Sanjay Datta
EDITOR

Anesthetic *and* Obstetric Management *of* High-Risk Pregnancy

THIRD EDITION

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With 85 Illustrations

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For my wife, Gouri,
and daughter, Nandini,
whose endless support and encouragement,
continued understanding, and valuable advice
helped to make this project possible.

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Preface

It has been enormously satisfying to prepare the third edition of *Anesthetic and Obstetric Management of High-Risk Pregnancy* because it fulfills the need for close communication between two specialties, anesthesiology and obstetrics. This relationship is necessary not only to take care of the sick parturient, but also to deliver a healthy baby.

New developments in obstetrics and in obstetric anesthesia necessitated this third edition. Most of the contributors to this edition are new, and they have provided information on the latest approaches, as well as updated information. In addition, Chapter 13, "Critical Care Anesthesia for High-Risk Parturients," is completely new.

Like earlier editions, the third edition includes contributions from an international team of experts in the field of obstetric anesthesia and obstetrics. I thank all the authors for their valuable contributions. The authors have expressed their own opinions and recommendations, which do not necessarily reflect my own views. I also wish to thank Ms. Elizabeth Kiernan for her endless help in completing the new edition.

I sincerely hope this edition will further reinforce the concept of the team approach for taking care of the high-risk parturient.

Boston, Massachusetts *Sanjay Datta, MD, FFARCS(ENG)*

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1
Prepartum and Intrapartum Fetal Monitoring

Ramon Martin

Anesthesia for the obstetric patient is an integral part of labor and delivery. For routine, normal deliveries, anesthesia usually involves providing pain relief with an epidural technique. In pregnancies complicated by either maternal or fetal disease, the role of anesthesia is more central to patient care and can involve close monitoring with invasive lines during labor, fluid management, and discussion with the obstetricians about the timing and type of anesthesia.

Equally important in the dialogue with the obstetricians is an understanding of the techniques used to assess the fetus. During labor and delivery, the fetus is evaluated primarily by fetal heart rate (FHR) monitoring, either electronically or with intermittent auscultation. This technique is only one of several methods to monitor the fetus from the midfirst trimester through birth. As pregnancy progresses, the prenatal record contains a wealth of information not only about the parturient but also about the fetus.

The monitoring of the mother and the fetus during this period of development has evolved considerably as a result of biochemical and technical advances that have yielded a better understanding of the fetus. Most pregnancies proceed and end with no complications. Monitoring techniques are used not only for diagnostic purposes, thereby serving a preventive role, but also are possibly useful in treatment when the fetus is stressed. Stress to the fetus is defined in this chapter as either hypoxia or asphyxia, because the supply of oxygen to the fetus is crucial. Any diminution or cessation of oxygen results in an immediate change in acid–base status, affecting all organs, particularly the heart and the brain. There are compensatory responses by the fetus, but fetal reserves are limited. It is therefore important to recognize the fetal response to stress and, if possible, to identify the cause of the stress and treat it.

This chapter reviews the relevant aspects of fetal respiratory and cardiac physiology to define the fetal response to stress (i.e., asphyxia or hypoxia). The techniques used to monitor the fetus during pregnancy, labor, and delivery are discussed in relation to their effectiveness in determining whether a fetus is stressed.

Fetal Cardiovascular System

Fetal gas exchange occurs via the placenta. Because the fetal lungs are nonfunctional, several shunts in the fetal circulation allow oxygenated blood to pass from the placenta to the systemic circulation. Streaming or laminar blood flow keeps oxygenated blood separate in the venous system and assumes great importance in preferentially supplying oxygenated blood to organs such as the heart, brain, and adrenal glands during periods of hypoxia.

Venous Flow from the Placenta to the Fetal Heart

Approximately 40% of fetal cardiac output goes to the placenta, with a similar amount returning to the right heart via the umbilical vein (Figure 1.1). The blood in the umbilical vein has the highest oxygen saturation in the fetal circulation, so its distribution is important for the delivery of oxygen to fetal tissues. Half the umbilical venous blood enters the ductus venosus, which connects to the inferior vena cava; the rest enters the hepatoportal venous system.[1]

Streaming, which is the separation of blood with differing oxygenation saturations as it flows through a single vessel, is an important determinant of oxygen delivery to fetal tissue. This effect is seen when the more highly saturated umbilical venous blood passes through the ductus venosus into the inferior vena cava to meet the desaturated venous drainage from the lower trunk. In the liver, umbilical venous return is directed toward the left lobe and then portal venous return to the right lobe, so that there is a marked difference in oxygen saturation (higher in the left hepatic lobe than the right).[2,3] Although both hepatic veins enter the inferior vena cava, the left hepatic vein streams preferentially with the blood flow from the ductus venosus[3] whereas the right hepatic vein flow follows the same route as that from the abdominal vena cava.

Preferential flow of the umbilical venous return to the left atrium occurs because of the crista dividens, which splits the

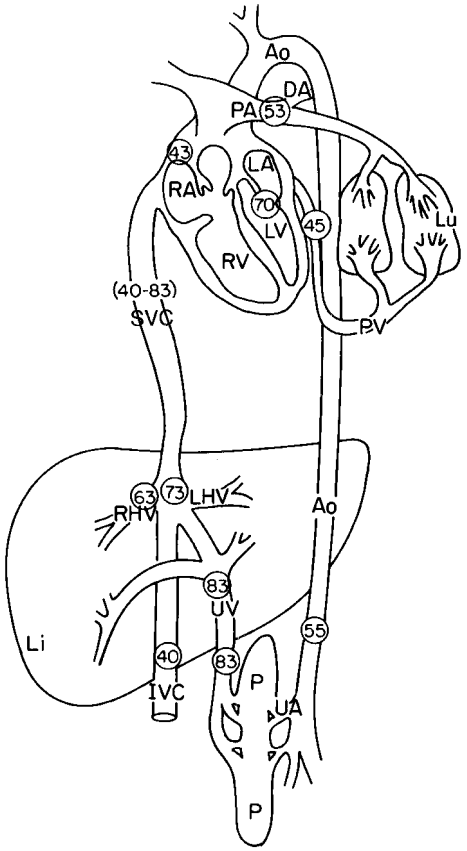

FIGURE 1.1. Normal fetal circulation with major blood flow patterns and oxygen saturation values (*circled numbers* indicate percent saturation). *IVC*, inferior vena cava; *P*, placenta; *Li*, liver; *RHV* and *LHV*, right and left hepatic veins; *SVC*, superior vena cava; *RA* and *LA*, right and left atria; *RV* and *LV*, right and left ventricles; *DA*, ductus arteriosus; *PA*, pulmonary artery; *Ao*, aorta; *Lu*, lung; *DV*, ductus venosus; *PV*, pulmonary vein; *UV*, umbilical vein; *UA*, umbilical artery.

inferior vena cava blood flow into two streams. One stream includes the oxygenated blood from the umbilical vein that is directed toward the foramen ovale and into the left atrium; the other stream consists of deoxygenated blood from the lower extremities and portal vein that enters the right atrium, resulting in a higher oxygen saturation in the left atrium than in the right. Blood flow through the superior vena cava is also preferentially streamed along with blood flow through the coronary sinus via the tricuspid valve. The desaturated blood from the right heart is directed toward the placenta for reoxygenation. The left heart supplies oxygenated blood for the brain.

Cardiac Output

Because of intracardiac and extracardiac shunts, the two ventricles do not work in series, as in adults. Therefore, they do not have the same stroke volume. The right ventricle ejects approximately two-thirds of fetal cardiac output (300 mL/kg/min), and the left ventricle ejects about one-third (150 mL/kg/min). Of the right ventricular output, only a small fraction (8%) flows through the pulmonary arteries. Most of the output crosses the ductus arteriosus and enters the descending aorta, allowing deoxygenated blood to return preferentially to the placenta. The left ventricular output enters the ascending aorta, and most of the output reaches the brain, upper thorax, and arms.[4–6]

TABLE 1.1. Distribution of cardiac output in fetal lambs.

Organ	Blood flow (mL/kg/min)	Cardiac output (%)
Heart	180	2
Brain	125	2
Upper body	25	16
Lungs	100	8
Gastrointestinal (GI) tract	70	5
Kidneys	150	2.5
Adrenals	200	0.1
Spleen	200	1.2
Liver	20	1.5
Lower body	25	20
Placenta	20	37

This distribution of cardiac output to individual organs is shown in Table 1.1. Because flow to the organs below the diaphragm is derived from both ventricles, flow is expressed as a percent of the combined ventricles.

Myocardial Function

The fetal myocardium, relative to the adult myocardium, is immature in structure, function, and sympathetic innervation. Although the length of the fetal sarcomere is the same as that in the adult,[7] the diameter of the fetal sarcomere is smaller, and the proportion of noncontractile mass to the number of myofibrils is less, 30% in the fetus versus 60% in adults.[8] Active tension generated is less than that in the adult heart at all lengths of a muscle along a length–tension curve. Passive or resting tension is higher in fetal myocardium than in the adult, suggesting lower compliance for the fetus.

A study of volume loading by infusion of blood or saline solution in fetal lambs showed that the right ventricle is unable to increase stroke work or output as much as that in the adult.[9] Cardiac output varies directly with heart rate, so an increase in rate from 180 to 250 beats/min will increase cardiac output 15% to 20%. Conversely, a decrease in heart rate below basal levels causes a decrease in ventricular output. Histochemical staining of the sympathetic nervous system demonstrates delayed development. Compared with the adult, isolated fetal cardiac tissue has a lower response threshold to the inotropic effects of norepinephrine, which is presumed to be secondary to the incomplete development of the sympathetic nervous system.[8] As a result, the fetal heart appears to operate at or near peak performance normally.

Control of the Cardiovascular System

The cardiovascular system is controlled by a complex interrelationship between autoregulation, reflex effects, hormonal substrates, and the autonomic nervous system. Although many organs in adults are able to maintain fairly constant blood flow over a wide range of perfusion pressures, the placental circulation does not exhibit autoregulation.[10] As a result, blood flow changes directly with changes in arterial perfusion pressure. Papile et al. demonstrated in fetal lambs that the cerebral circulation is autoregulated.[11] The baroreflex has also been shown to exist in fetal animals. In adults, it functions to stabilize heart rate and blood pressure, but in the fetus it is relatively insensitive. Marked changes in pressure are required to produce minor responses, so that the function of the baroreflex is probably minimal in utero.[12]

The chemoreceptor reflex is governed by receptors in either the carotid body or in the central nervous system (CNS) and causes hypertension and mild tachycardia with increased respiratory activity. Chemoreceptors in the aorta cause bradycardia with a slight increase in blood pressure. The former are less sensitive than the latter, so that bradycardia and hypertension are seen with hypoxia because of the overriding response of the aortic chemoreceptors.

The autonomic nervous system is fully developed in the fetus, as demonstrated by the presence of receptors and acetylcholinesterase and its response to cholinergic or adrenergic agonists. The renin-angiotensin system is also important in regulating the normal fetal circulation and the response to hemorrhage. Angiotensin II exerts a tonic vasoconstriction on the peripheral vasculature to maintain systemic arterial blood pressure and umbilical blood flow.[13] Vasopressin, although detectable in the fetus, probably has little regulatory function. Stress, that is, hypoxia, elicits an increase in vasopressin secretion and results in hypertension and bradycardia.[14] In the presence of decreased cardiac output, the renin-angiotensin system maintains the flow to the brain, heart, and placenta, while flow to the splanchnic bed decreases.[15] Circulating prostaglandins are present in high concentrations in the fetus[16,17] and are produced by both the placenta and the fetal vasculature. Prostaglandins (PGEs) have diverse effects on the cardiovascular system. Infusions of PGE_1, PGE_2, PGF_2, and thromboxane constrict the umbilical–placental circulation,[18,19] whereas prostacyclin has the opposite effect. Prostaglandin E_1, PGE_2, PGI_2, and PGD_2 cause pulmonary vasodilation in the fetus, and PGF_2 produces vasoconstriction.[20,21] Prostaglandins also relax smooth muscle in the ductus arteriosus so that it remains patent in utero.[22,23]

Placental Respiratory Gas Exchange and Fetal Oxygenation

Although fetal viability is seen at earlier gestational ages, a significant amount of morbidity results from the underdevelopment of the respiratory system. After the embryonic period, the airways proliferate and branch from 8 to 16 weeks gestation. Vascular channels appear from 17 to 27 weeks and approximate the potential air spaces; this is when effective gas exchange becomes possible. Surfactant appears and enhances adequate surface tension to keep the alveoli open. Type I and II epithelial cells are also identified. From 28 to 35 weeks gestation, the interstitial spaces thin and the peripheral air spaces develop. There is a gradual increase in the surface area for gas exchange. From 36 weeks on, the number of alveoli rapidly increases, and there is further differentiation of specific cell types.

The passage of oxygen from the atmosphere to the fetus can be described in a sequence of six steps. These steps alternate bulk transport of gases with diffusion across membranes. The first three steps are primarily maternal and the last three are fetal (Figure 1.2).

Transport of oxygen starts from the atmosphere to the maternal alveoli through the large airways by the respiratory muscles, in exchange for carbon dioxide. The pressure of oxygen in the alveoli is regulated by several mechanisms that respond to changes in the levels of the partial pressures of oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}), and the pH of maternal blood. Arterial P_{CO_2} in the parturient is regulated at a lower level than in the nonpregnant woman, secondary to the effects of progesterone.[24]

With the second step, oxygen diffuses rapidly across the alveoli to maternal erythrocytes. The PO_2 of maternal arterial blood is slightly less than that in the alveoli because of shunting and inequality of ventilation and perfusion throughout the lung fields. In the pregnant woman, the gradient of oxygen in the arterioles and alveoli is dependent on position and widens

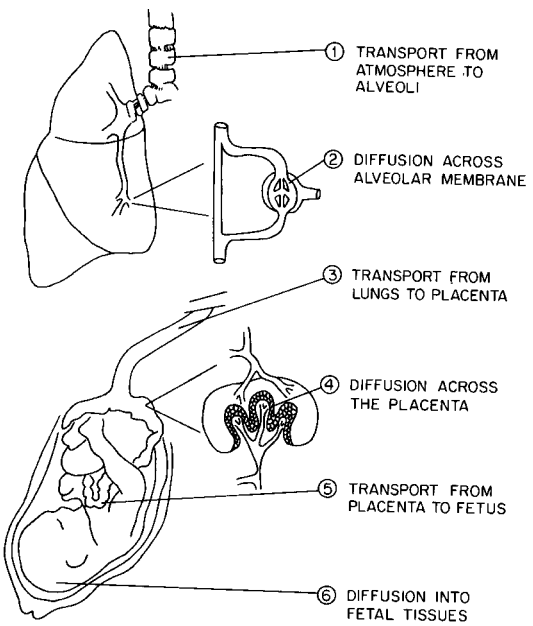

FIGURE 1.2. Six steps in the transport of oxygen from the atmosphere to the fetal tissues.

when she moves from the upright to the supine position. Maternal blood transports oxygen to the placenta in two forms, free and bound to hemoglobin. These two forms are in a reversible equilibrium.

In the diffusion of oxygen across the placenta, the oxygen uptake by the gravid uterus is greater than that by the fetus; this is because, compared with the fetus, the placenta and uterus extract oxygen and consume a relatively large fraction. In chronic sheep preparations, this has been calculated with the Fick principle: uterine oxygen consumption is measured by the difference in oxygen content between the maternal arterial blood (A) and uterine venous blood (V). Multiplying the difference by uterine blood flow (F) yields uterine oxygen uptake:

$$(A - V)F = O_2 \text{ uptake by the gravid uterus}$$

In a sheep study, the umbilical vein was observed to carry the highest concentrations of oxygenated blood delivered to the fetus, but this is low when compared with maternal Po_2. Attempts have been made to explain the low fetal Po_2 with either a concurrent or cross-current model of placental oxygen exchange, but the placenta is probably more complex. Nonetheless, the umbilical venous Po_2 depends on and is not higher than the venous Po_2 of the uterine circulation.[25] In addition, three other factors might contribute to the inefficiency of the exchange process:

1. Shunting: the diversion of blood away from the exchange surface to perfuse the myometrium and endometrium
2. Uneven perfusion: differences in the ratio of maternal–fetal blood flow in portions of the placenta
3. Oxygen-diffusing capacity: defined as the product of the quantity of oxygen transferred from maternal to fetal circulation divided by the mean Po_2 difference between maternal and fetal erythrocytes; this is the result of the permeability of the placental membrane to oxygen transport and the reaction rate of oxygen with hemoglobin.[26]

Uterine venous Po_2, a primary factor that determines umbilical venous Po_2, is in turn influenced by a number of other factors (Box 1.1). Chief among these are the oxygen saturation and the oxyhemoglobin dissociated curve of venous blood. The oxyhemoglobin dissociation curve is shifted by pH so that Po_2 is inversely related to pH (Bohr effect). As a result, maternal alkalosis will shift the curve to the left, decreasing oxygen delivery to the fetus. Other factors that can shift the curve are temperature, hemoglobinopathies, and the 2,3-diphosphoglycerate (2,3-DPG) content of erythrocytes. Oxygen saturation of uterine venous blood (Sv) is a function of four variables: maternal arterial oxygen saturation (Sa), oxygen capacity of maternal blood (O_2Cap), uterine blood flow (F), and the oxygen consumption rate (Vo_2) of the gravid uterus (including placental and fetal oxygen consumption; this can be formulated as follows:

$$Sv + Sa - Vo_2(O_2Cap)$$

which is an application of the Fick principle. Anemic, circulatory, or hypoxic hypoxia will decrease uterine venous saturation, leading to a decrease in fetal oxygenation.

Box 1.1. Factors that determine uterine venous Po_2.

- Oxyhemoglobin dissociation of maternal blood
  - Hemoglobin structure
  - Temperature
  - Erythrocyte pH [2,3-diphosphoglycerate, (2,3-DPG)]
- Oxygen saturation in uterine venous blood
  - Arterial O_2 saturation
  - Uteroplacental blood flow
  - O_2 capacity
  - Placental and fetal O_2 consumption

Although umbilical vein Po_2 is less than that in the maternal circulation, there are compensatory mechanisms to ensure adequate fetal oxygenation. Fetal erythrocyte hemoglobin has a high affinity for oxygen. The rate of perfusion of fetal organs, compared with adult organs, is high in relation to their oxygen requirements. Physiologically, the low level of Po_2 in fetal arterial blood is a part of the mechanism that keeps the ductus arteriosus open and the pulmonary vascular bed constricted.

Supplemental oxygen increases the Po_2 of maternal arterial blood, but causes only a small increase in fetal arterial Po_2, because of the differences in the oxyhemoglobin dissociation curves between mother and fetus (Figure 1.3). Increasing the fractional inspired oxygen (Fio_2) to 100% causes a rise in maternal Po_2 from 90 to 500 Torr, or an increase of 1 mmol for the arterial oxygen content.[27] Because there is no change in uterine blood flow and presumably in uterine oxygen consumption rate, uterine venous oxygen content also increases 1 mmol. The resulting increase in uterine venous Po_2 is 11.5 Torr, which is not to say that supplemental oxygen for the mother has no effect; it probably is more important when the fetus is hypoxic.

As in the mother, carbon dioxide is one end product of fetal metabolism. Carbon dioxide from the fetus diffuses across the placenta from the umbilical circulation to the maternal side for transport to the lungs and excretion. The diffusion process requires that the Pco_2 of fetal blood be higher than that on the maternal side. In sheep, the umbilical venous blood is approximately 5 Torr higher than that in the maternal vein. As a result, perturbations in the maternal acid–base balance are quickly reflected in the fetus. Therefore, fetal respiratory alkalosis (low fetal Pco_2) is secondary to a low maternal Pco_2. Although fetal respiratory acidosis can be caused by a high level of maternal Pco_2, decreased placental perfusion resulting in an adequate gas exchange can also play a role.

Fetal Heart Rate

The average FHR decreases from 155 beats/min at 20 weeks gestation to 144 beats/min at 30 weeks gestation and is 140 beats/min at term. The variability is 20 beats/min in a normal

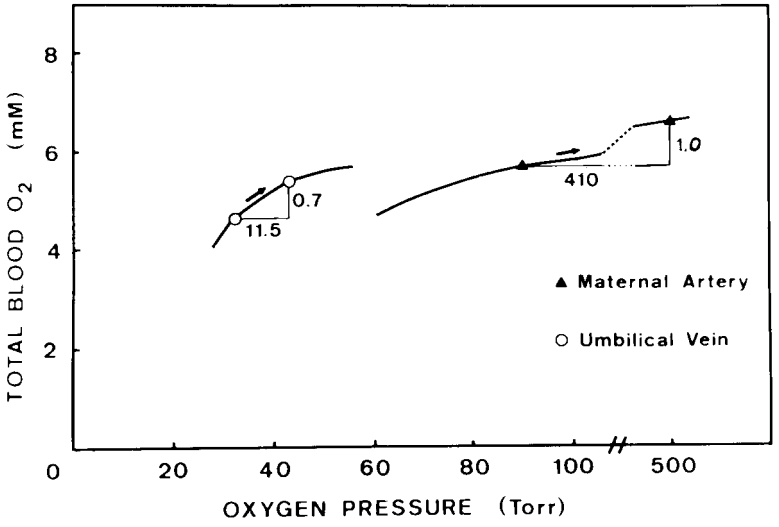

FIGURE 1.3. Relationship between oxygen content and P_{O_2} in maternal and fetal blood before and after maternal inhalation of 100% oxygen.

fetus. The sinoatrial (SA) and the atrioventricular (AV) nodes serve as intrinsic pacemakers, with the SA node setting the rate in the normal heart. Variability of the FHR is followed either beat to beat or over a longer period and is an important prognostic variable. Control of the FHR is the result of a number of factors, both intrinsic and extrinsic.

The parasympathetic nervous system contributes to cardiac regulation through the vagus nerve. It has endings in both the SA and AV nodes. Stimulation of the vagus nerve results in bradycardia through a direct effect on the SA node. Blocking the vagus nerve results in an increase in heart rate of approximately 20 beats/min,[28] so the vagus nerve exerts a constant influence to decrease a higher intrinsic rate. In addition, the vagus nerve transmits impulses that result in beat-to-beat variability of the FHR.[29]

The sympathetic nervous system has nerve endings throughout the myocardium at term. Stimulation of the sympathetic nerves causes release of norepinephrine and an increase in heart rate and contractility and therefore cardiac output. If the sympathetic nerves are blocked, there is an average decrease of 10 beats/min in the FHR.

The sympathetic and parasympathetic nervous systems are modulated by other factors. Chemoreceptors located in both the peripheral nervous system and the CNS exert their primary effect on the control of respiration, but they also have an effect on the circulation. With a decrease in arterial perfusion pressure or an increase in carbon dioxide content, a reflex tachycardia develops leading to an increase in blood pressure. Baroreceptors are located in the arch of the aorta and at the junction of the internal and external carotid arteries and are sensitive to increases in blood pressure. When pressure rises, impulses are sent via the vagus nerve to decrease the heart rate and cardiac output.

Of the possible hormones that can contribute to heart rate control, three have an effect during periods of stress. Epinephrine and norepinephrine are secreted by the adrenal medulla during stress. Their effects are similar to those caused by sympathetic stimulation: an increase in heart rate, contractility, and blood pressure. The adrenal cortex produces aldosterone in reaction to hypotension; this increases blood volume by slowing renal sodium output, leading to water retention.

Fetal Breathing and Body Movements

Fetal breathing and body movements are important functions during fetal life. The development of skeletal and diaphragmatic muscle is dependent on these movements in utero. Fetal lung development is also dependent on diaphragmatic motion. This movement does have its cost, consuming 15% to 30% of available fetal oxygen supplies.[30] Therefore, absence of either movement or breathing can be a sign of hypoxia.[31,32]

Fetal Breathing

Studies in lambs have demonstrated that breathing movements occur about 40% of the time during observation; this directly correlates with low-voltage electroencephalogram activity and electro-ocular activity.[33] Flow in and out of the trachea to the lungs occurs in conjunction with diaphragmatic motion.[34] In ewes, the frequency of fetal breathing movements decreases from 39% to 7% when hypoxia is induced.[31] Gasping movements occur with asphyxia in dying fetal animal preparations.[35] Two to 3 days before the onset of labor, fetal breathing movements decrease[36,37]; this is thought to be secondary to the rising concentration of PGE_2, which probably plays a role in the onset of labor.[38] Infusing PGE_2[39] or inducing labor with adrenocorticotropic hormone (ACTH),[37] with a subsequent rise in PGE_2, is associated with a drop in fetal breathing movements from 40% to 15% of the time.

A number of other factors can alter breathing activity (Table 1.2). The time of day is very important, particularly during the last trimester. In addition to circadian rhythms, 2

Table 1.2. Factors that alter fetal breathing.

Drug/condition	Effect
Hypoglycemia	Decrease
Glucose infusion	Increase
Ethanol	Decrease
Barbiturates	Decrease
Diazepam	Decrease
Catecholamines	Increase
PGE_2	Decrease
Indomethecin	Increase

PGE, prostaglandin.

to 3 h postprandial, fetal breathing movements increase significantly,[40–45] probably secondary to the increase in maternal blood glucose.[40–45] After either an oral[46] or an intravenous glucose[47] load to the mother, fetal breathing movements increase.[48] During the last 10 weeks of pregnancy, administration of carbon dioxide (5%) to healthy pregnant women results in increased breathing movements,[49] which is thought to represent maturation in the sensitivity of the fetal respiratory center. Maternal ingestion of drugs affects fetal breathing movements. After administration of ethanol[50] or methadone,[51] there is a marked decrease in breathing movements, whereas with maternal cigarette smoking,[52] there is a transient increase in the frequency of a fetal breathing activity. During the 3 days before the onset of spontaneous labor, fetal breathing movements decrease, and they are absent during active labor.[53]

Fetal Body Movements

Fetal body movements are considered significant when the body rolls and the extremities stretch. Isolated limb movement is not of any consequence. During the last trimester, fetal body movements occur on average 3 to 16 min in each hour during a 24-h period of observation.[54] The actual or mean number of fetal body movements ranges from 20 to 50 per hour, but up to 75-min spans of no movement have been recorded in healthy fetuses. Unlike fetal breathing movements, body movements are not influenced by maternal plasma glucose concentration[55] and maternal alcohol ingestion,[50] and they do not decrease during the last 3 days before onset of spontaneous labor.[56] Fetal body movements, however, are closely related to FHR accelerations. Reports show that from 91% to 99.8% of fetal movements are associated with FHR accelerations.[57]

Fetal Acid–Base Physiology

Fetal metabolism results in the production of carbonic and noncarbonic acids that require buffering. Carbonic acid is the hydration product of carbon dioxide, which in turn is the end product of the oxidative metabolism of glucose. Hemoglobin in the fetal erythrocyte buffers the carbonic acid and transports it to the placenta. Carbon dioxide is regenerated and diffuses quickly across the placenta. If maternal respiration and uteroplacental and umbilical blood flows are maintained, then large amounts of carbon dioxide can be eliminated rapidly. On a molar basis, the rate of fetal carbon dioxide production is basically equivalent to the oxygen consumption rate of the fetus.[58] The noncarbonic acids in the fetus include uric acid (from the metabolism of nonsulfur-containing amino acids), lactate, and keto acid (from the metabolism of carbohydrates and fatty acids). These noncarbonic acids are eliminated through the maternal kidneys, after diffusing slowly across the placenta. The maternal kidney regenerates bicarbonate from the excretion of the noncarbonic acids.

Box 1.2. Factors that affect fetal acid–base balance.

- Mother
  - Hypoxia
  - Hypoventilation
  - Altered hemoglobin
  - Metabolic acidosis
  - Decreased blood supply to placenta
- Placenta
  - Infarction or separation
  - Insufficiency
- Fetus
  - Obstruction of umbilical blood flow
  - Fetal anemia
  - Increased fixed acid production

A number of other factors that affect acid–base balance in the fetus disrupt either the supply of oxygen or the removal of the carbonic and noncarbonic acids through the placenta. The maternal, fetal, and placental factors listed (Box 1.2) can result in either respiratory or metabolic perturbations of fetal acid–base balance. Fetal respiratory acidosis is secondary to decreased carbon dioxide elimination, which is most commonly caused by either decreased minute ventilation or V/Q mismatch that results in maternal respiratory acidosis which is reflected in the fetus. As with primary fetal respiratory acidosis, rapidly reversing the cause in the mother restores fetal acid–base balance. Maternal respiratory alkalosis is caused by hyperventilation, which decreases the P_{CO_2}, increases the pH, and responds rapidly to reversal of the causes.

Fetal metabolic acidosis can result from either primary fetal or secondary maternal metabolic acidosis. The decreased pH is caused by loss of bicarbonate and is usually a result of chronic metabolic disorders. With prolonged fetal respiratory acidosis from cord compression or abruptio placentae, the accumulation of noncarbonic acids can result in a mixed respiratory-metabolic acidosis.

Fetal Temperature Regulation

Fetal temperature parallels that of the mother. Heat is produced as a by-product of metabolic processes that consume oxygen. Just as fetal oxygen consumption (approximately 6.8–8 mL/kg/min) is twice that of the adult (3–4 mL/kg/min), fetal heat production is also large compared to the adult. This

heat can be dissipated through either the umbilical circulation or the fetal skin; the former is the major source of heat loss. A decrease in uterine blood flow, as occurs during uterine contractions, might increase fetal temperature. Although this has not been shown directly, indirectly, the maternal and fetal temperature gradient does increase during labor.[59] Epidural anesthesia during labor has been associated with increased maternal temperature, but the mechanism has not been delineated, and there is no evidence so far of a detrimental effect on the fetus.[60]

Fetal Reaction to Stress

During labor and delivery, the main causes of stress for the fetus are hypoxia and asphyxia. Fetal hypoxia is caused by the mother breathing a hypoxic mixture of gases, which results in decreased oxygen tension. Asphyxia is secondary to a reduction of at least 50% in uterine blood flow. In addition to decreased oxygen tension there is also increased carbon dioxide tension, leading to both metabolic and respiratory acidosis. With prolonged asphyxia, the fetus switches to anerobic metabolism and produces a buildup of lactate. Metabolic acidosis subsequently develops. The fetal responses to hypoxia or asphyxia are as follows:

1. Bradycardia (due to increased vagal activity) with hypertension
2. Slight decrease in ventricular output
3. Redistribution of blood from the splanchnic bed to the heart, brain, placenta, and adrenals[61]
4. Decrease in fetal breathing movements (from 7% to 39% of the time)
5. Terminal gasping movements with asphyxia
6. Increased circulating catecholamine levels in fetal sheep
7. Increased alpha-adrenergic activity

In chronically instrumented sheep, fetal oxygen consumption drops by as much as 60% of control values with hypoxia[62]; this is accompanied, as already described, by fetal bradycardia, an increase in blood pressure, and progressive metabolic acidosis. The fetal sheep can tolerate this for approximately 1 h; these changes are rapidly reversed with restoration of oxygenation.[63] Fetal cerebral[64] and myocardial[65] oxygen consumption has been shown to remain constant. When hypoxia is prolonged or proceeds to asphyxia, these compensatory mechanisms are lost.

Transition from Fetus to Neonate

With labor and birth, the fetus becomes a neonate and undergoes a series of physiologic changes. Although these changes affect every major organ system, this section considers primarily the cardiovascular and respiratory systems. With the separation of the placenta, the changes that occur include the following:

1. Blood flow through the inferior vena cava decreases, with a resultant decrease in right atrial blood flow and pressure.
2. Pulmonary blood flow increases as pulmonary vascular resistance falls (secondary to lung expansion and vasodilation of the pulmonary vascular bed).
3. Venous return to the left atrium increases, as well as left atrial pressure.

These changes produce a "series" flow pattern from the fetal "parallel" flow pattern.

Closure of Fetal Shunts

The ductus arteriosus closes in response to a rise in oxygen tension and decreased levels of circulating prostaglandins. The former effect is age dependent, so that premature infants have a decreased response to a rise in P_{O_2}. Glucocorticoids, which are used in premature infants to accelerate fetal lung maturation, decrease this effect. The ductus venosus closes with the fall in partial venous and sinus pressures. Unlike the ductus arteriosus, the ductus venosus is not dependent on changes in P_{O_2} or endogenous levels of catecholamines. The foramen ovale closes because the pressure in the left atrium rises above that in the right atrium. Anatomic closure of all three shunts, although begun at birth, is not completed until 24 h to 3 months after birth.

Cardiac Output

Neonatal cardiac output is 600 to 850 mL/kg/min, a small increase over fetal cardiac output of 500 mL/kg/min. The left ventricular output increases to 2 to 2.5 times that of the fetal left ventricular output, whereas the output from the right ventricle remains basically the same. Neonatal heart rate decreases from fetal levels but can vary from 140 beats/min in the awake infant to 90 to 120 beats/min during sleep.

Respiratory Changes

The intermittent, rhythmic respiratory movements of the fetus become continuous after birth and ensure gas exchange. A number of factors exert an effect:

1. Changes in the physical environment (temperature, sound, and tactile stimulation)
2. Preconditioning changes during labor (increase in P_{CO_2} and a decrease in pH)
3. Increase in P_{O_2} secondary to the cardiovascular changes

With a vaginal delivery, the compression of the head and thorax during the passage through the vaginal canal followed by the sudden expansion with the delivery of the trunk results in an elastic recoil of the thorax and active contraction of the respiratory muscles. This change also stimulates two reflexes:

1. The Herring Breuer inflation reflex: lung inflation results in inspiratory inhibition, which causes a higher respiratory

rate in the neonate and may be important in maintaining a higher functional residual capacity (FRC).
2. Head's reflex: an increase in inspiratory effort with rapid lung inflation.

Reabsorption of amniotic fluid from alveolar air spaces, along with an increase in lung volume, results in a rise in lung compliance with birth that gradually continues to rise in the hours after birth. In premature infants, both lung volume and compliance are decreased and are further decreased in infants with respiratory distress syndrome (RDS). Airway and pulmonary resistance, although initially high at birth, decreases with age as the diameter of the airways becomes larger. FRC increases quickly after birth as amniotic fluid is reabsorbed. The respiratory rate, initially 60 to 80 breaths/min, gradually decreases to 30 to 40 breaths/min. Tidal volume is 5 to 7 mL/kg body weight. Minute ventilation ranges from 150 to 250 mL/kg/min.

During labor and delivery, uterine contractions decrease uterine blood flow, which in turn can decrease fetal gas exchange. This effect can also be produced by cord compression or partial separation of the placenta, resulting in relative hypoxia and hypercapnia at birth in neonates. These effects are transient in most neonates because the start of regular breathing improves oxygenation.

Perinatal Mortality

According to the National Center for Health Statistics,[66] the perinatal mortality rate (PMR) is defined as the number of late fetal deaths (>28 weeks gestation) plus early neonatal deaths (infants 0–6 days of age) divided by 1000 live births plus the fetal and neonatal deaths. In the United States, the PMR has declined by an average of 3% per year since 1965.[67] Over the past 6 years, fetal death rate alone has decreased 16%, and neonatal mortality has fallen 21%. Of all fetal deaths, 22% occur between the 36th and 40th weeks of gestation and another 10% occur beyond the 41st week of gestation.

Congenital anomalies account for 25% of perinatal mortality and are the leading cause.[68] Premature labor and delivery was the most common event leading to death in this group. Overall, prematurity with associated RDS was the next most common cause of perinatal death. Intrauterine hypoxia and birth asphyxia account for 3% of the PMR, and placenta or cord complications accounted for 2% of the PMR. Several associated factors identified by Lammer et al.[69] were race (African-American), marital status (single), age (>34 or <20 years), parity (>5), and lack of prenatal care. Multiple gestations were associated with 10% of all fetal deaths, giving a PMR of 50/1000, which is seven times that of singleton pregnancies. More than half of all fetal deaths were associated with asphyxia or maternal causes such as pregnancy-induced hypertension (PIH) or placental abruption.

If the first step to reducing the PMR further is recognizing the causes, then the next step is prevention. A study of perinatal mortality in the Mersey region of England showed that of 309 perinatal deaths, 182 or 58.9% were due to avoidable causes, primarily a delayed response to abnormalities of the progress of labor or FHR tracing during labor and delivery, maternal weight loss with a resulting growth-retarded fetus, and reductions in fetal movement.[70] Antepartum fetal monitoring is the means to decrease these fetal deaths; this is most useful when targeting specific groups of parturients who are at increased risk of perinatal mortality (Table 1.3).

TABLE 1.3. Parturients at increased risk of perinatal mortality.

Maternal disease	Fetal disease
Post-dates gestation	Neonatal asphyxia
Diabetes	Perinatal death
Previous stillbirth	Perinatal death
Pregnancy-induced hypertension	Fetal distress in labor
Maternal age >35 years	Congenital anomalies
Maternal weight loss	IUGR
Premature labor	RDS

IUGR, intrauterine growth restriction; RDS, respiratory distress syndrome.

Techniques of Fetal Assessment

Before 20 weeks gestation, tests are done to assess the fetus for fetal anomalies.

Amniocentesis

Performed before 15 weeks gestation, early amniocentesis is an alternative to chorionic villus sampling to obtain fetal cells for diagnosis of genetic or morphologic abnormalities. The indications for amniocentesis are listed in Box 1.3. Although the success of obtaining cells is the same as for chorionic villus sampling, the disadvantages are primarily those of withdrawal of amniotic fluid. The volume of fluid removed is a much greater proportion of the total fluid volume, which could increase fetal loss.

After 16 weeks gestation, midtrimester amniocentesis with ultrasound guidance is safe with a rate of fetal loss of 0.5% to 1.0%.[71,72] The amniotic fluid is used to grow fetal cells, which in turn are scanned for chromosomal aberrations. During the third trimester, amniocentesis is used to obtain fluid to assess fetal lung maturity.

Box 1.3. Indications for amniocentesis.

- Maternal age 35 years or older at delivery
- History of any chromosomal abnormality in a family member
- Birth of a previous child with Down syndrome or other chromosomal disorder
- Parents at risk for being carriers of X-linked disorders or inborn errors of metabolism
- History of recurrent spontaneous abortions
- Family history of neural tube defects

Chorionic Villus Sampling

Performed between 9 to 12 weeks of gestation, chorionic villus sampling allows early determination of chromosomal abnormalities. Under ultrasound guidance, this technique is simply the aspiration of villi through either the cervix or the abdomen. Because actual tissue is obtained, results from cells are available as early as 24 to 48 h and can also be analyzed for abnormalities in DNA or specific enzymatic reactions. Fetal loss was 2.3% to 2.5% in one randomized trial.[73] Limb reduction defects and oromandibular hypogenesis have been reported in a small number of infants after chorionic villus sampling,[74] but other studies[75,76] have not demonstrated any difference between the expected rates of appearance of these developmental aberrations.

Percutaneous Umbilical Blood Sampling

Starting at 18 weeks gestation, fetal blood can be obtained transabdominally under ultrasound guidance by needle puncture of the umbilical cord, a method useful in diagnosing a range of problems[77]:

1. Hematologic abnormalities, such as hemoglobinopathies, isoimmunization, thrombocytopenia, and coagulation factor deficiencies
2. Inborn errors of metabolism
3. Infections by viruses, bacteria, or parasites
4. Chromosomal abnormalities, especially mosaicism

The risk to the fetus is greater than other tests, with an increase in fetal loss of 2%.[77] As a result, this test is usually reserved for situations in which information cannot be obtained by other means.

Ultrasonography

During the past three decades, ultrasound has become an important method of antepartum fetal assessment. Useful throughout gestation, it gives an accurate measurement of gestational age and provides an assessment of fetal growth as well as developmental abnormalities. It is also an important guide in the performance of amniocentesis, chorionic villus sampling, and cordocentesis. Real-time ultrasound permits a dynamic assessment of fetal well-being by following, over time, fetal breathing activity, movements, and tone.

Despite its importance as a method of fetal assessment, there is still controversy about the routine use of ultrasound in pregnancy. In Helsinki, Finland, which like many other European countries advocates routine ultrasound screening, a randomized trial showed a significant decrease in perinatal mortality in the screened group compared to the control group,[78] primarily due to early detection of fetal malformations. A number of other studies have not found a benefit from routine ultrasound screening.[79,80] A recent large-scale study of 15,151 pregnant women demonstrated no difference in adverse perinatal outcome. Subgroups of women with post-dates gestation, multiple pregnancies, or infants who are small for gestational age did not differ in perinatal outcome between the control and study populations.[81] This controversy is also fueled by the desire to contain medical costs by decreasing unnecessary testing.

During the first trimester, ultrasonography, particularly transvaginal sonography, can help determine whether a fetus is viable, when there is vaginal bleeding, or determine the presence of other processes: ectopic pregnancy, uterine anomaly, or an adnexal mass. In addition, it can provide the first measurement of fetal crown-rump length as a measure of fetal age. During the second trimester, ultrasound assessment of biparietal diameter becomes an accurate measure of gestational age.[82] From 12 to 28 weeks of gestation, the relation between biparietal diameter and gestation is linear.[83] Ultrasound assessment of fetal growth, when continued into the third trimester, is important in diagnosing deviations from normal growth such as growth retardation, macrosomia, or developmental anomalies. Diagnoses of oligohydramnios or polyhydramnios are made by ultrasound. Real-time ultrasound measures variables that are the components of the Biophysical Profile (amniotic fluid volume, fetal breathing, limb movement, and tone). All these measurements can affect the course of labor and delivery.

Doppler Ultrasound Velocimetry

Blood flow in fetal and maternal vessels, particularly the umbilical artery, can be assessed by Doppler ultrasound velocimetry. The Doppler principle is the use of focused sound waves of a known frequency, directed at blood moving in a vessel. The sound waves that are reflected back have a different frequency and are converted to a visual displacement of blood velocity. This technique has been used since 1978 to measure fetal–placental circulation, particularly in high-risk disease states that result in vascular changes.

In a normal pregnancy, blood flows through the umbilical artery even during diastole because of decreased placental resistance. Increased placental vascular resistance, as seen with preeclampsia and resultant intrauterine growth restriction (IUGR), might result in decreased umbilical artery blood flow during diastole. Decreased diastolic flow results in an increased ratio of systolic to diastolic flows (S/D). Absent or reversed diastolic flow is considered potentially ominous and might be associated with either a fetal anomaly or severe IUGR. This finding usually indicates the need for further testing and possible delivery of a fetus. Several other blood vessels in the uterus and fetus have been studied but so far have had few useful clinical correlates.

Analysis of Maternal Serum

Maternal serum is routinely sampled during the first trimester to assess the possibility of neural tube defects and Rh sensitization. Neural tube defects are one of the most frequent con-

genital abnormalities, with an incidence of 1 to 2 per 1000 live births in the United States.

Alpha fetoprotein (AFP) is elevated in the fetal serum during the first trimester when the neural tube fails to close, resulting in anencephaly, meningomyelocele, or encephalocele. Alpha fetoprotein passes through the placenta into the maternal serum and can be measured with a radioimmunoassay. Alpha fetoprotein is also elevated in malformations of the gastrointestinal tract, as well as in fetal death, decreasing the specificity of the test. Despite this, it is still used as a general screening test; with any abnormal values, ultrasonography and amniocentesis are performed for confirmation.

The Triple Screen blood test attempts to predict whether a fetus is at higher risk of having Down syndrome, anencephaly, or neural tube defects such as spina bifida. This test, however, may miss 15% to 40% of fetuses with Down syndrome and has a false-positive rate as high as 8%. As a result, this test is of decreasing interest to both clinicians and patients. Other tests, such as fetal nucleated red cells and urinary hyperglycosalated human chorionic gonadotropin (HCG), are being studied.

Maternal Assessment of Fetal Activity and Uterine Contractions

Asking a parturient to count fetal activity over a period of time provides a simple and sensitive test of fetal well-being. It is based on the fact that from 28 weeks of gestation on, the fetus makes approximately 30 body movements each hour (about 10% of the total time), and the parturient is able to appreciate most of these.[84] Although fetal movement is reassuring, lack of movement can indicate either a quiet period, which can usually last 20 min (but can last as long as 75 min), or fetal compromise secondary to asphyxia. Factors that can decrease maternal appreciation of fetal activity are an anterior placenta, polyhydramnios, and obesity.[85] Several studies have demonstrated that when patients reliably count fetal movements according to a set protocol, there is a significant reduction in fetal death.[86–88]

Because premature labor with resultant delivery of a premature infant is a leading cause of neonatal morbidity and mortality, it was thought that monitoring uterine contractions might predict women at increased risk of preterm labor. Several studies have demonstrated that ambulatory monitoring of uterine contractions does not reduce the rate of preterm delivery.

Assessment of Fetal Lung Maturity

Because fetal chronologic age does not necessarily correlate with functional maturity, particularly in respect to the pulmonary system, methods of assessing fetal lung maturity are important adjuncts in clinical decision making. The majority of perinatal morbidity and mortality results from complications of premature delivery. The most frequently seen complication is the RDS. This disorder is caused by a deficiency of a surface-active agent (surfactant) that prevents alveolar collapse during expiration. Phospholipids produced by fetal alveolar cells are the major component of lung surfactant and are produced in sufficient amounts by 36 weeks gestation. The most commonly used technique measures the lecithin–sphingomyelin ratio (L/S). The concentration of lecithin, a component of surfactant, begins to rise in the amniotic fluid at 32 to 33 weeks gestation and continues to rise until term. The concentration of sphingomyelin remains relatively constant, so that the ratio of the two provides an estimate of surfactant production that is not affected by variations in the volume of amniotic fluid. The risk of neonatal RDS when the L/S ratio is greater than 2 is less than 1%. If the ratio is less than 1.5, approximately 80% of neonates will develop RDS.

Disaturated phosphatidylcholine (SPC) is the major component of fetal pulmonary surfactant. The technique that separates SPC from lecithin in amniotic fluid is complicated, and the results can be altered by abnormalities in amniotic fluid production and excretion (i.e., oligohydramnios or polyhydramnios). A value greater than 500 μg/dL for SPC concentration in amniotic fluid is consistent with mature fetal lungs and a small risk for RDS. However, in diabetic parturients, the SPC value should be 1000.

The disadvantages in measuring the L/S ratio include a long turnaround time, the use of toxic reagents, a lack of technical expertise, and the inability to standardize the test. As a result, few hospitals are able to perform the test. Another test, the TDx fetal lung maturity test, is automated and avoids the technical involvement of sample preparation and measurement. The test relies on the fluorescence polarization of a dye added to a solution of amniotic fluid that is then compared with values on a standard curve to determine the relative concentration of surfactant and albumin. The determined values are expressed in milligrams of surfactant per gram of albumin. With a cutoff of 50 mg/g for maturity, the TDx test was equal in sensitivity (0.96) and more specific (0.88 versus 0.83) when compared with the L/S ratio in one multicenter study.[89]

Biophysical Profile

The biophysical profile involves evaluation of immediate biophysical activities (fetal movement, tone, breathing movements, and heart rate activity) as well as semiquantitative assessment of amniotic fluid. The biophysical parameters reflect acute CNS activity and when present correlate positively with the lack of depression (secondary to asphyxia) of the CNS. Amniotic fluid volume represents long-term or chronic fetal compromise. Major indications for referral for biophysical profile include suspected IUGR, hypertension, post-dates gestation, and diabetes.

The biophysical evaluation of the fetus is done by ultrasound with the sole purpose of detecting changes in fetal activity due to asphyxia. Changes in fetal breathing movements, heart rate, and body movements are indicators of the state of fetal oxygenation. Superimposed on these factors are the nonrandom pattern of CNS output and the sleep state, with effects that might be mistaken for hypoxia. However, extend-

TABLE 1.4. Biophysical profile scoring.

Variable	Score = 2	Score = 0
Fetal breathing movements	One episode, 30-s duration in 30 min	Absent
Gross body movement	Three discrete body/limb movements in 30 min	More than two episodes in 30 min
Fetal tone	One episode of extension/flexion of hand, limb, or trunk	Absent or slow movement
Fetal heart rate (FHR)	Two episodes of acceleration with fetal movement in 30 min	More than two episodes
Amniotic fluid volume	One pocket, 1 × 1 cm	No amniotic fluid or a pocket <1 × 1 cm

ing the period of observation to find a period of normal recovery for the latter conditions helps to differentiate asphyxia from normal variants.

The scoring of the fetal biophysical profile is an assessment of five variables (Table 1.4), four of which are monitored simultaneously by ultrasound. The variables are said to be normal or abnormal and are assigned a score of 2 for normal and 0 for abnormal. The nonstress test (NST) is monitored after the biophysical evaluation. When the test score is normal, conservative therapy is indicated, with some exceptions:

1. Post-date gestation with a favorable cervix
2. Growth-retarded fetus with mature pulmonary indices and a favorable cervix
3. Insulin-dependent diabetic woman at 37 weeks gestation or more with mature pulmonary indices
4. Class A diabetic woman at term with a favorable cervix
5. Women with medical disorders (e.g., asthma, preeclampsia, PIH) that might pose a threat to maternal and fetal health

Table 1.5 lists recommendations for management of biophysical profile scores.

Several prospective studies (Table 1.6) have shown that the majority of women studied (>97%) have normal test results and delivery outcome. Perinatal mortality varies inversely with the last score before delivery. In 1981 and 1985, in large groups of patients, Manning et al.[94,95] found that the gross perinatal mortality rate decreased from 11.7 to 7.4 per 1000 and the corrected value decreased from 5 to 1.9 per 1000. In Manitoba, since the use of this testing, the stillbirth rate has decreased by 30%. A stillbirth occurring within a week of a normal test result is defined as a false negative; this ranges from 0.41 to 1.01 per 1000 with a mean of 0.64 per 1000.

The false-negative rate, although small, directly reflects the negative predictive accuracy of the test. Manning et al.[90] calculated from a study of 19,221 pregnancies a negative predictive accuracy of 99.224%, or the probability of fetal death after a normal test result as 0.726 per 1,000 patients.

Because the ideal testing method would result in no false-negative deaths, the biophysical profile is not perfect. The cause of the imperfection is the probability of change in the fetal status from either a chronic condition or an acute variable. Although more frequent testing of all patients would decrease the false-negative rate, this has not been attempted because of the increased workload. The proper selection of patients requiring more vigilant monitoring (those judged to be at risk, e.g., an immature fetus with growth retardation, preeclampsia, diabetes) would render this more feasible.

Nonstress Testing

Nonstress testing is the external detection of FHR and fetal movement in relation to uterine contractions, noting accelerations of FHR with fetal movement. These parameters are predictors of fetal outcome.

With the parturient recumbent in the semi-Fowler's position and left lateral tilt (to displace the uterus from the inferior vena cava and aorta), 20 min of consistent FHR tracing is followed, and a tocodynamometer is used to measure uterine contractions. Fetal movement is noted either in the mother by external palpation of the maternal abdomen or by spikes in the tocodynamometer tracing.

The test is usually interpreted as either reactive, nonreactive, or of uncertain reactivity[96,97]:

1. Reactive: at least two fetal movements in 20 min with acceleration of the FHR by at least 15 beats/min, with long-term variability of at least 10 beats/min and a baseline rate within the normal range (Figure 1.4)

TABLE 1.5. Interpretation and management of biophysical profile score.

Score	Interpretation	Recommended management
8–10	Normal infant	Repeat test in 1 week[a]
6	Suspect asphyxia	Repeat test in 4–6 h[b]
4	Suspect asphyxia	If >36 weeks, deliver
		If <36 weeks, repeat in 24 h
0–2	Probable asphyxia	Deliver

[a]Repeat test twice a week if diabetic or >42 weeks gestation.
[b]Deliver if oligohydramnios is present.

TABLE 1.6. Biophysical profile and perinatal mortality.

Study	No. patients	No. deaths	Perinatal mortality
Manning et al.[90]	19,221	141	1.92
Baskett et al.[91]	5,034	32	3.10
Platt et al.[92]	286	4	7.0
Schiffrin et al.[93]	158	7	12.6

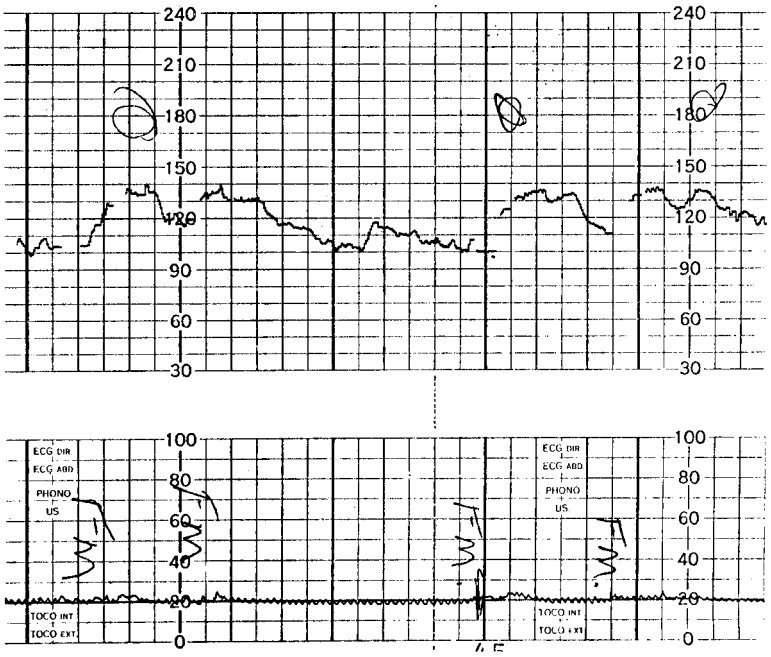

FIGURE 1.4. Reactive nonstress test, characterized by accelerations in the fetal heart rate (*FHR*) (top chart) with fetal movement (*FM*).

2. Nonreactive: no fetal movement or acceleration of the FHR with movement, poor to no long-term variability, baseline FHR may be within or outside the normal range (Figure 1.5)
3. Uncertain reactivity: fewer than two fetal movements in 20 minutes or acceleration of less than 15 beats/min, long-term variability amplitude less than 10 beats/min, baseline heart rate outside of normal limits

Fetuses have sleep or inactive cycles that can last as long as 80 min. The test administrator can either wait for a while or manually stimulate the infant.

A reactive test is associated with survival of the fetus for 1 or more weeks in more than 99% of cases.[96,98] A nonreactive test is associated with poor fetal outcome in 20% of cases.[99] Although the false-positive rate of this technique is high (80%), further evaluation is needed when a nonreactive result is obtained. The next step is usually a contraction stress test (CST). Similarly, an uncertain reactive pattern needs to be followed up with either another NST or a CST.

Contraction Stress Test

As its name implies, the CST assesses the fetal response (heart rate pattern) to regular uterine contractions. Using the same technique as the NST, the CST requires three adequate contractions within a 10-min period, each with a duration of 1 min. If there are not enough spontaneous contractions, augmentation with intravenous oxytocin is indicated. Beginning at a rate of 1.0 mU/min, the infusion is increased every 15 min until the requisite number of contractions is obtained. It is rarely necessary to exceed 10 mU/min.

Certain clinical situations present contraindications to CSTs: prior classical cesarean section, placenta previa, and women at risk of premature labor (premature rupture of membranes, multiple gestations, incompetent cervix, and women undergoing treatment for preterm labor).

CSTs are interpreted as follows:

1. Negative: no late deceleration and normal baseline FHR

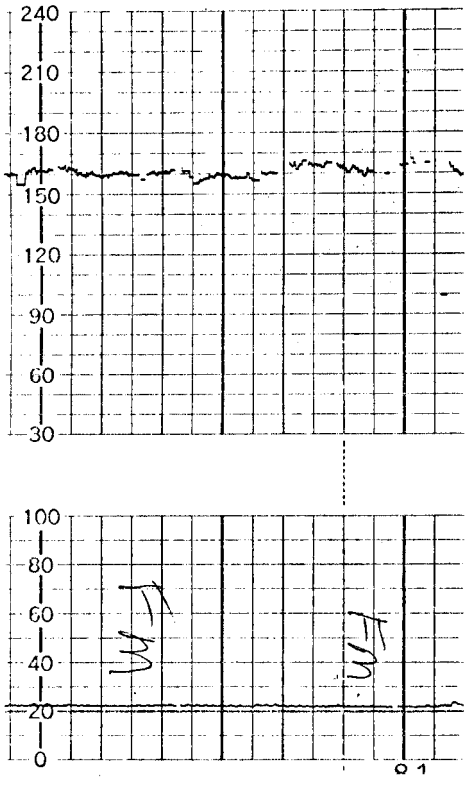

FIGURE 1.5. Nonreactive nonstress test, with no accelerations in fetal heart rate with fetal movement (*FM*).

2. Positive: persistent late decelerations (even when the contractions are less frequent than three contractions within 10 min), possible absence of FHR variability.
3. Suspicious: intermittent late deceleration or variable decelerations, abnormal baseline FHR
4. Unsatisfactory: poor quality recording or inability to achieve three contractions within 10 min
5. Hyperstimulation: excessive uterine activity (contractions closer than every 2 min or lasting longer than 90 s), resulting in late decelerations or bradycardia

A negative CST is associated with fetal survival for a week or more in 99% of cases,[96,97] whereas a positive CST is associated with poor fetal outcome in 50% of cases.[99] As does the NST, the CST also has a high false-positive rate (50%), but the treatment, if delivery is indicated, can be a trial of induction of labor.

Fetal Heart Rate Monitoring

In conjunction with fetal scalp sampling and possibly fetal pulse oximetry to measure acid–base balance, FHR monitoring provides the main method of evaluating the fetus during the antepartum period as a part of nonstress testing, contraction stress testing, and biophysical profile and during labor and delivery. A review by Fenton and Steer[100] documented the historical use of FHR auscultation. FHR auscultation was first described by Marsac in 1650. A number of clinical studies have shown that perinatal morbidity and mortality are increased when the FHR is greater than 160 to 180 beats/min or less than 100 to 120 beats/min. Beginning in the 1940s, FHR was followed over a period of time as a more sensitive indicator of fetal well-being; this developed into continuous FHR monitoring, which charted beat to beat changes in the FHR.

Intermittent auscultation of the FHR is still a widely used means to monitor the fetus. In low-risk patients, this is done every 30 min, listening for 30 s during and after a contraction, when the parturient is in the first stage of labor, and every 15 min during the second stage of labor. In high-risk patients, the frequency of listening is shortened to every 15 min during the first stage of labor and every 5 min during the second stage. Auscultation with a fetoscope or Doppler can detect changes in basal heart rate, variability, and decelerations in relation to uterine contractions. When abnormalities are noted, either fetal scalp sampling or continuous FHR monitoring or both are indicated.

Continuous FHR monitoring entails measuring each fetal heartbeat as well as the interval between two beats, calculating the FHR, and then plotting each successive rate. This procedure can be done externally on the mother's abdomen with a Doppler ultrasound, a phonocardiographic monitor, or an electrocardiogram. An electrode attached to the fetal scalp after rupture of the amniotic membranes provides an internal or direct recording of FHR. Similarly, uterine contractions are measured either externally with a tocodynamometer or internally with a saline-filled catheter placed into the uterine cavity.

Fetal Heart Rate Patterns

The FHR pattern is characterized by its baseline between contractions and periodic changes in association with uterine contractions.[101] The baseline and periodic changes are further broken down into FHR and variability. This section considers the baseline FHR and its variants as well as variability.

Fetal heart rate from 120 to 160 beats/min between contractions is normal (Figure 1.6). Rates greater than 160

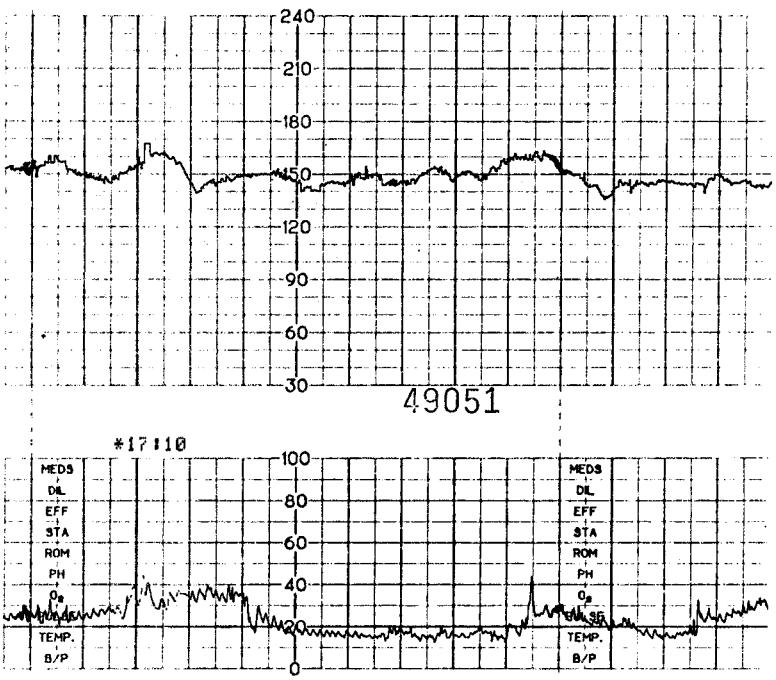

FIGURE 1.6. Normal fetal heart rate (*FHR*) pattern. The heart rate (140 beats/min) and short-term and long-term variability are normal. There are no periodic changes.

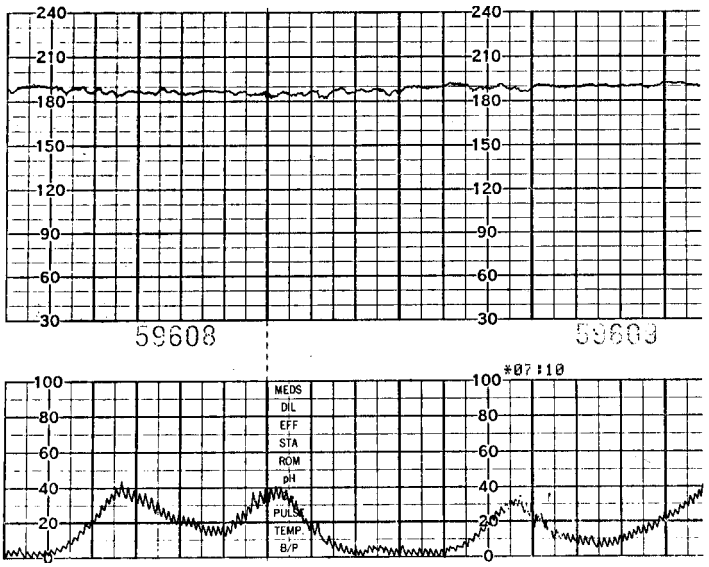

FIGURE 1.7. Tachycardia. In this case, there was a maternal fever secondary to chorioamnionitis.

beats/min are described as tachycardia (Figure 1.7) and those less than 120 beats/min as bradycardia (Figure 1.8). If the alteration in rate is less than 2 min in duration, it is called either an acceleration or a deceleration.

The usual, initial response of the normal fetus to acute hypoxia or asphyxia is bradycardia. A heart rate between 100 and 120 beats/min might either signify a compensated, mild hypoxic stress or be idiopathic and benign. When the heart rate falls below 60 beats/min, the fetus is in distress and requires either reversal of the cause of the bradycardia or emergency delivery. Other causes of bradycardia that are nonasphyxic in origin are bradyarrhythmias, maternal drug ingestion (especially beta blockers), and hypothermia. Tachycardia is occasionally seen with fetal asphyxia or with recovery from asphyxia, but is more likely seen secondary to these events:

1. Maternal or fetal infection, especially choriamnionitis
2. Maternal ingestion of beta mimetic or parasympathetic blockers
3. Tachyarrhythmias
4. Prematurity
5. Thyrotoxicosis

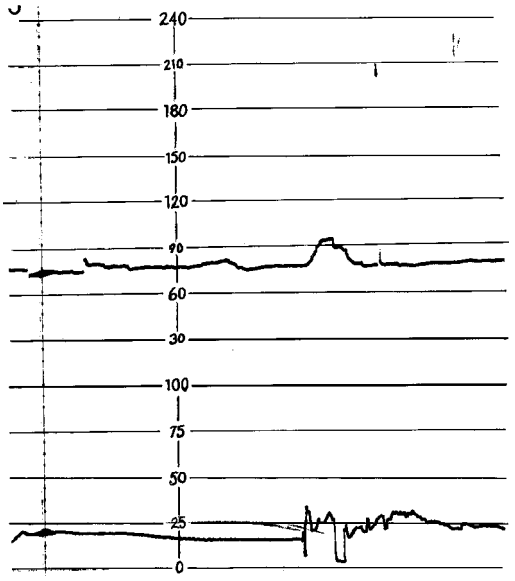

FIGURE 1.8. Bradycardia, accompanied by absence of FHR variability.

Variability in the FHR tracing describes the irregularity or the difference in interval from beat to beat. If the intervals between heartbeats were identical, then the tracing would be smooth (Figure 1.9). In most healthy fetuses, one notes an irregular line, thought to be secondary to an intact nervous pathway through the cerebral cortex, midbrain, vagus nerve, and the cardiac conduction system. It is thought that when asphyxia affects the cerebrum there is decreased neural control of the variability, made worse by the failure of fetal hemodynamic compensatory mechanisms to maintain cerebral oxygenation. With normal variability, therefore, irrespective of the FHR pattern, the fetus is not suffering cerebral anoxia.

Variability is described as being either short term or long term. Short-term variability is the beat-to-beat difference, and it requires accurate detection of the heart rate. Because this can only be obtained with the fetal electrocardiogram, external monitors cannot be used to describe short-term variability, which is characterized as either present or absent. Long-term variability looks at a wider window of the FHR, between 3 and 6 beats/min. It can be detected using either internal or external methods of FHR monitoring and is described by the approximate amplitude range in beats per minute as follows:

1. Normal: amplitude range 6 beats/min or greater
2. Decreased: amplitude range between 2 and 6 beats/min
3. Absent: amplitude range less than 2 beats/min
4. Saltatory: amplitude greater than 25 beats/min.

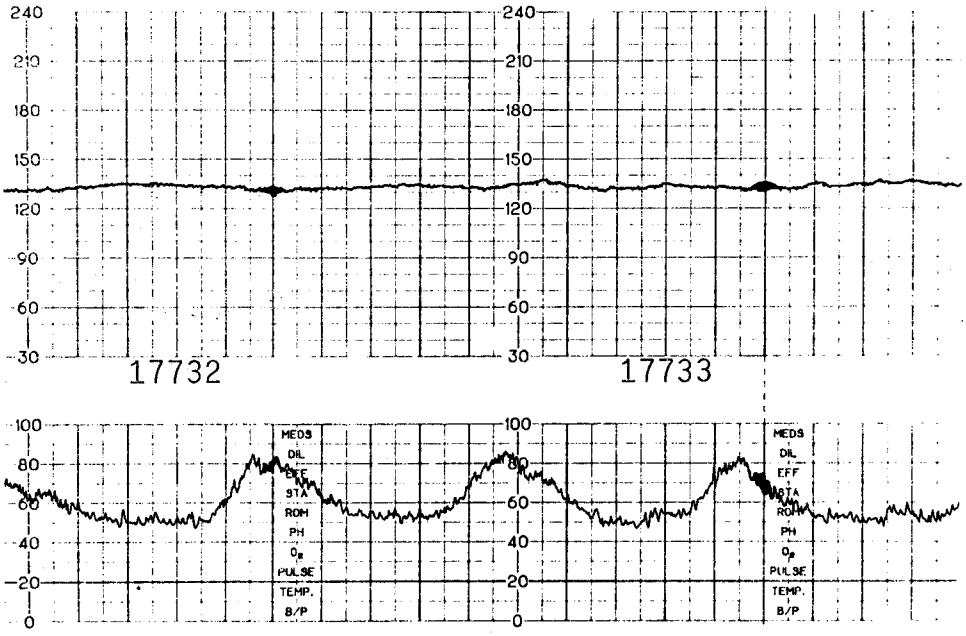

FIGURE 1.9. Decreased variability of the fetal heart rate (*FHR*).

In addition to asphyxia, other causes of altered variability include anencephaly, fetal drug effect (secondary to morphine, meperidine, diazepam, and magnesium sulfate), vagal blockade (due to atropine or scopolamine), and interventricular conduction delays (complete heart block).

Periodic changes in FHR occur in association with uterine contractions. Early decelerations that occur concomitantly with a uterine contraction have a smooth contour and are a mirror image of the contraction (Figure 1.10). The descent of the FHR is usually not more than 20 beats/min below the baseline. The cause is presumed to be a vagal reflex caused by a mild hypoxia but is not associated with fetal compromise. Late decelerations are also smooth in contour and mirror the contraction, but they begin 10 to 30 s after the onset of the contraction (Figure 1.11). The depth of the decline is inversely related to the intensity of the contraction.

Late decelerations have been classified as either reflex or nonreflex. Reflex late decelerations are caused by maternal hypotension, which acutely decreases uterine perfusion to an otherwise healthy fetus. A uterine contraction added to this insult further reduces oxygen flow, causing cerebral hypoxia, which then leads to deceleration. Between contractions, the FHR returns to baseline with good variability. The nonreflex late deceleration is the result of prolonged hypoxia that leads to myocardial depression. Cerebral function is also depressed, as is seen with preeclampsia, IUGR, and prolonged repetitive

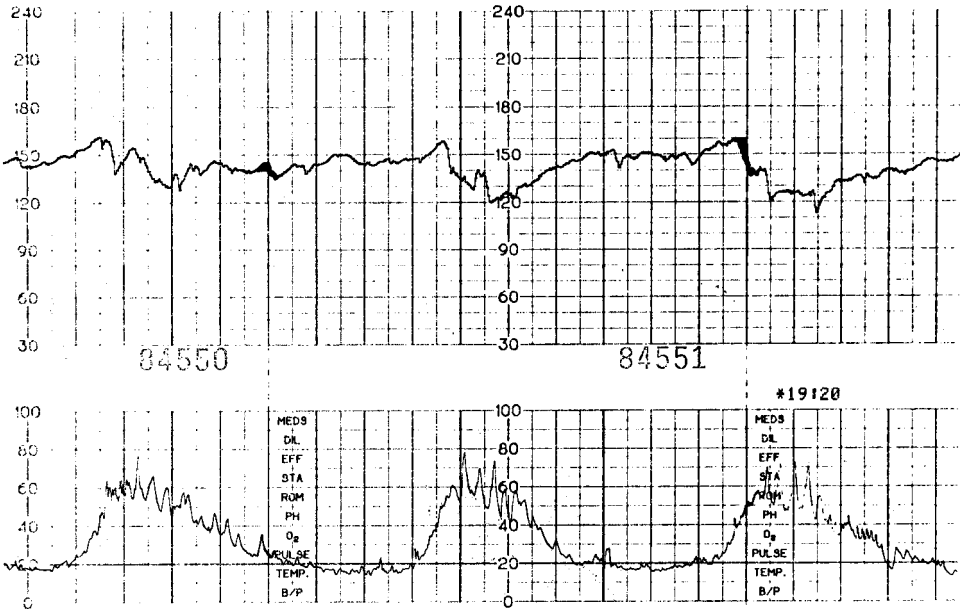

FIGURE 1.10. Early decelerations.

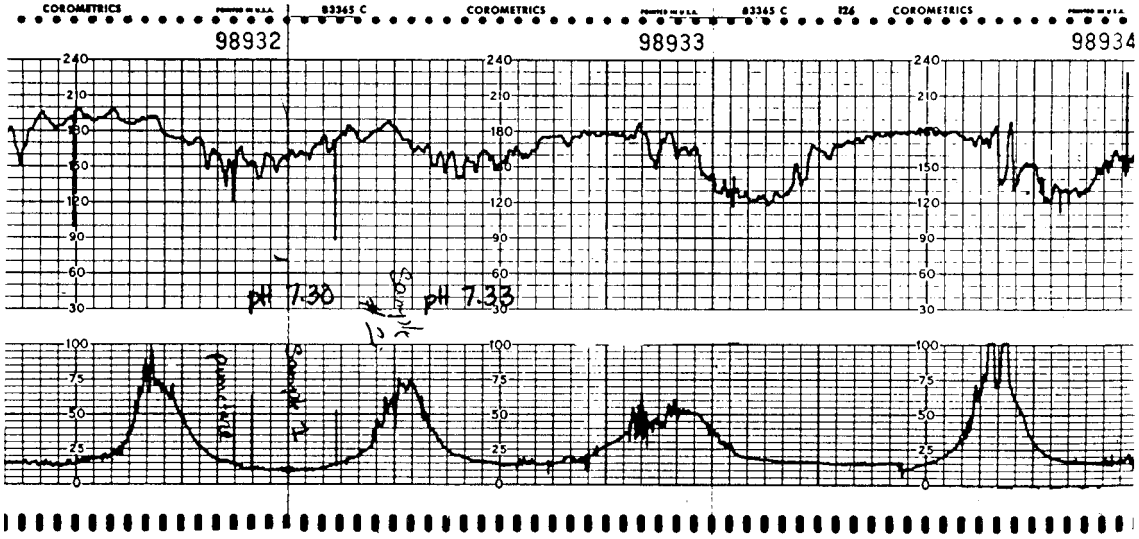

FIGURE 1.11. Late decelerations, with decreased variability of the fetal heart rate (*FHR*) between contractions.

late decelerations. Fetal heart rate variability is either decreased or absent.

Variable decelerations differ in duration, shape, and amount of decrease in FHR from contraction to contraction. The abrupt onset and cessation of deceleration is thought to result from increased vagal firing in response to either compression of the umbilical cord (during early labor) or dural stimulation with head compression (during the second stage of labor). The vagal activity causes bradycardia, which decreases cardiac output as well as umbilical blood flow. Variable decelerations are described as severe when they fall to 60 beats/min below the baseline FHR or last longer than 60 s (Figure 1.12). Otherwise, they are classified as mild to moderate (Figure 1.13). The normal fetus is generally able to tolerate mild to moderate variable decelerations for prolonged periods of time; however, severe variable decelerations eventually result in fetal compromise unless reversed.

Accelerations with uterine contractions represent the greater effect of sympathetic activity over the parasympathetic nervous system (Figure 1.14); these indicate a reactive, healthy fetus and have a good prognostic significance.

The components of FHR just described comprise a normal pattern of a baseline rate of 120 to 160 beats/min, which has a variability of greater than 6 beats/min. One can see either

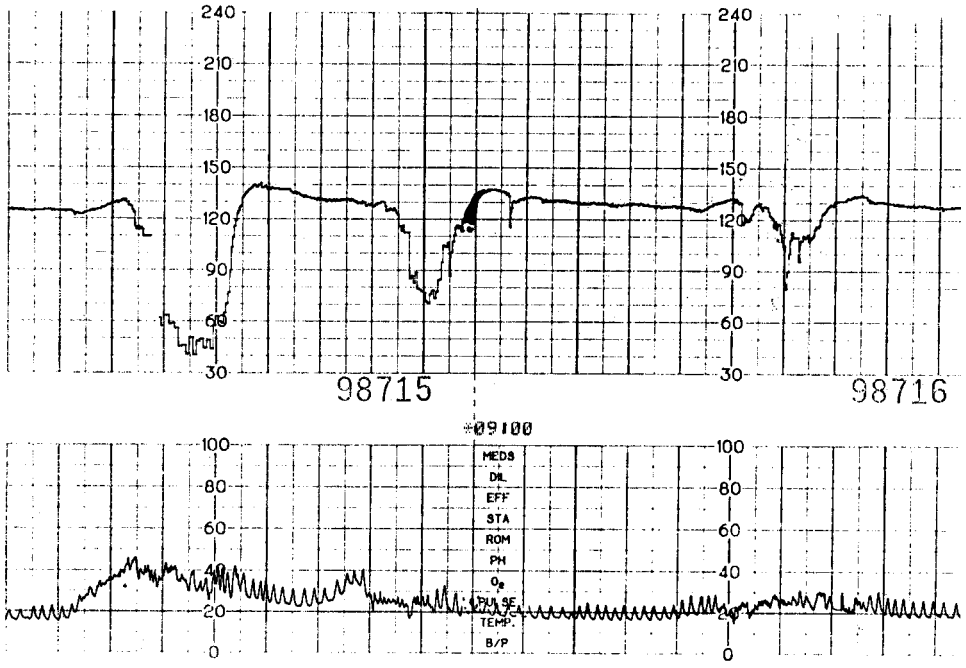

FIGURE 1.12. Severe, deep variable decelerations, with decreased variability of the fetal heart rate (*FHR*) between contractions.

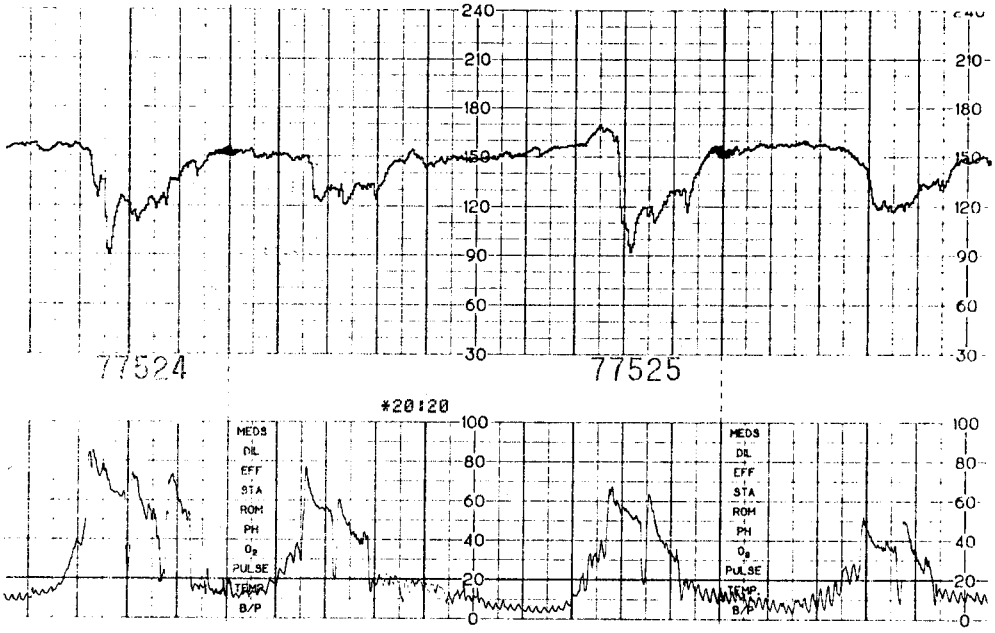

FIGURE 1.13. Mild to moderate variable decelerations with pushing during the second stage of labor.

no decelerations, early decelerations, or accelerations with contractions; this is associated with a good fetal outcome (i.e., Apgar score > 7 at 5 min).[101,102] Depending on the severity and duration of the stress, other FHR patterns are seen.

The acute stress pattern is a compensatory reaction in an otherwise healthy fetus to a short-lived period of asphyxia or hypoxia. The FHR usually demonstrates bradycardia, although tachycardia is also seen, but the most important fact noted is that variability remains normal. There can be either late or variable decelerations. The fetal outcome is generally good,[103] because the impact of the asphyxia is brief, with possible depression from carbon dioxide narcosis, which is rapidly reversible.

When the stress persists, bradycardia is more profound and is associated with decreased variability as well as late or deep variable decelerations. This is a prolonged stress pattern that indicates mounting hypoxic damage to the heart and brain, resulting in the loss of compensatory mechanisms. Unless corrected, fetal death in utero can occur.

For a growth-retarded fetus, already compromised by a placenta with marginal function, persistent asphyxia results in a

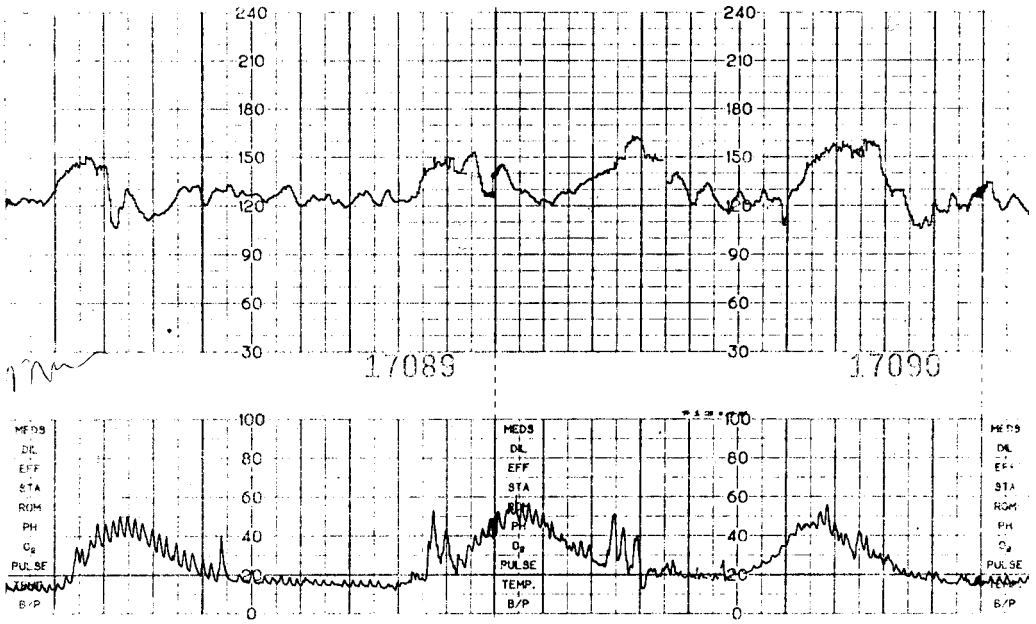

FIGURE 1.14. Accelerations with uterine contractions.

sinister pattern that is characterized by absent variability. The FHR displays severe variable or late decelerations with a smooth rather than abrupt decrease and recovery in heart rate. Persistent bradycardia without variability is also called sinister.

Nonreassuring Fetal Status

In an American College of Obstetrics and Gynecology (ACOG) technical bulletin on Fetal Heart Rate Patterns in 1995, it was pointed out that the term fetal distress is imprecise and inaccurate.[104] Instead of this general label, it was recommended that the term nonreassuring fetal status be used initially, followed by a description of the FHR pattern in terms of type and severity. This recommendation was reaffirmed in February 1998 with an ACOG Committee Opinion that fetal distress implies an ill fetus but has a low predictive value even in high-risk populations.[105] The preferred term, nonreassuring fetal status with a further description (i.e., fetal bradycardia, persistent late decelerations, etc.), imparts more information to the pregnant woman and other care providers. The implications of this are important to anesthesiologists because the description will affect the degree of urgency, mode of delivery, and type of anesthesia needed.

Treatment of Fetal Heart Rate Patterns

The first step in treatment is to recognize and describe an abnormal FHR pattern. The cause must then be identified, and it should be corrected as quickly as possible. Causes and treatment of FHR patterns are presented in Table 1.7. If the pattern does not improve with these measures, then one needs to acquire more direct evidence of the fetal status (i.e., fetal scalp sampling) or to deliver the fetus immediately.

Summary of Electronic Fetal Heart Rate Monitoring

Electronic FHR monitoring is now an important part of fetal assessment during the antepartum period. Its use to diagnose nonreassuring fetal status, whether acute or chronic, has directly affected labor and delivery practice in an attempt to decrease fetal morbidity and mortality. An analysis of the literature by Parer and King, however, suggests that electronic monitoring has poor sensitivity in identifying morbidity and limited sensitivity in predicting its absence.[106] To determine if neonatal neurologic damage could be correlated with FHR tracing, this review of 10 studies found the following:

1. There were several definitions of FHR patterns, making a comparison of data from various centers difficult.
2. Fetal heart rate patterns had a poor predictive value on outcome.
3. A significant number of neonates with poor outcome had no monitoring abnormalities.
4. Monitoring FHR did not lead to effective treatment that had a significant impact on neonatal morbidity.

Although electronic FHR monitoring has been used for more than 30 years, there is no standard associating brain damage with a specific FHR tracing. There has not yet been a study to demonstrate that FHR monitoring either predicts or prevents neurologic morbidity, but this does not deny that electronic FHR monitoring has merit. Rather, it needs to be further refined, standardized, and applied to particular clinical situations where physiologic correlations are possible.

In a technical bulletin,[104] ACOG reviewed the physiologic basis for monitoring FHR patterns, provided guidelines for performing the monitoring, and discussed interpretation and management; this is an attempt to provide standards so that FHR monitoring can be more useful. Despite the questions about its utility, FHR monitoring is still the predominate tool to monitor the fetus during labor and, as such, requires a basic understanding.

Table 1.7. Treatment of fetal heart rate patterns.

Pattern	Cause	Treatment
Bradycardia, late decelerations	Hypotension	IV fluids, ephedrine, change position
	Uterine hyperstimulation	Decrease oxytocin
Variable decelerations	Umbilical cord compression	Change position
	Head compression	Continue pushing if variability good
Late decelerations	Decreased uterine blood flow	Change position, O_2 for mother
Decrease in variability	Prolonged asphyxia	Change position, O_2 for mother

Effects of Epidural Anesthesia on Fetal Heart Rate

The definite effects of epidural anesthesia/analgesia on maternal blood pressure and uterine smooth muscle contractility have also raised concerns about the potential effects on FHR. In addition to local anesthetics (bupivicaine, lidocaine, and chloroprocaine), narcotics are also injected into the epidural space. A number of studies in humans[107–110] have demonstrated no deleterious effects on FHR. Studies[111–114] using Doppler velocimetry of umbilical and uterine arteries demonstrated that epidural anesthesia causes no change in the mean uterine and umbilical artery systolic–diastolic (S-D) ratios in normal parturients at term. In women with preeclampsia, epidural blockade caused a significant decrease in mean uterine artery S-D ratios without a change in the umbilical artery S-D ratio, indicating a decrease in uterine artery vasospasm. There were no changes in FHR. Alahuhta et al.[115] also used M-mode echocardiography to assess fetal myocardial function. Except for an increase in right ventricular end-diastolic dimensions, there was no effect on the fetal myocardial function.

Fetal Scalp Sampling

Since first introduced by Saling[116] in 1967, fetal blood sampling has become the final determinant in making a diagnosis of fetal hypoxia or asphyxia. The fetal blood sample is obtained from the presenting part (scalp or buttock) during labor. The instrumentation and technique of fetal blood collecting are described in many standard textbooks. In this brief discussion, mention is made of the indications for sampling as well as the prognostic significance of values obtained.

Although a full set of blood gas determinations (pH, P_{CO_2}, and P_{O_2}) can be done on as little as 0.25 mL of blood, most institutions obtain a minimal amount of blood for pH determination. The pH value alone does not allow differentiation between respiratory and metabolic acidosis. Treatments of the causes of acidosis are theoretically different. Metabolic acidosis requires immediate delivery, whereas respiratory acidosis should respond to standard resuscitation. In reality, the initial resuscitation measures (oxygen for the mother, uterine displacement, intravenous fluid bolus) are generally begun immediately with any severe deceleration. If a deceleration does not respond quickly to resuscitation, the clinical situation (stage of labor, presence of meconium, estimated fetal weight, gestation age, parity, etc.) will determine whether fetal scalp sampling is needed or if delivery is necessary immediately.

In human newborns, there is good correlation between the pH of scalp blood taken shortly before delivery and that of umbilical cord samples. Beard et al.,[117] correlating scalp blood pH and 2-min Apgar scores, showed that a scalp pH above 7.25 was associated with an Apgar score greater than 7 in 92% of infants. When the scalp pH was less than 7.15, the Apgar score was less than 6 in 80% of cases. Fetal heart rate deceleration has also been found to correlate with pH values (Table 1.8). This correlation is not always close, so fetal scalp sampling is used when there is any question about the FHR tracing.

Winkler et al.[119] evaluated the degree of umbilical artery acidemia with newborn morbidity. Comparing a group of 358 term infants with an umbilical artery pH below 7.20 to a matched control group, they found that only when the pH decreased to less than 7.00 did the incidence of complications increase. For 23 infants with umbilical artery pH less than 7.00, the average 1- and 5-min Apgar scores were significantly lower than the rest of the study and control infants. Only 2 of the 23 infants developed complications (seizures, persistent hypotonia, renal and cardiac dysfunction) secondary to asphyxia. Although both fetal scalp and umbilical artery sampling serve to indicate asphyxia, only the former allows one to alter the management of labor to either reverse the asphyxia or deliver the infant emergently.

There are other FHR patterns that signal the need for fetal scalp sampling in addition to persistent late decelerations:

1. Absent or decreased short-term variability, which might be caused by CNS depressants given to the mother
2. Variable deceleration when combined with reduced or absent short-term variability
3. Severe, persistent, variable decelerations

The clinical situation provides indications for fetal scalp sampling, especially if there is decreased variability or severe decelerations.

TABLE 1.8. Correlation of fetal scalp pH and fetal heart rate pattern.

Deceleration pattern	Scalp pH
Early, mild variable	7.30 ± 0.04
Moderate variable	7.26 ± 0.04
Mild, moderate late	7.22 ± 0.06
Severe late, variable	7.14 ± 0.07

Source: From Kubli FW, Hon EW, Khazin AF, et al. Observations on heart rate and pH in the human fetus during labor. Am J Obstet Gynecol 1969;104:1190.

Pulse Oximetry

Fetal pulse oximetry is being used increasingly as an ancillary test to FHR monitoring to measure fetal oxygen stores, particularly when there might be concern for hypoxia/asphyxia.

Reflectance pulse oximetry is a refinement of conventional pulse oximetry that requires transmitted light and provides a noninvasive method to assess fetal oxygenation. A study by Johnson and McNamara[120] demonstrated, in healthy parturients in labor, that when the sensor was placed between the cervix and the fetal presenting part, there was a significant correlation between fetal oxygen saturation and umbilical vein saturation and pH as well as umbilical artery pH. The relationship of umbilical artery pH and saturation to fetal O_2 saturation was not significant. The range of the values was large: for a fetal oximetry value of 60%, the umbilical vein saturation ranged from 30% to 70% and the pH from 7.25 to 7.38. Values for fetal pulse oximetry varied from 50% to 90% when, with delivery, the umbilical vein pH was generally greater than 7.24. Although there were statistical correlations, the wide range of values suggests a low specificity of the oximeter. Dildy et al. studied 73 healthy parturients in labor and was unable to obtain a reliable signal 50% of the time.[121]

In an ACOG Committee Opinion,[122] Federal Drug Administration (FDA) approval of a fetal pulse oximeter was noted, but the issue of reliability of readings remains an issue. A multicenter trial of fetal pulse oximetry and its usefulness in the management of nonreassuring FHR patterns resulted in an overall reduction (>50%) in the incidence of cesarean births due to nonreassuring fetal status.[123] There was, however, no overall difference in the rate of cesarean birth between the study and control groups because there was an increase in cesarean births secondary to dystocia in the study group.

These studies suggest that the use of the pulse oximeter shows promise, but more prospective, randomized control studies are needed.

Summary

The reduction of perinatal morbidity and mortality is the sole purpose of fetal assessment, which spans the three trimesters of gestation. Chromosomal and developmental abnormalities are the focus of first and early second trimester studies. During the late second and third trimesters, the emphasis shifts to detecting causes of asphyxia and hypoxia. These problems tend to occur more frequently in parturients who have underlying diseases such as diabetes, pregnancy-induced hypertension, drug addiction, malnutrition, and obesity. Although now no single technique can reliably detect asphyxia/hypoxia in a fetus, the potential usefulness and limitations of current monitoring techniques must be understood.

