, including Apgar scoring.
   - 3.2 Knowledge of the pathogenesis of a depressed newborn (acidosis, drugs, hypovolemia, trauma, anomalies, and infection), as well as specific indications for resuscitation.
   - 3.3 Proficiency in newborn airway management, laryngoscopy, endotracheal intubations, suctioning of airways, artificial vertilation, cardiac massage, and maintenance of thermal stability.

In larger maternity units and those functioning as high-risk centers, 24-hour in-house anesthesia, obstetric and neonatal specialists are usually necessary. Preferably, the obstetric anesthesia services should be directed by an anesthesiologist with special training or experience in obstetric anesthesia. These units will also frequently require the availability of more sophisticated monitoring equipment and specially trained nursing personnel.

A survey jointly sponsored by ASA and ACOG found that many hospitals in the United States have not yet achieved the goals mentioned previously. Deficiencies were most evident in smaller delivery units. Some small delivery units are necessary because of geographic considerations. Currently, approximately 34% of hospitals providing obstetric care have fewer than 500 deliveries per year.[2] Providing comprehensive care for obstetric patients in these small units is extremely inefficient, not cost-effective and frequently impossible. Thus, the following recommendations are made:

1. Whenever possible, smaller units should consolidate.
2. When geographic factors require the existence of smaller units, these units should be part of a well-established regional perinatal system.

The availability of the appropriate personnel to assist in the management of a variety of obstetric problems is a necessary feature of good obstetric care. The presence of a pediatrician or other trained physician at a high-risk cesarean delivery to care for the newborn or the availability of an anesthesiologist during active labor and delivery when TOLAC is attempted and at a breech or multifetal delivery are examples. Frequently, these physicians spend a considerable amount of time standing by for the possibility that their services may be needed emergently, but may ultimately not be required to perform the tasks for which they are present. Reasonable compensation for these standby services is justifiable and necessary.

A variety of other mechanisms have been suggested to increase the availability and quality of anesthesia services in obstetrics. Improved hospital design, to place labor and delivery suites closer to the operating rooms, would allow for safer and more efficient anesthesia care, including supervision of nurse anesthetists. Anesthesia equipment in the labor and delivery area must be comparable to that in the operating room.

Finally, good interpersonal relations between obstetricians and anesthesiologists are important. Joint meetings between the two departments should be encouraged. Anesthesiologists should recognize the special needs and concerns of the obstetrician and obstetricians should recognize the anesthesiologist as a consultant in the management of pain and life-support measures. Both should recognize the need to provide high quality care for all patients.

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1. Vaginal birth after previous cesarean delivery. ACOG Practice Bulletin No. 115. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010; 116: 450-63.
2. Bucklin BA, Hawkins JL, Anderson JR, et al. Obstetric anesthesia workforce survey: twenty year update. Anesthesiology 2005; 103: 645-53.

APPENDIX D

Information Technology Resources for Obstetric Anesthesia Providers

William Camann, MD • Larry F. Chu, MD, MS (BCHM), MS (Epidemiology)

A variety of information technology–based resources exist for obstetric anesthesia providers. These websites offer information regarding clinical practice, ongoing research, and recent publications. This appendix should serve as a brief guide to some of these resources, which include websites, mobile computing applications, and social media resources such as Facebook and Twitter.

These sites were active at the time that this guide was prepared (October, 2013). The authors of this appendix, and the editors and publisher of this textbook, bear no responsibility for the accuracy (or lack thereof) of any information found in these sites. Publication of this list does not imply endorsement of these sites.

We have also included QR code technology that will allow users with mobile computing devices such as smartphones and tablets to scan the links of the printed page into their web browsers. Numerous QR code scanning applications are available for iOS and Android platforms. Finally, for long web addresses, we have used URL-shortening (Bit.ly) to facilitate web browser entry.