References

1. Edelstone DI, Rudolph AM, Heymann MA. Liver and ductus venosus flows in fetal lambs in utero. Circ Res 1978;42:426–433.
2. Bristow J, Rudolph AM, Itskovitz J. A preparation for studying liver blood flow, oxygen consumption in the fetal lamb in utero. J Dev Physiol 1981;3:255–266.
3. Bristow J, Rudolph AM, Istkovitz J. Hepatic oxygen and glucose metabolism in the fetal lamb. J Clin Invest 1983;71:1047–1061.
4. Rudolph AM, Heymann MA. Circulatory changes during growth in the fetal lamb. Circ Res 1970;26:289–299.
5. Peeters LL, Sheldon RE, Jones MD Jr, et al. Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 1979;135:637.
6. Peeters LL, Sheldon RE, Jones MD Jr, et al. Redistribution of cardiac output and oxygen delivery in the hypoxic fetal lamb. Am J Obstet Gynecol 1979;135:1071–1078.
7. Sheldon CA, Friedman WF, Sybers HD. Scanning electron microscopy of fetal and neonatal lamb cardiac cells. J Mol Cell Cardiol 1976;8:853–862.
8. McPherson RA, Kramer MF, Covell JW, et al. A comparison of the active stiffness of fetal and adult cardiac muscle. Pediatr Res 1976;10:660–664.
9. Heyman MA, Rudolph AM. Effects of increasing preload on right ventricular output in fetal lambs in utero. Circulation 1973;48:IV–37.
10. Berman W Jr, Goodlin RC, Heymann MA, et al. Pressure flow relationships in the umbilical and uterine circulations of the sheep. Circ Res 1976;38:262–266.
11. Papile L, Rudolph AM, Heymann MA. Autoregulation of cerebral blood flow in the preterm fetal lamb. Pediatr Res 1985;19:159–161.
12. Dawes GS, Johnston BM, Walker DW. Relationship of arterial pressure and heart rate in fetal newborn and adult sheep. J Physiol (Lond) 1980;309:405–417.
13. Iwamoto HS, Rudolph AM. Effects of angiotensin II on the blood flow and its distribution in fetal lambs. Circ Res 1982;48:183.
14. Drummond WH, Rudolph AM, Keil LC, et al. Arginine vasopressin and prolactin after hemorrhage in the fetal lamb. Am J Physiol 1980;238:E214–219.
15. Iwamoto HS, Rudolph AM, Keil LC, et al. Hemodynamic responses of the sheep fetus to vasopressin infusion. Circ Res 1979;44:430–436.
16. Challis JRG, Patrick JE. The production of prostaglandins and thromboxanes in the feto-placental unit and their effects on the developing fetus. Semin Perinatol 1980;4:23–33.
17. Mitchell MD, Flint AP, Bibby J, et al. Plasma concentrations of prostaglandins during late human pregnancy: influence of normal and preterm labor. J Clin Endocrinol Metab 1978;46:947–951.
18. Novy MJ, Piasecki G, Jackson BT. Effect of prostaglandins E2 and F2 alpha on umbilical blood flow and fetal hemodynamics. Prostaglandins 1974;5:543–555.
19. Berman W Jr, Goodlin RC, Heymann MA, et al. Effects of pharmacologic agents on umbilical blood flow in fetal lambs in utero. Biol Neonate 1978;33:225–235.
20. Cassin S. Role of prostaglandins and thromboxanes in the control of the pulmonary circulation in the fetus and newborn. Semin Perinatol 1980;4:101–107.
21. Cassin S. Role of prostaglandins, thromboxanes and leukotrienes in the control of the pulmonary circulation in the fetus and newborn. Semin Perinatol 1987;11:53–63.
22. Clyman RI. Ontogeny of the ductus arteriosus response to prostaglandins and inhibitors of their synthesis. Semin Perinatol 1980;4:115–124.
23. Clyman RI. Ductus arteriosus: current theories of prenatal and postnatal regulation. Semin Perinatol 1987;11:64–71.
24. Prowse CM, Gaensler EA. Respiratory and acid base changes during pregnancy. Anesthesiology 1965;26:381–392.
25. Rankin JHG, Meschia G, Makowski EL, et al. Relationship between uterine and umbilical venous PO_2 in sheep. Am J Physiol 1971;220:1688–1692.
26. Longo LD, Hill EP, Power GG. Theoretical analysis of factors affecting placental O_2 transfer. Am J Physiol 1972;222:730–739.
27. Meschia G. Transfer of oxygen across the placenta. In: Gluck L (ed) Intrauterine Asphyxia and the Developing Fetal Brain. Chicago: Year Book Medical, 1977:109–115.
28. Russell JC, Cooper CM, Ketchum CH, et al. Multicenter evaluation of TDx test for assessing fetal lung maturity. Clin Chem 1989;35:1005–1010.
29. Mendez-Bauer C, Poseirio JJ, Arellano-Hernandez G, et al. Effects of atropine on the heart rate of the human fetus during labor. Am J Obstet Gynecol 1963;85:1033–1053.
30. Vapaavouri EK, Shinebourne EA, Williams RL, et al. Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs. Biol Neonate 1973;22:1177–1188.
31. Rurak DW, Cooper CC, Taylor SM. Fetal oxygen consumption and PO_2 during hypercapnia in pregnant sheep. J Dev Physiol 1986;8:447–459.
32. Boddy K, Dawes GS, Fisher R, et al. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J Physiol (Lond) 1974;243:599–618.
33. Natale R, Clewlow F, Dawes GS. Measurement of fetal forelimb movements in lambs in utero. Am J Obstet Gynecol 1981;140:545–551.
34. Dawes GS, Fox HE, Leduc BM, et al. Respiratory movements and rapid eye movements in the foetal lamb. J Physiol (Lond) 1972;220:119–143.
35. Maloney JE, Adamson TM, Brodecky V, et al. Diaphragmatic activity and lung liquid flow in unanesthetized fetal sheep. J Appl Physiol 1975;39:423–428.
36. Patrick JE, Falton KJ, Dawes GS. Breathing patterns before death in fetal lambs. Am J Obstet Gynecol 1976;125:73–78.
37. Patrick J, Challis JRG, Cross J, et al. The relationship between fetal breathing movements and prostaglandin E_2 during ACTH-induced labour in sheep. J Dev Physiol 1987;9:287–293.
38. Thorburn GD, Challis JRG. Control of parturition. Physiol Rev 1979;59:863–918.
39. Kitterman JA, Liggins GC, Fewell JE, et al. Inhibition of breathing movements in fetal sheep by prostaglandins. J Appl Physiol 1983;54:687–692.
40. Richardson B, Hohimer AR, Mueggler P, et al. Effects of glucose concentration on fetal breathing movements and electrocortical activity in fetal lambs. Am J Obstet Gynecol 1982;142:678–683.
41. Patrick J, Richardson B, Hasen G, et al. Effects of maternal ethanol infusion on fetal cardiovascular and brain activity in lambs. Am J Obstet Gynecol 1985;151:859–867.
42. Boddy K, Dawes GS, Fisher RL, et al. The effects of pentobarbitone and pethidine on foetal breathing movements in sheep. Br J Pharmacol 1976;57:311–317.

43. Piercy WN, Day MA, Neims AH, et al. Alteration of ovine fetal respiratory-like activity by diazepam, caffeine and doxapram. Am J Obstet Gynecol 1977;127:43–49.
44. Kitterman JA, Liggins GC, Clements JA, et al. Stimulation of breathing movements in fetal sheep by inhibitors of prostaglandin synthesis. J Dev Physiol 1979;1:453–466.
45. Patrick J, Natale R, Richardson B. Pattern of human fetal breathing activity at 34 to 35 weeks' gestational age. Am J Obstet Gynecol 1978; 132:507–513.
46. Lewis PJ, Trudinger BJ, Mangey J. Effect of maternal glucose ingestion on fetal breathing and body movements in late pregnancy. Br J Obstet Gynecol 1978;85:86–89.
47. Boddy K, Dawes GS. Fetal breathing. Br Med Bull 1975;1:3–7.
48. Natale R, Patrick J, Richardson B. Effects of maternal venous plasma glucose concentrations on fetal breathing movements. Am J Obstet Gynecol 1978;132:36–41.
49. Richie K. The fetal response to changes in the composition of maternal inspired air in human pregnancy. Semin Perinatol 1980;4:295–299.
50. McLeod W, Brien J, Carmichael L, et al. Maternal glucose injections do not alter the suppression of fetal breathing following maternal ethanol ingestion. Am J Obstet Gynecol 1984;148:634–639.
51. Richardson B, O'Grady JP, Olsen GD. Fetal breathing movements and the response to carbon dioxide in patients on methadone maintenance. Am J Obstet Gynecol 1984;150:400–405.
52. Thaler I, Goodman JDS, Dawes GS. The effect of maternal smoking on fetal breathing rate and activity patterns. Am J Obstet Gynecol 1980; 138:282–287.
53. Richardson B, Natale R, Patrick J. Human fetal breathing activity during induced labor at term. Am J Obstet Gynecol 1979;133:247.
54. Manning FA, Platt LD, Siopos L. Fetal movements in human pregnancies. Obstet Gynecol 1979;54:699–702.
55. Bocking A, Adamson L, Cousin A, et al. Effects of intravenous glucose injections on human fetal breathing movements and gross fetal body movements at 38 to 40 weeks' gestational age. Am J Obstet Gynecol 1982;142:606–611.
56. Carmichael L, Cambell K, Patrick J. Fetal breathing, gross body movements and fetal heart rates before spontaneous labor at term. Am J Obstet Gynecol 1984;148:675–679.
57. Timor-Tritsch IE, Dierker LJ, Zador I, et al. Fetal movements associated with fetal heart rate accelerations and decelerations. Am J Obstet Gynecol 1978;131:276–280.
58. Schiffrin BS. The rationale for antepartum fetal heart rate monitoring. J Reprod Med 1979;23:213–221.
59. Rooth G, Huch A, Huch R, et al. Fetal-maternal temperature differences during labor. Contrib Gynacol Obstet 1977;3:54–62.
60. Power GG. Fetal thermoregulation: animal and human. In: Poulin WW, Fox RA (eds) Fetal and Neonatal Physiology. Philadelphia: Saunders, 1998:671–676.
61. Cohn HE, Piasecki GJ, Jackson BT. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 1974;129: 817–824.
62. Parer JT. The effect of acute maternal hypoxia on fetal oxygenation and the umbilical circulation in the sheep. Eur J Obstet Gynecol Reprod Biol 1980;10:125–136.
63. Mann LI. Effects in sheep of hypoxia on levels of lactate, pyruvate and glucose in blood of mothers and fetus. Pediatr Res 1970;4:46–54.
64. Jones MD, Sheldon RE, Peeters LL, et al. Fetal cerebral oxygen consumption at different levels of oxygenation. J Appl Physiol 1977;43: 1080–1084.
65. Fisher DS, Heymann MA, Rudolph AM. Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. Am J Physiol 1982;242:H657–H651.
66. Friede A, Rochat R. Maternal mortality and perinatal mortality: definitions, data and epidemiology. In: Sachs B (ed) Clinical Obstetrics. Littleton, MA: PSG, 1985:1–33.
67. Vital Statistics of the United States, vol II. Mortality, section 4. Washington, DC: U.S. Department of Health and Human Services, Public Health Services, 1988, 1–7.
68. CDC. Contribution of birth defects to infant mortality—United States, 1986. MMWR 1989;38:633.
69. Lammer EJ, Brown LE, Anderka MT, Guyer B. Classification and analysis of fetal deaths in Massachusetts. JAMA 1989;261:1757.
70. Mersey Region Working Party on Perinatal Mortality. Perinatal health. Lancet 1982;1:491–494.
71. Working Party on Amniocentesis. An assessment of the hazards of amniocentesis. Br J Obstet Gynecol 1978;85(suppl 2):1–41.
72. Taber A, Philip J, Madsen M, et al. Randomised, controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;1:1287–1293.
73. Jackson LG, Zachary JM, Fowler SE, et al. A randomized comparison of transcervical and transabdominal chorionic villus sampling. N Engl J Med 1992;327:594–598.
74. Burton BK, Schulz CJ, Burd LI. Limb anomalies associated with chorionic villus sampling. Obstet Gynecol 1992;79:726–730.
75. Monni G, Ibba RM, Lai R, et al. Limb-reduction defects and chorionic villus sampling. Lancet 1991;337:1091.
76. Mahoney MJ. Limb abnormalities and chorionic villus sampling. Lancet 1991;337:1422.
77. Shulman LP, Elias S. Percutaneous umbilical blood sampling, fetal skin sampling and fetal liver biopsy. Semin Perinatol 1990;14:56–64.
78. Saari-Kemppainen A, Karjalainen O, Ylostalo P, et al. Ultrasound screening and perinatal mortality: controlled trial of systemic one-stage screening in pregnancy: the Helsinki Ultrasound Trial. Lancet 1990; 336:387–391.
79. Ewigman B, LeFevre M, Hesser J. A randomised trial of routine prenatal ultrasound. Obstet Gynecol 1990;76:189–194.
80. Bekketeig LS, Eik-Nes SH, Jacobsen G, et al. Randomised controlled trial of ultrasonographic screening in pregnancy. Lancet 1984;2:207–211.
81. Ewigman B, Crane JP, Frigoletto FD, et al. Effect of prenatal ultrasound screening on perinatal outcome. N Engl J Med 1993;329:821–827.
82. Campbell S, Warsof S, Little D, et al. Routine ultrasound screening for the prediction of gestational age. Obstet Gynecol 1985;65:613–620.
83. Kurtz A, Wapner R, Kurtz R, et al. Analysis of biparietal diameter as an accurate indicator of gestational age. J Clin Ultrasound 1980;8:319–326.
84. Patrick J, Campbell K, Carmichael L, et al. Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. Am J Obstet Gynecol 1982;142:363–371.
85. Srokin Y, Dierker L. Fetal movement. Clin Obstet Gynecol 1982; 25:719–734.
86. Neldam S. Fetal movements as an indicator of fetal well being. Lancet 1980;1:1222–1224.
87. Rayburn W. Antepartum fetal assessment. Clin Perinatol 1982;9:231–252.
88. Liston R, Cohen A, Mennui M, Gabbe S. Antepartum fetal evaluation by maternal perception of fetal movement. Obstet Gynecol 1982;60: 424–426.
89. Russell JC, Cooper CM, Ketchum CH, et al. Multicenter evaluation of TDx test for assessing fetal lung maturity. Clin Chem 1989;35:1005–1010.
90. Manning FA, Morrison I, Harmon CR, et al. Fetal assessment by fetal BPS: experience in 19,221 referred high-risk pregnancies. II. The false negative rate by frequency and etiology. Am J Obstet Gynecol 1987; 157:880–884.
91. Baskett TF, Allen AC, Gray JH, et al. The biophysical profile score. Obstet Gynecol 1987;70:357–360.
92. Platt LD, Eglington GS, Scorpios L, et al. Further experience with the fetal biophysical profile score. Obstet Gynecol 1983;61:480–485.
93. Schiffrin BS, Guntes V, Gergely RC, et al. The role of real-time scanning in antenatal fetal surveillance. Am J Obstet Gynecol 1981;140:525–530.
94. Manning FA, Baskett TF, Morrison I, et al. Fetal biophysical profile scoring: a prospective study in 1184 high-risk patients. Am J Obstet Gynecol 1981;140:289–294.
95. Manning FA, Morrison I, Lange IR, et al. Fetal assessment based on

fetal biophysical profile scoring: experience in 12,620 referred high-risk pregnancies. I. Perinatal mortality by frequency and etiology. Am J Obstet Gynecol 1985;151:343–350.
96. Schiffrin BS. The rationale for antepartum fetal heart rate monitoring. J Reprod Med 1979;23:213–221.
97. Keegan KA, Paul RH. Antepartum fetal heart rate testing. IV. The nonstress test as a primary approach. Am J Obstet Gynecol 1980;136:75–80.
98. Evertson LR, Gauthier RJ, Collea JV. Fetal demise following negative contraction stress test. Obstet Gynecol 1978;51:671–673.
99. Ott WJ. Antepartum cardiotachometry for fetal evaluation. South Med J 1981;74:310–314.
100. Fenton AN, Steer CM. Fetal distress. Am J Obstet Gynecol 1962;83:354.
101. Hon EH, Quilligan EJ. The classification of fetal heart rate. Conn Med 1967;31:779.
102. Schiffrin BS, Dame L. Fetal heart rate patterns: prediction of Apgar score. JAMA 1972;219:1322.
103. Krebs HB, Petres RE, Dunn LJ, et al. Intrapartum fetal heart rate monitoring. I. Classification and prognosis of fetal heart rate patterns. Am J Obstet Gynecol 1979;133:762.
104. ACOG Technical Bulletin. Fetal heart rate patterns: monitoring, interpretation and management. Int J Obstet Gynecol 1995;51:65.
105. ACOG Committee Opinion. Inappropriate use of terms fetal distress and birth asphyxia. Int J Obstet Gynecol 1998;61:309.
106. Parer JT, King T. Fetal heart rate monitoring: is it salvageable? Am J Obstet Gynecol 2000;182:982.
107. Lavin JP, Samuels SV, Miodovnik M, et al. The effects of bupivicaine and chloroprocaine as local anesthetics for epidural anesthesia on fetal heart rate monitoring parameters. Am J Obstet Gynecol 1981;141:717.
108. Abboud TK, Afrasiabi A, Zhu J, et al. Bupivicaine/butorphanol/epinephrine for epidural anesthesia in obstetrics: maternal and neonatal effects. Reg Anesth 1989;14:219.
109. McLintic AJ, Danskin FH, Reid JA, et al. Effect of adrenaline on extradural anesthesia, plasma lignocaine concentrations and the feto-placental unit during elective caesarean section. Br J Anesth 1991;67:683.
110. Loftus JR, Holbrook RH, Cohen SE. Fetal heart rate after epidural lidocaine and bupivicaine for elective caesarean section. Anesthesiology 1991;75:406.
111. Ramos-Santos E, Devoe LD, Wakefield ML, et al. The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal and hypertensive patients during active term labor. Obstet Gynecol 1991;77:20–26.
112. Hughes AB, Devoe LD, Wakefield ML, et al. The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal term labor. Obstet Gynecol 1990;75:809–812.
113. Lindblad A, Bernow J, Vernersson E, et al. Effects of extradural anesthesia on human fetal blood flow in utero. Comparison of three local anesthetic solutions. Br J Anesth 1987;56:1265–1272.
114. Turner GA, Newnham JP, Johnson C, et al. Effects of extradural anesthesia on umbilical and uteroplacental arterial flow velocity waveforms. Br J Anesth 1991;67:306–309.
115. Alahuhta S, Rasanen J, Jouppila R, et al. Uteroplacental and fetal haemodynamics during extradural anesthesia for caesarean section. Br J Anesth 1991;66:319–323.
116. Saling E, Schneider D. Biochemical supervision of the foetus during labor. J Obstet Gynecol Br Commonw 1967;74:799–811.
117. Beard RW, Morris ED, Clayton SE. pH of fetal capillary blood as an indicator of the condition of the foetus. J Obstet Gynecol Br Commonw 1967;74:812–822.
118. Kubli FW, Hon EW, Khazin AF, et al. Observations on heart rate and pH in the human fetus during labor. Am J Obstet Gynecol 1969; 104:1190–1206.
119. Winkler CL, Hauth JC, Tucker JM, et al. Neonatal complications at term as related to the degree of umbilical artery acidemia. Am J Obstet Gynecol 1991;164:637–641.
120. Johnson N, McNamara H. Monitoring the fetus with a sensor coverred with an irregular surface can cause scalp ulceration. Br J Obstet Gynecol 1993;100:961–962.
121. Dildy GA, Clark SL, Loucks CA. Preliminary experience with intrapartum fetal pulse oximetry in humans. Obstet Gynecol 1993;81:630–635.
122. ACOG Committee Opinion. Fetal pulse oximetry. Obstet Gynecol 2001;98:523–524.
123. Garite TJ, Dildy GA, McNamara H, et al. A multicenter controlled trial of fetal pulse oximetry in the intrapartum management of nonreassuring fetal heart rate patterns. Am J Obstet Gynecol 2000;183:1049–1058.

2
Prenatal Diagnosis of Fetal Disorders

Sunil Eappen and Susan E. Ponkey

The medical science of genetics continues to advance at a rapid pace with new techniques and discoveries being made constantly. The U.S. genome project,[1] begun in 1990 as a joint effort between the National Institutes of Health and the U.S. Department of Energy, has further accelerated the progress of identifying more metabolic and genetic diseases at an even earlier stage of development. After the working draft of the entire human genome sequence was published recently,[2] researchers have become very excited about the potential to uncover the genetic basis of many diseases—this is particularly interesting in the context of prenatal diagnosis of diseases. A number of methods are currently being utilized to evaluate the fetus, and the future will yield more reasons to exploit this technology. In caring for these patients, we need to understand this technology not only to better care for our patients now but because we will soon be treating more and more fetuses as a result of the prenatal diagnosis.

Approximately 3% to 5% of all neonates have a known birth defect,[3] and although most of these do not have known causes (Table 2.1), many can be detected before birth. The incidence of chromosomal abnormalities in live-born infants is estimated to be approximately 1 of 170 births.[4] Since the discovery in the 1950s that Down syndrome is caused by an extra chromosome 21, the field of cytogenetics has grown enormously. Chromosomal abnormalities have been divided into three groups: numerical, structural, and mosaic.

Types of Abnormalities

Numerical Chromosomal Abnormalities

In this group, the number of chromosomes is either more or less than 46. Down syndrome is the most common numerical chromosomal abnormality. Klinefelter syndrome (47, XXY) and Turner syndrome (46, X) are other examples. Trisomy 13 and trisomy 18 also have recognizable patterns of malformations; other autosomal trisomies are rarely seen in live births.

Structural Chromosomal Abnormalities

Here, a specific region on a particular chromosome is altered in some way. Structural chromosomal abnormalities can occur in a variety of ways when chromosomal material is deleted, duplicated, or rearranged. For example, cri du chat syndrome is caused by the deletion of genetic material on chromosome 5. Translocations, rearrangements of material between chromosomes, are probably the most clinically significant type of chromosomal rearrangement that cause structural chromosomal changes.

Mosaic Chromosomal Abnormalities

Chromosome mosaicism is the presence of two (or more) cytogenetically distinct cell lines in the same individual caused by an error during early mitosis of the zygote after conception. A number of techniques, including ultrasound, amniocentesis, chorionic villus sampling, fetal blood sampling, maternal blood sampling, and magnetic resonance imaging (MRI), are currently in use to make accurate prenatal diagnosis of fetal disorders.

Ultrasound

High-resolution ultrasonography has had a profound impact on the practice of obstetrics in a variety of applications, including the detection of fetal anomalies. Although most experts have traditionally recommended employing ultrasound after 18 weeks of gestation because of better visualization of the major organs, other authors have been utilizing ultrasound at even earlier ages.[5] Many authorities have reported successful imaging of the major organ systems at 14 weeks or earlier.[5,6] Continued advances in technology and in our understanding of fetal anomalies, will allow earlier and earlier detection of fetal defects.

Ultrasound works by generating intermittent high-frequency sound waves by applying an alternating electrical current to a transducer made of piezoelectric material.[7] The transducer

Table 2.1. Suspected etiologies of fetal congenital birth defects.

Cause	Percentage (%) of all birth defects[a]
Genetic	20–25
Fetal infections	3–5
Maternal diseases	3–5
Medications/drugs	1
Unknown	70–75

[a]Genetic causes include chromosomal anomalies and gene defects; common fetal infections include cytomegalovirus, toxoplasmosis, rubella, zoster, and syphilis; maternal diseases include diabetes and illicit drug or alcohol abuse. *Source:* From Beckman DA, Brent RL. Mechanisms of known environmental teratogens: drugs and chemicals. Clin Perinatol 1986;13:649–687.

sends a pulse of sound waves that passes through the skin and soft tissues until it encounters an interface of different tissue densities. When this happens, a portion of the sound energy, proportional to the difference in densities at the interface, is reflected back to the transducer. This reflection of sound at the transducer creates an electrical voltage that is amplified onto a screen. In current ultrasonography, multiple transducers generate many sound waves simultaneously or in sequence to create real-time images to detect movement. This method allows monitoring not only of static fetal defects but also of fetal movements, breathing, or cardiac motions, and even blood vessel pulsation deficits.

The number of fetal anomalies detectable by high-resolution ultrasonography continues to grow (Table 2.2).[8] Ultrasound has become popular because of its utility as well as because this information can be gathered with no known side effects to the mother or the fetus.[7]

Amniocentesis

Amniocentesis is the invasive prenatal diagnostic test most commonly used for genetic disease. The technique is considered to be relatively simple and is performed transabdominally with the use of ultrasonography. A 20- or 22-gauge needle is inserted into the amnionic cavity, withdrawing 20 to 30 mL of fluid to garner cells to culture. The fluid can also be used, for example, to assess fetal lung maturity. Amniocentesis for culturing cells is most commonly performed at midtrimester (16–18 weeks gestation). The most commonly cited risks are as follows[8,9]:

- Preterm premature rupture of membranes (and possible resultant fetal loss)
- Infection
- Fetal trauma

Another risk involves bleeding into the placenta and into the amnionic sac. Any perforation of the placenta can lead to transfer of fetal blood to the mother and cause maternal isoimmunization. Ultrasonic localization of the placenta can reduce the incidence of placental perforation, but anti-D globulin must be administered prophylactically to Rh-negative women at the time of amniocentesis.

Table 2.2. Fetal anomalies detectable by high-resolution ultrasonography.

Cardiac (using echocardiography)
Atrial septal defect/ventriculus septal defect
Valvular lesions
Pulmonary artery stenosis
Transposition of the great vessels
Hypoplastic left heart
Pericardial and pleural effusion
Fetal arrhythmias
Combined lesions (e.g., tetralogy of Fallot)
Central nervous system
Hydrocephalus
Anencephaly
Encephalocele
Intracranial lesions
Meningocele
Meningomyelocele
Choroid plexus cysts
Gastrointestinal
Diaphragmatic hernia
Omphalocele
Gastroschisis
Transesophageal fistula
Esophageal atresia
Duodenal atresia
Urinary tract
Hydronephrosis/hydroureter
Renal agenesis/hypoplasia
Urethral valves
Polycystic/multicystic kidneys
Skeletal
Achondroplasia
Osteogenesis imperfecta
Agenesis/hypoplasia of bones
Other
Teratomas
Cleft lip
Fetal growth retardation

Chorionic Villus Sampling

Chorionic villus biopsies involve a similar approach to that of amniocentesis, except that a sample of the chorionic villus is aspirated by placing a transabdominal needle or a transvaginal catheter into the center of the chorion. The chorion is of fetal origin, and biopsies thus can be evaluated as can those obtained via amniocentesis. The advantage of chorionic villus biopsy is that fetal cells are obtained quickly and the normally long culture procedure is not needed because these chorion cells divide rapidly. Chorionic villus sampling has become the standard for either a first trimester alternative to amniocentesis or when amniocentesis has failed to yield adequate cells. There has been some controversy as to whether chorionic villus sampling is as safe as amniocentesis and whether the transcervical or transabdominal approach is better. It appears that chorionic villus sampling places the mother at slightly higher risk of fetal loss than amniocentesis.[10,11] Another problem associated with chorionic villus sampling is

an increased frequency of chromosomal mosaicism that ultimately may not be found in the baby at birth.

Chorionic villus sampling has been used to diagnose a great number of diseases[12,13]:

- Lysosomal storage diseases such as Tay-Sachs or Gaucher's disease
- Amino acid disorders
- Congenital adrenal hypoplasia
- Hemoglobinopathies
- Cystic fibrosis
- Hemophilia A and B
- Duchenne's muscular dystrophy

Cordocentesis

Cordocentesis is also known as percutaneous umbilical blood sampling (PUBS) or umbilical cord blood sampling. A needle is inserted through the abdominal wall and the uterine wall into the umbilical vein to withdraw fetal blood directly with the aid of ultrasound to localize the cord and placenta. The fetal blood can then be evaluated for fetal hematologic diseases as well as other disorders such as the following[14]:

- Many metabolic disorders
- Anemia
- Hemophilia A and B
- von Willebrand's disease
- Sickle cell anemia
- Thalassemias
- Autoimmune thrombocytopenia
- Alloimmune thrombocytopenia
- CDE disease
- Fetal infections such as toxoplasmosis, rubella cytomegalovirus (CMV), varicella-zoster virus)

In addition, this procedure can be used to treat anemia and thrombocytopenia by infusing blood or platelets.

The major drawback of this technique remains the slightly increased incidence of fetal death.[15] Other complications such as bleeding and fetal bradycardia have also been reported.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been used for diagnosing or confirming fetal anatomic and structural defects, especially brain abnormalities.[16] With the continuous improvement of ultrasonography and an earlier warning by the National Institutes of Health Consensus Development Conference that pregnant women should not undergo MRI unless they have a clear medical need that cannot be resolved by other means,[17] MRI probably has not been utilized as much as it could be. No documented adverse fetal effects have been reported from the use of MRI. Currently, it appears to be used mostly for identifying maternal anatomic pathology (e.g., pelvic mass) or in special circumstances such as verifying a placenta accreta before delivery.

Maternal Blood Sampling

There are a number of screening programs that sample maternal blood to detect congenital fetal disorders. The most common prenatal screening test for pregnant women is alpha fetoprotein (AFP). Alpha fetoprotein is a glycoprotein synthesized by the fetus that peaks in the fetus and the amniotic fluid around the 13th week of gestation. Although the maternal plasma concentration of AFP is 1/1000 that of the fetal circulation, these levels can be accurately assessed. Routine screening is usually carried out between 15 and 18 weeks of gestation. Approximately 5% of these women have abnormal values for which ultrasound and possibly amniocentesis are recommended for a definitive diagnosis.[18,19] Common reasons for abnormal maternal AFP levels with "normal" fetuses include multiple gestation, decreased/increased maternal weight, or inaccurate gestational age. Although the major reason for instituting generalized AFP screening was to detect neural tube defects, there are a variety of causes for abnormal maternal AFP values[20–22]:

Decreased maternal AFP
- Down syndrome
- Trisomy 18
- Gestational trophoblastic disease
- Fetal death

Increased maternal AFP
- Neural tube defects
- Gastrointestinal obstruction
- Abdominal wall defects (e.g., omphalocele)
- Renal anomalies or renal obstruction
- Osteogenesis imperfecta
- Oligohydramnios
- Pilonidal cysts
- Liver disease
- Cystic hygroma

Maternal age and low AFP are used together to predict the risk of Down syndrome. The addition of maternal estriol and human chorionic gonadotropin to AFP greatly increases the ability to predict the chances of fetal Down syndrome, and this triple screen is currently the recommended screening device.

Summary

As technology continues to advance, we will be diagnosing more and more abnormalities in utero. It behooves all of us to follow this progress so we can offer the optimal care to our patients.

References

1. Roberts L, Davenport RJ, Pennisi E, Marshall E. A history of the human genome project. Science 2001;291:1195–1196.
2. Baltimore D. Our genome unveiled. Nature (Lond) 2001;409:814–816.
3. Beckman DA, Brent RL. Mechanism of known environmental teratogens: drugs and chemicals. Clin Perinatol 1986;13:649–687.
4. Jacobs PA, Melville M, Ratcliff S, Keay AJ, Syme J. A cytogenetic survey of 11,680 newborn infants. Ann Human Genet 1974;37:359–376.
5. Green JJ, Hobbins JC. Abdominal ultrasound examination of the first-trimester fetus. Am J Obstet Gynecol 1988;159:165–175.
6. Quashie C, Weiner S, Bolgonese R. Efficacy of first trimester transvaginal sonography in detecting normal fetal development. Am J Perinatol 1992;9:209–213.
7. Reece EA, Assimakopoulos E, Zheng XZ, Hagay Z, Hobbins JC. The safety of obstetric ultrasonography: concern for the fetus. Obstet Gynecol 1990;76:139–146.
8. Vintzileos AM, Campbell WA, Nochimson DJ, Weinbaum PJ. Antenatal evaluation and management of ultrasonically detected fetal anomalies. Obstet Gynecol 1987;69:640–660.
9. Hanson FW, Happ RL, Tennant FR, Hune S, Peterson AG. Ultrasonography guided early amniocentesis in singleton pregnancies. Am J Obstet Gynecol 1990;162:1376–1381.
10. Lippman A, Tomkins DJ, Shime J, Hammerton JL. Canadian multicentre randomized clinical trial of chorion villus sampling and amniocentesis. Final report. Prenatal Diagn 1992;12:385–408.
11. Rhoads GG, Jackson LG, Schlesselman SE, et al. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. N Engl J Med 1989;320:609–617.
12. Desnick RJ, Schuette JL, Golbus MS, et al. First-trimester biochemical and molecular diagnoses using chorionic villi: high accuracy in the US Collaborative Study. Prenatal Diagn 1992;12:357–372.
13. Isada NB, Paar DP, Johnson MP, et al. In utero diagnosis of congenital varicella zoster virus infection by chorionic villus sampling and polymerase chain reaction. Am J Obstet Gynecol 1991;165:1727–1730.
14. Copel JA, Cullen MT, Grannum PA, Hobbins JC. Invasive fetal assessment in the antepartum period. Obstet Gynecol Clin N Am 1990;17:201–221.
15. Daffos F, Forestier F, Capella-Pavlosky M. Fetal blood sampling during the third trimester of pregnancy. Br J Obstet Gynaecol 1984;91:118–121.
16. Powell MC, Worthington BS, Buckley JM, Symonds EM. Magnetic resonance imaging (MRI) in obstetrics. II. Fetal anatomy. Br J Obstet Gynaecol 1988;95:38–46.
17. Marx JL. Imaging technique passes muster. Science 1987;238:888–889.
18. Lindfors KK, Gorczyca DP, Hanson FW, Tennant FR, McGahan JP, Peterson AG. The roles of ultrasonography and amniocentesis in evaluation of elevated maternal serum alpha-fetoprotein. Am J Obstet Gynecol 1991;164:1571–1576.
19. Hogge WA, Thiagarajah S, Ferguson JE Jr, Schnatterly PT, Harbert GM. The role of ultrasonography and amniocentesis in the evaluation of pregnancies at risk for neural tube defects. Am J Obstet Gynecol 1989;161:520–524.
20. Katz VL, Chescher NC, Cefalo RC. Unexplained elevations of maternal serum alpha-fetoprotein. Obstet Gynecol Surv 1990;45:719–726.
21. New England Regional Genetics Group Prenatal Collaborative Study of Down Syndrome Screening. Combining maternal serum AFP and age to screen in pregnant women under age 35. Am J Obstet Gynecol 1989;160:575–581.
22. Milunsky A, Jick SS, Bruell CL, et al. Predictive values, relative risks, and overall benefits of high and low maternal serum alpha-fetoprotein screening in singleton pregnancies: new epidemiologic data. Am J Obstet Gynecol 1989;161:291–297.

3
Fetal Congenital Abnormalities

Ronald J. Hurley and Linda J. Heffner

Advances in perinatology during the past two decades have resulted in dramatic changes in the diagnosis and management of fetal abnormalities. Antenatal diagnosis of a variety of congenital problems has resulted in the development of fetal therapeutics that may improve neonatal outcome. Perinatologists and pediatric surgeons continue to identify those fetal conditions that may benefit from intrauterine therapy and those for which treatment after delivery is indicated. The identification of these fetal conditions may dictate timing and mode of delivery; in utero treatment may affect maternal physiology. This chapter briefly reviews the diagnostic and therapeutic options available for prenatal diagnosis and then addresses the anesthetic considerations when specific conditions are identified.

Pathophysiology

Conditions affecting the fetus may be thought of broadly as anatomic, physiologic, or both. Examples of anatomic abnormalities include neural tube defects (e.g., meningomyelocele, spina bifida), congenital heart defects (transposition of the great vessels, tetralogy of Fallot, hypoplastic left heart syndrome), large masses (teratomas, cystic hygromas), abdominal wall defects (gastroschisis, omphalocele), and conjoined twins. Examples of physiologic conditions include cardiac arrhythmias, immune and nonimmune hydrops, fetal Graves' disease, and intrauterine growth restriction (IUGR). Combined disorders include multiple congenital malformations secondary to chromosomal defects and macrocrania secondary to severe hydrocephalus.

Diagnosis

Currently available techniques for the detection of abnormalities include maternal serum screening, chorionic villus sampling (CVS), amniocentesis, ultrasound, Doppler velocimetry, percutaneous umbilical blood sampling, and antenatal fetal heart rate monitoring. Maternal serum screening uses concentrations of estriol, chorionic gonadotropin (β-hCG), and alpha fetopotein (AFP) in maternal serum to predict risk for Down syndrome, trisomy 18, and open neural tube defects.[1] Screening is currently offered at 16 to 18 weeks gestation. Other disorders that may elevate maternal serum AFP include gastroschisis, omphalocele, cystic hygroma, Finnish nephrosis, and placenta accreta/percreta/increta.[1–3]

Chorionic villus sampling is a first trimester technique for obtaining trophoblast for use in chromosomal, enzymatic, and DNA-based assays.[4–7] Midtrimester amniocentesis is the technique most widely used to obtain fetal cells for chromosomal, DNA, or chemical study; indications include advanced maternal age, abnormal maternal serum screen, previous trisomy, parental chromosomal translocation, sex-linked genetic disorders, and an expanding number of identifiable single gene defects. The recent addition of fluorescent in situ hybridization (FISH) using DNA probes for chromosomes 13, 18, 21, X, and Y provides rapid identification of the most commonly occurring chromosomal aneuploidies.[8] FISH can be performed directly on amniocytes at any gestational age, thereby serving as an alternative to the more invasive procedure, percutaneous umbilical blood sampling, in some cases. Amniocentesis also may be used in the third trimester to assay fetal lung maturity before anticipated delivery.

Ultrasound is used as a primary diagnostic method and as a necessary adjunct to intrauterine techniques such as CVS, amniocentesis, and percutaneous umbilical blood sampling. Examples of indications for prenatal ultrasound currently include uncertain pregnancy dating, vaginal bleeding, abnormal maternal serum screen, size–date discrepancies, suspected polyhydramnios, suspected IUGR, and family history of congenital malformations. Many congenital malformations are diagnosed incidentally on scans obtained for another reason, but the use of routine ultrasound as a prenatal screening tool remains controversial. Ultrasound technology continues to improve. The ability to perform Doppler velocimetry on the umbilical vasculature is now widely available; normative data

have been established, and certain abnormalities, particularly reversed end-diastolic flow, have been correlated with significant risk for fetal death.[9] Umbilical Doppler would appear useful in the management of pregnancies suspected to have IUGR.

Currently less widely available than Doppler velocimetry, percutaneous umbilical blood sampling (PUBS) is a highly invasive but useful technique for directly accessing the fetal blood stream.[10,11] Percutaneous umbilical blood sampling can be used in the midtrimester to establish risk of congenital toxoplasmosis when maternal infection is present, in the third trimester to permit rapid lymphocytic karyotyping when a lethal trisomy is suspected, and to manage isoimmunized pregnancies including those complicated by potential fetal alloimmune thrombocytopenia. Percutaneous umbilical blood installation has been suggested as a way of delivering medications that cannot cross the placenta to the fetus; this application remains largely theoretical.

Once congenital abnormalities are diagnosed, many options are available to handle them. Early diagnosis maximizes the range of available options to include termination of the pregnancy should that be the patient's choice. For late diagnoses and pregnancies continuing into viability, in utero treatment may be indicated. Procedures currently under investigation include urinary tract drainage procedures for obstructive uropathy, administration of cardioactive drugs for supraventricular arrhythmias, percutaneous drainage of ascites or hydrothoraces before delivery, and intrauterine transfusion. Infants may benefit from premature or timed delivery, from delivery by cesarean section, or by delivery using a specialized technique at cesarean called the ex utero intrapartum treatment (EXIT) procedure.

Box 3.1. Fetal abnormalities potentially requiring cesarean delivery.

Anatomic
Macrocrania
Teratoma
Conjoined twins
Cystic hygroma
Arthrogryposis multiplex congenita
Ovarian cyst
Omphalocele
Gastroschisis
Osteogenesis imperfecta types I, III, IV
Spina bifida
Cephalocele
Diabetic macrosomia
Physiologic
Fetal distress
Thrombocytopenia
Congenital heart block
Ascites

Source: Main DM, Mennuti MT. Neural tube defects: issues in prenatal diagnosis and counseling. Obstet Gynecol 1986;67:1–16.

Obstetric Management

Cesarean Delivery

Cesarean delivery is sometimes indicated to prevent fetal somatic dystocia that might occur with the vaginal delivery of conjoined twins or a very large body part (Box 3.1). Similarly, it may be necessary to prevent traumatic injury to exposed tissue, such as in neural tube defects or abdominal wall defects containing liver. Cesarean delivery may also be recommended for similar reasons when fetal thrombocytopenia is present, especially in cases of alloimmune thrombocytopenia, as discussed in detail in Chapter 17.

In instances in which the presence of a congenital anomaly may preclude vaginal delivery, the anesthesiologist must attempt to optimize abdominal relaxation while minimizing anesthetic risk for mother and fetus. The degree of abdominal muscle relaxation provided by a spinal anesthetic or by the usual concentration of local anesthetics used for epidural anesthesia for cesarean section is generally adequate.

It must be remembered, however, that the use of a major regional anesthetic does not provide uterine relaxation. Should extraction of the fetus prove difficult and complete uterine relaxation be required, an anesthesiologist should be prepared for rapid induction of general anesthesia with thiopental, succinylcholine, endotracheal intubation, nitrous oxide, and a volatile anesthetic such as sevoflurane, desflurane, or isoflurane to provide maximal uterine relaxation. Halothane has been traditionally used for this purpose. However, because of concerns regarding hepatotoxicity associated with this agent,[12] it is no longer used by many anesthesiologists. In vitro studies on human uterine muscle have shown that equipotent concentrations of enflurane, isoflurane, and halothane depress myometrial muscle equally.[13] No studies have been performed to date on the newer agents desflurane and sevoflurane, although both have been used clinically. A combination vapor and intravenous nitroglycerin in doses up to 20 μg/kg/min has been proposed but without documented additional benefit.[14]

Cesarean delivery of a fetus with some of the anomalies listed in Box 3.1 may necessitate delivery through a larger uterine incision than is usually used. Thus, the obstetrician may choose a vertical, rather than a transverse, hysterotomy. Also, the time from uterine incision to delivery may be extended as the fetal parts are extracted. For these reasons, the anesthesiologist should be prepared for increased blood loss by establishing adequate large-bore intravenous access before the start of the procedure. Adequate preoperative volume loading with 1500 to 2000 mL intravenous fluids is particularly important.

Anesthetic Management

Several specific fetal conditions may be affected by drugs normally administered during the course of obstetric anesthesia. This section specifically addresses these issues for cases of fetal arrhythmias, maternal Graves' disease, fetal IUGR, and

nonimmune hydrops. The issues of nonreassuring fetal status, whether acute or manifested by peripartum evaluations such as the fetal heart rate tracing or biophysical profile, are discussed in Chapters 1 and 29.

Fetal Arrhythmias

Most antenatally diagnosed arrhythmias are supraventricular tachycardias, most commonly paroxysmal supraventricular tachycardia and, less frequently, atrial flutter and fibrillation. These rhythm abnormalities may be caused by anatomic abnormalities, defects in the conduction system, or viral infection. If rhythm abnormalities remain untreated, congestive heart failure and fetal hydrops may occur. To prevent or treat congestive heart failure, antiarrhythmic agents are administered maternally[15] because survival is improved if hydrops is not present. Prognosis is poor once hydrops has developed.[16]

Successful in utero conversion of fetal supraventricular tachycardia has been accomplished by administration of cardioactive drugs, usually digoxin or verapamil, and occasionally quinidine, procainamide, or propranolol, to the mother.[17] Conversion presumably occurs when therapeutic concentrations of drug are obtained in the fetal circulation; this may require administration of very large doses of these drugs to the mother. Premature delivery is effected only if transplacental therapy is unsuccessful in the face of persistent or worsening hydrops fetalis.

The use of these cardiogenic medications in the presence of fetal arrhythmias has several implications for the anesthesiologist. Therapeutic levels for the fetus often would be considered high therapeutic plasma concentrations for an adult. Maternal plasma levels need to be monitored to ensure that toxic levels of digoxin are not reached. During the period in which the parturient receives nothing by mouth, digoxin is administered intravenously. Maternal plasma potassium levels should also be followed, because low potassium levels may exacerbate digoxin toxicity.

Regional anesthesia is frequently used for labor and delivery in these patients. If a parturient has been treated with beta blockers such as propranolol for fetal supraventricular tachycardia, maternal heart rate may not increase if local anesthetic containing epinephrine is accidentally injected into an epidural vessel. Subjective symptoms should be carefully assessed to avoid inadvertent intravascular injection.

The effects of vasopressors such as ephedrine and phenylephrine, which are commonly used to treat the hypotension accompanying the induction of regional anesthesia, must also be considered. Maternal treatment with propranolol may make ephedrine therapy less effective because the contribution of heart rate to increasing maternal blood pressure may be diminished. In these cases, larger doses of ephedrine may be required to restore maternal blood pressure. The use of a pure alpha agonist such as phenylephrine may be more effective.

Fetal supraventricular arrhythmias may be associated with ventricular response rates well above 200 beats/min. Maternal ephedrine administration is associated with significant increases in fetal heart rate.[18] Therefore, large doses of ephedrine may exacerbate these abnormally fast ventricular rates and cause fetal decompensation. Although stroke volume can recharge in response to hemodynamic needs, fetal cardiac output is normally dependent on heart rate.[19] However, at the exacerbated fast heart rates seen with tachyarrhythmias, time provided for ventricular filling may be inadequate, and further deterioration may result.

Chronic fetal bradyarrhythmias are most often secondary to complete heart block, a condition with implications for both mother and fetus. Neonatal consequences vary from minimal to lethal complex structural heart disease; mothers of these infants have an increased risk of collagen vascular disease.[20] Most cases reported delivery at term without intrauterine treatment. Intrapartum monitoring in these fetuses is difficult and dependent on fetal capillary blood gas measurement rather than the usual heart rate monitoring. For this reason, cesarean delivery may be unavoidable. Fetal echocardiography and umbilical Doppler assessment may be useful to avoid cesarean delivery.[21]

In these cases, maternal hypotension encountered during regional anesthesia should be treated in the standard manner with ephedrine, because the ephedrine that passively crosses the placenta would not be expected to adversely affect these fetuses. Maternal administration of phenylephrine causes a reflex maternal bradycardia. Although this effect on fetal heart rate has not been reported, one may postulate that this drug could worsen the degree of fetal bradycardia and should be avoided. There is no advantage in these cases to increasing the fetal heart rate with atropine because the fetus has chronically compensated for the persistent bradycardia. Atropine is used only for specific maternal indications, such as maternal bradycardia. Cases in which the heart block is accompanied by hydrops fetalis have not benefited from an increase in fetal heart rate up to 50% associated with maternal administration of beta agonists.[22]

Graves' Disease

When maternal Graves' disease is present, even when well controlled after ablative therapy, there is a risk of fetal Graves' disease and the possibility of thyroid storm induced by delivery of the neonate. Fetuses affected by Graves' disease in utero can usually be identified by a mild fetal tachycardia (180–200 beats/min) and by IUGR. Parturients with active maternal Graves' disease may be treated with beta blockers such as propranolol. Regional anesthesia is generally preferred for labor and delivery because the sympathetic block attenuates adrenal release of catecholamines and minimizes the hypertension and tachycardia that may be produced by the stress of delivery.[23,24] Vasopressors such as ephedrine, which may increase both fetal and maternal heart rate, should be carefully titrated; an alpha agonist such as phenylephrine may be a better choice. The fetus may be born with a large goiter in these cases, and the anesthesiologist should ensure that personnel responsible for delivery room care of the neonate are prepared to manage neonatal respiratory obstruction.

Intrauterine Growth Restriction

Intrauterine growth restriction is an abnormality of fetal growth affecting approximately 3% of pregnancies. Causes are diverse and include chronic uteroplacental insufficiency, congenital infection, and genetic and anatomic abnormalities. Uteroplacental insufficiency accounts for at least 50% of confirmed cases. Once uteroplacental insufficiency is diagnosed as the probable cause, aggressive obstetric management is indicated, because these cases benefit from optimization of the intrauterine environment and timed delivery. Aggressive use of ultrasound, including Doppler velocimetry, and antepartum fetal heart rate testing are helpful. Delivery should be considered when fetal lung maturity is obtained.

No literature exists specifically addressing the anesthetic considerations for the IUGR fetus. In these cases, as in all cases of suspected uteroplacental insufficiency, maintenance of optimal placental perfusion is paramount. Abrupt changes in maternal blood pressure should be avoided. Adequate volume loading before the induction of anesthesia and prompt administration of vasopressors to treat maternal hypotension are essential. The presence of an IUGR fetus should alert the anesthesiologist to search for associated maternal conditions such as chronic hypertension, toxemia, cigarette smoking, or alcoholism.[25]

Fetal Hydrops

Nonimmune fetal hydrops, a condition of generalized edema of fetal soft tissues in utero, with or without effusions in serous cavities, and with no hematologic evidence of isoimmunization, may be caused by numerous maternal, fetal, and placental disorders.[26] Ultrasound identification of the condition and extensive antenatal evaluation can correctly identify the cause in about 85% of cases, and in some, specific therapy can be directed to the problem. Overall survival is less than 25%. In those cases in which the fetus is potentially salvageable but the hydrops is still present, care must be taken at delivery to prevent generalized depression in the neonate.

As in the IUGR fetus, maintenance of optimal placental perfusion is extremely important. Maternal narcotic administration should be avoided if possible, because the respiratory status of the fetus with nonimmune hydrops may be extremely precarious, and further depression could result. Regional anesthesia is preferred for labor and delivery because this will minimize the administration of systemic agents that transfer across the placenta. Aggressive resuscitation may be needed in the delivery room.

Fetal Conditions Incompatible with Extrauterine Life

Some fetal abnormalities are incompatible with extrauterine life. Anesthetic implications for the patient with intrauterine fetal death are discussed in Chapter 32. The following is a list of lethal malformations for which no therapeutic interventions currently exist.[27]

Extreme sensitivity to the emotional state of the parents is essential, because some families will choose aggressive therapies even if the prognosis for long-term survival is extremely poor. In these situations, appropriate consultations with the neonatologist are needed to ensure that the family is fully aware of the condition of the fetus and able to decide appropriately about the use of aggressive resuscitation after delivery. After all the information regarding the fetal condition and the options for management have been presented, a course of nonaggressive management may be chosen. Obstetric ethicists support nonaggressive management as a reasonable alternative.[28]

If a plan of nonaggressive management is selected, the anesthesiologist should make the parturient aware that her emotional and physical comfort are of paramount importance. Regional analgesic can be used for labor and delivery. Intravenous supplementation with narcotics, diazepam, or midazolam can be added as required to maintain the patient's comfort. Because some of these agents have an amnestic effect, it is important to discuss with the parturient the amount of recall that she may have of the event and to select agents on the basis of the patient's wishes and emotional state. Similar guidelines apply concerning anesthetic choices for patients undergoing destructive fetal procedures such as cephalocentesis in the case of severe hydrocephalus. General anesthesia may be desired by the patient in some of these cases, and the risks and benefits should be discussed. Respect for the families' choices and concerns is essential when dealing with these sensitive issues.

Box 3.2. Lethal congenital malformations diagnosable.

Anencephaly
Iniencephaly
Hydranencephaly
Alobar or semilobar holoprosencephaly
Acrania
Ectopia cordis
Body stalk anomaly
Meckel's syndrome
Bilateral renal agenesis
Infantile polycystic kidney disease
Bilateral multicystic kidney disease
Achondrogenesis
Thanatophoric dwarfism
Short rib-polydactyly syndromes
Osteogenesis imperfecta, type II
Hypophosphatasia

Summary

Anesthetic management in these cases may be challenging as expectant mothers might be on different medications in high doses for fetal well-being.

References

1. Zelop C, Nadel A, Frigoletto FD, Ponkey S, Macmillan M, Benacerraf BR. Placenta accreta/percreta/increta: a cause of elevated maternal serum alpha-fetoprotein. Obstet Gynecol 1992;80:693–694.

2. Main DM, Mennuti MT. Neural tube defects: issues in prenatal diagnosis and counseling. Obstet Gynecol 1986;67:1–16.
3. Kupferminc MJ, Tamura RK, Wigton TR, Glassenberg R, Socol ML. Placenta accreta is associated with elevated maternal serum alpha-fetoprotein. Obstet Gynecol 1993;82:266–269.
4. DiMaio MS, Baumgarten A, Greenstein RM, et al. Screening for fetal Down's syndrome in pregnancy by measuring maternal serum alpha-fetoprotein levels. N Engl J Med 1987;317:342–346.
5. Hogge WA, Schomberg SA, Galbus MS. Chorionic villus sampling: experience of the first 1000 cases. Am J Obstet Gynecol 1986;154:1249–1252.
6. Elias S, Simpson JL, Martin AO, et al. Chorionic villus sampling in continuing pregnancies. I. Low fetal loss rate in initial 109 cases. Am J Obstet Gynecol 1986;154:1349–1352.
7. Martin AO, Simpson JL, Rosinsky B, et al. Chorionic villus sampling in continuing pregnancies. II. Cytogenetic reliability. Am J Obstet Gynecol 1986;154:1353–1358.
8. Ward BE, Gersen SL, Carelli MP, et al. Rapid prenatal diagnosis of chromosomal aneuploidies by fluorescence in situ hybridization: clinical experience with 4,500 specimens. Am J Hum Genet 1993;52:854–865.
9. Trudinger B. Doppler ultrasound assessment of blood flow. In: Creasy RK, Resnik R (eds) Maternal-Fetal Medicine: Principles and Practice. Philadelphia: Saunders, 1989:254–267.
10. Hobbins JC, Grannum PA, Romero R, et al. Percutaneous umbilical blood sampling. Am J Obstet Gynecol 1985;152:1–6.
11. Daffos F, Capella-Pavlovsky M, Forestier F. Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: a study of 606 consecutive cases. Am J Obstet Gynecol 1985;153:655–660.
12. Bottinger LE, Dalen E, Halen B. Halothane-induced liver damage: an analysis of the material reported to the Swedish Adverse Drug Reaction Committee. 1966–1973. Acta Anaesth Scand 1976;20:40.
13. Munson ES, Embro WJ. Enflurane, isoflurane and halothane and isolated human uterine muscle. Anesthesiology 1977;46:11–14.
14. Cauldwell CB, Rosen MA, Harrison MR. The use of nitroglycerin for uterine relaxation during fetal surgery. Anesthesiology 1995;83:A929
15. Wladimiroff JW, Stewart PA. Diagnosis and treatment of fetal tachyarrhythmias. In: Maeda K (ed) The Fetus as a Patient. New York: Elsevier, 1987:335–342.
16. Klein AM, Holyman IR, Austin EM. Fetal tachycardia prior to development of hydrops. Am J Obstet Gynecol 1979;134:347.
17. Kleinman CS, Copel JA, Weinstein EM, et al. In utero diagnosis and treatment of fetal SCT. Semin Perinatol 1985;9:113–129.
18. Wright RG, Shnider SM, Levinson G, et al. The effect of maternal administration of ephedrine on fetal heart rate and variability. Obstet Gynecol 1981;57:734–738.
19. Gilbert RD. Effects of afterload and vasoreceptors on cardiac function in fetal sheep. J Dev Physiol 1982;4:299–309.
20. Reid RL, Pancham SR, Kean WF, et al. Maternal and neonatal implications of congenital complete heart block in the fetus. Obstet Gynecol 1979;54:470–474.
21. Kleinman CS, Copel JA, Hobbins JC. Combined echocardiographic and Doppler assessment of fetal atrioventricular block. Br J Obstet Gynaecol 1987;94:967.
22. Kleinman CS, Copel JA. Fetal cardiac dysrhythmias. In: Creasy RK, Resnik R (eds) Maternal Fetal Medicine: Principles and Practice. Philadelphia: Saunders, 1989:344–356.
23. Bullock JL, Harris RE, Young R. Treatment of thyrotoxicosis during pregnancy with propranolol. Am J Obstet Gynecol 1975;121:242–245.
24. Halpern SH. Anaesthesia for cesarean section in patients with uncontrolled hyperthyroidism. Can J Anaesth 1989;36:454–459.
25. Cohen SF. Evaluation of the neonate. In: Shnider S (ed) Anesthesia for Obstetrics. Baltimore: Williams & Wilkins, 1987:489–507.
26. Norton ME. Nonimmune hydrops fetalis. Semin Perinatol 1994;18: 321–332.
27. Romero R, Pilu G, Jeanty P, et al., eds. Prenatal Diagnosis of Congenital Anomalies. Norwalk: Appleton-Lange, 1988.
28. Chervenak FA, McCollough LB. Nonaggressive obstetric management: an option for some fetal anomalies during the third trimester. JAMA 1989;261:3439–3440.

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4
Intrauterine Fetal Manipulation

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Successful fetal intervention was first described by Dr. Liley in 1963 for the treatment of infants with erythroblastosis fetalis.[1] In the early 1960s, the treatment for neonates with severe hydrops fetalis secondary to maternal Rh sensitization was so dismal that Liley attempted to transfuse the fetus while in the uterus. He wrote that "for a variety of disorders, the physician and the parents are no longer helplessly dependent on what time, luck and intrauterine life present with birth . . . some day, for a wider range of fetal illness, we may be able to offer a brighter prospect than the present dismal alternative of neonatal death, abnormality or abortion."[2] However, it was not until 1982 that Harrison and colleagues performed the first open fetal operative procedure.[3] Today, with major advances in prenatal imaging and tocolytic therapy and refinements in surgical and anesthetic techniques, many once life-threatening fetal anomalies are now correctable.

It must be remembered, however, that in all selected cases for fetal intervention, there are two patients—the mother and her fetus. In every case, certain risks and benefits must be thoroughly assessed. For the fetus, any prenatal therapy should ultimately be judged by its ability to improve upon the natural history of the disease, and the benefit to the fetus should greatly outweigh the risk. The mother, although usually healthy, must understand and accept the inherent risks of anesthesia, surgery, and the complications related to the control of preterm labor. She will undergo certain physical risks for the psychologic benefit of a potentially more healthy fetus. Furthermore, because many open fetal procedures are performed with a low uterine hysterotomy, a cesarean delivery is usually required in all future pregnancies to avoid the possibility of uterine rupture. Fortunately, retrospective data suggest that prior open fetal surgery has a negligible impact on future maternal fertility.[4]

Surgical Management

The key to the successful management of many fetal anomalies is early and accurate diagnosis. With marked improvements in prenatal sonographic imaging, Doppler sonography, and ultrafast fetal magnetic resonance imaging, the fetus is no longer a hidden mystery in the mother's womb.

It is true that, with most fetal anomalies, the appropriate medical and surgical treatment involves near-term or term delivery of the affected fetus at an experienced tertiary care center. Other congenital malformations, if not terminated, may be incompatible with extrauterine life and may benefit from prenatal surgical intervention.

Fetal Obstructive Uropathy

Most fetal urinary tract obstructions do not require prenatal intervention. It is usually the fetus with bilateral hydronephrosis caused by an urethral obstruction who may develop severely impaired renal function (i.e., posterior urethral valves). Decreases in fetal urine output lead to oligohydramnios with potentially life-threatening pulmonary hypoplasia. Decompression of bilateral hydronephrosis may improve lung development and preserve renal function.[5–7]

The diagnosis of a significant urinary tract obstruction is usually made early in the second trimester on the basis of sonographic measurements. Decreasing amniotic fluid volume on serial ultrasound examinations in the setting of bilateral hydronephrosis is usually a late indicator of deteriorating renal function. Eligibility for fetal intervention is based on indices of renal function as assessed by the sonographic appearance of the renal parenchyma and by the analysis of the fetal urine.[8] The presence of cortical cysts or increased echogenicity is highly predictive of renal dysplasia, yet the absence of these findings does not preclude renal damage.[9] Poor renal function can reliably be predicted with elevations in fetal urinary electrolytes (sodium and chloride) and β_2-microglobulin.[10]

If the lungs are mature in the setting of oligohydramnios, and there is preserved renal function, early delivery should be considered for postnatal decompression (Figure 4.1). If the lungs are immature, fetal intervention to decompress the bladder can be considered. Percutaneous vesicoamniotic shunting,[11,12] fetoscopic vesicostomy,[13,14] and endoscopic ablation of posterior urethral valves[15,16] have had favorable outcomes.

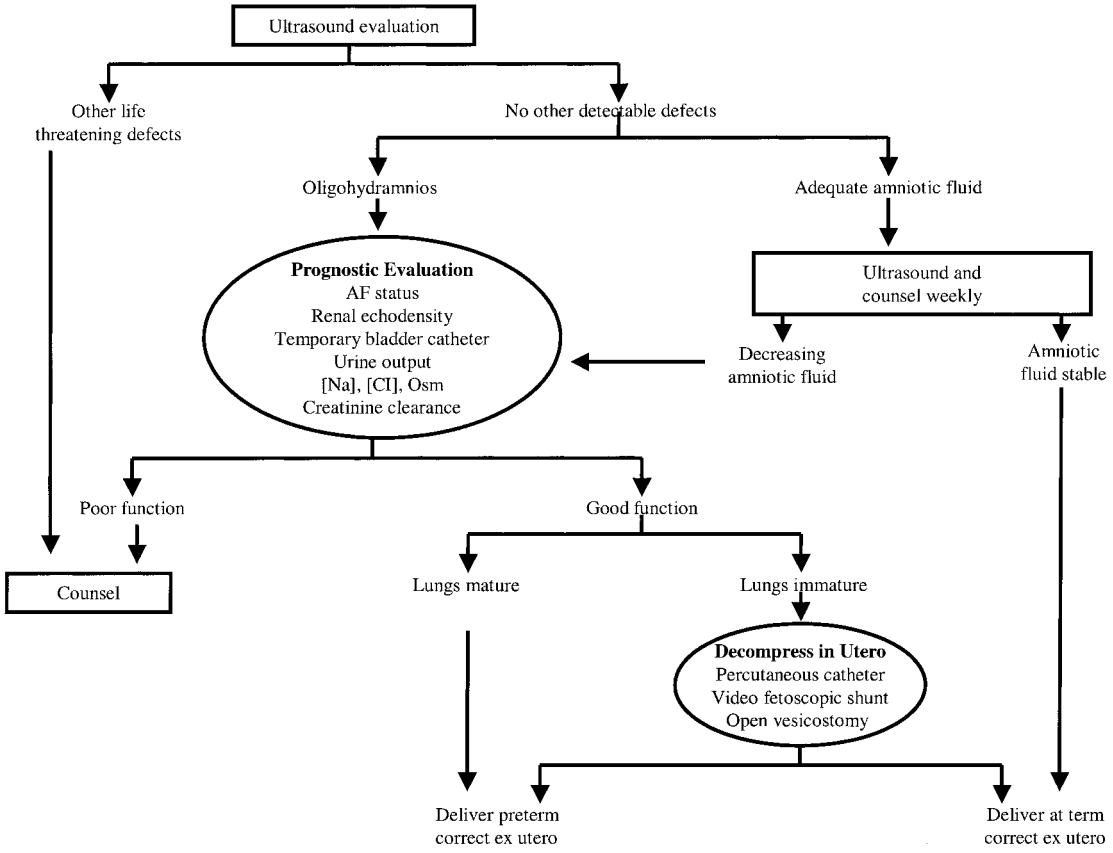

FIGURE 4.1. Management of the fetus with bilateral hydronephrosis. *AF*, amniotic fluid; *Osm*, osmolality. (From Quinn TM, Adzick NS. Fetal surgery. Obstet Gynecol Clin N Am 1997;24:152, with permission.)

Despite advances in prenatal intervention for obstructive uropathy, there is still a considerable risk to the fetus. Long-term outcomes indicate that fetal intervention may not reverse the renal dysplastic changes or be a predictor for possible urinary diversion.[17]

Fetal Lung Masses

In many cases, a fetal lung mass that is diagnosed in utero may either be a bronchopulmonary sequestration (BPS) or a congenital cystic adenomatoid malformation (CCAM). Serial ultrasound examinations of fetuses with lung masses has helped define the natural history of these lesions, identify the pathophysiology that will affect clinical outcome, and formulate the management on the basis of prognosis.[18] Experience suggests that the overall prognosis depends on the size of the lung mass and the secondary pathophysiologic effects. A large lung mass can cause a mediastinal shift with subsequent hypoplasia of normal lung tissue, polyhydramnios, and vena caval and cardiac compression, leading to fetal hydrops and death.

Hydrops fetalis is a condition characterized by an abnormal accumulation of fluid and edema in the fetus.[19] Placentomegaly and polyhydramnios may be additional findings. Fetal hydrops or progressive placentomegaly are highly predictive of imminent in utero demise.[20] Large fetal lung masses with hydrops can also have life-threatening consequences for the mother. A maternal hyperdynamic state referred to as the "mirror syndrome" may develop.[21] The mother develops worsening symptoms of preeclampsia (i.e., hypertension, proteinuria, and peripheral and pulmonary edema). Unfortunately, the treatment of the underlying fetal condition does not reverse the mother's compromised state.[19]

Bronchopulmonary sequestration is a cystic mass of nonfunctional lung tissue that lacks an obvious communication with the tracheobronchial tree and receives all or most of its blood supply from anomalous systemic vessels.[22] Color flow Doppler ultrasound demonstrating an echodense pulmonary mass with a systemic blood supply usually confirms the diagnosis.[23] Adzick and colleagues reported that 75% of cases of prenatally diagnosed BPS resolve spontaneously.[18,24] Fetal hydrops can result either from compression by the mass or from a tension hydrothorax caused by fluid or lymph secretion from the BPS.[25]

Congenital cystic adenomatoid malformation of the lung is a multicystic pulmonary mass with a proliferation of bronchial structures.[26,27] Unlike BPS, most CCAMs derive their arterial blood supply and venous drainage from the normal pul-

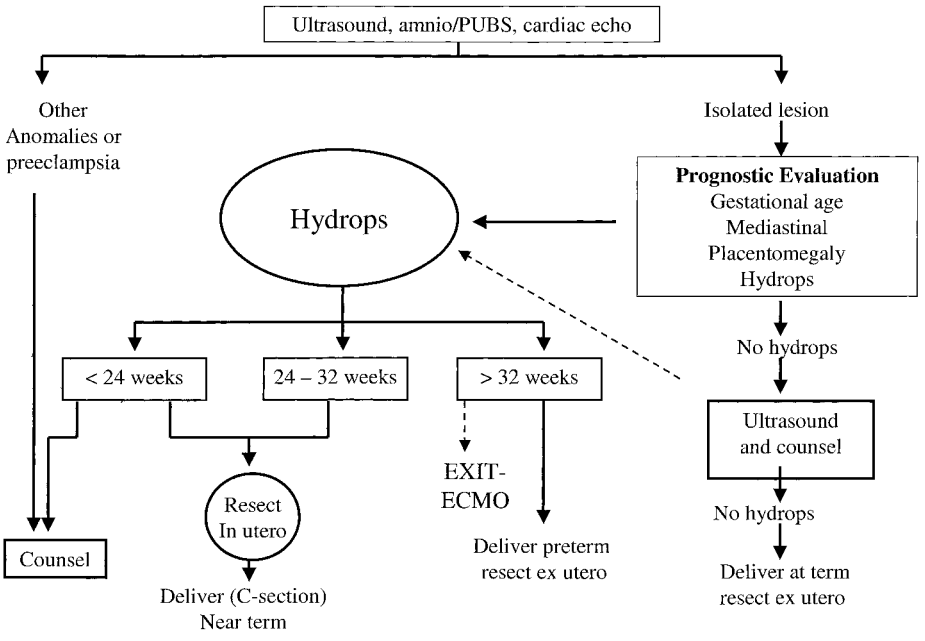

FIGURE 4.2. Management of the fetus with a fetal lung mass. *PUBS*, percutaneous umbilical cord sampling; *EXIT-ECMO*, ex utero intrapartum treatment-extracorporeal membrane oxygenation. (From Quinn TM, Adzick NS. Fetal surgery. Obstet Gynecol Clin N Am 1997; 24:148, with permission.)

monary circulation.[28] Prenatally diagnosed CCAMs have a broad spectrum of clinical severity ranging from benign to life threatening. Some very large CCAMs can decrease in size and even disappear before birth.[29] Others may remain stable, increase without adverse consequences, or increase to the size at which mediastinal shift, vena caval compression, and fetal hydrops develop.

The treatment for each fetus with a lung mass must be individualized (Figure 4.2). Because the outcome for fetuses with developing hydrops is so dismal, fetal intervention may be warranted. If the fetus develops hydrops before 32 weeks gestation, several options exist. Fetal surgical resection (lobectomy) was performed in 13 cases at 21 to 29 weeks gestation with 8 survivors.[30] Hydrops reversed over 1 to 2 weeks, and further lung growth allowed for normal postnatal development. Thoracoamniotic shunting may be effective in cases of a single large cyst.[31,32] More recently, using a fetal sheep model, radiofrequency thermal ablation was used to create a controlled area of lung tissue ablation. In the future, this may offer a potential treatment for hydropic fetuses with a large chest mass.[33]

For hydropic fetuses greater than 32 weeks gestation, early delivery should be encouraged for extracorporeal membrane oxygenation (ECMO) placement[33,34] while on placental support, using the EXIT (*ex utero* intrapartum treatment) procedure followed by delivery and resection or, if stable, for resection following delivery.

If the fetus is not hydropic, the growth of the lesion and the fetus's condition are monitored by serial ultrasounds.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is an anatomically simple defect in which the abdominal viscera herniate into the hemithorax. Herniated bowel, stomach, and liver compress the growing ipsilateral fetal lung and shift the mediastinum, compromising development of the contralateral lung. As a result, these infants are born with variable degrees of pulmonary hypoplasia and respiratory failure. Despite continuing advances in prenatal care, delivery at experienced tertiary care centers, improved neonatal resuscitation, and the ready use of ECMO, postnatal mortality from the resultant pulmonary hypoplasia and pulmonary hypertension is still disturbingly high.[35]

Prenatally diagnosed CDH is associated with a much higher mortality than postnatally diagnosed CDH.[36–41] In those fetuses who are diagnosed in utero, the clinical severity of CDH varies from those with a relatively "good" prognosis who will usually do well with aggressive postnatal care to those with a "grim" prognosis who may benefit from prenatal intervention. The prognosis is primarily related to the position of the liver; those fetuses with liver herniation into the hemithorax have about a 50% survival, whereas those with the liver in the normal anatomic position have a greater than 90% chance of survival.[42]

A second prognostic indicator for fetal patients with CDH is the lung-to-head ratio (LHR), which measures the cross-sectional area of the contralateral lung and indexes it to head circumference to adjust for gestational age.[43] Fetuses with an LHR greater than 1.4 and liver located below the diaphragm have a good prognosis with experienced postnatal medical and surgical treatment at a tertiary neonatal care center and thus are not candidates for fetal intervention. Fetuses with an LHR less than 1.4 and liver herniation into the chest have a grimmer prognosis and may benefit from fetal intervention.

A third prognostic indicator is simply the time of diagnosis. The outcome for patients with an early (less than 24 weeks

gestation) diagnosis of an isolated CDH is generally worse than the outcome of patients detected later by population-based studies or by studies of patients who present in the postnatal period.[44]

Fetal surgery for CDH is ideally performed at 24 to 26 weeks gestation, which allows the decompressed lungs sufficient time to develop and avoids the increased uterine irritability and hence preterm labor that occurs later in gestation. Initial attempts to save severely affected fetuses were made with open fetal surgery and repair of the diaphragmatic defects.[45,46] However, early experience proved that complete surgical repair of the diaphragmatic defect in fetuses without liver herniation into the chest did not improve the survival rate over standard postnatal care.[47]

The problem of "liver up" CDH into the chest still remains challenging. Open surgical attempts to reduce the incarcerated liver kinked the umbilical vein, resulting in fetal deaths.[45,46] Animal studies with CDH have shown that impeding the normal egress of fetal lung fluid by controlled tracheal occlusion enlarges the hypoplastic lungs and pushes the abdominal viscera back into the abdomen.[48–50] Temporary tracheal occlusion, either by fetoscopy or by open dissection in humans, accelerates fetal lung growth and ameliorates the often fatal pulmonary hypoplasia that affects this high-risk group of fetuses.[51,52] These fetuses are then delivered by the EXIT procedure to remove the tracheal clips and obtain a patent airway.

The fetal care program at Children's Hospital Boston, has also treated the "liver up" CDH with a low LHR using the EXIT-ECMO procedure with favorable results. This procedure allows a "smooth" transition from intrauterine to extrauterine life with essentially no barotrauma or prolonged resuscitation.

In summary, at the Advanced Fetal Care Center at Children's Hospital Boston, when a CDH is diagnosed early in gestation with poor prognostic indicators, the family has four choices: (1) terminate the pregnancy, (2) carry to term and deliver in a tertiary neonatal center for postnatal intensive care, (3) undergo the EXIT-ECMO procedure at or near term; or (4) have *in utero* tracheal occlusion at 24 to 26 weeks gestation followed by the EXIT procedure at delivery (Figure 4.3).

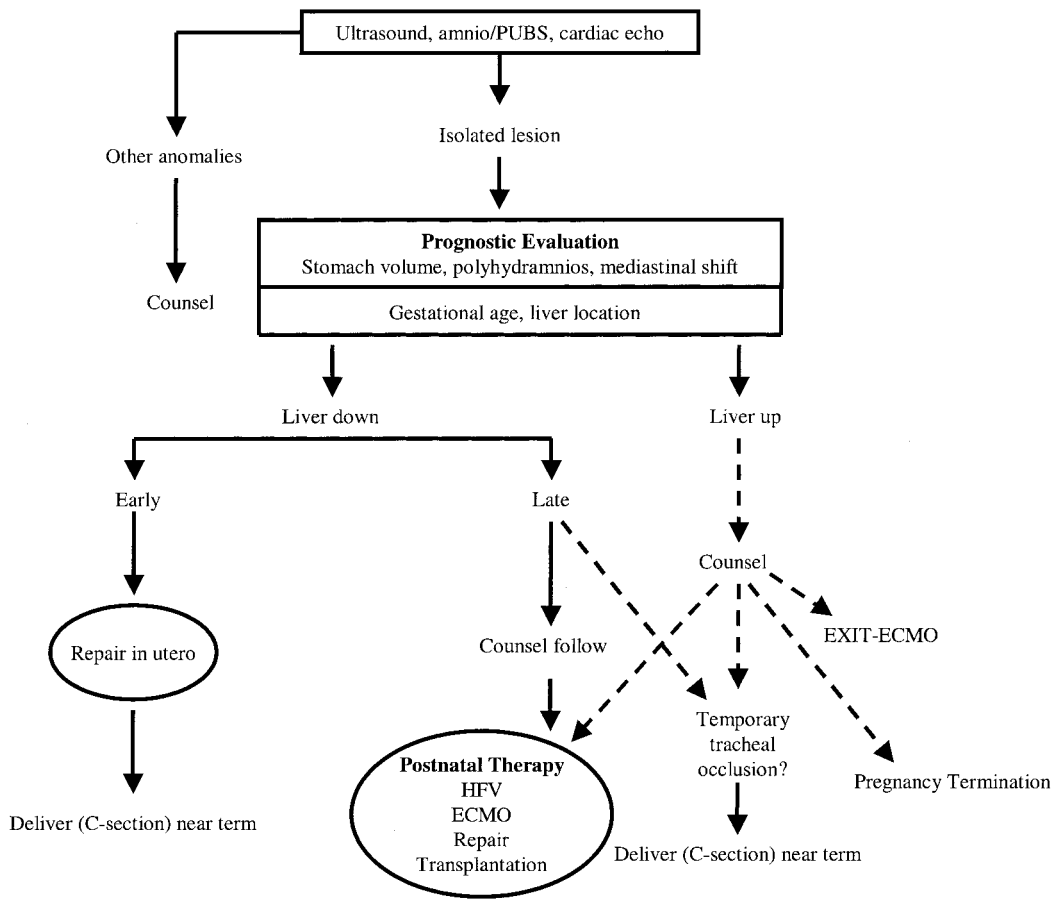

FIGURE 4.3. Management of the fetus with congenital diaphragmatic hernia. *HFV*, high-frequency ventilation; *EXIT*, ex utero intrapartum treatment; *ECMO*, extracorporeal membrane oxygenation; *PUBS*, percutaneous umbilical cord sampling. (From Quinn TM, Adzick NS. Fetal surgery. Obstet Gynecol Clin N Am 1997;24:150, with permission.)

Sacrococcygeal Teratoma

Sacrococcygeal teratoma (SCT), although a rare diagnosis, is the most common neonatal tumor. Although malignant spread is unusual, the outcome for prenatally diagnosed SCT is often not favorable. Because this is a highly vascular lesion, a vascular steal syndrome may develop, in which the tumor "steals" blood flow from the fetus and placenta. There may also be spontaneous internal or external hemorrhage from the SCT, resulting in fetal anemia.[53] High-output cardiac failure and hydrops rapidly progress to fetal death.[20,54,55] The anemic, hydropic fetus with SCT secondary to hemorrhage may be treated by an *in utero* blood transfusion, whereas the only hope for a hydropic fetus with vascular steal from the tumor may be either early delivery or fetal intervention.

Most fetuses with a diagnosis of SCT can be managed by a planned delivery followed by postnatal resection of the tumor (Figure 4.4). Any indication of fetal hydrops should trigger prompt delivery or fetal intervention. If placentomegaly and hydrops develop after pulmonary maturity is established, the fetus should be delivered by emergent cesarean section and treated *ex utero*. If high-output cardiac failure and placentomegaly develop in cases with immature lungs, *in utero* tumor resection has been successful.[56,57] Radiofrequency ablation to interrupt blood flow to an SCT was recently attempted in four fetuses, with survival in two fetuses.[58] The other two cases experienced hemorrhage into the tumor, leading to unfavorable outcomes.

Airway Obstruction

The causes of fetal airway obstruction may be either extrinsic to the airway or intrinsic to the larynx or trachea. Extrinsic causes of fetal airway obstruction are usually the mass effect of a large cervical teratoma or lymphangioma. Less common causes include fetal goiter, hemangioma, epignathus, neuroblastoma, choristoma, mucocele, laryngocele, or a bronchial cleft cyst.[59–63] Intrinsic causes of fetal airway obstruction usually fall under the category of congenital high airway obstruction syndrome (CHAOS).[64] The airway obstruction in CHAOS may be caused by tracheal or laryngeal atresia or a laryngeal cyst.

Detection of a giant neck mass is usually discovered at a prenatal ultrasound. Magnetic resonance imaging using fast scanning techniques may help identify the diagnosis. Polyhydramnios may be present if the mass is large enough to cause esophageal obstruction and inhibit fetal swallowing.[65,66] Complete obstruction of the larynx or trachea in CHAOS results in elevated intratracheal pressures and dilation of the tracheobronchial tree because of the accumulation of fetal lung fluid. The results are large hyperechogenic lungs, a flattened or inverted diaphragm, ascites, and hydrops.[64] There has never been a fetus diagnosed with CHAOS and hydrops who has survived without intervention.[67] Furthermore, up to 30% of neonates with cervical and 21% with oropharyngeal teratomas died of airway obstruction shortly following birth.[68] Because many of these lesions are incompatible with extrauterine life, the EXIT procedure has proved to be lifesaving.[61,62,69–71] While the fetus is partially delivered and is on placental support, the airway is secured by other means such as direct laryngoscopy, bronchoscopy, tracheostomy,[72] or the initiation of ECMO.

Twin–Twin Transfusion Syndrome

Twin–twin transfusion syndrome (TTTS) is a relatively common complication of monochorionic twin pregnancies.[73] The condition usually presents in the second trimester with an obvious discordance in amniotic fluid volume. Blood is shunted by placental vascular anastomosis from one twin (the "donor") to the cotwin (the "recipient"), resulting in a net imbalance of blood flow. The "recipient" twin develops polyhydramnios as a result of atrial natriuretic peptide (ANP)-mediated polyuria[74–76] while the "donor" twin develops oligohydramnios/

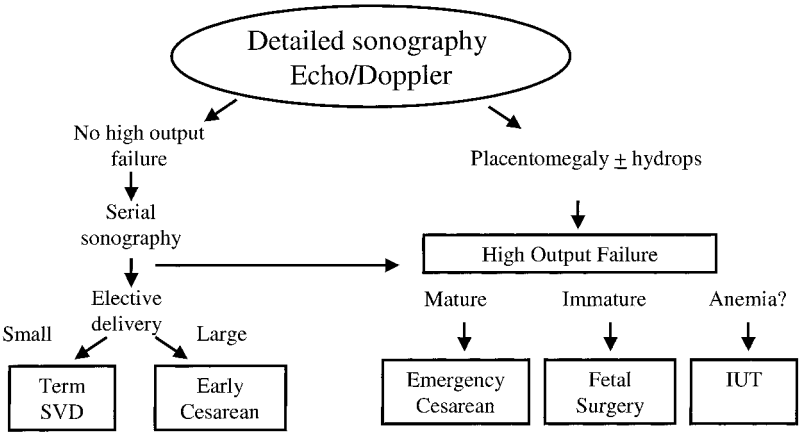

FIGURE 4.4. Algorithm for management of the fetus with sacrococcygeal teratoma. (From Flake AW. The fetus with sacrococcygeal teratoma. In: Harrison MR, Evans MI, Adzick NS, Holzgreve W, eds. The Unborn Patient. The Art and Science of Fetal Therapy. Philadelphia: Saunders, 2001:321, with permission.)

anhydramnios from hypovolemic oliguria.[77,78] Furthermore, the "recipient" may go on to develop hypertrophic cardiomyopathy and hydrops, followed by death.[79,80] Besides a high morality of 17% in these twins overall,[80,81] there is also a risk of long-term neurologic sequelae.[82] Treatment options in cases with cardiac failure include serial amniocenteses of the polyhydramniotic sac, [83] percutaneous umbilical cord occlusion, and fetoscopic laser ablation of the abnormal vascular anastomosis.[84–86]

Myelomeningocele

Myelomeningocele (MMC) is the congenital failure of the neural tube to close, which most commonly occurs in the middle or caudal groove of the spinal canal, resulting in a thoracic or lumbosacral defect. Most children with MMC also have an associated Arnold–Chiari type II malformation (hindbrain compression) that may contribute to the development of ventriculomegaly and hydrocephalus.[87–89] Although severely disabling, MMC is not a lethal congenital defect. Patients with MMC, depending on the level of the defect, may develop paraplegia, urinary and fetal incontinence, sexual dysfunction, and skeletal deformities and thus require multiple surgical and medical interventions in their lifetime.

A "two-hit" hypothesis has been described to explain the etiology of neural tissue damage in cases of MMC.[90] The first "hit" may be the result of an embryologic defect in spinal cord development. The second "hit" may result from prolonged exposure of the open spinal cord to in utero trauma or to the composition of the amniotic fluid.[91] This secondary event may be prevented if early coverage or closure of the cord defect could be provided. The hope of fetal intervention is to correct the defect before significant neural damage occurs or to reverse the damage that may have already occurred.

Animal studies have indeed shown that in utero repair of surgically created MMC did prevent certain neurologic defects.[92–95] The data in humans is less convincing. The fetal surgical group from the Children's Hospital of Pennsylvania reported on a single case of a T11–S1 myelomeningocele who had an open repair at 23 weeks gestation. The child's neurologic level at birth was better than predicted, and a postnatal MRI revealed no evidence of the Chiari malformation and no hydrocephalus.[96] Follow-up studies in patients having in utero MMC repair have not shown dramatic improvements in sensorimotor function, yet unexpectantly have shown a substantial reduction in hindbrain herniation[97–99] and also a modestly reduced incidence of shunt-dependent hydrocephalus.[99–101]

It is unknown at this time whether fetal surgery for myelomeningocele is truly beneficial, considering maternal and fetal morbidity, as compared to term delivery and standard postnatal care.[102] A large, multicenter prospective randomized clinical trial comparing open fetal repair at a certain range of gestational ages (<27 weeks) with routine postnatal care is now underway to answer this complex question.[102]

Future Therapy

The accomplishments achieved during the past two decades in the surgical management of previously lethal congenital defects are truly amazing. Other areas of ongoing research such as valvuloplasty for fetuses with severe aortic valve obstruction,[103] scarless wound healing in fetuses with cleft lips/palates,[104–107] and in utero stem cell therapy for hemoglobinopathies, immunodeficiency diseases, and metabolic disorders[108,109] are just beginning to be discovered and understood for future fetal intervention.

Anesthetic Management

Many of the anesthetic considerations for fetal intervention are similar to those for nonobstetric surgery during pregnancy. An understanding of the many physiologic changes that occur during pregnancy is necessary to ensure maternal safety. Because the fetus is also a patient, fetal well-being must be considered, and potential teratogenic agents should be avoided. Finally, because the fetus may remain in the womb following a surgical intervention, preterm labor should be controlled to lessen the morbidity and mortality associated with prematurity.

Unlike other nonobstetric surgery during pregnancy, the fetus must also be anesthetized and appropriately monitored. In addition, because of inadvertent uterine manipulation, there is an increased likelihood of inducing intraoperative or postoperative preterm labor, and the uterus must be adequately relaxed for surgical exposure.

The Mother

Pregnancy is associated with major physiologic changes that involve essentially every organ system, most of which are induced by placental hormones or by the mechanical effects of the gravid uterus. With these physiologic changes in mind, it is important to remember that fetal well-being is directly dependent on maternal well-being. Any compromise in maternal oxygenation or hemodynamics can have disastrous consequences on the developing fetus.

Fetal oxygenation depends on maternal arterial oxygen content, the maternal hemoglobin concentration, the fetal hemoglobin concentration, and uteroplacental perfusion. Although the anesthetic technique in itself has no effect on the maternal or fetal hemoglobin concentration, the delivered anesthetic should optimize maternal arterial oxygen content and maintain adequate uteroplacental blood flow.

The causes of maternal hypoxia during general anesthesia are similar to those of any ventilated patient. However, because acute maternal hyperventilation can result in fetal hypoxemia and acidosis,[110] a normal $Paco_2$ for pregnancy (30–33 Torr) should be maintained. Maternal alkalosis reduces uterine and umbilical blood flow by direct vasoconstriction[111] and also increases the affinity of maternal hemo-

Box 4.1. Anesthetic management and uterine blood flow

1. Maternal hypotension caused by vasodilation from high concentrations of inhalation agents, sympathectomy from regional blockade, aortocaval compression, or hypovolemia
2. Vasoconstriction from maternal hypoxia, hypocarbia, hypertension, toxemia, or increased catecholamines
3. Elevated venous pressure from caval compression or uterine contractions
4. Excessive positive pressure ventilation that impedes maternal venous return and cardiac output

Source: Adapted with permission from Rosen MA. Anesthesia and monitoring for fetal intervention. In: Harrison MR, Globus MS, Filly RA (eds) The Unborn Patient: Prenatal Diagnosis and Treatment, 2nd edn. Philadelphia: Saunders, 1991:174.

globin for oxygen, which results in less transfer of oxygen across the placenta.[112] Although the uterine vasculature is maximally dilated under normal conditions, the vessels are capable of significant vasoconstriction that can impair fetal oxygenation.

Uterine blood flow may be decreased by several factors relating to anesthetic management, which include those listed in Box 4.1.[113]

Normal fetal growth and development can be compromised by the inadvertent use of teratogenic agents. All human studies to date indicate that surgery and anesthesia during pregnancy are not associated with an increased incidence of congenital anomalies yet may cause a greater chance of miscarriage and preterm delivery.[114–118]

The most significant challenge to the success of invasive fetal therapy today is preterm labor. Any uterine stimulation or manipulation will initiate uterine contractions. Besides directly reducing uteroplacental blood flow, strong uterine contractions may cause placental separation, which obviously compromises fetal well-being.

Various drugs are available to achieve tocolysis. Preoperatively, an indomethacin suppository is administered to the mother for procedures involving most fetal surgical interventions. While the mother is anesthetized under general anesthesia, high concentrations of an inhaled agent are delivered intraoperatively to optimize uterine relaxation as well as to inhibit uterine contractions. The profound uterine relaxation provided by these agents can contribute to significant uterine bleeding with surgical incision.[119–121] Following the fetal intervention, intravenous magnesium sulfate is administered as the inhalation agent is tapered with uterine closure. Occasionally, bolus doses of intravenous nitroglycerin may be needed to further inhibit uterine contractions intraoperatively or upon emergence of the mother from anesthesia.

Pulmonary edema has been reported in obstetric patients who received nitroglycerin for tocolysis after open fetal surgery.[122,123] Magnesium sulfate and low-dose beta-adrenergic agonists can also cause pulmonary edema in pregnant patients.[124–126] Because of these concerns, intraoperative intravenous fluids to the mother should be limited. Postoperatively, an intravenous magnesium infusion is continued for several days. Afterwards, subcutaneous or oral terbutaline or calcium channel blockers are given to the mother for the remainder of the pregnancy.

For surgeries involving a major fetal intervention, general anesthesia is most commonly preferred. Following a rapid sequence induction, anesthesia is maintained with oxygen, an inhaled agent, and a neuromuscular blocker. Before uterine incision and the inhaled agent is increased to at least 2 (MAC) minimal alveolar concentrations titrated to satisfactory uterine relaxation. Ephedrine or phenylephrine is given as needed to maintain a maternal systolic blood pressure of greater than 100 mm Hg.[127] Again, intravenous fluids are restricted to minimize the risk of postoperative pulmonary edema.

For most invasive fetal procedures other than the EXIT procedure, intravenous magnesium sulfate is bolused with closure of the hysterotomy and the inhaled agent is reduced. If the mother remains hemodynamically stable, narcotics may be given, or an epidural, if placed preoperatively, may be dosed. Upon skin closure, the inhalation agent is discontinued, the neuromuscular blockade is reversed, and the mother is extubated when fully awake and responsive.

For less invasive fetal procedures that do not involve a hysterotomy, the choice of a regional anesthetic accompanied by intravenous sedation for the mother may be acceptable. However, it must be remembered that although the placental transfer of drugs administered to the mother may sedate the fetus, an anesthetized or immobile fetus is not guaranteed. Excessive fetal movement, besides making the procedure technically more difficult, can also result in displacement of a needle or catheter, leading to significant trauma to the fetus or to the placenta. If a regional anesthetic is chosen, it may be wise to deliver an intramuscular or intravascular injection of pancuronium[128] and fentanyl to the moving fetus.

For the EXIT procedure, the fetus is partially delivered and the necessary operation is performed on placental support. As in other open fetal procedures, anesthesia for the fetus and satisfactory uterine relaxation are extremely important for the pediatric surgeon to perform the often lifesaving procedure. After delivery of the infant, uterine tone must return quickly to avoid the risk of significant maternal hemorrhage and uterine atony. With clamping of the umbilical cord, oxytocin is administered intravenously and the inhaled agent is decreased. For postoperative pain relief, narcotics are given or the epidural is dosed. If uterine atony persists, intravenous/intrauterine methergine or intrauterine prostaglandin $F_{2\infty}$ must be administered immediately, or rapid blood loss will follow.

The Fetus

The combination of underdeveloped organ function and the usually life-threatening congenital malformation places the fetus at a considerable anesthetic risk. Unlike that of adults

and older children, fetal cardiac output is more dependent on heart rate than on stroke volume.[129] Because fetal myocardial contractility is probably maximally stimulated, the fetus has a limited ability to increase stroke volume. Furthermore, in the fetal lamb, increases in preload had little effect on cardiac output[130] as volume loading increased cardiac output by only 15% to 20%.[131] Anesthetic-induced decreases in contractility combined with surgical fetal manipulation can result in fetal hypotension, bradycardia, and eventual cardiac collapse.

It is generally accepted that neonates manifest a greater degree of hypotension in response to isoflurane and halothane at equipotent anesthetic concentrations as compared with older children.[132,133] Rao and others found the isolated neonatal rat atria to be more sensitive to the myocardial depressant effects of halothane, enflurane, and isoflurane than the adult rat atria.[134] The authors concluded that the greater degree of hypotension seen in younger animals was caused by a more pronounced direct depression on myocardial contractility in the younger as compared with the older rat.

All inhaled anesthetics rapidly cross the placenta.[135] However, the uptake of inhaled anesthetics occurs more slowly in the fetus than in the mother. When pregnant ewes were anesthetized with 1.5% halothane in oxygen, halothane appeared in the fetal blood by 2 minutes, but equilibrium with the maternal blood was not reached until 24 minutes later.[136] Fetal blood pressure decreased by 27%, yet there were no changes in fetal heart rate or acid–base status.[136] Isoflurane was also present in the fetal circulation within 2 minutes.[137] However, even after 96 minutes of anesthesia, fetal levels were significantly less than maternal levels.[137] Although there were no significant changes in fetal blood pressure or heart rate, the pH, base excess, and cardiac output were decreased.[137]

During light or moderately deep (1.0–1.5 MAC) isoflurane or halothane anesthesia, maternal arterial pressure was lowered and uterine vasodilation occurred, however, uteroplacental perfusion was maintained. Fetal oxygenation and acid–base status were also maintained.[138] However, at higher concentrations of the inhaled anesthetic (2.0 MAC), maternal hypotension resulted in decreased uteroplacental perfusion despite uterine vasodilation, leading to fetal hypoxia and acidosis.[138]

The effects of halothane anesthesia on fetal physiology during fetal surgery have also been studied. Pregnant ewes received either halothane or intravenous ketamine anesthesia, and the fetuses were then instrumented for cardiovascular evaluation. In the stressed fetus undergoing fetal surgery, halothane anesthesia significantly reduced fetal cardiac output and placental blood flow, while fetal vascular resistance increased.[139] Placental vascular resistance increased out of proportion to systemic vascular resistance, which led to a shunting of blood away from the placenta, resulting in a detrimental effect on fetal respiratory gas exchange.[139]

Name_____

Estimated Fetal Weight_____

Code Medications	Comes As	Dose	Patients Dose
Atropine	0.1 mg/mL	0.01 mg/kg	=_____mg =_____mL
Tromethamine (THAM)	0.3M/L	3 mM/kg (= 10 mL/kg)	=_____mmol/L =_____mL
Calcium gluconate	100 mg/mL	100 mg/kg	=_____mg =_____mL
Epinephrine 1:10,000	0.1 mg/mL	0.02 mg/kg	=_____mg =_____mL

Compression – 100-150/minute

Packed red blood cell (PRBC) Transfusion

Following THAM and dilution, Hematocrit = _____, pH = _____.

Warm to 37°C.

PRBC 15 ml X -_____ kg = _____ ml. Give blood SLOWLY over several minutes.

Monitor heart rate during and after transfusion.

After transfusion, Calcium Gluconate 100 mg X _____ kg = _____ mg = _____ mL

FIGURE 4.5. Fetal surgery emergency sheet. (From Graf JL, Paek BW, Albanese CT, et al. Successful resuscitation during fetal surgery. J Pediatr Surg 2000;35:1389, with pemission.)

Preterm neonates feel pain. Cutaneous sensory receptors are present in the human fetus by the 20th week of gestation.[140] By the 30th week of gestation, the brainstem and thalamus are completely myelinated,[140] and EEG patterns show a distinction between wakefulness and sleep.[141] Obviously, the second trimester fetus needs anesthesia to eliminate pain and to induce unconsciousness. However MAC, at least in fetal lambs, is significantly less than that of neonatal lambs or the mother.[142] This lower MAC may be secondary to incomplete myelination of nerve fibers and immature neurotransmission pathways in the developing fetus. MAC may also be decreased by high levels of progesterone in the fetus, as progesterone has anesthetic properties when administered in pharmacologic doses.[143]

Anand and others have demonstrated that preterm neonates undergoing surgery had substantial hormonal responses indicative of stress when given minimal anesthesia.[144] These responses resulted in a catabolic response characterized by glycogenolysis, gluconeogenesis, and lipolysis in the postoperative period, which caused circulatory and metabolic complications in the neonate.[145] The prevention of this exaggerated stress response with fentanyl anesthesia improved postoperative outcome following surgery.[145]

The fetus has little subcutaneous tissue or fat and is therefore prone to significant hypothermia. To avoid this problem during open fetal procedures, the fetus must be minimally exposed, the operating room should be kept as warm as possible, and the uterus should be continually irrigated with warmed saline solution.

Fetal distress can most effectively be avoided by having reliable and continuous fetal monitoring. Pulse oximetry is probably the most useful monitor currently available to evaluate fetal well-being as it measures both fetal heart rate and oxygenation.[146] It provides a rapid response time (less than 5 seconds) and has a high sensitivity and a high negative predictive value.[146] If the fetal saturation is less than 50%, maternal hemodynamics should be optimized, uterine tone assessed, and the umbilical cord checked for kinks, spasm, or obstruction. Fetal saturations of less than 30% suggest profound hypoxia with impending cardiovascular collapse.

Fetal echocardiogram (ECG), using either surface or percutaneously placed electrodes, has often proven to be unreliable and difficult to interpret. Implantable subcutaneous radiotelemeters that continuously monitor the fetal ECG as well as the amniotic pressure may prove useful in the future.[147] Whenever technically feasible, fetal echocardiography should be readily available to access fetal myocardial contractility, heart rate, and volume status.

Access to the fetal circulation may be needed during fetal surgery for blood sampling, drug administration, or transfusion. Puncture of the umbilical vessels can lead to cord spasm, hematoma, embolism, and fetal death and is therefore usually avoided. Central line placement prolongs open fetal exposure and is, in itself, another surgical intervention. Dorsal or saphenous vein cannulation may be the preferred and most reliable technique at the present time for vascular access in the fetus.

A resuscitation protocol has recently been developed for fetal surgery patients.[148] Cases of intraoperative fetal cardiac arrest usually arise from three scenarios (Figure 4.5).[148]

1. The compromised fetus is not able to sustain the stress of the surgical procedure.
2. There is significant intraoperative blood loss.
3. Metabolic or electrolyte abnormalities are present.

Calculated resuscitation drug dosages and packed red blood cell volumes treated with tromethamine (THAM) must be readily available for all procedures involving a major fetal intervention.

Summary

Little is known about fetal anesthesia, and much is still to be learned. However, it is known that although inhaled anesthetics rapidly cross the placenta, fetal levels remain below maternal levels for a prolonged period of time.[136,137] Fentanyl (10–20 μg/kg) and a muscle relaxant such as vecuronium (0.1 mg/kg)[149] or pancuronium (0.1 mg/kg)[128] can be given to provide additional anesthesia to the fetus.

Fetal surgery is a young and exciting field of medicine that involves many subspecialties. Although many hurdles are being conquered in terms of maternal and fetal obstetric, surgical, and anesthetic management, diagnostics, and monitoring, many hurdles still remain to allow these once-doomed fetuses another chance.

References

1. Liley AW. Intrauterine transfusion of foetus in haemolytic disease. Br Med J 1963;2:1107.
2. Liley AW. Foreword. In: Harrison MR, Globus MS, Filly RA (eds). The Unborn Patient: Prenatal Diagnosis and Treatment, 2nd edn. Philadelphia: Saunders, 1991:XI.
3. Harrison MR, Globus MS, Filly RA. Fetal surgery for congenital hydronephrosis. N Engl J Med 1982;306:591–593.
4. Farrell JA, Albanese CT, Jennings RW, et al. Maternal fertility is not affected by fetal surgery. Fetal Diagn Ther 1999;14:190–192.
5. Harrison MR, Ross N, Noall R, et al. Correction of congenital hydronephrosis in utero. I. The model: fetal urethral obstruction produces hydronephrosis and pulmonary hypoplasia in fetal lambs. J Pediatr Surg 1983;18:247–256.
6. Harrison MR, Nakayama DK, Noall R, et al. Correction of congenital hydronephrosis in utero. II. Decompression reverses the effects of obstruction on the fetal lung and urinary tract. J Pediatr Surg 1982;17: 965–974.
7. Glick PL, Harrison MR, Noall R, et al. Correction of congenital hydronephrosis in utero. III. Early mid-trimester ureteral obstruction produces renal dysplasia. J Pediatr Surg 1983;18:681–687.
8. Adzick NS, Harrison MR, Flake AW, et al. Fetal urinary tract obstruction: experimental pathophysiology. Semin Perinatol 1985;9:79–80.
9. Mahony BS, Filly RA, Callen PW, et al. Fetal renal dysplasia: sonographic evaluation. Radiology 1984;152:143–146.
10. Upitz S, Ryan G, Samuell C, et al. Fetal urine analysis for the assessment of renal function in obstructive uropathy. Am J Obstet Gynecol 1993;168:174–179.

11. Manning FA, Harrison MR, Rodeck CM, et al. Special report: catheter shunts for fetal hydronephrosis and hydrocephalus. N Engl J Med 1986;315:336–340.
12. McLorie G, Farhat W, Khoury A, et al. Outcome analysis of vesicoamniotic shunting in a comprehensive population. J Urol 2001;166: 1036–1040.
13. MacMahan RA, Renou PM, Shekelon PA, et al. In utero cystostomy. Lancet 1992;340:1234.
14. Quintero RA, Morales WJ, Allen MH, et al. Fetal hydrolaparoscopy and endoscopic cystostomy in complicated cases of lower urinary tract obstruction. Am J Obstet Gynecol 2000;183:324–330.
15. Quintero RA, Shukla AR, Homsy YL, et al. Successful in utero endoscopic ablation of posterior urethral valves: a new dimension in fetal urology. Urology 2000;55:774.
16. Quintero R, Johnson M, Romero R, et al. In utero percutaneous cystoscopy in the management of fetal lower obstructive uropathy. Lancet 1995;346:537–540.
17. Holmes N, Harrison MR, Baskin LS. Fetal surgery for posterior urethral valves: long-term postnatal outcomes. Pediatrics 2001;108:E7.
18. Adzick NS, Harrison MR, Crombleholme TM, et al. Fetal lung lesions: management and outcome. Am J Obstet Gynecol 1998;179:884–889.
19. Bullard KM, Harrison MR. Before the horse is out of the barn: fetal surgery for hydrops. Semin Perinatol 1995;19:462–473.
20. Flake AW, Harrison MR, Adzick NS, et al. Fetal sacrococcygeal teratoma. J Pediatr Surg 1986;21:563–566.
21. Quinn TM, Adzick NS. Fetal surgery. Fetal Diagn Ther 1997;24: 143–157.
22. Carter R. Pulmonary sequestration. Ann Thorac Surg 1959;7:68.
23. Eisenberg P, Cohen HL, Coren C. Color doppler in pulmonary sequestration diagnosis. J Ultrasound Med 1992;12:179–183.
24. Hernanz-Schulman M, Stein M, Neblett WW, et al. Pulmonary sequestration: diagnosis with color flow doppler sonography and a new theory of associated hydrothorax. Radiology 1991;180:817–821.
25. Adzick NS, Harrison AR, Flake AW, et al. Fetal lung lesions: management and outcome. Am J Obstet Gynecol 1994;170:399.
26. Miller RK, Sieber WK, Yunis EJ. Congenital cystic adenomatoid malformation of the lung: a report of 17 cases and review of the literature. Pathol Annu 1980;1:387–407.
27. Stocker JT, Madewell JER, Drake RM. Congenital cystic adenomatoid malformation of the lung: classification and morphologic spectrum. Hum Pathol 1977;8:155–171.
28. Bianchi W, Crombleholme TM, D'Alton ME, eds. Cystic adenomatoid malformation. In: Fetology: Diagnosis and Management of the Fetal Patient. New York: McGraw-Hill, 2000:289–297.
29. MacGillivray TE, Harrison MR, Goldstein RB, et al. Disappearing lung lesions. J Pediatr Surg 1993;28:1321–1324.
30. Adzick NS, Harrison MR, Flake AW, et al. Fetal surgery for cystic adenomatoid malformation of the lung. J Pediatr Surg 1993;28:806–812.
31. Blott M, Nicolaides KH, Greenough A. Postnatal respiratory function after chronic drainage of a fetal pulmonary cyst. Am J Obstet Gynecol 1988;159:858–859.
32. Clark SL, Vitale DJ, Minton SD, et al. Successful fetal therapy for cystic adenomatoid malformation associated with second-trimester hydrops. Am J Obstet Gynecol 1987;157:294–295.
33. Milner R, Kitano Y, Olutoye O, et al. Radiofrequency thermal ablation: a potential treatment for hydropic fetuses with a large chest mass. J Pediatr Surg 2000;35:386–389.
34. Mychaliska GB, Bealer JF, Rosen MA, et al. Operating on placental support: the ex utero intrapartum treatment procedure. J Pediatr Surg 1997;32:227–230.
35. Harrison MR, Adzick NS, Estes JM, et al. A prospective study of the outcome of fetuses with congenital diaphragmatic hernia. JAMA 1994;271:382–384.
36. Atkinson JB, Ford EG, Humphries B, et al. The impact of extracorporeal membrane support in the treatment of congenital diaphragmatic hernia. J Pediatr Surg 1991;26:791–793.
37. Heiss K, Manning P, Oldham KT, et al. Reversal of mortality for congenital diaphragmatic hernia with ECMO. Ann Surg 1989;209:225–230.
38. Stolar C, Dillon P, Reyes C. Selective use of extracorporeal membrane oxygenation in the management of congenital diaphragmatic hernia. J Pediatr Surg 1988;23:207–211.
39. Van Meurs KP, Newman KD, Anderson KD, et al. Effect of extracorporeal membrane oxygenation on survival of infants with congenital diaphragmatic hernia. J Pediatr 1990;117:954–960.
40. Adzick NS, Harrison MR, Glick PL, et al. Diaphragmatic hernia in the fetus: prenatal diagnosis and outcome in 94 cases. J Pediatr Surg 1985;20:357–361.
41. Sharland GK, Lockhart SM, Heward AJ, et al. Prognosis in fetal diaphragmatic hernia. Am J Obstet Gynecol 1992;166:9–13.
42. Albanese CJ, Lopoo J, Goldstein RB, et al. Fetal liver position and perinatal outcome for congenital diaphragmatic hernia. Prenatal Diagn 1998;18:1138–1142.
43. Lipshutz GS, Albanese CT, Feldstein VA, et al. Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg 1997;32: 1634–1636.
44. Flake AW. Fetal surgery for congenital diaphragmatic hernia. Semin Pediatr Surg 1996;5:266–274.
45. Harrison MR, Langer JC, Adzick NS, et al. Correction of congenital diaphragmatic hernia in utero. V. Initial clinical experience. J Pediatr Surg 1990;25:47–55.
46. Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero. VI. Hard earned lessons. J Pediatr Surg 1993;28:1411–1417.
47. Harrison MR, Adzick NS, Bullard KM, et al. Correction of congenital diaphragmatic hernia in utero. VII. A prospective trial. J Pediatr Surg 1997;32:1637–1642.
48. DiFiore JW, Fauza DO, Slavin D, et al. Experimental fetal tracheal ligation reverses the structural and physiologic effects of pulmonary hypoplasia in congenital diaphragmatic hernia. J Pediatr Surg 1994;29: 248–257.
49. Hendrick MH, Estes JM, Sullivan KM, et al. Plug the lung until it grows (PLUG): a new method to treat congenital diaphragmatic hernia in utero. J Pediatr Surg 1994;29:612–617.
50. Harrison MR, Bressack MA, Churg AM, et al. Correction of congenital diaphragmatic hernia in utero. II. Simulated correction permits fetal lung growth with survival at birth. Surgery (St. Louis) 1980;88:260–268.
51. Harrison MR, Mychaliska GB, Albanese CT, et al. Correction of congenital diaphragmatic hernia in utero. IX. Fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic tracheal occlusion. J Pediatr Surg 1998;33:1017–1023.
52. Flake AW, Crombleholme TM, Johnson MP, et al. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. Am J Obstet Gynecol 2000;183:1059–1066.
53. Alter DN, Reed RL, Marx GR, et al. Prenatal diagnosis of congestive heart failure in a fetus with a sacrococcygeal teratoma. Obstet Gynecol 1988;71:978–981.
54. Langer JC, Harrison MR, Schmidt KG, et al. Fetal hydrops and death from sacrococcygeal teratoma: rationale for fetal surgery. Am J Obstet Gynecol 1989;160:1145–1150.
55. Bond SJ, Harrison MR, Schmidt KG, et al. Death due to high-output cardiac failure in fetal sacrococcygeal teratoma. J Pediatr Surg 1990;25:1287–1291.
56. Adzick NS, Crombleholme TM, Morgan MA, et al. A rapidly growing fetal teratoma. Lancet 1997;349:538.
57. Gray JL, Albanese CT, Jennings RW, et al. Successful fetal sacrococcygeal teratoma resection in a hydropic fetus. J Pediatr Surg 2000;35: 1489–1491.
58. Paek BW, Jennings RW, Harrison MR, et al. Radiofrequency ablation of human fetal sacrococcygeal teratoma. Am J Obstet Gynecol 2001;184:503–507.
59. Sauter ER, Diaz JH, Arensman RM, et al. The perioperative manage-

ment of neonates with congenital oropharyngeal teratomas. J Pediatr Surg 1990;25:925–928.
60. Catalono PJ, Urken ML, Alvarez M, et al. New approach to the management of airway obstruction in "high risk" neonates. Arch Otolaryngol Head Neck Surg 1992;118:306–309.
61. Langer JC, Tabb T, Thompson R, et al. Management of prenatally diagnosed tracheal obstruction: access to the airway in utero prior to delivery. Fetal Diagn Ther 1992;7:12–16.
62. Shulman SR, Jones BR, Slotnick N, et al. Fetal tracheal intubation with intact uteroplacental circulation. Anesth Analg 1993;76:197–199.
63. Ferlito A, Deveney KO. Developmental lesions of the head and neck: terminology and biologic behavior. Ann Otolaryngol Head Neck Surg 1994;120:444–448.
64. Hedrick MH, Ferro MM, Filly RA, et al. Congenital high airway obstruction syndrome (CHAOS): a potential for perinatal intervention. J Pediatr Surg 1994;29:271–274.
65. Lloyd JR, Clatworthy HW. Hydramnios as an aid to the early diagnosis of congenital obstruction of the alimentary tract: a study of the maternal and fetal factors. Pediatrics 1958;21:903–909.
66. Rosenfeld CR, Coln CD, Duenhoelter JH. Fetal cervical teratomas as a cause of polyhydramnios. Pediatrics 1979;64:174–179.
67. Crombleholme TM, Albanese CT. The fetus with airway obstruction. In: Harrison MR, Evans MI, Adzick NS, Holzgreve W (eds) The Unborn Patient: The Art and Science of Fetal Therapy, 3rd edn. Philadelphia: Saunders, 2001:357–371.
68. Zerella JT, Finberg FJ. Obstruction of the neonatal airway from teratomas. Surg Gynecol Obstet 1990;170:126–131.
69. Tanaka M, Sato S, Naito H, et al. Anaesthetic management of a neonate with prenatally diagnosed cervical tumour and upper airway obstruction. Can J Anaesth 1994;41:236–240.
70. Bui TH, Grunewald C, Frencker B, et al. Successful EXIT (ex utero intrapartum treatment) procedure in a fetus diagnosed prenatally with congenital high-airway obstruction syndrome due to laryngeal atresia. Eur J Pediatr Surg 2000;10:328–333.
71. Ward VM, Langford K, Morrison G. Prenatal diagnosis of airway compromise: EXIT (ex utero intra-partum treatment) and foetal airway surgery. Int J Pediatr Otorhinolaryngol 2000;53:137–141.
72. Liechty KW, Crombleholme TM. Management of fetal airway obstruction. Semin Perinatol 1999;23:496–506.
73. Sebire N, Snijders R, Hughes R, et al. The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynaecol 1997;104:1203–1207.
74. Nageotte MP, Hurwitz SR, Vaziri ND, et al. Atriopeptin in the twin transfusion syndrome. Obstet Gynecol 1989;73:867–870.
75. Wieacker P, Wilhelm C, Prömpeter H, et al. Pathophysiology of polyhydramnios in twin transfusion syndrome. Fetal Diagn Ther 1992;7:87–92.
76. Rosen D, Rabinowitz R, Beyth Y, et al. Fetal urine production in normal twins and in twins with acute polyhydramnios. Fetal Diagn Ther 1990;5:57–60.
77. Fisk N. The scientific basis of feto-fetal transfusion syndrome and its treatment. In: Ward H, Whittle M (eds): Proceedings of the RCOG Study Group on Multiple Pregnancy. London: RCOG Press, 1995:235–250.
78. Duncan KR, Denbow M, Risk NM. The aetiology and management of twin-twin transfusion syndrome. Prenatal Diagn 1997;17:1227–1236.
79. Zosmer N, Bajoria R, Weiner E, et al. Clinical and echographic features of in utero cardiac dysfunction in the recipient twin in twin-twin transfusion syndrome. Br Heart J 1994;72:74–79.
80. Hecher K, Ville Y, Snijders R, et al. Doppler studies of the fetal circulation in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 1995;5:318–324.
81. Steinberg LH, Hurley VA, Desmedt E, et al. Acute polyhydramnios in twin pregnancies. Aust NZ J Obstet Gynaecol 1990;30:196–200.
82. Denbow ML, Battin MR, Cowan F, et al. Neonatal cranial ultrasonographic findings in preterm twins complicated by severe fetofetal transfusion syndrome. Am J Obstet Gynecol 1998;178:479–483.
83. Saunders NJ, Snijders RJM, Nicolaides KH. Therapeutic amniocentesis in twin-twin transfusion syndrome appearing in the second trimester of pregnancy. Am J Obstet Gynecol 1992;166:820–824.
84. DeLia JE, Cruikshank D, Keye W. Fetoscopic neodymium: YAG laser occlusion of placental vessels in severe twin-twin transfusion. Obstet Gynecol 1990;75:1046–1053.
85. DeLia JE, Kuhlman RS, Lopez KP. Treating previable twin-twin transfusion syndrome with fetoscopic laser surgery: outcomes following the learning curve. J Perinatal Med 1999;27:61–67.
86. Hecher K, Plath H, Bregenzer T, et al. Endoscopic laser surgery versus serial amniocentesis in the treatment of severe twin-twin transfusion syndrome. Am J Obstet Gynecol 1999;180:717–724.
87. Babcook CJ, Goldstein RB, Barth RA, et al. Prevalence of ventriculomegaly in association with myelomeningocele: correlation with gestational age and severity of posterior fossa deformity. Radiology 1994;190:703–707.
88. Gorden JE, Maloney FJ. The association with hydrocephalus and Arnold-Chiari malformation with spina bifida in the fetus. Neuropathol Appl Neurobiol 1980;6:29–39.
89. McLone DG, Kneper PA. The cause of Chiari II malformation and syringomyelia. A unified theory. Pediatr Neurosci 1989;15:1–12.
90. Heffez DS, Aryanpur J, Hutchins GM, et al. The paralysis associated with myelomeningocele: clinical and experimental data implicating a preventable spinal cord injury. Neurosurgery (Baltim) 1990;26:987–998.
91. Hutchins GM, Meuli M, Meuli-Simmon C, et al. Acquired spinal cord injury in human fetuses with myelomeningocele. Pediatr Pathol Lab Med 1996;16:701–712.
92. Meuli M, Meuli-Simmon C, Hutchins GM, et al. In utero surgery rescues neurologic function at birth in sheep with spina bifida. Nat Med 1995;1:342–347.
93. Meuli M, Meuli-Simmon C, Yingling CD, et al. In utero repair of experimental myelomeningocele saves neurological function at birth. J Pediatr Surg 1996;31:397–402.
94. Paek BW, Farmer DL, Wilkinson CC, et al. Hindbrain herniation develops in surgically created myelomeningocele but is absent after repair in fetal lambs. Am J Obstet Gynecol 2000;183:1119–1123.
95. Heffez DS, Aryanur J, Rotellin NA, et al. Intrauterine repair of experimental surgically created dysraphism. Neurosurgery (Baltim) 1993;32:1005–1010.
96. Michejeda M. Intrauterine treatment of spina bifida primate model. Z Kinderchir 1984;39:259–261.
97. Adzick NS, Sutton LN, Crombleholme TM, et al. Successful fetal surgery for spina bifida. Lancet 1998;352:1675–1676.
98. Sutton CN, Adzick NS, Bilaniuk LT, et al. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. JAMA 1999;282:1826–1831.
99. Bruner JP, Tulipan N, Paschall RC, et al. Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. JAMA 1999;282:1819–1825.
100. Tulipan N, Hernanz-Schulman M, Lowe CH, et al. Intrauterine myelomeningocele repair reverses preexisting hindbrain herniation. Pediatr Neurosurg 1999;31:137–142.
101. Tulipan N, Bruner JP, Hernanz-Schulman M, et al. Effect of intrauterine myelomeningocele repair on central nervous system structure and function. Pediatr Neurosurg 1999;31:183–188.
102. Hirosen S, Farmer DL, Albanese CT. Fetal surgery for myelomeningocele. Curr Opin Obstet Gynecol 2001;13:215–222.
103. Kohl T, Sharland G, Allan LD, et al. World experience of percutaneous ultrasound-guided balloon valvuloplasty in human fetuses with severe aortic valve obstruction. Am J Cardiol 2000;85:1230–1233.
104. Ozturk S, Deveci M, Sangezer M, et al. Results of artificial inflammation in scarless foetal wound healing: an experimental study in foetal lambs. Br J Plast Surg 2001;54:47–52.
105. Levine JP, Bradley FP, Shahinian HK, et al. Nasal expansion in the fetal lamb: a first step toward management of cleft nasal deformity in utero. Plast Reconst Surg 1999;103:761–767.
106. Weinzweig J, Panter KE, Pantaloni M, et al. The fetal cleft palate. II.

Scarless healing after in utero repair of a congenital model. Plast Reconst Surg 1999;104:1356–1364.
107. Stelnicki EJ, Lee S, Hoffman W, et al. A long-term, controlled-outcome analysis of in utero versus neonatal cleft lip repair using an ovine model. Plast Reconst Surg 1999;104:607–615.
108. Pschera H. Stem cell therapy in utero. J Perinatal Med 2000;28:346–354.
109. Hayashi S, Flake AW. In utero hematopoietic stem cell therapy. Yonsei Med J 2001;42:615–629.
110. Levinson G, Shnider SM, Delorimer AA, et al. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology 1974;40:340–347.
111. Motoyama ED, Rivard G, Acheson F, et al. The effect of changes in maternal pH and PCO_2 on the PO_2 of foetal lambs. Anesthesiology 1967;28:891–903.
112. Kamban JR, Handte RE, Brown WU, et al. The effect of normal and preeclamptic pregnancies on the oxyhemoglobin dissociation curve. Anesthesiology 1986;65:426–427.
113. Rosen MA. Anesthesia and monitoring for fetal intervention. In: Harrison MR, Globus MS, Filly RA (eds) The Unborn Patient: The Art and Science of Fetal Therapy, 2nd edn. Philadelphia: Saunders, 1990: 172–181.
114. Shnider SM, Webster GM. Maternal and fetal hazards of surgery during pregnancy. Am J Obstet Gynecol 1965;92:891–900.
115. Brodsky JB, Cohen EN, Brown BW Jr, et al. Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 1980;138:1165–1167.
116. Mazze RI, Kallem B. Reproductive outcome after anesthesia and operation during pregnancy: a registry of 5405 cases. Am J Obstet Gynecol 1989;161:1178–1185.
117. Ad Hoc Committee on the effect of trace anesthetics on the health of operating room personnel. Anesthesiology 1974;41:321–340.
118. Duncan PG, Pope WDB, Cohen MM, et al. The safety of anesthesia and surgery during pregnancy. Anesthesiology 1986;64:790–794.
119. Harrison MR, Globus MS, Filly RA. Fetal surgery for congenital hydronephrosis. N Engl J Med 1982;306:591–593.
120. Naftalin N, McKay DM, Phear WPC, et al. The effects of halothane on pregnant and nonpregnant human myometrium. Anesthesiology 1977; 46:15–19.
121. Nakayama DK, Harrison MR, Sevon-Ferre M, et al. Fetal surgery in the primate. II. Uterine electromyographic response to operative procedures and pharmacologic agents. J Pediatr Surg 1984;19:333–339.
122. DiFederico EM, Burlingame JM, Kilpatrick SF, et al. Pulmonary edema in obstetric patients is rapidly resolved except in the presence of infection or of nitroglycerin tocolysis after open fetal surgery. Am J Obstet Gynecol 1998;179:925–932.
123. DiFederico EM, Harrison MR, Natthay MA. Pulmonary edema in a woman following fetal surgery. Chest 1996;109:1114–1117.
124. Elliot JP. Magnesium sulfate as a tocolytic agent. Am J Obstet Gynecol 1983;147:277–284.
125. Katz M, Robertson PA, Creasy RK. Cardiovascular complications associated with terbutaline treatment for preterm labor. Am J Obstet Gynecol 1981;139:605–608.
126. Jacobs MM, Knight AB, Anas F. Maternal pulmonary edema resulting from betamimetic and glucocorticoid therapy. Obstet Gynecol 1980;56: 56–99.
127. Shih GH, Boyd GL, Vincent RD, et al. The EXIT procedure facilitates delivery of an infant with a pretracheal teratoma. Anesthesiology 1998;89:1573–1575.
128. Copel JA, Grannum PA, Harrison D, et al. The use of intravenous pancuronium bromide to produce fetal paralysis during intravascular transfusion. Am J Obstet Gynecol 1988;158:170–171.
129. Rudolph AH, Heymann MA. Cardiac output in the fetal lamb: the effects of spontaneous and induced changes of heart rate on right and left ventricular output. Am J Obstet Gynecol 1976;124:183–192.
130. Friedman WF. The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87–111.
131. Gilbert RD. Control of fetal cardiac output during changes in blood volume. Am J Physiol 1980;238:1180–1186.
132. McGregor M, Davenport HT, Jegier W, et al. Cardiovascular effects of halothane in normal children. Br J Anaesth 1958;30:398–408.
133. Lichtor JL, Beher BE, Ruschhaupt DG. Myocardial depression during induction in infants (abstract). Anesthesiology 1983;59:A452.
134. Rao CC, Boyer MS, Krisha G, et al. Increased sensitivity of the isometric contraction of the neonatal isolated rat atria to halothane, isoflurane and enflurane. Anesthesiology 1986;64:13–18.
135. Warren TW, Datta S, Ostheimer GW, et al. Comparison of the maternal and neonatal effects of halothane, enflurane and isoflurane for cesarean delivery. Anesth Analg 1983;62:516–520.
136. Biehl DR, Côté J, Wade JD, et al. Uptake of halothane by the foetal lamb. Can Anaesth Soc J 1983;30:24–27.
137. Biehl DR, Yarnell R, Wade JG, et al. The uptake of isoflurane by the foetal lamb in utero: effect on regional blood flow. Can Anaesth Soc J 1983;30:581–586.
138. Palahniuk RJ, Shnider SM. Maternal and fetal cardiovascular and acid-base changes during halothane and isoflurane anesthesia in the pregnant ewe. Anesthesiology 1974;41:462–472.
139. Sabik JF, Assad RS, Hanley FL. Halothane as an anesthetic for fetal surgery. J Pediatr Surg 1993;28:542–547.
140. Anand KJS, Hickey PR. Pain and its effect in the human neonate and fetus. N Engl J Med 1987;317:1321–1329.
141. Torres F, Andersen C. The normal EEG of the human newborn. J Clin Neurophysiol 1985;2:89–103.
142. Gregory GA, Wade JG, Biehl DR, et al. Fetal anesthetic requirement (MAC) for halothane. Anesth Analg 1983;62:9–14.
143. Drury RA, Gold RM. Differential effects of ovarian hormones on reactivity to electric foot shock in the rat. Physiol Behav 1978;20:187–191.
144. Anand KJS, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1:243–248.
145. Anand KJS, Brown MJ, Bloom SR, et al. Studies on hormonal regulation of fuel metabolism in the human newborn infant undergoing anesthesia and surgery. Horm Res 1985;22:115–128.
146. Luks F, Johnson BD, Papadakis K, et al. Predictive value of monitoring parameters in fetal surgery. J Pediatr Surg 1998;33:1297–1301.
147. Jennings RW, Adzick NS, Longaker MT, et al. New techniques in fetal surgery. J Pediatr Surg 1992;27:1329–1333.
148. Graf JL, Paek BW, Albanese CT, et al. Successful resuscitation during fetal surgery. J Pediatr Surg 2000;35:1388–1389.
149. Levesque C, Murat I, Toubus F. Fetal neuromuscular blockade with vecuronium bromide: studies during intravascular intrauterine transfusion in isoimmunized pregnancies. Anesthesiology 1992;76:642–644.

5
The Pregnant Teenager

Linda S. Polley and Cosmas J.M. van de Ven

Approximately 500,000 births result from the 1,000,000 adolescent pregnancies that occur each year in the United States. Although the overall birthrates for adolescents are declining, teenage pregnancy remains widespread, with 12.2% of all births in the United States to mothers less than 20 years old.[1] Historically, most societies have condoned marriages and childbirth during the later teenage years. The salient issue is that most of today's pregnant adolescents become pregnant without a stable relationship and face a multitude of social complications and potential medical complications. Adolescent mothers are significantly less likely to receive a high school diploma and are more likely to receive public assistance with long periods of welfare dependency. The children born to adolescents are at higher risk for health problems and cognitive impairment as well as abuse and neglect. Studies estimate that the elimination of adolescent pregnancy in the United States would result in a net gain to society of $4 billion annually, after consideration of medical expenses, public assistance, and social service costs.[2]

Epidemiology

The problem of adolescent pregnancy gained widespread media attention during the late 1980s and early 1990s and was commonly referred to as an epidemic. In 1986, the birthrate was 50.2 live births per 1000 women aged 15 to 19, which increased to a recent high point of 62.1 in 1991. Reports for 1999 reveal a teenage birthrate of 49.6 per 1000 births for women aged 15 to 19 years, which represents a 3% decline compared with the 1998 rate and a 20% decline from 1991. The 1999 rate is an all-time low, but it is important to realize that this improvement is not the same for all subgroups of the adolescent population.[1]

Rates vary with age, race and Hispanic origin, marital status, socioeconomic status, and geographic location. The age-specific birthrate for the youngest teenage group, those 10 to 14 years, was 1.0 per 1000 women, which has changed very little from 1998 when it was 0.9 per 1000 women. More improvement was seen in older teens: the 1999 rate for teenagers 15 to 17 years has declined 6% compared to 1998, and the rate for teenagers 18 to 19 years declined 2% during the same period. Between 1991 and 1999, there was a 26% decrease in the birthrate for teenagers 15 to 17 years and a 15% decrease for teenagers 18 to 19 years (Figure 5.1).[1]

Examination of adolescent birthrates by race and Hispanic origin revealed that all groups showed decreases in 1999. The largest decrease was seen in American Indian teenagers (6%, with a rate of 67.7 per 1000 in 1999). There was a 5% decrease in African-American teenagers (1999 rate, 81.1 per 1000) and a 3% decrease for non-Hispanic white teenagers (34.1 per 1000). The birthrate for Hispanic teenagers is substantially higher than that of other racial and ethnic groups and declined by less than 1% compared to 1998 (93.1 per 1000). Between the years of 1991 and 1998, birthrates dropped most sharply for African-American women (30%) and least for Hispanic women (13%) (Table 5.1).[1]

Seventy-eight percent of all teenage births occurred to unmarried teenagers, which is unchanged from 1998. The percentage of births to unmarried teenagers is also age specific and varies from 73.9% of 18- to 19-year-olds to 96.4% of women under 15 years of age. Birthrates for unmarried teenagers are not yet available for 1999. Births to adolescents also vary a great deal by geographic location, from a high of 19.7% of total births in Mississippi to 6.9% of all births in Massachusetts.[1] Last, socioeconomic status is also a determinant of teenage birthrates. In 1988 the Rand Study reported a teenage parenthood rate of 1 in 1000 for Caucasian teenagers with high socioeconomic status and intact family structure as opposed to 1 in 4 for African-American teenagers with low socioeconomic status and single-parent households.[3]

Compared to other developed countries, the adolescent birthrate in the United States is four times higher than in Germany, six times higher than in France, and eight times higher than in the Netherlands.[4] Abortion rates are also higher in the United States. Researchers cite poor contraceptive use as the primary reason for the higher adolescent pregnancy rates in the United States because sexual activity rates are similar.[5]

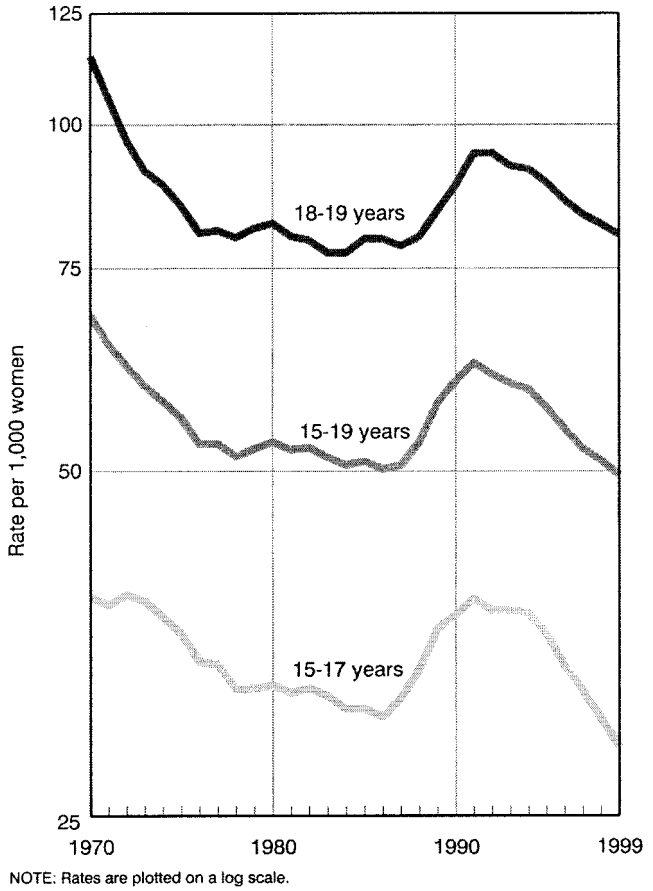

FIGURE 5.1. Birth rates for teenagers by age in the United States, 1970 to 1999. (From Curtin SC, Martin JA. Births: preliminary data for 1999. Natl Vital Stat Rep 2000:48:1–20.)

Reasons for Adolescent Pregnancy

The explanation for pregnancy during the teenage years appears obvious: early sexual activity and low rates of contraceptive use. Between ages 15 and 19, at least 50% of both females and males report having had sexual intercourse.[6,7] One study found that adolescents at highest risk for early sexual intercourse are those who live in rural areas, have parents who receive public assistance, are African-American, or are from the southern part of the United States.[8] In addition, when there is a large age difference between the female adolescent and her partner, she is more likely to have early first intercourse with a lower likelihood of contraceptive use, higher likelihood of adolescent birth, higher likelihood of unforced but unwanted sexual intercourse, and a higher number of sexual partners during the teenage years.[9] Teenagers younger than age 15 at first intercourse are more likely to report that it was nonvoluntary.[6]

Many adolescents do not use contraception consistently. However, an increase in the use of contraceptives was identified in a 1997 survey, mostly due to greater use of condoms. Reported use of condoms in sexually active adolescents has increased from 46.2% in 1991 to 56.8% in 1997.[10] Both early sexual activity and poor contraception have been linked to lack of a supportive family and social environment, poor educational experience, high-risk lifestyle behaviors, peer pressure, and depression.[11] A final consideration is the earlier onset of menarche, which exposes girls to pregnancy at increasingly younger ages.

Prenatal Care

At least in part because of denial of pregnancy, adolescents do not seek prenatal care as early in their pregnancies as older women do. In 1996, only 67% of adolescents received any prenatal care during the first trimester compared with 77% of women 20 to 24 years old and 89% of women 30 to 34 years old. Less than 26% of teenagers began prenatal care during their second trimester, and 7% received late or no prenatal care during their pregnancy.[12] Late presentation minimizes opportunities for interventions including nutritional counseling, detection and treatment of sexually transmitted diseases, ultrasound diagnosis of fetal anomalies, and preparation for childbirth and addition to the family.

Low Birth Weight

The proportion of low birth weight (LBW) births, that is, neonates who weigh less than 2500 g at birth, was 7.6% for 1999.[1] The LBW rate is higher among adolescents. In 1996, 12.8% of neonates born to mothers less than 15 years old had LBW compared to 9.3% of neonates born to mothers 15 to 19 years old.[12] LBW babies may be preterm and/or small for gestational age, a distinction that may be difficult to make in the absence of early and adequate prenatal care. It has been difficult to determine if age is an independent risk factor for LBW because many risk factors associated with adolescent pregnancy are also associated with LBW, including tobacco use, substance abuse, poor nutrition, and low prepregnancy maternal body weight. Adolescents are more likely to smoke during pregnancy than are older women. The rate of smoking during pregnancy increased from 16.7% to 17.2% from 1994 to 1996. During the same time period, the rate of smoking during pregnancy fell in all other maternal age groups.[13] Studies of the incidence of substance abuse during pregnancy are difficult to interpret because of the problems with testing, self-reporting, and polysubstance abuse. Alcohol consumption is a serious health problem among adolescents. In the United States, the average age of initial alcohol use outside the family is 12.7 years for girls.[14] One study found that 40% of teenagers aged 14 to 19 drank during pregnancy.[15] Other commonly used substances that may adversely effect birth weight include marijuana, cocaine, and amphetamines.

Sexually Transmitted Diseases

Adolescent sexual activity commonly leads to sexually transmitted disease (STD) as well as pregnancy. Of the 15 million new cases of STD each year, 25% or 4 million cases are di-

TABLE 5.1. Birth rates for women aged 15–19 years, by age, race, and Hispanic origin: United States, final 1990–1998 and preliminary 1999, and percent change in rates, 1991–1999.

Age, race, and Hispanic origin of mother	1999	1998	1997	1996	1995	1994	1993	1992	1991	1990	Percent change, 1991–1999
15–19 years											
All races[a]	49.6	51.1	52.3	54.4	56.8	58.9	59.6	60.7	62.1	59.9	−20.1
White, total[b]	44.5	45.4	46.3	48.1	50.1	51.1	51.1	51.8	52.8	50.8	−15.7
White, non-Hispanic	34.1	35.2	36.0	37.6	39.3	40.4	40.7	41.7	43.4	42.5	−21.4
Black, total[a]	81.1	85.4	88.2	91.4	96.1	104.5	108.6	112.4	115.5	112.8	−29.8
Hispanic[c]	93.1	93.6	97.4	101.8	106.7	107.7	106.8	107.1	106.7	100.3	−12.7
15–17 years											
All races[a]	28.7	30.4	32.1	33.8	36.0	37.6	37.8	37.8	38.7	37.5	−25.8
White, total[b]	24.8	25.9	27.1	28.4	30.0	30.7	30.3	30.1	30.7	29.5	−19.2
White, non-Hispanic	17.1	18.4	19.4	20.6	22.0	22.8	22.7	22.7	23.6	23.2	−27.5
Black, total[b]	52.1	56.8	60.8	64.7	69.7	76.3	79.8	81.3	84.1	82.3	−38.0
Hispanic[c]	61.2	62.3	66.3	69.0	72.9	74.0	71.7	71.4	70.6	65.9	−13.3
18–19 years											
All races[a]	80.2	82.0	83.6	86.0	89.1	91.5	92.1	94.5	94.4	88.6	−15.0
White, total[b]	73.4	74.6	75.9	78.4	81.2	82.1	82.1	83.8	83.5	78.0	−12.1
White, non-Hispanic	59.0	60.6	61.9	63.7	66.1	67.4	67.7	69.8	70.5	66.6	−16.3
Black, total[b]	122.9	126.9	130.1	132.5	137.1	148.3	151.9	157.9	158.6	152.9	−22.5
Hispanic[c]	139.0	140.1	144.3	151.1	157.9	158.0	159.1	159.7	158.5	147.7	−11.6

Data are rates per 1000 women in specified group.
[a]Includes races other than white and black.
[b]Race and Hispanic origin are reported separately on the birth certificate. Data for persons of Hispanic origin are included in the data for each race group according to the mother's reported race.
[c]Includes all persons of Hispanic origin of any race.
Source: From Curtain SC, Martin JA. Births: preliminary data for 1999. Natl Vital Stat Rep 2000;48:1–20.

agnosed in teenagers. Both LBW and premature delivery have been associated with STD. Chlamydia is the most common, with more than 500,000 cases reported in 1997. Female adolescents aged 15 to 19 years had the highest infection rates and accounted for 43.6% of all case reports. The Centers for Disease Control and Prevention has estimated that of the sexually active female adolescents tested for chlamydia, 1 in 10 are infected. Rates of gonorrhea infection have steadily declined since 1975, but females aged 15 to 19 years have the highest age-specific rates.[16,17] Of greater concern are the 586 new cases of human immunodeficiency virus (HIV) infection reported among adolescents 13 to 19 years old in 1997. African-American teenagers are at highest risk and account for 65% of these cases. In the 20- to 24-year-old age group, 1,855 new cases of acquired immunodeficiency syndrome (AIDS) were reported in 1997.[18] Because AIDS has a latency period of up to 10 years, most of these young people were infected with HIV as adolescents or even preadolescents.

Preeclampsia

The rate of preeclampsia appears to be higher in adolescent pregnancy when controlled for race and parity. The incidence of preeclampsia in parturients less than 15 years old has been reported to be as high as 35%.[19,20] Risk factors for preeclampsia, including primigravidity, primipaternity (first pregnancy with male partner), and African-American race, are more common in pregnant adolescents.

Obstetric Management

When the pregnant teenager is admitted to the labor and delivery unit, a relatively poor preparation for childbirth should be anticipated. Adolescents frequently have a poor understanding of the birth process and a poor psychosocial support structure. A multidisciplinary team of obstetricians, anesthesiologists, nurses, and social workers provides optimal management.

Is the outcome of labor and delivery different for the teenager than for the older mother? There has been controversy regarding poor outcomes that have been observed in teenage deliveries. The central question is whether the observed outcomes are the result of young maternal age alone or the consequence of sociodemographic factors generally associated with adolescent pregnancy. Is young age alone an independent risk factor? It is important to make a distinction between younger and older teenagers. In multiple studies, adolescent parturients over 15 years of age have improved obstetric outcomes when compared to women in their twenties including decreased cesarean section rates, decreased oxytocin requirements, decreased duration of the active phase of labor, and decreased rates of prematurity.[21,22]

It is not surprising that these older adolescents would not suffer reproductive disadvantages during pregnancy solely based on age because, in general, they are at the peak of lifetime health. However, the situation differs for the younger adolescent (less than 15 years of age) who is generally no

more than 2 years post menarche and likely has not completed her own growth at the time of pregnancy. Adverse outcomes that have been reported in this age group include prematurity, LBW, and small-for-gestational-age neonates.[21–23] It has been hypothesized that the metabolic demands of the young mother still in her growth phase take precedence over the nutritional needs of the fetus. Maternal growth may interfere with the normal physiology of pregnancy, possibly by decreased uterine blood flow and nutrient transfer. The presence of maternal growth during pregnancy has been associated with reduced levels of micronutrients in umbilical cord blood samples.[24]

In summary, it appears that adolescents generally have normal labor and deliveries but their babies may be premature, small for gestational age, or have low birth weights. The neonatal consequences may be the result of ongoing maternal growth with competition for nutrients.

Anesthetic Considerations

The Minor Patient and Informed Consent

Many obstetric centers obtain separate, written consent before administration of analgesia for labor and planned vaginal delivery. The traditional legal view is that a minor cannot give legal consent for medical or surgical treatment and that consent must be obtained from a parent or guardian.[25] However, most states consider the parturient who has not reached the age of majority, an "emancipated minor" for purposes of giving consent; emancipation confers the full legal capacity of an adult for medical decisions. Laws vary from state to state and may consider issues such as the patient's marital status, whether she resides separately from her parents, and whether she manages her own legal and financial affairs.[26]

Psychosocial Support for the Pregnant Teenager

Psychosocial support is crucial for all parturients, but this issue is particularly important for the teenager who must prepare for impending motherhood while also meeting the developmental challenges of adolescence. The importance of emotional support to a positive childbirth experience cannot be overstated, and this support is typically provided by the father of the baby, family members, or friends. At least one study of women of all ages has found that husband participation during labor was associated with decreased maternal anxiety and medication requirements.[27] The very young father may be less well equipped for this task or may not have ongoing involvement with the pregnancy. Of interest, a recent study of 46,500 births to school-age mothers in California revealed that two-thirds of the fathers are adult men who averaged 4.2 years older than high school age mothers and 6.7 years older than junior high school age mothers.[28] Other studies have demonstrated beneficial effects of emotional support. Decreases in the length of labor, analgesic requirements, oxytocin use, and the incidence of operative delivery have been shown.[29–32] Regardless of the degree of family support, the pregnant adolescent requires extra time and attention from the labor and delivery staff with consideration of her level of maturity and anxiety at the time of parturition. Labor may be a very frightening experience for the young parturient. Anesthetic interventions must be considered an adjunct to ongoing encouragement, support, and reassurance.

Sexual Abuse

A recent questionnaire-based study highlighted the importance of a history of sexual abuse in adolescent pregnancy. In a cohort of 200 sexually active women aged 13 to 18 years, 20% reported a prior history of sexual abuse.[33] Sexually abused teenagers may present late in pregnancy and be markedly fearful of vaginal examination. Social work referral for psychologic support during pregnancy and the transition to motherhood can be helpful. During labor, the sensory blockade provided by epidural analgesia can make it possible for the abused adolescent to tolerate vaginal examinations and is the optimal method of pain management. The adolescent parturient should be asked in a private setting whom she wishes to be present during her labor. She may choose someone other than a family member as a labor support person if the pregnancy is the result of sexual abuse or incest.

Anesthetic Management

Many adolescent parturients are fearful of epidural catheter placement and may initially decline this form of analgesia. Parenteral opioids may be used during early labor to provide analgesia and mild sedation. As labor progresses, many patients reconsider their analgesic options and may request epidural analgesia. Epidural and spinal analgesia are clearly the most effective methods of pain relief in current practice for both the first and second stages of labor.[34–37] To obtain the cooperation of the young mother, careful explanation of the procedure to both the patient and support person is necessary. At the University of Michigan Health System, the support person is allowed to remain in the room during epidural placement to assist with positioning and coaching. Young fathers may be relatively more "needle phobic" and are instructed to notify the anesthesiologist of any lightheadedness or other presyncopal symptoms. With patience and encouragement, most young parturients do very well with the procedure. It is important that the young mother has realistic expectations regarding the target level of analgesia. The anesthetic goal is not to provide total sensory loss, and the parturient must expect to feel pressure sensations that will increase with the progress of labor.

The principles of obstetric anesthesia for cesarean section are the same for the teenage parturient as for older women. The anesthesiologist must provide safe and effective anesthesia for the mother without compromising the fetus.

Preanesthetic Medication

Most women do not require sedative or anxiolytic medications before cesarean delivery. Sedatives, which undergo placental transfer, are typically avoided until the infant is delivered and the umbilical cord clamped. However, pregnant adolescents may occasionally require premedication. In instances of panic disorder or prior sexual abuse, judicious doses of an anxiolytic in combination with verbal reassurance may allow the anxious teenager to tolerate the positioning and draping required for the procedure. Small doses of a benzodiazepine (e.g., midazolam 1–2 mg) and/or an opioid (e.g., fentanyl 25–50 μg) given intravenously are unlikely to result in neonatal depression.[38,39] At the University of Michigan, a pediatrician attends cesarean deliveries in which the mother received intravenous sedatives or narcotics before clamping of the umbilical cord. A disadvantage of benzodiazepine administration is the potential for anterograde amnesia.[40] Because most women want to remember the childbirth experience, opioids may be a better first choice for preoperative sedation.

The anesthesiologist plays a pivotal role in helping allay the fears of the adolescent mother. This role is especially important in the scenario of urgent or emergent cesarean section when other members of the health care team are focused on preparation of equipment and personnel for the surgical procedure. Calm explanations and reassurance by the anesthesiologist can be very helpful to a frightened teenager. The presence of a family member or support person in the operating room can also provide emotional comfort.

Choice of Anesthetic Technique

Anesthetic-related deaths during obstetric delivery have declined significantly in recent years. In the first analysis of U.S. data, the anesthesia-related maternal mortality rate decreased from 4.3 per million live births in the period 1979 to 1981 to 1.7 per million during 1988 to 1990. Anesthesia-related deaths primarily occur during cesarean section. The mortality decrease appears to be due to a decrease in complications of regional anesthesia. The number of deaths involving general anesthesia has remained stable.[41] In general, most obstetric anesthesiologists prefer regional techniques for cesarean section. For any individual parturient, the choice of anesthetic technique is influenced by the indication for cesarean delivery, the urgency of the procedure, maternal and fetal status, and the desires of the mother. The adolescent may request general anesthesia because of fear of pain associated with both placement of the regional block and the surgical procedure. The anesthesiologist should give a clear age-appropriate explanation of the risks and benefits of regional versus general anesthesia to the parturient and her family.

Anesthetic Administration

Regional anesthesia, either epidural or subarachnoid block, is the most commonly used method of anesthesia for cesarean delivery. The teenage parturient requires emotional support and careful explanations for a positive experience. Specifically, the adolescent should be counseled to expect pressure and pulling sensations during abdominal delivery and that a subjective sensation of dyspnea may occur with cephalad progression of regional blockade.

There is a theoretical concern that the adolescent parturient may require smaller doses of local anesthetics for spinal and epidural anesthesia because of her short stature.[42] In our experience, pregnant adolescents often appear markedly mature for their age and are not shorter than older parturients. Regardless of patient stature, epidural dosing is not a problem with an incrementally dosed catheter technique. For spinal anesthesia, patient variables such as spinal column length and height may influence dose requirement for isobaric solutions[43,44] but not for the hyperbaric solutions[45–47] typically used for cesarean section. Norris and coworkers have investigated the effect of height on cephalad sensory levels with spinal anesthesia for cesarean section and reported no differences in level obtained in women ranging between 4 feet 10 in. and 5 feet 8 in. in height using 15 mg hyperbaric bupivacaine.[45]

In the event that general anesthesia is required for cesarean delivery, the same anesthetic principles apply to teenage parturients as to older women; these include premedication with a nonparticulate antacid, left uterine displacement, careful preoxygenation, and rapid sequence induction. The patient should be told to expect pressure on her anterior neck as she loses consciousness. It is reasonable to have smaller-sized endotracheal tubes available for younger parturients.

Postpartum and Postoperative Care

Adolescents recovering from cesarean delivery should not have to experience significant discomfort. Effective methods of pain management include neuraxial opioids, intravenous patient-controlled analgesia (PCA), and continuous epidural analgesia. Subarachnoid morphine is a particularly attractive choice for the young mother, as there is no effect on patient mobility and minimal sedation during the mother–infant bonding period. Potential side effects include pruritus, nausea and vomiting, and respiratory depression, which are effectively treated with μ-opioid antagonists.[48] This method of pain management requires vigilant nursing observation of respiratory status, appropriate nursing staff education, and standardized protocols. An anesthesia care provider should be readily available to manage any complications that may occur. Postoperative epidural analgesia for the immediate postpartum period is also safe and effective in institutions that are equipped to provide this service. Last, intravenous PCA has the advantage of providing control to the patient although it

also requires her participation. PCA is the technique of choice for parturients who received general anesthesia without an epidural in place and for parturients who received epidural chloroprocaine because epidural opioids are antagonized by previous administration of chloroprocaine.[49,50]

Summary

The teenager deserves extra attention in the postpartum period to promote early interaction and bonding with her infant. The young mother will benefit from instruction in infant care and breast-feeding. In the current era of rapid hospital discharge after delivery, the available time for teaching and support is short. Ideally, the adolescent mother will receive home visits by nursing and/or social workers after hospital discharge to assist with infant care, adjustment to motherhood, and contraception. Arguably, the most important postpartum goal is to assist the young mother in building her self-esteem and continuing her education.

References

1. Curtin SC, Martin JA. Births: preliminary data for 1999. Natl Vital Stat Rep 2000;48:1–20.
2. Maynard RA. Kids having kids: economic costs and social consequences of teen pregnancy. Washington, DC: Urban Institute Press, 1997.
3. Abrahamse AF, Morrison PA, Waite LJ. Beyond stereotypes: who becomes a single teenage mother? Santa Monica, CA: Rand Corp., 1988.
4. Berne L, Huberman B. European approaches to adolescent sexual behavior and responsibility. Washington, DC: Advocates for Youth, 1999.
5. Jones EF, Forrest JD, Goldman N, et al. Teenage pregnancy in developed countries: determinants and policy implications. Fam Plann Perspect 1985;17:53–63.
6. Abma JC, Chandra A, Mosher WD, et al. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. Vital Health Stat 1997;27:1–114.
7. Sonenstein F, Ku L, Lindberg L, et al. New data on sexual behaviors of teenage males: sexual activity declines, contraceptive use increases from 1988–1995. Washington, DC: Urban Institute, 1997.
8. Resnick MD, Bearman PS, Blum RW, et al. Protecting adolescents from harm: findings from the national longitudinal study on adolescent health: JAMA 1997;278(10):823–832.
9. Moore K, Driscol A. Partners, predators, peers, protectors: males and teen pregnancy. Washington, DC: Child Trends Inc., 1997.
10. Center for Disease Control and Prevention. Trends in sexual risk behaviors among high school students—United States, 1991–1997. MMWR 1998;47:749–752.
11. Jaskiewicz JA, McAnarney ER. Pregnancy during adolescence. Pediatr Rev 1994;15:32–38.
12. Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1996. Mon Vital Stat Rep 1998;46:1–99.
13. Mathews TJ. Smoking during pregnancy, 1990–96. Natl Vital Stat Rep 1998;47:1–12.
14. Alexander B. Alcohol abuse in adolescents. Am Fam Physician 1991; 43:527–532.
15. Streissguth AP, Grant TM, Barr HM, et al. Cocaine and the use of alcohol and other drugs during pregnancy. Am J Obstet Gynecol 1991;164: 1239–1243.
16. Center for Disease Control and Prevention. Tracking the hidden epidemics. Trends in STDs in the United States 1998. Atlanta, GA: CDC, 1998.
17. Center for Disease Control and Prevention. Sexually transmitted disease surveillance 1997. Atlanta, GA: CDC, 1998.
18. Center for Disease Control and Prevention. HIV/AIDS surveillance report, vol 9. Atlanta, GA: CDC, 1997:1–37.
19. Battaglia FC, Frazier TM, Hellegers AE. Obstetric and pediatric complications of juvenile pregnancy. Pediatrics 1963;32:902.
20. Duenhoelter JH, Jimenez JM, Baumann G. Pregnancy performance of patients under fifteen years of age. Obstet Gynecol 1975;46:49–52.
21. Satin AJ, Leveno KJ, Sherman ML, et al. Maternal youth and pregnancy outcomes: middle school versus high school age groups compared with women beyond the teen years. Am J Obstet Gynecol 1994;171:184–187.
22. Amini SB, Catalano PM, Dierker LJ, Mann LI. Births to teenagers: trends and obstetric outcomes. Obstet Gynecol 1996;87:668–674.
23. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med 1995;332:1113–1117.
24. Scholl TO, Hediger ML, Schall JI, et al. Maternal growth during adolescent pregnancy [letter]. JAMA 1995;274:26–27.
25. In re Hudson, 126 P. 2d 765, 781 (Wash. 1942).
26. Holder AR. Minors' rights to consent to medical care. JAMA 1987; 257:3400–3402.
27. Henneborn WJ, Cogan R. The effect of husband participation on reported pain and probability of medication during labor and birth. J Psychosom Res 1975;19:215–222.
28. Males M, Chew KS. The ages of fathers in California adolescent births, 1993. Am J Public Health 1996;86(4):565–568.
29. Sosa R, Kennell J, Klaus M, et al. The effect of a supportive companion on perinatal problems, length of labor, and mother-infant interaction. N Engl J Med 1980;303:597–600.
30. Kennell J, Klaus M, McGrath S, et al. Continuous emotional support during labor in a US hospital. A randomized controlled trial. JAMA 1991; 265:2197–2201.
31. Skibsted L, Lange AP. The need for pain relief in uncomplicated deliveries in an alternative birth center compared to an obstetric delivery ward. Pain 1992;48:183–186.
32. Hofmeyr GJ, Nikodem VC, Wolman WL, et al. Companionship to modify the clinical birth environment: effects on progress and perceptions of labour, and breastfeeding. Br J Obstet Gynaecol 1991;98:756–764.
33. Rainey DY, Stevens-Simon C, Kaplan DW. Are adolescents who report prior sexual abuse at higher risk for pregnancy? Child Abuse Neglect 1995;19:1283–1288.
34. Howell CJ, Chalmers I. A review of prospectively controlled comparisons of epidural with non-epidural forms of pain relief during labour. Int J Obstet Anesth 1992;1:93–110.
35. Morgan B, Bulpitt CJ, Clifton P, Lewis PJ. Effectiveness of pain relief in labour: survey of 100 mothers. Br Med J (Clin Res Ed) 1982;285: 689–690.
36. Robinson JO, Rosen M, Evans JM, et al. Maternal opinion about analgesia for labour. A controlled trial between epidural block and intramuscular pethidine combined with inhalation. Anaesthesia 1980;35: 1173–1181.
37. Paech MJ. The King Edward Memorial Hospital 1,000 mother survey of methods of pain relief in labour. Anaesth Intensive Care 1991;19: 393–399.
38. Kanto J, Sjovall S, Erkkola R, et al. Placental transfer and maternal midazolam kinetics. Clin Pharmacol Ther 1983;33:786–791.
39. Eisele JH, Wright R, Rogge P. Newborn and maternal fentanyl levels at cesarean section. Anesth Analg 1982;61(2):179.
40. Camann W, Cohen MB, Ostheimer GW. Is midazolam desireable for sedation in parturients? [letter]. Anesthesiology 1986;65:441.
41. Hawkins JL, Koonin LJ, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.

42. Jones MM, Taslimi MM. The pregnant teenager. In: Datta S (ed) Anesthetic and Obstetric Management of High-Risk Pregnancy. St. Louis: Mosby, 1996:48–51.
43. Pitkänen MT. Body mass and spread of spinal anesthesia with bupivacaine. Anesth Analg 1987;66:127–131.
44. Schnider TW, Minto CF, Bruckert H, Mandema JW. Population pharmacodynamic modeling and covariate detection for central neural blockade. Anesthesiology 1996;85:502–512.
45. Norris MC. Patient variables and the subarachnoid spread of hyperbaric bupivacaine in the term parturient. Anesthesiology 1990;72:478–482.
46. Norris MC. Height, weight and the spread of spinal anesthesia for cesarean section. Anesth Analg 1988;67:555–558.
47. Hartwell BL, Aglio LS, Hauch MA, Datta S. Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. Reg Anesth 1991;16:17–19.
48. Rawal N, Schott U, Dahlstrom B, et al. Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 1986;64(2):194–201.
49. Eisenach JC, Schlairet TJ, Dobson CE, Hood DH. Effect of prior anesthetic solution on epidural morphine analgesia. Anesth Analg 1991;73(2): 119–123.
50. Camann WR, Hartigan PM, Gilbertson LI, et al. Chloroprocaine antagonism of epidural opioid analgesia: a receptor-specific phenomenon? Anesthesiology 1990;73(5):806–863.

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6
The Morbidly Obese Pregnant Woman

Bhavani Shankar Kodali and Aviva Lee-Parritz

Obesity in women of childbearing years is increasing exponentially. Obstetric and anesthesia management of morbidly obese pregnant women poses a great challenge to both obstetricians and anesthesiologists alike, because obesity is a significant risk factor for adverse perinatal outcome mediated through increased risk of hypertension, diabetes, coronary disease, respiratory dysfunction, and thromboembolic complications.[1,2] Equally important is the effect of maternal overweight on the pregnancy outcome. Obesity increases antepartum stillbirths, especially at term.[2,3] It is estimated that 34 million adults in the United States are overweight to a significant degree.[4] These patients require communication and cooperation of the entire health care team to prevent catastrophic complication and improve outcome.

The purpose of this chapter is to define and quantify obesity, describe the pathologic alterations in obesity, outline the influence of physiologic changes of pregnancy on the pathologic alterations of obesity, and elucidate obstetric and anesthetic management of morbidly obese parturient.

Definition and Prevalence of Obesity

There is disagreement about a precise definition of obesity, but in general terms a person must be considered obese when the amount of fat tissue is increased beyond the point compatible with physical and mental health and normal life expectancy.[5] The most important health risks of obesity are distinctly related to excessive weight, with a progressive and disproportionate increase as the patient's weight rises. A 10% overweight carries an excess mortality of 33% and a 20% or more overweight a 50% excess mortality.[6] At a weight of 60% above standard insurance tables, disease risk is doubled as compared with the general population.[7] However, this excess mortality risk appears to be more pronounced in men compared to women.[8,9] Given that there is a positive relationship between excess weight and morbidity, it becomes important to quantify obesity and its gradations. Some define morbid obesity as a doubling of the person's predicted ideal weight.[10] Ideally, an index of obesity should be independent of height, muscularity, and skeletal mass; it should reflect fatness only.[11] Body mass index (BMI) is defined as weight (kg)/height^2(m). Normal values range between 22 and 28 in the United States.[12] A BMI greater than 28 for women is considered obese and greater than 35 to 40 as morbidly obese. Weight greater than 300 pounds in a gravida at term is also considered to be morbidly obese.[13] There are other ways of defining morbid obesity. Bendexin stated that a morbidly obese individual is one who weighs twice the predicted weight for sex, age, and height as prescribed in the Metropolitan Life Insurance Company table. Garbaciak et al. thought that the definition should be reserved for parturients who were 150% above ideal body weight.[14] A simple method of identifying this group of women is to state every pregnant patient who is 100 pounds overweight is morbidly obese. Mason et al. described obese pregnant women who exceed 225% of ideal body weight ($>$123 kg, BMI $>$ 46) as super obese.[15]

The prevalence of obesity varies depending on the definition, the criteria used, and the cultural and economic area studied. In the United States, a National Institute of Health consensus defined obesity as 20% above relative weight[5]; by this criterion, 30% to 40% of women are obese.[16]

Pathophysiology

Cardiovascular Changes

Nonpregnant, morbidly obese, normotensive persons have increased pre- and afterload, increased mean pulmonary artery pressure, and elevated right and left ventricular stroke work. The total peripheral resistance is slightly decreased in normotensive obese persons.[17,18] The cardiac diameter is usually increased by 20% to 55%, and the ventricles are hypertrophied with increased cardiac weight.[19,20] Cardiac output is increased due to larger stroke volume.[19,21] Increments in cardiac output are well correlated to weight and proportional to the increasing oxygen consumption that is associated with

obesity.[12,17,21,22] Left ventricular function, as measured by the left ventricular systolic work/pulmonary artery wedge pressure (LVSW/PAWP) ratio, is about 57% of normal in asymptomatic obese persons.[23] In response to exercise, cardiac output (CO) rises faster in the morbidly obese than in normal persons and is often associated with a rise in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure.[12] Hypertension is significantly correlated with obesity, and an increased systolic pressure of 3 mm Hg and a rise in diastolic pressure of 2 mm Hg is associated with every 10-kg increase in body weight.[17,24,25]

A body mass index greater than 30 is associated with a threefold increase in the incidence of hypertension.[26] The total blood volume is increased in obese persons, but on a volume/weight basis it is decreased, compared to lean persons (50 versus 75 mL/kg body weight).[27] Most of the expanded volume is distributed in the adipose tissue.[28] Splanchnic blood flow is about 20% higher, whereas cerebral and renal blood flow is found to be normal.[12] A 30-fold increase in premature ventricular contractions is seen in obese patients with eccentric left ventricular contractions when compared with lean subjects.[29] Left ventricular hypertrophy (LVH) occurs in response to increased workload. However, there is an association between increased left ventricular mass and increased weight, even after controlling for age and blood pressure, in patients with BMI greater than 30.[30] Excess pericardial fat is not a prominent feature in obese patients with cardiac enlargement.[31] Fatty infiltration of the heart can occur, especially in the right ventricle and perhaps in the conduction system. Eccentric LVH is the major cause of increased heart size in obesity. Inadequate hypertrophy and chamber size may predispose patients to myocardial decompensation.[32] The hemodynamic and respiratory changes seen in morbidly obese persons upon change of posture has been examined in 11 patients before upper abdominal surgery.[33] Change of posture from sitting to supine position was accompanied by a significant increase in CO, cardiac index (CI), PAWP, and mean pulmonary artery pressure, and a significant decrease in heart rate and peripheral resistance. There were no differences in pulmonary vascular resistance (PVR) or mean arterial pressure (MAP).

Hypoxemia, if present, causes increased pulmonary vascular resistance. Airway obstruction may also increase pulmonary artery pressure. It was observed that a decline in PAWP occurred from 38 to 5 mm Hg on relieving airway obstruction in an obese patient.[34]

Respiratory Changes

Respiratory changes in morbid obese persons can be differentiated into mechanical, pulmonary, and airway changes.

Mechanical Changes

Total respiratory compliance is decreased mainly due to decreased chest wall compliance and, to lesser extent, decreased lung compliance. The reduction in chest wall compliance is caused by fat accumulation around the ribs, under the diaphragm, and intraabdominally. The increase in pulmonary blood volume is responsible for the decrease in lung compliance.[35]

Pulmonary Changes

Reduced respiratory compliance and mass loading of the lungs result in reduction of functional residual capacity (FRC) caused by a decreased expiratory reserve volume (ERV).[12,36] A progressive reduction in ERV is seen when the person is brought from a standing position via the seated position to the supine and, further, to the Trendelenburg position. This movement causes a FRC reduction, which may fall within the closing volume and lead to airway closure (gas trapping), especially in dependent lung regions. A ventilation/perfusion mismatch thereby develops, which gives rise to the low Pa_{O_2} values seen in many morbidly obese persons.[12,35–37]

Bodell differentiated simple gross obesity and the Pickwickian (obesity-hypoventilation) syndrome by classifying obese individuals into three relatively distinct groups according to pulmonary function[38]:

1. Patients with normal arterial saturation but with reduced expiratory capacities
2. Patients with no lung disease who have arterial hypoxemia
3. Patients with intrinsic lung disease with hypoxemia and hypercarbia as a result of alveolar hypoventilation

Relatively young morbidly obese patients can adjust to their hypoxemia with an increase in CO and by the development of polycythemia. With the passage of time, carbon dioxide may be retained and somnolence may ensue. Pulmonary hypertension may occur from the increased blood volume and hypoxic vasoconstriction, and thus cor pulmonale develops. This "Pickwickian" syndrome, as described by Burnwell et al., represents the end stage of cardiopulmonary disease for the morbidly obese individual[39], this occurs in about 7% to 10% of massively obese patients.

Airway Changes

Obese patients are likely to develop airway obstruction and apnea during sleep, resulting hypercapnia and hypoxia. Some individuals require a continuous airway positive pressure device to overcome airway obstruction.[40,41]

Gastrointestinal Changes

It is generally believed that the morbidly obese patient is at increased risk for pulmonary aspiration of gastric contents. Hiatal hernia is more common in obese patients than in nonobese patients. Obese patients have delayed gastric emptying, and often the combination of a low gastric pH (<2.5) and a large volume (>2.5 mL) of gastric juice.[42,43] In a study that compared gastric contents in obese and nonobese subjects,[44] BMI was 46 ± 8 in the obese subjects and 22 ± 2 in the lean subjects. The groups were similar for age (35 ± 12 years and $40 \pm$

16 years in the obese and lean subjects, respectively), gender (5/25 obese men and 7/23 lean men), and smoking status (6 smokers in each group). ASA grade was I or II in all subjects. Gastric content volume was identical in the obese and lean subjects (26 ± 13 mL and 26 ± 8 mL, respectively). The pH values were 2.3 (1.3–7.1) and 2.8 (1.6–7.1) in obese and lean patients, respectively. Therefore in this study, gastric content volumes in fasting obese and lean subjects were similar. However, pH was lower in obese individuals.

Endocrine Changes

Diabetes mellitus occurs more frequently among obese patients, and there may be decreased insulin sensitivity with upper body obesity.[45]

Coagulation Changes

Obese patients are at increased risk for deep vein thrombosis and pulmonary thromboembolism.

Implications of Obesity in Pregnancy

Pregnancy in obese parturients may have four important implications. First, some of the physiologic changes associated with pregnancy (such as increases in blood volume and CO, reduction in FRC) may further exacerbate deleterious effects produced by pathophysiologic alterations of obesity (Box 6.1). Second, obese pregnant women are susceptible to pregnancy-related diseases and complications (preeclampsia, gestational diabetes). Third, there is an association between increased incidence of obstetric and perinatal complications and morbid obesity. Finally, a combination of these three factors may lead to the fourth implication: an unfavorable outcome of pregnancy for the morbidly obese.

Box 6.1. Pathophysiologic changes in morbidly obese pregnant women.

- Cardiovascular system
  - Enlarged heart
  - Eccentric hypertrophy
  - Fatty infiltration
  - Diastolic dysfunction
  - Usually preserved systolic function
  - Increased cardiac output
  - Hypertension
  - Increase in MPAP
  - Increase in PAWP
  - Increased blood volume
  - Increased plasma and RBC volume
  - Increased splanchnic blood flow
  - Increases in CO, CI, PAWP, MPAP in assumption of supine position
- Respiratory system
  - Decreased respiratory compliance
  - Increased minute volume
  - Decreased FRC
  - Hypoventilation
  - Pickwickian syndrome
- Airway changes
  - Prone to develop airway obstruction and apnea during sleep
- Blood gases
  - Arterial hypoxemia
  - Normo or hypercarbia
- Gastrointestinal
  - Low gastric pH
  - Hiatus hernia
- Pregnancy-related diseases and complications
  - Increased incidence of chronic hypertension
  - Increased incidence of preeclampsia and diabetes
  - Susceptible to increased thrombosis and embolism
  - Increased cesarean delivery rate
  - Increased incidence of postpartum hemorrhage, genital tract infection, urinary infection, fetal macrosomia, and late intrauterine fetal death
  - Increased risk of maternal death during pregnancy

Cardiovascular

Maternal plasma volume increases starting in the first trimester and peaks between 32 and 36 weeks gestation, resulting in an overall increase of 45% above nonpregnant values. Red cell mass also increases by approximately 25%. Together, these factors cause a 45% increase in circulating blood volume. Mabie et al. studied cardiovascular function in obese hypertensive pregnant women and found increased left ventricular mass and abnormal diastolic function but preserved systolic function.[46] The authors postulated that this might reflect volume overload in the presence of inadequate left ventricular relaxation. Primary therapy for this type of patient would be directed toward volume reduction using diuretic therapy.[46]

Respiratory

Pregnancy causes further decline in the abnormal posture associated with obesity, resulting in the frequent finding of thoracolumbar lordosis and modified thoracic curve. The large and protuberant abdomen diminishes rib movement, and the patient's ability to raise the lower end of the sternum is jeopardized. The excess layers of fat on the chest wall and abdomen limit respiratory excursion. This mechanical deficit leads to increased work of breathing.

Pregnancy is normally associated with a 30% to 40% increase in minute ventilation, with only a 15% to 30% increase in oxygen consumption. Eng et al. measured lung volumes in obese pregnant women during the third trimester and again postpartum.[47] Lung volumes were comparable to nonobese pregnant women except for the FRC, which was decreased less than expected compared to the normal controls. This preservation of FRC may offer some protection from premature airway closure frequently found in obese patients.

The Pa_{O_2} in obese pregnant women is increased from the nonpregnant state at 80 to 85 mm Hg; however, this is lower

than the 104 to 108 mm Hg found in pregnant women of normal weight.[47,48] This modest increase in Pa_{O_2} in obese pregnant women can be attributed to increased minute ventilation and CO.

Pregnancy also produces changes in the oropharynx. Pilkington et al. demonstrated a progression in the Mallampati airway classification with advancing gestation.[49] Therefore, pregnancy can be expected to exacerbate airway obstruction already present in obese women. Pulmonary hypertension resulting from sleep apnea has been described during pregnancy.[50]

Gastrointestinal

It is unclear whether obesity worsens pregnancy-associated changes in lower esophageal sphincter tone.[51,52] However, it seems likely that the morbidly obese patient is at increased risk for pulmonary aspiration of gastric contents.

Pregnancy-Related Diseases and Complications

Obesity is associated with an increased incidence of chronic hypertension, pregnancy-induced hypertension (PIH), and diabetes mellitus during pregnancy.[53–57] Hood and Dewan observed a 14-fold increase in the incidence of chronic hypertension (28% versus 2%) among parturients whose weight exceeded 300 pounds at the time of delivery when compared with a control group of nonobese pregnant women.[13] Similarly, the incidence of preeclampsia was 16% in obese versus 10% among a control group of nonobese pregnant women.[13] Obesity results in a 2- to 8-fold increase in the incidence of insulin-dependent diabetes mellitus during pregnancy.[53,55,58] The distribution of the patient's fat may play a role in the risks of obesity. Krotkiewski et al. showed that in those patients whose fat was more centrally located and not equally distributed (the more usual situation for women), abnormal glucose tolerance tests and hypertension were more common.[59] In the final analysis, it is important to know that obesity increases the risk of death during pregnancy. Several factors that contribute to this adverse outcome include advanced age, diabetes, hypertension, thromboembolic diseases, and infection.[60–65] Studies have also shown that obesity increases the likelihood of maternal death during anesthesia.[63–66]

Obstetric and Fetal Complications in the Morbidly Obese Gravida

An obstetric problem in the morbidly obese parturient is the difficulty with sonographic diagnosis of the fetus. Maternal weight has been found to be a good predictor for sonographic visualization of the fetus, with increasing weight making the ultrasound examination more difficult. This lack of visualization is inversely related to maternal weight and does not change with increasing gestational age or prolongation of examination.[67]

Increased BMI, increased prepregnancy weight, and excessive maternal weight gain increase the risk of cesarean section.[1] Abnormal presentations, fetal macrosomia, and prolonged labor are predisposing factors associated with increased incidence of cesarean delivery among obese women. There is evidence that obese parturients are at increased risk for abnormal labor.[68,69] The incidence of cesarean delivery for failure to progress was much higher in the morbidly obese group than in the control group, although the difference was not statistically significant.[13] Hypertension and diabetes often prompt elective induction of labor, which increases the risk of cesarean delivery.[55] There is evidence that weight gain during pregnancy also may affect the risk of fetal macrosomia, and this is likely to increase the incidence of cesarean delivery.[70] Ratner et al. determined that the incidence of primary cesarean delivery was statistically greater in those obese women gaining more than 24 pounds as compared to obese women gaining less than 24 pounds.[70] However, there is a considerable debate on this subject; some authors state that prepregnancy weight has a more important bearing on the incidence of cesarean delivery than the weight gain during pregnancy in morbidly obese gravid women.[70–72]

Some studies have noted an increased incidence of meconium-stained amniotic fluid, umbilical cord accidents, and late fetal heart rate decelerations during labor in obese patients.[58,68] However, the incidence of fetal distress as an indication for cesarean delivery was remarkably similar for both normal weight and morbidly obese patients.[13] The success rate of vaginal delivery after prior cesarean delivery in parturients who weighed at least 300 pounds at the first prenatal visit is about 13% as compared to 60% to 80% in nonobese pregnant subjects,[73] which may be an additional factor contributing to an overall increased cesarean delivery rate in obese pregnant subjects.

Some studies suggest that abnormal presentations and multiple gestations are more common in obese parturients than in nonobese pregnant women.[53,69] Furthermore, compared to women with normal BMI, the following outcomes (induction of labor, postpartum hemorrhage, genital tract infection, urinary tract infection, wound infection, birth weight above 90th percentile, and intrauterine late fetal death) were significantly more common in obese pregnant women, and morbid obesity appeared to be an independent risk factor for adverse perinatal outcome.[1,74,75] The increased risk of fetal macrosomia predisposes obese women to trauma at delivery.[53] Fetal macrosomia also increases the likelihood of shoulder dystocia during vaginal delivery.[57] Johnson et al. noted an association between fetal macrosomia and an increased incidence of shoulder dystocia in pregnant women weighing more than 250 pounds.[68]

There is high incidence of umbilical arterial pH less than 7.10 among obese women, regardless of whether they had a trial of labor or elective cesarean delivery.[73] There is significantly higher incidence of neonates with Apgar score at 1 min less than 5, Apgar score at 5 min less than 7, birth weight greater than 4500 g, birth weight less than 2500 g, intrauter-

ine growth retardation, and neonatal intensive care unit admissions among babies born to obese parturients as compared to those born to nonobese parturients.[57] There seem to be an association between gravid obesity and congenital anomalies in infants born to gravid obese parturients. Waller and associates found these infants are at a greater risk for developing neural tube defects and other congenital malformations.[76]

Weight Reduction Surgery

Fertility and pregnancy rates improve following weight reduction operations in obese women.[77] Successful pregnancies have been reported even in the initial period of rapid, postoperative weight loss.[78] Moreover, there is a reduction in obstetric complications in individuals who conceived after weight reduction surgery as compared to the presurgical gravid obese state.[79]

Obstetric and Anesthetic Management

The obese parturient is classified as a high-risk patient. Counseling must start during the preconception period to fully explain the potential maternal and fetal risks of obesity. This is a good opportunity to screen for medical conditions that may complicate ensuing gestation. Weight reduction should be encouraged before conception to reduce the complications of gestation.

A complete physical examination should be performed with special attention to the patient's cardiovascular and pulmonary status to determine if coronary artery disease or intrinsic pulmonary disease exists. A 12-lead ECG to evaluate ischemic heart disease and rhythm abnormalities and a chest X-ray to determine heart size should be obtained. During pregnancy, an elevated diaphragm may cause a QRS shift to the left. In addition, other minor alterations produced by gestation may be seen on the ECG that should not be construed as evidence of heart disease. However, the ECG may reflect evidence of long-standing hypertension (left ventricular hypertrophy), ischemia, and changes suggesting the presence of pulmonary hypertension.

A history of excessive snoring and sleep apnea should be sought. If obesity-hypoventilation syndrome is suspected, a cardiologist consultation is necessary that may further evaluate cardiac function using echocardiography. The timing of this consultation at this stage offers an opportunity to optimize cardiovascular function before labor and delivery.

Pulmonary status must be investigated by means of pulmonary function testing and an arterial blood gas test, if indicated. Pulmonary function testing may be repeated during the third trimester to determine the effect of pregnancy. Testing should also be performed with the patient in the supine position to determine the effect of decreasing FRC. Hypoxia, if previously present, will become worse; if not present, it will develop. This concern is important if the obese woman must subsequently undergo a cesarean delivery because this procedure would be done in the supine position with left uterine displacement. Pulse oximetry is a useful device to assess the effect of changing posture on oxygenation. Initial assessment of airway as well as periodic assessment of airway is mandatory to determine the implications of airway changes produced by advancing pregnancy.

In addition to routine laboratory tests, liver function tests and blood glucose levels should be determined. Slight elevations of the transaminases may be observed in the pregnant women. If the rise in transaminases is greater than 30 IU, or if there are abnormalities in coagulation tests, a more thorough investigation into the possibility of hepatic disease is warranted. Diabetes should be tightly controlled during pregnancy. Nutrition therapy is an essential element of prenatal care for these patients.

An important consideration during the predelivery care is proper understanding of her psychologic makeup.[80] Depression and low self-esteem are clearly associated with obesity. This lack of understanding may lead to the loss of the parturient's cooperation in both prenatal care and the intrapartum period. Obese pregnant women frequently have a distorted view of their weight and body image. It is not unusual for women to significantly understate their weight and at the same time acknowledge that they are indeed overweight. The understanding of this psychological makeup and sensitive communication will build a cooperative relationship between pregnant women and care providers.

Because of significant comorbid associations and increased risk of preterm labor, consultation with the anesthesiologists should take place at the beginning of the third trimester. Four important issues should be addressed at this stage. First, this is the period during which cardiovascular changes of pregnancy will have maximum impact on the pathophysiologic changes of obesity. A detailed history and physical examination is performed, focusing on the systems most likely to be compromised by obesity. All laboratory values are reviewed. If further cardiac consultation is deemed necessary, then it should be obtained at this stage to allow enough time for optimizing cardiorespiratory functional status before delivery. Second, the anesthesiologist should assess the status of the airway and look for factors that could complicate intubation, remembering that the airway can worsen as the pregnancy advances to term.

Third, review options of labor and delivery analgesia and anesthesia techniques with the parturient. She should be informed that epidural/spinal techniques could take longer than usual to perform and that the anesthesiologist will work with the women to achieve a satisfactory placement of the epidural/spinal. This review will psychologically prepare the parturient to face up to the reality of performing spinal/epidural techniques that could be difficult in obese parturients. Fourth, one should communicate a provisional plan of anesthesia for labor and delivery with the obstetrician and other relevant care providers. For example, for the pregnant women with a difficult airway, a plan emphasizing early epidural placement may be considered.

Management of Labor and Delivery

For reasons of the high incidence of comorbidities in obese pregnant women and the increased risks of operative delivery for either cephalopelvic disproportion or a nonreassuring fetal state, continuous maternal and fetal monitoring is essential.

Noninvasive blood pressures should be recorded with a blood pressure cuff large enough to obtain accurate readings. If a blood pressure cuff large enough for the woman's upper arm cannot be obtained, one should place a cuff in the region of the radial artery; this will allow trends to be followed during labor. If an adequate blood pressure reading cannot be obtained, one should consider placement of an arterial line, which will also provide periodic monitoring of arterial blood gases. If a parturient is known to have hypoxia or hypercarbia, an arterial line is necessary. Despite morbid obesity, radial artery cannulation is rarely difficult.

Pulse oximetry should be used in all obese women. Pulse oximetry will also guide the use of supplemental oxygen during labor. Further monitoring will depend on the cardiorespiratory status of the pregnant woman, and the risk of any monitoring procedure should be weighed against the extra benefit obtained in an individual pregnant woman.

Obstetric Management

The indications for labor induction are the same for the obese parturient as for nonobese parturients. Maximize pulmonary function by avoiding the lithotomy position for a vaginal delivery; the woman can labor and deliver in the semierect position. Operative vaginal delivery should also be performed in this position. The upright positioning helps prevent a further decrease in the FRC and the consequent hypoxia associated with the supine or lithotomy position.

The incidence of cesarean delivery for failure to progress is higher in morbidly obese than in nonobese parturients.[13] If the pregnant woman cannot safely fit on the operating room table, one should consider performing the cesarean delivery in a labor bed (in an operating suite) or on a special operating room table capable of bearing heavier weights. In addition to left uterine displacement, a 10° reverse Trendelenburg position will help facilitate better oxygenation.

The type of incision normally selected is the high transverse incision. It is generally believed that with this incision the pregnant woman appears better able to cough and deep breathe postoperatively, thus helping to prevent atelectasis, pneumonia, and hypoxia. Vertical midline and paramedian incisions have also been used. A case-control retrospective study to determine the differences in postoperative morbidity in obese women who had a supraumbilical or a Pfannenstiel incision at cesarean delivery showed no difference in postoperative morbidity.[81] However, it is generally believed that the Pfannenstiel incision has the advantage of reduced thickness of adipose tissue above the pubis and decreased wound dehiscence, as these women will require increased coughing and deep breathing to prevent atelectasis postoperatively.

There are several methods by which a panniculus can be retracted to facilitate incision. All of them are associated with varying degrees of adverse effects on cardiovascular (compression of inferior vena cava) and respiratory function.[82] Caudal retraction permits a vertical incision. The Pfannenstiel incision can be performed following cephalad retraction. A Pfannenstiel incision has been associated with a longer operating time, greater blood loss, and poorer exposure.[83] Whether the panniculus is retracted by a surgical assistant or by use of tape, caution should be exercised to minimize vena caval compression.

After either vaginal delivery or cesarean delivery, it is important that the pregnant woman ambulate as quickly as feasible, preferably during the first 24 h postpartum; this will decrease the incidence of thromboembolic phenomena.

Anesthetic Management

Principles of anesthetic management that apply to labor and delivery in nonobese parturients are also valid in obese parturients. However, special considerations in the anesthetic management of obese parturients should be addressed.

Management of obese parturients for labor delivery depends upon several factors such as the degree of obesity, airway problems, and the cardiorespiratory status (Box 6.2). The usual antacid prophylaxis precautions should be applied before administration of analgesia/anesthesia. It is advisable to administer oxygen via nasal cannula or face mask because of the common occurrence of hypoxia. Regional anesthesia is probably the best method of providing analgesia for labor and delivery. Regional analgesia reduces oxygen consumption and attenuates the increase in cardiac output that occurs during labor and delivery. Moreover, successful use of regional anesthesia has been described in morbidly obese parturients with significant systemic derangements such as dilated cardiomyopathy, angina, and asthma.[84–86] Furthermore, regional anesthesia does not affect the likelihood of vaginal delivery in patients who weighed more than 300 pounds when compared with similar parturients who did not receive epidural analgesia during labor.[13] Among regional techniques, which include epidural, continuous spinal, and combined epidural spinal techniques, epidural analgesia seems to be the best technique for providing not only a well-controlled analgesia for labor delivery but also good anesthesia for unexpected or expected cesarean delivery.

If an obese mother chooses natural childbirth, the anesthesiologist and obstetrician should ensure that a quick regional anesthesia or safe general anesthesia could be provided in the event of fetal distress. However, if there is reason to believe that anesthesia cannot be provided expeditiously due to the body habitus, then the obstetrician in conjunction with the anesthesiologist should encourage the patient to receive an early epidural placement. The location of the epidural catheter can be tested with lidocaine 1.5% to 2% or a local anesthetic regimen to which the individual anesthesiologist is accustomed.

Box 6.2. Anesthetic management of labor and delivery.