OBSTETRIC ANESTHESIOLOGY SOCIETIES

http://www.oaa-anaes.ac.uk

The Obstetric Anaesthetists Association (OAA). The OAA provides both education and training for anesthesia practitioners in the United Kingdom and other countries, and serves as a resource for women seeking information about analgesia for labor and anesthesia for cesarean delivery. Significant amounts of educational material are freely available for all users.

http://www.soap.org

The Society for Obstetric Anesthesia and Perinatology (SOAP). The SOAP is a subspecialty anesthesiology society based in the United States that promotes excellence in research, education and the clinical practice of obstetric anesthesiology and perinatology. Significant amounts of educational material are freely available for all users.

OTHER PROFESSIONAL SOCIETIES OF INTEREST

http://www.aap.org

The American Academy of Pediatrics (AAP). The AAP promotes the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults. Significant amounts of educational material are freely available.

http://www.acog.org

The American College of Obstetricians and Gynecologists (ACOG). The ACOG promotes health care for women through policy and guideline development, education, and advocacy. A password is required for access to much of the online information, including committee opinions and practice bulletins and guidelines.

http://www.asahq.org

ASA OB Anesthesia practice guidelines

The American Society of Anesthesiologists (ASA). The ASA encourages education, research, and scientific progress in anesthesiology. The ASA strives to be an advocate for all patients who require anesthesia or relief from pain. The majority of documents, policies, and guidelines are freely available; some sections require a password for access. The ASA practice guidelines for obstetric anesthesia can be found at https://ecommerce.asahq.org/p-119-practice-guidelines-for-obstetric-anesthesia.aspx (shortened URL: http://bit.ly/SnsTWu).

http://www.asra.com

The American Society of Regional Anesthesia and Pain Medicine (ASRA). The ASRA provides clinical and professional education for physicians and scientists, promotes excellence in patient care, and encourages research to advance the scientific basis of regional anesthesia and pain medicine. The ASRA consensus statement on regional (neuraxial) anesthesia in the anticoagulated patient can be found at http://www.asra.com/consensus-statements/2.html. The ASRA consensus statements regarding infectious complications of neuraxial blockade can be found at http://asra.com/consensus-statements/3.html.

http://www.apsf.org/

The Anesthesia Patient Safety Foundation (APSF). The APSF seeks to improve patient safety during anesthesia care by encouraging and conducting research and education, programs and campaigns, and national and international exchange of information and ideas. Significant amounts of educational material are freely available for all users. The APSF Newsletter can be found at http://www.apsf.org/resource_center/newsletters.mspx.

http://bit.ly/bTdBYs

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). The AWHONN seeks to improve the health of women and newborns and to strengthen the nursing profession through advocacy, research, education, and provision of other professional and clinical resources for nurses and other health care professionals. Some content is freely available for all users. The AWHONN position statement on the role of the registered nurse in the care of the pregnant woman receiving analgesia/anesthesia by neuraxial catheter techniques is available at http://bit.ly/XtA1P5.

http://www.cas.ca/

The Canadian Anesthesiologists' Society (CAS). The CAS promotes science, vigilance, and compassion in the practice of anesthesiology. Significant amounts of information (including practice guidelines) are freely available for all users. The CAS guidelines for regional (neuraxial) analgesia in obstetric patients can be found at http://www.cas.ca/members/sign_in/guidelines/practice_of_anesthesia/default.asp?load=obstetrical_regional_analgesia.

http://www.iars.org

The International Anesthesia Research Society (IARS). The IARS encourages the development and dissemination of current, state-of-the-art basic and clinical research data and the newest advances in all areas of clinical anesthesia care.

http://www.ifmss.org

The International Fetal Medicine and Surgery Society (IFMSS). The IFMSS promotes education and research related to the field of fetal diagnosis and therapy.

http://www.nasom.org

The North American Society of Obstetric Medicine (NASOM). The NASOM promotes and supports research collaboration, communication, and teaching concerning the medical care of pregnant women. General internists from the United States and Canada form the core membership of the society.

http://www.smfm.org

The Society for Maternal-Fetal Medicine (SMFM). The SMFM seeks to promote and expand education and research in maternal-fetal medicine and encourages the exchange of new ideas and research concerning the most recent approaches and treatments for obstetric problems.

http://www.somanz.org

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ). The SOMANZ seeks to advance clinical and scientific knowledge of hypertensive diseases and medical disorders in pregnancy and to foster collaboration with other regional and international societies interested in hypertension in pregnancy and obstetric medicine.

GOVERNMENTAL REGULATORY AND INFORMATIONAL WEBSITES

http://www.cdc.gov/

The Centers for Disease Control and Prevention (CDC). The CDC provides extensive information on most health-related subjects. For example, information is available on assisted reproductive technologies, birth rates, birth defects, breast-feeding, medication use during pregnancy, nutrition in pregnancy, preterm labor, maternal mortality, and various disease processes in pregnancy.

http://www.cemach.org.uk

The Confidential Enquiries into Maternal and Child Health (CEMACH). The CEMACH provides extensive information on maternal and perinatal mortality statistics, including anesthesia-related deaths, in the United Kingdom.

JOURNALS AND SCIENTIFIC LITERATURE

http://www.ajog.org

***The American Journal of Obstetrics and Gynecology* (the official journal of the SMFM).** A subscription is required for most text.

http://www.anesthesiology.org

***Anesthesiology* (the official journal of the ASA).** Content more than 6 months old is freely available without a subscription or password.

http://bit.ly/cyxxMe

***Anesthesia & Analgesia* (the official journal of the IARS and the SOAP).** Content more than 12 months old is freely available without a subscription or password.

http://www.cja-jca.org/

***The Canadian Journal of Anesthesia* (the official journal of the CAS).** Content more than 12 months old is freely available without a subscription or password.

http://www.cochrane.org

The Cochrane Collaboration. The Cochrane Collaboration provides frequently updated reviews of current literature in a variety of medical specialties, including anesthesiology and obstetrics. Most information in abstract form is freely available; however, a subscription is required for access to full-text documents.

http://bit.ly/11mKCzQ

***The International Journal of Obstetric Anesthesia* (the official journal of the OAA).** This is the only peer-reviewed journal devoted solely to obstetric anesthesia. A subscription is required for most text.

http://bit.ly/VXCVcH

***The Obstetric Anesthesia Digest*.** Recent publications of interest to obstetric anesthesia providers are cited, reviewed, and discussed by a panel of experts. A subscription is required for access to full text.

http://www.greenjournal.org

***Obstetrics & Gynecology* (the official journal of the ACOG).** New or updated ACOG practice bulletins and committee opinions are frequently published in *Obstetrics & Gynecology*. A subscription is required for most text.

http://bit.ly/cxXOG

***Pediatrics* (the official journal of the AAP).** Content more than 12 months old is freely available without a subscription or password (for a rolling 8-year period).

http://1.usa.gov/19bas8

PubMed (a medical literature search resource supported by the National Institutes of Health). This site provides citations and abstracts; the user must go to the original source to obtain the full text of most articles.

iTUNES PODCASTS

http://bit.ly/XW1MUj

Openanesthesia.org Podcast. Drs. Edward Nemergut and Robert Thiel from the Department of Anesthesiology at the University of Virginia host this podcast from Openanesthesia.org, an organization dedicated to promoting evidence-based medicine in anesthesiology, critical care, and pain management.

http://bit.ly/10lTg2p

The World of Anesthesia Podcast. Drs. Rajnish Gupta and Nahel Saied from the Department of Anesthesiology at Vanderbilt University host this podcast that discusses topics of general anesthesiology, critical care, and pain medicine.

http://bit.ly/ZQ1r5X

Medscape Anesthesia Podcasts. A collection of podcasts that cover various aspects of the specialty of anesthesiology, including clinical care, research, and politics.

http://bit.ly/11mNq06

The ASA Podcast Series. A series of podcasts from the American Society of Anesthesiologists that highlight the society's accomplishments and topics from its journal, *Anesthesiology*.

http://bit.ly/XW3sNt

The California Society of Anesthesiologists Podcasts. A collection of lectures from annual meetings of the California Society of Anesthesiologists.