- Anesthesiology consultation at 28 weeks gestation
- Evaluation of cardiorespiratory status and airway
- Multidisciplinary team approach

- Labor analgesia
  - Labor and delivery in semierect position
  - Monitor oxygenation via pulse oximetry
  - Supplemental oxygen may be required
  - Additional monitoring as required

- Early placement and confirmation of optimal epidural analgesia
  - Midline approach in sitting position
  - Strapping excess fat away from the midline
  - Greater failure rate of initial insertion of epidural catheters may be anticipated
  - A CSE needle can be used as a guide in the localization of epidural space
  - Longer epidural needle may be required
  - To minimize catheter displacement, catheters should be secured on assumption of upright or lateral position from the initial flexed position
  - Restrain from using opioids until confirmation of the proper location of epidural catheter
  - Diligent periodic monitoring of labor and delivery analgesia is mandatory
  - Continuous spinal analgesia is an option when epidural space cannot be localized successfully
  - CSE is an option with few caveats

- Cesarean delivery
  - Diligent positioning of patient's head and neck in optimal position for intubation even in patients undergoing cesarean delivery under regional anesthesia
  - Precautions against inadvertent high block
  - Meticulous left uterine displacement
  - Exercise caution with retraction of panniculus to avoid cardiovascular compromise
  - Duration of cesarean delivery may be longer

- General anesthesia
  - Examination of airway and anticipation of difficult intubation
  - Diligent positioning of head and neck
  - An extra pair of hands is a boon
  - An additional airway should be readily available, particularly an LMA
  - Adequate preoxygenation
  - Rapid sequence anesthesia
  - Hypoxemia may ensue quickly during apnea in obese gravida.
  - Large tidal volume ventilation with or without PEEP

- Postoperative
  - Adequate pain control to assure postoperative deep breathing
  - Thromboprophylaxis

CSE, combined spinal epidural technique

Thereafter, the mother could proceed with her intended desire of natural childbirth while the epidural catheter remains as a backup to provide epidural anesthesia for unforeseen fetal emergencies. For women desiring analgesia for labor and delivery, early epidural placement should be encouraged; this will provide ample time for attempting a difficult placement and also saves time because the parturient is more cooperative in the initial stages of labor as compared to the painful later stages.

Discussing their experience with regional anesthesia, Hood and Dewan stated that morbidly obese parturients required more repeat epidural catheters to achieve success.[13] They also reported a much greater failure rate with the initial insertion as compared with attempts on normal-sized individuals. Although Buckley et al. reported a failure rate of about 20% for epidural anesthesia in morbidly obese patients, Hood and Dewan had a much higher success rate (94%) for providing satisfactory epidural anesthesia in parturients weighing more than 300 pounds.[13,87] Poor localization of landmarks, increased depth of the epidural space, and failure to identify the epidural space are a few of the factors contributing to a high failure rate for epidural anesthesia as well as a higher incidence of unilateral blockade. Increased depth of epidural space exaggerates minor directional errors and increases the likelihood of identifying a lateral portion of the epidural space.[88] The application of ultrasonic guidance to facilitate localization of epidural space is an option, but its applicability to a busy obstetric unit is questionable.[89]

A few important precautions may improve the success rate of epidural technique. A sitting position is preferred in the morbidly obese for placing regional anesthesia. This position allows the body fat of the back and upper buttocks to fall away from the midline, not overlapping the access site for needle placement. Our practice is to have the patient sit up and hug a pillow or two to achieve as much flexion as possible. Occasionally, fat pads have to strapped away from the midline using tape.[86] If bony landmarks cannot be delineated on palpation, a 25-gauge infiltration needle can be used to localize spinous processes. Occasionally, the epidural needle itself must be used to feel the deeper bone landmarks to locate the intervertebral space. Conversation with the patient during placement can also help in localizing the probable midline. Once the probable midline is demarcated, the epidural needle is directed to locate the epidural space. If a bone is encountered, the angulations of the direction of the needle can be changed in the usual manner. However, in persistent difficult circumstances, I often succeed by moving the point of insertion of the epidural needle in 1-cm increments up or down the probable midline to facilitate the location of the interlaminar space between the two vertebrae. When the feel of the epidural needle movement is not like the usual firm ligamentous feel (but feels mushy), a 25-gauge Whittaker spinal needle can be introduced through the epidural needle [as in the combined spinal epidural technique, (CSE)], to determine what is ahead of the epidural needle. If no cerebrospinal fluid (CSF) is obtained, the epidural needle can be advanced further until the epidural space is localized; this will allow a cautious approach to the epidural space and avoid an accidental wet tap with the 17-gauge needle. This approach can also be used to confirm the epidural space when a false loss of re-

sistance is encountered in fat pockets during epidural space location. A longer spinal needle to facilitate the "needle through needle" technique is being developed for clinical use. Occasionally, a longer epidural needle (16 cm) is required when the traditional length of 10 cm cannot reach the epidural space.

Once the epidural space is localized, the epidural catheter is inserted approximately 4 to 5 cm into the space. Caution must be exercised while securing the catheter to the skin. It has been demonstrated that epidural catheters frequently appear to be drawn inward with position change from the sitting flexed to lateral decubitus position, with greatest change seen in patients with a BMI greater than 30.[90] To minimize the catheter displacement, Hamilton et al. recommended that the epidural catheters be inserted at least 4 cm into the epidural space and that patients assume the upright or lateral position before the catheter is secured to the skin.[90]

Once the epidural catheter is introduced, the test dose and local anesthetic regimen to which an individual anesthesiologist is accustomed can be followed with the caveat that it is prudent to avoid narcotic in the initial loading dose of the local anesthetic. Because the administration of opioid by any route provides some pain relief, the anesthesiologist may be misled to believe that the catheter is positioned correctly in the epidural space. However, large doses of local anesthetics subsequently administered for cesarean delivery will not result in a satisfactory anesthesia.

If the epidural space cannot be localized to facilitate epidural analgesia, an intentional spinal is attempted, and a catheter is introduced into the subarachnoid space. In cases of unintentional wet dural puncture, continuous spinal anesthesia can be provided. Our practice is to provide initial analgesia with a usual spinal dose of 0.25% bupivacaine 1 mL and fentanyl 25 μg; this is followed by an infusion of bupivacaine 0.125% with 2 μg/mL fentanyl at 1 ml/h to maintain analgesia. *"Spinal catheter" should be prominently displayed at the port of injection to avoid accidental injection of large epidural quantities of medications by anesthesia care providers.* The author's observations concur with the reported findings that the incidence of postdural puncture headache following dural puncture is lower in the morbidly obese than in the nonobese group.[13,91]

Traditionally, the standard area for epidural placement is L2–L3 or L3–L4. These sites are chosen ostensibly to avoid damage to the spinal cord, which in most people ends at L1. Occasionally, a lower thoracic approach for epidural placement can be considered when lumbar access is difficult. Lower thoracic vertebrae may be palpable because of a frequently occurring convexity in the parturient's back. Moreover, with the more cephalad approach to the woman's back, the midline may be identified more easily. For more effective labor analgesia, the epidural catheter should be threaded in a caudad direction approximately 2 to 3 cm.[92]

Combined spinal epidural is an option that can be considered for labor analgesia. However, two caveats should be taken into consideration. First, intrathecal narcotics are associated with depressed ventilation in normal-weight parturients; morbid parturients can also be susceptible to this effect.[93] Second, although there is no difference in the success rate between the epidural analgesia that follows the spinal part of the CSE and the regular epidural (epidural) technique in nonobese parturients, it should not be assumed that this could be true in morbidly obese parturients, who are likely to have a higher incidence of failed epidural catheters.[13,94] Moreover, in the Norris study, approximately 5% of catheters that produced effective labor analgesia failed to produce adequate surgical anesthesia, independent of insertion technique (epidural or CSE group).[94] These patients could have a difficult airway that preclude safe administration of general anesthesia for an immediate cesarean section in the event of an unsatisfactory epidural anesthesia. Therefore, it is the author's practice not to perform CSE as a universal technique in all parturients requiring labor and delivery analgesia, particularly in the presence of morbid obesity, preferring early confirmation of the efficacy of epidural analgesia. Occasionally, an intentional dural puncture is performed with a 25-gauge spinal needle (without introducing subarachonoid medications) to confirm the location of the epidural needle in the epidural space. Furthermore, our beliefs concur with findings that a dural hole enhances the efficacy of epidural analgesia and anesthesia.[95]

A single injection of subarachonoid blockade for vaginal delivery in morbidly obese parturients should be restricted to operative obstetrics (massive repair of perineal tear, etc.). It is probably unnecessary and unwise, however, for normal vaginal deliveries, unless the patient is toward the end of impending vaginal delivery or forceps/vacuum application. A diligent periodic monitoring of labor and delivery analgesia is mandatory in morbidly obese parturients. The cause of inadequate and suboptimal analgesia should be investigated as there is a possibility that catheters can be dislodged from the epidural space. Early detection of such events provides ample time to replace nonfunctional and suboptimal epidural catheters.

Anesthesia for Cesarean Delivery

Careful attention should be paid to positioning the parturient for cesarean section. The protuberant abdomen may shift remarkably when the woman is tilted toward the left for facilitating left uterine displacement. Therefore, the woman should be well secured. There should be enough padding over the arm boards (blankets) to keep the arms at the same level as the body; this will further help to stabilize the parturient on the operating table, also improving her general comfort level. Irrespective of the type of anesthesia (regional or general), it is the author's practice to diligently position the woman's head and neck as optimally as possible for probable intubation, achieved by gradually elevating the upper back and neck with blankets arranged in a stepwise fashion (8–10 blankets may be required). This method will facilitate a clear demarcation of head and neck from the chest and result in a gentle

flexion of the cervical spine. After achieving this position, an extension at the atlanto-occipital joint will provide the optimum condition for intubation. Diligent body positioning will also help to ensure the patient's comfort and secure her confidence and cooperation; moreover, this will help to facilitate breathing when the panniculus is retracted and secured to the operating table to make way for a surgical incision.

It is important to initiate left uterine displacement as soon as the parturient is in the supine position. Cardiovascular collapse after placement in a supine position has been reported in two cases in obese patients.[96] Careful attention must be paid during cephalad retraction of the large panniculus. The tethered retractors are secured to the ether screen or to a stable object. Cephalad retraction of the panniculus in morbidly obese parturients can result in hypotension and fetal compromise. Intraoperative fetal death has been reported in one parturient who received epidural anesthesia for cesarean delivery, apparently as a result of a prolonged episode of hypotension associated with cephalad retraction of a large panniculus.[82]

Cesarean delivery in the morbidly obese can be performed under spinal, epidural, continuous spinal, or combined spinal/epidural anesthesia. General anesthesia is at best reserved for emergency circumstances and when regional techniques fail or are contraindicated. The basic principles guiding the choice of anesthesia for cesarean delivery in morbidly obese parturients depend on the circumstances of presentation and are similar to those in nonobese parturients: namely, elective or emergency, presence of prior epidural/continuous spinal catheters, airway issues, length of anticipated procedure, and the ease of conversion from regional to general anesthesia if a need arises. It is important to know that the duration of cesarean delivery can exceed 2 h in 55% of women who weigh more than 250 pounds.[54] Another factor that assumes an important place in decision making is the cardiopulmonary status of the morbidly obese parturient.

Spinal Anesthesia

If spinal anesthesia is chosen, we use a hyperbaric bupivacaine and fentanyl combination. Epinephrine can be added (200 μg) to enhance the density, effectiveness, and duration of the block.[97] There is a controversy over the relationship between obesity and the height of the spinal anesthetic block.[98–101] The preponderance of evidence suggests little correlation between patient weight and the spread of anesthesia; however, the consequences of extensive blockade dictate caution when selecting single-shot spinal anesthesia. Green has suggested that although obesity per se does not alter local anesthetic dose requirement during the administration of spinal anesthesia, large buttocks, often present in obese patients, place the vertebral column in a Trendelenburg position, resulting in an exaggerated spread of anesthesia.[99] Therefore, it is our practice to maintain head and back elevation as previously described with or without a 10° to 15° reverse Trendelenburg position. Venous return can be maintained by a slight elevation of the lower limbs. The height of the block is closely monitored until a desired level is achieved by adjusting the degree of the reverse Trendelenburg position.

Spinal anesthesia produces more profound loss of thoracic motor function and may pose a problem in morbidly obese parturients. Although the peak expiratory flow rate decreases, the reduction in Pa_{O_2} is small.[48,100] Due to loss of sensation in the lower chest and thoracic motor function, morbid parturients may panic from a subjective sensation of shortness of breath. Reassurance plays a dominant role in these circumstances. Although 25-gauge spinal needles are usually used for spinal placement, in difficult circumstances a 22-gauge spinal needle can be used, as the incidence of postdural puncture headache is small in obese parturients.

Epidural Anesthesia

Studies have shown that obesity results in a more extensive spread of epidurally administered 20 mL bolus bupivacaine, but bolus administration of anesthetic agents into the epidural space is unacceptable in current clinical practice settings. On the other hand, neither woman position nor obesity affects the height of the sensory block when 12 mL 0.25% bupivacaine is administered for epidural analgesia during labor.[102] Incremental doses of anesthetic agent (2% lidocaine with epinephrine) are administered until a desired level (T4) of anesthesia is obtained.

Continuous Spinal Anesthesia

Continuous spinal anesthesia can be used if epidural placement is difficult. Incremental doses of hyperbaric bupivacaine (0.75%) up to a total 1.6 mL are sufficient to achieve the desired level of anesthesia.

Infiltration Anesthesia

Successful use of infiltration block for cesarean delivery in a morbidly obese parturient (150 kg) with severe preeclampsia, generalized edema, and acute respiratory failure has been described.[103] The incision line was infiltrated with 8 mL lidocaine 1% with epinephrine (1:200,000). The rectus sheath and peritoneum were infiltrated with 0.5% lidocaine with epinephrine with a total dose of 300 mg. Anesthesia was supplemented with nitrous oxide in oxygen (50:50).

General Anesthesia for Cesarean Delivery

Airway considerations play a dominant role when considering general anesthesia for cesarean delivery. There is the potential for difficult intubation, difficult mask ventilation, and susceptibility for aspiration. Endotracheal intubation may be difficult or impossible with standard techniques. There is an association between obesity, short neck, and Mallampati class and intubation.[104] Lee et al. reported a incidence of difficult intubation of 2.4% among patients whose weight was 1.5 to 1.75 times the ideal; this incidence was tripled to 7.3% when

the weight of the patients increased to 1.75 to 2 times the ideal body weight.[105] Buckley et al. reported 9 difficult intubations among 65 morbidly obese nonpregnant subjects (13%).[87] The incidence of difficult intubation is even higher in pregnant morbidly obese subjects. Hood and Dewan reported 33% incidence of difficult intubation in their series in which patients received general anesthesia for cesarean delivery.[13] Furthermore, the history of previous successful intubation does not guarantee the same result during a subsequent procedure.[13]

In elective cesarean delivery, there is ample time for careful airway analysis and planning. However, cesarean delivery for urgent indications may impose considerable pressure on the anesthesiologists to proceed in haste. Despite urgency, careful anesthetic planning based on the airway assessment probably should take precedence over the fetal indication of urgency. A hasty move under these circumstances can culminate in both fetal and maternal disaster. An additional pair of experienced hands is a boon in the management of a difficult airway in morbidly obese subjects. Two hands may be required for either jaw thrusting or holding the face mask while the second person can assist in ventilation. Additional equipment to assist difficult intubation is required, including a short handled Datta–Briwa laryngoscope,[106] assorted laryngoscope blades, a variety of endotracheal tubes, and equipment to facilitate transtracheal jet ventilation and percutaneous cricothyroidotomy. A laryngeal mask airway (LMA) should always be available in all obstetric suites for situations when a patient cannot be ventilated or intubated.[107]

If the preanesthetic assessment does not suggest a difficult intubation, rapid sequence induction can be performed after adequate denitrogenation of lungs. Parturients can become hypoxemic rapidly during apnea.[108] Obese parturients can also become hypoxemic during apnea.[109] The combination of obesity and pregnancy can further increase the susceptibility of an obese parturient to become hypoxemic rapidly during apnea. Hence, it is prudent to grasp every opportunity before induction to preoxygenate the obese parturient while the woman is being positioned and monitors applied. Parturients should be encouraged to take a few deep breaths during this process of preoxygenation. Under emergency circumstances, a four-breath method of denitrogenation can be used. However, it should be noted that a study showed that nonobese parturients with the four-breath method developed hypoxemia more rapidly than parturients who received 3-min tidal preoxygenation.[110]

For an unforeseen difficult intubation, management follows the usual difficult airway algorithm. In our institution, a code-airway is called in the event of a difficult intubation; this summons, among others, a surgical senior who can expeditiously perform a tracheotomy/tracheostomy, if required. The American Society of Anesthesiologists (ASA) and the ASA task force on obstetric anesthesia have developed guidelines to deal with unexpected airway difficulty.[111] If initial attempts at intubation are unsuccessful after inducing anesthesia, a few additional attempts at intubation are appropriate using different laryngoscope blades, anesthesiologists, and head positions before considering the case to be difficult. If the trachea cannot be intubated, one should not persist with intubation but begin mask ventilation, because parturients die of hypoxemia not of failure to intubate. If the mask ventilation is not successful despite an oral airway, a LMA or Combitube is inserted to facilitate ventilation. An LMA is our first choice because anesthesiologists have considerable experience with the LMA in routine anesthetic practice. If ventilation cannot be accomplished with an LMA/Combitube (cannot intubate, cannot ventilate), transtracheal jet ventilation, cricothyrotomy, or tracheostomy must be considered. On the other hand, if ventilation is successful with an LMA (cannot intubate, can ventilate), the decision to continue anesthesia depends on the indication for the cesarean delivery.[112] If the cesarean delivery is being performed for elective indications, there is no justification for jeopardizing the mother's life by continuing with general anesthesia without a tracheal tube. On the other hand, general anesthesia with LMA can be continued when the mother's life depends on the completion of cesarean delivery (as in massive antepartum hemorrhage). A fiberoptic intubation through an LMA can help secure the airway under these circumstances. It is prudent to acquire difficult airway equipment and surgical help as a backup until the termination of anesthesia has culminated in the safe recovery of the pregnant woman.

If a difficult intubation is anticipated preoperatively, a fiberoptic intubation should be performed before induction of general anesthesia. Godley et al. described the use of LMA for awake fiberoptic intubation under topical anesthesia in a morbidly obese parturient considered to be a difficult intubation.[113] Cohn et al. achieved successful awake intubation in a 240-kg morbidly obese parturient using Bullard's laryngoscope.[114]

There is a relative dearth of scientific work regarding potential problems with thiopentone sodium for induction of general anesthesia in the morbidly obese parturient. The dose of induction agent should be increased in morbidly obese patients because blood volume, muscle mass, and cardiac output show linear increase with the degree of obesity.[10] However, in clinical practice, thiopentone 4 mg/kg lean body mass to a maximum 500 mg provides satisfactory induction for cesarean delivery. Etomidate in a dose of 0.1 to 0.3 mg/kg may be used for obese patients with cardiac problems. Propofol 2 mg/kg is another alternative for induction. Although propofol is highly lipophilic with a distribution volume of about 40 L, it does not appear to accumulate in the body. However, it has marked hemodynamic effects, and an excessive dosage for induction may lead to cardiovascular depression. When hemodynamics are unstable, ketamine 1 mg/kg of lean body mass is a suitable option. If a patient has history of bronchial asthma, ketamine is frequently used because of its bronchodilatory effects. Hypertension is a relative contraindication to the choice of ketamine, as is a history of mental aberrations and hypertonicity of uterus. Midazolam is generally not used for induction; it may be used after delivery of the

baby. It should be remembered that elimination half-life is prolonged significantly from a mean 2.7 h in controls to 8.4 h in the obese.[115]

Succinylcholine, in a dose of 1 to 1.5 mg/kg, is the drug of choice for the facilitation of intubation. In regard to the nondepolarizing muscle relaxants, the recovery time from atracurium is not prolonged in obese patients, but there is prolongation of recovery time from vecuronium (0.1 mg/kg).[116] This difference is a result of impaired hepatic clearance in the grossly overweight. A peripheral nerve stimulator should be used no matter which muscle relaxant is used. Regardless of the relaxant used, it is probably wiser to reverse its effects with neostigmine in the usual fashion.

Morbidly obese patients are known to metabolize inhalational agents such as halothane and enflurane more rapidly than nonobese patients.[117,118] However, these agents are no longer used in obstetric practice. Serum inorganic fluoride concentrations in obese patients increase more rapidly and remain higher than in nonobese patients following similar exposure of sevoflurane during general anesthesia.[119] As the fluoride level after isoflurane anesthesia is not significantly increased, isoflurane is the drug of choice because of lesser organ toxicity.[120] A study comparing the postoperative recovery after propofol, isoflurane, and desflurane in morbidly obese patients receiving general anesthesia showed that sedation was significantly less pronounced with desflurane at 30 and 120 min postoperatively.[121] Postoperative immediate and intermediate recoveries were more rapid after desflurane than after propofol or isoflurane anesthesia. This advantage of desflurane persisted at least for 2 h after surgery and is associated with both an improvement in patient mobility and a reduced incidence of postoperative desaturation.[121] Thus, desflurane seems to be an ideal inhalational agent for obese subjects. The theory that lipid solubility of volatile anesthetics prolongs the recovery period in morbidly obese patients has been challenged.[122] Because of its low fat solubility and lack of metabolism, nitrous oxide would appear to be a logical choice, but because of the high demands of oxygen in many morbidly obese patients its usefulness is limited.

All obese patients should receive high tidal volume ventilation. Large tidal volume coupled with low chest wall compliance and elevation of the diaphragm means that high peak inspiratory pressures are often necessary. Ventilation with large tidal volumes aims at moving tidal ventilation above the closing volume and consequently increasing arterial oxygen tension.[36]

Ventilation adjustments can be guided by capnography. End-tidal carbon dioxide reflects arterial carbon dioxide in nonobese parturients undergoing cesarean delivery.[123] There are no such data in morbid parturients undergoing cesarean delivery, but the arterial to end-tidal carbon dioxide difference may be expected to increase due to an increase in alveolar dead space.[124] Maintaining an end-tidal carbon dioxide around 32 mm Hg should at least avoid hypocarbia, which may reduce uterine blood flow.

Application of moderate positive end-expiratory pressure (PEEP) can improve oxygenation, although this may not always be the case.[125] Even if PEEP does increase Pa_{O_2}, it may do so at the expense of CO, resulting in a net fall in oxygen delivery. Although it is probably preferable to extubate the obese parturient in the operating room, if there is any doubt as to the patient's ability to maintain adequate ventilation and oxygenation, one should continue mechanical ventilation in the postanesthesia care unit. Extubation depends on the usual criteria for termination of endotracheal intubation.

Postoperative Care

Morbidly obese patients are greatly at risk from postoperative respiratory insufficiency, and supplemental oxygen must be given throughout the recovery period. The head and upper body should be elevated 30° to 45° to facilitate better oxygenation. Shivering must be prevented because this will cause a marked increase in oxygen demand. After abdominal surgery, a 45% incidence of atelectasis has been reported,[126] and continuous positive airway pressure (CPAP) treatment should be initiated in the recovery room. Recently, bilevel CPAP has been shown to significantly reduce pulmonary dysfunction after upper abdominal surgery in obese patients.[127] Restoration of normal pulmonary function following intraabdominal surgery may take 4 to 5 days.[128]

Thromboembolic complications contribute greatly to the increased morbidity and mortality in postoperative obese patients. Prolonged immobilization should be avoided as it can lead to phlebothrombosis. Pregnancy can further increase the risk of thrombosis in the morbidly obese patient. Pulmonary emboli, often fatal, occur in 5% to 12% of obese patients undergoing surgery.[36,129] The increased risk of phlebothrombosis can be prevented by miniheparinization (Heparin 5000 units*2), elastic stockings or frequent leg lifts, and pneumoboots (sequential compression devices). Regional anesthesia offers some protection as well, facilitating early mobilization. The method of providing postoperative analgesia for these patients can have a major effect on their early ambulation and recovery.

Extreme caution is necessary when parenteral opioids are administered postoperatively to morbidly obese patients because respiratory insufficiency and circulatory collapse may result. Patient-controlled analgesia (PCA) may also cause serious respiratory depression.[130] Epidural or intrathecal administration of opioids is far superior to parenteral analgesic regimes. Epidural morphine ensures longer duration of pain relief, earlier mobilization, earlier normalization of intestinal motility, improved pulmonary function, and shorter hospital stay.[131] Our practice is to administer 3 mg morphine via the epidural route or 0.2 mg via the intrathecal route. It would be prudent to utilize pulse oximetry in the postsurgical period for at least 24 h to monitor oxygenation for obese women receiving neuroaxial opioids. Additionally, apnea monitors can

be used to monitor respiration. When epidural opioids are given, most authors argue against the concomitant use of intravenous opioids, but supplementary administration of a peripherally acting analgesic can be useful to augment postoperative pain relief.

Summary

Obese women should be strongly encouraged to lose weight before conceiving to decrease obstetric and perinatal morbidity and mortality. Careful systemic evaluation should be performed at the first opportunity during pregnancy in morbidly obese women to determine the systemic pathophysiologic alterations of obesity. It is strongly recommended that the pregnant woman should be seen by an anesthesiologist at around 28 weeks gestation to determine the effect of pregnancy on various systems. A multidisciplinary approach should be instituted depending on the systemic findings. Careful evaluation of the airway should be performed, and an anesthetic plan formulated and communicated to the patient as well as the obstetrician. Regional anesthesia is most appropriate for labor and delivery. An early administration of epidural anesthesia is recommended, which will provide ample time to negate difficulties encountered during epidural placements. Continuous spinal anesthesia is a reasonable alternative. If general anesthesia is contemplated, a second pair of hands is a boon, and necessary airway backup equipment should be at hand. A multidisciplinary approach is the key to a successful outcome of pregnancy in morbidly obese women.

References

1. Sebire N, Jolly M, Harris J, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord 2001;25:1175–1182.
2. Baeten J, Bukusi E, Lambe M. Pregnancy complications and outcomes among overweight and obese nulliparous women. Am J Public Health 2001;91:436–440.
3. Stephansson O, Dickman P, Johansson A, Cnattingius S. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. Am J Obstet Gynecol 2001;184:463–469.
4. Frankel H. Determination of body mass index. JAMA 1986;255:1292.
5. National Institute of Health Consensus Development Conference Statement. Health implications of obesity. Ann Intern Med 1985;103:147–151.
6. Strauss R. Operative risk of obesity. Surg Gynecol Obstet 1978;146: 286–290.
7. Kral J. Morbid obesity and related health risks. Ann Intern Med 1983;103:1043.
8. Must A, Jacques P, Dallal G, et al. Long term morbidity and mortality of overweight adolescents. N Engl J Med 1992;327:1350–1355.
9. Kushner R. Body weight and mortality. Nutr Rev 1993;51:127–136.
10. Brodsky J. Anesthetic management of the morbidly obese patient. Int Anesthesiol Clin 1986;24:93–103.
11. Mann G. The influence of obesity on health (first of two parts). N Engl J Med 1974;291:178–185.
12. Buckley F. Anesthetizing the morbidly obese patient. ASA Refresher Courses 1989;243:1–6.
13. Hood D, Dewan D. Anesthesia and obstetric outcome in morbidly obese parturients. Anesthesiology 1993;79:1210–1218.
14. Garbaciak JJ, Richter M, Miller S, et al. Maternal weight and pregnancy complications. Am J Obstet Gynecol 1991;164:1306.
15. Mason E, Doherty C, Maher J, et al. Super obesity and gastric reduction procedure. Gastroenterol Clin N Am 1987;16:495.
16. Bray GA. Obesity. In Fauci AS, Marlin JB, Braunwald E, et al. (eds) Harrison's Principles of Internal Medicine, 14th Ed. New York: McGraw-Hill, 1998:454–462.
17. Reisin E, Frohlich E. Cardiovascular and respiratory pathophysiological alterations. Arch Intern Med 1981;141:431–434.
18. Oberg B, Poulsen T. Obesity: an anesthetic challenge. Acta Anaesthesiol Scand 1996;40:191–200.
19. Albert M, Hashimi M. Obesity and the heart. Am J Med Sci 1993; 306:117–123.
20. Amad K, Brennan J, Alexander J. The cardiac pathophysiology of chronic exogenous obesity. Circulation 1959;32:740–745.
21. Alaxander J. Obesity and cardiac performance. Am J Cardiol 1964; 14:860–865.
22. De Divitiis O, Fazion S, Petitto M, et al. Obesity and cardiac function. Circulation 1981;4:477–482.
23. Aggarwal N, Shibutani K, SanFilippo J, Del Guercio L. Hemodynamic and respiratory changes in surgery of the morbidly obese. Surgery (St. Louis) 1982;92:226–234.
24. Bjerkedal T. Overweight and hypertension. Acta Med Scand 1957;159: 13–26.
25. Kannel W, Brand N, Skinner J, et al. The relation of adiposity to blood pressure and development of hypertension: The Framingham study. Ann Intern Med 1967;67:48–59.
26. Malcom R, Von J, O'Neil PM, et al. Update on the management of obesity. South Med J 1988;81:632–639.
27. Backman L, Freyschuss V, Hallberg D, Melcher A. Cardiovascular function in extreme obesity. Acta Med Scand 1973;193:437–446.
28. Alexander J. Obesity and the circulation. Mod Concepts Cardiovasc Dis 1963;32:799–803.
29. Messerli P, Nunez B, Ventura H, Snyder D. Overweight and sudden death. Increased ventricular ectopy in cardiopathy of obesity. Arch Intern Med 1987;147:1725–1728.
30. Lauer M, Anderson K, Kannei W, Levey D. The impact of obesity on left ventricular mass and geometry. JAMA 1991;266:231–236.
31. Alaxander J. The cardiomyopathy of obesity. Prog Cardiovasc Dis 1985;27:325–334.
32. Ford L. Heart size. Circ Res 1976;39:297–303.
33. Paul D, Hoyt J, Boutros A. Cardiovascular and respiratory changes in response to change of posture in the very obese. Anesthesiology 1976; 45:73–78.
34. Teeple E, Ghia J. An elevated pulmonary wedge pressure resulting from an upper respiratory obstruction in an obese patient. Anesthesiology 1983;59:66–68.
35. Luce J. Respiratory complication in obesity. Chest 1980;78:626–631.
36. Fox G. Anaesthesia for intestinal short circuiting in hte morbidly obese with reference to the pathophysiology of gross obesity. Can Anaesth Soc J 1975;22:307–322.
37. Anderson J, Rasmussen J, Eriksen J. Pulmonary function in obese patients scheduled for jejuno-ileostomy. Acta Anaesthesiol Scand 1977; 21:346–351.
38. Bodell GN. Pulmonary function in obese persons. J Clin Invest 1955; 37:1049.
39. Burnwell CS, Raben ED, Whaley RD, et al. External obesity associated with alveolar hypoventilation: a Pickwickian syndrome. Am J Med Sci 1956;21:811.
40. Berger K, Ayappa I, Chatr-Amontri B, et al. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. Chest 2001;120:1231–1238.
41. Montserrat J, Ferrer M, Hernandez L, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized

controlled study with an optimized placebo. Am J Respir Crit Care Med 2001;164:608–613.
42. Lam A, Grace D, Penny F, Vezina W. Prophylactic intravenous cemitidine reduces the risk of acid aspiation in morbidly obese patients. Anesthesiology 1983;59:A242.
43. Vaughan R, Bauer S, Wise L. Volume and pH of gastric juice in obese patients. Anesthesiology 1975;43:686–689.
44. Philippe J, Guillaume F, Mohamed M, et al. Gastric residue is not more copious in obese patients. Anesth Analg 2001;93:1621–1622.
45. Kissebah A, Bydelingum N, Murray R, et al. Relation of body height and fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982:130–144.
46. Mabie W, Ratts T, Ramanathan K, Sibai B. Circulatory congestion in obese hypertensive women. A subset of pulmonary edema in pregnancy. Obstet Gynecol 1988;72:553–558.
47. Eng M, Butler J, Bonica JJ. Respiratory function in pregnant obese women. Am J Obstet Gynecol 1975;123:241–245.
48. Blass NH. Regional anesthesia in the morbidly obese patient. Reg Anesth 1979;4:20–22.
49. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth 1995;74:638–642.
50. Lewis D, Chessor A, Edwards M, et al. Obstructive sleep apnea during pregnancy resulting in pulmonary hypertension. South Med J 1998;91:761–762.
51. O'Brien TF. Lower esophageal sphincter pressure (LSP) esophageal function in obese humans. J Clin Gastroenterol 1980;2:145–148.
52. Brock-Utne J, Dow T, Dimopoulos G, et al. Evidence refuting a role for increased abdominal pressure in the pathogenesis of heartburn associated with pregnancy. Br J Anaesth 1981;53:381–384.
53. Kliegman R, Gross T. Perinatal problems of the obese mother and her infant. Obstet Gynecol 1985;66:299–306.
54. Johnson S, Kolberg B, Verner M, Railsback L. Maternal obesity in pregnancy. Surg Gynecol Obstet 1987;164:431–437.
55. Gross T, Sokol R, King K. Obesity and pregnancy: risk and outcome. Obstet Gynecol 1980;56:446–450.
56. Tracey T, Miller G. Obstetric problems of the massively obese. Obstet Gynecol 1968;33:204–208.
57. Perlow J, Morgan M, Montgomery D, et al. Perinatal outcome in pregnancy complicated by massive obesity. Am J Obstet Gynecol 1992; 167:958–962.
58. Garbaciak J, Richter M, Miller S, et al. Maternal weight in pregnancy complications. Obstet Gynecol 1985;152:238–245.
59. Krotkiewski M, Bjornetorp P, Sjostrom L, et al. Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. J Clin Invest 1983;72:1150.
60. Maeder E, Barno A, Mecklenburg F. Obesity: a maternal high risk factor. Obstet Gynecol 1975;45:669–671.
61. Kaunitz A, Hughes J, Grimes D, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–612.
62. Rochat R, Koonin L, Atrash A, Jewett J. Maternal mortality in the United States: report from the maternal mortality collaborative. Obstet Gynecol 1988;72:91–97.
63. May W, Greiss F. Maternal mortality in North Carolina: a four year experience. Am J Obstet Gynecol 1989;161:555–561.
64. Endler G, Mariona F, Solol R, Stevenson L. Anesthesia-related mortality in Michigan 1972–1984. Am J Obstet Gynecol 1988;158:187–193.
65. Sachs B, Oriol N, Ostheimer G, et al. Anesthetic related maternal mortality 1954–1985. J Clin Anesth 1989;1:333–338.
66. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
67. Wolfe HM, Sokol RJ, Marties SM, et al. Maternal obesity: A potential source of error in sonographic prenatal diagnosis. Obstet Gynecol 1990;76:339.
68. Johnson JW, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. Am J Obstet Gynecol 1992;167:353–372.
69. Peckham CH, Chrstianson RE. The relationship between pre-pregnancy weight and certain obstetric factors. Am J Obstet Gynecol 1971;111:1–7.
70. Ratner RE, Hamme LH, Isada NB. Effects of gestational weight gain in morbidly obese women. 1. Maternal morbidity. Am J Perinatol 1991;8:21–24.
71. Kaiser PS, Kirby RS. Obesity as a risk for cesarean section in a low-risk population. Obstet Gynecol 2001;97:39–43.
72. Crane SS, Wojtowycz MA, Dye D, et al. Association between pre-pregnancy obesity and the risk of cesarean delivery. Obstet Gynecol 1997; 89:213–216.
73. Chauhan SP, Magann EF, Carroll CS, et al. Mode of delivery for the morbidly obese with prior cesarean delivery: vaginal versus repeat cesarean section. Am J Obstet Gynecol 2001;185:349–354.
74. Kumari AS. Pregnancy outcome in women with morbid obesity. Int J Gynaecol Obstet 2001;73:101–107.
75. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med 1998;338:147–152.
76. Waller DK, Millis JL, Simpson JL, et al. Are obese women at higher risk for producing malformed offspring? Am J Obstet Gynecol 1994;170:541.
77. Bilenka B, Ben-Shlomo I, Cozacov C, et al. Fertility, miscarriage and pregnancy after vertical banded gastroplasty operation for morbid obesity. Acta Obstet Gynecol Scand 1995;74:42–44.
78. Printen KJ, Scott D. Pregnancy following gastric bypass for the treatment of morbid obesity. Am Surg 1982;48:363–365.
79. Deital M, Stone E, Kasssaml HA, et al. Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. J Am Coll Nutr 1988;7:147–153.
80. Satmar-Fones G. Some psychiatric aspects of morbidly obese patients in relation to jejunoileal and gastric bypass procedures. Can J Surg 1984;27:133.
81. Houston M, Raynor B. Postoperative morbidity in the morbidly obese parturient woman: supraumbilical and low transverse abdominal approaches. Am J Obstet Gynecol 2000;182:1033–1035.
82. Hodgkinson R, Hussain FJ. Cesearean section associated with gross obesity. Br J Anaesth 1980;52:919–923.
83. Morrow C, Hernandez W, Townsend D, Disaia P. Pelvic celiotomy in the obese patient. Obstet Gynecol 1977;127:335.
84. Douglas MJ, Flanagan ML, McMorland GH. Anesthetic management of a complex morbidly obese parturient. Can J Anaesth 1991;38:900–903.
85. Shnaider R, Ezri T, Szmuk P, Larson S. Combined spinal-epidural anesthesia for cesarean section in a patient with peripartum dilated cardiomyopathy. Can J Anaesth 2001;48:681–683.
86. Patel J. Anaesthesia for LSCS in a morbidly obese patient. Anaesth Intensive Care 1999;27:216–219.
87. Buckley FP, Robinson NB, Simonowitz DA, Dellinger ED. A comparison of anesthetic and analgesic regimens for upper abdominal surgery. Anesthesia 1983;38:840–851.
88. Narang VP, Linter SP. Failure of extradural blockade in obstetrics: a new hypothesis. Br J Anaesth 1988;60:402–404.
89. Wallace DH, Currie JM, Gilstrap LC, Santos R. Indirect sonographic guidance for epidural anesthesia in obese pregnant patients. Reg Anesth 1992;17:233–236.
90. Hamilton CL, Riley ET, Cohen SE. Changes in the position of epidural catheters associated with patient movement. Anesthesiology 1997;86: 778–784.
91. Faure E, Moreno R, Thisted R. Incidence of postdural puncture headache in morbidly obese parturients. Reg Anesth 1994;19:361–363.
92. Blass NH, Abouleish A, Dalmeida R. Low thoracic epidural anesthesia for massively obese parturients. Anesthesiology 1994;81:A1172.
93. Bailey PL, Lu JK, Pace NL, et al. Effects of intrathecal morphine on the ventilatory response to hypoxia. N Engl J Med 2000;343:1228–1234.
94. Norris MC. Are combined spinal-epidural catheters reliable? Int J Obstet Anesth 2000;9:3–6.
95. Suzuki N, Koganemaru M, Onizuka S, Takasaki M. Dural puncture with a 26-gauge spinal needle affects spread of epidural anesthesia. Anesth Analg 1996;82:1040–1042.

96. Tseuda K, Debrand M, Zeok SS, et al. Obesity supine sudden death syndrome: report of two morbidly obese patients. Anesth Analg 1979;58: 345–347.
97. Abouleish EI. Epinephrine improves the quality of spinal hyperbaric bupivacaine for cesarean section. Anesth Analg 1987;66:395–400.
98. Norris MC. Height, weight and the spread of subarachnoid hyperbaric bupivacaine in the term parturient. Anesth Analg 1988;67:555.
99. Green NM. Distribution of local anesthetics within the subarachnoid space. Anesth Analg 1985;64:715–730.
100. Pitkanen MT. Body mass and spread of spinal anesthesia with bupivacaine. Anesth Analg 1987;66:127–131.
101. McCullogh W, Littlewood DG. Influence of obesity on spinal anesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1986;58:610–614.
102. Milligan KR, Cramp P, Schatz D, et al. The effect of patient position and obesity on the spread of epidural analgesia. Int J Obstet Anesth 1993; 2:134–136.
103. Gautam PL, Kathuria S, Kaul TK. Infiltration block for cesarean section in morbidly obese parturient. Acta Anaesthesiol Scand 1999;43: 580–581.
104. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetrics anesthesia. Anesthesiology 1992;77:67–73.
105. Lee JJ, Larson RH, Buckley JJ, Roberts RB. Airway maintenance in the morbidly obese. Anesthesiol Rev 1980;7:33–36.
106. Datta S, Briwa J. Modified laryngoscope for endotracheal intubation of obese patients. Anesth Analg 1981;60:120.
107. Parmet JL, Colonna-Romano P, Horrow JC, et al. The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult tracheal intubation along with difficult mask ventilation. Anesth Analg 1998;87:661–665.
108. Archer GW, Marx GF. Arterial oxygen tension during apnea in parturient women. Br J Anaesth 1974;46:358–360.
109. Berthould M, Peacock J, Reilly C. Effectiveness of preoxygenation in morbidly obese patients. Br J Anaesth 1991;67:464–466.
110. Gambee M, Hetzka R, Fisher D. Preoxygenation techniques: comparison of three minutes and four breaths. Anesth Analg 1987;1987: 468–479.
111. Practice guidelines for management of the difficult airway: a report by the American Society of Anesthesiologists task force on management of the difficult airway. Anesthesiology 1993;78:597–602.
112. Harmer M. Difficult and failed intubation in obstetrics. Int J Obstet Anesth 1997;6:25–31.
113. Godley M, Ramachandra Reddy AR. Use of LMA for awake intubation for cesarean section. Can Anaesth Soc J 1996;43:299–302.
114. Cohn AI, Hart RT, McGraw SR, Blass NH. The Bullard laryngoscope for emergency airway management in a morbidly obese parturient. Anesth Analg 1995;81:872–873.
115. Greenbelt DJ, Abernethy DR, Locniskar A, et al. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 1984;61:27–35.
116. Weinstein JA. Pharmacodynamics of vecronium and atracurium in the obese surgical patient. Anesth Analg 1988;67:1149.
117. Bentley JB, Vaughan RW, Gandolfi AJ, Cork RC. Halothane biotransformation on obese and nonobese patients. Anesthesiology 1982;57:94–97.
118. Bentley JB, Vaughan RW, Miller MS, et al. Serum inorganic fluoride levels in obese patients during and after enflurane aneshesia. Anesth Analg 1979;58:409–412.
119. Higuchi H, Satoh T, Arimura S, et al. Serum inorganic fluoride levels in mildly obese patients during and after sevoflurane anesthesia. Anesth Analg 1993;77:1018–1021.
120. Strube PJ, Hulands GH, Halsey MJ. Serum fluoride levels in morbidly obese patients: enflurane compared with isoflurane anaesthesia. Anaesthesia 1987;42:685–689.
121. Juvin P, Vadam C, Malek L, et al. Postoperative recovery after desflurane, propofol, or isoflurane anesthesia among morbidly obese patients: a prospective, randomized study. Anesth Analg 2000;91:714–719.
122. Cork RC, Vaughan RW, Bentley JB. General anesthesia for morbidly obese patients—an examination of postoperative outcomes. Anesthesiology 1981;54:310–313.
123. Shankar KB, Moseley H, Kumar Y, Vemula V. Arterial to end-tidal carbon dioxide tension difference during Caesarean section anaesthesia. Anaesthesia 1986;41:698–702.
124. Hedenstierna G, Santesson J. Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. Acta Anaesthesiol Scand 1976;20:248–254.
125. Salam MR, Dalal FY, Zygmunt MP, et al. Does PEEP improve intraoperative arterial oxygenation in grossly obese patients? Anesthesiology 1978;48:280–281.
126. Soderberg M, Thompson D, White T. Respiration, circulation and anaesthetic management in obesity. Investigation before and after jejunal bypass. Acta Anaesthesiol Scand 1977;21:55–61.
127. Joris J, Sottiaux T, Chiche JD, et al. Bi-level CPAP (BIPAP) reduces the postoperative restrictive pulmonary syndrome in obese patients afer gastroplasty. Br J Anaesth 1994;72(suppl 1):A111.
128. Eriksen J, Andeson J, Rasmussen JP. Postoperative pulmonary function in obese patients after upper abdominal surgery. Acta Anaesthesiol Scand 1977;21:336–341.
129. Fox GS, Whaley DG, Beven D. Anaesthesia for the morbidly obese. Br J Anaesth 1981;53:811–816.
130. VanDercar DH, Martinez AP, DeLisser EA. A potential contraindication for patient-controlled analgesia. Anesthesiology 1991;74:623–624.
131. Rawal N, Sjostrand U, Christofferson E, et al. Comparison of intramuscular and epidural morphine for postoperative ambulation and pulmonary function. Anesth Analg 1984;63:583–592.

7
Breech Presentation, Malpresentation, and Multiple Gestation

Rakesh B. Vadhera and Gregory J. Locksmith

Malpresentation

Before labor, the fetus normally assumes a vertex presentation characterized by vertical orientation in the maternal abdomen with a flexed head leading the rest of the body through the maternal pelvis (Figure 7.1). A malpresentation refers to any deviation in fetal orientation or cephalic flexion. Malpresentation is estimated to occur in 5% of all deliveries[1] and is associated with increased maternal and perinatal morbidity and mortality (Table 7.1).

Numerous factors are associated with malpresentation, the most common being prematurity. Of all deliveries performed before 32 weeks gestation, approximately 10% are nonvertex, and of all those performed before 28 weeks, up to 33% are malpresentations. At term, this figure decreases to 3%.[2,3] Other predisposing conditions include intrauterine factors such as multiple gestation, grandmultiparity, polyhydramnios, oligohydramnios, Mullerian anomalies, tumors, and high or low placental implantation. Malpresentation also is associated with fetal congenital anomalies such as myotonic dystrophy, aneuploidy, or other disorders that impair motor function or muscle tone. Cephalopelvic disproportion, either from an enlarged fetal head or a contracted maternal pelvis, is also related to nonvertex presentations.

Most of the increase in perinatal morbidity and mortality can be explained by prematurity, but congenital anomalies also play a role. Other untoward outcomes include birth trauma and asphyxia secondary to umbilical cord prolapse. The major maternal complications associated with malpresentation are related to cesarean delivery. Trauma to the maternal pelvis with instrumental vaginal delivery is also probably more likely.

Noncephalic Presentations

Breech Presentation

In the breech presentation, the fetal axis is longitudinal with its caudal pole in the lower uterine segment and the head in the fundus. The breech-presenting fetus is categorized as one of three types (Figure 7.2). The frank breech has the hips flexed and the knees extended. The feet typically are located high in the uterine fundus near the head. The complete breech has the hips and knees flexed with the feet in the lower portion of the uterus. The incomplete (footling) breech has one or both hips extended, with one or both feet presenting in the lowest portion of the uterus.

The diagnosis of breech may be made by abdominal palpation or by digital vaginal examination. During labor, the astute labor and delivery nurse may become suspicious after noting unusually copious amounts of thick meconium passing from the vagina. Location of the fetal heart rate high in the maternal abdomen may also prompt wariness in the attendant. Physical examination, however, has been found to be inaccurate for detection of malpresentation.[4] Ultrasound is recommended for confirmation when any malpresentation is even slightly suspected.

Intrapartum Management

In the United States, the vaginal delivery rate for breech presentation has decreased dramatically, from 88% in 1970 to 21% in 1985.[5] Since 1985, the rate probably has fallen even further. Similar trends have been reported in Canada[6] and in Europe.[7] The decline in opportunities for vaginal breech delivery has created concern about whether young physicians today can acquire the experience and skill to perform the procedure safely. In a 1993 survey of faculty physicians from the National Institute of Child Health and Human Development-sponsored Maternal-Fetal Medicine Units Network, 55% responded that residency training for vaginal breech delivery was inadequate, and 39% believed that residents were adequately trained.[8] Because of concerns about its relative safety, the erosion in skill for performing this technique among obstetricians-in-training, and the relative safety and convenience of cesarean delivery, the vaginal breech delivery is fast becoming a dying art.

The reported perinatal mortality rate for breech-presenting fetuses varies from 9% to 25%,[9–11] three to five times that of nonbreech, term infants. The excess deaths associated with

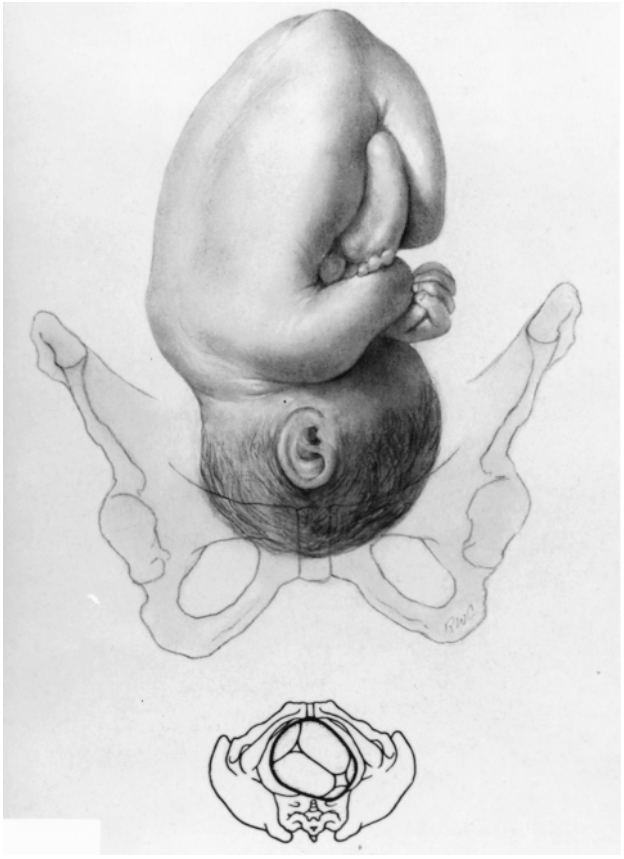

FIGURE 7.1. Fetus in the vertex presentation. The head is the leading body part, and the neck is flexed. (From Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, Clark SL, eds. Williams Obstetrics, 20th edn. Norwalk, CT: Appleton & Lange, 1997, p. 256. Used by permission.)

TABLE 7.1. Risks associated with malpresentation.

Maternal	Fetal
Cesarean delivery	Preterm delivery
Genital tract trauma	Congenital anomalies
	Birth trauma
	Umbilical cord prolapse

breech presentation may be completely explained by lethal anomalies or prematurity, both of which are strongly correlated with breech presentation. Whether route of delivery independently influences the outcome of the term breech infant is a matter of great interest and debate.

Large systematic reviews, mostly of retrospective cohort studies, have concluded that planned vaginal delivery, compared with planned cesarean delivery, is associated with small but statistically significant increases in neonatal morbidity and mortality.[12,13] A retrospective analysis of the Swedish Medical Birth Registry demonstrated increased rates of mortality, low 5-min Apgar scores, and birth injury in breech infants born vaginally compared to those born by elective cesarean.[14]

Two randomized, controlled studies of reasonable methodologic quality were published in the early 1980s that compared planned vaginal delivery with planned cesarean in women with breech presentation at term.[15] In a study of women with frank breech presentation,[16] maternal morbidity was increased in the elective cesarean group, and no difference was noted in neonatal outcomes. In another study of women with nonfrank breech presentation,[17] maternal outcomes were not clearly documented, and no difference was noted in neonatal outcomes. Both these studies were restricted to fetuses with an estimated weight between 2500 and 3800 g and mothers with adequate X-ray pelvimetry. Although these studies were prospective, and the subjects were randomly allocated to treatment and control groups, the results need to

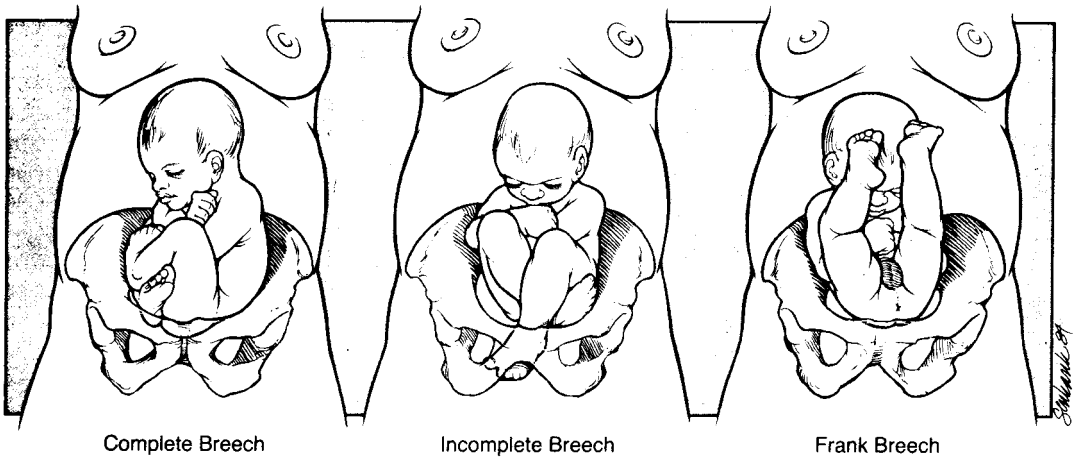

FIGURE 7.2. Types of breech presentation. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 479. Used by permission.)

Box 7.1. Essential requirements for planned vaginal breech delivery.

At least two operators experienced in vaginal breech delivery
Continuous fetal monitoring
Continuous capability to perform cesarean delivery
Anesthesia staff available at all times
Neonatal resuscitation team present at birth

be reviewed with some skepticism. The method of randomization was not specified in either study, and more than half the subjects who were allocated to the vaginal delivery groups were delivered ultimately by cesarean. Furthermore, the sample sizes in both studies were insufficient to detect small but perhaps clinically important differences in neonatal outcomes.

A recent study that drew 2088 subjects from 121 centers and 26 countries compared maternal and neonatal outcomes in those who had planned vaginal versus planned cesarean delivery.[18] In this study, adverse neonatal outcome was significantly less frequent in the planned cesarean group, and no difference was found in the incidence of adverse maternal outcome. This study can be questioned primarily with regard to the generalizability of its results because more than half its subjects delivered in countries with high perinatal mortality rates. Nevertheless, at the present time, the preponderance of the evidence supports a policy of planned cesarean for breech presentation at term.

Vaginal Breech Delivery

In some circumstances, a woman will give informed consent for vaginal delivery or may present to the hospital with the breech already partly delivered. Detailed descriptions of techniques for vaginal breech delivery are presented in obstetrical textbooks.[1,19,20] Several elements are essential if vaginal breech delivery is planned (Box 7.1). Well-trained and experienced operators should be in attendance and should have continuous capability to perform immediate cesarean. Anesthesiologists should be promptly available at all times during labor with the operating room readied. Although controversial in the past, epidural anesthesia is likely to improve parturient comfort and cooperation, particularly in the second stage if Piper forceps are required to assist with delivery of the aftercoming head. Attendants skilled in neonatal assessment and resuscitation should be present at the birth.

Piper forceps (Figure 7.3) can be an invaluable tool for facilitating delivery of the aftercoming head. A reduction of 50% in the morbidity of breech delivery has been ascribed to forceps use.[21] The risk of hyperextension injury is reduced because the forceps maintain flexion of the fetal head during descent through the pelvis, thus obviating traction force on the trunk and spine. Furthermore, delivery may be completed earlier after proper application of forceps. By reducing the amount of time from delivery of the trunk to delivery of the head, the risk of hypoxia may be lowered. Some obstetricians advocate the routine use of Piper forceps for vaginal breech to ensure controlled delivery of the head and to maintain optimal operator skill for deliveries that will actually require their use.

Perinatal morbidity can be minimized if certain criteria are met before deciding to proceed with vaginal breech delivery (Box 7.2). The type of breech greatly influences the potential complications. The frank breech is associated with the most favorable outcome rates. Because the feet occupy less space in the maternal pelvis than the buttocks, the risk of umbilical cord prolapse or entanglement is higher with the footling breech.[22] Additionally, the feet are not as effective for cervical dilation as the wedge created by the frank breech. The risk of head entrapment within an incompletely dilated cervix, therefore, is higher in the footling breech. The complete breech typically converts spontaneously to footling or frank

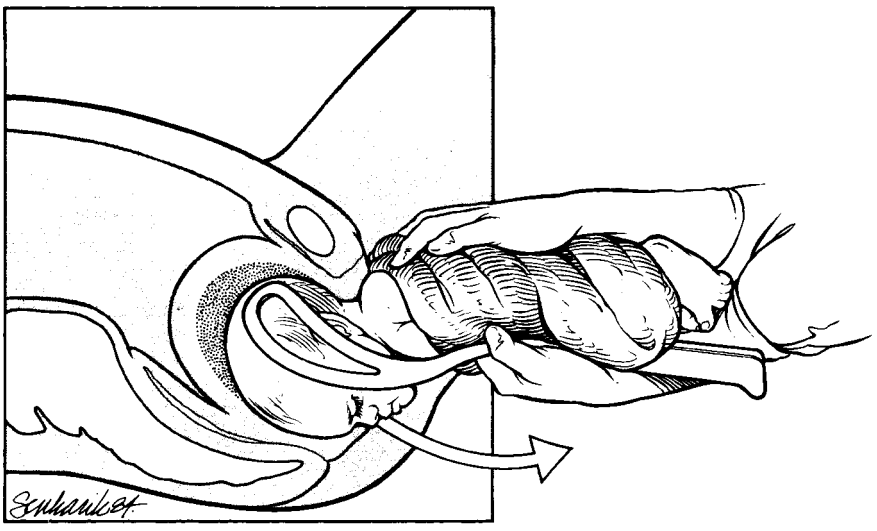

FIGURE 7.3. Extraction of the aftercoming head of a breech-presenting fetus using Piper forceps. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 484. Used by permission.)

Box 7.2. Contraindications to planned vaginal breech delivery of a viable fetus.

Estimated fetal weight less than 1500 g
Incomplete (footling) breech presentation
Contracted maternal pelvis
Hyperextension of the fetal neck
Fetal hydrocephalus

presentation. Consequently, the complete breech is at lower risk for complications than the footling breech but is at higher risk than the frank breech.

The weight of the fetus is also an important consideration. Most of the data and the studies of highest methodological quality are analyses of term breech infants of normal birth weight. Improved survival has been demonstrated with cesarean delivery for breech infants weighing between 1000 and 1500 g.[23–27] Retrospective evidence suggests that vaginal breech delivery before 32 weeks is associated with a higher risk of neonatal intraventricular hemorrhage.[28] Although data regarding vaginal breech delivery of macrosomic infants are scarce, a fetal weight greater than 4000 g presents concerns about the potential for dystocia, head entrapment, and neonatal injury. The generally preferred route of delivery for breech infants estimated to weigh less than 1500 g or more than 4000 g, therefore, is cesarean section. To compensate for potential errors in fetal weight estimation, many obstetricians raise the lower limit to 2000 g and decrease the upper limit to 3500 g.

An assessment of adequacy of the maternal pelvis should be made either clinically or with radiographic studies. The radiographic studies provide the advantage of objective and easily reproducible measurements but are costly and expose the mother and fetus to radiation. Computed tomography is preferred over X-ray pelvimetry because of its lower dose of radiation (250 mrad versus 1–5 rad)[29] and its capability to measure diameters in the axial plane. No studies have ever demonstrated that outcome with vaginal breech delivery is improved when radiographic pelvimetry is used as an alternative to simple clinical pelvimetry.

Finally, before proceeding with vaginal delivery, the obstetrician should ascertain that the fetal neck is not hyperextended and that hydrocephalus is not present. Hyperextension of the neck is associated with high risk of fetal spinal cord injury during vaginal breech delivery.[30–32] Excessive enlargement of the fetal head presents theoretical concerns about an increased risk of head entrapment in the maternal pelvis.

With planned vaginal breech delivery, cesarean should be performed for arrest of dilation in the active phase of labor, arrest of descent in the second stage, fetal compromise as demonstrated by fetal heart rate monitoring, or any other condition that would prompt section of a vertex-presenting infant. Presumably because of the higher rates of adverse perinatal outcome, obstetricians tend to have a lower threshold for performing intrapartum cesarean in the breech that was originally intended to be delivered vaginally. Some authors recommend cesarean delivery rather than oxytocin for augmentation of labor when an arrest is attributed to inadequate uterine contractions.[20]

Fetal Head Entrapment

Entrapment of the fetal head is a true obstetric emergency. Head entrapment occurs when the fetal legs and torso deliver through an incompletely dilated cervix, and the head becomes stuck. Encountered most often in preterm and incomplete (footling) breech presentations, it can result in birth trauma, asphyxia, and perinatal death. The anesthesiologist is a valuable ally in managing fetal head entrapment. Administration of nitroglycerine or a halogenated anesthetic agent often provides a sufficient amount of uterine relaxation to allow the head to pass through the cervix. If the cervix cannot be reduced over the fetal head after attempts at uterine relaxation, Dührssen's incisions in the cervix may be required. This technique requires the operator to make two to three incisions in the cervix at 2, 6, or 10 o'clock (Figure 7.4). Excellent exposure is critical, and general or dense regional anesthesia is necessary for the patient to be able to tolerate the procedure.

Transverse and Oblique Presentation

Abnormalities in axial lie are rare, occurring in approximately 1 in 300 deliveries.[3,33] Perinatal mortality is increased with transverse and oblique presentation, primarily from complications of prematurity, but also because of congenital anomalies, umbilical cord prolapse, and traumatic delivery. Maternal mortality and morbidity are also increased and are usually related

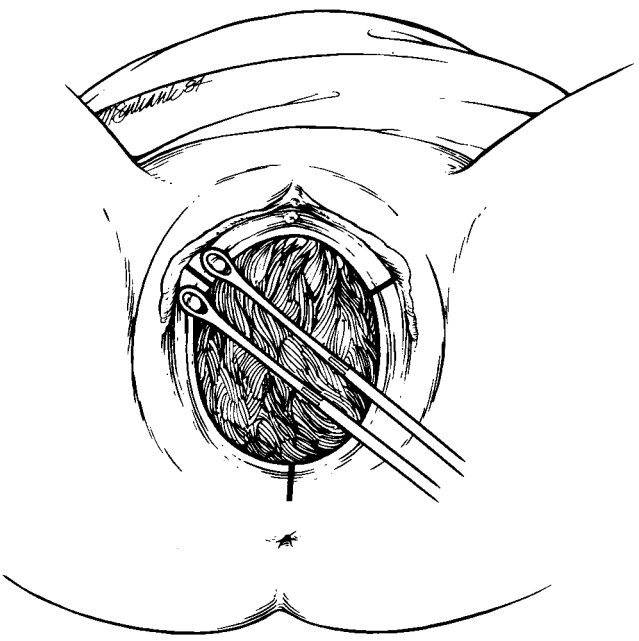

FIGURE 7.4. Proper location for Dührssen's incisions. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 633. Used by permission.)

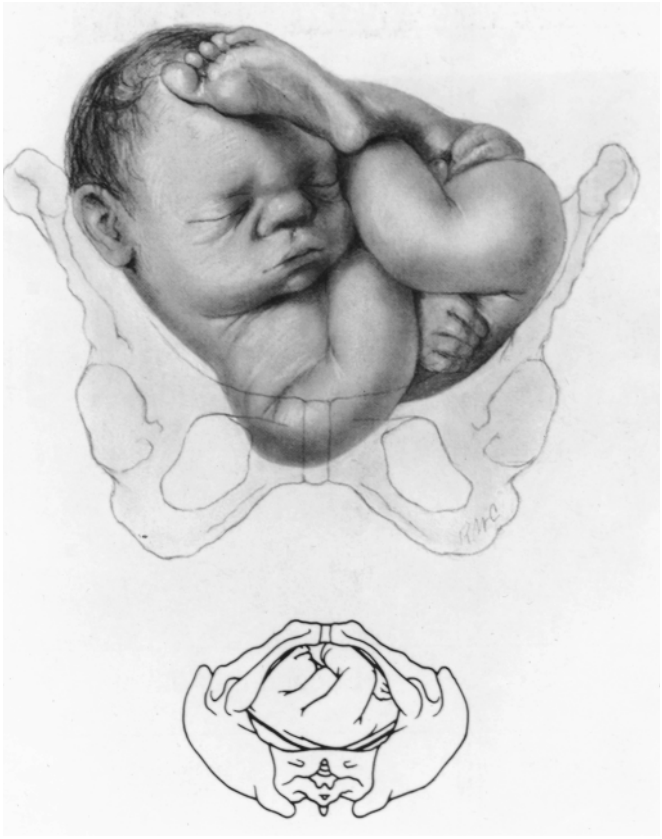

FIGURE 7.5. Transverse presentation. (From Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, Clark SL, eds. Williams Obstetrics, 20th edn. Norwalk, CT: Appleton & Lange, 1997, p. 257. Used by permission.)

to postcesarean infection, hemorrhage, or traumatic delivery. A transverse-presenting fetus is shown in Figure 7.5.

Vaginal delivery from a transverse or oblique presentation is a high-risk venture and should not be undertaken. Attempts of internal podalic version and breech extraction are unlikely to be successful and are associated with high perinatal mortality.[3,34] External cephalic version (ECV) at term, before onset of labor, and before rupture of membranes is a reasonable alternative to planned cesarean delivery for transverse-presenting fetuses. One group[35] found that 86 of 96 women with transverse presentations that were converted to cephalic and who subsequently had labor induced were able to deliver vaginally. The woman with transverse or oblique presentation of a viable fetus who is in active labor or with ruptured membranes should be delivered by cesarean section.

External Cephalic Version

External cephalic version can be performed on breech, oblique, and transverse-presenting fetuses. It offers the potential for vaginal delivery while minimizing the risks of cord prolapse, head entrapment, and other complications that are often attributed to vaginal breech delivery. The Cochrane Library review of six prospective, randomized studies found that ECV was associated with a 58% reduction in noncephalic births and a 48% reduction in cesarean delivery.[36] The investigators also concluded, however, that not enough evidence existed to assess the risks of the procedure.

During ECV, the operator applies gentle constant pressure over the fetal head and breech to rotate the fetus into a cephalic presentation (Figure 7.6). The procedure should be performed at 36 to 38 weeks. Before 36 weeks fetuses often convert to cephalic presentation spontaneously, obviating the need for the procedure. After 38 weeks the fetus continues to grow, but the amniotic fluid volume begins to decline, reducing the likelihood for success. Reported success rates vary between 40% and 75%.[37]

Complications associated with external version include umbilical cord compression, placental abruption, fetal-to-maternal hemorrhage, and uterine rupture. On rare occasions, prolonged fetal bradycardia develops during the procedure, requiring emergency cesarean. Possibilities for failure or

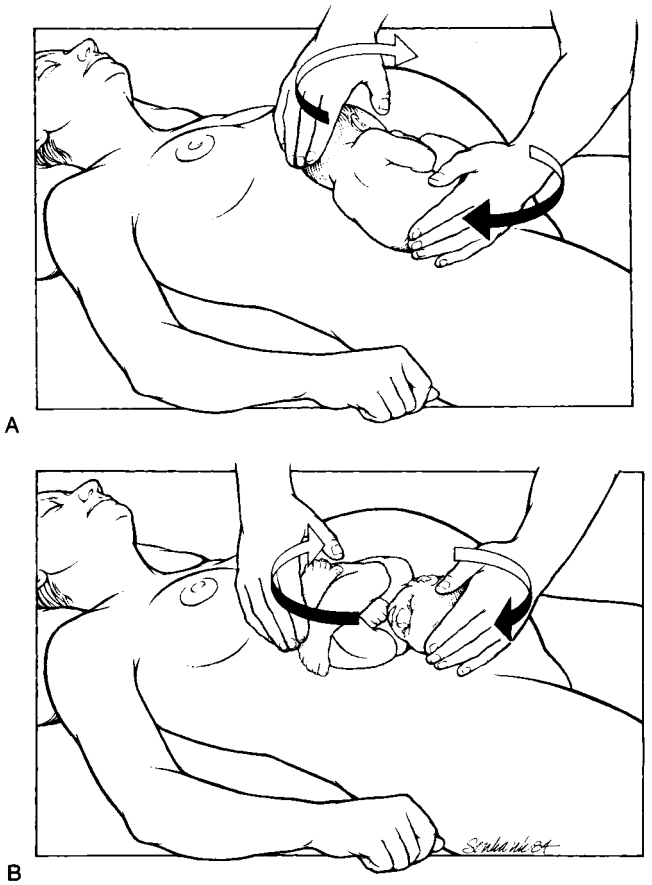

FIGURE 7.6. Technique for external cephalic version (*ECV*). Fetal presentation before (**A**) and after (**B**) successful external version. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 489. Used by permission.)

spontaneous reversion to a noncephalic presentation also exist. Factors associated with reduced likelihood of success include oligohydramnios, anterior placental location, maternal obesity, deep pelvic engagement of the breech, and posterior positioning of the fetal back.[38]

Various adjunctive techniques such as tocolytic drugs, fetal acoustic stimulation, and epidural anesthesia have been used to facilitate ECV. Of these techniques, tocolysis is the best studied. The rationale for using tocolytic medications before attempting external version is to maintain relative uterine relaxation during external manipulation of the uterus. The largest randomized trials initiated to evaluate tocolysis as an adjunct to external version have demonstrated a modest improvement in successful version but no ultimate lowering of the cesarean rate.[39–41] In one study of fetal acoustic stimulation, exposed women had six times the successful version rate compared to those who were not exposed.[42]

Anesthesia Considerations for a Breech Delivery

Although the latest data suggest a better fetal outcome with a planned cesarean delivery,[18] the different options possible when a parturient presents with a breech at or near term are the following:

- ECV
- Proceed with vaginal delivery, mostly assisted to avoid or limit fetal hypoxia
- Planned cesarean section
- Emergency cesarean section if there is any danger to maternal or fetal well-being during vaginal delivery

The ideal time to discuss anesthetic and analgesic management of a breech delivery with the parturient is when the obstetrician discusses the various options of breech delivery with the parturient. Preoperative evaluation in such high-risk patients can minimize maternal and fetal risks. A good and early communication between the obstetric and anesthesia teams is paramount in counseling and providing a care plan catered to the specific needs of a particular woman and also in formulating a secondary plan if the obstetric management changes because of the safety of mother or the fetus.

Anesthetic services may be required for ECV, normal or assisted vaginal breech delivery, complete breech extraction, delivery of entrapped fetal head, or elective or emergency cesarean section (Figure 7.7). Acute fetal distress, sudden cord

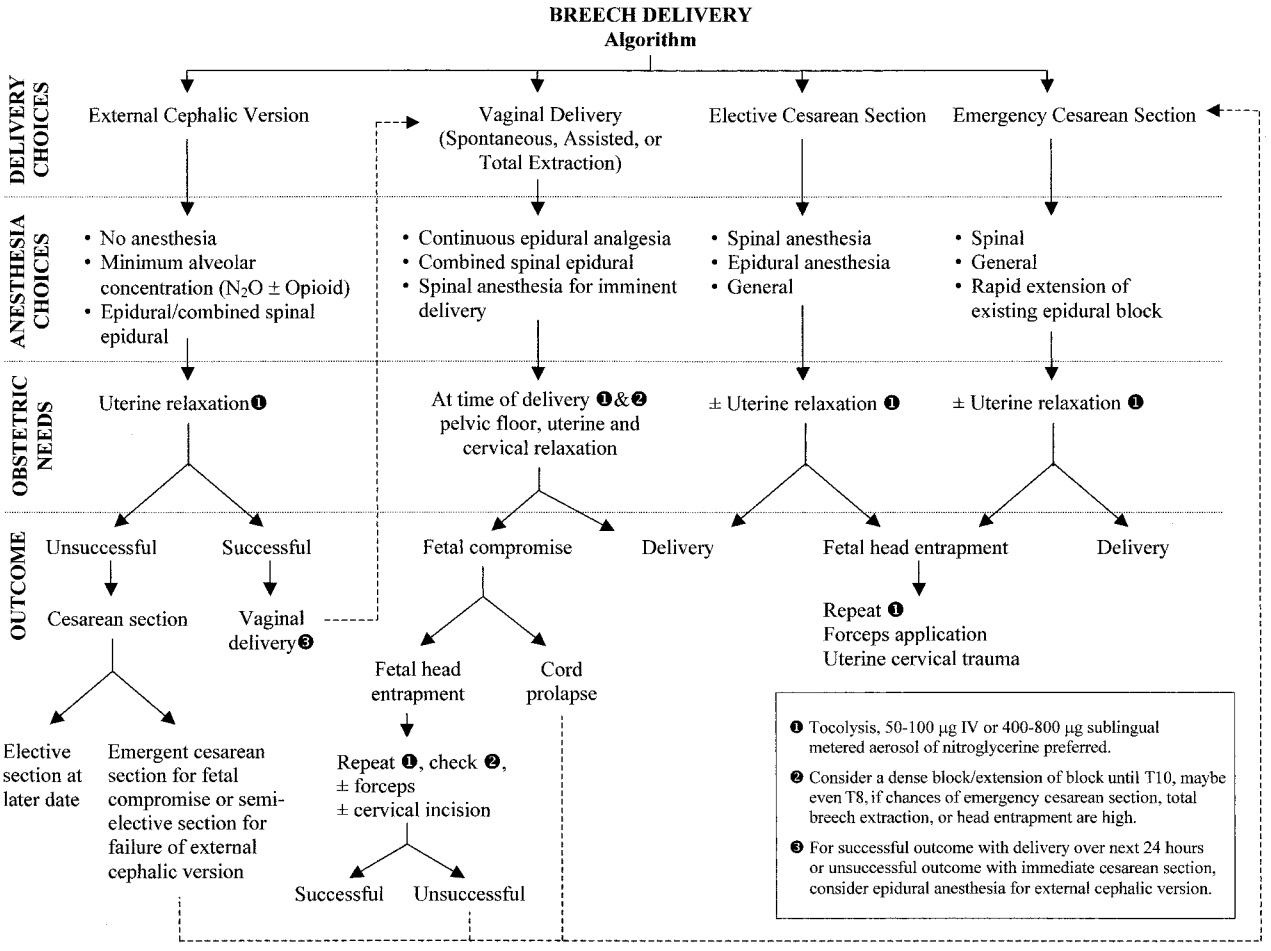

FIGURE 7.7. Breech delivery algorithm.

TABLE 7.2. Preanesthetic preparation for breech and multiple gestation.

Discussion
With obstetrician to formulate a detailed plan
With patient of all the options available for different delivery plans
Preanesthetic evaluation
Must include airway assessment
Symptoms and signs of supine hypotension and hydration status
Preparation
Large-bore intravenous line
Aspiration prophylaxis
Blood for emergency transfusion (at least typed and screened, autologous, or crossmatched if uterine atony or hemorrhage expected)
Equipment and drugs for the following:
Additional IV line, fluid and blood warmer, and rapid infusion pumps
Subarachnoid block
Rapid sequence induction of general anesthesia
Treatment of hypotension (vasopressors, left uterine displacement)
Possible uterine relaxation (nitroglycerine, terbutaline, halogenated anesthetic agents)
Uterine contraction (pitocin, methergine, prostaglandin $F_{2\alpha}$)
Neonatal resuscitation
Extension of epidural analgesia for cesarean section
Execution
Good functioning labor epidural, especially if airway assessment points to difficult airway management
When delivery is imminent, extend the block with higher concentration local anesthetics, and be ready for assisted breech delivery, delivery of aftercoming head including forceps application, or cesarean section for any fetal compromise

prolapse, or entrapment of fetal head can lead to emergency fetal delivery by cesarean section, which makes it absolutely necessary that adequate time is spent for the patient, equipment, and drug preparation, which should include airway assessment, keeping woman NPO but hydrated with a large-bore IV placement, and giving aspiration prophylaxis (Table 7.2).

External Cephalic Version

Successful ECV helps reduce the perinatal mortality and morbidity associated with breech delivery or cesarean section. Most obstetric unit protocols now demand that an anesthesiologist be present during the procedure, ready for emergency cesarean section. The role of anesthesiologists has changed in the last decade from being just a standby monitoring service to actively providing analgesia and assuring the safety of the mother during the procedure. The widespread use of tocolytic agents, β-sympathomimetics or nitroglycerine, and immediate confirmation of successful version and fetal well-being with Doppler ultrasonography have increased the success rate of vaginal delivery.[43,44] Depending on the gestational age and fetal maturity, the outcomes for ECV are: successful version with expectant delivery immediately or at a later date; unsuccessful version with expectant vaginal breech delivery or cesarean section, the latter being a more likely option; or emergency cesarean section for fetal distress. The anesthetic involvement during ECV is challenging, as the analgesic technique needs to offer the flexibility to cover most of these outcomes, if possible.

Parturient comfort can be provided with either an intravenous opiate, with or without inhalational analgesia with nitrous oxide in oxygen, or with epidural analgesia. The limitation of using the former technique is the amount of opiates that can be given safely, which must be monitored closely in case the fetus is to be delivered urgently and to ensure that the patient remains awake and conscious. However, there is some controversy regarding whether regional anesthesia, whether epidural or combined spinal epidural, substantially increases the success rate of ECV. Anesthesia care providers are reluctant to offer an invasive procedure with associated complications and risks for such a procedure, whereas some obstetricians fear that administration of regional anesthesia may encourage them to use excessive force, which may increase the risk of perinatal morbidity and mortality.

Epidural anesthesia is still infrequently used for ECV, even after several recent studies that have demonstrated that epidural or combined spinal epidural anesthesia during ECV significantly increases the success rate. Three of these studies, one retrospective and two prospective, compared the success rate of ECV with or without epidural anesthesia.[45–47] The success rate significantly increased, by 26% to 37% when ECV was performed with epidural anesthesia as compared to ECV performed without epidural anesthesia. Two other studies evaluated ECV performed under epidural anesthesia after a previous failed attempt when epidural anesthesia was not used. Neiger et al.[48] and Rozenberg et al.[49] were successful in turning 9 of 16 and 27 of 68 patients, respectively, where ECV had failed previously performed under no anesthesia. In a recent study, Birnbach et al.[50] reported a success rate of 80% when ECV was performed under combined spinal epidural block, compared to a 33% success rate in patients who did not receive any analgesia. Opponents of the use of regional anesthesia for ECV find the success rates in control groups in these studies uncharacteristically low. A review by Zhang et al.[37] of United States literature, which included 15 articles, showed an average success rate of 65% when ECV was performed without any regional anesthesia. In a prospective trial of ECV performed with or without spinal anesthesia, spinal anesthesia demonstrated no increase in the ECV success rate (44% in the spinal group versus 42% in controls).[51] With the amount of information available so far, The American College of Obstetricians and Gynecologists concluded, "there is not enough information available to make a recommendation supporting or opposing use of epidural anesthesia."[52] Complications during ECV (i.e., changes in the fetal heart rate patterns in as many as 10% of cases, fetal–maternal transfusion in 18% of cases, and placental separation in 0.2%–2% of cases) might necessitate emergency cesarean delivery.

Labor Analgesia

Labor analgesia for an expectant vaginal breech delivery ideally should be discussed with the parturient and obstetrician as soon as such a decision is made. Epidural analgesia for breech labor and delivery has been controversial in the past.

This controversy arose from the fear of some obstetricians that epidural analgesia prolongs the second stage of labor, inhibits the woman's ability to push effectively, increases the incidence of complete breech extraction with increased perinatal morbidity and mortality, and may cause fetal and neonatal depression. This belief has changed so much in the last decade that, in most of the modern high-risk obstetric units, epidural analgesia is the preferred technique if a vaginal delivery, either spontaneous or assisted, is expected. The belief changed over time because of the observations that epidural analgesia offers the advantage of superior and optimal pain relief, inhibition of early pushing (especially in a premature breech), an alert and cooperative patient who can push adequately with proper coaching, perineal relaxation that helps breech extraction and application of forceps to extract the aftercoming head, improved neonatal status, and the option to extend anesthesia for emergency cesarean section and therefore avoid the need for general anesthesia.

Boyson and Simpson[53] in 1960 noted a decrease in neonatal morbidity when breech births were managed with caudal anesthesia. Crawford[54] reported a slightly prolonged second stage of labor (10 min), a decreased incidence of low Apgar scores at 5 min, and no increase in the incidence of fetal extraction in parturients who received epidural analgesia. A number of studies in the 1970s confirmed that epidural analgesia is the analgesic method of choice in breech labor and vaginal delivery.[55–58] Although the second stage of labor is lengthened slightly (10–30 min),[54,59] most of these studies found that the incidence of breech extraction or cesarean section is not increased by the use of epidural analgesia.[56,59] In fact, the incidence of breech extraction or cesarean section may be decreased because of effective controlled pushing efforts by an alert, cooperative patient.[54] In most of these studies, epidural analgesia did not influence the Apgar scores, umbilical cord acid–base values, or neonatal outcome.[54,55,57,59] Breeson et al.[58] found improved neonatal condition when the breech was delivered with epidural analgesia, whereas Confino et al.[59] reported lower 1-min Apgar scores in fetuses weighing more than 2500 g (however, 5-min Apgar scores, perinatal morbidity, and maternal complications were the same in both groups). Darby and Hunter[57] reported that epidural analgesia, compared to either narcotics or N_2O inhalation analgesia, was associated with a higher 5-min Apgar scores. Van Zundert et al.[60] reported a retrospective review of the expulsion time, the interval between the first expulsive effort by the mother, and the delivery of the baby as indicators of fetal risk. In their study, patients received an intermittent bolus injection of 0.125% bupivacaine with 1:800,000 epinephrine. The expulsion time was remarkably short (mean time, only 8.7 min). In contrast, Chadha et al.,[61] in a retrospective review, observed that epidural analgesia was associated with an increased need for oxytocin augmentation of labor, longer first (approximately 3 h) and second stages (approximately 18–30 min) of labor, and a greater cesarean section rate if cesarean section was performed during the second stage of labor.

Establishment of a good functioning epidural block, in early stages of labor, is desirable and mostly rewarding. An epidural block should be initiated and titrated to desired dermatome, with a low concentration of local anesthetic. Either bupivacaine less than 0.25% or ropivacaine less than 0.2% produces the desired analgesic effect without much motor block. Addition of an opioid can reduce the concentration of local anesthetic. In the parturient who is at high risk of operative or assisted deliveries or who is expected to present with a difficult airway management, it is advisable to initiate the block with only a local anesthetic to achieve a desired sensory level to confirm the placement of the epidural catheter before starting the infusion. If there is any doubt regarding the efficacy of the block, the catheter should be replaced. For continued labor analgesia, most anesthesiologists administer the lower concentrations of local anesthetics (bupivacaine 0.0625%–0.125% or ropivacaine 0.1%), with an opioid (fentanyl 2.5 μg/mL) by continuous infusion to avoid extensive motor block. For parturients with earlier complaints of rectal pressure and wanting to push prematurely during the late first stage of labor, or for intrauterine manipulation, breech extraction, or applications of forceps to aftercoming head during the second stage of labor, the epidural block can be rapidly augmented with 1.5% to 2% lidocaine with 1:200,000 epinephrine, 2% to 3% 2-chloroprocaine, 0.5% ropivacaine, or 0.25% to 0.5% bupivacaine to provide sacral analgesia. Augmenting the block with higher concentrations is justifiable if the parturient is more likely to deliver by a cesarean section. It is important that parturients with breech presentation deliver in an operating room in case an emergency abdominal delivery must be performed.

Occasionally, a subarachnoid block can be administered during the late first stage or second stage of labor for breech extraction or to prevent precipitous delivery, especially of a premature fetus. Although the subarachnoid route provides rapid onset of excellent analgesia and perineal relaxation without any fetal depression, it can also cause excessive motor block with higher concentrations of local anesthetics and can limit the patient's ability to push effectively. For pregnant women in advanced labor with no epidural, a combined spinal anesthesia technique with 2.5 mg bupivacaine with or without an opiate provides a rapid analgesia without any motor block.[62]

Fetal Head Entrapment

Fetal head entrapment of the aftercoming head is the greatest fear involved with a vaginal breech delivery. A parturient with a low birth weight breech may experience a premature urge to push. Premature babies, breeches less than 32 weeks, and incomplete breeches are more likely to suffer from fetal head entrapment because of a smaller body (compared to size of the head) that may deliver before the cervix is fully dilated. The presence of an anesthesia care provider for all deliveries, even if the epidural analgesia does not exist, is important. Once the fetal head is entrapped, the time to accomplish fetal head delivery is extremely limited; otherwise, fetal well-

being is severely compromised. The choices, under such limiting circumstances, are to either relax the cervical muscles, uterine smooth muscle, and pelvic floor muscles or to proceed with an operative delivery—the former choice being more commonly practiced before the obstetricians proceed with the operative delivery.

In the past, general anesthesia was more commonly used in these situations. Succinylcholine provided the perineal relaxation, while the high concentration of a volatile halogenated agent (e.g., halothane, enflurane, isoflurane) provided uterine and cervical relaxation.[63] However, administration of high concentrations of volatile agents without airway protection or rapid sequence induction of anesthesia in a lithotomy position is unsafe and hazardous. Delivery of the entrapped head can also be achieved safely by providing a dense and adequate T10 level of analgesia with epidural analgesia and uterine relaxation with a tocolytic. A well-functioning lumbar epidural not only provides sacral analgesia—it inhibits early pushing during the first state of labor before the cervix is completely dilated and allows intrauterine manipulations—but also causes adequate pelvic floor and perineal relaxation for the aftercoming head and probably reduces the incidence of fetal head entrapment. If diluted solutions of bupivacaine, either 0.0625% with an opioid or 0.125% with or without an opioid, are inadequate to prevent pushing during the first stage of labor, or if the delivery is imminent, the epidural analgesia can be augmented with higher concentrations (0.25%) of bupivacaine, with or without an opioid. For breech extraction, head entrapment, applications of forceps for the aftercoming head, or cesarean sections, 2% lidocaine with epinephrine 1:200,000, with or without sodium bicarbonate, or 3% 2-chloroprocaine may be administered to rapidly augment the block to a desired appropriate level. If uterine and cervical relaxation becomes necessary, a rapid and transient effect can be produced by amyl nitrate or nitroglycerine.[64–66] Either 50 to 100 μg intravenous nitroglycerine or 400 to 800 μg sublingual aerosol spray of nitroglycerine will mostly produce a reliable result.[67,68] In the absence of hypovolemia, neither of the routes or doses cause a clinically significant hypotension.

Cesarean Section

For a breech-presenting fetus, many obstetricians consider an elective cesarean section to be the safest route of delivery[18]; this is particularly true in North America today as the technique of vaginal breech delivery becomes less and less frequently practiced and taught. If the breech is to be delivered by elective cesarean section, regional anesthesia, either a subarachnoid or lumbar epidural block, has become the preferred technique over general anesthesia. Breech cesarean delivery performed under general anesthesia not only carries a 17-fold greater risk of morbidity when compared to the regional anesthesia techniques,[69] it has also been shown to result in lower Apgar scores in 41% of parturients, when compared to only 7% of parturients who received regional anesthesia.[70] Crawford and Davies[70] in this study also observed that epidural anesthesia protected the neonate when uterine incision to delivery time exceeds 90 s. A fetal compromise, either because of severe fetal distress, a prolapsed cord, or fetal head entrapment, might necessitate induction of general anesthesia to expedite the delivery. Many anesthesiologists now believe that a subarachnoid block may be administered just as rapidly. General anesthesia is still preferred by many obstetricians. The reluctance of obstetricians to deliver the fetus under regional anesthesia comes not only from the possibility of a delay in delivering an already compromised fetus, but also from the notion that general anesthesia might provide the uterine relaxation, if needed, for controlled assisted delivery of the aftercoming head with or without the application of forceps. Darby and Hunter,[57] however, noted no difference in the neonatal outcome after epidural or general anesthesia. An adequately dense epidural block near delivery can be safely extended rapidly to perform a cesarean section if the need arises from any fetal compromise. 2-Chloroprocaine (3%) or lidocaine (2%) with epinephrine, 1:200000, and sodium bicarbonate can augment the block, from an existing T10 to the T4–T5 level, for a rapid operative delivery. Relaxation of uterus with a tocolytic might be required for the aftercoming head.

Abnormal Cephalic Presentations

Face Presentation

Normal vertex presentation requires the neck to be fully flexed during active labor. Full flexion permits the smallest diameter of the fetal skull, the suboccipitobregmatic diameter (Figure 7.8), to pass through the maternal pelvis. Full flexion also

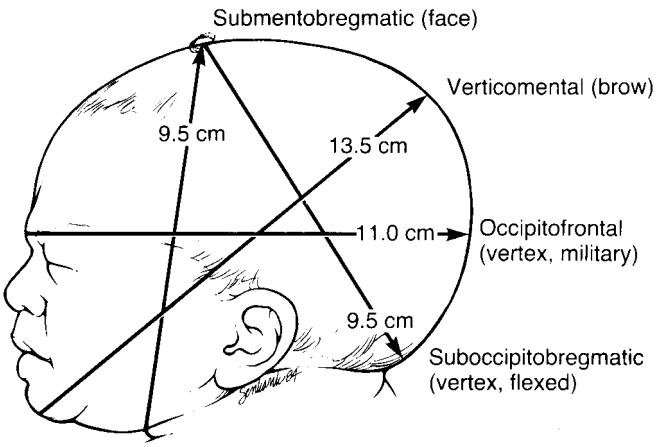

FIGURE 7.8. Diameters of the typical fetal skull. The shortest diameter passed through the head with the fetal neck either full flexed (vertex presentation) or extended (face presentation). (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 372. Used by permission.)

allows the neck to extend during expulsion of the head. The face presentation is characterized by full extension of the fetal neck as the head descends through the pelvis (Figure 7.9). The incidence of face presentation is approximately 1 in 500 live births.[1] Risk factors for face presentation are similar to those for other malpresentations. One review found that 60% of infants who presented with face presentation were malformed,[71] whereas another study found that either a fetal anomaly or a contracted maternal pelvis was associated with 90% of face presentations.[72]

Normally, the face presentation is diagnosed during active labor, after the cervix has dilated appreciably. The face-presenting fetus can deliver vaginally, but cesarean delivery is ultimately required in up to 60% of cases.[72] The mechanism of labor is critical for success. In contrast to the vertex-presenting infant, who can deliver vaginally from an occiput-anterior or -posterior position, the face-presenting infant can deliver safely only from a mentum-anterior position (Figure 7.10). Additionally, the incidence of fetal heart rate[47] and labor[33] abnormalities is probably higher among face presentations.

Pitocin may be used with face presentation for labor abnormalities that are secondary to inadequate uterine contractions. The progress of labor and fetal condition, however, require intensive monitoring. Attendants must be able to recognize problems promptly and make quick and decisive actions to correct disorders. Prolonged labor has been associated with markedly increased perinatal mortality for face-presenting infants.[73] Cesarean delivery should be performed for labor abnormalities, nonreassuring fetal heart rate patterns, and persistent mentum-posterior position. Some infants in the mentum-posterior position rotate spontaneously to the mentum-anterior position. Attempts to manually rotate the position to mentum-anterior or to flex the head into a vertex presentation increase both maternal and perinatal risks needlessly.[74]

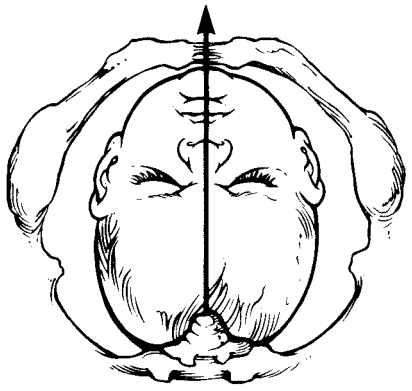

FIGURE 7.10. Mentum-anterior position of the face presentation. The face-presenting infant can deliver safely only from this position. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 473. Used by permission.)

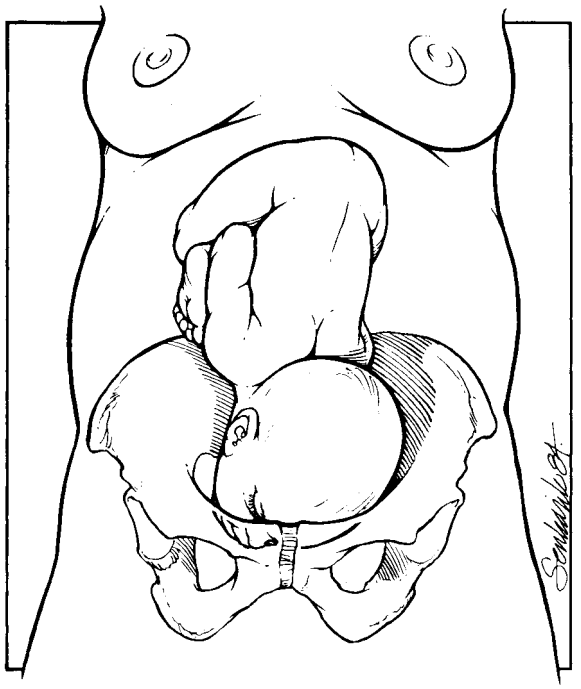

FIGURE 7.9. Face presentation. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 473. Used by permission.)

Brow Presentation

The fetal neck in the brow presentation is deflexed but not as fully extended as in the face presentation (Figure 7.11). The reported incidence varies widely, probably because it is not easily detected early in labor and because it typically converts spontaneously to vertex or face presentation. Risk factors for brow presentation are cephalopelvic disproportion, prematurity, and multiparity.[33,75]

As with face presentation, brow presentation is usually detected during digital vaginal examination, relatively late in labor. Usually the brow presentation converts to vertex or, less often, to face presentation. Persistent brow presentation generally requires cesarean delivery for arrest of labor: the diameter of the fetal skull traversing the pelvis (the verticomental diameter; see Figure 7.8) is typically too wide to permit passage if the infant is near term. Attempting to flex the head into a vertex presentation, either manually or with forceps, is discouraged. Pitocin may be used with brow pre-

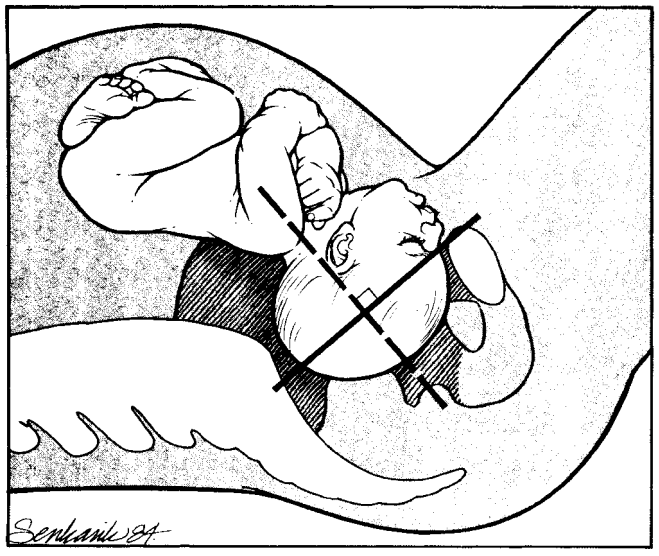

FIGURE 7.11. Brow presentation. The neck is extended but not as fully extended as with a face presentation. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 475. Used by permission.)

sentation for labor abnormalities that are secondary to inadequate uterine contractions.

Compound Presentation

Compound presentation refers to the situation in which an extremity presents simultaneously with the head or breech. Most commonly, an arm presents along with the vertex (Figure 7.12). The incidence of compound presentation is approximately 1 in 1000 live births.[33,76] Risk factors include prematurity, multiparity, and large maternal pelvic size. Prematurity is the most consistently associated factor. Perinatal mortality associated with compound presentation is approximately 10%.[33] This rate is mostly related to prematurity, but asphyxia resulting from umbilical cord prolapse is also probably a contributing factor. Less commonly, neurologic or musculoskeletal injury of the presenting extremity can result. Protracted labor also has been reported.[77]

Compound presentation is often occult, with the diagnosis made at delivery. In other instances, it is recognized during active labor during digital vaginal examination. During labor, the accompanying extremity usually retracts spontaneously as the major pole descends through the pelvis. Even without spontaneous retraction, safe vaginal delivery can be accomplished. Practitioners should not attempt to manually replace the extremity higher in the pelvis because of the potential for maternal and perinatal morbidity.[76] Indications for cesarean delivery include cord prolapse, fetal heart rate abnormalities, and arrests of labor.

Multifetal Gestation

Twins

Twinning can occur by one of two mechanisms. Monozygotic twins result from a single fertilized ovum dividing into two distinct individuals after a variable number of cellular divisions. As a rule, such twins are genetically identical. Dizygotic twins result from two separate sperm fertilizing two distinct ova. These twins are typically as genetically similar as other true siblings. The incidence of monozygotic twinning is approximately 4 per 1000 live births.[19,78] This rate is virtually constant throughout the world and is not affected by maternal age, race, parity, or genetics. In the United States, the frequency of dizygotic twinning is approximately twice the rate of monozygotic twinning.

Dizygotic twinning is affected by many factors, particularly maternal use of ovulation-inducing drugs and assisted reproductive technologies such as in vitro fertilization. The frequency of dizygotic twinning is low in Asians, intermediate in Caucasians, and high in Africans.[78] The incidence of dizygotic twinning also increases with maternal age and parity.

Monozygotic twinning was once thought to be unaffected by infertility therapy; however, evidence now suggests that

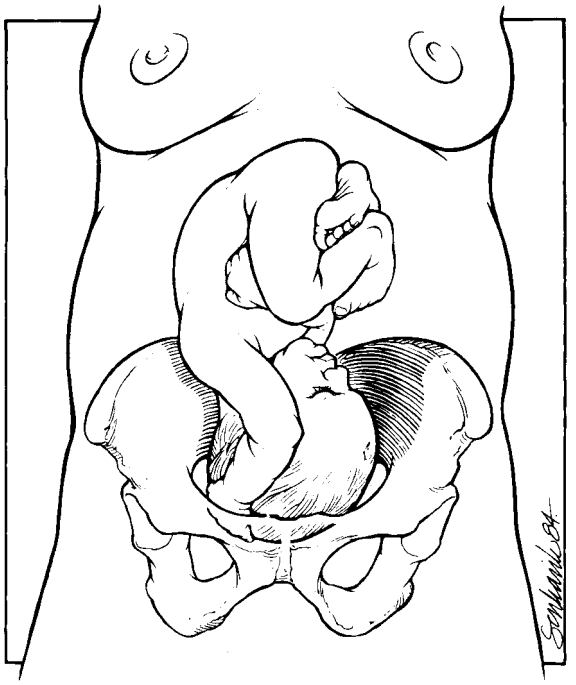

FIGURE 7.12. Compound presentation. The left arm is presenting along with the vertex. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 477. Used by permission.)

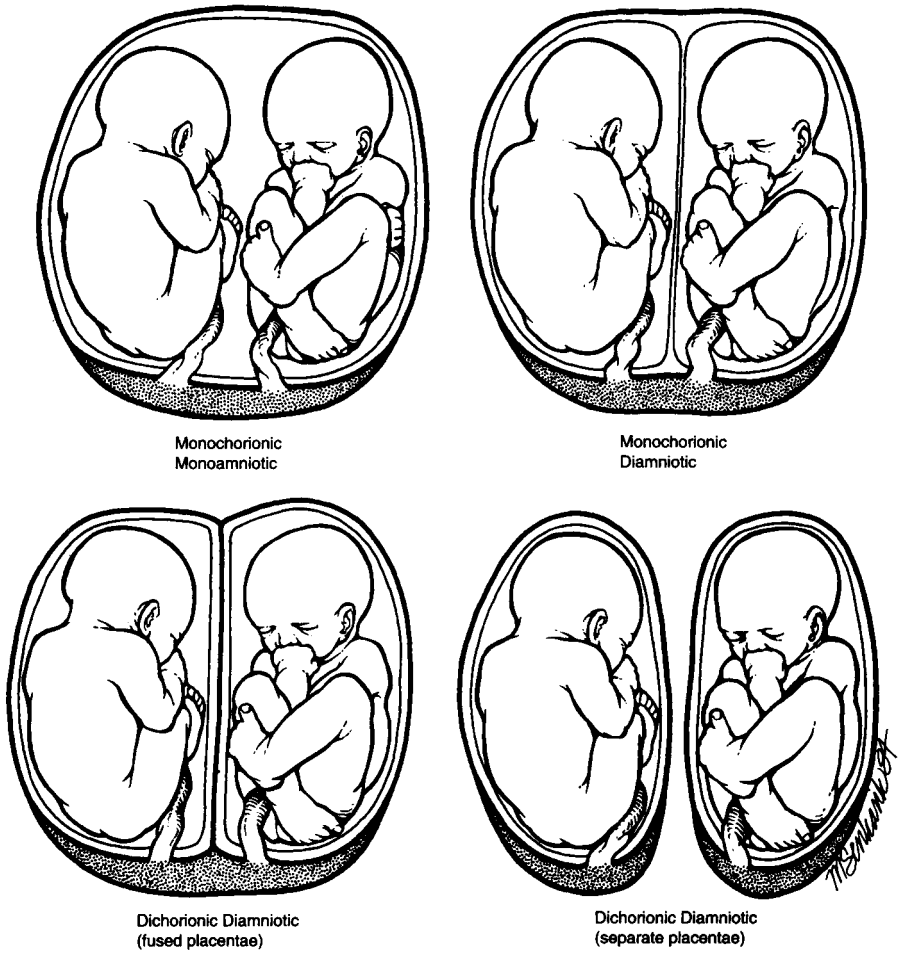

FIGURE 7.13. Placental types of twin pregnancies. (From Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996, p. 822. Used by permission.)

monozygotic twinning is doubled in association with use of ovulation-inducing agents.[79] From the mid-1970s through 1990, the use of ovulation-inducing agents and assisted reproductive technologies has actually led to a growth in the number of multiple births, which is rising faster than the number of singleton births associated with fertility therapy.[80] This increase in multiple births is seen primarily in older, typically white, highly educated women.[81]

Placentation

Twins can be described in terms of the degree of fusion between the placentas and membranes (Figure 7.13). These distinctions are important determinants of risk for the pregnancy. The membranes of every pregnancy consist of an outer chorion and an inner amnion. In dizygotic twin pregnancies, each twin is surrounded by its own separate amniochorionic shell. This membrane pattern is known as dichorionic-diamniotic placentation. The placentas may be fused or separate. In monozygotic twins, depending on the amount of time that has elapsed from fertilization until division into distinct individuals, placentation could be dichorionic diamniotic, monochorionic diamniotic, or monochorionic monoamniotic (Table 7.3).

Perinatal risk rises substantially with greater sharing of amniochorionic compartments. In general, dichorionic twins have the lowest risk and monoamniotic twins have the highest. Regardless of the placental type, perinatal morbidity and mortality are far greater in twins than in singletons (Table 7.4). The principal factor responsible for the increase in ad-

TABLE 7.3. Relationship between the time of embryonic cleavage and placentation of monozygotic twins.

Placentation	Days from fertilization to cleavage
Dichorionic, diamniotic	2–3
Monochorionic, diamniotic	3–8
Monochorionic, monoamniotic	8–13
Conjoined twins	13–15

TABLE 7.4. Risks associated with multiple gestation.

Maternal	Fetal
Preeclampsia	Preterm delivery
Gestational diabetes	Growth restriction
Anemia	Birth defects
Postpartum hemorrhage	Placenta previa
	Placental abruption
	Cord accidents
	Malpresentation
	Twin–twin transfusion syndrome[a]

[a]Seen only in monochorionic, diamniotic twins.

verse outcomes is preterm delivery. Twins are also at increased risk for intrauterine growth restriction, birth defects, placenta previa and abruption, umbilical cord accidents, and malpresentation. Because of the increased placental mass associated with multiple gestation, mothers are at increased risk for preeclampsia and gestational diabetes. Anemia is also much more common, because blood volume is increased in mothers with twins compared to those with singletons. Postpartum hemorrhage secondary to uterine atony is also more common, presumably because the overdistended uterus may not involute properly after delivery.

Monochorionic twins, as a rule, have numerous vascular communications between them. Because of this phenomenon, growth disparity is much greater between monochorionic versus dichorionic twins. The growth disparity in monochorionic twins varies continuously from a few grams to the extreme discordance noted in the twin–twin transfusion syndrome (TTS). This condition is found only in monochorionic-diamniotic twins. The pathologic findings underlying TTS are anastomoses between high-pressure arterial systems of one twin and low-pressure venous systems of the other. The twin on the arterial side becomes a donor that transfuses the cotwin. The donor twin is typically anemic, growth restricted, and has oligohydramnios. The recipient often has polycythemia and polyhydramnios. Increased morbidity and mortality in monochorionic-diamniotic twins are related primarily to higher rates of stillbirths and preterm delivery, usually as a consequence of TTS. Preterm delivery in TTS results from spontaneous preterm labor, premature rupture of membranes, and induced delivery for fetal indications. Mortality rates range from 60% to 100%.[82,83]

Various procedures have been devised to improve outcome in twin pregnancies affected by TTS, such as serial amnioreduction, septostomy,[84] and laser occlusion of the communicating vessels. Serial amnioreduction has the advantages of being the most widely studied of these procedures and the easiest to perform. This procedure involves performing amniocentesis at selected intervals to remove large proportions of fluid surrounding the twin with polyhydramnios. A compilation of four descriptive studies published in the early 1990s has demonstrated a neonatal survival rate of 68% for 72 women with TTS treated with repeated amnioreduction.[85–88] The exact reason why this procedure is effective is unclear but probably involves reduced intraamniotic pressure resulting in better perfusion of one or both twins. The pathophysiology of polyhydramnios in TTS is not well understood.

Fetoscopically directed laser occlusion of the communicating vessels holds promise as a therapeutic option because it attempts to correct the underlying problem. Descriptive studies of TTS-affected pregnancies treated by fetoscopic laser have shown that neonatal outcome is similar to that achieved with therapeutic amniocentesis.[89–91] Disadvantages of this procedure are expense, complexity, and limited availability. Furthermore, because the fetoscope must be introduced through the anterior uterine wall and the vessels must be visualized and contacted directly by the laser source, patients with anteriorly oriented placentas are not good candidates for the procedure. Currently, the procedure is considered experimental.

Monoamniotic twins have the highest mortality rates. Most recent studies report the survival rate in monoamniotic twin pregnancies to be 40%.[92] Fortunately, monoamniotic twinning occurs very rarely, with an estimated incidence of less than 1% of all monozygotic twins. The high mortality occurs primarily because of umbilical cord occlusion, usually as a result of entanglement. Cord entanglement has been reported to occur in 70% of all monoamniotic twin pregnancies.[93] Cords can be intertwined, or one twin's cord can be wrapped around itself or around the cotwin.

Optimal management for monoamniotic twins has not been determined. Controversy surrounds the issues of monitoring for fetal well-being and timing of delivery. Some advocate continuous fetal monitoring starting at 24 weeks gestation and ending at 32 weeks with cesarean delivery. Others believe monitoring can be less intensive and that delivery can be delayed, at least until fetal lung maturity is confirmed. Cesarean section is generally agreed upon as the delivery mode of choice because the risk of cord entanglement between the twins is so high.

Diagnosis

Ideally, the diagnosis of twin gestation will have been made before the patient reports to the hospital for delivery. The degree to which twins are diagnosed antenatally varies between practices and is probably most strongly dependent on the frequency of a particular practice's use of antenatal ultrasound. A strong argument made in support of universal ultrasound screening for all pregnant women is that multiple gestation could be diagnosed early in pregnancy with near-100% accuracy. Patients could then receive specialized prenatal care, and planning for intrapartum management could be instituted well before delivery.

Multiple gestation is often suspected when the uterus measures large relative to the patient's menstrual dates. It may also

be suspected in a pregnant woman with an abnormally elevated serum alpha fetoprotein level during her second trimester. Ultrasound has the greatest sensitivity and specificity for diagnosing multiple gestation and should be performed to confirm the diagnosis in all cases where the suspicion is aroused.

Intrapartum Management

The plan for delivery of twins should take into consideration gestational age, estimated fetal weights, each twin's presentation, and the availability of adequate monitoring throughout labor. Vaginal delivery may be planned if the heart rates of both twins can be monitored continuously throughout labor. Additionally, real-time ultrasound should be available in the delivery room to assess the second twin's presentation immediately after the delivery of the first twin.

The presentation of each twin at the start of labor is an important consideration. Twin presentation combinations are generally classified into one of three groups: twin A vertex and twin B vertex (42%), twin A vertex and twin B nonvertex (38%), and twin A nonvertex (19%) (Figure 7.14).[94] If the criteria for monitoring during labor can be met, vaginal delivery should be planned if both twins present vertex. When the first twin presents nonvertex, most authorities agree that cesarean delivery should be planned regardless of the second twin's presentation. Intrapartum management for vertex–nonvertex twins is problematic because of the difficulties inherent in delivering the second twin.

After vaginal delivery of the first twin, three options exist for management of the second, nonvertex twin: cesarean delivery, ECV with anticipated vaginal delivery, and breech extraction. The first of these options is a poor choice because it subjects the parturient to the disadvantages of a full course of labor with vaginal delivery and to the morbidity of cesarean sections. Breech extraction of the second twin is probably the best choice if a skilled and experienced operator is on hand for the delivery. External cephalic version of the second twin would seem to be a prudent plan but is successful only 50% to 75% percent of the time, and the time spent attempting this maneuver diminishes the amount of time the operator has to perform breech extraction. One study has demonstrated that attempted external version of the second twin is associated with a higher rate of fetal distress, umbilical cord prolapse, and compound presentation compared to breech extraction of the second twin or cesarean delivery of both twins.[7,95] Another study comparing the same three management plans found that vaginal delivery of the first twin and breech extraction of the second twin was associated with the lowest hospital costs, the shortest durations of maternal and neonatal hospital stay, and the lowest rates of neonatal pulmonary and infectious disease.[96] In the absence of an obstetrician who is skilled at external version and vaginal breech delivery, any twin gestation in which one or more is presenting nonvertex should be delivered by cesarean section.

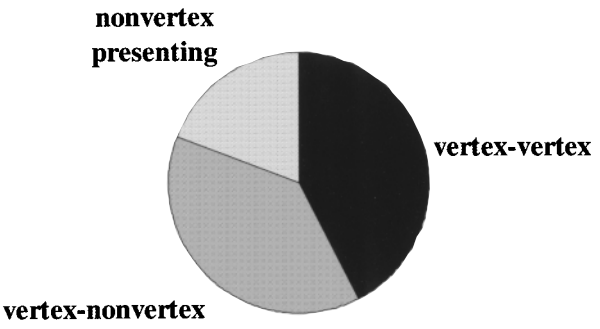

FIGURE 7.14. Potential combinations for twin presentation during labor and their relative frequencies of occurrence. (Data from Redick LF, Livington E. A new preparation of nitroglycerin for uterine relaxation. Int J Obstet Anesth 1995;4:14.)

Of all the complications associated with multifetal pregnancy, postpartum hemorrhage is among the most likely to result in maternal death. It is also one that is likely to take the physicians by surprise if they are not prepared. Regardless of the mode of delivery, uterotonic agents should be on hand. Oxytocin (20–40 units in 1000 mL crystalloid solution, rapidly) should be given prophylactically after all fetuses have been delivered. Second-line therapies include methylergonovine (0.2 mg intramuscularly), 15-methyl-prostaglandin $F_{2\alpha}$ (0.2 mg intramuscularly), or misoprostol (1000 mg rectally) (Table 7.5).

Vaginal Breech Delivery of the Second Twin

The controversy surrounding vaginal breech delivery of the second twin is similar to that concerning breech delivery of singletons. Several retrospective analyses suggest that outcome of the second twin is no different when breech extraction and planned vaginal delivery are compared.[97–101] One small prospective trial has been performed in women with twins at 35 weeks or greater.[100] No difference was noted in neonatal outcome, but a three- to fourfold increase in the rate of maternal infection was noted in mothers delivered by cesarean section.

The same criteria for vaginal breech delivery of a singleton can be applied for vaginal delivery of a nonvertex second twin. Estimated fetal weight should be between 1500 and 4000 g, maternal pelvimetry should be judged adequate, the neck of the breech-presenting fetus should not be extended, and two operators who are experienced in vaginal breech delivery should be present. Adequate regional or general anesthesia is essential for the extraction.

The initial step in the breech extraction of a second twin is known as internal podalic version. This step requires the operator to insert a hand into the uterus, identify and grasp the feet, and gently pull the feet to the introitus. Ideally, the membranes should remain intact. Real-time ultrasound may be use-

TABLE 7.5. Standard uterotonic agents for treatment of postpartum hemorrhage caused by uterine atony.

Agent	Dose	Route
Oxytocin	40 units in 1000 mL crystalloid solution	Rapid intravenous infusion
Methylergonovine (Methergine®)	0.2 mg	Intramuscularly
15(*s*)-Methyl prostaglandin $F_{2\alpha}$ (Hemabate®)	250 mg	Intramuscularly
Prostaglandin E_1 (misoprostol)	1000 mg	Rectally

ful in cases where identification of the feet is difficult. A systemic agent to effect uterine relaxation can also greatly facilitate the procedure. Once the feet have reached the introitus, the membranes can be ruptured, and maternal expulsive efforts should be the primary force to achieve further descent. The technique for the remainder of the delivery is the same as with a singleton vaginal breech.

Time Interval Between First and Vertex-Presenting Second Twin

After vaginal delivery of the first twin, the second usually delivers spontaneously within 15 min. In an observational study of 115 second twins at 34 or more weeks who were delivered vaginally, 70 delivered within 15 min of the first twin, 28 delivered between 16 and 30 min later, and 17 delivered more than 30 min after delivery of the first twin (Figure 7.15).[101] In this study, intravenous oxytocin was given to mothers whose uterine contractions became inadequate within 10 minutes after delivery of the first twin.

Theoretical concerns about prolonged delay between the first and second twin include the development of uterine inertia, rapid closing of the cervix, umbilical cord prolapse, and placental abruption. Before continuous fetal monitoring was widely available, these concerns prompted several authorities to recommend expediting delivery of the second twin so that the time interval between the first and second twins was no more than 30 min. Subsequent studies have demonstrated that with continuous fetal heart rate surveillance, safe vaginal delivery of the second twin can take place after an indefinite period of time.[101,102] If necessary, expeditious delivery can be achieved either by internal podalic version with breech extraction or by cesarean section. Caution should be exercised, however, with breech extraction of a second twin that was originally being managed expectantly. Over time, the cervix will begin to close even if a fetus remains in utero. Head entrapment may be encountered if breech extraction is performed when the cervix is incompletely dilated.

FIGURE 7.15. Average amount of time from vaginal delivery of the first twin to spontaneous vaginal delivery of the second twin. (Data from Skalley TW, Kramer TF. Brow presentation. Obstet Gynecol 1960;15:616–620.)

Higher-Order Multiple Gestations

Multifetal gestations with three or more fetuses face the same risks as twins but on a much larger scale. As with twins, the most common source of morbidity and mortality among higher-order multiples is prematurity. The average gestational age at spontaneous delivery for singletons is 40 weeks, for twins it is 37 weeks, and for triplets it is 33 to 35 weeks. Accordingly, the infant mortality rate has been calculated as 9 per 1000 for singletons, 57 per 1000 for twins, and 168 per 1000 for triplets (Figure 7.16A). Among survivors, the incidence of severe handicaps was 20, 34, and 58 per 1000 for singletons, twins, and triplets, respectively (Figure 7.16B).[103]

Retrospective analyses of 14[104] and 33[105] patients in addition to a prospective study of 8 patients [106] with triplet pregnancies concluded that vaginal delivery is safe in selected cases, but the collective experience is limited. Theoretically, the risks of cord accident, malpresentation, and interlocking fetuses are increased with a greater number of fetuses in the uterus. Most authorities believe that cesarean section is the safest route of delivery for all pregnancies with three or more fetuses. If vaginal delivery is planned, the delivering obstetrician should possess great skill and experience with ECV and with vaginal breech delivery.

Anesthesia Considerations for Multiple Gestations

Depending upon the number of fetuses and their presentation, obstetric indications, or the preference of obstetrician and mother, delivery may be either by vaginal route or by cesarean

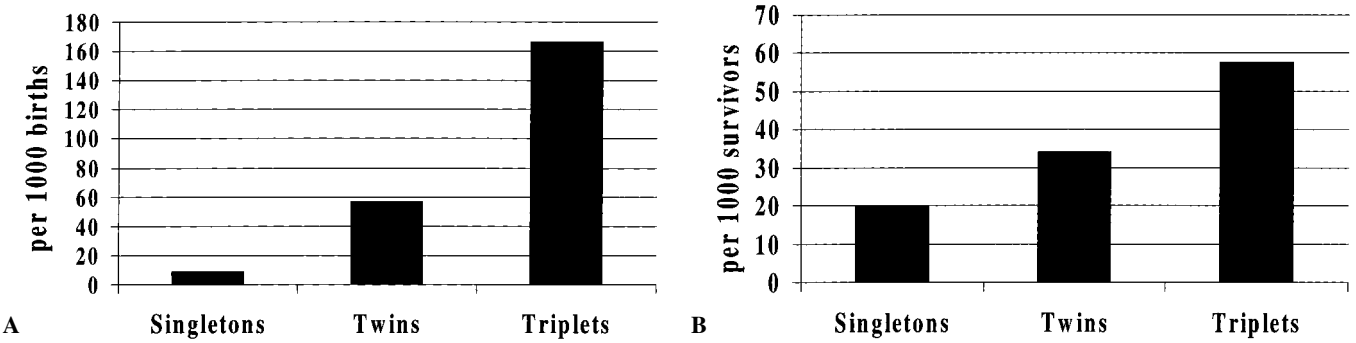

FIGURE 7.16. (**A**) Mortality rates for singletons, twins, and triplets. (**B**) Rates of severe handicaps in surviving singletons, twins, and triplets. (Data from Breen JL, Wiesmeier E. Compound presentation: a survey of 131 patients. Obstet Gynecol 1968;32:419–422.)

section. Major considerations in regard to choice of anesthesia for multiple gestations are the frequent occurrence of prematurity, pregnancy-induced hypertension, breech presentation, aortocaval compression and hypotension during regional anesthesia, and uterine atony immediately postpartum. Even if the mother and obstetrician opt for a vaginal delivery, the anesthesiologist may have to rapidly provide anesthesia for internal podalic version or ECV of breech or transverse presentation, assisted breech delivery or breech extraction, midcavity forceps delivery, or cesarean section, especially for the fetal compromise of twin B. Therefore, early preoperative evaluation, preparation, and formulation of an extended plan with the parturient and obstetrician are essential (see Table 7.2). The anesthetic management of multiple births is similar to that of breech delivery in many ways, and the number of fetuses largely determines the mode of delivery. Most women with three or more fetuses are delivered by cesarean section.[107] Other factors that affect the route of delivery include complications of pregnancy (particularly pregnancy-induced hypertension), noncephalic presentations, fetal distress, and complications of labor.

Labor and Vaginal Delivery

During the past 25 years, the analgesic requirement for the parturients with multiple gestations has changed. During the 1950s and 1960s, safety of regional anesthesia was controversial. Twins delivered under caudal anesthesia—a popular form of regional anesthesia at that time—were reported to have a higher mortality rate.[108,109] Little and Friedman[108] reported a higher mortality in twin B, and Guttmacher and Kohl[109] reported a higher perinatal death rate in either twin when the mother received caudal anesthesia. On the other hand, Aaron and Halperin[110] reported a much lower mortality rate (5.4% versus 14%) in twins whose mothers received caudal anesthesia. Large doses of local anesthetics used and hypotension, combined with the inability to monitor fetal heart rate continuously, might have been the contributing factors for increased mortality. Fear of prolongation of labor, increased risk of aortocaval compression and subsequent maternal hypotension, reduced placental perfusion, increased need for forceps, and breech delivery were the reasons for avoiding regional analgesic techniques. Hypotension, associated with increased risk of aortocaval compression and sympathectomy, is easily prevented with adequate hydration, left uterine displacement, and the aggressive use of ephedrine. Many obstetricians preferred local infiltration or pudendal nerve block during the second stage of labor. Although these techniques safeguard somewhat against neonatal depression, they obviously do not provide analgesia during the first stage of labor.

In 1975, Crawford[111] noted in a retrospective review of outcome of 102 multiple pregnancies with or without epidural anesthesia that the mean interval between full dilatation of the cervix and delivery of the first twin was 10 to 15 min greater in the epidural series, but the mean interval between delivery of the first and second infant was shorter by 2 to 4 min in the epidural series. One-minute Apgar scores were lower in twin B, but Apgar scores for twin A did not differ. There were only 2 deaths in the group who received epidural analgesia, compared with 5 deaths in the group who did not. Crawford concluded that the provision of an epidural block for labor and delivery to patients with a multiple pregnancy is beneficial to the infants. Crawford and Weaver[112] reported the safety and benefit of epidural analgesia during vaginal delivery of twins when the bearing-down reflex was totally abolished and the perineum relaxed. They also noted its effect on the maintenance of the acid–base status, especially of the second twin. The safety of this technique has been confirmed by others.[113–116] Weekes et al.[114]compared the labor course of parturients with or without epidural analgesia (50 patients versus 92 patients) and found that the duration of the first and second stages of labor, the incidence of assisted deliveries when the head presented, the proportion of breech extractions when either the first or second twin presented by the breech, the incidence of low Apgar scores, and perinatal mortality were not significantly different in the two groups. They concluded that not only did these findings suggest that lumbar epidural analgesia is safe for providing pain relief in labor for patients with a twin pregnancy, but also that it is preferable

to conventional analgesia in these cases, as it allows prompt intervention to effect delivery of the second twin.

Because of increased risk of hypotension, emergency operative delivery, and uterine atony and postpartum hemorrhage, placement of a large-bore intravenous catheter, giving patient aspiration prophylaxis, and sending blood for type and screen are essential prerequisites for establishing an epidural block (see Table 7.2). The sitting position might be preferable, as pronounced lumbar lordosis makes the epidural needle placement technically more difficult in a lateral position. Hypotension associated with increased risk of aortocaval compression and sympathectomy should be avoided with adequate left uterine displacement and prehydration and should be treated aggressively with vasopressors. One should try to establish a good functioning epidural analgesia in early stages of labor with a low concentrations of local anesthetic, 0.125% to 0.25% bupivacaine or 0.2% ropivacaine, to provide adequate analgesia with minimal motor block. After establishing the efficacy of the block, continuous infusion of lower concentrations of bupivacaine (0.0625%–0.125%) or ropivacaine (0.1%) with an opioid usually provides adequate first-stage analgesia. The delivery should always take place in an operating room with facilities for cesarean section. Twin A with cephalic presentation and expected vaginal delivery might not require additional analgesia. For twin B, a noncephalic presentation with a higher chance of intrauterine manipulation, assisted delivery or operative delivery will require augmentation of the epidural block with higher concentrations of local anesthetics. Some anesthesiologists might augment the block when the delivery of first twin is imminent, whereas some might wait until after the delivery of twin A. Chloroprocaine (2%–3%) or lidocaine (1.5%–2.0%) augments the block rapidly for assisted delivery, especially of twin B. If operative delivery is expected, higher concentrations of these local anesthetics with a block of bilateral T4 will be adequate.

Cesarean Section

For a scheduled, nonurgent cesarean section, any of the anesthesia techniques, from spinal to epidural to general anesthesia, can be safely administered. Over the past 20 years regional anesthesia has become a preferred technique over general anesthesia. Although no prospective study has compared the maternal safety and neonatal outcome of the different techniques, the safety of regional anesthesia in these cases has been reported by Crawford.[116] Crawford observed similar neonatal outcome, Apgar scores, umbilical artery pH, and acid–base status in twins delivered by epidural on general anesthesia. General anesthesia is usually reserved for some patients requiring emergency cesarean section for sudden fetal distress, cord prolapse, or maternal hemorrhage, or where regional anesthesia is contradicted. Large uterine mass associated with multiple gestation may further decrease functional residual capacity, increase oxygen consumption, delay gastric emptying, and worsen aortocaval compression, thus making these parturients more prone to aspiration, risk of hypoxemia during periods of apnea, failed intubation, and hypotension. The administration of depressant drugs, such as narcotics and other general anesthetic agents, can have a deleterious effect on premature infants and should be carefully titrated. As a result, adequate denitrogenation, left uterine displacement, and protection against aspiration are essential. General anesthesia is also associated with increased morbidity and mortality in parturients.[69]

Among regional anesthesia techniques, some anesthesiologists prefer epidural to spinal anesthesia. Spinal anesthesia and a rapid onset of sympathectomy can cause severe hypotension in a patient with a massive enlarged uterus and aggravated aortocaval compression. Increasing the left uterine tilt, aggressive use of ephedrine, and fluids usually resolve the hypotension. Jawan et al[117] observed that spinal anesthesia in patients with multiple gestations has a more rapid onset and a higher cephalad spread (T3 versus T5) than in patients with a singleton fetus. A slow, incremental, careful titration of local anesthetics, a gradual onset of sympathecotomy, and a better maintained blood pressure and uteroplacental perfusion are the distinct advantages of an epidural, especially when the uterine incision-to-delivery interval (of all infants) might be prolonged and placental blood flow might be placed in jeopardy. Overall, regional anesthesia is less likely to cause neonatal depression and also offers the distinct advantages of early maternal–infant bonding and superior pain control.[112] Sometimes, obstetricians may request an adequate uterine relaxation to avoid early placental separation until all the fetuses are delivered. Nitroglycerine (50–100 μg IV) is preferred because of its quick onset and a short duration of action. Fetal jeopardy of twin B or arrest of labor following successful vaginal delivery of the first infant, prolapsed cord, and unfavorable presentation of twin B might necessitate an urgent or emergent delivery. Yarnell et al.[118] compared maternal and neonatal outcomes of 55 triplets delivered under spinal, epidural, or general anesthesia. Except for an easily treatable hypotension in the spinal group, no differences were noted in neonatal outcome.

Summary

Increased risk of operative or assisted deliveries, with an increased incidence of preterm labor and perinatal morbidity and mortality, places both malpresentation and multiple gestation in a high-risk category. An early and close interaction between the obstetrician, the anesthesiologist, and the neonatologist is essential for ideal planning and management of these cases. These patients should always deliver in a room with facilities for a cesarean section, and an anesthesiologist should always be present and prepared to handle sudden changes in fetal well-being, including the need for uterine relaxation and emergent assisted or operative delivery. Epidural anesthesia offers several advantages and is flexible enough to cover most of the

changing needs at the time of delivery, including an emergent operative delivery, and thus avoids the need for rapid induction of general anesthesia with its associated morbidity.

References

1. Seeds JW, Walsh M. Malpresentations. In: Gabbe SG, Niebyl JR, Simpson JL (eds) Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996:469–498.
2. Weisman AI. An antepartum study of fetal polarity and rotation. Am J Obstet Gynecol 1944;48:550–552.
3. Johnson CE. Transverse presentation of the fetus. JAMA 1964;187: 642–646.
4. Thorp JM Jr, Jenkins T, Watson W. Utility of Leopold maneuvers in screening for malpresentation. Obstet Gynecol 1991;78:394–396.
5. Croughan-Minihane MS, Petitti DB, Gordis L, Golditch I. Morbidity among breech infants according to method of delivery. Obstet Gynecol 1990;75:821–825.
6. The Cesarean Birth Quality Assurance Committee. Cesarean birth in Ontario. Appropriate use of cesarean section: recommendations for a quality assurance program. Toronto, Canada: Ministry of Health of Ontario, 1991:6–7.
7. Thiery M. Management of breech delivery. Eur J Obstet Gynecol Reprod Biol 1987;24:93–103.
8. Eller DP, VanDorsten JP. Route of delivery for the breech presentation: a conundrum. Am J Obstet Gynecol 1995;173:393–396.
9. Hibbard LT, Schumann WR. Prophylactic external cephalic version in an obstetric practice. Am J Obstet Gynecol 1973;116:511–518.
10. Kauppila O, Gronroos M, Aro P, et al. Management of low birth weight breech delivery: should cesarean section be routine? Obstet Gynecol 1981;57:289–294.
11. Rovinsky JJ, Miller JA, Kaplan S. Management of breech presentation at term. Am J Obstet Gynecol 1973;115:497–513.
12. Cheng M, Hannah M. Breech delivery at term: a critical review of the literature. Obstet Gynecol 1993;82:605–618.
13. Gifford DS, Morton SC, Fiske M, Kahn K. A meta-analysis of infant outcomes after breech delivery. Obstet Gynecol 1995;85:1047–1054.
14. Roman J, Bakos O, Cnattingius S. Pregnancy outcomes by mode of delivery among term breech births: Swedish experience 1987–1993. Obstet Gynecol 1998;92:945–950.
15. Hofmeyr GJ, Hannah ME. Planned caesarean section for term breech delivery. In: Cochrane Review (ed) The Cochrane Library. Oxford: Update Software, 2000.
16. Collea JV, Chein C, Quilligan EJ. The randomized management of term frank breech presentation: a study of 208 cases. Am J Obstet Gynecol 1980;137:235–244.
17. Gimovsky ML, Wallace RL, Schifrin BS, Paul RH. Randomized management of the nonfrank breech presentation at term: a preliminary report. Am J Obstet Gynecol 1983;146:34–40.
18. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. Lancet 2000;356:1375–1383.
19. Cunningham FG, MacDonald PC, Gant NF, et al. Lie, presentation, attitude, and position of the fetus. In: Williams Obstetrics, 20th edn. Norwalk: Appleton & Lange, 1997:251–260.
20. Gilstrap LC III. Breech delivery. In: Hankins GDV, Cunningham FG, Clark SL, Gilstrap LC III (eds) Operative Obstetrics, 1st edn. Norwalk: Appleton & Lange, 1995:191–208.
21. Dennen PC. Special instruments: piper forceps for the aftercoming head. In: Dennen's Forceps Deliveries, 3rd edn. Philadelphia: Davis, 1989: 159–167.
22. Collea JV, Rabin SC, Weghorst GR, Quilligan EJ. The randomized management of term frank breech presentation: vaginal delivery vs. cesarean section. Am J Obstet Gynecol 1978;131:186–195.
23. Goldenberg RL, Nelson KG. The premature breech. Am J Obstet Gynecol 1977;127:240–244.
24. Bodmer B, Benjamin A, McLean FH, Usher RH. Has use of cesarean section reduced the risks of delivery in the preterm breech presentation? Am J Obstet Gynecol 1986;154:244–250.
25. Ingemarsson I, Westgren M, Svenningsen NW. Long-term follow-up of preterm infants in breech presentation delivered by caesarean section. A prospective study. Lancet 1978;2:172–175.
26. Morales WJ, Koerten J. Obstetric management and intraventricular hemorrhage in very-low-birth-weight infants. Obstet Gynecol 1986;68:35–40.
27. Westgren LM, Songster G, Paul RH. Preterm breech delivery: another retrospective study. Obstet Gynecol 1985;66:481–484.
28. Weiner CP. Vaginal breech delivery in the 1990s. Clin Obstet Gynecol 1992;35:559–569.
29. Moore MM, Shearer DR. Fetal dose estimates for CT pelvimetry. Radiology 1989;171:265–267.
30. Abroms IF, Bresnan MJ, Zuckerman JE, et al. Cervical cord injuries secondary to hyperextension of the head in breech presentations. Obstet Gynecol 1973;41:369–378.
31. Caterini H, Langer A, Sama JC, et al. Fetal risk in hyperextension of the fetal head in breech presentation. Am J Obstet Gynecol 1975;123: 632–636.
32. Daw E. Hyperextension of the head in breech presentation. Am J Obstet Gynecol 1974;119:564–565.
33. Cruikshank DP, White CA. Obstetric malpresentations: twenty years' experience. Am J Obstet Gynecol 1973;116:1097–1104.
34. Cackins LA, Pearce EWJ. Transverse presentation. Obstet Gynecol 1957;9:123–125.
35. Edwards RL, Nicholson HO. The management of the unstable lie in late pregnancy. J Obstet Gynaecol Br Commonw 1969;76:713–718.
36. Hofmeyr GJ, Kulier R. External cephalic version of breech presentation at term. In: The Cochrane Library. Oxford: Update Software, 2000.
37. Zhang J, Bowes WA Jr, Fortney JA. Efficacy of external cephalic version: a review. Obstet Gynecol 1993;82:306–312.
38. Fortunato SJ, Mercer LJ, Guzick DS. External cephalic version with tocolysis: factors associated with success. Obstet Gynecol 1988;72:59–62.
39. Chung T, Neale E, Lau TK, Rogers M. A randomized, double blind, controlled trial of tocolysis to assist external cephalic version in late pregnancy. Acta Obstet Gynecol Scand 1996;75:720–724.
40. Marquette GP, Boucher M, Theriault D, Rinfret D. Does the use of a tocolytic agent affect the success rate of external cephalic version? Am J Obstet Gynecol 1996;175:859–861.
41. Stock A, Chung T, Rogers M, Ming WW. Randomized, double blind, placebo controlled comparison of ritodrine and hexoprenaline for tocolysis prior to external cephalic version at term. Aust N Z J Obstet Gynaecol 1993;33:265–268.
42. Johnson RL, Elliott JP. Fetal acoustic stimulation, an adjunct to external cephalic version: a blinded, randomized crossover study. Am J Obstet Gynecol 1995;173:1369–1372.
43. Robertson AW, Kopelman JN, Read JA, et al. External cephalic version at term: is a tocolytic necessary? Obstet Gynecol 1987;70:896–899.
44. Tan GW, Jen SW, Tan SL, Salmon YM. A prospective randomised controlled trial of external cephalic version comparing two methods of uterine tocolysis with a non-tocolysis group. Singap Med J 1989;30: 155–158.
45. Carlan SJ, Dent JM, Huckaby T, et al. The effect of epidural anesthesia on safety and success of external cephalic version at term. Anesth Analg 1994;79:525–528.
46. Schorr SJ, Speights SE, Ross EL, et al. A randomized trial of epidural anesthesia to improve external cephalic version success. Am J Obstet Gynecol 1997;177:1133–1137.
47. Mancuso KM, Yancey MK, Murphy JA, Markenson GR. Epidural anal-

gesia for cephalic version: a randomized trial. Obstet Gynecol 2000;95: 648–651.
48. Neiger R, Hennessy MD, Patel M. Reattempting failed external cephalic version under epidural anesthesia. Am J Obstet Gynecol 1998;179: 1136–1139.
49. Rozenberg P, Goffinet F, de Spirlet M, et al. External cephalic version with epidural anaesthesia after failure of a first trial with beta-mimetics. Br J Obstet Gynaecol 2000;107:406–410.
50. Birnbach DJ, Matut J, Stein DJ, et al. The effect of intrathecal analgesia on the success of external cephalic version. Anesth Analg 2001;93: 410–413.
51. Dugoff L, Stamm CA, Jones OW III, Mohling SI, Hawkins JL. The effect of spinal anesthesia on the success rate of external cephalic version: a randomized trial. Obstet Gynecol 1999;93:345–349.
52. American College of Obstetricians and Gynecologists. External Cephalic Version: ACOG Practice Patterns No. 4. Washington, DC: ACOG, 1997.
53. Boyson WA, Simpson JW. Breech management with caudal anesthesia. Am J Obstet Gynecol 1960;79:1121.
54. Crawford JS. An appraisal of lumbar epidural blockade in patients with a singleton fetus presenting by the breech. J Obstet Gynaecol Br Commonw 1974;81:867–872.
55. Bowen-Simpkins P, Fergusson IL. Lumbar epidural block and the breech presentation. Br J Anaesth 1974;46:420–424.
56. Donnai P, Nicholas AD. Epidural analgesia, fetal monitoring and the condition of the baby at birth with breech presentation. Br J Obstet Gynaecol 1975;82:360–365.
57. Darby S, Hunter DJ. Extradural analgesia in labour when the breech presents. Br J Obstet Gynaecol 1976;83:35–38.
58. Breeson AJ, Kovacs GT, Pickles BG, Hill JG. Extradural analgesia—the preferred method of analgesia for vaginal breech delivery. Br J Anaesth 1978;50:1227–1230.
59. Confino E, Ismajovich B, Rudick V, David MP. Extradural analgesia in the management of singleton breech delivery. Br J Anaesth 1985;57:892–895.
60. Van Zundert A, Vaes L, Soetens M, et al. Are breech deliveries an indication for lumbar epidural analgesia? Anesth Analg 1991;72:399–403.
61. Chadha YC, Mahmood TA, Dick MJ, Smith NC, Campbell DM, Templeton A. Breech delivery and epidural analgesia. Br J Obstet Gynaecol 1992;99:96–100.
62. Campbell DC, Camann WR, Datta S. The addition of bupivacaine to intrathecal sufentanil for labor analgesia. Anesth Analg 1995;81:305–309.
63. Munson ES, Embro WJ. Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 1977;46:11–14.
64. Donchin, Y, Evron S. Relaxation of the uterus with amyl nitrite in cases of multiple deliveries and breech presentation. In: Abstracts of the 13th Annual Meeting. Society for Obstetric Anesthesia and Perinatology, San Diego, CA, 1981, p. 29.
65. Peng AT, Gorman RS, Shulman SM, et al. Intravenous nitroglycerine for uterine relaxation in the postpartum patient with retained placenta. Anesthesiology 1989;71:172–173.
66. DeSimone CA, Norris MC, Leighton BL, et al. Intravenous nitroglycerin for manual extraction of a retained placenta. In: Abstracts of the 20th Annual Meeting, Society for Obstetric Anesthesia and Perinatology, San Francisco, CA, 1988, p. 112.
67. Effer SB, McMorland GH. Breech presentation, malpresentation, multiple gestation. In: Datta S (ed) Anesthetic and Obstetric Management for High-Risk Pregnancy. Chicago: Mosby-Year Book, 1991:74.
68. Redick LF, Livington E. A new preparation of nitroglycerin for uterine relaxation. Int J Obstet Anesth 1995;4:14.
69. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
70. Crawford JS, Davies P. Status of neonates delivered by elective Caesarean section. Br J Anaesth 1982;54:1015–1022.
71. Browne ADH, Carney D. Management of malpresentations in obstetrics. Br Med J 1964;5393:1295–1298.
72. Duff P. Diagnosis and management of face presentation. Obstet Gynecol 1981;57:105–112.
73. Copeland GN Jr, Nicks FI Jr, Christakos AC. Face and brow presentations. NC Med J 1968;29:507–510.
74. Benedetti TJ, Lowensohn RI, Truscott AM. Face presentation at term. Obstet Gynecol 1980;55:199–202.
75. Skalley TW, Kramer TF. Brow presentation. Obstet Gynecol 1960;15:616–620.
76. Weissberg SM, O'Leary JA. Compound presentation of the fetus. Obstet Gynecol 1973;41:60–64.
77. Breen JL, Wiesmeier E. Compound presentation: a survey of 131 patients. Obstet Gynecol 1968;32:419–422.
78. Chitkara U, Berkowitz RL. Multiple gestations. In: Gabbe SG, Niebyl JR, Simpson JL (eds) Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996:821–862.
79. Derom C, Vlietinck R, Derom R, Van den BH, Thiery M. Increased monozygotic twinning rate after ovulation induction. Lancet 1987;1: 1236–1238.
80. Luke B. The changing pattern of multiple births in the United States: maternal and infant characteristics, 1973 and 1990. Obstet Gynecol 1994;84:101–106.
81. Jewell SE, Yip R. Increasing trends in plural births in the United States. Obstet Gynecol 1995;85:229–232.
82. Chescheir NC, Seeds JW. Polyhydramnios and oligohydramnios in twin gestations. Obstet Gynecol 1988;71:882–884.
83. Bebbington MW, Wittmann BK. Fetal transfusion syndrome: antenatal factors predicting outcome. Am J Obstet Gynecol 1989;160:913–915.
84. Saade GR, Belfort MA, Berry DL, et al. Amniotic septostomy for the treatment of twin oligohydramnios-polyhydramnios sequence. Fetal Diagn Ther 1998;13:86–93.
85. Elliott JP, Urig MA, Clewell WH. Aggressive therapeutic amniocentesis for treatment of twin-twin transfusion syndrome. Obstet Gynecol 1991;77:537–540.
86. Saunders NJ, Snijders RJ, Nicolaides KH. Therapeutic amniocentesis in twin-twin transfusion syndrome appearing in the second trimester of pregnancy. Am J Obstet Gynecol 1992;166:820–824.
87. Pinette MG, Pan Y, Pinette SG, Stubblefield PG. Treatment of twin-twin transfusion syndrome. Obstet Gynecol 1993;82:841–846.
88. Reisner DP, Mahony BS, Petty CN, et al. Stuck twin syndrome: outcome in thirty-seven consecutive cases. Am J Obstet Gynecol 1993; 169:991–995.
89. De Lia JE, Cruikshank DP, Keye WR Jr. Fetoscopic neodymium:YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. Obstet Gynecol 1990;75:1046–1053.
90. Hecher K, Plath H, Bregenzer T, et al. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. Am J Obstet Gynecol 1999;180:717–724.
91. Ville Y, Hyett J, Hecher K, Nicolaides K. Preliminary experience with endoscopic laser surgery for severe twin-twin transfusion syndrome. N Engl J Med 1995;332:224–227.
92. Colburn DW, Pasquale SA. Monoamniotic twin pregnancy. J Reprod Med 1982;27:165–168.
93. Nyberg DA, Filly RA, Golbus MS, Stephens JD. Entangled umbilical cords: a sign of monoamniotic twins. J Ultrasound Med 1984;3:29–32.
94. Chervenak FA, Johnson RE, Youcha S, et al. Intrapartum management of twin gestation. Obstet Gynecol 1985;65:119–124.
95. Gocke SE, Nageotte MP, Garite T, et al. Management of the nonvertex second twin: primary cesarean section, external version, or primary breech extraction. Am J Obstet Gynecol 1989;161:111–114.
96. Mauldin JG, Newman RB, Mauldin PD. Cost-effective delivery management of the vertex and nonvertex twin gestation. Am J Obstet Gynecol 1998;179:864–869.
97. Blickstein I, Schwartz-Shoham Z, Lancet M, Borenstein R. Vaginal de-

livery of the second twin in breech presentation. Obstet Gynecol 1987;69:774–776.
98. Laros RK Jr, Dattel BJ. Management of twin pregnancy: the vaginal route is still safe. Am J Obstet Gynecol 1988;158:1330–1338.
99. Fishman A, Grubb DK, Kovacs BW. Vaginal delivery of the nonvertex second twin. Am J Obstet Gynecol 1993;168:861–864.
100. Rabinovici J, Barkai G, Reichman B, et al. Randomized management of the second nonvertex twin: vaginal delivery or cesarean section. Am J Obstet Gynecol 1987;156:52–56.
101. Rayburn WF, Lavin JP Jr, Miodovnik M, Varner MW. Multiple gestation: time interval between delivery of the first and second twins. Obstet Gynecol 1984;63:502–506.
102. Chervenak FA, Johnson RE, Berkowitz RL, Hobbins JC. Intrapartum external version of the second twin. Obstet Gynecol 1983;62:160–165.
103. Luke B, Keith LG. The contribution of singletons, twins and triplets to low birth weight, infant mortality and handicap in the United States. J Reprod Med 1992;37:661–666.
104. Loucopoulos A, Jewelewicz R. Management of multifetal pregnancies: sixteen years' experience at the Sloan Hospital for Women. Am J Obstet Gynecol 1982;143:902–905.
105. Grobman WA, Peaceman AM, Haney EI, et al. Neonatal outcomes in triplet gestations after a trial of labor. Am J Obstet Gynecol 1998;179:942–945.
106. Alamia V Jr, Royek AB, Jaekle RK, Meyer BA. Preliminary experience with a prospective protocol for planned vaginal delivery of triplet gestations. Am J Obstet Gynecol 1998;179:1133–1135.
107. MacGillivray I. Twins and other multiple deliveries. Clin Obstet Gynaecol 1980;7:581–600.
108. Little WA, Friedman EA. Anesthesia for the twin delivery. Anesthesiology 1958;19:515.
109. Guttmacher AF, Kohl SG. The fetus of multiple gestations. Gynecology 1958;12:528.
110. Aaron JB, Halperin J. Fetal survival in 376 twin deliveries. Am J Obstet Gynecol 1955;69:794.
111. Crawford JS. An appraisal of lumbar epidural blockade in labour in patients with multiple pregnancy. Br J Obstet Gynaecol 1975;82:929–935.
112. Crawford JS, Weaver JB. Anaesthetic management of twin and breech deliveries. Clin Obstet Gynaecol 1982;9:291–296.
113. James FM III, Crawford JS, Davies P, Naiem H. Lumbar epidural analgesia for labor and delivery of twins. Am J Obstet Gynecol 1977; 127:176–180.
114. Weekes AR, Cheridjian VE, Mwanje DK. Lumbar epidural analgesia in labour in twin pregnancy. Br Med J 1977;2:730–732.
115. Gullestad S, Sagen N. Epidural block in twin labour and delivery. Acta Anaesthesiol Scand 1977;21:504–508.
116. Crawford JS. A prospective study of 200 consecutive twin deliveries. Anaesthesia 1987;42:33–43.
117. Jawan B, Lee JH, Chong ZK, Chang CS. Spread of spinal anaesthesia for caesarean section in singleton and twin pregnancies. Br J Anaesth 1993;70:639–641.
118. Yarnell RW, Steinbok VS, Goudas LC, et al. Maternal and fetal outcomes following regional anesthesia for triplet births: a review of 55 consecutive cases. In: Abstracts, Society for Obstetric Anesthesia and Perinatology, April 13–17, 1997, p. 113.

8
Antepartum Hemorrhage

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Hemorrhage of Pregnancy

Defining antepartum hemorrhage carries with it conceptual problems. First, hemorrhage is defined simply as the escape of blood from vessels. The term hemorrhage is not meant to be quantitative, yet the image of an excessive amount of blood loss comes to mind. There is also a unique problem in applying a temporal qualifier to the term hemorrhage in clinical obstetrics. Intrapartum hemorrhage is the bleeding that takes place as a normal consequence of labor. Antepartum and postpartum hemorrhage can be further subdivided. Twenty-two weeks gestation divides the early and late antepartum period, whereas the postpartum can be further subdivided into immediate (first 24 h) and late (beyond 24 h) periods. Discussing hemorrhage within these time frames is problematic because the risks of a serious bleeding episode in the late antepartum, intrapartum, or immediate postpartum period are often related (e.g., placenta previa). Furthermore, the antepartum period is addressed without ignoring the contributions made by specific clinical entities to bleeding during labor and immediately after delivery.

Classification of Hemorrhage in the Parturient

Hemorrhage in the pregnant patient is categorized into one of four classes, depending on the degree of blood loss.[1] The average 70-kg pregnant woman's blood volume is 6000 mL at 30 weeks gestation. Patients with class I hemorrhage (900 mL/15% blood loss) rarely have an acute volume deficit. Class II hemorrhage (1200–1500 mL/20%–25% blood loss) leads to orthostatic blood pressure changes, positive tilt test, narrowing of pulse pressure, decreased peripheral perfusion, and prolonged capillary refill time. Pulse pressure of 30 mm Hg or less in a patient with a class II hemorrhage indicates a diastolic pressure increase (a sign of peripheral vasoconstriction) and should prompt a search for other signs of acute volume loss. Class III hemorrhage (1800–2000 mL/30%–35% blood loss) causes overt hypotension with tachycardia, tachypnea, and cold, clammy skin. Class IV hemorrhage (2400 mL/40% blood loss) results in profound shock and a nonpalpable blood pressure. This condition leads to circulatory arrest and death if untreated.

A key point to remember is that hematocrit alone is not a good indicator of blood loss. Significant changes in hematocrit after an acute blood loss may take 4 h; complete compensation may not occur until 48 h after. Urine output is a superior indicator, and adequate urine production reflects adequate renal perfusion after hemorrhage.

Incidence and Etiology of Obstetric Hemorrhage

The most common causes of third trimester hemorrhage are abruptio placentae (31%) and placenta previa (22%). Thus, 53% of patients with antepartum hemorrhage are at risk for severe, and often life-threatening, blood loss.[2] In the remaining 47% of cases, local genital tract lesions, marginal placental sinus bleeding, and uterine rupture may be responsible. However, in a significant number of women, no obvious source is ever determined.

Impact on Mother, Fetus, and Neonate

Late antepartum hemorrhage is a complication observed in 2% to 5% of pregnancies. Its clinical significance results from blood loss in sufficient quantity to threaten the continuation of the pregnancy or the health of the mother or fetus. During the period 1974 to 1978, hemorrhage from causes other than abortion, ectopic pregnancy, and molar pregnancies (early antepartum) accounted for a maternal mortality rate of 2.1 per 100,000 live births.[3] A similar calculation for the period 1979 to 1992 revealed a death rate secondary to hemorrhage of 1.3/100,000 live births.[4] It is theorized that this nearly 50% reduction in maternal mor-

tality rates can be attributed to improved prenatal care, improved blood banking techniques, better appreciation for the risks of hemorrhage, and improved anesthetic and obstetric management approaches to excessive blood loss during pregnancy. Although overall maternal death rates attributable to hemorrhage continue to decline, hemorrhage moved from the third leading cause of maternal death (13.4%) between 1974 and 1978 to the leading cause (30.2%) between 1979 and 1986.[5] It was a leading cause, again, between 1987 and 1990 (28.7%).[6] These data serve as a reminder that there remains no room for complacency when considering the problem of obstetric hemorrhage. Fetal well-being is also threatened by obstetric hemorrhage. Although 56% of pregnancies that culminate in maternal death due to hemorrhage result in a live-born fetus, stillbirths were observed in nearly 16%, and the fetus was never delivered in 6.3% of cases.[4] The neonatal consequences from antepartum maternal hemorrhage are largely a result of early delivery.

Physiology of Pregnancy and Hemorrhage

Keeping in mind the ABCs of resuscitation—airway, breathing, and circulation—as these relate to the management of hemorrhage, we are reminded of the important changes in airway anatomy, respiratory physiology, and circulatory physiology that occur in response to pregnancy.

Airway

Anatomic and physiologic factors alter the airway during pregnancy, placing the parturient at risk for difficult laryngoscopy and difficult tracheal intubation. Estrogen increases the interstitial water in the ground substance of the connective tissues, resulting in edema of the upper and lower respiratory tract. Increased nasal congestion predisposes to epistaxis during nasotracheal or nasogastric intubation. Pharyngolaryngeal and vocal cord edema may hinder passage of a tracheal tube size that would easily pass in a nonpregnant female. Tongue enlargement and immobility of the floor of the mouth may cause difficult laryngoscopy.[7] Preeclamptic women are at greater risk for pharyngolaryngeal edema, resulting in difficult and complicated tracheal intubation.[8–12] In this population, the difficulty is attributed to reduced plasma proteins and marked fluid retention, especially in the head and neck region.[13]

A correlation between weight gain and an increase in the Mallampati score suggests that fluid retention causing pharyngolaryngeal edema is responsible for difficult tracheal intubation.[14] Furthermore, the course of labor and bearing down in labor may worsen the Mallampati score, thus requiring reevaluation of the airway before induction of general anesthesia.[15] Peripartum airway changes that were detected during cesarean hysterectomy with massive fluid resuscitation gradually returned to normal within 48 h after surgery.[16]

Pregnancy also results in breast engorgement. In the recumbent position, the enlarged breasts tend to fall against the neck, hindering laryngoscope insertion. Solutions to minimize difficulty in laryngoscopy include taping of breasts laterally and caudally, proper sniff position with a shoulder roll, use of a short laryngoscope handle, or insertion of the laryngoscope blade alone followed by attachment of the handle later.[17]

Breathing

Respiratory parameters are altered during pregnancy by two principal factors. One is an endocrinologic effect resulting from progesterone-mediated increased sensitivity to carbon dioxide by chemoreceptors; the latter results in an increased tidal volume (at the expense of the expiratory reserve volume) with no change in respiratory rate and, subsequently, an increase in minute ventilation. Increased minute ventilation is teleologic in view of the oxygen demands of the developing fetus; however, minute ventilation exceeds oxygen consumption (48% versus 21%) during pregnancy. When viewed using blood gas parameters, the increase in minute ventilation is seen as a compensated respiratory alkalosis (pH 7.40–7.47, P_{CO_2} 25–32 mm Hg). This fact needs to be considered when interpreting blood gas values during attempts to resuscitate patients in shock.[18–22]

The second factor is the mechanical effect imposed by an enlarging fetal–placental unit that results in an enlarging uterus, and cephalic displacement of the diaphragm as pregnancy progresses until just before delivery when lightening (engagement of the fetal head) occurs. These mechanical changes translate into a near-18% reduction in functional residual capacity. This change, in combination with the increase in tidal volume and reduced expiratory reserve volume, requires consideration in the adjustment of mechanical ventilation settings.[23] The increased oxygen consumption and decreased functional residual capacity predispose parturients to rapid arterial oxygen desaturation during periods of apnea. Apnea may occur during rapid sequence induction of anesthesia and during seizures associated with eclampsia or local anesthetic toxicity.

Circulation

Many parameters are used to assist the evaluation of cardiovascular function during pregnancy. The heart is often described as being hyperdynamic, which refers to the mechanics behind the observed increase in cardiac output (30%–45%) during normal pregnancy.[24] Early in pregnancy, this increase results from an increase in stroke volume, and later from a more rapid heart rate.[25] By the second trimester, the stroke volume increases from about 65 mL to 85 mL, where it stays until near term, at which time there is a slight decline. The

maternal pulse increases gradually to a mean value in the high 80s by 32 weeks.[25] Together, these changes result in an increase in cardiac output from 4.5 to about 6 L/min.[26] Significantly, the kidneys and uterus experience the greatest gains in blood flow as a result of the increase in cardiac output.[27,28] There is little change in blood flow to the brain or liver.

Blood pressure during pregnancy, as in the nonpregnant women, is dependent on a number of factors such as maternal age, body mass index, and perhaps ethnicity. There is no clearer example than to consider that the 90th percentile blood pressure in females 13–18 years old is about 120/80 mm Hg; this would not be an alarming blood pressure in a 40-year-old gravida. For this reason, it is important to keep the aforementioned variables in mind during resuscitative efforts when baseline blood pressure information is not available. A general dictum holds that pregnancy imparts a biphasic change in blood pressure. The first change that occurs is a decline, which begins by about 7 weeks gestation and becomes maximal during the second trimester such that a nadir is achieved between 24 and 32 weeks; this is followed by a gradual return to baseline from 32 weeks to term.[29] The fall in diastolic blood pressure is greater than that recorded for systolic blood pressure. Thus, the calculated pulse pressure is widened in the late second and early third trimester.

It has been speculated that the physiologic changes that result in the increased cardiac output and biphasic blood pressure changes during pregnancy are caused by reduced systemic vascular resistance (800–1200 dynes/s/cm^5 nonpregnant).[30] A number of vasoactive autacoids and hormonal changes are thought to account for this reduction. The reduction in systemic vascular resistance reaches a nadir between 14 and 24 weeks (25%). Pulmonary vascular resistance undergoes a similar change in direction and magnitude (20–120 dynes/s/cm^5 nonpregnant).[24] There is no measurable change in central venous pressure (1–7 mm Hg), pulmonary capillary wedge pressure (6–12 mm Hg), or mean pulmonary artery pressure (9–16 mm Hg) as a result of pregnancy.[24]

Blood Components

Blood components are altered as a result of pregnancy. The circulating blood volume increases 46% (approximately 1500 mL) over the nonpregnant baseline.[31] Plasma volume and red cell mass increase disproportionately, creating a physiologic hemodilution effect; this may decrease the thromboembolism tendency that accompanies the coagulation system changes of pregnancy. Changes occur within the blood-clotting cascade as a consequence of pregnancy. Fibrinogen increases throughout pregnancy by about 50% (300–600mg/dL). Factors VII through X are also appreciably increased. Factors II and XI are decreased during pregnancy. Overall, these changes result in a slight decrease in prothrombin and partial thromboplastin times during pregnancy. The platelet count and size can each undergo a moderate reduction during pregnancy. These changes in platelet parameters result in no change in the bleeding time. Among the inhibitors of coagulation (i.e., antithrombin III, protein C, and protein S), only protein S appears to have a reduced activity despite normal antigen levels. The reduction in activity is in the neighborhood of 50% (26–0.14 U/mL).[32] Antithrombin III and protein C activity remain unchanged throughout normal pregnancy. Antithrombin III is, however, reduced in severe preeclampsia. Plasminogen levels are increased considerably during pregnancy; however, fibrinolytic activity is prolonged. It has been suggested that the placenta is responsible for the reduced fibrinolysis.[33]

The thromboelastogram (TEG) is a quick, whole blood viscoelastic test and provides global assessment of functional hemostasis. The principle and its interpretation have been well described.[34] Using celite activation, most results are available within 15 to 20 min. TEG has shown that pregnancy is a hypercoagulable state and remains so for 24 h after delivery.[35] Various parameters include *r* (reaction time; range, 5–7 min), which measures clotting factor activity; *K* (clot formation time; range, 1–3 min), and α angle (speed of clot formation; range, 53°–67°), which primarily indicate fibrinogen activity and secondarily some platelet function; *MA* (maximum amplitude; range, 59–68 mm), which primarily measures platelet function and secondarily fibrinogen activity; *G* (elastic shear modulus; range, 7,195–10,625 dynes/cm^2; and *LY 60* (reduction in *MA* after 60 min), which indicates fibrinolytic activity. TEG coagulation index (*CI*), which is a composite value derived from a simple linear equation that combines *r, K*, α angle, and *MA,* helps to measure overall blood coagulability. Figure 8.1 shows a typical, hypercoagulable TEG pattern during pregnancy along with measured variables.

This chapter describes different causes of antepartum hemorrhage and their obstetric and anesthetic management.

Abruptio Placentae

Abruptio placentae is defined as the premature separation of a normally situated placenta from its attachment to the decidua basalis before the birth of the fetus. It is also called placental abruption, accidental hemorrhage, or placental separation. The placental separation may be complete, partial, or may involve only the placental margin. A number of different classification schemes for placental abruption have been suggested. Some were based on sonographic features, some on clinical findings, and others on the pathologic review of placental specimens. None have gained widespread use, as their clinical utility is limited. One type of abruption that deserves special mention is the "marginal sinus abruption"; this results from tears in marginal placental veins and is regarded as a "low-pressure" abruption.[36–38] The bleeding seen in this type of abruption is usually associated with dissection of the placental membranes from the myometrial wall and not from a separation of the placenta from the myometrium.[39] The result is a collection of blood separate from the placenta. The clinical symptoms are usually mild and thus may result in fail-

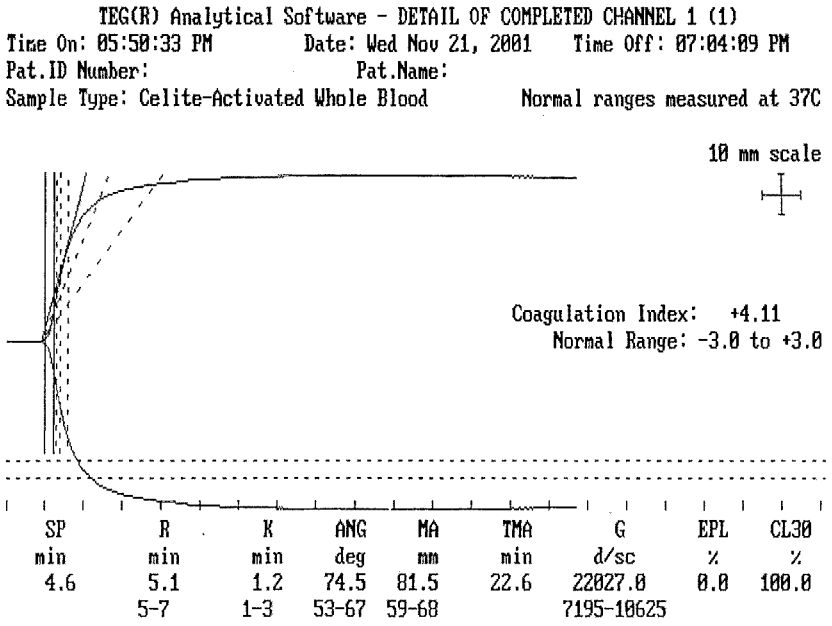

FIGURE 8.1. Typical thromboelastogram (*TEG*) changes during pregnancy (hypercoagulable).

ure to make an early diagnosis.[38] Retroplacental abruption is thought to result from rupture of spiral arteries producing a "high pressure" bleed. Complete detachment of the placenta with either concealed or torrential hemorrhage can be fatal to the mother and fetus (Figure 8.2).

Placental abruption occurs in 0.5% to 1.8% of all pregnancies.[40,41] When cases of abruptio placentae were reviewed, it appeared that about 40% occurred after 37 weeks and another 40% between 34 and 37 weeks; less than 20% of abruptions occurred before 32 weeks gestation.[42] The observation that nearly 60% of the cases of placental abruption occur at preterm gestational ages and an understanding of the theorized etiologies of abruption explains why birth weights of neonates delivered from mothers diagnosed with placental abruption are lower compared to mothers without placental abruption. Adjusted relative risk for a low birth weight infant (<2500 g) was 4.6 (4.0–5.3). There was a 4.1 (3.4–4.8) risk for a birth weight between 1500 and 2499 g. At weight less than 1500 g, this figure increased 11.4 (8.6–15.0) fold.[41]

Risk Factors

The exact etiology of placental separation before delivery often cannot be pinpointed in individual cases. Circumstances that lead to placental abruption and their associated increased risks are listed in Table 8.1.

Recently, interest in genetic risk has been reviewed with regard to pregnancy outcome. Several genes are thought to be important in the process of placental implantation. The relative risk for placental abruption has been shown to increase when genetic polymorphisms or mutations are identified (Table 8.2).

Factors stated in Tables 8.1 and 8.2 have been well substantiated by epidemiologic and association studies, although other factors have been identified. Independent of the etiology, the resultant placental separation may result in antepartum hemorrhage, fetal distress, preterm labor, or postpartum uterine atony.

Diagnosis

The classic signs and symptoms of abruptio placentae include abdominal pain, uterine tenderness, uterine irritability/tetany, vaginal bleeding, coagulopathy, and fetal distress/death. Of note, 65% to 80% of the time, vaginal bleeding is not present, and placental site bleeding remains concealed.[43] When bleeding is excessive, whether it is concealed or evident, patients may present with hypotension.[44]

Ultrasound examination has been reported to be of little use in the diagnosis of clinically suspected abruption, due to the absence of identifiable blood within the uterus, because of free passage through the cervix.[38] Others believe that ultrasonography is useful to exclude placenta previa[45] and to assess the age of the blood clot.[39] Acute hemorrhage is hyperechoic or isoechoic relative to the placenta, whereas an older clot (more than 2 weeks) is almost sonolucent. An acute abruption may occasionally be seen as a discrete collection of blood between the placenta and myometrium, but more often than not, the blood dissects into the placenta or myometrium and is difficult to recognize sonographically. In these cases, the placenta may appear to be heterogeneously thickened.[39,44,46,47] The normal placenta should not measure more than 5 cm in thickness, so that a placenta with a thickness of 8 to 9 cm should raise suspicion of an abruption, especially in an appropriate clinical scenario.[46]

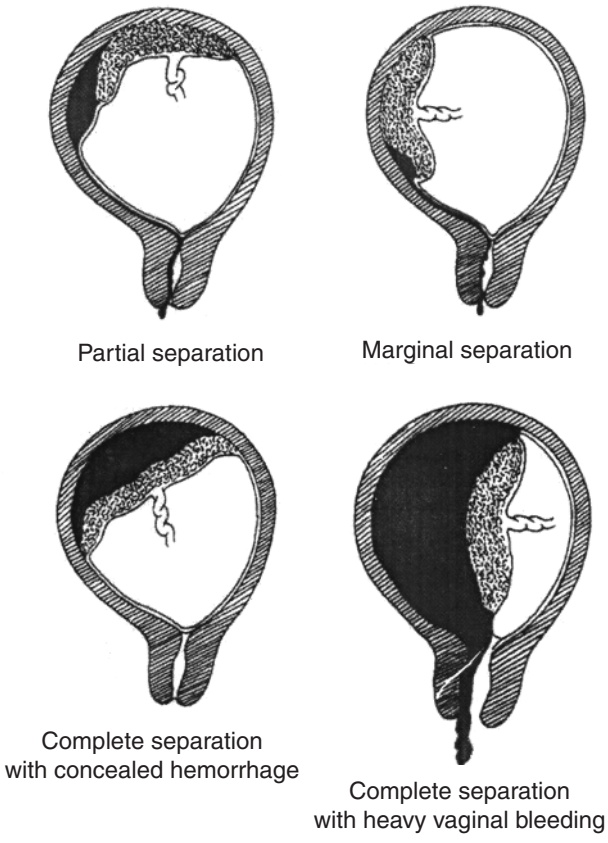

FIGURE 8.2. Degrees of separation of normally implanted placenta. (Drawn by Medical Illustration Unit, Baylor College of Medicine, Houston, TX.)

The differential diagnosis of placental abruption includes all clinical entities in which vaginal bleeding alone or in combination with uterine contractions or fetal compromise/death occurs. In cases in which there is obvious vaginal bleeding, the differential diagnosis must include genital tract trauma/lesions, hematuria, marginal sinus rupture, placenta previa, preterm labor, vaginal or vulvar varicosities, and vasa previa. In patients who have no visible bleeding, the differential diagnosis should include acute appendicitis, chorioamnionitis, fibroid degeneration, hematoma of the rectus sheath, ovarian cyst complications (hemorrhage, rupture, and torsion), pyelonephritis, retroplacental hemorrhage, uterine rupture, medical causes of acute abdominal pain, (diabetes, herpes zoster, myocardial infarction, pneumonia, porphyria, and sickle cell disease), and orthopedic causes such as lumbar or sacral strain.

TABLE 8.1. Risk factors for abruptio placentae.

Category	Example	Risk (%)
Physical forces	Trauma[a]	1–50[160–162]
	Membrane rupture	4[163]
Exposures	Cocaine	17[164]
	Methadone	1[164]
	Tobacco	3[78]
Medical disease	Hypertension with superimposed preeclampsia	10[40,49,78]
	Severe preeclampsia	3[40,49,78]
	Fibroid uterus	3–57[165]

[a]Highly dependent on specific nature of the trauma.

TABLE 8.2. Genetic risk factors for abruptio placentae.

Example	Relative risk (%)[a]
Hypofibrinolysis	16[166]
MTHFR deficiency	2–2.5[167,168]
Factor V Leiden	4.9[167]
Prothrombin mutation	8.9[167]

MTHFR, 5,10-methylenetetrahydrofolate reductase.
[a]All values are significantly different than baseline.

Obstetric Management

Major factors in the obstetric management of abruptio placentae are the severity of the abruption as determined by the presence or absence of hypotension and coagulopathy, the gestational age, and the condition of the fetus. Making the decision to allow vaginal delivery or to proceed with cesarean section, in cases in which the fetus is still alive, has been facilitated by the advent of electronic fetal monitoring. In most situations, consideration of maternal hemodynamic and coagulation status, coupled with fetal well-being and expected time to delivery, should guide clinical decision making.

Cesarean section is reserved for the usual obstetric indications as well as for severe hemorrhage or worsening coagulopathy remote from expected delivery. In the absence of fetal distress and maternal decompensation, vaginal delivery may be pursued. Judicious use of abdominal delivery may well increase the chances of a viable fetus and reduce the degree of coagulopathy. The literature suggests that nearly 75% of fetal deaths occur more than 90 min after admission.[48] Continuous electronic fetal monitoring is essential. Blood products should be available on short notice. Oxytocin augmentation is not contraindicated, although when indicated, it should be used judiciously. Labor frequently progresses more rapidly among patients with placental abruption, mitigating the need for oxytocin.[49] Vaginal delivery should be attempted in cases of severe abruption associated with fetal demise and coagulopathy. Under such circumstances, appropriate component replacement therapy with blood products and oxytocin augmentation is required.

Special Anesthetic Considerations

Anesthetic management, in abruptio placentae, is influenced by the hemodynamics and volume status of the mother. Initial evaluation and treatment emphasize eliminating hypovolemia and assessing the magnitude of blood loss from hema-

tologic studies and coagulation profile. Patient preparation includes large-bore intravenous catheters, aspiration prophylaxis, left uterine displacement, and supplementary oxygen. Urinary output monitoring, via an indwelling catheter, serves as a valuable indicator of renal perfusion.

Evaluation

Overt hypotension and tachycardia are signs of dangerous hypovolemia that cannot be ignored. In a parturient, normal vital signs can be misleading because of the enormous reserve of additional blood volume acquired during pregnancy. Hypertension, either pregnancy induced or chronic, is associated with abruption of the placenta. Normal or even hypertensive blood pressure does not preclude imminently dangerous hypovolemia. Serious hemorrhage and hypovolemia result in blood pressure drop to normotensive levels. This normotensive reading in hypertensive parturients creates false security and delays identification of compromised vital organs. The pulse rate may be equally misleading.[50] Some parturients who have bled appreciably may be able to maintain normal blood pressure and pulse rate, when recumbent. If sitting, they are hypotensive or develop tachycardia. There are several reasons to maintain caution when applying and interpreting the tilt test in a parturient. The tilt test is needless and potentially dangerous for parturients who are hypotensive when recumbent. In parturients with an epidural who subsequently develop abruption, sympathetic blockade exaggerates the hypotension in the sitting position. The hypervolemic parturient may lose excessive blood before demonstrating orthostatic hypotension.

Monitoring and Fluid Management

Maternal hypotension and hypovolemia are assessed and corrected by guidance from invasive arterial blood pressure, central venous pressure (CVP), and urine output monitoring. Urine output below 0.5 mL/kg/h, despite adequate volume replacement, merits placing a CVP catheter. A review of 36 patients with severe abruptio placentae[51] showed CVP monitoring resulted in better volume resuscitation. Average hemoglobin concentration 24 h postpartum was 11 g/dL, compared to 8 g/dL in the unmonitored group. Further, the monitored group had greater urine output. Significant coagulopathy or disseminated intravascular coagulopathy (DIC) precludes the cannulation of subclavian or internal jugular venous sites, and an antecubital venous site is preferable. Absolute CVP level is less important than the CVP response to volume infusion and monitoring trends of CVP serially. The fluid challenge test helps in the diagnostic assessment of volume replacement. The hemodynamic pressures are measured before and after an intravenous fluid challenge of 10 to 20 ml/min is administered over 10 to 15 min. An increase greater than 5 cm H_2O in CVP or an increase greater than 7 mm Hg in pulmonary capillary wedge pressure is significant and indicates cardiac failure or excessive volume replacement.[52]

Serious hemorrhage demands prompt, adequate refilling of the intravascular compartment. Two general guidelines determine the amount and kind of fluids needed to combat hypovolemia: lactated Ringer's solution and blood or blood component replacement should be adequate to maintain the urine output at 0.5 to 1 mL/kg/h and the hematocrit above 30%.[53]

Anesthesia for Vaginal or Cesarean Delivery

Avoiding anesthetic drugs or techniques that exaggerate hypotension protects maternal and fetal safety. The use of regional anesthesia is contraindicated in parturients with abruptio placentae and associated acute fetal distress, coagulopathy, or hypovolemia. In the absence of these complications, a continuous epidural analgesia technique may be used for labor, vaginal delivery, or cesarean section.

Most cases of severe abruption with acute fetal distress require abdominal delivery. General anesthesia, with rapid sequence induction and intubation under cricoid pressure, is recommended. Ketamine (0.75–1 mg/kg) is the optimum induction agent if uterine tone is normal or decreased. Theoretically, larger doses of ketamine, in abruption, increase uterine tone and further compromise a stressed fetus. However, a study proved ketamine at 2 mg/kg increased uterine tone only in the first trimester; there were no effects on uterine tone at term.[54] Etomidate (0.3 mg/kg) is recommended if uterine tone is increased, or if hemodynamic instability exists.[55] Uterine relaxation with inhalation anesthetics helps increase placental perfusion. Low doses of inhalational anesthetics also maintain circulatory hemostasis and allow for administration of high-inspired oxygen concentration (Fio_2). Cesarean section with general anesthesia, supplemented by a halogenated agent, increases the risk for blood loss.[56] Although under normal clinical circumstances it is not significant, hemorrhage may be substantial in parturients with severe abruption.

Complications of Placental Abruption

The most important sequelae of severe abruption in the postpartum period are acute renal failure, anemia, coagulopathy with DIC, postpartum hemorrhage, pituitary necrosis or Sheehan's syndrome, and uterine atony.

Acute Renal Failure

The overall incidence of renal failure in abruptio placentae is 1.2% to 8.9%. Acute renal failure occurs in severe abruption with or without DIC. It is believed to be secondary to hypotension and hemorrhagic shock (prerenal), microvascular clotting, fibrin deposition in periglomerular arterioles, and myoglobinuria alone or in combination. Some degree of renal ischemia occurs in 10% of patients with severe hemorrhage. Renal failure may manifest as transient oliguria or anuria accompanied by renal tubular or cortical necrosis. Renal cortical necrosis associated with placental abruption is caused by severe intrarenal vasospasm from massive hemor-

rhage. The key to preventing acute renal failure is aggressive blood, fluid, and volume resuscitation to prevent hypovolemic shock and renal ischemia. With acute blood loss, renal blood flow is reduced, glomerular filtration rate (GFR) is decreased, sodium and water absorption is increased, urine sodium content is decreased, and urine osmolality is increased. Urine sodium concentration of 20 mEq/L, urine/serum osmolar ratio greater than 2, and urine osmolality greater than 500 mOsm/kg indicate reduced renal perfusion and prerenal failure. Monitoring of volume status is important in these patients to ensure adequate circulating volume without precipitating pulmonary edema.

Persistent oliguria, in the past, had mandated invasive hemodynamic monitoring. If oliguria persisted despite a CVP reading of 7 cm H_2O, a pulmonary artery (PA) catheter was usually placed, especially in a patient with severe preeclampsia and placental abruption. The PA catheter allowed assessment of preload, afterload, cardiac output, and other variables. More recently, noninvasive cardiac monitoring with echocardiography has been used and is extremely useful in situations such as coagulopathy. Myocardial performance and ventricular filling pressures can be determined.[57] Fluid management decisions may also be based on echocardiography, in lieu of PA catheter data.[57] Diuretics should be used only under exceptional circumstances and with caution. These patients may require inotropic support or the administration of low-dose (2.5 μg/kg/min) dopamine. Use of renal-dose dopamine has been questioned recently.

Fenoldopam mesylate, a benzazepine derivative, is the first selective dopamine D_1 receptor agonist that has been approved for clinical use.[58] It acts on the cerebral, coronary, renal, and splanchnic vasculature and offers better renal protection. It is a rapidly acting peripheral vasodilator that acts primarily on the postsynaptic dopaminergic D_1 receptors, has moderate affinity for the α_2 adrenergic receptors, and lowers mean arterial pressure. Fenoldopam has no significant activity at the dopaminergic D_2 receptor, α_1 and β-adrenoreceptors, $5HT_1$ and $5HT_2$ receptors, or muscarinic receptors. It also acts as a diuretic in the kidneys.[58] Fenoldopam is a racemic mixture with the *R* isomer having 250-fold-higher activity as compared to the *S* isomer. It was found to preserve renal perfusion, GFR, and natriuresis without causing hypotension in dogs at an infusion rate of 0.1 μg/kg/min.[59] Fenoldopam also ablates the tubular prerenal response to profound hypovolemia, suggesting that it may have a renoprotective effect during acute ischemic injury in dogs.[59] The human studies were performed in both normotensive and hypertensive patients. The recommended infusion rates for treating malignant hypertension are 0.01 to 1.6 μg/kg/min. Elimination half-life in mild to moderate hypertensives was about 5 min. Clearance of fenoldopam is not affected by end-stage renal disease, continuous ambulatory peritoneal dialysis, or severe hepatic failure. In a study of 12 patients with hypoxemia due to multiple trauma or bowel surgery requiring ventilatory support, intravenous fenoldopam (0.2 μg/kg/min) increased renal perfusion, urine flow, and urinary excretion of potassium and sodium.[60] Beneficial renal effects have been shown at infusion rates as low as 0.03 μg/kg/min, which are well below the rates required to lower systemic arterial blood pressure.[61]

Consumptive Coagulopathy

One special concern surrounding the management of placental abruption relates to the comorbidity from DIC, which complicates approximately 20% of cases of placental abruption.[62] Multiple theories exist to explain the etiology of DIC in cases of abruptio placentae, and many of these hinge on the fluctuations of fibrin split products (FSP). Placental separation is associated with significant elevations in maternal serum FSP, independent of whether this occurs as a consequence of normal labor and delivery or after abruptio placentae. In vitro studies suggest that FSP inhibit myometrial contractility.[63] In vivo local concentrations of FSP are greater than those measured systemically, and FSP in lochia, after abruptio placentae, are much higher than those found after normal vaginal delivery.[63] Antifibrinolytic agents have been shown to improve myometrial contractility in cases of abruptio placentae.[64] In summary, excessive hemorrhage resulting from placental abruption appears to be in part due to uterine atony. The latter occurs as a result of elevated FSP. These speculations aside, the principles that guide management of associated DIC and hemorrhage are not different from DIC and hemorrhage observed in other clinical settings.

Disseminated intravascular coagulation, which produces a dramatic decline in coagulation factors and platelets, occurs because of retroplacental consumption of fibrinogen or from the release of an unidentified thrombogenic substance into the circulation. The thrombogenic substance, thought to be thromboplastin, triggers extrinsic coagulation pathway activation. Thrombin converts fibrinogen to fibrin and initiates intravascular clotting. DIC ends in consumption of factors I, II, V, and VIII and platelets. Thrombi and fibrin are reportedly deposited in the microcirculation thus interrupting blood flow to vital organs. The fibrinolytic system activates to lyse the excessive fibrin almost simultaneously; this is termed secondary fibrinolysis.

Retroplacental consumption of clotting factors also causes DIC by deposition of substantial fibrin in the uterine cavity. This process stimulates the secondary activation of circulating plasminogen to plasmin, which enzymatically destroys circulating fibrinogen. Thromboplastin release into the maternal circulation from a retroplacental clot is a possible cause of consumption of coagulation factors and platelets. DIC develops rapidly in the obstetric population and is accentuated with placental abruption or amniotic fluid embolism. Laboratory evidence of prolonged prothrombin time (PT) and partial prothrombin time (PTT), hypofibrinogenemia, thrombocytopenia, elevated fibrin degradation products (FDPs), and TEG pattern confirms DIC.

Differentiating a consumptive from a dilutional coagulopathy is difficult. DIC complicates approximately 10% of all placental abruptions, but is more common in those where fetal death has occurred.[50] Overt hypofibrinogenemia (<150 mg/dL of plasma), elevated levels of FDPs, and variable decreases in other coagulation factors occur in 30% of women with placental abruption that is severe enough to kill the fetus. Such coagulation defects may not occur in cases with fetal survival.

Fibrinogen seems to be the commonest procoagulant needed in obstetric hemorrhage with DIC. Serial determination of fibrinogen level is a sensitive indicator of DIC.[64] Approximately 4 g of fibrinogen are required to increase the fibrinogen concentration by 100 mg/dL in a healthy 70-kg adult. Fibrinogen may be administered in the form of cryoprecipitate or fresh-frozen plasma (FFP). Cryoprecipitate contains 3- to 10-fold more fibrinogen per unit volume as compared to FFP.[65] Each bag of cryoprecipitate contains fibrinogen (250–300 mg), factor VIII, von Willebrand factor, and factor XIII in 15 to 25 mL plasma. Thus, 13 to 16 bags of cryoprecipitate are needed to increase the fibrinogen concentration by 100 mg/dL.[65] The fibrinogen level of 100 mg/dL safely produces hemostasis in the nonpregnant individual. A fibrinogen level of 150 to 200 mg/dL is probably necessary to prevent hemorrhage in the obstetric population. Cryoprecipitate, frozen and stored at 19°C, must be thawed for 30 to 40 min at 37°C before use.

Fresh-frozen plasma contains all the clotting factors except platelets. Most of the factors are stable in stored blood with two exceptions: factors V and VIII. Factors V and VIII are not stable in stored blood and decrease to 15% and 50% of normal, respectively, after 21 days storage. Packed RBCs have even fewer coagulation factors; consequently, FFP is recommended if (1) generalized bleeding cannot be controlled with surgical hemostasis or cautery; (2) PTT is at least 1.5 times control or more; or (3) factors V and VIII are deficient, based on laboratory evidence. However, factors V and VIII rarely decrease below those levels required for hemostasis.

Dilutional Coagulopathy

Massive transfusion can be defined as the transfusion of 10 or more units of blood or an amount greater than one blood volume. During storage, the pH of blood drops, potassium increases, 2,3-diphosphoglycerate decreases, factor V and VIII degrade, platelets are lost, and red cells lyse, resulting in complications associated with massive transfusion.

Dilutional coagulopathy causes hemorrhagic diathesis in patients receiving multiple units of blood. Platelets are damaged by storage at 4°C and are trapped before being absorbed by the reticuloendothelial system. Total platelet activity lessens to 50% to 70% of original in vivo activity after 6 h. After 24 or 48 h, platelet activity reduces to 5% to 10% of normal. Transfusion of multiple units of stored blood (>24 h) dilutes the patient's available platelet pool.

Platelet count rarely decreases to predicted lows from dilution alone.[66] Prophylactic platelet administration during massive transfusion has no benefit. The practice of giving platelets to treat laboratory evidence should be discouraged. Platelet concentrates contain a few erythrocytes and may cause sensitization even though the blood banks ensure blood group and Rh compatibility. Platelet transfusion should be administered only to prevent or correct hemorrhage associated with thrombocytopenia or platelet dysfunction.[67] However, preoperatively, platelet therapy is needed when the platelet count is below 50,000/mm^3.[2] According to others, the threshold for platelet transfusion may be safely lowered to 30,000/mm^3 if the patient is not hemorrhaging.[65] Patients with acutely induced thrombocytopenia develop a hemorrhagic diathesis at a much higher platelet count than patients with chronically induced thrombocytopenia. Adequate hemostasis from a surgical incision or trauma requires a higher platelet count to plug the holes in damaged capillaries. Each platelet concentrate, in a 70-kg patient, increases platelet count by 10,000 to 12,000/mm^3.[2] However, others believe that each platelet concentrate increases the platelet count by only 8,000 to 10,000/mm^3 in the average adult woman.[65] In any event, average platelet storage period is 72 h because platelets are difficult to store. Most blood banks have an inadequate supply of platelets.

Intraoperative Monitoring of Coagulopathy

If a coagulopathy is suspected, the diagnosis should be confirmed with laboratory data including PT, activated PTT, platelet count, FSP, and TEG, if available. TEG has been used for detection of coagulation defects associated with intraoperative blood loss in parturients.[68] TEG has been shown to reduce use of blood and blood components during liver transplantation.[69] TEG is an extremely useful tool and, if readily available, may help in monitoring coagulation parameters and in reducing usage of blood and blood components in hemorrhaging parturients. Examples of some abnormal TEG tracings are shown in Figure 8.3. Bleeding time is no longer used and does not correlate with adequacy of either platelet count or function.