SOCIAL MEDIA AND VIDEO PAGES

http://on.fb.me/XW4dWQ

The SOAP Facebook Page. The Society for Obstetric Anesthesia and Perinatology (SOAP) was founded in 1968 to provide a forum for discussion of problems unique to the peripartum period. Their Facebook page brings their community into the social media age with regular postings of SOAP-related information for their members and the public at large.

http://bit.ly/UR1wkI

The SOAP Video Page (Anesthesia Illustrated). This website has a large number of obstetric anesthesia videos including many of the major presentations from the Sol Shnider and SOAP annual meetings.

http://on.fb.me/XqaNRz

Obstetric Anesthesia Facebook Interest Page. This Facebook page is dedicated to the science, practice, and research of obstetric anesthesia and is hosted by Dr. Alex Butwick from the Department of Anesthesia, Stanford University School of Medicine.

http://on.fb.me/13mfzno

***The Obstetric Anesthesia Digest* Facebook Page.** *Obstetric Anesthesia Digest* posts frequent updates linking to original research studies from the peer-reviewed literature on topics related to the practice of obstetric anesthesia.

http://twitter.com/acognews

The American College of Obstetricians and Gynecologists (ACOG) Twitter Page. The ACOG uses Twitter to post updates related to ACOG's activities, as well as popular news items related to obstetric medicine.

http://on.fb.me/VPSrdL

The American College of Obstetricians and Gynecologists (ACOG) Facebook Page. On its Facebook page, the ACOG updates the public on ACOG activities, research findings, and public health initiatives related to obstetric and gynecologic medicine.

iOS AND ANDROID APPLICATIONS

http://bit.ly/WJjLGB

***Anesthesiology* iOS Application.** This application provides iPad access to journal subscribers of the journal *Anesthesiology*. Issues older than 6 months are available to non-subscribers free of charge.

http://bit.ly/13mgzrt

***Anesthesia & Analgesia* iOS Application.** This application provides iPad access to journal subscribers of *Anesthesia & Analgesia*. Issues older than 6 months are available to non-subscribers free of charge.

http://bit.ly/13nHfHt

Anesthesia 411 iOS Application. Anesthesia 411 provides information on 125 of the most common cases seen in the practice of anesthesiology. Topics include intravenous access, drug and drug administration, monitors, and specialized equipment.

http://bit.ly/XqcGgU

Crisis Code iOS Application. This application teaches the principles of crisis management for Advanced Cardiac Life Support.

http://bit.ly/UV2Fvu

CommunicatOR iOS Application. The application enhances communication between the anesthesia care providers and patients who do not speak the same language. Recordings of phrases commonly used during induction, emergence, and the provision of neuraxial anesthetic techniques are communicated to patients in their native language. This application also allows the patient to anticipate what is going to happen during a procedure.

http://bit.ly/WXbJuE

Pain Relief OAA: Android Application. This application gathers the Obstetric Anaesthetists' Association's information leaflets (translated into 35 languages) about pain relief and anesthesia for use by anesthesia providers, obstetricians, midwives, and mothers and their partners.

http://bit.ly/ZC37eC

Miniatlas Anesthesia Android Application. The application provides a library of detailed, high-quality images to support the daily clinical practice of anesthesiology by allowing patients to visualize procedures while the anesthesia provider is discussing them. These images can also be used for peer presentations or teaching and are supplemented with referenced texts.

http://bit.ly/Ubd6aw

Anesthesia Core Journals. This RSS-reader list provides summary headlines and/or abstracts of recent anesthesiology articles that have been indexed within journals under the category of Anesthesia and Emergency Medicine in the Abridged Index Medicus (AIM).

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