Placenta Previa

Placenta previa is defined as implantation of the placenta in the lower uterine segment in advance of the fetal presenting part. The placenta is normally placed in the body of the uterus and away from the cervical internal os. If the placenta obstructs the descent of the fetus, there is potential for maternal hemorrhage. There are a number of different classifications for placenta previa, most of which depend on a description of the placenta in relation to the internal os. This description may, however, be confusing because there is a potentially changing relationship between the location of the placenta and the uterus during the third trimester and particularly during labor. Thus, most grad-

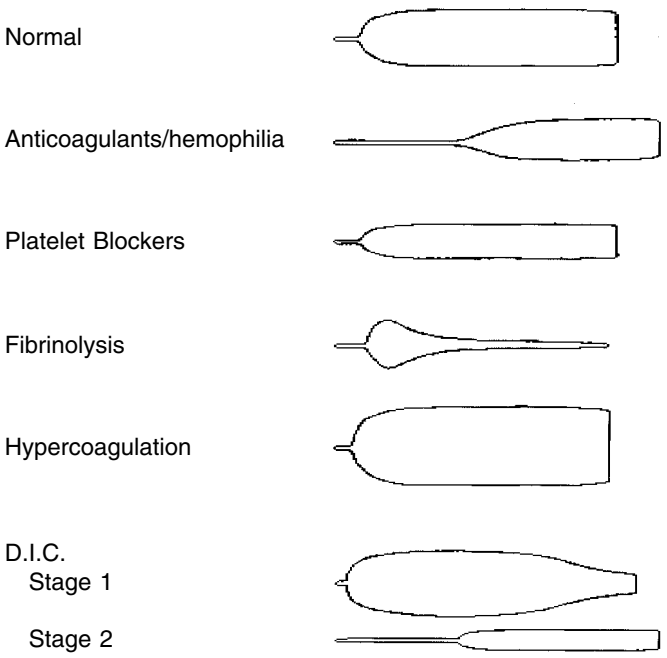

FIGURE 8.3. Abnormal typical thromboelastogram (*TEG*) tracings. (With permission from Eli Cohen, Ph.D., Haemoscope Corporation, Niles, IL.)

ing systems pertain to the antepartum period. The incidence of placenta previa varies from 0.1% to 1.0% of third trimester pregnancies. Maternal mortality may reach 0.9%.[70]

The placenta may occupy one of at least four different positions within the lower portion of the womb (Figure 8.4). The low-lying placenta does not encroach upon the internal os but is implanted in the lower uterine segment. The marginal placenta previa encroaches without covering it. The placental edge may be as much as 2 cm from the internal os for the term marginal placenta previa to apply. A partial placenta previa exists when the placenta is partially covering the internal os. The latter accounts for about 30% of cases of placenta previa. Complete placenta previa comprises 40% of cases and signifies complete covering of the internal os with the placenta concentrically placed.[70]

There are two potential patterns of placental growth after central placental implantation, centripetal (resulting in complete placenta previa) and unidirectional (toward the more vascularized fundal region). The unidirectional growth may be the cause of the resolution as the placenta favors the more vascularized fundal region of the uterus rather than the more fibrous lower segment. Evidence for this mode of growth is provided by the eccentric placement of the cord insertion on the placental plate (eccentric, marginal, or in some cases velamentous). The insertion point of the cord in the membranes marks the original placental location. A fundal placenta in the second trimester is evidence that there will not be placenta previa at term.

Risk Factors

The association of increasing parity with placenta previa suggests that damage to the endometrium during a prior pregnancy may be an etiologic factor. Furthermore, a poorly developed decidua in the lower segment results in an abnormally firm attachment of the placenta and an increased risk of placenta accreta (24% with one previous cesarean section and up to 67% with four or more prior cesarean sections).[71] Table 8.3 lists well-established risk factors for placenta previa.

Diagnosis

Clinically, the diagnosis of placenta previa is supported by palpation of a relaxed uterus. The presenting part is usually

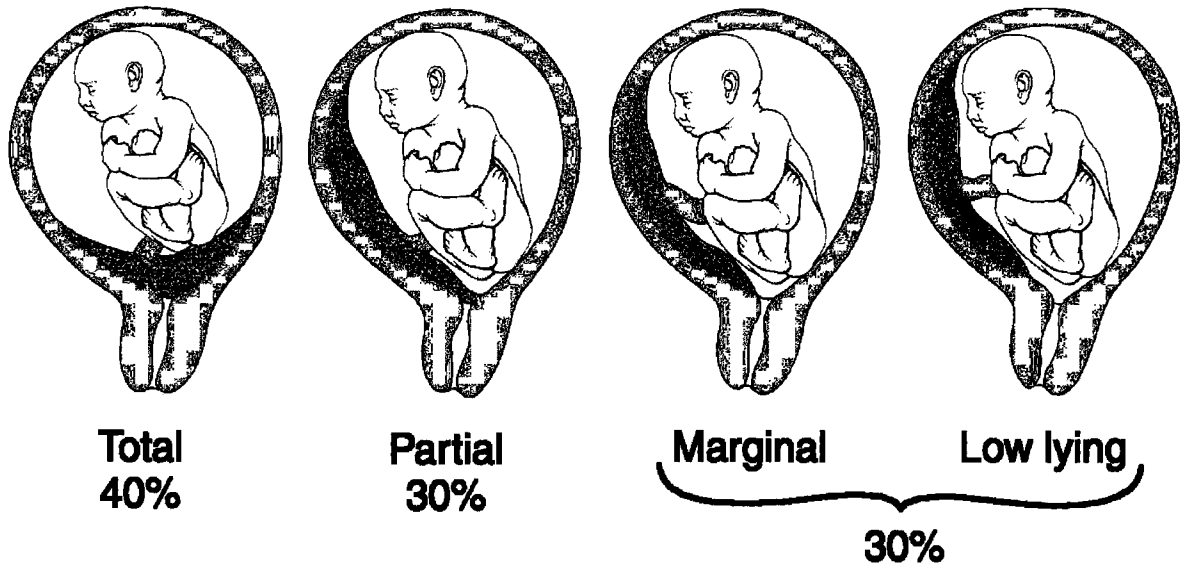

FIGURE 8.4. Grading of placenta previa. (Drawn by Medical Illustration Unit, Baylor College of Medicine, Houston, TX.)

TABLE 8.3. Risk factors for placenta previa.

Category	Example	Increased risk (%)
Parity	0	<0.01[169]
Grand multiparity		5[169]
Maternal age	35 years	2.35[170]
	40 years	4.5[171]
Prior placenta previa		4–8[172]
Prior cesarean section[a]	0	0.26[71]
	4	10[71]

[a]Multiparous.

in the upper uterine segment because of the presence of the placenta in the lower uterine segment. An abnormal presentation is very common, with the fetus being in the breech or transverse position in 33% of cases.[72,73] In fetuses with a cephalic presentation, the presenting part is frequently high above the pelvic brim and difficult to palpate, especially when there is an anterior placenta previa.

Although clinical findings are important, the definitive diagnosis is made by ultrasound examination. With transabdominal ultrasound and a full maternal urinary bladder, the accuracy of diagnosis approaches 93% to 97%.[74,75] Transvaginal ultrasound has been shown to be safe in the diagnosis and management of patients with placenta previa, despite the risk of probe-induced trauma. This approach allows superior definition of the lower segment and has been reported to be 100% sensitive.[76] Most agree that either sonographic approach can result in false-positive and false-negative results. Therefore, these modalities are complementary. One approach to the diagnosis of placenta previa is to first perform transabdominal ultrasound and proceed to the transvaginal route for imaging only if uncertainty remains.

Magnetic resonance imaging (MRI) has been used to diagnose placenta previa because it provides excellent resolution of the cervical–placental interface.[77] Cost and ready availability of this modality have limited the usefulness of this technique. A "double-setup" examination refers to the use of a digital examination of the vaginal fornices in an actively bleeding patient. This examination is performed in an operating room setting, and all those involved in the patient's care (including nursing and blood bank personnel) are prepared for emergency intervention in the event that the examination results in excessive bleeding and the need for cesarean section. The utility of this approach is limited to those actively bleeding patients in whom fetal well-being is established but ultrasound remains equivocal or is unavailable. If the fetal presenting part can be felt in all four quadrants, vaginal delivery is usually feasible and the membranes can be ruptured. If there is bogginess suggestive of placenta previa, the procedure should be abandoned and abdominal delivery performed. Digital exploration of the cervical canal is not advised because of the danger of precipitating severe hemorrhage.

When one considers only the patient's presentation—vaginal bleeding with or without labor—before performing an ultrasound, the differential diagnosis is similar as for abruptio placentae. After abruptio placentae, lesions of the cervix, vagina, or vulva including ectropion, lacerations, and neoplasms must be considered. Molar pregnancy and labor (normal or preterm) must also be considered. Given the definitive role of ultrasonography in establishing the diagnosis of placenta previa, one must consider reasons for erroneous ultrasound diagnosis of this condition. Nearly 3% to 7% of incorrect ultrasound diagnoses are a result of either failure to search the lateral aspects of the uterus (false negative) or urinary bladder overdistension, which causes apposition of the anterior and posterior walls of the lower segment (false positive).[78]

Obstetric Management

In general, the diagnosis of placenta previa mandates cesarean section. Rare cases of marginal placenta previa, with compression of the lateral edges of the placenta by the descending fetal head (thus minimizing bleeding), can result in vaginal delivery. Elective cesarean section is preferred. Nearly one-third of neonates born after emergency cesarean section are anemic compared with only 3% born after elective surgery.[73]

Previously taught dogma with respect to the management of placenta previa remote from term is being reevaluated. The efficacy of expectant management is highly dependent on the gestational age at the time of presentation. A 2-week prolongation of pregnancy is much more likely at early (<32 weeks) compared to later gestational ages (>35 weeks).[79] However, about one-quarter of those expectantly managed can anticipate blood transfusion therapy to attain such gains. Expectant therapy starts with hospitalized bedrest for a minimum of 72 h. During this period of time, continuous monitoring for contractions and fetal well-being often results in the observations of sufficient contraction activity, causing one to consider the use of tocolytic agents. The controversy exists primarily due to the cardiovascular effects caused by these agents. A rule of thumb has been to aggressively tocolyze before 32 weeks gestation in cases where the patient and her fetus are hemodynamically stable.

After this gestational age, care has to be individualized after a discussion with the patient. Rules for home management of placenta previa have been suggested.[80–82] These rules include the following: (1) the patient must be able to reach a hospital in 15 min or less at all hours of the day; (2) an adult capable of driving must be with the patient at all times; (3) the patient's blood can be typed and crossmatched without difficulty; and (4) the patient agrees to minimize activity and to abstain from intercourse. In cases where any of these criteria cannot be met, the patient must remain hospitalized until after delivery. The decision to move from expectant management to delivery in an actively bleeding patient remote from term is not easy. The risk of pregnancy prolongation with possible maternal and neonatal morbidity must be weighed against potential neonatal benefits derived from

Table 8.4. Obstetric management of placenta previa.

Presentation	Controversy	Approach to patient
Remote from term	Aggressive transfusion therapy	Individualize with patient input.
	Tocolytic therapy	Gestational age rules (keep in mind cardiovascular effects): Aggressive tocolysis if <32 weeks. Consideration between 32 and 35 weeks
	Single versus repeated courses of antenatal steroids	According to recognized guidelines
	Home versus hospitalized bedrest	Individualize with patient input Assess patient's ability to comply with guidelines (see text)
Near term	Timing of delivery	Consider dating criteria, neonatal services
	Type of skin and uterine incision	Vertical skin, individualize uterine
Postpartum	Routine use of uterotonic agents	If lower segment bogginess, use $PGF_{2\alpha}$, 0.25 mg intramuscularly or intrauterine (minimal cardiovascular effects); methylergonovine (methergine), 0.2 mg intramuscularly (remember cardiovascular effects); and/or misoprostol (cytotec), 0.4–1.0 mg per rectum (less experience)

transfusion therapy. Among the factors to consider are mobility of the surgical and anesthesia teams, blood banking capability, and availability of neonatology services.

Obstetric management can be considered within the context of gestational age at presentation: remote from term, near term, or postpartum (Table 8.4). With regard to the immediate postpartum period, special attention needs to be paid to the increased risk of placenta accreta/increta/percreta (described in a subsequent section of this chapter).

Anesthetic Management

Anesthetic management of placenta previa should take into consideration three different scenarios: (1) double setup for vaginal delivery/cesarean section, (2) cesarean section in hemodynamically stable patients, or (3) cesarean section in actively bleeding and hemodynamically unstable patients.

Double Setup

Ultrasonography and MRI have made the use of "double setup" examination for diagnosing placenta previa obsolete. However, if necessary, anesthetic preparation for double setup entails (1) simultaneously preparing for emergency cesarean section in a patient with placenta previa and ongoing hemorrhage and (2) having crossmatched blood immediately available. This procedure may result in torrential hemorrhage, mandating immediate delivery. Consequently, the examination is safer when performed in the operating room, under continuous fetal and maternal monitoring.

Hemodynamically Stable Patient

Anesthetic management for cesarean section in confirmed placenta previa depends on the presence or absence of active bleeding. Either regional or general anesthesia is acceptable in the parturient who bled several weeks before delivery and is normovolemic. With large-bore intravenous catheters in place and crossmatched blood present in the operating room, one can proceed with anesthesia and surgery.

General anesthesia for women with placenta previa undergoing cesarean section is favored. These parturients are at risk for intraoperative excessive blood loss for three reasons. First, the placenta may be located anteriorly so that the obstetrician incises through the placenta. Second, after delivery, the distended lower uterine segment does not contract as well as the fundus. Third, placenta previa parturients with previous cesarean sections have added risk for placenta accreta. All factors precipitate extensive postpartum bleeding. However, regional anesthesia for cesarean section in placenta previa patients is shown to decrease blood loss, lower the incidence of hysterectomy, and result in better neonatal outcome.[83] However, hypotension induced by regional anesthesia in the parturient results in decreased placental perfusion. As stated previously, patients with placenta previa on $MgSO_4$ tocolytic therapy may have exaggerated hypotension.[84] In hypermagnesemic gravid ewes, ephedrine and phenylephrine provided similar restoration of maternal mean arterial pressure, ephedrine being superior to phenylephrine in restoring uterine blood flow during anesthesia-induced hypotension.[85]

In hemodynamically stable parturient, regional anesthesia such as epidural and combined spinal epidural can be used.

Actively Bleeding/Hemodynamically Unstable Parturients

Copious bleeding and hemorrhagic shock make resuscitating the mother extremely difficult. Completely correcting blood loss before surgery is not always possible because bleeding continues until the placenta is removed. Evaluation of the

woman, surgical preparation, aspiration prophylaxis, monitoring, and volume resuscitation should proceed as previously outlined. Preparations for volume resuscitation and induction of anesthesia should proceed simultaneously.

Left uterine displacement and preoxygenation (denitrogenation) precede induction of general anesthesia. Using a rapid sequence induction and utilizing cricoid pressures, anesthesia is induced with either 0.5 to 1.0mg/kg ketamine or 0.3 mg/kg etomidate. Ketamine produces sympathetic nervous system stimulation and maintains blood pressure. Etomidate causes minimal cardiac depression and is safe in obstetrics.[55] Sodium pentothal or propofol are not the induction agents of choice in a hypovolemic patient because of the potential for exaggerated hypotension. General anesthetic administration may further reduce fetal oxygen and placental blood flow. Rapid infusion of crystalloid, hetastarch, colloid, and RBCs helps restore circulatory volume status.

Some patients on arrival to the operating room are hypotensive and moribund. In such cases, the airway should be secured before anesthesia induction. Patients in severe hemorrhagic shock with a maximally stimulated sympathetic system will have a direct myocardial depressant effect from ketamine. Ketamine, under such circumstances, exacerbates the hypotension and should be avoided. Immediate surgical intervention should stop the blood loss. Etomidate can be an ideal induction agent.

Selection of maintenance agents depends on the degree of cardiovascular compromise. Halogenated agents administered during balanced general anesthesia for cesarean section cause uterine muscle relaxation and increased blood loss.[56] In a bleeding woman, it is prudent to eliminate halogenated agents and uterine relaxants. Anesthesia maintenance is achieved with oxygen, benzodiazipines, small doses of short-acting narcotics, and nitrous oxide as tolerated.

Delivery of the fetus and removal of the placenta minimize the threat to the mother. If bleeding continues from the atonic lower uterine segment, oxytocin, methylergonovine, and/or 15-methyl prostaglandin $F_{2\alpha}$ may be necessary to establish uterine tone. As assessed by blood pressure, CVP measurements, and urine output, adequate resuscitation normalizes the blood volume. The neonate also requires intensive resuscitation at birth if asphyxiated, acidotic, or hypovolemic.

Disseminated intravascular coagulopathy, characteristic of consumptive coagulopathy, is common with severe abruptio placentae but rare with placenta previa. Dilutional thrombocytopenia and coagulopathy may also follow massive transfusion in placenta previa parturients; these conditions are discussed earlier in this chapter, in the section on abruptio placentae.

Alternatives to Allogeneic Blood Transfusion in Parturients Predisposed to Hemorrhage

Although fatal obstetric hemorrhage is rare, obstetric cases receive 4% of blood components used annually in the United States. The incidence of multiunit (defined as more than two units) transfusion during a primary and repeat cesarean section is 0.37% and 1.47%, respectively.[86] Improvements in obstetric surgical techniques and practice have decreased the use of homologous blood transfusions at the time of cesarean section; however, in high-risk cases (i.e., placenta previa, large fibroids, preoperative anemia, repeat cesarean section, and premature delivery by cesarean section), the risk of requiring a transfusion is still significant. Studies show that 33% to 80% of parturients with placenta previa receive predonated autologous blood, and 27% are given homologous blood.[87]

One may choose one or more of the following alternatives to allogeneic transfusion depending on the time available before delivery, because most placenta previa women are diagnosed antepartum: (1) lowering the acceptable hematocrit for transfusion; (2) erythropoietin; (3) acute normovolemic hemodilution (ANH); and (4) erythrocyte salvage.

Lowering the Acceptable Hematocrit for Transfusion

A Consensus Development Conference on Perioperative Red Cell Transfusion was sponsored by the National Institutes of Health in 1988. They suggested that the usual transfusion trigger for hematocrit of 30% was too high and stated that healthy, nonpregnant women may not need transfusion until the hematocrit is 21%, or even less.[88] These findings really apply only when euvolemia (normovolemia) is present. The American Society of Anesthesiologists has also published guidelines for conservation of blood and blood products.[89] Based on these guidelines, most anesthesia care providers have abandoned a single transfusion trigger in favor of an individual patient assessment and now accept much lower hematocrit levels. Preoperatively, in a pregnant woman, we recommend a starting hematocrit of at least 30%. However, postoperatively, it may be reasonable not to transfuse blood if the woman is euvolemic, hemodynamically stable, and maintaining adequate mentation and urine output, and there is no ongoing or anticipated hemorrhage, even though the hematocrit is less than 20%.

Erythropoietin

Erythropoietin is an endogenous hematopoietic factor that behaves like a hormone. It is a glycoprotein elaborated by the kidney in adults, and minimally by the liver. In response to tissue hypoxia, erythropoietin production and, subsequently, plasma erythropoietin levels are increased, stimulating bone marrow erythropoiesis almost 100- to 1000 fold.[90] Currently, erythropoietin is manufactured commercially by using recombinant genetic technology and has similar biological effects as endogenous erythropoietin.[91] Recombinant human erythropoietin (rh-EPO), in a study, was administered as 50 to 300 units/kg, intravenously or subcutaneously, thrice weekly, in anemic patients and produced a dose-dependent increase in reticulocyte count within 10 days, followed by increases in red cell count, hemoglobin, and hematocrit within

2 to 6 weeks.[92,93] Body iron stores are sufficient for a maximal response to rh-EPO if the baseline serum ferritin level is greater than 100 ng/ml.[94] This contention has been confirmed in a number of clinical trials.[95–97] A greater biologic response is not observed at doses exceeding 300 units/kg.[93] Peak effects, that is, a clinically significant increase in hematocrit, may take 2 to 6 weeks because of the time required for erythroid progenitors to mature and be released into the circulation. As a result, rh-EPO has a limited role during acute hemorrhage but can be used effectively in an anemic parturient with placenta previa who is remote from delivery. A convenient dosing schedule for surgical patients is 600 units/kg, subcutaneously, once weekly (21 days, 14 days, and 7 days) before surgery and a fourth dose on the day of surgery.[98] rh-EPO has been used to treat chronically anemic conditions such as autoimmunodeficiency syndrome (AIDS), chronic renal insufficiency, malignancy, prematurity, and rheumatoid arthritis. Side effects include hypertension, seizures, and thrombotic crises.

Acute Normovolemic Hemodilution

Dodril and colleagues first described ANH in 1957.[99] ANH is associated with a reduced loss of red cells during surgical hemorrhage.[100] The available fresh, whole blood containing coagulation factors, platelets, and red blood cells is spared for transfusion, later, during surgery.[101] Cost savings with ANH have been questioned recently,[102] even though ANH has been shown to decrease intraoperative blood transfusion requirements.[100–103] ANH usage has been mostly restricted to healthy, nonpregnant adults because the physiologic anemia of pregnancy and the peripartum fluid shifts have precluded its use in obstetrics in the past. However, the technique, which has been used extensively in children and in the elderly, has only recently been reported in obstetrics.[104–106]

During ANH, the volume of blood to be withdrawn is adapted from the formula described by Gross.[107]

$$V = EBV \times \frac{H_i - H_f}{H_{av}}$$

where V = volume to be removed, EBV = estimated blood volume (average, ~85 mL/kg in pregnant adults; range, 76–94 mL/kg)[31]; H_i = initial hematocrit, H_f = final hematocrit, and H_{av} = average hematocrit (average of H_i and H_f). In a 75-kg adult with EBV = 6375 mL, H_i = 35%, and H_f = 25%, the allowable blood for withdrawal is

$$6375 \times \frac{0.35 - 0.25}{0.30} = 2125 \text{ mL}$$

Blood is withdrawn through a catheter inserted into an artery, central vein, or a large peripheral vein and simultaneously replaced with a precalculated volume of crystalloid or colloid.[108] The ensuing increase in cardiac output and decrease in afterload, arterial oxygen content, and blood viscosity is identical to the normal pregnancy-related hemodynamic and hematologic changes. Reduction in coagulation factors is also observed.[109] Coagulation parameters return to baseline by the end of the 24 h. However, operative blood loss remains similar to that seen without ANH.

Acute normovolemic hemodilution is undertaken in the operating room under continuous monitoring because of the major fluid shifts involved and decreases seen in afterload and arterial oxygen content. ANH is started immediately before or after induction of anesthesia. Blood is collected in standard blood receptacles containing an anticoagulant, usually citrate phosphate dextrose adenine (CPDA), over a 10- to 15-min period.[105] Serum hematocrit is determined after each receptacle collection; we aim for a target hematocrit of 25%. The volume of blood removed may be measured using a syringe for withdrawal or by weighing each unit. The blood may be kept in the operating room at room temperature for up to 6 h. Hemodilution kits are available commercially.[110] Fetal heart rate monitoring is done before the surgery.

Crystalloid solutions, three times the volume of the blood withdrawn, must be simultaneously infused during blood withdrawal and are removed by administration of diuretics before transfusion. Colloid solutions such as albumin, dextran, and hydroxyethyl starch are retained longer in the intravascular compartment and help to reduce the volume replacement requirements equal to the blood volume removed.[111] The blood collected in the receptacles is transfused back in reverse order from withdrawal. Consequently, the last unit withdrawn that has the lowest hematocrit, contains the least platelets, and has the lowest concentration of clotting factors is administered first. Also, the first unit withdrawn that has the highest hematocrit, contains the most platelets, and has the highest concentration of clotting factors is administered last.

Advantages of ANH include reducing blood loss and homologous blood transfusion requirements; improving tissue perfusion and oxygen delivery at a hematocrit of 25%; allowing administration of fresh, whole blood with normal levels of ATP, 2,3-DPG, p50, and normal platelet function; and enabling acceptance of closed-circuit ANH by Jehovah's Witnesses patients. It also avoids disease transmission, transfusion reactions, blood bank compatibility problems, clerical errors, and logistic problems of intraoperative blood salvage.[110] Informed consent for ANH may not be required, but is advisable, especially in patients whose religious beliefs preclude the use of blood transfusion.

Indications for ANH include adults with a hematocrit of 35% or higher who are expected to lose more than 2 L of blood during surgery, patients with rare antibodies or unusual blood types, poor blood banking facilities, and Jehovah's Witnesses (who accept closed-circuit ANH). Hematocrit decreases by approximately 3% per unit of blood removed. Contraindications to ANH include anemia, cardiac dysfunction, impaired coagulation profile, and renal dysfunction. ANH

may not be very effective, if used alone. Blood conservation programs designed to reduce the use of homologous blood transfusion are most successful when two or more components are used in a multimodality technique.[110]

Erythrocyte Salvage

The use of intraoperative erythrocyte salvage has increased substantially during the past decade. Its popularity is likely propelled by a perception of its effectiveness and safety and the desire to avoid potential complications following transfusion of allogeneic blood.[112] However, with nucleic acid testing, the risks attendant with the transfusion of allogeneic blood are decreasing.[113]

The literature contains four reports of 174 patients, including a woman with placenta previa, who underwent transfusion with washed erythrocytes after salvage during cesarean section.[114–117] With the exception of one case of heparin overdose, no other adverse events were reported. In 1994, the National Institute of Health, National Heart, Lung, and Blood Institute (Bethesda, MD) convened a panel to evaluate autologous transfusion and provided their recommendations. This panel endorsed the expanded use of intraoperative erythrocyte salvage,[118] but did not recommend this practice during cesarean section. This view was prompted by both a concern that an amniotic fluid embolism might occur and a lack of data from prospective randomized studies documenting the safety of this practice.

As with any therapy, the use of intraoperative erythrocyte salvage during cesarean section should be based on considerations of effectiveness and safety compared with the available alternatives. Investigations examining the product of erythrocyte salvage and processing during cesarean section generally have produced results consistent with these expectations. Tissue factor,[119] free fetal hemoglobin,[114,120] and α-fetoprotein[120,121] have been reduced or eliminated from the final erythrocyte suspension, whereas substantial concentrations of fetal erythrocytes,[114,121–123] fetal squamous cells,[121,122] and lamellar bodies (composed of phospholipids[122]) still remain. Recently, Waters and colleagues were able to almost completely eliminate fetal squamous cells from a filtered erythrocyte salvaged suspension by using a leukocyte reduction filter.[122]

The reports published during the past several years have begun the process of evaluating the safety of erythrocyte salvage and processing during cesarean section. However, larger prospective randomized studies are necessary to document the safety of this technique for the occasional bleeding obstetric case for whom erythrocyte salvage technique may be efficacious and needed. Until then, the use of this technique during cesarean section should be limited to those times when it is the only way to augment the parturient's oxygen-carrying capacity or when it is necessary to preserve function or life.[124] The need may become more frequent if the predicted shortage of blood in the United States[125] becomes a reality.

In recent years, transcatheter arterial embolization has emerged as a highly effective technique for controlling obstetric hemorrhage.

Vasa Previa

Vasa previa occurs when the fetal vessels present over or near the internal os and are presenting before the fetal parts. In this condition, the fetal vessels course through the fetal membranes as they leave the discoid, placental, velamentous insertion of the umbilical cord. The frequency of velamentous insertion of the umbilical cord is near 1% for singleton pregnancies,[126] making the frequency of vasa previa considerably less than 1%.

Risk Factors

Factors that increase the risk for vasa previa are directly related to those that increase the risk for velamentous insertion of the umbilical cord. The only known factors for this are multiple gestation. With increasing fetal number, the risk for velamentous insertion of the umbilical cord increases proportionately. Nevertheless, vasa previa remains uncommon.

Diagnosis

The diagnosis of vasa previa, when made before hemorrhagic complications, is by palpation or ultrasound. During digital examination, a pulsation in the fetal membranes offers a clue to the diagnosis that can later be confirmed using ultrasound. Color Doppler ultrasound is particularly useful in confirming the diagnosis. Once the membranes have ruptured and bleeding has been identified, clues to the diagnosis may be observed in the fetal heart rate tracing (e.g., bradycardia, sinusoidal pattern, and/or late decelerations) or through the use of chemical tests for fetal blood. The chemical tests most often mentioned are a Wright stain or the Apt test. In the former, blood per vagina is smeared onto a slide, and a Wright stain is performed in an effort to detect nucleated RBCs (fetal blood). The Apt test takes advantage of the resistance to denaturation of fetal hemoglobin under alkaline conditions. Using either a filter paper or test tube, a few drops of blood are collected (it is a good idea to use adult blood as a control). A few drops of alkaline solution (either 10% NaOH or 10% KOH) are applied to the filter paper or to the test tubes. Adult hemoglobin is rapidly denatured, and the color of the filter paper of the tube containing blood turns brown. Fetal hemoglobin maintains its cherry-red color under the same conditions. Despite the available chemical approaches for confirmation, it may be impossible to wait for reagents needed to definitively establish this diagnosis. When vaginal bleeding occurs after ruptured fetal membranes, preparation for cesarean section should begin and be resisted only if fetal heart

rate tracings remain reassured and observed blood is determined to be maternal in origin.

Obstetric Management

A high index of suspicion is required for optimizing the fetal outcomes in cases of bleeding vasa previa. Cesarean section is the only accepted mode of delivery for patients with a known vasa previa. It is preferential to perform cesarean delivery electively, perhaps even before term. When this diagnosis is suspected or confirmed in the presence of hemorrhage during labor or at the time of membrane rupture, emergency cesarean section should be implemented. Despite these efforts, outcomes are often dismal[127] even when delivery occurs minutes after the onset of bleeding[128]; because of the insufficient fetal blood volume, compensation for what appears to be a fairly small amount of hemorrhage, compared to placental abruption or placenta previa, is not possible.

Special Anesthetic Considerations

Anesthetic management is similar to patients with placenta previa, which is discussed earlier in the chapter.

Uterine Atony

Uterine atony is the condition wherein the uterine smooth muscle fails to contract sufficiently after delivery of the fetus, resulting in hemorrhage from dilated venous and arterial bleeders within the placental bed. Most important to the obstetrician and the anesthesia teams are factors that place the gravida at risk for this life-threatening condition.

Risk Factors

Many risk factors for uterine atony are well appreciated and can be thought of as those occurring as a consequence of routine management of labor gone awry or those that present with antecedent fetal or maternal risk factors. These risks are listed in Table 8.5.

TABLE 8.5. Risk factors for uterine atony.

Association	Risk factor
Labor	Protracted or arrested active phase of labor requiring oxytocin augmentation
	Chorioamnionitis
	Obstructed labor
Fetal complication	Fetal macrosomia
	Polyhydramnios
	Abruptio placentae (Couvelaire uterus)
	Placenta previa (lower segment atony)
Maternal	Family history
	Grand multiparity
	Laceration at cesarean section (hypoxic uterine muscle)
	Tocolytic therapy

Diagnosis

Of all the conditions that cause obstetric hemorrhage, uterine atony can be the most straightforward to diagnose. However, because this condition can coexist with others that result in excessive bleeding, each must be meticulously sought before concluding that the bleeding is the result of uterine atony alone. Uterine atony requires inspection of the placenta (for fragmentation), uterus (for retained placental fragments), cervix (for lacerations), and vagina (for lacerations). Pharmacologic therapy is initiated once bleeding from such sources is excluded. The diagnosis of placenta accreta is entertained if the uterine cavity feels "gritty" to palpation on manual exploration of the uterus. A gentle curettage of the uterus in search of accessory lobes of the placenta or missed retained fragments is performed when an adequate manual exploration cannot be completed. Although performing a curettage may be helpful for removing a minimally adherent placental fragment, care should be taken to avoid too vigorous a curettage, as bleeding from placenta accreta may be exacerbated.

Obstetric Management

Obstetric management can be thought of as fitting into one of three general categories: pharmacologic, uterine manipulation, or surgical (Table 8.6).

Although pharmacologic and uterine manipulations are administered simultaneously, when to proceed to surgical methods may not be readily apparent. The anesthesia and obstetric team must maintain careful communication regarding the patient's response to noninvasive treatments. Failure to respond to pharmacologic therapy, persistent uterine atony, ongoing hemorrhage, and hemodynamic compromise may require surgical intervention with more invasive procedures, including hysterectomy.

The B-Lynch procedure was described as a method of suturing the uterus with a single long suture in an effort to avoid

TABLE 8.6. Pharmacologic interventions for uterine atony.

Pharmacologic
Oxytocin (Pitocin)
Methylergonovine (Methergine)
15-Methyl $PGF_{2\alpha}$ (Hemabate)
Misoprostol (Cytotec)
Uterine manipulation
Superior displacement of uterus
Uterine muscle massage
Surgical
B-Lynch procedure[129,130]
Hysterectomy

hysterectomy in cases of uterine atony.[129] It has had moderate success.[130] The suture used is absorbable and it causes the uterus to compress or fold over onto itself, while compressing blood vessels coursing from the cornual region of the uterus. More widespread use and acceptance of this method will establish its utility.

Anesthetic Management

Anesthetic management of uterine atony involves pharmacologic therapy for improving uterine tone (see Table 8.6) and volume replacement with crystalloids, colloids, and blood components, as mentioned earlier.

Placenta Accreta, Placenta Increta, and Placenta Percreta

Placenta accreta is defined as an abnormal adherence of the placenta to the uterine wall after the birth of the newborn. The underlying pathology in this condition is absent decidua, allowing the placental villi to attach directly to the myometrium. The terms placenta increta and placenta percreta specify the degree of invasion into the myometrium or through the myo-metrium, respectively. Independent of the degree of invasion, the placental involvement may be focal or more widespread. The amount of hemorrhage may correlate to some extent with the degree of placental involvement. The uteroplacental relationships found in these conditions are diagrammed in Figure 8.5.

Risk Factors

The reported frequency of this condition varies from 1 in 1,667 to 1 in 70,000. Clearly, risk factors (Table 8.7) that enhance risk for this condition are known and, in some cases, more precise figures are available to the delivery team and the patient.

TABLE 8.7. Risk factors for placenta accreta.

Risk factor	Placenta accreta (%)
No placenta previa and no uterine scar	<1[173]
Placenta previa and no prior cesarean section	4[174]
Placenta previa and one prior cesarean section	10–25[174]
Placenta previa and multiple prior cesarean sections	67[174]

Although some have suggested a positive association between maternal age and parity with subsequent placenta accreta, others do not agree.[131,132] There is no dispute that the presence of a placenta previa and the presence of a uterine scar (most frequently from cesarean section) are the most important risk factors for placenta accreta.

Diagnosis

The diagnoses of placenta accreta, placenta increta, and placenta percreta require histologic confirmation for maximal precision. However, clinical suspicion and diagnosis are often stated even before the pathologic diagnosis and are rarely proven wrong. Clinical clues to the diagnosis of placenta accreta include a retained placenta, a uterine cavity that is rough to palpation after manual removal of the placenta (indicating eroded myometrium and possible small pieces of retained placental fragments), uterine inversion, hematuria, and massive hemorrhage after manual removal of the placenta.

Several radiologic modalities (gray-scale ultrasound, color Doppler imaging, and MRI) have each been described in the antepartum diagnosis of placenta accreta, increta, and percreta.[133–139] In our experience, MRI readings have been inconsistent in establishing the diagnosis of placenta accreta. Although antepartum diagnosis is always preferred, the reality is that quite often this abnormality of placental implantation occurs without the opportunity for antepartum preparation. Thus, a review of risk factors and a general plan of action are warranted.

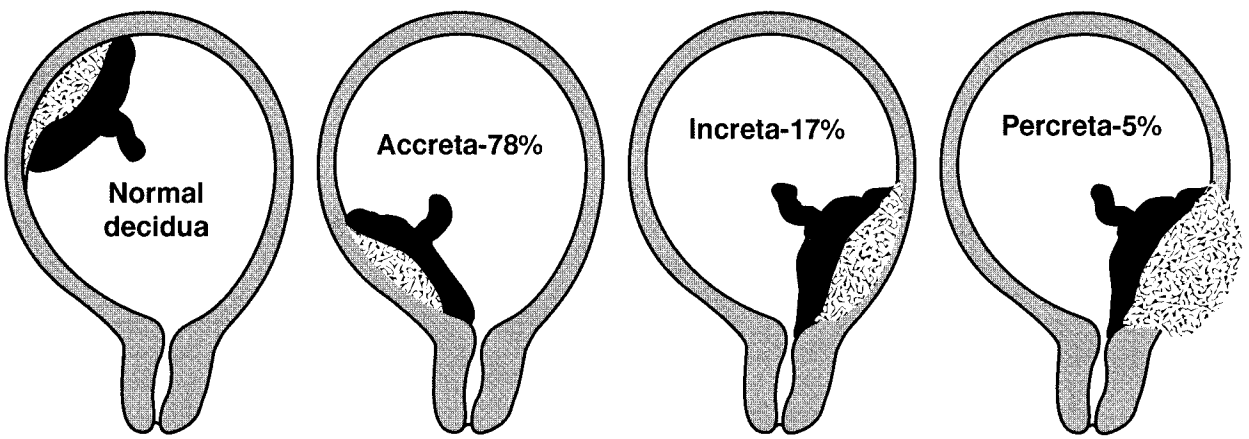

FIGURE 8.5. Uteroplacental relationships in placenta accreta. (Drawn by Medical Illustration Unit, Baylor College of Medicine, Houston, TX.)

Obstetric Management

The antepartum diagnosis of placenta accreta has the capacity to alter the intrapartum management plan. Antepartum preparation starts by providing educational information to the parturient and the family. Providing information and the consent process are helpful in establishing a rapport with family members that assists in future efforts to manage the woman both intraoperatively and postoperatively. A parturient with a known or suspected placenta accreta is delivered by scheduled cesarean hysterectomy. Cesarean delivery of the newborn takes place through a midline vertical skin incision. The type of hysterotomy is dictated by the placental location; in cases of a low-lying placenta or placenta previa, a classical (high vertical) hysterotomy is performed to avoid going through the placenta and to prevent torrential hemorrhage. After delivery, the placenta should not be manipulated. Instead, the hysterotomy edges are oversewn with running locking suture while the placenta remains in situ. Disturbing the placenta can result in unnecessary and excessive blood loss. A vascular surgeon can expose the aorta and pass an umbilical tape beneath the aorta that may be used to temporarily occlude the aorta in the event of massive and uncontrolled hemorrhage during hysterectomy. Transient occlusion of the aorta may help in maintaining cerebral and coronary perfusion during episodes of hemorrhagic hypotension. The hypogastric artery catheters are inflated only if there is uncontrolled hemorrhage, deep in the pelvis. A supracervical hysterectomy is preferred, although this may not be always possible in cases where the placenta is low lying or in cases of placenta previa with placenta accreta.

Other Nonsurgical and Surgical Interventions

Time-tested measures used to treat uncontrolled hemorrhage in obstetrics include dilation and curettage, repair of lacerations, administration of various uterotonic agents, placement of Oleary stitches, uterine isolation, hypogastric artery ligation, and hysterectomy. The methods presented in the following section have unproven efficacy, but each has been extensively reported and we believe that all or some may have a place in the management of obstetric hemorrhage.

Nonsurgical Interventions

Case reports demonstrate the utility of hypogastric artery catheterization using balloon-tipped catheters as a means of reducing blood loss at the time of hysterectomy. In the previously described cases, the balloons were inflated when excessive, uncontrollable hemorrhage occurred (estimated blood loss, 1100–4000.[140,141] In select cases in which massive hemorrhage is anticipated, we have utilized interventional radiology services to introduce the balloon-tipped catheters into the hypogastric arteries. The catheters should not be inflated unless uncontrollable hemorrhage is apparent. Inflation of the balloon-tipped catheter, when bleeding is not of concern, may result in the completion of the hysterectomy with a false sense of security. Subsequent deflation of the balloon tips may result in immediate or delayed hemorrhage from pedicles whose vessels previously supplied blood to the uterus. In our experience of 10 cases, we have not had to inflate the catheters to control bleeding (unpublished data). We have also had no complications from their placement, and total fluoroscopy time has been approximately 1 min.

Misoprostol administered as a therapeutic intervention during the third stage of labor has been recommended (1000 μg per rectum) as a means to control excessive blood loss.[142] However, most studies that explored the use of misoprostol during the third stage of labor have been studied largely under the setting of hemorrhage prophylaxis. Recommended doses, 400 to 600 μg (oral or per rectum), have met with some success when compared to placebo.[143–145] A World Health Organization study concluded oxytocin (10 IU, intramuscularly or intravenously) was most appropriate to use for prophylaxis against postpartum hemorrhage. Blood loss was greater in the misoprostol group, and more subjects enrolled in the misoprostol group required additional uterotonic agents.[146]

Special Anesthetic Considerations

Cesarean hysterectomy is more difficult than hysterectomy in a nonpregnant woman because of the adhesions from previous surgery, difficult exposure, edematous tissues, engorged vasculature, enlarged uterus, and slipped ligatures.[147] Consequently, surgery is prolonged and may lead to massive hemorrhage. Preoperatively, the risks and benefits of various anesthetic options are discussed with the patient.

Anesthetic Management

The choice of anesthetic technique between regional or general anesthesia for cesarean hysterectomy in placenta accreta must consider the potential for uncontrollable hemorrhage and the ABCs of hemodynamic resuscitation. Some other important factors includes evaluation of the parturient's airway, preferences of the pregnant woman and the anesthesiologist, skills and experience of the obstetrician, and availability of manpower. The hypotensive woman may not be able to maintain and protect her airway. Securing an airway and simultaneously being involved in massive volume resuscitation can be a tenuous situation, if manpower is inadequate.

The option, therefore, is limited to either general anesthesia or continuous epidural anesthesia. Spinal anesthesia, due to its limited duration, is not a viable option unless it is delivered by continuous spinal anesthesia technique or a combined spinal epidural technique. General anesthesia offers the advantage of evaluating the parturient's airway, securing the airway, and establishing ventilation. Peripheral large-bore catheters should be used for vascular access for large-volume resuscitation. Central venous access and radial arterial cannulation is also estab-

lished before surgery. Blood is typed, crossmatched, and made immediately available. Securing the airway and having central venous access, peripheral venous access, and arterial pressure monitoring established electively allows the anesthesia care team to concentrate on volume resuscitation, blood component replacement, and hemodynamic stability.

Alternatively, continuous epidural, continuous spinal, or combined spinal epidural techniques of anesthesia may be used in these women. The use of regional anesthesia avoids the risks of general anesthesia in pregnancy, allows titratability of the epidural anesthetic during surgery, and enables postoperative analgesia. In select cases undergoing interventional radiology procedures, the catheter is sited and activated before scheduled surgery. The patient is then taken to the radiology suite where balloon-tipped catheters are placed into the hypogastric arteries under fluoroscopic guidance. The mother and the fetus are continuously monitored during the procedure. The patient is then transferred to the operating room. Ureteral stents are placed by the urologists, under direct visualization, in patients with suspected placenta percreta.

The decision to administer continuous epidural anesthesia is based on a multiinstitutional study of elective or emergency cesarean hysterectomy involving 12 patients. For none of the patients was it necessary that their anesthetic be converted to general anesthesia with maintenance of a T4 sensory level. The authors noted that many parturients wish to be awake during cesarean delivery. Prophylaxis against nausea and vomiting and judicious sedation reduce the need for intraoperative induction of general anesthesia.[148] However, if uncontrollable, massive hemorrhage leads to hypotension, one must proceed with securing the patient's airway using preoxygenation and rapid sequence induction/intubation with cricoid pressure. The hypotensive patient may not be able to maintain and protect her airway.

The development of intraoperative bleeding diathesis can worsen complications markedly. The anesthesiologist may be faced with a dilemma when to remove an epidural catheter in a parturient with DIC. Sprung et al.[149] made the following recommendations. (1) If there is no evidence of intraspinal bleeding, the catheter must be removed as early as possible because of the potential for intravascular catheter migration and initiation of bleeding. (2) If bleeding is present around the catheter insertion site and possibly in the epidural or subarachnoid space, the catheter must be left in place. (3) Frequent assessment of neurologic status is important until the underlying cause of the coagulopathy is treated and the bleeding is resolved. (4) In case of intraspinal hematoma, leading to neurologic deficit, immediate neurologic consultation and decompression surgery are needed.

The anesthesiologist and obstetrician must constantly communicate to determine anticipated risks and extent of bleeding. Special obstetric skills coupled with expert anesthetic management are needed to secure hemostasis. Patients with placenta percreta are not only at high risk for extensive hemorrhage but also for sepsis and DIC. Postoperative management after cesarean hysterectomy involves close monitoring in an intensive care unit. Monitoring should include assessment of analgesia, coagulation profile, core temperature, hematocrit, hemodynamics, sedation, urine output, ventilatory status, and volume status.

Uterine Rupture

Uterine rupture, separation of the unscarred uterine muscle or a previous cesarean section scar, can occur before or during labor resulting in massive hemorrhage.[150] Furthermore, isolated case reports document the occurrence of this condition with and without a prior uterine scar.[151–153]

Risk Factors

Although spontaneous uterine rupture (with no prior uterine scar) has been reported, it is rare.[154] Clearly, the most common antecedent to uterine rupture is a previous cesarean section. Although a complete discussion of a trial of labor (TOL) is beyond the scope of this chapter, the basic approach we use in thinking about uterine rupture is presented.

We dichotomize the thought process and, as a result, our approach to these patients. We first consider the chances for a successful vaginal birth after cesarean section (VBAC). Without further stratification, success rates have varied, with a range of 60% to 80% reported.[155] To provide more parturient-specific information, we consider the reason for the initial cesarean section. A prior cesarean section for a true second stage of labor arrest disorder probably bodes more poorly than a cesarean section for severe preeclampsia or breech presentation.[156,157] After refining the risk toward either end of the reported range of success, we next consider the risk of uterine rupture. In considering this risk, recent evidence suggests that when patients present in spontaneous labor, the risk of uterine rupture is less than when prostaglandins are used for cervical ripening and induction.[158] The relative risk of rupture after spontaneous labor compared to nonlaboring patients was 3.3 (95% CI, 1.8–6.0), and when prostaglandins were used for labor induction, the relative risk was 15.6 (95% CI, 8.1–30). The effect of oxytocin on rupture rates remains unclear.[159] Thus, if parturients are willing to further consider a TOL after learning where they fall on the spectrum of likelihood for success (some request a cesarean section after the initial discussion focusing on chances of success), we ask the woman to reconsider depending on whether she presents in labor or if labor induction is indicated.

Diagnosis

The diagnosis of uterine rupture is confirmed visually or by palpation during cesarean section or after a vaginal birth, respectively. It is controversial as to whether manual palpation should be performed in all cases of successful vaginal deliv-

ery after cesarean section.[155] Opponents argue that manual palpation carries with it the possibility of extending an asymptomatic (stable mother and no evidence of active bleeding) dehiscence. Proponents argue that failure to recognize dehiscence early can put the mother at greater risk for morbidity from hypotension.

Clues to the diagnosis may be evident before its confirmation. These clues are highly dependent on the degree to which uterine bleeding or fetal distress occurs as a consequence of the bleeding that follows uterine rupture. Rupture without evidence of maternal hypovolemia and no abnormality on the fetal heart rate tracing during labor is on the mild end of the spectrum. Under these circumstances, the diagnosis of uterine rupture may never be made (no reason to perform palpation of a prior uterine scar after vaginal birth or rupture may be a coincidental finding at the time of cesarean section). The clinically significant end of the spectrum includes abnormalities on the fetal heart rate tracing that necessitate cesarean section, evidence of maternal hypovolemia, or heavy vaginal bleeding after vaginal birth. Certainly, the presence of any of these last three clues mandates anticipation of ongoing heavy bleeding and the potential for serious maternal or fetal morbidity and mortality.

Obstetric Management

There are two possible approaches to the management of uterine rupture. When the rupture is found as an incidental finding after vaginal delivery, we advocate a watchful, waiting approach for signs and symptoms of concealed bleeding (abdominal pain or hypotension). When evidence suggesting uterine rupture occurs during labor, exploratory laparotomy with delivery of the fetus and repair of the uterine rent is warranted. In some cases, hysterectomy is required to manage bleeding complications.

Treatment of uterine rupture should be individualized. Abdominal hysterectomy is no longer advocated in all cases. If the fetus is still undelivered, or if uterine bleeding is believed to be secondary to a uterine or cervical defect, immediate laparotomy is indicated. If a defect is found at the time of postpartum examination after a VBAC, but no bleeding is noted, and the patient is hemodynamically stable, close observation is warranted. Laparotomy is indicated only if the patient shows signs of hematologic or hemodynamic decompensation.

Special Anesthetic Considerations

Anesthetic management considerations are similar to those described in an earlier section on placental abruption.

Summary

Hemorrhage in the obstetric cases occurs unexpectedly and potentially causes serious maternal and fetal morbidity and mortality. Various aspects of antepartum hemorrhage, current obstetric guidelines including nonsurgical and surgical interventions during obstetric hemorrhage, and special anesthetic considerations have been reviewed. Excellent critical care management minimizes postoperative morbidity and mortality after obstetric hemorrhage. A well-equipped labor and delivery operative suite staffed by expert obstetric, anesthesia, neonatal, and nursing teams leads to successful outcome for the mother and baby in obstetric hemorrhagic emergencies.

References

1. Baker RJ. Hemorrhage in obstetrics. Obstet Gynecol Annu 1977;6:295.
2. American College of Obstetricians and Gynecologists. Hemorrhagic Shock, vol 1. ACOG Tech Bull 1984;82.
3. Kaunitz AM, Hughes JM, Grimes DA, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65(5):605–612.
4. Chichakli LO, Atrash HK, MacKay AP, et al. Pregnancy-related mortality in the United States due to hemorrhage: 1979–1992. Obstet Gynecol 1999;94(5 pt 1):721–725.
5. Atrash HK, Koonin LM, Lawson HW, et al. Maternal mortality in the United States, 1979–1986. Obstet Gynecol 1990;76(6):1055–1060.
6. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987–1990. Obstet Gynecol 1996;88(2): 161–167.
7. Cheek TG, Gutsche BB. Maternal physiologic alterations during pregnancy. In: Shnider SM, Levinson G (eds) Anesthesia for Obstetrics. Baltimore: Williams & Wilkins, 1993.
8. Brock-Utne JG, Downing JW, Seedat F. Laryngeal oedema associated with pre-eclamptic toxaemia. Anaesthesia 1977;32(6):556–558.
9. Seager SJ, Macdonald R. Laryngeal oedema and pre-eclampsia. Anaesthesia 1980;35(4):360–362.
10. Hein HA. Cardiorespiratory arrest with laryngeal oedema in pregnancy-induced hypertension. Can Anaesth Soc J 1984;31(2):210–212.
11. Brimacombe J. Acute pharyngolaryngeal oedema and pre-eclamptic toxaemia. Anaesth Intensive Care 1992;20(1):97–98.
12. Rocke DA, Scoones GP. Rapidly progressive laryngeal oedema associated with pregnancy-aggravated hypertension. Anaesthesia 1992;47(2): 141–143.
13. Jouppila R, Jouppila P, Hollmen A. Laryngeal oedema as an obstetric anaesthesia complication: case reports. Acta Anaesthesiol Scand 1980; 24(2):97–98.
14. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth 1995;74(6):638–642.
15. Farcon EL, Kim MH, Marx GF. Changing Mallampati score during labour. Can J Anaesth 1994;41(1):50–51.
16. Bhavani-Shankar K, Lynch EP, Datta S. Airway changes during Cesarean hysterectomy. Can J Anaesth 2000;47(4):338–341.
17. Suresh MS. Difficult airway in the parturient. In: Fleisher LA, Prough DS (eds) Problems in Anesthesia. Airway Management. Hagerstown, MD: Lippincott/Williams & Wilkins, 2001:88–99.
18. Prowse CM. Respiratory and acid-base changes during pregnancy. Anesthesiology 1965;26(4):381–392.
19. Andersen GJ. The maternal oxygen tension and acid-base status during pregnancy. J Obstet Gynaecol Br Commonw 1969;76:16–19.
20. Lucius H, Gahlenbeck H, Kleine HO, et al. Respiratory functions, buffer system, and electrolyte concentrations of blood during human pregnancy. Respir Physiol 1970;9(3):311–317.
21. Lim VS, Katz AI, Lindheimer MD. Acid-base regulation in pregnancy. Am J Physiol 1976;231(6):1764–1769.
22. Templeton A, Kelman GR. Maternal blood-gases, PAO_2—PaO_2): Hysiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976; 48(10):1001–1004.

23. Leontic EA. Respiratory disease in pregnancy. Med Clin N Am 1977; 61(1):111–128.
24. Kirshon B, Cotton DB. Invasive hemodynamic monitoring in the obstetric patient. Clin Obstet Gynecol 1987;30(3):579–590.
25. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol 1989;256(4 pt 2):H1060–H1065.
26. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161(6 pt 1):1439–1442.
27. Gant NFWR. Measurement of uteroplacental blood flow in the human. In: Rosenfeld CR (ed) The Uterine Circulation. Ithaca: Perinatology Press, 1989:53–73.
28. Chesley LC. The effect of posture on renal function in late pregnancy. Am J Obstet Gynecol 1964;89(6):754–759.
29. Wilson M, Morganti AA, Zervoudakis I, et al. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. Am J Med 1980;68(1):97–104.
30. Duvekot JJ, Cheriex EC, Pieters FA, et al. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol 1993;169(6):1382–1392.
31. Lund CJ. Blood volume during pregnancy: significance of plasma and red cell volumes. Am J Obstet Gynecol 1967;98:393–403.
32. Gatti L, Tenconi PM, Guarneri D, et al. Hemostatic parameters and platelet activation by flow-cytometry in normal pregnancy: a longitudinal study. Int J Clin Lab Res 1994;24(4):217–219.
33. Astedt B. Significance of placenta in depression of fibrinolytic activity during pregnancy. J Obstet Gynaecol Br Commonw 1972;79(3):205–206.
34. Chandler WL. The thromboelastograph and the thromboelastograph technique. Semin Thromb Hemost 1995;21:1–6.
35. Sharma SK. Thromboelastographic changes in healthy parturients and postpartum women. Anesth Analg 1997;85:94–98.
36. Gruenwald P, Levin H, Yousem H. Abruption and premature separation of the placenta. The clinical and the pathologic entity. Am J Obstet Gynecol 1968;102(4):604–610.
37. Harris BA. Marginal placental bleeding. Anatomical and pathological considerations. Am J Obstet Gynecol 1952;64(1):53–61.
38. Harris BA Jr, Gore H, Flowers CE Jr. Peripheral placental separation: a possible relationship to premature labor. Obstet Gynecol 1985;66(6): 774–778.
39. Nyberg DA, Cyr DR, Mack LA, et al. Sonographic spectrum of placental abruption. AJR Am J Roentgenol 1987;148(1):161–164.
40. Pritchard JA, Mason R, Corley M, Pritchard S. Genesis of severe placental abruption. Am J Obstet Gynecol 1970;108(1):22–27.
41. Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. JAMA 1999;282(17):1646–1651.
42. Paterson ME. The aetiology and outcome of abruptio placentae. Acta Obstet Gynecol Scand 1979;58(1):31–35.
43. Pritchard JA, Brekken AL. Clinical and laboratory studies on severe abruptio placentae. Am J Obstet Gynecol 1967;97(5):681–700.
44. Hurd WW, Miodovnik M, Hertzberg V, Lavin JP. Selective management of abruptio placentae: a prospective study. Obstet Gynecol 1983; 61(4):467–473.
45. Spirt BA, Kagan EH, Rozanski RM. Abruptio placenta: sonographic and pathologic correlation. AJR Am J Roentgenol 1979;133(5):877–881.
46. Jaffe MH, Schoen WC, Silver TM, et al. Sonography of abruptio placentae. AJR Am J Roentgenol 1981;137(5):1049–1054.
47. McGahan JP, Phillips HE, Reid MH, Oi RH. Sonographic spectrum of retroplacental hemorrhage. Radiology 1982;142(2):481–485.
48. Abdella TN, Sibai BM, Hays JM Jr, Anderson GD. Relationship of hypertensive disease to abruptio placentae. Obstet Gynecol 1984;63(3): 365–370.
49. Hibbard BM, Jeffcoate TN. Abruptio placentae. Obstet Gynecol 1966; 27(2):155–167.
50. Green JR. Placental abnormalities: placenta previa and abruptio placentae. In: Creasy RKR (ed) Maternal Fetal Medicine: Principles and Practice. Philadelphia: Saunders, 1994:592–612.
51. Muldoon MJ. The use of central venous pressure monitoring in abruptio placentae. J Obstet Gynaecol Br Commonw 1969;76:225.
52. Shoemaker WC. Resuscitation of the critically ill patient. Use of branched-chain decision trees to improve outcome. Emerg Med Clin N Am 1986;4(4):655–694.
53. Czer LS, Shoemaker WC. Optimal hematocrit value in critically ill postoperative patients. Surg Gynecol Obstet 1978;147(3):363–368.
54. Oats JN, Vasey DP, Waldron BA. Effects of ketamine on the pregnant uterus. Br J Anaesth 1979;51(12):1163–1166.
55. Suresh MS. Comparison of etomidate with thiopental for induction of anesthesia at cesarean section. Anesthesiology 1986;65(3A):A400.
56. Andrews WW. Effect of type of anesthesia on blood loss at elective repeat cesarean section. Am J Perinatology 1992;9(3):197–200.
57. Belfort MA, Rokey R, Saade GR, Moise KJ Jr. Rapid echocardiographic assessment of left and right heart hemodynamics in critically ill obstetric patients. Am J Obstet Gynecol 1994;171(4):884–892.
58. Murphy MB, Murray C, Shorten GD. Fenoldopam—a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. N Engl J Med 2001;345(21):1548–1557.
59. Halpenny M, Markos F, Snow HM, et al. Effects of prophylactic fenoldopam infusion on renal blood flow and renal tubular function during acute hypovolemia in anesthetized dogs. Crit Care Med 2001;29(4): 855–860.
60. Poinsot O, Romand JA, Favre H, Suter PM. Fenoldopam improves renal hemodynamics impaired by positive end-expiratory pressure. Anesthesiology 1993;79(4):680–684.
61. Mathur VS, Swan SK, Lambrecht LJ, et al. The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. Crit Care Med 1999;27(9):1832–1837.
62. Douglas RG, Buckman MI, MacDonald PF. Premature separation of the normally implanted placenta. J Obstet Gynaecol Br Emp 1955;62:710.
63. Basu HK. Fibrinolysis and abruptio placentae. Br J Obstet Gynaecol 1969;76:481.
64. Sher G. Pathogenesis and management of uterine inertia complicating abruptio placentae with consumption coagulopathy. Am J Obstet Gynecol 1977;129(2):164–170.
65. Clark SL, Cotton DB, Hankins G, Phelan JP. Critical Care Obstetrics, 3rd edn. Oxford: Blackwell Publishing 1997.
66. Collins JA. Recent developments in the area of massive transfusion. World J Surg 1987;11(1):75–81.
67. Consensus Conference. Platelet transfusion therapy. JAMA 1987;257: 1777–1780.
68. Sharma SK. Assessment of parturients with TEG during massive hemorrhage. In: Abstracts, Society for Obstetric Anesthesiology and Perinatology 27th Annual Meeting, 1995;132.
69. McNicol PL, Liu G, Harley ID, et al. Blood loss and transfusion requirements in liver transplantation: experience with the first 75 cases. Anaesth Intensive Care 1994;22(6):666–671.
70. Wilson RJ. Bleeding during late pregnancy. In: Wilson RJ (ed) St. Louis: Mosby, 1983.
71. Clark SL, Koonings PP, Phelan JP. Placenta previa/accreta and prior cesarean section. Obstet Gynecol 1985;66(1):89–92.
72. Silver R, Depp R, Sabbagha RE, et al. Placenta previa: aggressive expectant management. Am J Obstet Gynecol 1984;150(1):15–22.
73. Cotton DB, Read JA, Paul RH, Quilligan EJ. The conservative aggressive management of placenta previa. Am J Obstet Gynecol 1980;137(6): 687–695.
74. Wexler P, Gottesfeld KR. Second trimester placenta previa. An apparently normal placentation. Obstet Gynecol 1977;50(6):706–709.

75. Wexler P, Gottesfeld KR. Early diagnosis of placenta previa. Obstet Gynecol 1979;54(2):231–234.
76. Farine D, Peisner DB, Timor-Tritsch IE. Placenta previa—is the traditional diagnostic approach satisfactory? J Clin Ultrasound 1990;18(4): 328–330.
77. Powell MC, Buckley J, Price H, et al. Magnetic resonance imaging and placenta previa. Am J Obstet Gynecol 1986;154(3):565–569.
78. Naeye RL, Harkness WL, Utts J. Abruptio placentae and perinatal death: a prospective study. Am J Obstet Gynecol 1977;128(7):740–746.
79. Brenner WE, Edelman DA, Hendricks CH. Characteristics of patients with placenta previa and results of "expectant management." Am J Obstet Gynecol 1978;132(2):180–191.
80. Droste S, Keil K. Expectant management of placenta previa: cost-benefit analysis of outpatient treatment. Am J Obstet Gynecol 1994; 170(5 pt 1):1254–1257.
81. Mouer JR. Placenta previa: antepartum conservative management, inpatient versus outpatient. Am J Obstet Gynecol 1994;170(6):1683–1685.
82. Wing DA, Paul RH, Millar LK. Management of the symptomatic placenta previa: a randomized, controlled trial of inpatient versus outpatient expectant management. Am J Obstet Gynecol 1996;175(4 pt 1): 806–811.
83. Abboud TK. Anesthesia for placenta previa at Women's Hospital: 3 year survey. In: Abstracts, 25th Annual Meeting, 1993;19.
84. Chestnut DH, Thompson CS, McLaughlin GL, Weiner CP. Does the intravenous infusion of ritodrine or magnesium sulfate alter the hemodynamic response to hemorrhage in gravid ewes? Am J Obstet Gynecol 1988;159(6):1467–1473.
85. Sipes SL, Chestnut DH, Vincent RD Jr, et al. Which vasopressor should be used to treat hypotension during magnesium sulfate infusion and epidural anesthesia? Anesthesiology 1992;77(1):101–108.
86. Sherman SJ, Greenspoon JS, Nelson JM, Paul RH. Identifying the obstetric patient at high risk of multiple-unit blood transfusions. J Reprod Med 1992;37(7):649–652.
87. McVay PA, Hoag RW, Hoag MS, Toy PT. Safety and use of autologous blood donation during the third trimester of pregnancy. Am J Obstet Gynecol 1989;160(6):1479–1486.
88. Consensus conference. Perioperative red blood cell transfusion. JAMA 1988;260(18):2700–2703.
89. Practice Guidelines for blood component therapy. A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996;84(3):732–747.
90. Graber SE, Krantz SB. Erythropoietin and the control of red cell production. Annu Rev Med 1978;29:51–66.
91. Egrie JC. Characterization and biological effects of human recombinant erythropoietin. Immunobiology 1986;172:213–224.
92. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med 1987; 316(2):73–78.
93. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med 1989;111(12): 992–1000.
94. Rutherford CJ, Schneider TJ, Dempsey H, et al. Efficacy of different dosing regimens for recombinant human erythropoietin in a simulated perisurgical setting: the importance of iron availability in optimizing response. Am J Med 1994;96(2):139–145.
95. Abraham PA, Halstenson CE, Macres MM, et al. Epoietin enhances erythropoiesis in normal men undergoing repeated phlebotomies. Clin Pharmacol Ther 1992;52:205.
96. Fishbane S, Maesaka JK. Iron management in end-stage renal disease. Am J Kidney Dis 1997;29(3):319–333.
97. Sowade O, Warnke H, Scigalla P, et al. Avoidance of allogeneic blood transfusions by treatment with epoetin beta (recombinant human erythropoietin) in patients undergoing open-heart surgery. Blood 1997;89(2): 411–418.
98. Goldberg MA, McCutchen JW, Jove M, et al. A safety and efficacy comparison study of two dosing regimens of epoetin alfa in patients undergoing major orthopedic surgery. Am J Orthop 1996;25(8):544–552.
99. Dodril FD. The use of the heart-lung apparatus in human cardiac surgery. J Thorac Cardiovasc Surg 1957;33:60–74.
100. Helm RE, Klemperer JD, Rosengart TK, et al. Intraoperative autologous blood donation preserves red cell mass but does not decrease postoperative bleeding. Ann Thorac Surg 1996;62(5):1431–1441.
101. Kochamba GS, Pfeffer TA, Sintek CF, Khonsari S. Intraoperative autotransfusion reduces blood loss after cardiopulmonary bypass. Ann Thorac Surg 1996;61(3):900–903.
102. Stehling L, Zauder HL. Acute normovolemic hemodilution. Transfusion 1991;31(9):857–868.
103. Stehling L. Alternatives to allogeneic transfusion. In: Petz LD (ed) Clinical Practice of Transfusion Medicine. New York: Churchill Livingstone, 1996:539–561.
104. Stehling L, Zauder HL. Controversies in transfusion medicine. Perioperative hemodilution: pro. Transfusion 1994;34(3):265–268.
105. Estella NM. Normovolemic hemodilution before cesarean hysterectomy for placenta percreta. Obstet Gynecol 1997;89:1–2.
106. Grange CS, Douglas MJ, Adams TJ, Wadsworth LD. The use of acute hemodilution in parturients undergoing cesarean section. Am J Obstet Gynecol 1998;178(1 pt 1):156–160.
107. Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983;58(3):277–280.
108. Monk TG, Goodnough LT, Birkmeyer JD, et al. Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropubic prostatectomy. Transfusion 1995;35(7):559–565.
109. Monk TG, Goodnough LT. Blood conservation strategies to minimize allogeneic blood use in urologic surgery. Am J Surg 1995;170(6A suppl):69S–73S.
110. Baker BW. Blood Conservation, obstetrics, and Jehovah's Witnesses. Anesthesiol Clin N Am 1998;16(2):375–384.
111. Messmer K, Kreimeier U, Intaglietta M. Present state of intentional hemodilution. Eur Surg Res 1986;18(3–4):254–263.
112. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts—blood transfusion. N Engl J Med 1999; 340(6):438–447.
113. Stramer SL, Caglioti S, Strong DM. NAT of the United States and Canadian blood supply. Transfusion 2000;40(10):1165–1168.
114. Rainaldi MP, Tazzari PL, Scagliarini G, et al. Blood salvage during caesarean section. Br J Anaesth 1998;80(2):195–198.
115. Jackson SH, Lonser RE. Safety and effectiveness of intracesarean blood salvage. Transfusion 1993;33(2):181.
116. Rebarber A, Lonser R, Jackson S, et al. The safety of intraoperative autologous blood collection and autotransfusion during cesarean section. Am J Obstet Gynecol 1998;179(3 pt 1):715–720.
117. Potter PS, Waters JH, Burger GA, Mraovic B. Application of cell-salvage during cesarean section. Anesthesiology 1999;90(2):619–621.
118. National Heart La. Transfusion alert: use of autologous blood. National Heart, Lung, and Blood Institute Expert Panel on the Use of Autologous Blood. Transfusion 1995;35(8):703–711.
119. Bernstein HH, Rosenblatt MA, Gettes M, Lockwood C. The ability of the Haemonetics 4 Cell Saver System to remove tissue factor from blood contaminated with amniotic fluid. Anesth Analg 1997;85(4):831–833.
120. Fong J, Gurewitsch ED, Kump L, Klein R. Clearance of fetal products and subsequent immunoreactivity of blood salvaged at cesarean delivery. Obstet Gynecol 1999;93(6):968–972.
121. Cattling SJ. Cell salvage in obstetrics: an evaluation of the ability of cell salvage combined with leucocyte depletion filtration to remove amniotic fluid from operative blood loss at cesarean section. Int J Obstet Anesth 1999;8:79–84.

122. Waters JH, Biscotti C, Potter PS, Phillipson E. Amniotic fluid removal during cell salvage in the cesarean section patient. Anesthesiology 2000;92(6):1531–1536.
123. Durand FD. Rheologic and cytologic study of autologous blood collected with cell savers during cesarean. Rev Fr Transfusion Hemobiol 1989;32:179–191.
124. Weiskopf RB. Erythrocyte salvage during cesarean section. Anesthesiology 2000;92(6):1519–1522.
125. Nightingale SD. Summary of Meeting of the DHSS Advisory Committee on Blood Safety and Availability, 29–30 May 1999. Washington, DC: U.S. Department of Health and Human Services, Office of the Secretary.
126. Cunningham FG, MacDonald PC, Gant NF. Diseases and abnormalities of the fetal membranes. In: Cunningham FG and Williams SW, (eds) Williams Obstetrics, 20th edn. Stamford, CT: Appleton & Lange, 1997:674.
127. Antoine C, Young BK, Silverman F. Sinusoidal fetal heart rate pattern with vasa previa in twin pregnancy. Obstet Gynecol 1982;27:295.
128. Benirschke K, Kaufmann P. The Pathology of the Human Placenta. New York: Springer-Verlag, 1995.
129. Lynch C, Coker A, Lawal AH, et al. The B-Lynch surgical technique for the control of massive postpartum haemorrhage: an alternative to hysterectomy? Five cases reported. Br J Obstet Gynaecol 1997;104(3): 372–375.
130. Ferguson JE, Bourgeois FJ, Underwood PB. B-Lynch suture for postpartum hemorrhage. Obstet Gynecol 2000;95(6 pt 2):1020–1022.
131. Clark SL. Placenta previa and abruptio placentae. In: Creasy RK, Resnik R (eds) Maternal-Fetal Medicine. Philadelphia: Saunders, 1999:620.
132. Zaki ZM, Bahar AM, Ali ME, et al. Risk factors and morbidity in patients with placenta previa accreta compared to placenta previa non-accreta. Acta Obstet Gynecol Scand 1998;77(4):391–394.
133. Kay HH, Spritzer CE. Preliminary experience with magnetic resonance imaging in patients with third-trimester bleeding. Obstet Gynecol 1991;78(3 pt 1):424–429.
134. Levine D, Barnes PD, Edelman RR. Obstetric MR imaging. Radiology 1999;211(3):609–617.
135. Ha TP, Li KC. Placenta accreta: MRI antenatal diagnosis and surgical correlation. J Magn Reson Imaging 1998;8(3):748–750.
136. Hudon L, Belfort MA, Broome DR. Diagnosis and management of placenta percreta: a review. Obstet Gynecol Surv 1998;53(8):509–517.
137. Maldjian C, Adam R, Pelosi M, et al. MRI appearance of placenta percreta and placenta accreta. Magn Reson Imaging 1999;17(7):965–971.
138. Ito T, Katagiri C, Ikeno S, et al. Placenta previa increta penetrating the entire thickness of the uterine myometrium: ultrasonographic and magnetic resonance imaging findings. J Obstet Gynaecol Res 1999;25(5): 303–307.
139. Chou MM, Ho ES, Lee YH. Prenatal diagnosis of placenta previa accreta by transabdominal color Doppler ultrasound. Ultrasound Obstet Gynecol 2000;15(1):28–35.
140. Kidney DD, Nguyen AM, Ahdoot D, et al. Prophylactic perioperative hypogastric artery balloon occlusion in abnormal placentation. AJR Am J Roentgenol 2001;176(6):1521–1524.
141. Dubois J, Garel L, Grignon A, et al. Placenta percreta: balloon occlusion and embolization of the internal iliac arteries to reduce intraoperative blood losses. Am J Obstet Gynecol 1997;176(3):723–726.
142. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med 2001;344(1):38–47.
143. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;179(4):1043–1046.
144. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105(9):971–975.
145. Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94(2):255–258.
146. Gulmezoglu AM, Villar J, Ngoc NT, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358(9283):689–695.
147. Chestnut DH. Obstetric Anesthesia. Principles and Practice, 2nd edn. St. Louis: Mosby, 1999.
148. Chestnut DH, Dewan DM, Redick LF, et al. Anesthetic management for obstetric hysterectomy: a multi-institutional study. Anesthesiology 1989;70(4):607–610.
149. Sprung J, Cheng EY, Patel S. When to remove an epidural catheter in a parturient with disseminated intravascular coagulation. Reg Anesth 1992;17(6):351–354.
150. Abbi M, Misra R. Rupture of uterus in a primigravida prior to onset of labor. Int J Fertil Womens Med 1997;42(6):418–420.
151. Milon D, Chevrant-Breton O, Tekam S, et al. Rupture of the uterus during labor without apparent cause. Eur J Obstet Gynecol Reprod Biol 1983;15(1):1–4.
152. Nel JT. An unusual case of uterine rupture. A case report. S Afr Med J 1984;65(2):60–61.
153. Langton J, Fishwick K, Kumar B, Nwosu EC. Spontaneous rupture of an unscarred gravid uterus at 32 weeks gestation. Hum Reprod 1997; 12(9):2066–2067.
154. Fischer RL. Spontaneous rupture of an unscarred uterus in a primigravid woman. Am J Obstet Gynecol 1996;175(2):504–505.
155. American College of Obstetricians and Gynecologists. Vaginal birth after previous cesarean delivery. In: The American College of Obstetricians and Gynecologists (ed) 2001 Compendium of Selected Publications. Washington, DC: The American College of Obstetricians and Gynecologists, 1999:1106–1112.
156. Holt VL, Mueller BA. Attempt and success rates for vaginal birth after caesarean section in relation to complications of the previous pregnancy. Paediatr Perinat Epidemiol 1997;11 Suppl 1:63–72.
157. Hoskins IA, Gomez JL. Correlation between maximum cervical dilatation at cesarean delivery and subsequent vaginal birth after cesarean delivery. Obstet Gynecol 1997;89(4):591–593.
158. Lydon-Rochelle M, Holt VL, Easterling TR, Martin DP. Risk of uterine rupture during labor among women with a prior cesarean delivery. N Engl J Med 2001;345(1):3–8.
159. Zelop CM, Shipp TD, Repke JT, et al. Uterine rupture during induced or augmented labor in gravid women with one prior cesarean delivery. Am J Obstet Gynecol 1999;181(4):882–886.
160. Crosby WMCJ. Safety of lapbelt restraint for pregnant victims of automobile collisions. N Engl J Med 1971;284:6326–6329.
161. Rothenberger D, Quattlebaum FW, Perry JF Jr, et al. Blunt maternal trauma: a review of 103 cases. J Trauma 1978;18(3):173–179.
162. O'Keeffe DF. When the accident victim is pregnant. Contemp Ob Gyn 1985;148–163.
163. Nelson DM, Stempel LE, Zuspan FP. Association of prolonged, preterm premature rupture of the membranes and abruptio placentae. J Reprod Med 1986;31(4):249–253.
164. Chasnoff IJ, Burns KA, Burns WJ. Cocaine use in pregnancy: perinatal morbidity and mortality. Neurotoxicol Teratol 1987;9(4):291–293.
165. Rice JP, Kay HH, Mahony BS. The clinical significance of uterine leiomyomas in pregnancy. Am J Obstet Gynecol 1989;160(5 pt 1): 1212–1216.
166. Glueck CJ, Kupferminc MJ, Fontaine RN, et al. Genetic hypofibrinolysis in complicated pregnancies. Obstet Gynecol 2001;97(1):44–48.
167. Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999;340(1):9–13.
168. van der Molen EF, Arends GE, Nelen WL, et al. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene as a new risk fac-

tor for placental vasculopathy. Am J Obstet Gynecol 2000;182(5): 1258–1263.
169. Hibbard LT. Placenta previa. In: Sciarra JJ, editor. Gynecology and Obstetrics. New York: Harper & Row, 1981.
170. Iyasu S, Saftlas A, Rowley D. The epidemiology of placenta previa in the United States, 1979 though 1987. Am J Obstet Gynecol 1993;168: 1424.
171. Ananth CV, Wilcox A, Savitz DA. Effect of maternal age and parity on the risk of uteroplacental bleeding disorders in pregnancy. Obstet Gynecol 1996;88:511.
172. Kelly JV IL. Placenta Previa. In: Iffy L KH, editor. Principles and Practice of Obstetrics and Perinatology. New York: John Wiley & Sons, 1981.
173. To WW, Leung WC. Placenta previa and previous cesarean section. Int J Gynaecol Obstet 1995;51(1):25–31.
174. Clark SL, Koonings PP, Phelan JP. Placenta previa/accreta and prior cesarean section. Obstet Gynecol 1985;66(1):89–92.

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9
Postpartum Hemorrhage

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The tremendous reduction in maternal mortality in developed countries has been one of the great achievements in obstetrics this century. In the United Kingdom, for example, between 1952 and 1954 there were approximately 70 deaths per 100,000 deliveries; in 1994 to 1996, maternal deaths fell to 11 per 100,000 deliveries.[1] In the United States, the past 50 years have seen a similar reduction in maternal deaths achieved by improvements in antenatal and intrapartum obstetric care, the establishment of blood banks, and improved treatment of peripartum hemorrhage.[2] Although maternal mortality rates have plummeted in the developed world, global mortality for mothers in childbirth remains between 500,000 and 600,000 annually, with postpartum hemorrhage accounting for an estimated 125,000 deaths worldwide each year.[3] The improvements that have saved thousands of lives in the developed world have not been adequately translated for many reasons. The cost of some services, inability to maintain a safe blood supply, and lack of resources have continued to cost the lives of thousands of women worldwide.

Postpartum hemorrhage remains one of the greatest risks facing the parturient, representing a large proportion of maternal mortality and peripartum complications. In the most recent evaluation from the United Kingdom, hemorrhage was the third leading cause of death at term and accounted for 50% of maternal deaths after childbirth.[1] In the United States, one investigation found that postpartum hemorrhage was one of the leading indications for admission to intensive care units, and that obstetric shock was one of the largest risk factors for mortality.[4] A recent evaluation of the causes of maternal mortality in the state of Maryland found that postpartum hemorrhage represented the third leading cause of pregnancy-related deaths and was equal to preeclampsia as the leading cause of in-hospital mortality among parturients between 1984 and 1997.[5]

The Postpartum Period

Maternal Physiology

In normal pregnancy, maternal blood volume is increased by 30% to 40% over the nonpregnant baseline. This change is accomplished by an expansion of 50% in the plasma volume but an increase of only 30% in red blood cell mass.[6,7] This expansion of blood volume and physiologic anemia buffers the blood loss that occurs during parturition, protecting maternal hemodynamics and oxygen-carrying capacity, respectively.[8] The average loss of blood in a normal vaginal delivery appears to be in the range of 500 mL.[9] Similarly, the acute loss of blood that occurs with cesarean delivery is reported to be 1000 mL.[8,10] Regardless of the exact amount, the blood lost during delivery is approximately equal to the pregnancy-induced expansion; central blood volume after delivery remains at or above prepregnancy levels.[8] This change has little effect on maternal hemodynamics and well-being. Robson et al.[11] studied the hemodynamics of 10 women who had postpartum hemorrhage and compared them to 30 controls who did not. Among women with significant hemorrhage, cardiac stroke volume decreased and heart rate increased in the immediate postpartum period, and these changes lasted for approximately 48 h. However, maternal blood pressure and cardiac output were similar to the control group. The physiologic anemia of pregnancy acts to protect the vital cells of oxygen transport from blood lost during hemorrhage. In the early postpartum period, circulating plasma volume contracts, producing a hemoconcentration. As a result, the maternal hematocrit decreases by only 2% to 4% after vaginal or cesarean deliveries, respectively.[12]

The gravid uterus receives approximately 600 to 700 mL blood per minute at term pregnancy.[13] After delivery, the intense contraction of the myometrium causes the large amount of blood flowing through the uterus to be returned to the maternal circulation, a process termed autotransfusion. This autotransfusion can deliver 500 mL blood to the central circulation, which helps balance maternal losses. Failure of the myometrium to contract prevents this autotransfusion, which could potentially affect maternal hemodynamics. In addition, some investigators have noted that the arteries supplying the uterus taken from parturients who suffered a significant postpartum hemorrhage may be less reactive to vasoconstrictors than those found in the normal population.[14] Uterine artery vasoconstriction would limit blood flow to the site of

hemorrhage, and loss of vascular reactivity could worsen the rate of blood loss. Whether the loss of normal reactivity in the vasculature is a cause of maternal hemorrhage or a consequence of prolonged sympathetic stimulation and receptor downregulation is not known.

Uterine Retraction and Hemostasis

The primary mechanism for hemostasis in the postpartum period is the retraction of the uterine musculature. At term pregnancy, the individual smooth muscle cells of the uterine musculature develop gap junctions between cell walls, creating a network of communication that coordinates uterine activity. The smooth muscle cells of the myometrium are organized differently than either skeletal or cardiac striated muscles; the formations of actin and myosin fibrils are not linear, but arranged at random.[15] The force of uterine contraction is vectored in all directions, facilitating simultaneous uterine contraction and increase in intramyometrial pressure. During labor, this organization produces an effective force to properly expel the fetus.[15] It is likely that the same structure aids in producing uterine retraction in the immediate postpartum period. The intense intramyometrial pressure generated by the hypertrophied uterus causes a physical constriction of the small uterine arterioles, cutting off blood flow.

The classical hemostatic mechanisms, such as the intrinsic and extrinsic pathways, platelet aggregation, and fibrin formation, play a secondary but important role for maintaining hemostatic control of uterine bleeding. During pregnancy, there is a significant increase in the amount and activity of most coagulation factors, with the result that most parturients have a prothrombotic state. Dysfunction of the coagulation system does not affect the ability of the uterus to constrict the blood vessels during retraction but can lead to poor clot formation, early breakdown, and rebleeding. Parturients with coagulation disorders are at considerably higher risk of delayed hemorrhage.

The Third Stage of Labor

The third stage of labor extends from delivery of the neonate to passage of the placenta. In most cases, the third stage of labor proceeds without complication; in some women, however, placental separation is delayed or fails, and subsequent uterine atony may result in significant hemorrhage. Studies of the natural history of the third stage of labor suggest that delayed placental delivery of more than 30 min is associated with a greater incidence of maternal complications, including blood transfusions and curettage.[16,17] Because the active contraction of the uterus and delivery of the placenta are essential components in limiting maternal hemorrhage, a significant amount of research has focused on the management of the third stage of labor. Two methods of management have been described: conservative and active management. Conservative management is an expectant process, allowing the normal physiologic separation and delivery of the placenta. Active management of the third stage of labor is designed to promote placental delivery and to decrease the duration of the third stage of labor. Active management of the third stage of labor has been shown to decrease the severity of maternal blood loss, the duration of the third stage, and the incidence of postpartum hemorrhage; whether this prevents maternal transfusion and hysterectomy is unclear.[18,19]

The Fourth Stage of Labor

The fourth stage of labor extends from placental delivery to approximately 1 to 2 h postpartum and represents a period of increased risk of uterine atony and maternal hemorrhage. Careful observation of all parturients in the immediate postpartum period should be encouraged, as bleeding in the fourth stage can occur in otherwise low-risk patients, despite successful initial contraction. The parturient should remain in a supervised location during the fourth stage of labor and should receive frequent evaluation and massage of the uterus to prevent accumulation of blood clots and relaxation of the uterus. Continuation of uterotonic agents, such as oxytocin, will ensure that the uterus remains firm and contracted. Compression of the fundus helps in evacuating clots and debris. Maternal hemodynamics should be periodically monitored to help identify parturients with an occult blood loss. The causes of bleeding in the fourth stage of labor are similar to those in the third stage.

Postpartum Hemorrhage

Definition and Incidence

Postpartum hemorrhage is a clinical event occurring in the parturient. Although definitions vary, postpartum hemorrhage may occur in as many as 5% of all deliveries.[3] Historically, postpartum hemorrhage was defined as a blood loss of greater than 500 mL in the first 24 h after birth. It is now recognized that this definition is inadequate and clinically irrelevant. Visual estimates of bleeding become more inaccurate with greater amounts of blood loss and are approximately twice what experienced clinicians would report.[9] Some authors have suggested the definition of greater than 1000 mL blood loss during delivery. This definition is more relevant for investigations, as approximately 1% to 3% of women lose more than 1000 mL of blood after a vaginal delivery.[20,21] Because the amount of blood loss is difficult to measure accurately while administering care, other authors have suggested a clinical definition for hemorrhage as that which has or would produce hemodynamic instability.[22] The American College of Obstetrics and Gynecology has proposed a definition of a decrease in hematocrit of at least 10%, or the need for blood transfusion in the postpartum setting.[23] This definition identifies more than 97% of women experiencing more than 1000 mL blood loss but can only do so in hindsight.

Etiology

The etiology of postpartum hemorrhage can be separated into uterine and nonuterine causes, with the former accounting for most cases.[20] Uterine atony is the foremost cause of uterine bleeding (Table 9.1). Atony may be the primary cause of bleeding or may be associated with other causes such as retained placenta or endometrial uterine inversion. Other sources of uterine bleeding include lacerations that can result from vaginal deliveries but more commonly arise during cesarean delivery. Bleeding that originates from a nonuterine source is most commonly found in the genital tract and associated structures. Traumatic lacerations and hematomas are not uncommon and are usually identifiable and easily repaired. Uterine atony is the most common cause of hemorrhage; however, because genital tract trauma is often a delayed diagnosis, its prognosis may be worse.[24]

Prompt and accurate identification of the cause of postpartum hemorrhage is essential for treatment. Slow and persistent bleeding is a serious complication, as the recognition of excessive blood loss may remain obscured and treatment delayed until the onset of hypovolemic shock. Additionally, some parturients may have intraperitoneal bleeding or may accumulate a large amount of blood in the uterus before the diagnosis of hemorrhage is made. Unexplained hypotensive episodes or poor urine output in the postpartum woman should raise a high degree of suspicion for occult hemorrhage.

Table 9.2. Causes of postpartum hemorrhage.

Uterine
Antepartum hemorrhage
Atony
Placenta accreta
Retained placenta
Placenta fragments
Uterine laceration
Uterine rupture
Nonuterine
Genital tract trauma
Vaginal laceration
Cervical laceration
Genital tract hematomas
Intraabdominal or pelvic laceration (after cesarean delivery)
Coagulation disorders

Classification

Primary Postpartum Hemorrhage

Primary postpartum hemorrhage, which is also referred to as early hemorrhage, describes a significant blood loss in the first 24 h after delivery. Primary postpartum hemorrhage most often results from uterine atony. The etiology of uterine atony can be an intrinsic failure of the uterine musculature to contract, as may be found with overdistension, infection, or after dysfunctional labor; or the etiology may be extrinsic factors that prevent the uterus from completely contracting, such as retention of placental fragments, uterine clots, or an enlarged bladder (Table 9.2). Some cases of postpartum hemorrhage are uncontrollable by any means, requiring a hysterectomy to save the mother's life. With the dramatic overall increase in cesarean deliveries, abnormal placentation, such as placenta accreta, has become the most common cause of hemorrhage of great enough severity to necessitate hysterectomy.[25,26] A minority of cases of severe postpartum hemorrhage (approximately 20%) are caused by genital tract trauma; however, maintaining clinical suspicion of nonuterine etiology is of utmost importance.

Table 9.1. Etiology of uterine atony.

Disorder	Examples	Possible mechanism	Treatment options
Uterine over distension	Multiple gestation	Excessive stretch of actin–myosin complexes	Uterine massage
	Macrosomia		Uterotonics
	Polyhydramnios		
Intrinsic uterine dysfunction	Prolonged labor	Poor contractility	Uterotonics
	Prolonged second stage	Poor coordination	Second-line agents often required
Extrinsic uterine dysfunction	Retained placenta	Physical barrier to contraction	Evacuate the cavity
	Placental fragments		Uterine massage
	Blood and clots		Fundal pressure
	Bladder distension		Bladder catheterization
Prolong exposure to oxytocin	Induction of labor	Receptor down regulation	Uterotonics
	Labor augmentation		Second-line agents often required
Uterine or placental abnormalities	Surgical scars	Noncontractile tissue	Invasive therapy often required
	Placenta accreta		Devascularization
	Endometritis		Hysterectomy
	Chorioamnionitis		
Iatrogenic	Magnesium sulfate	Direct antagonism	Discontinue agents
	Terbutaline		Uterotonics
	Volatile anesthetics		Calcium gluconate

Secondary Postpartum Hemorrhage

Secondary postpartum hemorrhage describes a significant blood loss occurring more than 24 h after delivery and up to 6 weeks postpartum. For many patients, secondary postpartum hemorrhage can be life threatening because identification and treatment can be delayed. The parturient with secondary postpartum hemorrhage is likely to require intensive medical care for hypovolemic shock, including vasopressors, transfusion, and intubation, and is very likely to have an associated coagulopathy.[27] Causes of secondary postpartum hemorrhage are similar to the causes of primary hemorrhage; however, there is a greater likelihood that invasive or surgical procedures will be required for treatment.[28]

Treatment

The goals in the treatment of postpartum hemorrhage are as follows:

1. Identify and correct the cause of hemorrhage.
2. Resuscitate the patient.
3. Prevent further complications including rebleeding and infection.

Three components are essential for a successful outcome in the treatment of any uncommon life-threatening emergency: planning, communication, and teamwork. No obstetric center should wait for a life-threatening hemorrhage to develop a treatment plan or to determine the availability of resources. Primary planning, available resources, and alternative plans must be created, identified, and practiced before any emergency situation arises. The tremendous effectiveness of modern pharmacologic agents has made intractable postpartum hemorrhage a rare event; the ubiquitous good outcomes in obstetrics have become the norm, with the result that clinicians may become complacent. Developing a step-by-step treatment plan for these rare events is essential to ensure the highest level of success. All members of the team should be well versed in the steps involved and aware of the next phase of the plan if the current treatment should fail. It is also incumbent on the clinicians to communicate effectively with the other members of the team to ensure that the entire plan is being implemented appropriately. A plan for obstetric, medical, and anesthetic management of postpartum hemorrhage is shown in Table 9.3.

Several components of the care of the parturient must be assessed, and if these are not immediately available, alternatives should be prepared. Although it is unlikely that small centers can have immediate availability to all the necessary components, patient transport to a tertiary facility can be arranged; however, these plans should be made well in advance of an emergency event. Vital components of care include the following:

1. Prompt access to resuscitative equipment
2. Availability of blood products
3. Availability of an operating room and surgical personnel
4. Rapid return of laboratory results
5. Availability of intensive care facilities
6. Availability of an angiography suite and trained personnel

Most cases of postpartum hemorrhage respond to medical and obstetric management, including manual extraction, dilation, and curettage. Cases that remain unresponsive to these treatments may require interruption of the vascular supply to the uterus by either surgical arterial ligation or arterial embolization under angiography, and these steps can often salvage fertility in the mother. The final, lifesaving step in the treatment of postpartum hemorrhage is hysterectomy, which should be performed when other treatments fail or are unavailable.

Pharmacology

Oxytocin

Oxytocin is a nanopeptide hormone released by the posterior pituitary after being produced in the hypothalamus. Currently commercial preparations of oxytocin are produced synthetically, resulting in a highly purified molecule with minimal amounts of vasopressor and antidiuretic effects (Table 9.4). Historically, preparations of oxytocin were derived from animal extracts and naturally included a small amount of the other hormone produced in the posterior pituitary, vasopressin or antidiuretic hormone. Thus, old case reports of complications due to oxytocin administration included occasional hypertension. However, the two hormone molecules are similar enough that some cross-activity does exist.

Oxytocin injectate should be stored in a room temperature or cooler environment and is stable, depending on the manufacturer, for up to 3 months or 5 years. Oxytocin is distributed throughout the extracellular fluid and is metabolized by chymotrypsin in the gastrointestinal tract and oxytocinase, an enzyme produced in early pregnancy. The plasma half-life is approximately 3 to 5 min; the duration of action of oxytocin is 1 to 2 h after intramuscular injection. Response by the myometrium following intravenous injection or oxytocin is almost immediate. Adverse effects of oxytocin include maternal hypotension, tachycardia, and arrhythmias. With very high doses, the minor activation of vasopressor and antidiuretic hormone that can be found even in synthetic solutions may produce hypertension, pulmonary hypertension, and water intoxication. Oxytocin can be given intramuscularly, intravenously, or intranasally but not orally because it is metabolized in the gastrointestinal tract. It is strongly recommended to dilute the injection before intravenous use to avoid excessive dosages.

In the final trimester of pregnancy, the number of oxytocin receptors increases dramatically, peaking around term. Oxytocin acts to increase the frequency and duration of myometrial contraction, which is likely mediated through increased intracellular calcium concentrations. Oxytocin also has effects

TABLE 9.3. Treatment of postpartum hemorrhage.

Obstetric management	Medical management	Anesthetic management
Evacuate the uterine cavity	Administer uterotonics	Obtain adequate venous access
Deliver the placenta	Oxytocin (IM or IV) as first-line agent	Two large-bore peripheral IV catheters
Manual extraction if unresolved at 30 min	5–10 U IM	
Manual extraction at *any* time if actively bleeding	Continuous infusion of oxytocin	Volume resuscitation
Evacuate placental fragments	10–40 U in 1000 mL IV infusion	Crystalloid solution 10–15 mL/kg bolus
Curettage	Second-line agents if uterus remains atonic	Repeat bolus infusion per assessment of requirements
Consider ultrasound	15-Methyl-prostaglandin $F_{2\alpha}$	Transfusion for physiologic requirement
Massage the uterus	250 μg IM	
	Misoprostol	Monitor resuscitation
Inspect genital tract	400–1000 μg PR or PO	Maternal vital statistics
Repair lacerations	Methylergonovine	Blood pressure
Consider vaginal packing	200 μg IM	Pulse
		Oxygen saturation
Insert Foley catheter	Maternal blood analysis	Urine output
Reduce bladder size	Type and crossmatch	Maternal oxygen delivery
Monitor urine output	Hemoglobin or hematocrit	Pulse oxymetry
	Platelet count	Hemoglobin or hematocrit concentrations
Obtain assistance	Coagulation studies	Arterial blood gas analysis
Anesthesia	Arterial blood gas	Oxygen tension (Po_2)
Additional personnel		Acid–base status
	Prevent complications	Central hemodynamic monitoring
Additional support	Coagulation disorders	Central venous access
Blood bank availability	Dilution coagulopathy	Pressure monitoring
Operating room	Disseminated intravascular coagulopathy	Central administration of vasopressor agents
Surgical personnel	Hypothermia	Large-bore venous access
Ultrasonography	Infection	Pulmonary artery measurements
Angiographic suite and personnel		Diagnosis of intractable hypotension, hypoxia, low urine output
	Disposition	Measure adequacy of resuscitaton via mixed venous saturation
Intractable hemorrhage	Maintain observation for resumption of hemorrhage	
Consider bimanual compression	Transfer to intensive care unit	
Consider uterine packing		
Interrupt arterial supply		
Embolization		
Surgical ligation		
Hysterectomy		

on vascular smooth muscle, where in low concentrations the hormone acts as a vasodilator. Weis et al.[29] studied the effect of a bolus injection of 0.1 IU/kg of oxytocin in healthy first trimester parturients under general anesthesia; they demonstrated a decrease in maternal blood pressure of 30%, decrease in peripheral vascular resistance of 50%, and a subsequent increase in heart rate and cardiac output. The duration of these changes was short (5–10 min). Continuous intravenous infusion of a small dose of oxytocin does not elicit the same degree of vasodilation and hypotension.

Ergot Alkaloids

Several ergot derivatives are commercially available, but these agents are similar in their action and profiles (Table 9.4). Methylergonovine is an amine ergot alkaloid that differs structurally from the natural ergonovine by the addition of a methylene group. Ergot alkaloids should be protected from light and stored at cool temperature (8°C) for longer shelf life. Ergot alkaloids stored at room temperature have a shelf life of 60 to 90 days. Ergot alkaloids are rapidly absorbed after intramuscular administration, with distribution throughout the extracellular fluid; however, very low levels are detected in the milk of lactating women, and ergot alkaloids appear to be safe for use with breast-feeding. The half-life of ergot alkaloids is 1 to 5 min, although the total body elimination may take 1 to 2 h because of the wide distribution.

Within 2 to 5 min of intramuscular injection, the uterus begins sustained contractions that can last from 2 to 3 h. Adverse effects include a high incidence of nausea and vomiting, dizziness, headache, and hallucinations in some patients. However, the most worrisome side effects of ergot alkaloids are on the cardiovascular system. Systemic hypertension can occur as a result of the intense vasoconstriction caused by these agents. Parturients who have pregnancy-induced hypertension or pregnant women with previous chronic hypertension may have unusually severe reactions to ergot alkaloids including myocardial infarctions, arrhythmias, and cerebrovas-

TABLE 9.4. Uterotonic agents.

Agent	Dosage	Route of administration	Side effects	Warnings
Oxytocin	10–40 IU in 1000 mL 5–10 IU	IV infusion IM injection	Hypotension Tachycardia Nausea	Avoid rapid IV bolus
Ergonovine Methylergonovine	200 μg	IM injection	Hypertension Vasoconstriction Nausea and vomiting	Avoid in hypertension, pulmonary hypertension
15-Methyl prostaglandin $F_{2\alpha}$	250 μg	IM injection IU injection	Hypotension Hypertension Bronchoconstriction	Avoid in reactive airway disease
Misoprostol	400–1000 μg	PO PR	Shivering Hyperthermia	

cular accidents. Ergot alkaloids are known to induce pulmonary artery vasoconstriction and pulmonary hypertension. Ergot alkaloids should not be administered intravenously, especially in undiluted form. Also, the simultaneous administration of an ergot derivative and a vasoconstrictor drug should be used only with extreme caution. Coronary artery spasm has been reported in patients with atypical or variant angina.

Prostaglandin Agonists

At term pregnancy, prostaglandin activity increases until the placenta is delivered. Administration of exogenous prostaglandin agonists produces intense, sustained contraction of the myometrium and can be very effective for the treatment of postpartum hemorrhage. Two classes of agents are available: parenteral agents, which must be administered via injection, and oral agents (Table 9.4).

Parenteral Agents. A large number of parenteral prostaglandin agonists are commercially available; the particular choice often depends on the local standard. The most studied agent is 15-methyl prostaglandin $F_{2\alpha}$, hemabate or carboprost, which is a synthetic analogue of the endogenous prostaglandin $F_{2\alpha}$ (dinoprost), having a methyl group added to the C-15 position, a change that results in a significantly longer duration of action. Carboprost must be stored in refrigerated conditions; otherwise, the agent undergoes spontaneous degradation. Intravenous administration should be avoided; carboprost can be given intramuscularly or via intrauterine injection. After intramuscular injection, the plasma peak is reached in approximately 30 min and is maintained for 1 to 2 h. A single 250-μg dose has been found to be effective in the treatment and prevention of postpartum hemorrhage, and this dose can be repeated in 15 to 90 min to a maximum dose of 2 mg. Intraumbilical injection has also been described for the treatment of retained placenta.[30] Early experience in the treatment of hemorrhage with carboprost suggested failures that occurred more commonly in women with chorioamnionitis.[31] The onset of action is very rapid, with sustained contractions occurring 3 to 5 min after administration. Side effects include bronchoconstriction, hypertension, vomiting, diarrhea, and increases in body temperature. Carboprost should be used with extreme caution in women with reactive airway diseases. Hypertension is more common when high doses are used because of the activity on the vascular smooth muscle.

Oral Agents. Misoprostol is a synthetic analogue of prostaglandin E_1 that differs only slightly from endogenous prostaglandin, resulting in an increased duration of action compared to its natural analogue. After oral administration, misoprostol undergoes significant first-pass effect, with minimal plasma concentrations occurring after a single oral dose. In the United States, the only approved use of misoprostol is for peptic ulcer disease, especially in ulcers caused by damage caused by nonsteroidal antiinflammatory agents, where its effect of decreasing gastric acid secretion protects the mucosa. Of note, most oral antacids are known to delay the onset of action and decrease the plasma concentrations of this agent. Misoprostol for postpartum hemorrhage has been administered orally, rectally, or vaginally, and is rapidly absorbed from the mucous membranes. Misoprostol is a very effective uterotonic agent, increasing both the frequency and amplitude of contractions. Small doses have been used with great success for the purpose of cervical ripening and induction of labor. More recently, misoprostol has been described for the prevention and treatment of postpartum hemorrhage. In the setting of postpartum hemorrhage, O'Brien et al.[32] reported the use of 1000 μg rectally administered misoprostol. All 14 women in their series were successfully treated, with sustained uterine contraction occurring within minutes of administration. Some authors have found that misoprostol is not as effective as a primary uterotonic agent as oxytocin but has similar potency to methylergonovine.[33,34]

Obstetric Management

Identification and Treatment

The initial management of primary postpartum hemorrhage consists of identifying and treating the cause of bleeding. A rapid differential diagnosis of the cause of hemorrhage can be obtained by a careful palpation of the fundus. Although not a perfect test, a soft, large, and boggy uterus indicates a primarily uterine origin of bleeding, whereas a firm fundus

suggests a laceration or tear in the genital tract. The cavity of the uterus must be meticulously emptied of all products of conception, either manually or via curettage. To this end, ultrasonography has become an invaluable tool for identifying placental fragments and directing their extraction. Thorough and complete inspection of the lower genital tract and cervix with adequate lighting is mandatory. Parturients who suffer uterine atony may have coexistent genital tract trauma.

To ensure that the uterus is able to contract appropriately, it must be emptied of all contents, not only placenta or fragments but also blood clots. If the placenta remains trapped in the uterus, manual extraction of the placenta is required. The placenta should be examined to ensure that it has been removed intact; however, this may not be possible during manual extraction as it may be necessary to remove it in pieces. Placental fragments can be difficult to detect or identify during external and internal digital exam. Continued bleeding or recurrent failure of the uterus to contract should raise suspicion of retained products. Exploration of the uterine cavity should be performed. If one is unable to manually identify and extract any remaining fragments, then curettage is indicated under ultrasound guidance. Once the uterus has been completely emptied, manual extraction and massage are often enough to produce adequate contractility of the uterus. Oxytocin is given at this time to maintain uterine contractility. Oxytocin can be given intramuscularly or intravenously and should be maintained until the uterus has contracted firmly and active bleeding has ceased. If this technique fails to produce adequate contraction and control of bleeding, second-line agents should be administered. Prostaglandin agonists, either 15-methyl prostaglandin $F_{2\alpha}$, 250 μg intramuscular, or misoprostol, 1000 μg given rectally, are excellent agents for refractory uterine atony. Oleen and Mariano[35] found that 15-methyl prostaglandin $F_{2\alpha}$ was successful in almost 90% of women in whom oxytocin did not produce the desired effect. Ergot alkaloids (ergonovine, methylergonovine), 200 μg given by intramuscular injection, can be used in patients for whom prostaglandins are contraindicated (e.g., asthmatics). Ergot alkaloids are known to have a powerful vasoconstrictor effect and should be used with extreme caution in parturients with hypertension.

Medical management is effective in many cases. Oleen and Mariano[35] found that medical management failed in only 5% of their 237 cases of postpartum hemorrhage. Among the 12 women who required surgical intervention, identifiable risk factors included peripheral coagulopathy, retained products of conception, lacerations, chorioamnionitis, oxytocin-induced or augmented labor, increased fetal weight, magnesium-treated preeclampsia, and cesarean delivery. Maternal hemorrhage that is unresponsive to conservative therapy, including oxytocics, uterine massage, and placental extraction, should be considered a life-threatening situation. Immediate request for help should be made. As a temporary measure, bimanual uterine compression can be used to tamponade the bleeding. Generally, this technique is adequate to stop the immediate bleeding and temporize until further, definitive therapies can be initiated.

In the past, uterine packing was used in an effort to tamponade maternal hemorrhage. However, packing was associated with a high incidence of infection; moreover, significant hemorrhage can be concealed in the distensible uterus. The issue of packing remained controversial.[20] The current era of obstetrics has seen several advances that make the historical reports of packing difficult to interpret. On the one hand, antibiotics are extremely effective in treating intrauterine infection. If packing is maintained for short periods of time, there should be a low risk of infection. On the other hand, the pharmacologic spectrum of oxytocic agents has led to a significant reduction in the incidence of intractable uterine atony, with the result that most of the cases that would have responded to uterine packing are now treated more conservatively. Recent reports of success with the use of uterine packing may suggest that there remains, albeit small, a place for this modality in the management of intractable postpartum hemorrhage.[20]

Arterial Embolization

Arterial embolization is an effective but less often used treatment for postpartum hemorrhage. Selective arterial embolization under angiographic guidance was first described for the treatment of postpartum hemorrhage in 1979 by Brown et al.[36] (Figure 9.1). Angiographic arterial embolization has comparable success to surgical ligation but may have some significant advantages. The procedure can be performed under local anesthesia, obviating the need for general anesthesia, which can be challenging in hemodynamically compromised patients.[37] However, angiography can be performed only in centers that have the available resources and personnel. It has been suggested that low blood flow states may increase the failure of embolization because of inability to identify extravasation of dye during the procedure.[38] Arterial embolization is useful for both uterine and genital tract sources of bleeding and has been reported to be successful when hysterectomy failed.[27,39–41]

The success rate for arterial embolization is very high. In a review of case reports and series, Vedantham et al.[37] found no failures among the 49 postpartum vaginal deliveries noted, with an overall success rate of 97%. The majority of reported cases had associated coagulopathies, most often disseminated intravascular coagulopathy, which was corrected on successful embolization. Pelage et al.[27] reported the results of 14 women who presented with secondary postpartum hemorrhage after both vaginal and cesarean deliveries. The sources of hemorrhage in these women were both uterine and genital tract, with several cases of endometrial infection likely caused by retained products of conception. Three of the 14 subjects were noted to have rare and unpredicted causes for hemorrhage, including two pseudoaneurysms and one arteriovenous fistula; these arteries were selectively embolized, resulting in

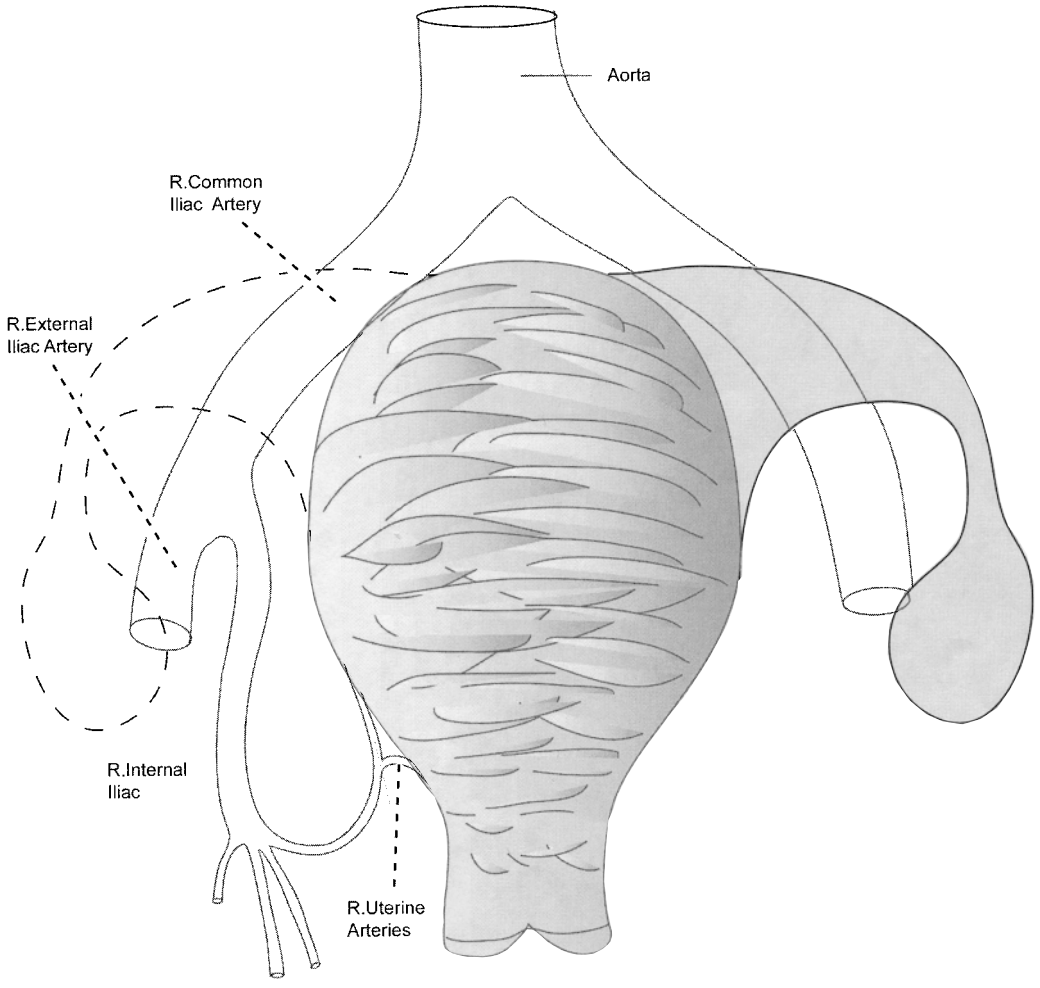

FIGURE 9.1. The vascular supply to the uterus and surrounding structures.

a cure. In most cases, the source of bleeding was identified by extravasation of dye; however, the operators were not able to identify the distal arterial extravasations in all cases and resorted to bilateral uterine artery embolization in these women. The authors reported complete success in all their patients, and all women had resumption of normal menstruation after therapy. Despite maximal medical and obstetric management, half the women in their cohort were suffering hypovolemic shock, and five had a significant coagulopathy; these complications resolved after successful embolization and replacement of blood loss. Deux et al.[39] reported the results of 25 women treated for intractable postpartum hemorrhage. Due to the severity of their conditions, two-thirds of these women were transferred from other centers for angiographic treatment. Associated disorders included multiple unit transfusion, intubation, vasopressor infusions, and coagulopathy. Embolization was successful in 24 women, resulting in cessation of blood loss, improvement in hemodynamics, and correction of coagulopathy. Of the 10 women who were followed, all resumed normal menstruation and 1 became pregnant.

Embolization is a very successful alternate therapy for intractable hemorrhage and may avoid the need for further surgical management in most cases. Failures are associated with unilateral embolization, proximal embolization, and cesarean delivery.[39] Several complications of arterial embolization should be considered. In parturients with poor blood flow or those in whom the vascular anatomy is poorly identified, reflux of the embolization material is a distinct and severe possibility. These materials could inadvertently lodge in alternate sites, leading to ischemic complications.[42] Other injuries and complications associated with pelvic arterial embolization include bladder necrosis, neurologic injury, and pelvic and arterial hematomas.[37,43,44]

Surgery

Surgical ligation of the arterial blood supply to the uterus is an effective and important treatment for intractable postpartum hemorrhage. The myometrium survives devascularization for several reasons. First, the uterine and ovarian arteries are

a dual, bilateral system of blood supply. Therefore, ligation of one artery will diminish the blood flow and perfusion of the uterus but usually does not place the myometrium at risk for infarction. Second, the uterus enjoys extensive collateralization of blood flow. Thus, even when extensive devascularization is required to control bleeding, the uterus can remain viable. The final advantage is that after a brief time the arterial supply to the uterus is renewed, allowing normal function to return, including fertility and pregnancy.

Ligation of the hypogastric arteries results in a diminution of blood flow to the uterus. Burchell[45] found that ligation of the hypogastric arteries decreased blood flow by 50% and, more important, reduced perfusion pressure by 85%. This partial interruption of perfusion can significantly decrease the rate of blood loss and allow medical and obstetric management to be successful. Ledee et al.[24] reported the results of their experience with bilateral hypogastric artery ligation in 49 women over 15 years of age. However, the value of hypogastric ligation may not be as high as these authors suggest; the rate of achieving a cure, as defined by not requiring a hysterectomy, is inferior to that of uterine artery ligation.[46,47] Clark et al.[46] reported a 42% success rate with 58% of their subjects requiring a hysterectomy to control bleeding. Blood loss, operating time, and morbidity were all greater than a cohort of patients who proceeded to hysterectomy on an emergent basis. Chattopadhyay et al.[47] reported a 65% success rate in 29 women, with the remaining 35% requiring an emergency hysterectomy. Failures in this cohort were more common among women with uterine atony. Vedantham et al.[37] recently reviewed the literature on hypogastric artery ligation, noting only a 65% success rate, with a 13% incidence of complications and two deaths (2%). Unlike the uterine and ovarian vessels, which are immediately available, the anatomy of the hypogastric arteries may be unfamiliar to the obstetrician. Hence, extensive dissection and additional time may be required, which may not be acceptable in the unstable patient. Because of the added difficulty of the technique and the significant failure rate and high complication rate, hypogastric artery ligation is not a preferred strategy for avoiding hysterectomy.

Ligation of the uterine arteries can be an effective and safe method of controlling obstetric hemorrhage (Figure 9.2). Ligation of the uterine artery is superior to the hypogastric artery because of the need for minimal dissection, familiarity of the anatomy to the surgeon, and lower rates of complications.[37] Although unilateral ligation may be successful in a minority of cases, such as those with an isolated trauma, bilateral uterine artery ligation is usually required for control of hemorrhage and generally successful. O'Leary[48] reported a series of 241 cases for the treatment of postpartum hemorrhage. They found a 96% success rate with only two complications (hematomas of the broad ligament). Fahmy[49] reported an 80% success rate of bilateral uterine artery ligation in 25

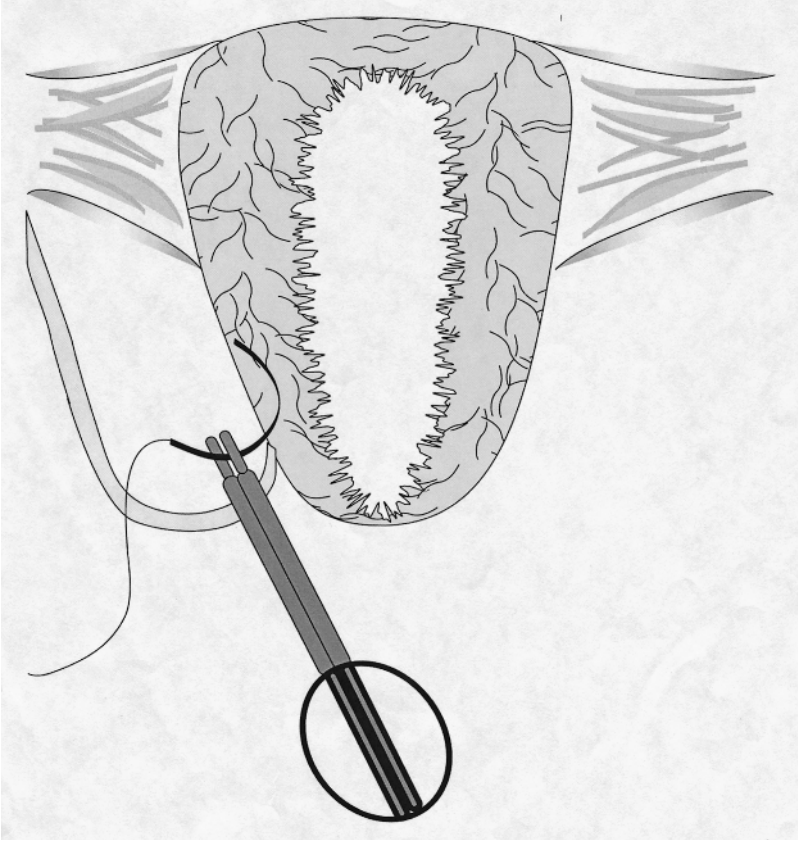

FIGURE 9.2. Ligation of the right uterine artery.

women. Failure of this technique was associated with coexistent coagulopathy in three women and a placenta previa in the remaining two patients. AbdRabbo[38] developed a systematic technique for surgical control of postpartum hemorrhage. In a stepwise fashion, the vessels supplying the uterus are ligated until bleeding is observed to stop. The author reported 100% success in treating parturients with postpartum hemorrhage, preventing hysterectomy in all 103 cases. Of the 45 patients with whom the authors could follow up, all resumed menstruation, and many became pregnant. The steps of arterial ligations are as follows:

1. Unilateral uterine vessel
2. Bilateral uterine vessels
3. Low uterine vessels
4. Unilateral ovarian vessel
5. Bilateral ovarian vessels
6. B-Lynch surgical technique

The initial steps are aimed at the uterine vessels, as these represent the majority of the blood supply to the myometrium. Failure of unilateral artery ligation to prevent further hemorrhage has often been noted, and the authors also found that the unilateral first step was successful in only 9% of their cases. Progressing to the second step, ligation of bilateral arteries raised the success to almost 75%. Patients with placenta previa were more likely to require further surgical ligation of the low uterine vessels, presumably preventing blood flow from the supply of the low uterine segment and collateral vessels. Of note, patients with abnormal uterine structure, placenta previa with accreta, or those with documented coagulopathies were less responsive to bilateral uterine artery ligation and required complete devascularization of the uterus via additional ovarian artery ligation. B-Lynch surgical suture may be helpful in this group of patients. Inherent to this systematic technique was an advance planning that allowed effective and timely treatment of emergency situations. Training for uncommon situations, such as intractable postpartum hemorrhage, certainly improves the success of management.

Hysterectomy

Obstetric hemorrhage that remains unresponsive to medical and obstetric management may require treatment via hysterectomy. The decision to proceed with a hysterectomy should take into account several factors. Obviously, the mother's life is of paramount concern. The option to proceed immediately with hysterectomy rather than attempting alternatives should be judged, taking into account maternal safety, the urgency of the situation, the likelihood of success with other options, and the desires of the patient to have additional children. This risk–benefit assessment is rarely easy.

Postpartum hysterectomy for uncontrolled hemorrhage is rarely a simple operation. The myometrium and its vessels are thickly engorged during pregnancy, making exposure and visualization difficult. The incidence of complications can be high, with reports of urinary tract injuries occurring in up to 5% of cases. Studies have demonstrated that the risk of complications associated with postpartum hysterectomy, including blood loss, is increased when the procedure is performed on an emergent rather than a planned basis. In their series of 42 patients, Chestnut et al.[50] found that patients undergoing emergency hysterectomy lost considerably more blood and were more likely to require transfusions in the perioperative period than those whose hysterectomy was planned. Emergency procedures were associated with about 2500 mL blood loss; approximately 86% of patients required transfusions with an average of 6.6 units per patient, compared with less than half the planned cases (48%) receiving blood products for an average of 1.6 units per patient. Castaneda et al.[51] reviewed 217 hysterectomies over an 18-year period. Although most of the planned procedures occurred at the beginning of the observed period and the emergency cases toward the end, the results were similar to those previously reported. Overall, 58% of the surgeries were planned and 42% were conducted on an emergent basis. Among the 126 planned surgeries, only 43% of the women required transfusion, whereas 84% of emergent hysterectomies did. Similarly, the estimated blood loss during surgery was approximately 3000 mL among the emergencies but only 1300 mL for the planned cases. Additionally, morbidity including infection, wound dehiscence, and bleeding was significantly more common in the emergent cases (23% versus 17%). It should also be mentioned that unless a careful inspection of the lower genital tract has been performed, hysterectomy may not be the correct solution to maternal hemorrhage.

Specific Causes

Atony

Uterine atony is the most common cause of postpartum hemorrhage and has been estimated to occur in approximately 2% to 5% of all deliveries. The cardinal feature of uterine atony is the presence of a flaccid or boggy uterus due to the failure of the myometrium to contract. The flow of blood through the gravid uterus can only be stopped by active muscular contraction. However, the uterus may hide up to 1000 mL blood, obscuring the degree of maternal hemorrhage. Manual palpation of the size and character of the uterus is mandatory after all deliveries. Although uterine atony is not common during elective term cesarean deliveries, it is a frequent feature of cesarean delivery after prolonged dysfunctional labor. Many causes of uterine atony have been identified, including overdistension of the uterus, dysfunctional labor, grand multiparity, and iatrogenic factors. In two different studies, atony was the most common indication for postpartum hysterectomy and for peripartum blood transfusion.[52,53]

Obstetric Management

Careful attention to the size and character of the uterus in the immediate postpartum period is mandatory.[54] The advances

in medical therapy, specifically uterotonic agents, have led to a significant decrease in the incidence and severity of uterine atony. Oxytocin should be administered as the first-line agent, and the contractility of the uterus continually assessed by palpation. If there is no response to this initial therapy, further uterotonic agents should be administered. Prostaglandin agonists (carboprost, misoprostol) can be used as the second-line agent and are effective in 90% of cases.[35] Prostaglandin agents are well tolerated but should be used with great caution in patients with asthma or pulmonary hypertension. Ergot alkaloids should be used in women for whom prostaglandins are contraindicated. In the rare cases that remain refractory to medical management, bimanual compression is often able to control the bleeding until invasive therapies can be initiated.[54]

During cesarean delivery, uterine atony can occur, but it is easily detectable. In low-risk patients, the uterus responds well to massage after elective cesarean delivery and may require a minimum of oxytocin infusion for contraction.[55] On the other hand, cesarean delivery performed after labor, especially after prolonged dysfunctional labor augmented with oxytocin infusion, may not completely respond to oxytocin and can require additional oxytocic drugs. Tocolytics administered before or during labor have been implicated as causative agents of uterine atony. Magnesium sulfate, beta-adrenergic agents (terbutaline, ritrodrine), and calcium channel antagonists cause significant uterine muscular relaxation. A careful review of the medications that the patient has received should be made, and all offending agents stopped immediately. Administration of calcium gluconate can be used to reverse the effects of magnesium on the myometrium.

Retained Placenta

After birth of the neonate, the placenta is spontaneously released from the surface of the uterine wall and delivered through the vaginal passage. Failure of the placenta to deliver promptly after childbirth may be a result of abnormal uterine function or abnormal placental attachment. During pregnancy, the uteroplacental surfaces are in contact and maintain a similar surface area. With the delivery of the neonate, the uterus is able to contract and reduce the size of its placental surface. The placenta, on the other hand, is unable to reduce its size, and it buckles and separates. Herman et al.[56] used ultrasonographic examinations to reveal four phases of the normal separation of the placenta: (1) the latent phase, with a thin placenta site wall; (2) the contraction phase, with thickening of the placenta site wall; (3) the detachment phase when the placenta separates; and (4) the expulsion phase, when the placenta slides free. In four of five women with a retained placenta, the failure appeared to be in the detachment phase, and the placenta was easily released with cord traction. The fifth case required manual extraction and demonstrated a failure of the contraction phase. Partial separation, in the face of uterine atony, may lead to extensive bleeding through open uterine arterioles that are not adequately constricted. If the separation of the placenta is incomplete, the placenta may tear during extraction, and fragments may be retained. Retained products of conception can lead to secondary postpartum hemorrhage; in some of these cases, a patient may return days or even weeks later with significant uterine bleeding, infection, and atony. Ultrasound examination is a valuable asset for identification of placental fragments and can aid in guidance during curettage.

Abnormal placental attachment occurs most commonly when the uterine cavity has been previously scarred, as with previous surgery, cesarean delivery, or curettage; however, a significant number of cases can occur without previous surgery, most often in multiparous patients.[57] There is a significant relationship between placenta previa and accreta, with at least 10% of women with placenta previa having an accreta and one-third of women with accreta having an associate placenta previa.[57,58] The lack of the normal uterine placental barrier leads to pathologic attachment of the placenta. The three grades of this disorder are placenta accreta, placenta increta, and placenta percreta. The definition of these three disorders is made by the depth to which the pathologic placenta invades the myometrium. Placenta accreta is a thinning or lack of separation between the placenta and uterine musculature. Placenta increta describes a placenta that has grown into the muscular wall of the myometrium. In placenta percreta, the placenta has invaded through the serosa of the uterus and may invade adjacent pelvic structures. Although a majority of cases of abnormal placental attachment can be identified via ultrasound, some cases remain unknown until after delivery and may lead to serious complications. Transvaginal ultrasound appears to be more effective in evaluation of accreta in the lower uterine segment, whereas magnetic resonance imaging depicts posterior placenta accreta.[59]

Obstetric Management

Postpartum hemorrhage is significantly more common when the placenta is retained for an inordinate period of time.[60] In some cases, the placenta fails to be delivered in a prompt and normal fashion. The definition of when a placenta is considered retained is disputed. Eighty-five percent of normal, term gestation deliveries complete the third stage of labor (placental delivery) within 15 min of delivery of the neonate, with the majority occurring in 5 to 10 min.[17] The normal placenta fails to separate by 30 min in less than 2% of term pregnancies and half of these fail at 60 min. In the absence of significant blood loss before the delivery of the placenta, the reasonable option is to allow 30 min before beginning manual removal of the placenta.[16] As the retained placenta prevents complete uterine contraction, the longer the placenta remains attached, the greater the risk of hemorrhage, with the frequency of hemorrhage increasing after approximately 10 min postpartum.[17]

When there is significant blood loss, the decision to manually extract the placenta should not be based on time but

rather on the assumption that removal of the placenta will allow the uterine muscles to contract. The incidence of hemorrhage from a retained placenta is approximately 3% to 4% and increases in premature deliveries.[17] Neither premature rupture of membranes nor chorioamnionitis appears to alter this risk.[61] Under adequate anesthesia, one hand maintains a firm, transabdominal hold of the fundus of the uterus for control, while the other hand is placed in the uterine cavity with extended fingers. Once the plane between the placenta and uterus is located, the placenta is manually removed from the uterine wall. Removal of any remaining membranes can be accomplished by grasping these with the hand, a sponge draped over fingers, or ring forceps.

Active Management of the Third Stage

Active management include several procedures: (1) the fundus of the uterus is held, but not actively massaged; (2) the cord is clamped, preventing the placenta from draining; (3) gentle traction is applied to the cord; and (4) an oxytocic agent is given, usually immediately on delivery of the anterior shoulder. Concern that an early administration of oxytocin results in trapping of the placenta does not appear to be validated by clinical trials. A number of early studies suggested that active management of the third stage of labor could shorten the duration for delivery of the placenta and decrease the incidence of maternal hemorrhage. Prendiville et al.[62] performed a meta-analysis of these studies and found a 40% reduction in the incidence of hemorrhage with active management of labor. Nordstrom et al.[63] randomized 1000 parturients to oxytocin 10 IU versus saline via bolus injection immediately after the birth of the neonate. Although the time to delivery of the placenta was not shortened, the amount of blood loss was significantly less in the group that received oxytocin. Gentle cord traction may reduce the incidence of retained placenta. Khan et al.[64] studied 1648 parturients randomized to either 10 IU of intramuscular oxytocin plus controlled cord traction versus a conservative control group. Women who receive oxytocin and traction had less estimated blood loss during the third stage, a smaller change in postpartum hematocrit, and a lower incidence of retained placenta at 30 min. In a trial by Rogers et al.,[65] parturients who were randomized to active or conservative management were additionally randomized to upright or supine maternal postures during the third stage. The authors reported a significant benefit to active management, but found no relationship between maternal posture and blood loss.

Oxytocin has been well established as the agent of choice for active management of the third stage of labor. Ergot alkaloids, do not appear to be better agents for use during active management of the third stage, as the incidence of retained placenta, nausea, and hypertension may be increased when compared with oxytocin.[66] The combination of oxytocin and ergonovine (Syntometrine), which is commonly used in the U.K., produces significantly greater side effects with no apparent advantage over the synthetic hormone alone.[67,68] Several prostaglandins have proven to be useful in the treatment of postpartum hemorrhage, but at the present time there is less evidence supporting their routine use as part of a third-stage active management protocol.[69] Prostaglandins are attractive, as they increase throughout labor and peak immediately before the separation of the placenta.[70] This observation suggests that prostaglandins play an important role during the third stage of labor. Unfortunately, because these agents are considerably more expensive than oxytocin, their ideal use may be as second-line agents when the uterus is refractory to oxytocin.

Misoprostol, a prostaglandin E_1 analogue, is an effective uterotonic agent, causing tonic contractions of the pregnant myometrium. Misoprostol is cheap, stable, and can be administered orally; therefore this agent could potentially be an effective agent in the areas where a lack of resources, including storage and refrigeration, may prohibit the use of some agents.[32,71] Hofmeyr et al.[72] compared oral misoprostol, 400 μg, versus placebo in the management of the third stage of labor. Fewer women who received misoprostol had significant hemorrhages, defined as greater than 1000 mL; however, this did not reach statistical significance because of the small number in the study. The World Health Organization conducted a multicenter, multination randomized trial comparing 600 μg oral misoprostol versus 10 IU intramuscular or intravenous oxytocin, with more than 18,000 women successfully randomized for treatment.[73] The misoprostol-treated women were significantly, although slightly, more likely to hemorrhage more than 1000 mL (4% in the misoprostol group versus 3% in the oxytocin group) and to require additional oxytocics (15% versus 11%). Additionally, the women in the misoprostol group were significantly more likely to shiver and have an elevated body temperature, above 38°C. Interestingly, this study did not find a difference in the need for either blood transfusions or for manual removal of the placenta. Prostaglandin $F_{2\alpha}$ (Prostin) and 15-methyl prostaglandin $F_{2\alpha}$ (Hemabate) have also been used. These agents are used intramuscularly or intramyometrially.

Genital Tract Trauma

Trauma to the genital tract, usually in the form of lacerations or hematomas of the perineum, vagina, or cervix, is the most common maternal injury during childbirth. Lacerations are almost always identifiable during inspection of the vagina and cervix after vaginal delivery. Depending on the size, depth, and amount of bleeding, a surgical repair with resorbable sutures may be necessary. Lower genital tract hematomas are common, usually quite painful, and can often be identified on inspection. Usually these cause only a small amount of bleeding, but they can occasionally result in a significant amount of blood loss. Early detection and prompt repair of genital tract trauma will prevent the need for transfusion. Unfortunately, diagnosis is often delayed, resulting in avoidable hemorrhage, delayed treatment, and potentially poor outcome.[24]

Vaginal and vulvar hematomas are not common, with a reported incidence between 1 in 310 and 1 in 7500 deliveries.[74] Soft tissue injury during delivery and inadequate repair result in a slowly expanding hematoma that produces pain and can lead to excessive blood loss. Associated risk factors include forceps delivery, episiotomy, and nulliparity. Because the bleeding may blend into the surrounding soft tissue, the diagnosis may be delayed until after significant blood has been lost. Vulvar hematomas arise from the branches of the pudendal artery, usually appearing immediately after delivery; however, some cases can be delayed for 3 days. Vaginal hematomas arise above the pelvic diaphragm and may be easily obscured by surrounding soft tissues. The most common presenting sign is pain.[74] Often, the presence of these hematomas is missed due to the presumption that perineal pain after delivery is normal.

Rare but life threatening, retroperitoneal hematomas arise from a laceration of one of the branches of the hypogastric artery during cesarean delivery or with uterine rupture. Because there is no external bleeding, identification of a retroperitoneal hematoma is often made after the onset of hypotension or hypovolemic shock. Diagnosis requires a high index of suspicion in parturients who have unexplained tachycardia, hypotension, low urine output, or falling hematocrit with no observable source of bleeding. Other signs and symptoms may include a tender mass in the inguinal area that may displace the uterus, lower abdominal tenderness, unilateral leg edema, and hematuria. Vaginal bleeding, if any, is usually small, and associated hypotension far out of proportion to the blood loss.

Lacerations and tears of the cervix, perineum, and vagina are common and can occur during normal and operative vaginal deliveries. Cervical lacerations are associated with operative deliveries (cesarean or forceps), but may also occur during spontaneous deliveries, especially during a rapid descent of the fetus before full cervical dilation. Brisk bleeding found despite a firmly contracted uterus should raise suspicion of an injury to the cervix. Inspection of the lower genital tract for the source of bleeding should be performed. It is essential to have adequate lighting and exposure during this exploration, as the soft tissue of the vagina may obscure a laceration.

Uterine Inversion

Uterine inversion is a rare but potentially devastating complication of the third stage of labor, with an incidence in the order of 1 in 2000 to 1 in 6400 vaginal deliveries.[75,76] Early reports described a mortality of up to 40%; however, it appears that prompt identification and aggressive resuscitation can be very successful.[76] The exact cause is not known but is probably a fundal implantation of the placenta. Most studies have identified a greater propensity among primigravidas. Several authors have implicated excessive fundal force during delivery or, more commonly, excessive cord traction during the third stage as the immediate cause of uterine inversion. Recent evidence suggests, however, that a structural abnormality may predispose some women to uterine inversion, with inversions occurring spontaneously during the third stage of labor. Additionally, some patients suffer repeated uterine inversion during subsequent deliveries, suggesting an abnormality in the uterine structure as the immediate cause.[76]

The presenting features of uterine inversion are acute hemorrhage and pain. The brisk bleeding after detachment of the placenta cannot be controlled by uterine contraction and requires prompt correction or hypovolemic shock will ensue. Despite aggressive treatment, shock may occur in 30% to 40% of patients.[77] In many cases, the amount of blood lost during inversion is greatly underestimated.[78] Abdominal palpation reveals a downward displacement of the fundus, if at all present, and a bimanual exam generally provides the diagnosis. The cervix may constrict shortly after inversion, preventing both venous drainage from the uterus and easy manual replacement.

Obstetric Management

After the diagnosis of uterine inversion, an immediate attempt to replace the uterus should be made before constriction of the cervical ring makes restoration more difficult. If done promptly, this may be successful in the majority of cases.[75] After failing the initial attempt, further attempts may delay treatment and risk significant morbidity. One should immediately call for assistance. If the placenta has not already been removed it should remain in place until further therapy has begun, because the continued attachment of the placenta may prevent further bleeding from the exposed uterine surface. Replacement of the uterus requires uterine and cervical relaxation, which can be accomplished with tocolytics such as nitroglycerine and terbutaline.[79–81] Disadvantages of the adrenergic agents include tachycardia, which may be undesirable in a hypotensive parturient.[54] In some cases the uterus remains trapped, and general anesthesia may be required for relaxation.

The palm of the hand should be placed on the internal fundus, and firm pressure should be applied to revert the uterus into this correct position. The placenta can be manually removed once the uterus has been repositioned, with care taken that a pathologic attachment may be present. After completing the procedure, the uterus must contract vigorously to prevent further atony and blood loss. Prostaglandins, in addition to oxytocin, have been found to be an excellent choice with a high success rate.[82] Bimanual compression should be performed to prevent further hemorrhage until the uterus is firm and fixed in position. In rare cases, if the uterus cannot be replaced manually, laparotomy may be performed for surgical repair.

Anesthetic Management

The ideal anesthetic should be individualized for each case, with evaluation of the hemodynamic status of the parturient

and ongoing blood loss, input from the obstetrician concerning the requirements for care, and consideration of backup plans in case of failure. In the parturient population, general anesthesia has been associated with higher mortality than regional anesthesia.[83] This idea must be tempered, however, by the observation that the parturient condition often determines the choice of anesthesia. Many of the comorbidities of pregnancy are relative contraindications to regional anesthesia, for example, coagulation disorders, uncorrected hypovolemia, and ongoing blood loss.

The choice of anesthetic technique depends on a number of factors, including the procedure being performed, the urgency of the case, the likelihood that further therapy may be required, and the condition of the parturient. The requirements for anesthesia differ among obstetric procedures. Manual extraction and curettage can be performed under general or regional anesthesia or under sedation. If the cervix has not yet constricted, minimal anesthesia may be required. If uterine relaxation is needed, nitroglycerine may be used as it produces rapid tocolysis of short duration.[84] Invasive surgical procedures including hysterectomy can be safety performed under regional or general anesthesia.[50] A single-shot spinal may not be adequate if the surgical procedure becomes protracted and complicated, or the anatomy is difficult. Thus, continuous epidural anesthesia would be a better option. Before performing regional anesthesia, intravascular volume must be adequately replaced. The sympathectomy associated with neuraxial local anesthetics may lead to severe decompensation in the hypovolemic patient. Significant postpartum hemorrhage is associated with the development of a coagulopathy. Adequate parameters of hemostasis must be evaluated in any patient who has lost a considerable amount of blood.

Airway

General anesthesia is frequently required during the management of postpartum hemorrhage. Advantages of general anesthesia include the ability to provide rapid surgical conditions for any operative procedure and definitive control of the airway in cases of severe illness where prolonged intensive care may be required. Clinical assessment of the airway, although not a reliable indicator, may aid in the prediction of difficult intubation.[85,86] Additional consideration should be given to changes in the airway during parturition. Prolonged labor and delivery have been noted to dramatically increase the amount of pharyngeal edema.[87,88] Moreover, with the loss of colloid oncotic pressure that occurs during large volume replacement, soft tissues tend to become edematous and friable. These changes may considerably increase the risk of failed intubation, which is already increased in the pregnant population. If control of the airway may be required for either general anesthesia or prolonged intensive care, then early intubation under elective conditions should be considered. A full range of airway tools should be available, including, if possible, a laryngeal mask airway and fiberoptic airway equipment.

Circulation

The maternal physiologic response to untreated hemorrhage can provide a guide to the assessment of blood loss and is an essential component in determining the requirement for and effectiveness of any therapy. A decrease in venous return caused by hemorrhage will elicit a reflex tachycardia designed to maintain an adequate cardiac output. These changes can occur with a 10% to 15% decrease in blood volume. After a 20% to 30% loss of volume, the parturient will develop a significant tachycardia, narrowing of pulse pressure, and peripheral vasoconstriction.[89] Further loss of blood, however, will overwhelm the physiologic reserve and lead to hypovolemic shock, characterized by hypotension, tachycardia, and poor perfusion. In contrast, if blood volume is replenished via an infusion of intravenous fluids, maternal perfusion and organ function can be maintained despite very low levels of hemoglobin.[90] Although blood pressure may be decreased by arteriolar vasodilation and decreased blood viscosity associated with acute hemodilution, maternal cardiac output and end-organ oxygen delivery are preserved. Therefore, the key to the treatment of acute obstetric hemorrhage is maintenance of isovolemia through aggressive infusion of crystalloid or colloid solutions.

Temporizing measures, including the administration of vasopressor agents, should be used for the treatment of hypotension until a definitive diagnosis can be made. Phenylephrine, a direct-acting alpha agent, is a good choice for the initial treatment of postpartum hemorrhage, as concerns over uterine artery vasoconstriction reducing blood flow to the placenta are no longer relevant. Phenylephrine can be given as an infusion or via bolus administration. In both cases, dilution of the high-concentration vial is required. If maternal hypotension continues despite aggressive volume replacement and vasopressor therapy, assessment of central hemodynamics may be required. A central venous catheter can give a rapid estimate of central venous pressure (CVP), which may help to assess cardiac preload, and allows the reliable central administration of vasopressor medications.

Differential Diagnosis of Hypotension

Most cases of hypotension during hemorrhage are caused by hypovolemia and inadequate resuscitation. Although tachycardia, narrowing of pulse pressure, and poor peripheral perfusion and capillary refill are common signs of early but significant blood loss, healthy parturients may not demonstrate overt symptoms of hypovolemia until 1 to 2 L of blood have been lost. Intractable hypotension or evidence of poor perfusion despite aggressive volume replacement is worrisome and may require a broadening of the differential diagnosis.

Hypotension may be caused by a derangement in preload, afterload, or cardiac dysfunction. Decreased preload may be due to misdiagnosis of the extent of hemorrhage. As was stated previously, visual estimate of bleeding is notoriously unreliable, especially in cases of severe bleeding.[9] If the clinical situation suggests severe hypovolemia, crystalloid, colloid, or blood should be given as guided by clinical signs and laboratory results. A decrease in maternal afterload should be considered if the severity of maternal hypotension is considerably greater than the degree of blood loss and remains refractory to volume administration. Consideration should be given to iatrogenic sources of vasodilation, including epidural local anesthetics and rapid administration of vasodilators such as oxytocin. Cardiac dysfunction can occur in the parturient with acute postpartum hemorrhage. Although inherent cardiac dysfunction is rare in the obstetric population, acute cardiac dysfunction can result from prolonged hypotension and hypoperfusion. Acute cardiac dysfunction can be caused by embolic disorders, including amniotic fluid or air. Decreases in central blood volume with open venous sinuses of an atonic uterus can result in aspiration of air, leading to an air embolism and cardiovascular collapse. Manipulation of the uterus can produce intense vagal stimulation resulting in bradycardia and hypotension, which may heavily impact the normal physiologic response to hypovolemia. Finally, pericardial tamponade is a rare, but devastating, complication that can occur during massive volume replacement in pregnancy. Placement of a pulmonary artery catheter may help differentiate among the less common causes of hypotension.

Massive Hemorrhage and Hypovolemic Shock

Massive hemorrhage is the loss of greater than one blood volume in a 24-h period. Patients who suffer a massive hemorrhage have several considerations that must be addressed. In addition to replacing red cell mass, the other components of blood must be administered. Loss of circulating plasma proteins and platelets can produce a coagulopathy that further complicates the maternal hemorrhage. The loss of plasma proteins decreases the oncotic pressure, causing third-space edema. The normal physiologic compensation for blood loss, which results in peripheral vasoconstriction and shunting of circulating blood volume to the major organs, can cause significant organ injury if left untreated for a prolonged period of time.

Hypothermia is dangerous for the critically ill parturient in hypovolemic shock. Core body temperatures of 34°C are associated with atrial arrhythmias, including atrial fibrillation, which may lead to further hemodynamic compromise. At a core temperature of 32°C, ventricular arrhythmias become more likely and life threatening. Additionally, hypothermia may be associated with the development of a coagulopathy resulting from platelet dysfunction. In cases in which large volumes of fluid are administered in a short period, intravenous fluids should be warmed to avoid hypothermia. If body temperature declines, active warming of the patient, using passive blankets or active forced-air warmers, should be instituted to avoid excessive heat loss.

Transfusion Medicine

The decision to transfuse blood products to the parturient is a complex one. The clinician must balance a desire to improve oxygen delivery and maintain hemodynamic stability with the concern that a devastating complication could result from blood transfusion. Most parturients are in a good state of health and can tolerate acute isovolemic anemia well. Fortunately, in the general obstetric population the need for blood transfusion is small, less than 1%, but the need for blood transfusion may be more common after cesarean than vaginal delivery.[89,91] Ransom et al.[92] reviewed more than 16,000 parturients admitted to their hospital over a 3-year period. Blood transfusions were given to only 76 women, with all but 4 having an identifiable risk. Cousins et al.[91] evaluated 1,111 parturients undergoing cesarean delivery for any reason and found an incidence of transfusion of 1.7% overall. Camann and Datta[93] reported a higher incidence of 3.5%, but noted that the incidence of transfusion decreased during the 3 years studied as clinicians became concerned with infectious disease transmission. Again, identifiable risk factors accounted for the majority of cases. Klapholz[94] reviewed more than 30,000 deliveries and found that approximately 2% of women require blood transfusion during the peripartum period, with only 0.09% requiring more than eight units. Thus, the requirement for blood products in parturition is quite low.

Most centers have modified or abandoned the previously used transfusion trigger of 10 g/dL hemoglobin concentration in favor of either symptomatic treatment or lower hemoglobin triggers. Published and disseminated transfusion guidelines can have a significant impact on the use of blood products with little or no impact on quality of care.[95,96] In the past, blood transfusions were given for hemoglobin concentration of 10 g/dL, which likely resulted in many unnecessary transfusions. In 1988, the Consensus Development Conference on perioperative red cell transfusion identified a hemoglobin concentration of 7 g/dL as tolerable in otherwise healthy patients, including parturients.[97] When blood volume is maintained with adequate intravenous fluid replacement, allowing for adequate oxygen delivery to vital organs, most investigations assessing well-being, morbidity, and mortality have found that even very low levels of hemoglobin concentration are tolerated.[12,98,99] The resistance to blood flow in the peripheral vasculature decreases in part because of decreases in blood viscosity and also by arterial vasodilation. This decreased resistance results in an increase in cardiac output and maintenance of tissue blood perfusion and oxygenation. Although the oxygen content in the blood is decreased in parturients with a lowered hematocrit, the increased blood flow to the tissues results in a maintenance of oxygen delivery. The minimum hemoglobin concentration that an otherwise healthy

parturient must maintain has not been determined; parturients with chronic anemia tolerate significant surgery without complications.[89] On the other hand, parturients who are unable to increase cardiac output in response to anemia will not be able to maintain oxygen delivery and may develop end-organ hypoxia. Pregnant women who demonstrate poor compensation or tissue hypoxia should be transfused despite a hemoglobin concentration greater than 7 g/dL.[100] In the parturient population, women who suffer postpartum hemorrhage tend to be significantly hypovolemic and are unable to increase cardiac output due to inadequate central volume. Hydration with crystalloid solution allows the physiologic compensation to occur. However, if active bleeding persists, transfusion of blood and blood products should be given, which can be guided by the clinical status and laboratory results. Hence, the decision to transfuse the parturient who has sustained a significant hemorrhage must take into consideration the amount of blood loss, the decrease in hematocrit that would result after hydration, and the continuation of blood loss.

No procedure or practice is totally without risk, and this realization must be balanced against the risk of inaction. Although the most feared risk associated with blood transfusion is the transmission of infectious diseases, these are not the most common or immediately dangerous risks. In the United States, the current risk of transmission of infectious disease is very low. Recent estimates report 1 in 677,000 units for human immunodeficiency virus and 1 in 60,000 to 1 in 100,000 for infectious hepatitis (B and C).[101] In addition to the high degree of laboratory testing, blood donor screening based on risk factors and a general decline in the prevalence of these diseases may account for the low rates.[102] Transfusion reactions, including mild reactions such as fever, rash, and urticaria and more severe reactions such as hemolysis and cardiovascular collapse, are more common. Mild reactions occur in 1% to 4% of transfusions, and severe reactions are, fortunately, rare with an incidence of 1 in 10,000 units.[103]

Autotransfusion in the Postpartum Period

The term autotransfusion defines the process of administering blood collected from the patient at some time before the administration. This description can refer to preoperative donation of blood, intraoperative collection with isovolemic hemodilution, or intraoperative collection via suction catheter and autotransfusion cell processor.

Autologous Donation

The spread of bloodborne infectious disease has been responsible for creating a tremendous interest in autologous blood banking and transfusion. Autologous blood, collected from a parturient well in advance of the need for transfusion, is safe and may prevent the need for homologous blood transfusion.[89] A small risk of clerical and other human error is impossible to abolish.[104] Autologous donation in the setting of the parturient is a procedure infrequently used for several reasons. Preoperative blood donation in obstetric population may not be feasible because of pregnancy-related anemia; a cutoff hematocrit of greater than 33% has been advocated.[105,106] In general, donations consist of only 1 unit of whole blood. Additionally, autologous donation requires sufficient lead time, which is often not available in most cases of obstetric hemorrhage. Early reports suggested that autologous donation was relatively contraindicated during pregnancy, as complications such as fetal distress and preterm labor were frequent. More recent investigations have demonstrated that this procedure can be conducted safely.[107] For example, O'Dwyer et al.[108] collected 105 units of autologous blood from 56 women undergoing elective cesarean delivery and transfused 65% of these units. Unfortunately, the need to transfuse blood in the obstetric population is very difficult to predict, making routine use of autologous donation impractical; however, there may be some situations where this procedure can be considered. For example, women with known placenta previa, or documented accreta, as well as women with known antibodies or rare blood types, may benefit from autologous blood collection well in advance of any surgical procedure; inclusion of less restrictive risk factors would be prohibitively expensive.[109] The absolute value of autologous donation can be argued, as most women do not need to receive their donation, and those who do require transfusion rarely receive only 1 unit. Without a doubt, routine use in advance of an expected vaginal delivery would seem prohibitively expensive, as the requirement for transfusion is so infrequent.[105,109]

Isovolemic Hemodilution

Intraoperative collection of whole blood with simultaneous reinfusion of a crystalline solution has been used in high-risk surgery. This technique requires adequate preprocedure hemoglobin concentrations, which are unusual to find in the parturient. Grange et al.[110] collected one or two units of whole blood during high-risk cesarean delivery in 38 patients. They found parturients can tolerate the procedure well, and, in combination with autologous donation, they were able to avoid transfusion in all but one parturient. It appears unlikely that this technique would be useful in the general armamentarium for treatment of postpartum hemorrhage.

Intraoperative Blood Salvage

Intraoperative blood salvage involves suction scavenging of blood loss during an operation and its centrifugation and washing, followed by reinfusion of the concentrated blood cells. During operative procedures where significant amount of blood can be lost, intraoperative blood salvage is a valuable technique to decrease the need for allogenic red cell transfusion therapy.

The use of blood-scavenging suction in the obstetric population has been controversial, with significant concern being

raised over the potential that amniotic fluid and other fetal debris that may be suctioned along with maternal blood would be reinfused to the parturient. Using reasonable guidelines to avoid fluid that would contain excessive amounts of amniotic fluid and fetal squamous cells, Rainaldi et al.[111] found that women randomized to intraoperative blood salvage had significantly higher hemoglobin concentrations postoperatively and were discharged from the hospital earlier. Rebarber et al.[112] reviewed the records of 139 women in whom intraoperative blood salvage was performed during cesarean delivery and compared them to a cohort of 89 subjects. The authors did not find a significant increase in postoperative complications among the women who received autotransfusions. One consequence of massive volumes of intraoperative blood salvage is the development of a coagulopathy, either dilutional as evidenced by increased prothrombin time (PT) and partial prothrombin time (PTT) and decreased fibrinogen and platelet count, or iatrogenic due to the heparin solution used to prevent clotting of the circuit. These problems are generally easily treated when diagnosed. Until more evidence on the safety of intraoperative blood salvage in the obstetric population is produced, strong consideration should be given to this technique in cases where massive hemorrhage and cesarean hysterectomy are likely. Some characteristics that would point to the use of this technique include women with positive antibodies in their blood screening and parturients who are Jehovah's Witnesses (a continuous circuit can be produced).

Homologous Transfusion

Donated blood is currently stored as individual components to maximize the ability to treat several parturients with individualized therapy. Red blood cells are maintained in a citrate phosphate dextrose adenine solution (CPDA), which acts as a preservative, allowing almost 2 months of storage. Each unit of packed red blood cells will raise the hemoglobin concentration by approximately 1.5 g/dL. Care must be taken in the case of massive and rapid transfusion as the citrate component of the preservative will decrease intravascular calcium. Hypocalcemia can have a significant detrimental effect on the ability of the myometrium to contract and may significantly worsen postpartum hemorrhage. Citric-induced hypocalcemia can be treated with calcium salts, such as 1 g intravenous calcium chloride.

Fresh-frozen plasma (FFP) consists of the plasma component of whole blood after extraction of red blood cells and platelets. Most clotting factors remain stable during storage of FFP; however, there is a decrease in factor V and factor VIII. Administration of FFP is recommended for parturients with known deficiency of clotting factors and evidence of bleeding. Prophylactic administration of FFP should be used only for those parturients who have documentation of severe shortage of factors (<20%). Normal hemostasis is believed to be adequate when clotting factors are at least 30% of normal; however, measurement of the levels of clotting factors is not a practical test for parturients with active bleeding. Available laboratory tests include PT, PTT, fibrinogen levels, fibrinogen degradation products levels, and D-dimer levels.

Donor platelets have a short shelf life during storage and are pooled immediately before usage. Each unit of platelets will raise the platelet count 5,000 to 10,000/mm^3. The use of platelets in a massive transfusion should only be done after documentation of thrombocytopenia and not based on a standard protocol. Platelet counts can be maintained due to their storage in the spleen until approximately one blood volume has been lost. Platelet transfusion should be given with evidence of nonsurgical bleeding or platelet counts less than 50,000/mm^3.

Dilutional coagulopathy can occur after the replacement of one blood volume with crystalline and packed red blood cells (PRBC). Because of the elimination of most coagulation factors during separation of red blood cells from whole blood, a patient may have a decrease in clotting factors with adequate blood volume. Clinical evidence of a dilutional coagulopathy consists of microvascular or nonsurgical bleeding; laboratory evidence will demonstrate an increased (>1.5 times normal) PT or PTT. Dilutional coagulopathies respond well to the administration of FFP, and further administration should be aimed at normalizing laboratory values.

Coagulopathy

Any evidence of excessive bleeding in the peripartum period should raise concerns regarding the development of a coagulopathy. Significant postpartum hemorrhage can result from, or be exacerbated by, a coagulopathy.[3] Parturients with preexisting coagulopathies, whether inherited or acquired, should be evaluated and treated before labor and delivery, whereas those with acute onset of coagulopathy, which are often related to pregnancy and labor, must be rapidly assessed and corrected. In the past, the high likelihood that parturients with significant hemorrhage would develop a coagulopathy was not appreciated.

Preexisting coagulopathies are ideally known ahead of time to allow adequate time for planning their management. These parturients often suffer from inherited disorders resulting in deficiencies of factors involved in the coagulation systems. Examples include von Willebrand's disease, hemophilia, or factor XI deficiency. A hematologist should be consulted early in the pregnancy in order to develop a plan for delivery, as careful monitoring of coagulation factor levels and activity, is essential to assess the risk of bleeding and the need for prophylaxis. For instance, the incidence of primary postpartum hemorrhage is significantly increased in women with von Willebrand's factor deficiency, with a reported incidence of 20%.[113] Equally important is the high incidence of secondary (>24 h) postpartum hemorrhage, as the pregnancy-induced increase in

factor levels fall rapidly after delivery.[114,115] Complete discussion of these inherited disorders can be found in Chapter 22, hematologic disease.

The parturient suffering a postpartum hemorrhage is at high risk for the development of a coagulopathy. As the level of blood loss approaches one blood volume, the loss of plasma proteins causes a depletion of the coagulation factors, resulting in a dilutional coagulopathy; this will produce a rise in the laboratory assessments of coagulation, PT, PTT, fibrinogen, and platelets.[89] Alternatively, the parturient whose vascular volume is inadequately corrected can develop a consumptive coagulopathy. Disseminated intravascular coagulopathy (DIC) is a consumptive coagulopathy that can occur in parturients. Because the pregnancy-induced changes of the hemostatic system result in a hypercoagulable state, subsequent disorders that fuel this active process can trigger a cascade of inappropriate intravascular coagulation. DIC has been associated with many disorders, including preeclampsia/eclampsia, amniotic fluid embolism, and massive blood transfusion.[116] DIC can result in a catastrophic loss of hemostatic components, including clotting factors, fibrinogen, and platelets.

Identification of a coagulopathy can be based in part on clinical evidence, such as bleeding at venous puncture sites or microvascular bleeding around the surgical wound. Laboratory confirmation is essential to allow the prompt and efficacious treatment of a coagulopathy. If the clinical suspicion of a coagulopathy is raised, the platelet count, PT, and PTT should be sent for evaluation. Abnormal elevations of the coagulation tests ($>$1.5 times normal) in the setting of significant hemorrhage should be considered confirmatory of coagulopathy.

Laboratory Assessment

Rapid and reliable laboratory assessment of certain parameters is an important component in the evaluation of the parturient with postpartum hemorrhage. Initial laboratory assessments should include hemoglobin or hematocrit concentrations, platelet count, coagulation studies, including PT, PTT, and fibrinogen level, and when appropriate, arterial blood gas analysis for the assessment of metabolic parameters. In the initial stage of acute hemorrhage, hematocrit does not change and therefore will not reflect the degree of blood loss. Volume replacement with crystalloid or colloid solution results in hemodilution of the red cell mass lowering the hematocrit. As noted previously, there is no reliable "trigger" at which transfusion of homologous red cells should be done; thus, assessment of physiologic parameters serves an important consideration. Parturients who are unable to maintain their blood pressure or urine output without continual boluses of intravenous fluid, or those who develop a metabolic acidosis with elevated lactate levels, should be considered for blood transfusion.

Cause-Specific Issues

Atony

In cases of severe, refractory atony, a surgical procedure is likely to be required; therefore, the major concern is replacement of the maternal blood volume to allow a safe anesthetic. Adequate intravenous access (two large-bore cannulas) and appropriate monitoring should be secured. Most women undergoing angiographic embolization of blood vessels can have the procedure done under sedation; general anesthesia is rarely required. However, the process of transporting and monitoring the parturient to the angiography suite can be a logistical nightmare and, therefore, should be undertaken by experienced personnel. Surgical procedures, on the other hand, require adequate anesthesia. Regional anesthesia can be used for exploration, arterial ligation, or hysterectomy but should be avoided in the hypovolemic patient. Uterine atony can be caused by, or worsened by, medications commonly administered to the parturient. It is well recognized that inhaled general anesthetics have a deleterious effect on uterine tone when used in high concentrations.[117–120] However, even low concentrations worsen an already flaccid uterus. Supplementation with short-acting narcotics and hypnotics reduces the required inhaled concentrations and limits the deleterious effects on uterine tone.

Retained Placenta

The choice of anesthetic technique should be based upon the clinical situation. When the parturient's cervix has not yet contracted, extraction or curettage under sedation and paracervical block is well tolerated. Volatile anesthetics are excellent agents for uterine relaxation, which may be required to allow extraction of the placenta; however, high concentrations are often required that may not be well tolerated by a hypovolemic patient and may significantly worsen maternal blood loss.[117,118] Regional anesthesia may be the best option to minimize maternal risk. The parturient must be hemodynamically stable, without evidence of a coagulopathy, and able to tolerate the associated sympathectomy. Spinal anesthesia using a short-acting local anesthetic with the parturient in a seated position can produce a dense saddle block that will allow a painless procedure. In the parturient who received epidural analgesia for labor, careful extension of the blockade can produce effective sacral anesthesia in most women. Uterine relaxation may be required to allow placental extraction, and can be accomplished with the use of intravenous nitroglycerine at 50 to 100 μg.[84]

Genital Tract Trauma

In most cases, repair of the genital tract can be performed after adequate resuscitation. In parturients who received

epidural analgesia for labor, blockade may be extended and will in most cases provide excellent sacral anesthesia for repair. Spinal anesthesia using a hyperbaric local anesthetic solution combined with narcotics can provide excellent anesthesia, especially when the parturient is placed in a seated position. Some parturients are unable to tolerate regional anesthesia because of excessive bleeding; in such cases, general anesthesia may be the best option. Muscle relaxation is almost never required, and most pregnant women can be maintained on a 66% nitrous oxide and oxygen mixture with low concentrations of agents such as Sevoflurane or Isoflurane. The inhaled concentration of volatile anesthetics should be carefully monitored, as their effect on uterine relaxation may induce further bleeding because of their relaxant effects on the uterus. Short-acting narcotics such as fentanyl are extremely useful to decrease the required concentration of inhaled anesthetics. In the majority of cases, low concentrations of inhaled anesthetics are very well tolerated.

Uterine Inversion

Most descriptions of uterine inversion have documented rapid blood loss that leads to hypovolemic shock in a very short period of time.[54] Although some of the shock associated with uterine inversion may be caused by the intense vagal stimulation that occurs with uterine manipulation, most cases could be better explained by a gross underestimation of blood loss.[78] In this emergency situation, the anesthesiologist may not have sufficient time available to perform a regional anesthetic, in which case general anesthesia is required. Under general anesthesia, uterine relaxation can be achieved with the use of volatile anesthetics. The combined use of low-concentration inhaled anesthetics with a parenteral tocolytic agent provides adequate relaxation to allow uterine replacement. Nitroglycerine at 50 to 100 μg has been found to be useful for uterine relaxation during removal of retained placenta and has been used for acute inversions.[81,84] The combination of nitroglycerine with other tocolytic agents, such as magnesium sulfate or terbutaline, is generally enough to allow reinsertion of the uterus; however, a significant degree of maternal hypotension should be anticipated. Aggressive volume replacement and vasopressor agents should be administered to allow the use of uterine relaxants.

Summary

Although hemorrhage remains one of the two major complications in the field of obstetrics, new approaches to its control are continuously being developed and explored. This chapter summarizes the current management approach for the in-house obstetrician and anesthesiologist who are the first line of the management team.

References

1. De Swiet M. Maternal mortality: confidential enquiries into maternal deaths in the United Kingdom. Am J Obstet Gynecol 2000;182:760–766.
2. Sachs BP, Brown DA, Driscoll SG, et al. Maternal mortality in Massachusetts. Trends and prevention. N Engl J Med 1987;316:667–672.
3. Drife J. Management of primary postpartum haemorrhage. Br J Obstet Gynaecol 1997;104:275–277.
4. Panchal S, Arria AM, Harris AP. Intensive care utilization during hospital admission for delivery: prevalence, risk factors, and outcomes in a statewide population. Anesthesiology 2000;92:1537–1544.
5. Panchal S, Arria AM, Labhsetwar SA. Maternal mortality during hospital admission for delivery: a retrospective analysis using a state-maintained database. Anesth Analg 2001;93:134–141.
6. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. Am J Obstet Gynecol 1967;98:394–403.
7. Taylor DJ, Lind T. Red cell mass during and after normal pregnancy. Br J Obstet Gynaecol 1979;86:364–370.
8. Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. Am J Obstet Gynecol 1976;126:671–677.
9. Duthie SJ, Ven D, Yung GL, et al. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. Eur J Obstet Gynecol Reprod Biol 1991;38:119–124.
10. Duthie SJ, Ghosh A, Ng A, Ho PC. Intra-operative blood loss during elective lower segment caesarean section. Br J Obstet Gynaecol 1992;99:364–367.
11. Robson SC, Boys RJ, Hunter S, Dunlop W. Maternal hemodynamics after normal delivery and delivery complicated by postpartum hemorrhage. Obstet Gynecol 1989;74:234–239.
12. Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol 1991;77:69–76.
13. Thaler I, Manor D, Itskovitz J, et al. Changes in uterine blood flow during human pregnancy. Am J Obstet Gynecol 1990;162:121–125.
14. Nelson SH, Suresh MS. Lack of reactivity of uterine arteries from patients with obstetric hemorrhage. Am J Obstet Gynecol 1992;166:1436–1443.
15. Huszar GB, Walsh MP. Relationship between myometrial and cervical functions in pregnancy and labor. Semin Perinatol 1991;15:97–117.
16. Combs CA, Laros RK Jr. Prolonged third stage of labor: morbidity and risk factors. Obstet Gynecol 1991;77:863–867.
17. Dombrowski MP, Bottoms SF, Saleh AA, et al. Third stage of labor: analysis of duration and clinical practice. Am J Obstet Gynecol 1995; 172:1279–1284.
18. Elbourne DR, Prendiville WJ, Carroli G, et al. Prophylactic use of oxytocin in the third stage of labour (Cochrane Review). Cochrane Database Syst Rev 2001;4:CD001808.
19. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. Cochrane Database Syst Rev 2000;CD000007.
20. Roberts WE. Emergent obstetric management of postpartum hemorrhage. Obstet Gynecol Clin N Am 1995;22:283–302.
21. Stones RW, Paterson CM, Saunders NJ. Risk factors for major obstetric haemorrhage. Eur J Obstet Gynecol Reprod Biol 1993;48:15–18.
22. Gilstrap LC III, Ramin SM. Postpartum hemorrhage. Clin Obstet Gynecol 1994;37:824–830.
23. Alamia V Jr, Meyer BA. Peripartum hemorrhage. Obstet Gynecol Clin N Am 1999;26:385–398.
24. Ledee N, Ville Y, Musset D, et al. Management in intractable obstetric haemorrhage: an audit study on 61 cases. Eur J Obstet Gynecol Reprod Biol 2001;94:189–196.
25. Zelop CM, Harlow BL, Frigoletto FD Jr, et al. Emergency peripartum hysterectomy. Am J Obstet Gynecol 1993;168:1443–1448.
26. Chestnut DH, Eden RD, Gall SA, Parker RT. Peripartum hysterectomy: a review of cesarean and postpartum hysterectomy. Obstet Gynecol 1985;65:365–370.

27. Pelage JP, Soyer P, Repiquet D, et al. Secondary postpartum hemorrhage: treatment with selective arterial embolization. Radiology 1999; 212:385–389.
28. Heffner LJ, Mennuti MT, Rudoff JC, McLean GK. Primary management of postpartum vulvovaginal hematomas by angiographic embolization. Am J Perinatol 1985;2:204–207.
29. Weis FR Jr, Markello R, Mo B, Bochiechio P. Cardiovascular effects of oxytocin. Obstet Gynecol 1975;46:211–214.
30. Bider D, Dulitzky M, Goldenberg M, et al. Intraumbilical vein injection of prostaglandin F2 alpha in retained placenta. Eur J Obstet Gynecol Reprod Biol 1996;64:59–61.
31. Hayashi RH, Castillo MS, Noah ML. Management of severe postpartum hemorrhage with a prostaglandin F2 alpha analogue. Obstet Gynecol 1984;63:806–808.
32. O'Brien P, El Refaey H, Gordon A, et al. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998;92: 212–214.
33. Gerstenfeld TS, Wing DA. Rectal misoprostol versus intravenous oxytocin for the prevention of postpartum hemorrhage after vaginal delivery. Am J Obstet Gynecol 2001;185:878–882.
34. Amant F, Spitz B, Timmerman D, et al. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. Br J Obstet Gynaecol 1999;106:1066–1070.
35. Oleen MA, Mariano JP. Controlling refractory atonic postpartum hemorrhage with Hemabate sterile solution. Am J Obstet Gynecol 1990;162: 205–208.
36. Brown BJ, Heaston DK, Poulson AM, et al. Uncontrollable postpartum bleeding: a new approach to hemostasis through angiographic arterial embolization. Obstet Gynecol 1979;54:361–365.
37. Vedantham S, Goodwin SC, McLucas B, Mohr G. Uterine artery embolization: an underused method of controlling pelvic hemorrhage. Am J Obstet Gynecol 1997;176:938–948.
38. AbdRabbo SA. Stepwise uterine devascularization: a novel technique for management of uncontrolled postpartum hemorrhage with preservation of the uterus. Am J Obstet Gynecol 1994;171:694–700.
39. Deux JF, Bazot M, Le Blanche AF, et al. Is selective embolization of uterine arteries a safe alternative to hysterectomy in patients with postpartum hemorrhage? AJR Am J Roentgenol 2001;177:145–149.
40. Yamashita Y, Takahashi M, Ito M, Okamura H. Transcatheter arterial embolization in the management of postpartum hemorrhage due to genital tract injury. Obstet Gynecol 1991;77:160–163.
41. Villella J, Garry D, Levine G, et al. Postpartum angiographic embolization for vulvovaginal hematoma. A report of two cases. J Reprod Med 2001;46:65–67.
42. Greenwood LH, Glickman MG, Schwartz PE, et al. Obstetric and nonmalignant gynecologic bleeding: treatment with angiographic embolization. Radiology 1987;164:155–159.
43. Rosenthal DM, Colapinto R. Angiographic arterial embolization in the management of postoperative vaginal hemorrhage. Am J Obstet Gynecol 1985;151:227–231.
44. Sieber PR. Bladder necrosis secondary to pelvic artery embolization: case report and literature review. J Urol 1994;151:422.
45. Burchell RC. Physiology of internal iliac artery ligation. J Obstet Gynaecol Br Commonw 1968;75:642–651.
46. Clark SL, Phelan JP, Yeh SY, Bruce SR, Paul RH. Hypogastric artery ligation for obstetric hemorrhage. Obstet Gynecol 1985;66:353–356.
47. Chattopadhyay SK, Deb RB, Edrees YB. Surgical control of obstetric hemorrhage: hypogastric artery ligation or hysterectomy? Int J Gynaecol Obstet 1990;32:345–351.
48. O'Leary JA. Uterine artery ligation in the control of postcesarean hemorrhage. J Reprod Med 1995;40:189–193.
49. Fahmy K. Uterine artery ligation to control postpartum hemorrhage. Int J Gynaecol Obstet 1987;25:363–367.
50. Chestnut DH, Dewan DM, Redick LF, et al. Anesthetic management for obstetric hysterectomy: a multi-institutional study. Anesthesiology 1989;70:607–610.
51. Castaneda S, Karrison T, Cibils LA. Peripartum hysterectomy. J Perinat Med 2000;28:472–481.
52. Clark SL, Yeh SY, Phelan JP, et al. Emergency hysterectomy for obstetric hemorrhage. Obstet Gynecol 1984;64:376–380.
53. Kamani AA, McMorland GH, Wadsworth LD. Utilization of red blood cell transfusion in an obstetric setting. Am J Obstet Gynecol 1988;159: 1177–1181.
54. Ripley DL. Uterine emergencies. Atony, inversion, and rupture. Obstet Gynecol Clin N Am 1999;26:419–434, vii.
55. Sarna MC, Soni AK, Gomez M, Oriol NE. Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg 1997;84: 753–756.
56. Herman A, Weinraub Z, Bukovsky I, et al. Dynamic ultrasonographic imaging of the third stage of labor: new perspectives into third-stage mechanisms. Am J Obstet Gynecol 1993;168:1496–1499.
57. Fox H. Placenta accreta, 1945–1969. Obstet Gynecol Surv 1972;27:475.
58. Zaki ZM, Bahar AM, Ali ME, et al. Risk factors and morbidity in patietns with placenta previa accreta compared to placenta previa nonaccreta. Acta Obstet Gynecol Scand 1998;77:391–394.
59. Levine D, Hulka CA, Ludmir J, et al. Placenta accreta: evaluation with color Doppler US, power Doppler US, and MR imaging. Radiology 1997;205:773–776.
60. Hall MH, Halliwell R, Carr-Hill R. Concomitant and repeated happenings of complications of the third stage of labour. Br J Obstet Gynaecol 1985;92:732–738.
61. Romero R, Hsu YC, Athanassiadis AP, et al. Preterm delivery: a risk factor for retained placenta. Am J Obstet Gynecol 1990;163:823–825.
62. Prendiville W, Elbourne D, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1988;95:3–16.
63. Nordstrom L, Fogelstam K, Fridman G, et al. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997;104:781–786.
64. Khan GQ, John IS, Wani S, et al. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. Am J Obstet Gynecol 1997;177:770–774.
65. Rogers J, Wood J, McCandlish R, et al. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351:693–699.
66. Sorbe B. Active pharmacologic management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstet Gynecol 1978;52: 694–697.
67. McDonald S, Prendiville WJ, Elbourne D. Prophylactic syntometrine versus oxytocin for delivery of the placenta. Cochrane Database Syst Rev 2000;CD000201.
68. Soriano D, Dulitzki M, Schiff E, et al. A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1996;103:1068–1073.
69. Gulmezoglu AM. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev 2000;CD000494.
70. Sellers SM, Hodgson HT, Mitchell MD, et al. Raised prostaglandin levels in the third stage of labor. Am J Obstet Gynecol 1982;144:209–212.
71. Walley RL, Wilson JB, Crane JM, et al. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. Br J Obstet Gynaecol 2000;107:1111–1115.
72. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–975.
73. Gulmezoglu AM, Villar J, Ngoc NT, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689–695.

74. Ridgway LE. Puerperal emergency. Vaginal and vulvar hematomas. Obstet Gynecol Clin N Am 1995;22:275–282.
75. Shah-Hosseini R, Evrard JR. Puerperal uterine inversion. Obstet Gynecol 1989;73:567–570.
76. Wendel PJ, Cox SM. Emergent obstetric management of uterine inversion. Obstet Gynecol Clin N Am 1995;22:261–274.
77. Brar HS, Greenspoon JS, Platt LD, Paul RH. Acute puerperal uterine inversion. New approaches to management. J Reprod Med 1989;34: 173–177.
78. Watson P, Besch N, Bowes WA Jr. Management of acute and subacute puerperal inversion of the uterus. Obstet Gynecol 1980;55:12–16.
79. Catanzarite VA, Moffitt KD, Baker ML, et al. New approaches to the management of acute puerperal uterine inversion. Obstet Gynecol 1986;68:7S–10S.
80. Kovacs BW, Devore GR. Management of acute and subacute puerperal uterine inversion with terbutaline sulfate. Am J Obstet Gynecol 1984; 150:784–786.
81. Dayan SS, Schwalbe SS. The use of small-dose intravenous nitroglycerin in a case of uterine inversion. Anesth Analg 1996;82:1091–1093.
82. Thiery M, Delbeke L. Acute puerperal uterine inversion: two-step management with a beta-mimetic and a prostaglandin. Am J Obstet Gynecol 1985;153:891–892.
83. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
84. DeSimone CA, Norris MC, Leighton BL. Intravenous nitroglycerin aids manual extraction of a retained placenta. Anesthesiology 1990;73:787.
85. Rocke DA, Rout CC, Murray WB. Predicting difficulty of laryngoscopy. Anaesth Intensive Care 1993;21:260–261.
86. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 1992;77:67–73.
87. Jouppila R, Jouppila P, Hollmen A. Laryngeal oedema as an obstetric anaesthesia complication: case reports. Acta Anaesthesiol Scand 1980; 24:97–98.
88. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth 1995;74:638–642.
89. Naef RW III, Morrison JC. Transfusion therapy in pregnancy. Clin Obstet Gynecol 1995;38:547–557.
90. Babineau TJ, Dzik WH, Borlase BC, et al. Reevaluation of current transfusion practices in patients in surgical intensive care units. Am J Surg 1992;164:22–25.
91. Cousins LM, Teplick FB, Poeltler DM. Pre-cesarean blood bank orders: a safe and less expensive approach. Obstet Gynecol 1996;87:912–916.
92. Ransom SB, Fundaro G, Dombrowski MP. The cost-effectiveness of routine type and screen admission testing for expected vaginal delivery. Obstet Gynecol 1998;92:493–495.
93. Camann WR, Datta S. Red cell use during cesarean delivery. Transfusion 1991;31:12–15.
94. Klapholz H. Blood transfusion in contemporary obstetric practice. Obstet Gynecol 1990;75:940–943.
95. Mallett SV, Peachey TD, Sanehi O, et al. Reducing red blood cell transfusion in elective surgical patients: the role of audit and practice guidelines. Anaesthesia 2000;55:1013–1019.
96. BCSH Blood Transfusion and Haematology Task Forces. The estimation of fetomaternal haemorrhage. Transfus Med 1999;9:87–92.
97. Consensus Conference. Perioperative red blood cell transfusion. JAMA 1988;260:2700–2703.
98. Naef RW III, Washburne JF, Martin RW, et al. Hemorrhage associated with cesarean delivery: when is transfusion needed? J Perinatol 1995; 15:32–35.
99. Carson JL, Duff A, Berlin JA, et al. Perioperative blood transfusion and postoperative mortality. JAMA 1998;279:199–205.
100. Thurer RL. Evaluating transfusion triggers. JAMA 1998;279:238–239.
101. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996;334:1685–1690.
102. Glynn SA, Kleinman SH, Schreiber GB, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. Retrovirus Epidemiology Donor Study (REDS). JAMA 2000;284:229–235.
103. Ekeroma AJ, Ansari A, Stirrat GM. Blood transfusion in obstetrics and gynaecology. Br J Obstet Gynaecol 1997;104:278–284.
104. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 1990;30:583–590.
105. Kruskall MS, Leonard S, Klapholz H. Autologous blood donation during pregnancy: analysis of safety and blood use. Obstet Gynecol 1987; 70:938–941.
106. Andres RL, Piacquadio KM, Resnik R. A reappraisal of the need for autologous blood donation in the obstetric patient. Am J Obstet Gynecol 1990;163:1551–1553.
107. McVay PA, Hoag RW, Hoag MS, Toy PT. Safety and use of autologous blood donation during the third trimester of pregnancy. Am J Obstet Gynecol 1989;160:1479–1486.
108. O'Dwyer G, Mylotte M, Sweeney M, Egan EL. Experience of autologous blood transfusion in an obstetrics and gynaecology department. Br J Obstet Gynaecol 1993;100:571–574.
109. Combs CA, Murphy EL, Laros RK Jr. Cost-benefit analysis of autologous blood donation in obstetrics. Obstet Gynecol 1992;80:621–625.
110. Grange CS, Douglas MJ, Adams TJ, Wadsworth LD. The use of acute hemodilution in parturients undergoing cesarean section. Am J Obstet Gynecol 1998;178:156–160.
111. Rainaldi MP, Tazzari PL, Scagliarini G, et al. Blood salvage during caesarean section. Br J Anaesth 1998;80:195–198.
112. Rebarber A, Lonser R, Jackson S, et al. The safety of intraoperative autologous blood collection and autotransfusion during cesarean section. Am J Obstet Gynecol 1998;179:715–720.
113. Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol 1991;98:909–918.
114. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or factor XI deficiency. Br J Obstet Gynaecol 1998;105:314–321.
115. Mannucci PM. How I treat patients with von Willebrand disease. Blood 2001;97:1915–1919.
116. Letsky EA. Disseminated intravascular coagulation. Best Pract Res Clin Obstet Gynaecol 2001;15:623–644.
117. Gilstrap LC III, Hauth JC, Hankins GD, Patterson AR. Effect of type of anesthesia on blood loss at cesarean section. Obstet Gynecol 1987; 69:328–332.
118. Munson ES, Embro WJ. Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 1977;46:11–14.
119. Marx GF, Kim YI, Lin CC, Halevy S, Schulman H. Postpartum uterine pressures under halothane or enflurance anesthesia. Obstet Gynecol 1978;51:695–698.
120. Lynch CB, Adeyemi C, et al. Br J Obstet Gynaecol 1997;104:372–375.

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Neurologic and Muscular Disease

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Obstetricians and anesthesiologists are frequently asked to care for parturients with a variety of neurologic or neuromuscular syndromes. Many of these disorders are chronically debilitating and may progress over time; frequently therapies are merely palliative and not curative. Because of the chronic and degenerative nature of these diseases, the anesthesiologist is concerned about the effects of various anesthetic regimens on disease progression. It is difficult to base clinical decisions on the existing literature because information in this area is limited and frequently anecdotal. An understanding of the pathophysiology of the particular disorder is therefore essential as a basis for making anesthetic choices.

This chapter reviews the neurologic disorders more commonly seen in the parturient. The pathophysiology and obstetric issues are discussed, as well as the available literature regarding implications for anesthetic care.

Headache

Pathophysiology

Headache is one of the most common neurologic symptoms during pregnancy and may arise from a variety of etiologies. Treatment of headaches in the antepartum period requires consideration of effects of therapies on uterine physiology as well as fetal effects. The more common diagnoses include tension headache and migraine headache. Headache is also associated with subarachnoid or intracranial hemorrhage, brain tumor, and cortical vein thrombosis, which are discussed later in this chapter. Headaches associated with hypertensive disorders of pregnancy are not discussed in this section. Headaches can be placed in one of several categories; first-time severe headaches are the highest risk category. There may be a change in the quality of a chronic headache, or a chronic headache may require adjustments in pain control. The physical examination should include vital signs, particularly temperature, palpation over the head and sinuses, evaluation for meningismus, and a careful neurologic exam with fundoscopic evaluation. One should remember that severe headaches with rapid onset, change of consciousness, or focal findings may be a sign of life-threatening problems such as stroke, infarct, or meningitis.

Migraine headaches are generally considered to be the result of neurovascular vasospasm followed by cerebral vasodilation. Serotonin (5-hydroxytryptamine) is released from platelets at the onset of the attack and acts on a variety of receptors to cause vasodilation or vasospasm. Hormonal influences are significant; about 79% of women experience improvement in headache recurrence during pregnancy.[1] Postpartum migraine may be precipitated by the sharp decline in estrogen levels after delivery. Two-thirds of migraines are unilateral, but the side may vary.

Tension headache, the most commonly occurring headache in the parturient, is often associated with anxiety and may be a marker for postpartum depression.[2] Tension headaches commonly recur over years.

Obstetric Management

If medications must be used to treat migraine during pregnancy, potential fetal toxicity needs to be considered. Simple analgesics such as acetaminophen and low-dose caffeine are considered probably safe and are often effective; aspirin is usually avoided because higher doses may result in intrauterine growth retardation and increased risk of bleeding.[3] Nonsteroidal antiinflammatory agents are not used in the third trimester because they may inhibit labor and increase the risk of bleeding.[3] For more severe headaches, narcotics may be used.

Ergot alkaloids and sumatriptan, which are standard therapies in the nonpregnant patient, are contraindicated during pregnancy because of concern about increased risks of premature labor and fetal malformations.[3,4] In severe cases, low-dose prophylactic therapy with beta blockers may be considered. Data on sumatriptan, a newer selective serotonin agonist, are not yet available from parturients. In animal studies, however, an increased incidence of congenital defects has been

seen when high doses are used.[5] At this time, sumatriptan use is not recommended in pregnancy. One study has reported cerebral ischemia after terbutaline use in parturients with a history of migraine.[6]

Severe tension headaches during pregnancy may be treated with opioids, which have a long track record of safety in the parturient.

Anesthetic Management

There is no published evidence that choice of anesthetic during labor and delivery increases the relapse rate of migraine in the postpartum period. There is also no known relationship between the diagnosis of migraine headaches and an increased incidence of postdural puncture headache after regional anesthesia.

Multiple Sclerosis

Pathophysiology

Multiple sclerosis is a chronic demyelinating disease of the central nervous system that is characterized by relapses and remissions of neurologic deficits. The disease is most commonly acquired in young adults, with a 3:2 ratio of females to males.[7] The prevalence is lowest in populations closest to the equator and increases to about 3 per 1000 in the northern United States and Canada.[8]

The etiology remains unknown; it is believed that in susceptible hosts with specific histocompatibility antigens an infectious agent may trigger an autoimmune process that results in inflammatory demyelination.[9] Although no laboratory test yields a conclusive diagnosis, characteristic abnormalities include increased IgG and oligoclonal banding in the cerebrospinal fluid (CSF), multifocal abnormalities on magnetic resonance imaging (MRI) of the brain and spinal cord, and abnormalities in evoked potentials.[10]

The patterns of disability and prognosis are extremely variable. Remissions and exacerbations occur over time and, in a minority of cases, are rapidly progressive. Symptoms can involve all areas of the central nervous system, with motor weakness, impaired vision, bladder and bowel dysfunction, and emotional lability being among the most common.

Treatment is aimed at suppressing the immunologic response. High-dose pulses of intravenous methyl-prednisolone are usually associated with good outcome in the short term.[11] Recent work suggests that interferon-β_{1b} may decrease the relapse rate and number of active lesions.[12]

Obstetric Management

There is no documented effect of multiple sclerosis on fertility, pregnancy, or management of labor and delivery. Patients with the exacerbating, remitting type of multiple sclerosis have been reported to have a slightly decreased relapse rate during pregnancy and an increase in relapse rate during the first 3 to 6 months postpartum.[13–15] Stress, exhaustion, infection, and hyperpyrexia exacerbate this disorder, and these factors as well as the loss of antenatal immunosuppression may contribute to the increased relapse rate in the first 3 postpartum months. Some studies report that administration of intravenous immunoglobulin during the postpartum period may prevent acute childbirth-associated exacerbations in patients with a previous history of postpartum exacerbation.[15] Pregnancy does not appear to negatively affect the long-term outcome of multiple sclerosis. In fact, one study suggests that parturition may have a slightly favorable effect on long-term disease activity.[16]

Anesthetic Management

There has been great controversy regarding the appropriate anesthetic choice for the patient with multiple sclerosis. The concern has been that performing epidural or spinal anesthesia in these patients exposes demyelinated areas of the spinal cord to any potential neurotoxic effects of local anesthetics and may result in exacerbations of the disease. Diagnostic lumbar puncture itself has not been associated with an increase in relapse rate.[17] The two series that did report relapses after spinal anesthesia included very small numbers; in one report, one relapse after 9 spinal anesthetics, and in the second, two after 19 spinal anesthetics.[18,19] The relationship of these risk factors to other postoperative risk factors was not explored. Although most anesthesiologists consider general anesthesia safe to administer to patients with this disorder, there are scant data in the literature supporting this belief.

There have been several case reports of the safe use of epidural and spinal anesthesia in parturients with multiple sclerosis.[20,21] One study retrospectively reviewed 32 pregnancies in patients with multiple sclerosis and reported no greater incidence of relapse in women who received epidural anesthesia for vaginal delivery than in women who received only local infiltration.[22] One patient of the five who underwent cesarean delivery with epidural anesthesia had a relapse, which may have been associated with the higher concentrations of local anesthetic in the CSF during prolonged administration of epidural anesthesia. Because the addition of opioid reduces the concentration of local anesthetic required for labor analgesia, it may be prudent to use dilute solutions of local anesthetic in combination with opioid for labor analgesia in these parturients.

Confavreux et al. recently reported a study of 269 pregnancies in patients with multiple sclerosis, of whom 42 received epidural analgesia.[23] There was no adverse effect of epidural analgesia on the rate of relapse or on the progresion of disability in these parturients.

At our institution, anesthesia for cesarean delivery for these patients is usually performed with either spinal or epidural anesthesia because the limited duration of surgery does not

necessitate repeated dosing of local anesthetic. In conclusion, the use of regional anesthesia is not contraindicated in these parturients. The parturients should be aware of the increased relapse rate in the immediate postpartum period and that, despite this fact, pregnancy does not seem to adversely influence the overall progression of the disease.

Epilepsy

Pathophysiology

Epilepsy is one of the more common neurologic illnesses encountered in the parturient, with a reported incidence of about 1 in 200 women attending antenatal clinics.[24] A variety of seizure types exist, including both generalized and partial seizures. Generalized seizures may be either tonic-clonic (grand mal) or absence (petit mal). Partial seizures have a focal origin and may include motor, sensory, autonomic, or psychic components. Complex seizures, which include temporal lobe epilepsy, can be associated with impaired consciousness. These disorders are treated with a variety of medications, and the prognosis for medical control is dependent on seizure type.

Obstetric Management

Seizure frequency may increase in one-third to one-half of women during pregnancy.[25] Several mechanisms have been postulated. Antiepileptic drug levels decrease during pregnancy because of the increased volume of distribution, decreased plasma protein binding, decreased albumin concentration, and increased drug clearance.[26] Although progesterone has a mild antiepileptic effect, estrogen is known to decrease the seizure threshold.[26] Other mechanisms by which pregnancy may increase the seizure threshold include respiratory alkalosis, sleep deprivation, and stress and anxiety.

Although epilepsy is associated with an increased risk of certain obstetric complications, more recent studies have shown an overall decline in the complication rate. Women with epilepsy are reported to have about a twofold risk of preeclampsia, premature labor, and placental complications such as previa and abruption as compared to women without a seizure disorder.[27] Should a seizure occur, hypoxia and acidemia can have devastating fetal consequences. Although antiepileptic therapy is not without risk, maternal seizures can result in depression of the fetal heart rate and can be hazardous to both fetal and maternal health.

A number of retrospective studies show that infants of mothers with epilepsy are approximately twice as likely to have adverse pregnancy outcomes, including stillbirth, neonatal and perinatal death, low birth weight, and maldevelopment. Induction of labor and cesarean delivery is also about twice as common.[26] Congenital malformation rates are the most extensively studied complication; overall, the risk of malformations in a woman with epilepsy on a single antiepileptic agent at therapeutic levels is 4% to 6%, which is about twice that in the general population.[26] These malformations include cleft lip and palate as well as cardiac, neural tube, and urogenital defects.

Almost all currently used antiepileptic agents cross the placenta and have been associated with an increased risk of congenital malformations. The decreased teratogenic effect in animal studies of newer agents such as felbamate and gabapentin looks more promising, but adequate data in the human parturient are lacking.[28]

Anesthetic Management

Serum levels of antiepileptic agents should be monitored during labor to ensure the maintenance of therapeutic levels. There is no contraindication to regional anesthesia; some have suggested that epidural anesthesia may have an anticonvulsant effect.[29] Drugs known to be associated with a decrease in seizure threshold should probably be avoided; these include ketamine, enflurane, and meperidine.[30] Sevoflurane has also recently been associated with seizures in patients with epilepsy.[31] Low doses of propofol have also been shown to cause activation of the electrocorticogram in epileptic patients, but at higher doses burst suppression was induced.[32]

Myasthenia Gravis

Pathophysiology

Myasthenia gravis is an autoimmune disorder resulting in muscle weakness. Classically, patients suffer from fatigable weakness following repetitive activity. Abnormal T-cell regulation results in the production of antibodies against the nicotinic acetylcholine receptor on the neuromuscular endplate of skeletal muscle. The receptor on the endplate is destroyed through complement fixation and recruitment of inflammatory cells. The presence of antibody also causes blockade of the function of the remaining acetylcholine receptor molecules.[33] Smooth muscle and cardiac muscle are not affected. Thymomas are present in about 15% of patients. Thymectomy results in a decrease in symptoms in two-thirds of patients.[34]

Treatment is based on the administration of anticholinesterases, which inhibit the breakdown of acetylcholine and therefore alleviate the symptoms. Pyridostigmine (Mestinon) is commonly used because it is relatively long acting and has fewer muscarinic side effects. In more severe cases, immunosuppressive therapies such as corticosteroids, plasmapheresis, or intravenous human immunoglobulin may be used.

Two types of crises can be seen in these patients. Worsening of the disease results in myasthenic crises, whereas overdose of anticholinesterase agents can precipitate a cholinergic crisis resulting from an excess of muscarinic effects. The two crises can be distinguished by the administration of edro-

phonium, a short-acting anticholinesterase used for diagnostic purposes. Edrophonium will improve symptoms if a myasthenic crisis is present.

Obstetric Management

During pregnancy, 31% of patients experience no change in the status of the myasthenia and 28% show improvement. About 40% of patients experience worsening of symptoms during the pregnancy or immediate postpartum period.[35] Anticholinesterase drugs are continued during pregnancy, and intravenous formulations are continued during labor and delivery. These agents are quaternary ammonium compounds and have minimal placental transfer.

Pregnant myasthenics have an increased incidence of preterm labor, although overall length of labor is not affected.[36] Although uterine smooth muscle would not be affected, weakness of the voluntary muscles may result in some difficulties during the second stage of labor. Antibody to the acetylcholine receptor does cross the placenta, resulting in increased neonatal morbidity and mortality secondary to antenatal and neonatal myasthenia gravis. Neonatal symptoms may require treatment with anticholinesterases after birth and can persist for weeks until the antibody titers decrease.[37]

Anesthetic Management

A variety of drugs that may be used during labor and delivery can cause worsening of myasthenia gravis; these include aminoglycoside antibiotics, clindamycin, neuromuscular blocking agents, beta blockers, calcium channel blockers, quinidine, procainamide, trimethaphan, phenytoin, and tocolytic agents such as terbutaline and ritodrine.[38,39] Magnesium sulfate use may be detrimental in the myasthenic with preeclampsia, because it produces significant diminution of neuromuscular transmission.[40] Worsening of maternal symptoms after administration of betamethasone has also been reported.[38]

Regional anesthesia provides optimal pain relief for labor and delivery and avoids any potential respiratory depressant effects of opioids in myasthenics who may have some evidence of respiratory compromise.[41] Amide local anesthetics should be used, as esters may have a prolonged half-life in the presence of anticholinesterase agents. Regional anesthesia can also be used for cesarean delivery, unless the patient has severe bulbar involvement or respiratory compromise, and a high level of anesthesia may impair respiratory function.

Sodium thiopental, ketamine, and propofol have all been safely used in these patients.[41–43] Myasthenic patients are extremely sensitive to nondepolarizing muscle relaxants.[41] Close neuromuscular monitoring is essential regardless of which nondepolarizing agent is chosen. Response to succinylcholine is unpredictable; its action may be prolonged by the anticholinesterase. Muscles affected by the myasthenia have been reported to be more sensitive to depolarizing agents and unaffected muscles more resistant.[44]

The myasthenic parturient who requires general anesthesia may be at increased risk for requiring postoperative ventilation. A combination of determinants has been identified that predicts the need for postoperative ventilation: female sex; forced expiratory volume $(FEF)_{25\%–75\%}$ less than 3.3 L/s and less than 85% predicted; forced vital capacity (FVC) less than 2.6 L/s and less than 78% predicted; and maximum expiratory flow $(MEF)_{50\%}$ less than 3.9 L/s and less than 80% predicted.[45]

Myotonic Disorders

Pathophysiology

Myotonic disorders are a group of muscle diseases that are characterized by the symptom of myotonia, or prolonged contraction of certain groups of muscles after stimulation. There are two distinct disorders in this group, the first being myotonic dystrophy and the second myotonia congenita.

Myotonic Dystrophy

Also known as dystrophica myotonica, myotonia atrophica, or Steinert's disease, myotonic dystrophy is an autosomal dominant, slowly progressive disorder that usually becomes apparent during the second or third decade.[39] There is a wide range in severity of the disorder. Patients exhibit skeletal muscle weakness, smooth muscle weakness, and cardiac conduction abnormalities. Progressive deterioration occurs, and patients generally succumb to respiratory failure or cardiac arrhythmias. There is no curative treatment; however, quinine or procainamide may be used to relieve myotonic spasms. When myotonic dystrophy is present in utero or at birth, the symptoms are much more severe, and the disease is called congenital myotonic dystrophy.

Myotonia Congenita

Myotonia congenita can be inherited as either an autosomal recessive or autosomal dominant disorder. This disorder is more benign and is much less common than myotonic dystrophy. Skeletal muscles can experience myotonic spasms, but no other organ systems are involved.

Obstetric Management

Myotonic dystrophy has been reported to worsen during pregnancy.[46] Parturients with this disorder are also at increased risk for obstetric complications, including postpartum hemorrhage from failure of uterine contraction after delivery. Increased risk of prolonged labor, premature labor, placenta previa, retained placenta, and spontaneous abortion have also been reported.[39]

In contrast, obstetric problems in the parturient with myotonia congenita have not been described, probably because this disorder involves skeletal muscle only, and uterine smooth muscle would not be affected. Patients with myotonia congenita may also experience a worsening of symptoms during pregnancy.[39]

Anesthetic Management

Sedatives should be used cautiously in this group of parturients, particularly if significant muscle weakness is present. Depolarizing muscle relaxants have been reported to cause myotonic spasms in patients with both myotonic dystrophy and myotonia congenita[47]; this can result in extreme difficulty with ventilation. Nondepolarizing muscle relaxants do not cause spasms and can be used. Patients with significant muscle weakness should have careful dosage and neuromuscular monitoring. Although myotonic dystrophy has not been associated with increased risk for malignant hyperthermia, some cases of malignant hyperthermia in patients with myotonia congenita have been reported.[48]

Regional anesthesia is preferred for labor and delivery. However, because myotonia is an intrinsic muscle disorder, regional anesthesia will not relieve myotonic spasms; only local infiltration with a local anesthetic agent can directly relieve the myotonia. Both spinal and epidural anesthesia have been successfully used in these patients.[49,50] Parturients with severe muscle wasting may be at risk for hyperkalemic cardiac arrhythmias if depolarizing muscle relaxants are administered.[51]

Muscular Dystrophy

Pathophysiology

Disorders in the group of muscular dystrophies are usually inherited and are characterized by progressive degeneration of skeletal muscle with intact innervation.[39] The discovery of the subsarcolemmal muscle fiber protein dystrophin has led to a reclassification of these disorders as inherited dystrophinopathies.[52] Analysis of dystrophin quality and quantity can be used diagnostically both prenatally and antenatally and in some cases can predict carriers.

Duchenne's and Becker's muscular dystrophy are transmitted as allelic X-linked recessive disorders, and hence are seen almost exclusively in males. The more common dystrophies seen in females are discussed next.

Facioscapulohumeral dystrophy is an autosomal dominant disorder that results in progressive degeneration of the muscles of the shoulders and face. Pelvic muscles may be involved later in the course of the disease. This disorder is infrequently associated with ventricular and supraventricular arrhythmias.

Limb girdle dystrophy has a variable inheritance pattern and involves slow degeneration of the shoulder and pelvic muscles. Cardiac abnormalities are infrequent.

Obstetric Management

Because the variety of the dystrophinopathies is large, and the classification of these disorders continues to be defined by DNA and dystrophin analysis, management should focus on the individual parturient's symptoms and severity of disease.[53] If significant weakness is present, pulmonary function testing should be obtained to assess the extent of restrictive disease. An antepartum cardiogram should be considered. Severe pelvic muscle wasting may necessitate instrumental delivery.

Anesthetic Management

Regional anesthesia can be successfully administered for both vaginal and cesarean delivery. Severe disease may result in both airway abnormalities and spinal deformities, making administration of anesthesia more difficult.[53] Patients with these disorders are at increased risk for malignant hyperthermia, and triggering agents should be avoided if general anesthesia is required.[54] Patients with severe muscle wasting may also be at risk for hyperkalemic cardiac arrhythmias after the administration of depolarizing muscle relaxants.

Spinal Cord Injury

Pathophysiology

Improved handling and stabilization techniques at the site of an accident as well as advances in rehabilitation techniques have led to an increasing number of women who present for obstetric care after spinal cord injuries. The scope of problems encountered depends upon the relative timing of the injury and the level of spinal cord involved.[55]

Immediately following the injury, a loss of reflex function within the isolated spinal cord results in flaccid paralysis, which is accompanied by loss of vasomotor tone, resulting in hemodynamic instability and abnormal temperature regulation. After a period of weeks to months, reflex activity is regained and a chronic picture appears. These patients experience disuse atrophy, flexor spasms, and the mass motor reflex. The mass motor reflex consists of widespread contraction of entire muscle groups occurring after a stimulus that would normally result in the contraction of only a small area of muscle.

Patients with spinal cord transections at the level of the fifth to seventh thoracic vertebrae or higher will be at risk for the syndrome of autonomic hyperreflexia. The absence of central inhibition of the sympathetic neurons in the spinal cord below the level of the injury results in unopposed afferent transmission via the dorsal spinal root, which causes massive unopposed release of catecholamines from the sympathetic chain. Noxious stimuli such as bladder or bowel distension or uterine contractions can precipitate this response. Symptoms include headache, flushing above and vasoconstriction below the level of the lesion, cardiac arrhythmias, and hy-

pertension.[55] When severe, fatal cerebral hemorrhage from severe hypertension or cardiac arrhythmias can occur.

Patients with spinal cord lesions are also at increased risk for urinary infections, decubiti, anemia, and deep venous thrombosis. Restrictive pulmonary dysfunction is seen in a number of patients.[56]

Obstetric Management

Parturients with spinal cord lesions above the level of T10 will not experience labor pain. Patients with lesions at or above this level also have been reported to have an increased risk of preterm labor.[57] These parturients require careful obstetric monitoring during the last weeks of pregnancy so that a precipitous delivery can be avoided. Inability to push during the second stage of labor may necessitate the use of forceps.[58]

Anesthetic Management

Although patients with a lesion above T10 generally will not experience labor pain, unopposed sympathetic release of catecholamines caused by stimulation by uterine contractions must be treated. Because uterine contractions can therefore precipitate autonomic hyperreflexia during labor, administration of regional anesthesia is frequently used to prevent or treat this syndrome. Although single-dose spinal anesthesia has been successfully used to prevent this syndrome in patients undergoing surgical procedures, the use of a continuous technique may be more prudent in the parturient.[59] Caution should be taken with the administration of epidural anesthesia in these parturients, as the usual test dose may not identify accidental intrathecal injection. The cephalad sensory level can be evaluated only if it is higher than the level of the spinal cord transection. Evaluation of segmental reflexes such as the abdominal and knee-jerk reflexes can help to provide at least a partial assessment, as they will be absent below the level of the block.

Epidural anesthesia has been the most commonly used technique for the prevention of autonomic hyperreflexia during labor and delivery. The successful epidural use of 0.25% bupivacaine with or without fentanyl or morphine, 0.5% bupivacaine, and meperidine have all been reported, whereas epidural fentanyl alone failed to control symptoms.[60–64] If regional anesthesia fails to control symptoms, alternative methods such as the administration of intravenous antihypertensive agents must be used.[65]

Regional anesthesia can also be used for cesarean delivery. If general anesthesia is required, succinylcholine and other depolarizing muscle relaxants should be avoided during the period of denervation injury, which is conservatively estimated as beginning 24 h after the injury and lasting for 1 year.[66] Use of depolarizing relaxants during this period can result in severe hyperkalemia. Nondepolarizing agents can be safely used instead.

Brain Neoplasms

Pathophysiology

Although the incidence of brain tumor does not increase during pregnancy, pathophysiologic changes during pregnancy can have a significant effect on tumor growth and symptomatology.[67] The types of tumors seen are similar to those in nonpregnant patients of the same age, with low- and high-grade gliomas and meningiomas each representing about a third of the total. The remaining third includes tumors such as acoustic neuroma, cerebellar astrocytoma, pituitary tumors, and tumors metastatic to the brain. No particular systemic neoplasm with brain metastases is associated with pregnancy with the exception of choriocarcinoma, in which approximately 3% to 20% of patients have metastatic brain disease at the time of diagnosis.[67]

The treatment and prognosis of brain neoplasms seen during pregnancy is obviously dependent upon the particular cell type involved. Magnetic resonance scans, which do not involve radiation, have been safely used in the pregnant patient. Computed tomography (CT) scans require the use of conventional radiation.

Obstetric Management

Physiologic changes during pregnancy can exacerbate tumor symptomatology. Fluid retention and increases in blood volume can increase tumor edema and enlarge tumors. This effect will be more marked in vascular tumors such as meningiomas.[68] Tumors such as meningiomas and acoustic neuromas have been shown to demonstrate sex hormone receptors, which may result in accelerated growth of these tumors during gestation.[67] Previously asymptomatic pituitary tumors may first present during pregnancy, when the pituitary gland normally enlarges. Tumor symptomatology may necessitate the use of anticonvulsants or corticosteroids, and the implications of these treatments in the parturient need to be considered. Malignant tumors or tumors with resultant severe symptomatology (such as optic nerve compression) may require surgery during pregnancy; management of the parturient undergoing intracranial surgery is an extensive topic and is not discussed here.

In the normal parturient, CSF pressure has been reported to increase significantly with painful uterine contractions.[69] During the second stage of labor, CSF pressure increased an average of 7 to 10 mm H_2O above normal. In parturients with an intracranial mass lesion and decreased compliance, this can lead to concerns regarding brain herniation. Although some parturients with intracranial mass lesions have been reported to have successful vaginal deliveries, the location and size of the tumor needs to be assessed in each individual case so that an appropriate plan can be designed.[70,71] In general, either cesarean delivery or a painfree second stage with forceps delivery to avoid pushing is performed.

Anesthetic Management

The choice of anesthesia for labor and delivery in the parturient with an intracranial neoplasm is controversial and should be made in consultation with the parturient's neurologist based on the size and location of the particular tumor involved. There have been reports of the successful use of epidural anesthesia for labor and delivery in patients with intracranial tumors.[72,73] Spinal anesthesia for emergency cesarean delivery in a parturient with glioblastoma has also been reported.[74] If general anesthesia is chosen for cesarean delivery, the risks of increased intracranial pressure and the full stomach considerations in the parturient need to be considered. For induction, sodium thiopental and a short acting nondepolarizing agent may be administered if there is concern about succinylcholine increasing intracranial pressure. A combination of isoflurane, nitrous oxide, and low-dose narcotic may be used for maintenance of anesthesia.

Cerebral Hemorrhage

Pathophysiology

Cerebral hemorrhage has been reported to occur with an incidence between 1 and 5 per 10,000 pregnancies and has an associated mortality of 30% to 40%, making it responsible for nearly 1 in every 10 maternal deaths.[75] Cerebral hemorrhage can be divided into the categories of subarachnoid hemorrhage and intracerebral hemorrhage. Most intracerebral hemorrhages in the parturient are associated with pregnancy-related hypertensive disorders and are not discussed here. Intracerebral hemorrhages have also been associated with cocaine and alcohol abuse. Most subarachnoid hemorrhages are caused by either cerebral aneurysms or arteriovenous malformations. Misdiagnosis can occur from failure to appreciate the spectrum of signs and symptoms, failure to understand the limitations of computer-assisted tomography (CAT) scanning, or failure to perform and correctly interpret lumbar puncture results. Although a large number of parturients with subarachnoid hemorrhage have severe, abrupt headache or neck pain, a number of parturients may have episodes of minor bleeding, and symptoms may be misdiagnosed. The timing of CAT scanning is important; sensitivity decreases after the first day.

Obstetric Management

There is a definite association between aneurysmal bleeding and hypertension, and the incidence of aneurysmal bleeding increases throughout gestation in parallel with physiologic increases in blood volume. Fifty-five percent of initial aneurysmal bleeds occur during the third trimester, with surprisingly rare initial bleeding occurring during labor and delivery.[76] Rehemorrhage during the same pregnancy occurs in about half of patients with aneurysmal hemorrhages. Because of the risk of rehemorrhage, a parturient with a ruptured cerebral aneurysm is generally referred for surgical clipping. Once this procedure has been performed, there is no reason to treat this parturient any differently during labor and delivery. If an aneurysm is found incidentally during pregnancy and has not bled, management should be based on the specific clinical situation involved. The risks and benefits based on aneurysm size and location need to be considered.

In contrast, arteriovenous malformations are less often associated with hypertension and tend to bleed with equal frequency throughout pregnancy and the postpartum period.[77] Unlike aneurysms, arteriovenous malformations are associated with a high risk of bleeding during labor and delivery. Arteriovenous malformations have a 25% risk of rehemorrhage within the same pregnancy. The data regarding appropriate treatment of arteriovenous malformations during pregnancy vary, despite the high risk of rebleeding during the same pregnancy,[75] which may be due to the lower incidence of surgically curable lesions compared with aneurysms. The operability of these lesions is dependent upon their location, and therefore not all lesions presenting during pregnancy are surgically repaired before delivery. More data are required before the optimal surgical timing of ruptured arteriovenous malformations in pregnancy is determined.[75]

For both untreated arteriovenous malformations and aneurysms, hemodynamic stress during labor and delivery must be minimized. Some have advocated elective cesarean delivery at 38 weeks,[77,78] although retrospective studies suggest that vaginal delivery with epidural anesthesia and low forceps delivery does not have a higher complication rate than cesarean delivery in these parturients.[79] Current data do not demonstrate a definite advantage of cesarean delivery over modified vaginal delivery in the obstetrically stable parturients.[75] The decision as to type of delivery in the parturient with an untreated lesion needs to be based on the individual parturient and her previous pregnancy history.

Anesthetic Management

If the parturient has previously undergone surgical repair of either an aneurysm or arteriovenous malformation, anesthetic management need not differ from that of other parturients. The parturient with either an untreated aneurysm or arteriovenous malformation should be treated to maintain hemodynamic stability and avoid hypertension. If vaginal delivery is contemplated, epidural anesthesia and the use of low forceps will avoid increased intracranial pressure seen with pain or with straining during pushing. For cesarean delivery, epidural or spinal anesthesia can be used to avoid the hypertensive response to laryngoscopy.[78,80,81]

Cortical Vein Thrombosis

Pathophysiology

The incidence of cerebral venous thrombosis in parturients has been estimated to be between 1 in 2,500 to 1 in 10,000

deliveries.[82] Primary thrombosis of a cortical vein or thrombosis of the sagittal sinus with extension into the cortical veins is the most commonly seen site. The majority of cases (75%) are reported to occur between the second and third postpartum weeks.[83] Parturients may present with symptoms of progressive headache, nausea and vomiting, and blurred vision. In severe cases, lateralizing neurologic signs and seizures can occur. Diagnosis is generally made by MRI or CT with contrast. Anticoagulation therapy is used to prevent extension of the thrombus.[84]

Obstetric Management

The parturient may be particularly susceptible to this thrombotic disorder because of the hypercoagulable state of pregnancy and the loss of blood and fluid that accompanies delivery and the immediate postpartum period.[83]

Anesthetic Management

As most of these cases present in the postpartum period, it is important to take care to differentiate cortical vein thrombosis from postdural puncture headache.[85] In general, the headache with cortical vein thrombosis is more diffuse in location, and its intensity does not vary with position. Parturients may be lethargic. Associated symptoms of cranial nerve traction are usually not present.

Maternal Hydrocephalus with Shunt

Pathophysiology

The improved outcome of parturients with hydrocephalus who have shunting procedures has led to an increasing frequency of parturients presenting with this condition. Currently, most shunts seen in the parturient are ventriculoperitoneal because these have the lowest incidence of infection.[67]

Obstetric Management

Obstetric complications are not more common in this group of parturients.[86] Parturients with shunts that were previously functioning well may become symptomatic, particularly during the third trimester of pregnancy, because increases in blood volume and cardiac output can lead to an increase in intracranial pressure. If infection or shunt discontinuity is not present, daily pumping of the shunt may help to relieve this problem until delivery, after which most symptoms will resolve.[87]

Anesthetic Management

Theoretically, if regional anesthesia is performed, some of the local anesthetic entering the CSF may escape into the peritoneum, leading to inadequate analgesia. However, there are case reports of parturients with shunts successfully receiving regional anesthesia for labor and delivery.[88] Prophylactic antibiotics should be used to prevent shunt infection.

Common Mononeuropathies in the Parturient: Bell's Palsy

Pathophysiology

Bell's palsy is defined as paralysis of the facial nerve. When it is seen in the parturient, symptoms generally involve all three peripheral motor branches of the nerve and result in asymmetric facial expression and inability to close the eye.[89] Presumably, the increased interstitial edema that can be seen in the parturient causes compression of the nerve within the facial canal.

Obstetric Management

There are no reports of increased obstetric complications in parturients with this lesion, and symptoms generally resolve after delivery. A careful neurologic exam is important to exclude other causes of the facial nerve lesion.

Anesthetic Management

There are no contraindications to regional anesthesia in parturients with Bell's palsy if there are no other complicating neurologic or medical disease.[90]

Common Mononeuropathies in the Parturient: Carpal Tunnel Syndrome

Pathophysiology

Carpal tunnel syndrome results from compression of the median nerve in the carpal tunnel. Symptoms include paresthesias and weakness of the thumb and index and middle fingers and may be bilateral.

Obstetric Management

Carpal tunnel syndrome is the most frequently seen neuropathy during pregnancy, with some studies reporting an incidence as high as 35%.[91] Generalized edema during pregnancy can result in nerve compression in the carpal tunnel; symptoms generally resolve after delivery.

Anesthetic Management

No specific anesthetic issues exist in patients with carpal tunnel syndrome.

Common Mononeuropathies in the Parturient: Meralgia Paresthetica

Pathophysiology

Meralgia paresthetica is a sensory neuropathy that occurs when the lateral femoral cutaneous nerve is compressed under the inguinal ligament. Symptoms include dysesthesias in the upper and middle part of the lateral thigh.[89]

Obstetric Management

This mononeuropathy is more commonly seen in the parturient because of compression and nerve stretch caused by increased interstitial edema, weight gain, and exaggerated lordosis. Symptoms generally resolve within the first 3 postpartum months.[92]

Anesthetic Management

Careful positioning of the patient with meralgia paresthetica is essential after epidural analgesia is in place so that additional nerve stretch does not exaggerate symptoms.

Summary

An understanding of the basic pathophysiology of these neurologic conditions is essential for appropriate anesthetic care. Often, planned elective anesthetic consultation well in advance of delivery will ensure that all members of the team are knowledgeable and all issues regarding the particular condition are addressed.

References

1. Chen TC, Leviton A. Headache recurrence in pregnant women with migraine. Headache 1994;34:107–110.
2. Stein G, Morton J, Marsh A, et al. Headaches after childbirth. Acta Neurol Scand 1984;69:74–79.
3. Hainline B. Headache. Neurol Clin 1994;12:443–460.
4. Silberstein SD. Headaches and women: treatment of the pregnant and lactating migraineur. Headache 1993;33:533–540.
5. Silbersteon SD. Migraine and pregnancy. Neurol Clin 1997;15:209–231.
6. Rosene KA, Featherstone HJ, Benedetti TJ. Cerebral ischemia associated with parenteral terbutaline use in pregnant migraine patients. Am J Obstet Gynecol 1982;143:405–407.
7. Cook SD, Troiano R, Bansil S, Dowling PC. Multiple sclerosis and pregnancy. Adv Neurol 1994;64:83–95.
8. Kurland LT. The frequency and geographic distribution of multiple sclerosis as indicated by mortality statistics and morbidity surveys in the United States and Canada. Am J Hyg 1952;55:457–481.
9. McDonald WI. The mystery of the origin of multiple sclerosis. J Neurol Neurosurg Psychiatry 1986;49:113–123.
10. Cook SD, Troiano R, Bansil S, et al. Multiple sclerosis and pregnancy. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:83–95.
11. Brod SA, Lindsey JW, Wolinsky JS. Multiple sclerosis: clinical presentation, diagnosis and treatment. Am Fam Physician 1996;54:1301–1311.
12. Lublin FD, Whitaker JN, Eidelman BH, et al. Management of patients receiving interferon beta-1b for multiple sclerosis: report of a consensus conference. Neurology 1996;46:12–18.
13. Whitaker JN. Effects of pregnancy and delivery on disability from multiple sclerosis [editorial, comment]. N Engl J Med 1998;339:339–340.
14. Weinshenker BG, Hader W, Carriere W, et al. The influence of pregnancy on disability from multiple sclerosis: a population-based study in Middleswex County, Ontario. Neurology 1989;39:1438–1440.
15. Damek DM, Shuster EA. Pregnancy and multiple sclerosis. Mayo Clin Proc 1997;72:977–989.
16. Roullet E, Verdier-Taillefer MH, Amarenco P, et al. Pregnancy and multiple sclerosis: a longitudinal study of 125 remittent patients. J Neurol Neurosurg Psychiatry 1993;56:1062–1065.
17. Shapira K. Is lumbar puncture harmful in multiple sclerosis? J Neurol Neurosurg Psychiatry 1959;22:238.
18. Bamford C, Sibley W, Laguna J. Anesthesia in multiple sclerosis. Can J Neurol Sci 1978;5:41–44.
19. Stenuit J, Marchand P. Les sequelles de rachi-anesthesie. Acta Neurol Psychiatry Belg 1968;68:626–635.
20. Crawford JS, James FM, Nolte H, et al. Rgional analgesia for patients with chronic neurologic disease and similar conditions. Anaesthesia 1981; 36:821.
21. Warren TM, Datta S, Ostheimer GW. Lumbar epidural anesthesia in a patient with multiple sclerosis. Anesth Analg 1982;61:1022–1023.
22. Bader AM, Hunt CO, Datta S, et al. Anesthesia for the obstetric patient with multiple sclerosis. J Clin Anesth 1988;1:21–24.
23. Confavreaux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse on multiple sclerosis. N Engl J Med 1998;339:285–291.
24. Rutherford JM , Rubin PC. Management of epilepsy in pregnancy: therapeutic aspects. Br J Hosp Med 1996;55:620–622.
25. Sharp GB. Epilepsy and pregnancy: mother and child. J Ark Med Soc 1994;91:282–288.
26. Yerby MS, Devinsky O. Epilepsy and pregnancy. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:45–63.
27. Yerby MS. Pregnancy, teratogemesis and epilepsy. Neurol Clin 1994;12: 749–771.
28. Morrell MJ. The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy and fetal outcome. Epilepsia 1996;37:34S–44S.
29. Merrell DA, Koch MA. Epidural anaesthesia as an anticonvulsant in the management of hypertension and the eclamptic patient in labour. S Afr Med J 1980;58:875–877.
30. Modica PA, Tempelhoff R, White PF. Pro and anticonvulsant effect of anesthetics. Anesth Analg 1990;70:303–315.
31. Komatsu H, Taie S, Endo S, et al. Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. Anesthesiology 1994;81:1535–1537.
32. Smith M, Smith SJ, Scott CA, et al. Activation of the electrocortigram by propofol during surgery for epilepsy. Br J Anaesth 1996;76:499–502.
33. Richman DP, Agius MA. Acquired myasthenia gravis: immunopathology. Neurol Clin 1994;12:273–284.
34. Perlo VP, Arnason B, Poskanzer D, et al. The role of thymectomy in treatment of myasthenia gravis. Ann NY Acad Sci 1971;183:308–315.
35. Plauche WC. Myasthenia gravis in mothers and their newborns. Clin Obstet Gynecol 1991;34:82–99.
36. Giwa-Osagie OF, Newton JR, Larcher V. Obstetric performance of patients with myasthenia gravis. Int J Gynaecol Obstet 1981;19:267–270.
37. Namba T, Brown SB, Grob D. Neonatal myasthenia gravis: report of two cases and review of the literature. Pediatrics 1970;45:488–504.
38. Cantazarite VA, McHargue AM, Sandberg EC, et al. Respiratory arrest during therapy for premature labor in a patient with myasthenia gravis. Obstet Gynecol 1984;64:819–822.

39. Gilchrist JM. Muscle disease in the pregnant woman. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:193–208.
40. Ross RM, Baker T. An effect of magnesium on neuromuscular function in parturients. J Clin Anesth 1996;8:202–204.
41. Rolbin WH, Levinson G, Shnider SM, et al. Anesthetic considerations for myasthenia gravis and pregnancy. Anest Analg 1978;57:441–447.
42. Riegler R, Lishcka A, Neumark J. Problems of anesthesia for cesarean section in myasthenia gravis. Anaesthesist 1983;32:403–406.
43. O'Flaherty D, Pennant JH, Rao K, et al. Total intravenous anesthesia with propofol for transternal thymectomy in myasthenia gravis. J Clin Anesth 1992;4:241–244.
44. Foldes FF, McNall PG. Myasthenia gravis: a guide for anesthesiologists. Anesthesiology 1962;23:837–872.
45. Naguib M, el Dawlatly A, Ashour M, et al. Multivariate determinants of the need for postoperative ventilation in myasthenia gravis. Can J Anaesth 1996;43:1006–1013.
46. O'Brien TA, Harper PS. Course, prognosis and complications of childhood-onset myotonic dystrophy. Dev Med Child Neurol 1984;26:62–67.
47. Paterson IS. Generalized myotonia following suxamethonium: case report. Br J Anaesth 1962;34:340–342.
48. Saidman LJ, Harvard ES, Eger EI. Hyperthermia during anesthesia. JAMA 1964;190:1029–1032.
49. Campbell AM, Thompson N. Anaesthesia for caesarean section in a patient with myotonic dystrophy receiving warfarin therapy. Can J Anaesth 1995;42:409–414.
50. Takano Y, Okada K, Murata K, et al. Anesthetic management for cesarean section in patients with maternal myotonic dystrophy. Masui 1994;43:1348–1351.
51. Sullivan M, Thmpson WK, Hill G. Succinylcholine-induced cardiac arrest in children with undiagnosed myopathy. Can J Anaesth 1994;41:497–501.
52. Reitter B, Goebel HH. Dystrophinopathies. Semin Pediatr Neurol 1996;3: 99–109.
53. Pash MP, Balaton J, Eagle C. Anesthetic management of a parturient with severe muscular dystrophy, lumbar lordosis and a difficult airway. Can J Anaesth 1996;43:959–963.
54. Smith C, Bush GH. Anesthesia and progressive muscular dystrophy. Br J Anaesth 1985;57:1113–1118.
55. Young BK. Pregnancy in women with paraplegia. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:209–214.
56. Okuyama A, Ueda M, Morimoto Y. Anesthetic management for urologic surgery in patients with chronic spinal cord injury. Masui 1994;43: 1033–1037.
57. Cantazarite VA, Ferguson JE, Weinstein C, et al. Preterm labor in the quadriplegic parturient. Am J Perinatol 1986;3:115–118.
58. Greenspoon JS, Paul RH. Paraplegia and quadriplegia: special considerations during pregnancy and labor and delivery. Am J Obstet Gynecol 1986;155:738–741.
59. Lambert DH, Deane RS, Mazuzan JE. Anesthesia and the control of blood pressure in patients with spinal cord injury. Anesth Analg 1982;61:344–348.
60. Abouleish E, Hanley ES, Palmer SM. Can epidural fentanyl control autonomic hyperreflexia in a quadriplegic parturient? Anesth Analg 1989; 68:523–526.
61. Baraka A. Epidural meperidine for control of autonomic hyperreflexia in a paraplegic parturient. Anesthesiology 1985;62:688–690.
62. Paunzer D, Wolman I, Niv D, et al. Epidural morphine-bupivacaine combination for the control of autonomic hyperreflexia during labor. Gynecol Obstet Invest 1994;37:215–216.
63. Stirt JA, Marco A, Conklin KA. Obstetric anesthesia for a quadriplegic patient with autonomic hyperreflexia. Anesthesiology 1979;51:560–562.
64. Watson DW, Downey GO. Epidural anesthesia for labor and delivery of twins of a paraplegic mother. Anesthesiology 1980;52:259–261.
65. Kobayashi A, Mizobe T, Tojo H, et al. Autonomic hyperrelexia during labour. Can J Anaesth 1995;42:1134–1136.
66. Stone WA, Beach TP, Hamelberg W. Succinylcholine: danger in the spinal cord injured patient. Anesthesiology 1970;32:168–169.
67. De Angelis LM. Central nervous system neoplasms in pregnancy. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:139–152.
68. Simon RH. Brain tumors in pregnancy. Semin Neurol 1988;8:214–221.
69. Marx GF, Zemaitis MT, Orkin LR. Cerebrospinal fluid pressures during labor and obstetrical anesthesia. Anesthesiology 1961;22:348–354.
70. Crawford JS. Extradural blockade and intracranial pressure. Br J Anaesth 1987;59:1478.
71. Finfer SR. Management of labour and delivery in patients with intracranial neoplasms. Br J Anaesth 1991;67:784–787.
72. Boyd AH, Sigston PE, Pigston PE. Postpartum headache and cerebral tumour. Anaesthesia 1992;47:450–451.
73. Goroszenuik T, Howard RS, Wright JT. The management of labour using continuous lumbar epidural analgesia in a patient with a malignant cerebral tumour. Anaesthesia 1986;41:1128–1129.
74. Atanassoff PG, Alon E, Weiss E, et al. Spinal anaesthesia for caesarean section in a patient with brain neoplasma. Can J Anaesth 1994;41: 163–164.
75. Wilterdink JL, Feldman E. Cerebral hemorrhage. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:13–23.
76. Robinson J, Hall C, Sedzimir C. Arteriovenous malformations, aneurysms and pregnancy. J Neurosurg 1974;41:63–70.
77. Sadasivan B, Malik G, Lee C, et al. Vascular malformations and pregnancy. Surg Neurol 1990;33:305–313
78. Laidler J, Jackson I, Redfern N. The management of caesarean section in a patient with an intracranial arteriovenous malformation. Anaesthesia 1989;44:490–491.
79. Dias M, Sekhar L. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. Neurosurgery 1990;27:855–866.
80. Gupta A, Hesselnik F, Eriksson L, et al. Epidural anaesthesia for caesarean section in a patient with a cerebral artery aneurysm. Int J Obstet Anaesth 1993;2:49–52.
81. Sharma SK, Herrera ER, Sidawi JE, et al. The pregnant patient with an intracranial arteriovenous malformation: cesarean or vaginal delivery using regional or general anesthesia? Reg Anesth 1995;20:455–458.
82. Simolke G, Cox S, Cunningham F. Cerebrovascular accidents complicating pregnancy and the puerperium. Obstet Gynecol 1991;78:37–42.
83. Wilterdink JL, Easton JD. Cerebral ischemia. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:1–11.
84. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. Lancet 1991;338:597–600.
85. Ravindran RS, Zandstra GC. Cerebral venous thrombosis versus post lumbar puncture headache. Anesthesiology 1989;71:478–479.
86. Stevens E. Pregnancy in women with cerebrospinal shunts: a literature review and case report. J Perinatol 1996;16:374–380.
87. Kleinman G, Sutherling W, Martinez M, et al. Malfunction of ventriculoperitoneal shunts during pregnancy. Obstet Gynecol 1983;61:753–754.
88. Gast MJ, Grubb RL, Strickler RC. Maternal hydrocephalus and pregnancy. Obstet Gynecol 1983;62:29S–31S.
89. Beric A. Peripheral nerve disorders in pregnancy. In: Devinsky O, Feldmann E, Hainline B (eds) Neurologic Complications of Pregnancy. Advances in Neurology, vol 64. New York: Raven Press, 1994:179–192.
90. Dorsey DL, Camann WR. Obstetric anesthesia in patients with idiopathic facial paralysis (Bell's palsy): a 10-year survey. Anesth Analg 1993;77: 81–83.
91. McLennan HG, Oats JN, Walstab JE. Survey of hand symptoms in pregnancy. Med J Aust 1987;147:542–544.
92. Massey EW. Mononeuropathies in pregnancy. Semin Neurol 1988;8: 193–196.

11
Respiratory Disease

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Changes of the Respiratory System During Pregnancy

Physiologic Changes

During pregnancy, hyperemia of the mucous membranes occurs and causes gravidas to have an increased likelihood of experiencing epistaxis. The effect is caused primarily by the increased blood volume during pregnancy. This mucosal hyperemia also leads to increased mucous production and can cause symptomatic nasal congestion that can be confused with infection of the upper respiratory tract. Nasal steroids or decongestants may offer some relief. However, the condition will resolve postpartum.

Physiologic changes in both oxygenation and ventilation allow the pregnant woman to better take in oxygen and expel carbon dioxide. Minute ventilation progressively increases during gestation by 30% to 40% over baseline, whereas the increase in oxygen consumption is only 15% to 29%.[1] Because the respiratory rate changes very little, the tidal volume increases by 30% to 40%, from about 500 to 700 mL to achieve this increase in minute ventilation. Despite the increased tidal volume, the vital capacity is unchanged from the nonpregnant state. The increase in tidal volume is achieved at the expense of the expiratory reserve volume, which is decreased during pregnancy.

Forced vital capacity and forced expiratory volume reflect large airway function. These values are unchanged by pregnancy.[2] Similarly, despite the lowered expiratory reserve volume and residual volume, small airway function does not seem to be significantly impaired.[3]

Anatomic Changes

As pregnancy progresses, the diaphragm is elevated because of the expanding uterus. By the third trimester, the level of the diaphragm is 4 cm superior to its position in the nonpregnant state. In addition, the chest circumference increases 5 to 7 cm, and the subcostal angle increases from about 68° to approximately 103°.[4] Although the elevation of the diaphragm does not compromise its excursion, there is greater use of the accessory muscles of respiration. This change is one of the factors contributing to the dyspnea of pregnancy.

Changes in Blood Gas Values

As a result of the hyperventilation brought about by these changes in respiration, normal arterial blood gas values in pregnant women differ from those in the nonpregnant state (Table 11.1). The reduced maternal P_{CO_2} and the increased maternal P_{O_2} widen the gradients of these gases between the gravida and her fetus and enhance exchange.

Progesterone causes this partially compensated respiratory alkalosis by both increasing the sensitivity to P_{CO_2} and directly stimulating the respiratory center.[5,6] This decreased P_{CO_2} and the increased tidal volume account for the dyspnea reported by two thirds of pregnant women. The kidneys compensate for the reduced P_{CO_2} by excreting bicarbonate and reducing serum bicarbonate levels.

Asthma

Epidemiology

Asthma is among the most common respiratory illnesses encountered in pregnancy, complicating about 4% of pregnancies.[7] This estimate is conservative, and the true prevalence of asthma in pregnant women may well be higher.

Effects of Asthma on Pregnancy and the Fetus

Pregnant women with asthma are at substantially increased risk for several adverse outcomes for infant and mother, suggesting the need for extra attention to mothers with asthma.[8] Chronically poor control has been associated with pregnancy-induced hypertension, preeclampsia, and uterine hemorrhage,

Table 11.1. Normal blood gas parameters in nonpregnant and pregnant women.

Parameter	Nonpregnant	Pregnant
Arterial pH	7.35–7.45	7.40–7.47
Arterial pO_2 (mm Hg)	90–105	104–108
Arterial pCO_2 (mm Hg)	35–45	25–32
Serum HCO_3 (mEq/L)	24–31	18–21

mm Hg, millimeters of mercury; mEq/L, milliequivalents per liter.

as well as greater rates of cesarean section and preterm delivery.[9] Preterm labor is more common, perhaps markedly so, in corticosteroid-dependent patients.[10] The difference in outcomes may also be related to the severity of asthma and the need for steroid therapy rather than to the maternal effects of asthma.[11] In fact, there is little evidence of an association between asthma in pregnancy and maternal mortality.[12]

In a recent study, maternal asthma was associated with low birth weight, small size for gestational age, and congenital anomalies.[13] However, an increased incidence of congenital anomalies has not been shown to occur in most previous studies.[14–16] Fetal well-being may be related to the compliance with asthma treatment, and more consistent therapy during pregnancy has been associated with greater fetal weight and length at birth.[17]

Effects of Pregnancy on Asthma

The literature addressing the effect of pregnancy on asthma is conflicting, with no consistent trend toward improvement or worsening of disease severity. Two of the largest prospective studies, using diaries or medication requirements to assess severity, found similar proportions of women who deteriorated, remained the same, or improved.[18] Although the course of asthma in an individual pregnant woman is largely unpredictable,[19] women with mild disease are unlikely to experience problems.[20] More patients with severe asthma deteriorate during the course of their pregnancy, with a peak around the sixth month.[21] Symptoms decrease significantly during the last 4 weeks of pregnancy to a level below that seen at any other time during pregnancy, returning to the prepregnancy course within 3 months postpartum.[18]

Assessment and Diagnosis

Key indicators for the diagnosis of asthma are wheezing and a history of cough, chest tightness, or difficulty breathing. The reversible nature of the airflow limitation and its diurnal variation can be established by spirometry and peak flow monitoring. Spirometry is an objective assessment of pulmonary function and is recommended for the initial assessment of patients. Peak expiratory flow (PEF) measurement provides a simple measure of the existence and severity of airflow obstruction; it is primarily used for monitoring, not for the diagnosis of asthma. A classification of asthma severity is provided in Table 11.2.

Spirometry typically measures the maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity, FVC) and the volume of air exhaled during the first second of the FVC (forced expiratory volume in 1 s, FEV_1). Airflow obstruction is indicated by reduced FEV_1 and FEV_1/FVC values relative to reference or predicted values. Significant reversibility is indicated by an increase of greater than 12% and 200 mL in FEV_1 after inhaling a short-acting bronchodilator[22] (Figure 11.1).

Therapy

Changes in maternal physiology occur during pregnancy that have the potential to alter the absorption, distribution, and elimination of drugs used therapeutically in pregnant women. These physiologic changes include plasma volume expansion and increases in extracellular fluid space and total body water; decreased plasma albumin concentration; a compensated respiratory alkalosis; increased cardiac output with regional blood flow changes; increased renal blood flow associated with increased glomerular filtration; changes in hepatic drug-metabolizing enzymes; and changes in gastrointestinal function.[23] A reduction in plasma proteins is largely caused by a decrease in serum albumin concentration.[24] This change in protein binding implies that, for certain drugs, plasma concentrations should be reduced or kept at the lower end of the therapeutic range during pregnancy.[25] For example, the protein binding of theophylline decreases by 10% to 15% during pregnancy; therefore, the therapeutic range for theophylline needs to be modified to account for the corresponding

Table 11.2. Classification of asthma severity.

Classification	Symptoms	Lung function
Mild intermittent	≤ two exacerbations per week	FEV_1 or PEF ≥80% predicted PEF variability <20%
Mild persistent	More than two exacerbations per week but < once a day	FEV_1 or PEF >80% predicted PEF variability 20%–30%
Moderate	≥ two exacerbations per week, daily symptoms, daily use of inhalers	FEV_1 or PEF >60% predicted and <80% predicted PEF variability >30%
Severe	Continuous symptoms, limited physical activity, frequent exacerbations	FEV_1 or PEF ≤60% predicted PEF variability >30%

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow.

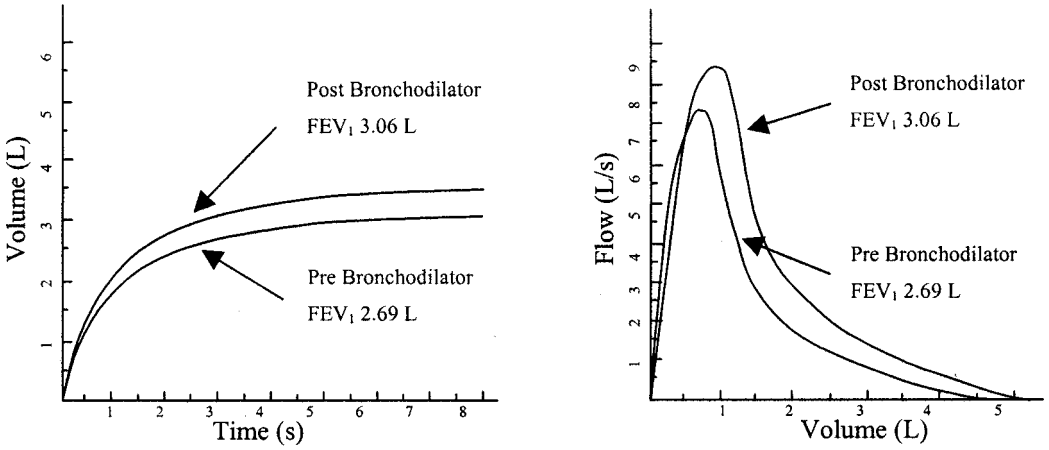


FIGURE 11.1. Result of a spirometry volume–time and flow–volume curve in a patient with bronchial asthma. The graphs illustrate reversible airflow limitation with a significant improvement after bronchodilator therapy.

increase in the free fraction of theophylline. During pregnancy, theophylline plasma concentrations between 8 and 12 g/mL are therapeutically equivalent to concentrations of 10 to 15 g/mL in the nonpregnant patient.

Asthma Drugs During Pregnancy

Antiinflammatory Agents

Corticosteroids. The risks associated with the gestational use of oral corticosteroids are probably still less than the potential risks to the mother and the fetus of severe uncontrolled asthma.[26,27] Chronic maternal administration of oral or parenteral (systemic) corticosteroids has been associated with decreased birth weight.[28–30] Animal studies show palatal clefting in species very sensitive to this anomaly, but no increase in birth defects has appeared in humans.[31] Because of extensive clinical experience with its use, beclomethasone is the preferred inhaled corticosteroid during pregnancy. Although systemic absorption of inhaled corticosteroids can occur, the low plasma levels achieved by inhalation make it unlikely that fetal effects will be seen.

Cromolyn Sodium. This drug is a nonsteroidal antiinflammatory agent for the chronic management of asthma. Acceptable animal studies and human experience suggest little potential for fetal harm from cromolyn sodium.[32]

Bronchodilators

β_2-Adrenergic Agonists (β_2-Agonists). β_2-Agonists relax airway smooth muscle and may modulate mediator release from mast cells and basophils. Inhaled β_2-agonists are the medications of choice for initial treatment of acute exacerbations of asthma and for the prevention of exercise-induced asthma. Metaproterenol (orciprenaline), albuterol (salbutamol), pirbuterol, bitolterol, and terbutaline are commonly used selective β_2-agonists.

Animal studies with β_2-agonists generally show no evidence of teratogenicity, although some of these agents produce anomalies at high doses.[33] Human experience is extensive but generally restricted to the latter part of pregnancy. There is no evidence of fetal injury from the use of these drugs systemically or by inhalation, and there is no contraindication to the use of these agents during lactation.[34] Nonselective β-agonists include epinephrine (adrenaline) and its isopropyl analogue, isoproterenol. Epinephrine given subcutaneously in severe acute exacerbations may be considered, although other therapies should be initiated first. Concern has been raised about uterine vasoconstriction caused by the α-adrenergic effects of epinephrine.[35,36]

Theophylline. Theophylline is the principal methylxanthine used in asthma therapy. Theophylline use during pregnancy has been extensive and without evidence of adverse effects to the neonate when doses are guided by appropriate serum levels (not exceeding 12 g/mL).[37] Approximately 1% or less of the maternal theophylline dose reaches the nursing infant; this level is usually not clinically significant.

Anticholinergics

Inhaled anticholinergic agents produce bronchodilation by reducing intrinsic vagal tone to the airways. Such agents also block reflex bronchoconstriction caused by inhaled irritants. Anticholinergic agents have been used during pregnancy without adverse effects.[38,39] Ipratropium produces less systemic effect than atropine and is not contraindicated in pregnancy, although it is generally not used except for patients with severe asthma.

Antihistamines

Antihistamines are used to block the action of histamine released during mast cell activation in response to an allergen or other stimulus. Antihistamines have been shown to be

safe during early pregnancy, and animal and human experience suggest little, if any, potential for human teratogenicity.[40] It seems reasonable to choose older antihistamines for which reassuring human data exist for use during pregnancy. Although concerns have been raised about antihistamine effects in young children, there are no data establishing adverse effects from use of these drugs in late pregnancy or during lactation.[41]

Decongestants

Decongestants are α-adrenergic drugs used to constrict blood vessels in the nasal mucosa. Agents in this class include oxymetazoline, phenylephrine, phenylpropanolamine, ephedrine, and pseudoephedrine. Because these drugs have α-adrenergic activity, there is concern about their potential to constrict the vascular supply involved in maternal–fetal gas and nutrient exchange.[42] However, pseudoephedrine appears not to produce this effect at therapeutic doses. Human experience with decongestants has not produced a consistent picture of birth defects.

General Asthma Treatment Recommendations

A stepwise approach to pharmacologic therapy is recommended, with the type and amount of medication dictated by asthma severity. To clarify this concept, medications are categorized into two general classes: long-term control medications to achieve and maintain control of persistent asthma and quick-relief medications to treat symptoms and exacerbations (Table 11.3). It should be emphasized that persistent asthma requires daily long-term therapy in addition to appropriate medications to manage asthma exacerbations (Table 11.4).

Obstetric Management

Fetal Surveillance and Asthma

The goal of managing pregnant women with asthma is to optimize maternal pulmonary function and to identify those fetuses at risk for intrauterine growth restriction and adverse outcome. Monitoring of pregnant patients with asthma starts with an evaluation of progressive fetal growth. Growth during the second and third trimesters should be determined by careful serial measurements of fundal height. Confirmation with sequential sonographic evaluations of fetal growth is indicated if the parturient's asthma is uncontrolled or if growth restriction is suspected by lagging fundal height. In the third trimester, antenatal surveillance with nonstress tests, contraction stress tests, or biophysical profiles may be used to ensure fetal well-being. Indications for antepartum fetal assessment include growth restriction, moderate to severe asthma, and decreased fetal movements.

Labor and Delivery

It is recommended that the patient's regularly scheduled asthma medications (inhaled cromolyn, beclomethasone, and/or oral theophylline) be continued during labor and delivery. The patient's peak expiratory flow rate (PEFR) should be measured upon admission to labor and delivery and subsequently every 12 h. If asthma symptoms develop, PEFR should be measured after asthma treatments. To limit the risk of bronchospasm, the patient should be kept well hydrated and be given adequate analgesia.

When women with asthma are admitted in labor, careful fetal monitoring is essential. During the course of labor, continuous fetal heart rate monitoring may be considered to guide appropriate obstetric and asthma management decisions. For labor induction, oxytocin is the drug of choice. Use of prostaglandin E_2 has been reported to cause bronchospasm.[43] However, it has been demonstrated that it can safely be used in the parturient with asthma for therapeutic abortion or labor induction with a dead fetus.[44] Use of intravaginal prostaglandin E_1 or intracervical E_2 gel for cervical ripening before labor induction has not been reported to cause bronchospasm.[45,46] The use of 15-methyl prostaglandin $F_{2\alpha}$, an agent used to treat postpartum uterine atony, should be avoided, because it is a synthetic analogue of prostaglandin $F_{2\alpha}$ that has been reported to cause bronchospasm in patients with asthma.[47]

Anesthetic Management

When choosing a narcotic analgesic for the patient with asthma, consideration must be given to the propensity of that

TABLE 11.3. Stepwise approach to managing asthma in the parturient.

Severity	Long-term control	Short-term control
Severe persistent	Inhaled corticosteroids (high dose) and long-acting bronchodilators (β_2-agonists) and corticosteroids by mouth	Inhaled β_2-agonist; the use of a short-acting β_2-agonist on a daily basis or increasing use indicates the need for additional long-term-control therapy.
Moderate persistent	Inhaled corticosteroids (medium dose) or long-acting inhaled (versus sustained-release), long-acting bronchodilators (β_2-agonists) or sustained-release theophylline	
Mild persistent	Inhaled corticosteroid or cromolyn or nedocromil, slow-release theophylline to serum concentration = 5–15 μg/mL; consider zafirlukast or zileuton	
Mild intermittent	No daily medication recommended	

TABLE 11.4. Management of asthma exacerbations in the parturient.

Mild exacerbation (FEV_1 or PEF >50% predicted)	Severe exacerbation (FEV_1 or PEF <50% predicted)	Respiratory arrest (severe dyspnea)
Inhaled β_2-agonist by metered- dose inhaler or nebulizer, up to three doses in first hour	Inhaled high-dose β_2-agonist and anticholinergic by nebulization every 20 min or continuously for 1 h	Intubation and mechanical ventilation with 100% O_2
Oxygen to achieve O_2 saturation 90%	Oxygen to achieve O_2 saturation 90%	Nebulized β_2-agonist and anticholinergic
Oral systemic corticosteroids if no immediate response or if patient recently took oral systemic corticosteroid	Systemic corticosteroids	Intravenous corticosteroid

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; O_2, oxygen.

agent to cause histamine release that may precipitate bronchospasm. Morphine and meperidine should therefore be avoided, and a preferred agent may be fentanyl. Narcotic analgesics do cause respiratory depression and should not be used if there is an acute asthma exacerbation.

Lumbar epidural analgesia reduces oxygen consumption and minute ventilation during the first and second stages of labor, which offers parturients with asthma considerable benefit.[48–50] Dilute concentrations of local anesthetics and narcotics administered by continuous epidural infusion technique offer consistent analgesia and minimize motor blockade for labor and delivery.[51] Even high thoracic epidural anesthesia appears to be safe in the asthmatic patient.[52] In the parturient with an asthma exacerbation, epidural analgesia has been reported to enhance the response to bronchodilator therapy.[50,53] However, bronchospasm has been reported in approximately 2% of patients with asthma receiving regional anesthesia.[54,55]

If a general anesthetic is necessary, preanesthetic use of atropine and glycopyrrolate may provide a bronchodilatory effect.[56,57] The preoperative inhalation of albuterol reduces the incidence of brochospasm.[58] For induction of anesthesia, ketamine is the agent of choice because it decreases airway resistance[59] and can prevent bronchospasm.[53,60] Propofol has also been used successfully.[61] Thiopental may cause histamine release and is therefore not the induction agent of choice in the asthmatic patient.[62] Muscle relaxants that can cause histamine release, such as atracurium or mivacurium, should be avoided.[63] Low concentrations of halogenated anesthetics can provide the patient with asthma with bronchodilation,[64,65] allowing high inspired concentrations of oxygen and avoiding maternal awareness of the surgery. Low concentrations do not appear to contribute to postpartum hemorrhage. However, high inspired concentrations of volatile agents may contribute to uterine hypotonia and should be avoided.

Adult Respiratory Distress Syndrome

Epidemiology and Definition

The adult respiratory distress syndrome (ARDS) is caused by increased microvascular permeability resulting in accumulation of excess lung water. ARDS can be defined as the acute onset of impaired oxygenation (widened arterial-to-alveolar oxygen gradient). Bilateral pulmonary infiltration is detected on chest radiograph without clinical evidence of elevated left atrial pressure (i.e., the pulmonary artery wedge pressure must be less than 18 mm Hg). Most frequently, patients with ARDS have evidence of multiorgan dysfunction. In fact, enormous overlap exists between ARDS, systemic inflammatory response syndrome (SIRS), and multiorgan system failure (MOF). Overall mortality for ARDS has recently been reported to range from 30% to 40%.[66–69] Factors such as the specific predisposing condition, comorbid diseases, and coexistence of MOF influence the expected outcome for a given patient. MOF is the most common cause of death in pregnant women with ARDS.[70]

Obstetric Management

The leading obstetric causes for ARDS in the parturient are infection (amnionitis and endometritis), preeclampsia and hemorrhage. The most common nonobstetric causes of ARDS are infection, aspiration, and trauma.[71] The development of pulmonary injury (with maternal infection) may be gestational age dependent and correlate with the known physiologic changes of pregnancy, which include increased blood volume, decreased colloid osmotic pressure, and unchanged critical lung-closing volume despite diminished functional residual capacity (FRC).[72] The pregnant state, per se, does predispose to pulmonary injury and ARDS in systemic sepsis of any cause.[73]

The obstetrician plays an important role in the diagnosis and differential diagnosis of ARDS and in management of pregnancy and fetal surveillance in the critically ill parturient patient. The type of fetal monitoring depends on the gestational age. Before fetal viability, the best available short-term assessment of fetal status is by means of monitoring of maternal cardiac output, mixed venous oxygenation, and intermittent fetal heart rate. Once the fetus is at a potentially viable gestational age, fetal heart rate monitoring is appropriate. The fetal heart rate may show diminished variability due to maternal drug therapy. Repetitive late decelerations that cannot be corrected are an indication for delivery. The therapy for ARDS is mostly supportive and consists of maternal stabilization, fetal monitoring, investigation and treatment of underlying causes, and evaluation for delivery.[74] The benefits of delivery on the course of ARDS have not been documented,

and indications for induction of labor or cesarean delivery in this setting are not well defined. Vaginal delivery during mechanical ventilation has been described, but most such patients undergo cesarean delivery.[75,76]

Anesthetic Management

The anesthesiologist/intensivist often participates in the care of parturients with ARDS, as mechanical ventilation is often required. Ventilatory management for parturients with ARDS presents a particular challenge. Although there are no studies of utilization of low tidal volumes in treatment of parturients with acute lung injury, the proven efficacy of this mode of ventilation in parturients with ARDS provides strong support for its universal use. In the ARDS Network study,[77] the delivered tidal volume was based on ideal body weight calculated from patient height. This ideal body weight may not be the same as the ideal body weight of a parturient, but it can be argued that it still should be used to calculate the delivered tidal volume. The goal of low tidal volume therapy is to avoid overdistension of the lung, and because total lung capacity varies little between the pregnant and nonpregnant state, it is reasonable to use this method of determining tidal volume. The ARDS Network study also limited maximum plateau pressures to 30 cm H_2O. It could be argued that the decreased chest wall compliance in the parturient would allow greater plateau pressures without exceeding a reasonable transpulmonary distending pressure. However, as lung compliance falls dramatically in acute lung injury, it becomes the overwhelming determinant of total respiratory compliance. For these reasons, there appears to be little reason to alter the alveolar plateau pressure guideline of the ARDS Network study.

The increased ventilation accompanying pregnancy produces respiratory alkalosis and a compensatory metabolic response. It is important to maintain maternal arterial P_{CO_2} in its usual range of 25 to 32 mm Hg. Permissive hypercapnia is not an attractive option for ventilating the parturient because maternal hypercapnia quickly results in fetal respiratory acidosis.[78] Acidosis also shifts the fetal oxygen dissociation curve to the right, limiting the ability to bind oxygen to fetal hemoglobin.

The type of maternal monitoring depends on the severity of symptoms. Invasive blood pressure monitoring is usually performed in ventilated patients to adjust ventilatory parameters according to arterial blood gas data. The need for pulmonary artery catheterization is controversial. Continuous mixed venous oxygen tension monitoring is considered a useful diagnostic tool by many intensivists in the hemodynamically unstable patient with ARDS. Nitric oxide (NO) has been utilized in the treatment of ARDS in nonpregnant patients, but there is still no consensus on whether inhaled NO improves clinical outcome as defined by oxygen requirements, ventilator days, or mortality.

Respiratory Infections

Bronchitis

Inflammation or infection of the large airways characterizes bronchitis. In parturients without chronic lung disease, suppressed immune systems, or malignancies, the etiology of acute bronchitis is viral in at least 90% of cases.[79] Therefore, there is no evidence that antibiotic therapy of acute bronchitis in healthy adults is beneficial. Furthermore, purulent sputum is not necessarily evidence of bacterial bronchitis and should not prompt antibiotic therapy.[80,81]

The foregoing recommendations apply only to parturients who demonstrate no evidence of pneumonia. The presence of fever, tachypnea, tachycardia, or evidence of focal consolidation on physical examination should heighten the clinician's suspicion for pneumonia. Furthermore, a cough lasting 3 weeks or longer may warrant chest radiography.[79] This test, with shielding of the pregnant uterus, may be performed with little exposure of the fetus to ionizing radiation. If antibiotic therapy were prescribed for chronic bronchitis or suspected bacterial bronchitis, reasonable choices would include erythromycin or amoxicillin-clavulanic acid.

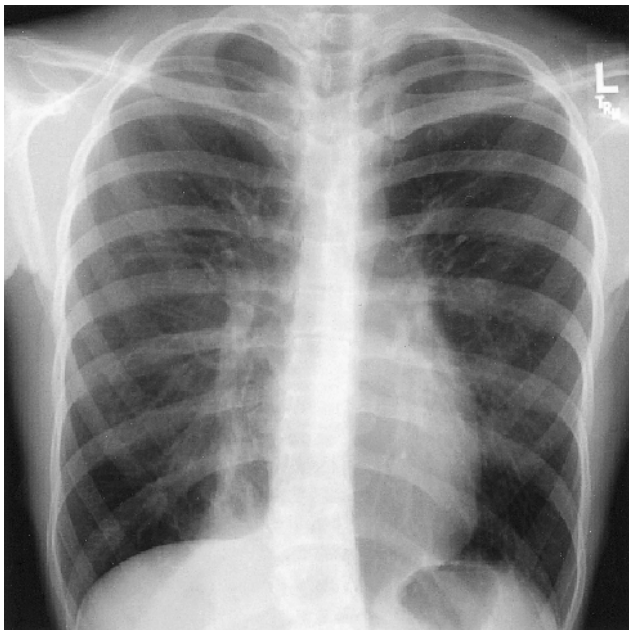
Pneumonia

Pneumonia is an infection or inflammation of the alveoli and small airways. This condition complicates 0.15% to 0.25% of pregnancies and can result in serious sequelae. Despite the fact that mortality rates have decreased dramatically since the advent of antibiotics, pneumonia is the most frequent non-obstetric infection causing maternal mortality.[82] Both the incidence and mortality rates from pneumonia in pregnancy are similar to rates in nonpregnant adults.[83] Figure 11.2 shows a subtle example of right lower lobe pneumonia.

Despite an appropriate diagnostic evaluation, the offending pathogen may not be identified in at least a third of cases,[84] and empiric therapy is often necessary. A β-lactam antibiotic with a β-lactamase inhibitor with or without a macrolide antibiotic such as erythromycin or azithromycin is suitable empiric therapy for most cases. However, resistant pneumococcal strains and atypical organisms are not well covered by such a regimen.

Medical complications associated with pneumonia during pregnancy include bacteremia, empyema, cardiac arrhythmias, and respiratory failure. During the latter half of pregnancy, coincident preterm labor and delivery occur frequently.[85] Furthermore, maternal hypoxia may lead to a nonreassuring fetal heart rate tracing. Treatment should include supplemental oxygen, and fetal heart rate monitoring should be considered.

Most cases of pneumonia during pregnancy are bacterial in etiology.[86] The most common pathogen in community-acquired pneumonias in pregnant women is *Streptococcus*



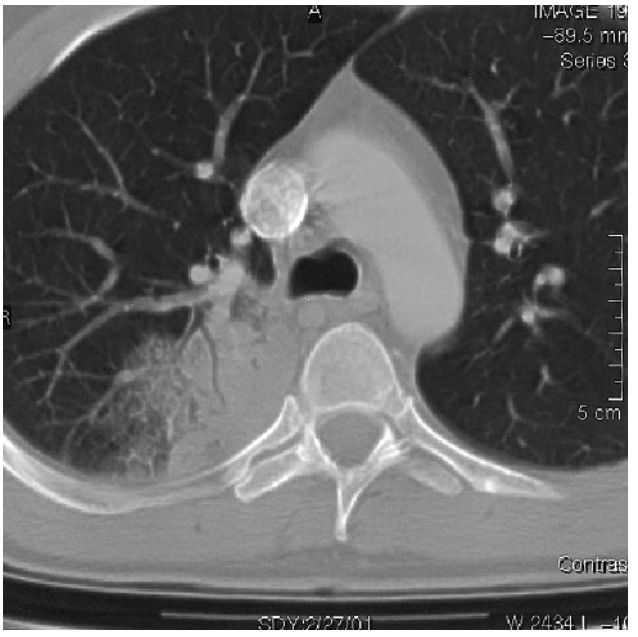


FIGURE 11.2. (A) Posteroanterior chest radiograph from a patient with right lower lobe pneumonia. Note that the inferior portion of the right heart border is obscured. **(B)** CT scan image at the level of the lung base taken from the same patient shows a consolidation in the right lung base consistent with pneumonia. (Courtesy of Chris Sistrom, M.D., Department of Radiology, University of Florida College of Medicine, Gainesville, FL.)

pneumoniae,[86–88] which is also the most common cause of bacterial pneumonia in the general population. Other common bacterial causes of pneumonia include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. Less common pathogens are *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Chlamydia* species.[89] Viral causes of pneumonia during pregnancy include influenza and varicella. The incidence of tuberculosis has also increased in recent years.

Anesthetic Management

There is general concern about the risk of bacterial contamination of the subarachnoid or epidural space during the placement of a neuraxial block in parturients with systemic bacteremia. Antibiotic treatment before the puncture appears to eliminate this risk.[90] Immunocompromised patients or patients receiving systemic corticosteroids appear to be at elevated risk for the development of an epidural abscess.[91]

Cigarette Smoking

Epidemiology

More than 20 million women in the United States smoke cigarettes.[92] Furthermore, approximately 80% of women who smoke continue to do so during pregnancy.[93] Smoking is a completely preventable cause of morbidity and has an adverse effect on virtually every other condition discussed in this chapter.

Pathophysiology

Smoking is associated with a variety of effects on other organ systems of the body. It is causally related to lung, oral, and esophageal cancer, coronary heart disease, atherosclerotic peripheral vascular disease, and chronic obstructive pulmonary disease.[94] The principal effects of smoking on the respiratory tract are caused by impairment of ciliary function, increased mucous production, and increased nonspecific airway reactivity.[95,96] The exact mechanism(s) causing these effects is not well understood.

Medical Management

Cessation of smoking should be encouraged throughout the prenatal course. A reduction in perioperative complications for nonobstetric surgical patients has been demonstrated with short-term abstinence from cigarettes.[96] Although there is no evidence that such an intervention in obstetrics is beneficial, extrapolation of these data to pregnant women seems reasonable.

Obstetric Management

In addition to the untoward effects already mentioned, cigarette smoking has been linked to an increased likelihood of

several conditions specific to pregnancy. Rates of spontaneous abortion, fetal death, and infant mortality are higher among women who smoke.[94,97,98] Obstetric complications such as abruptio placentae and placenta previa are more common in smokers than nonsmokers.[99]

Apart from effects in utero and in the immediate neonatal period, maternal smoking can have more long-lasting effects. Rates of certain childhood malignancies, asthma, strabismus, and attention deficit disorder have been linked with maternal smoking during pregnancy.[100–103]

Anesthetic Management

As mentioned, airway hyperreactivity is a concern when caring for a smoker. Smokers show increased mucous production, decreased mucociliary transport, and narrowing of the small airways.[104] Approximately 4 to 6 weeks of abstinence from cigarette smoking is required to allow a decrease in the risk of postoperative respiratory morbidity to that of a nonsmoker. After 48 h of abstinence, carboxyhemoglobin concentrations fall toward those of nonsmokers, and a few days of abstinence may improve mucociliary function. For labor and delivery, intravenous analgesia or regional anesthesia is preferable to general anesthesia because the latter involves instrumentation of the airway. If general anesthesia is required, the anesthesiologist should be prepared to encounter problems related to the increased airway reactivity seen in smokers.

Cystic Fibrosis

Epidemiology

Cystic fibrosis (CF) affects about 1 in 1800 Caucasians of European ancestry and is the most common recessively inherited disorder among these individuals.[105] The first description of pregnancy in a woman with CF occurred more than 40 years ago.[106] Since then, there have been many other reports of pregnancy in women with this condition as more of these patients survive into adulthood.

Pathophysiology

More than 600 mutations in the CF gene have been described.[107] These mutations result in defects in a chloride channel, causing abnormalities in epithelial electrolyte transport and in exocrine gland secretions. The disease results in both endocrine and exocrine pancreatic insufficiency and may be associated with impaired fertility.

The abnormally viscous secretions in the pulmonary tree result in airway inflammation, plugging, bronchiectasis, and obstructive lung disease. Recurrent and chronic pulmonary infections occur frequently in these patients. In particular, chronic infection with *Pseudomonas aeruginosa* is common and has been implicated as being responsible for a major portion of the morbidity and excess mortality in these patients.[108]

Obstetric Management

A multidisciplinary health care team should treat pregnant women with CF. This team should consist of a pulmonologist, respiratory therapist, dietician, maternal–fetal medicine specialist, and obstetrician.[109] The patient should understand that she might require multiple hospital admissions during pregnancy.

In addition to pancreatic enzyme substitution, pregnant women with CF need an additional 300 kcal/day to meet their energy needs.[110] Nutritional counseling and caloric supplementation are both important components of treatment because poor maternal weight gain has been reported to occur in more than 40% of patients.[111]

The cardiovascular and pulmonary status of patients with CF must be monitored with vigilance. As stated, lower respiratory infections may be frequent and chronic, and these patients may require multiple courses of antibiotics during gestation. Although the data are somewhat dated, congestive heart failure has been reported to occur in more than 10% of pregnancies in women with CF.[112]

In general, the course of CF does not seem to be affected by pregnancy.[111,112] However, prognosis seems to be related to prepregnancy status, and pregnancy is inadvisable in those women with significant airway obstruction, pancreatic insufficiency, or cor pulmonale at baseline. Genetic testing is available, and these patients should be offered genetic counseling and prenatal diagnosis. Ideally, care begins before conception, the woman receives optimal therapy, and she has ample time to consider carrier testing for her partner and prenatal diagnosis.

Preterm delivery and perhaps perinatal mortality occur with increased frequency during pregnancies complicated by CF.[111,112] Serial ultrasound surveillance for fetal growth restriction and antenatal testing are advisable. As stated previously, diabetes mellitus occurs commonly in women with CF. Those women with CF entering pregnancy without a diagnosis of diabetes should undergo early screening for gestational diabetes.

Anesthetic Management

Because pulmonary function is tenuous in parturients with CF, and oxygen requirements increase during painful labor, supplemental oxygen therapy should be used liberally in managing the labor and delivery of a pregnant women with CF. A lumbar epidural anesthetic can minimize the increased oxygen requirement during labor and can be used safely in women with CF.[113] Care must be taken to limit the level of the block so as to minimize chest wall motor weakness and respiratory compromise. If cesarean delivery becomes necessary, epidural anesthesia is the preferred method. General endotracheal anesthesia in women with CF may be associated with delayed uptake and prolonged elimination of inhalational agents as a result of ventilation/perfusion mismatch, endotracheal tube obstruction from profuse secretions, and pneumothoraces.[113]

Summary

Most parturients with mild to moderate respiratory disease are expected to do well during pregnancy, labor, and delivery. Both obstetrician and anesthesiologist should carefully evaluate parturients with advanced or severe respiratory problems in the antepartum period. These parturients are best served by a multidisciplinary team approach to patient care.

References

1. Hytten FE, Leitch I. The Physiology of Human Pregnancy, 2nd edn. Oxford: Blackwell, 1971.
2. Weinberger SE, Weiss ST, Cohen WR, et al. Pregnancy and the lung. Am Rev Respir Dis 1980;121:559–581.
3. Russell IF, Chambers WA. Closing volume in normal pregnancy. Br J Anaesth 1981;53:1043–1047.
4. Thomson KJ, Cohen ME. Studies on the circulation in pregnancy. II: Vital capacity observations in normal pregnant women. Surg Gynecol Obstet 1938;66:591–603.
5. Lyons HA, Antonio R. The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. Trans Assoc Am Physicians 1959;72:173–180.
6. Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanisms. J Appl Physiol 1978;44:939–944.
7. Woodruff PG, Fahy JV. Asthma: prevalence, pathogenesis, and prospects for novel therapies. JAMA 2001;286:395–398.
8. Liu S, Wen SW, Demissie K, et al. Maternal asthma and pregnancy outcomes: a retrospective cohort study. Am J Obstet Gynecol 2001;184: 90–96.
9. Tan KS, Thomson NC. Asthma in pregnancy. Am J Med 2000;109:727–733.
10. Perlow JH, Montgomery D, Morgan MA, et al. Severity of asthma and perinatal outcome. Am J Obstet Gynecol 1992;167:963–967.
11. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43:12–18.
12. Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. Obstet Gynecol 1998;92:435–440.
13. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998;158:1091–1095.
14. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J AlIergy Clin Immunol 1986;78:349–353.
15. Schatz M, Zeiger RS, Harden K, et al. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100:301–306.
16. Minerbi-Codish I, Fraser D, Avnun L, et al. Influence of asthma in pregnancy on labor and the newborn. Respiration 1998;65:130–135.
17. Olesen C, Thrane N, Nielsen GL, et al. A population-based prescription study of asthma drugs during pregnancy: changing the intensity of asthma therapy and perinatal outcomes. Respiration 2001;68:256–261.
18. Schatz M, Harden K, Forsythe A, et al. The course of asthma during pregnancy, postpartum, and with successive pregnancies: a prospective analysis. J Allergy Clin lmmunol 1988;81:509–517.
19. Schatz M. Interrelationships between asthma and pregnancy: a literature review. J Allergy Clin Immunol 1999;103:S330–S336.
20. White RJ, Coutts I, Gibbs C, et al. A prospective study of asthma during pregnancy and the puerperium. Respir Med 1989;83:103–106.
21. Gluck JC, Gluck P. The effects of pregnancy on asthma: a prospective study. Ann Allergy 1976;37:164–168.
22. American Thoracic Society. Lung function testing: selection of reference values and interpretive strategies. Am Rev Respir Dis 1991;144: 1202–1218.
23. Frederiksen MC. Physiologic changes in pregnancy and their effect on drug disposition. Semin Perinatol 2001;25:120–123.
24. Tsen LC, Tarshis J, Denson DD, et al. Measurements of maternal protein binding of bupivacaine throughout pregnancy. Anesth Analg 1999;89:965–968.
25. Connelly TJ, Ruo TI, Frederiksen MC, et al. Characterization of theophylline binding to serum proteins in pregnant and nonpregnant women. Clin Pharmacol Ther 1990;47:68–72.
26. The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). The use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunol 2000;84:475–480.
27. Schatz M. The efficacy and safety of asthma medications during pregnancy. Semin Perinatol 2001;25:145–152.
28. Pirson Y, Van Lierde M, Ghysen J, et al. Retardation of fetal growth in patients receiving immunosuppressive therapy. N Engl J Med 1985; 313:328.
29. Reinisch JM, Simon NG, Karow WG, et al. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978;202:436–438.
30. Scott JR. Fetal growth retardation associated with maternal administration of immunosuppressive drugs. Am J Obstet Gynecol 1977;128:668–676.
31. Bongiovanni AM, McPadden AJ. Steroids during pregnancy and possible fetal consequences. Fertil Steril 1960;11:181–186.
32. Cox JS, Beach JE, Blair AM, et al. Disodium cromoglycate (Intal). Adv Drug Res 1970;5:115–196.
33. Szabo KT, Difebbo ME, Kang YJ. Effects of several beta-receptor agonists on fetal development in various species of laboratory animals: preliminary report. Teratology 1975;12(3):336–337.
34. Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women: Kaiser-Permanente Asthma and Pregnancy Study Group. Chest 1990;98:389–392.
35. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation, 3rd edn. Baltimore: Williams & Wilkins, 1990:237–238, 520–521.
36. Adamsons K, Mueller-Heubach E, Myers RE. Production of fetal asphyxia in the rhesus monkey by administration of catecholamines to the mother. Am J Obstet Gynecol 1971;109:248–262.
37. Greenberger P, Patterson R. Safety of therapy for allergic symptoms during pregnancy. Ann Intern Med 1978;89:234–237.
38. Heinonen OP, Slone D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton, MD: Publishing Sciences Group, 1977.
39. Mellin GW. Drugs in the first trimester of pregnancy and the fetal life of *Homo sapiens*. Am J Obstet Gynecol 1964;90:1169–1180.
40. Aselton P, Jick H, Milunsky A, et al. First-trimester drug use and congenital disorders. Obstet Gynecol 1985;65:451–455.
41. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 1989;84:924–936.
42. Smith NT, Corbascio AN. The use and misuse of pressor agents. Anesthesiology 1970;33:58–101.
43. Fraser IS, Brash JH. Comparison of extra- and intra-amniotic prostaglandins for therapeutic abortion. Obstet Gynecol 1974;43:97–103.
44. Towers CV, Rojas JA, Lewis DF, et al. Usage of prostaglandin E_2 (PGE_2) in patients with asthma. Am J Obstet Gynecol 1991;164:295.
45. Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990;35:183–190.
46. Rayburn WF. Prostaglandin E_2 gel for cervical ripening and induction of labor: a critical analysis. Am J Obstet Gynecol 1989;160:529–534.
47. Fishburne JI Jr, Brenner WE, Braaksma JT, et al. Bronchospasm complicating intravenous prostaglandin F_2 for therapeutic abortion. Obstet Gynecol 1972;39:892–896.

48. Hagerdal M, Morgan CW, Sumner AE, et al. Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 1983;59:425–427.
49. Shnider SM, Abboud TK, Artal R, et al. Maternal catecholamines decrease during labor after lumbar epidural anesthesia. Am J Obstet Gynecol 1983;147:13–15.
50. Younker D, Clark R, Tessem J, et al. Bupivacaine-fentanyl epidural analgesia for a parturient in status asthmaticus. Can J Anaesth 1987;34: 609–612.
51. Chestnut DH, Laszewski LJ, Pollack KL, et al. Continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl during the second stage of labor. Anesthesiology 1990;72:613–618.
52. Groeben H, Schwalen A, Irsfeld S, et al. High thoracic epidural anesthesia does not alter airway resistance and attenuates the response to an inhalational provocation test in patients with bronchial hyperreactivity. Anesthesiology 1994;81:868–874.
53. Shono S, Higa K, Harasawa I, et al. Disappearance of wheezing during epidural lidocaine anesthesia in a patient with bronchial asthma. Reg Anesth Pain Med 1999;24:463–466.
54. Fung DL. Emergency anesthesia for asthma patients. Clin Rev Allergy 1985;3:127–141.
55. Eldor J, Frankel DZ, Barav E, et al. Acute bronchospasm during epidural anesthesia in asthmatic patients J Asthma 1989;26:15–16.
56. Gal TJ, Suratt PM. Atropine and glycopyrrolate effects on lung mechanics in normal man. Anesth Analg 1981;60:85–90.
57. Hurford WE. The bronchospastic patient. Int Anesthesiol Clin 2000;38: 77–90.
58. Maslow AD, Regan MM, Israel E, et al. Inhaled albuterol, but not intravenous lidocaine, protects against intubation-induced bronchoconstriction in asthma. Anesthesiology 2000;93:1198–1204.
59. Corssen G, Gutierrez J, Reves JG, et al. Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 1972;51:588–596.
60. Hirshman CA, Downes H, Farbood A, et al. Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth 1979;51:713–718.
61. Kakinohana M, Fujimine T, Kakinohana O. Propofol anesthesia for an emergent caesarean section in a patient with asthma. Masui 1999;48: 900–902.
62. Pizov R, Brown RH, Weiss YS, et al. Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. Anesthesiology 1995;82:1111–1116.
63. Caldwell JE, Lau M, Fisher DM. Atracurium versus vecuronium in asthmatic patients. A blinded, randomized comparison of adverse events. Anesthesiology 1995;83:986–991.
64. Maltais F, Sovilj M, Goldberg P, et al. Respiratory mechanics in status asthmaticus. Effects of inhalational anesthesia. Chest 1994;106:1401–1406.
65. Otte RW, Fireman P. Isoflurane anesthesia for the treatment of refractory status asthmaticus. Ann Allergy 1991;66:305–309.
66. Smith JL, Thomas F, Orme JF JT, et al. Adult respiratory distress syndrome during pregnancy and immediately postpartum. Am J Med 1990;153:508–510.
67. Mabie WC, Barton JR, Sibai BM. Adult respiratory distress syndrome in pregnancy. Am J Obstet Gynecol 1992;167:950–957.
68. Perry KC Jr, Martin RW, Blake PC, et al. Maternal mortality associated with adult respiratory distress syndrome. South Med J 1998;91: 441–444.
69. Catanzarite VA, Steinberg SM, Mosley CA, et al. Severe preeclampsia with fulminant and extreme elevation of aspartate aminotransferase and lactate dehydrogenase levels: high risk for maternal death. Am J Perinatol 1995;12:310–313.
70. Catanzarite V, Willms D, Wong D, et al. Acute respiratory distress syndrome in pregnancy and the puerperium: causes, courses, and outcomes. Obstet Gynecol 2001;97:760–764.
71. Hudson LD, Steinberg KP. Acute respiratory distress syndrome: clinical features, management, and outcome. In: Fishman AP, Elias JA, Fishman J, Kaiser R (eds) Fishman's Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1998:2549–2565.
72. Parsons PE. Mediators and mechanisms of acute lung injury. Clin Chest Med 2000;21:467–476.
73. de Veciana M, Towers CV, Major CA, et al. Pulmonary injury associated with appendicitis in pregnancy: who is at risk? Am J Obstet Gynecol 1994;171:1008–1013.
74. Hankins GDV. Acute pulmonary injury and respiratory failure during pregnancy. In: Clark SL, Cotton DB (eds) Critical Care Obstetrics, 2nd edn. Boston: Blackwell, 1991:340–370.
75. Sosin D, Krasnow J, Moawad A, et al. Successful spontaneous vaginal delivery during mechanical ventilatory support of the adult respiratory distress syndrome. Obstet Gynecol 1986;68:S19–S23.
76. Mabie WC, Barton JR, Sibai BM. Adult respiratory distress syndrome in pregnancy. Am J Obstet Gynecol 1992;167:950–957.
77. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301–1308.
78. Meschia G. Placental respiratory gas exchange and fetal oxygenation. In: Creasy RK, Resnik R, eds. Maternal-Fetal Medicine. Philadelphia: Saunders; 1999:260–266.
79. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for the treatment of uncomplicated acute bronchitis: background. Ann Intern Med 2001;134:521–529.
80. Robertson AJ. Green sputum. Lancet 1952;1:12–15.
81. Heald A, Auckenthaler R, Borst F, et al. Adult bacterial nasopharyngitis: a clinical entity? J Gen Intern Med 1993;8:667–673.
82. Kaunitz AM, Hughes JM, Grimes DA, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–612.
83. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. Thorax 2001;56:398–405.
84. Brown PD, Lerner SA. Community-acquired pneumonia. Lancet 1998;352:1295–1302.
85. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161:657–662.
86. Nolan TE, Hankins GD. Acute pulmonary dysfunction and distress. Obstet Gynecol Clin North Am 1995;22:39–54.
87. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med 1992;13:679–691.
88. Rigby FB, Pastorek JG. Pneumonia during pregnancy. Clin Obstet Gynecol 1996;39:107–119.
89. Goodrum LA. Pneumonia in pregnancy. Semin Perinatol 1997;21:276–283.
90. Carp H, Bailey S. The association between meningitis and dural puncture in bacteremic rats. Anesthesiology 1992;76:739.
91. Ngan Kee U, Jones MR, Thomas P, et al. Extradural abscess complicating extradural anaesthesia for Cesarean section. Br J Anaesth 1992;69:647.
92. Centers for Disease Control and Prevention. Cigarette smoking among adults—United States. 1994. MMWR (Morb Mortal Wkly Rep) 1995; 45:588–590.
93. Prager K, Malin H, Speigler D, et al. Smoking and drinking behaviour before and during pregnancy of married mothers of liveborn infants and stillborn infants. Public Health Rep 1984;99:117–127.
94. U.S. Department of Health and Human Services. Reducing the health consequences of smoking: 25 years of progress, a report of the Surgeon General. DHHS Publ (CDC) 89–8411. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989.
95. Gerrard JW, Cockcroft DW, Mink JT, et al. Increased nonspecific bronchial reactivity in cigarette smokers with normal lung function. Am Rev Respir Dis 1980;122:577–581.
96. Pearce AC, Jones RM. Smoking and anesthesia: preoperative abstinence and perioperative morbidity. Anesthesiology 1984;61:576–584.

97. DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. J Fam Pract 1995;40:385–394.
98. Kleinman JC, Pierre MB Jr, Madans JH, et al. The effects of maternal smoking on fetal and infant mortality. Am J Epidemiol 1988;127:274–282.
99. U.S. Department of Health and Human Services. The health consequences of smoking for women: a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980.
100. Stjernfeldt M, Berglund K, Lindsten J, et al. Maternal smoking during pregnancy and risk of childhood cancer. Lancet 1986;1:1350–1352.
101. Weitzman M, Gortmaker S, Walker DK, et al. Maternal smoking and childhood asthma. Pediatrics 1990;85:505–511.
102. Hakim RB, Tielsch JM. Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. Arch Ophthalmol 1992;110: 1459–1462.
103. Milberger S, Biederman J, Faraone SV, et al. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiatry 1996;153:1138–1142.
104. Pearce AC, Jones RM. Smoking and anesthesia: preoperative abstinence and perioperative morbidity. Anesthesiology 1984;61:576–584.
105. Goetzl L, D'Alton M. Prenatal diagnosis. In: Ling FW, Duff P (eds) Obstetrics and Gynecology: Principles for Practice. New York: McGraw-Hill, 2001:69–89.
106. Siegel B, Siegel S. Pregnancy and delivery in a patient with cystic fibrosis of the pancreas: report of a case. Obstet Gynecol 1960;16:438–440.
107. Genetic testing for cystic fibrosis. NIH Consensus Statement 1997;15:1.
108. Koch C, Hoiby N. Diagnosis and treatment of cystic fibrosis. Respiration 2000;67:239–247.
109. Samuels P. Pulmonary disease. In: Ling FW, Duff P (eds) Obstetrics and Gynecology: Principles for Practice. New York: McGraw-Hill, 2001:146–156.
110. Rush D, Johnstone FD, King JC. Nutrition and pregnancy. In: Burrow GN, Ferris TF (eds) Medical Complications During Pregnancy, 3rd edn. Philadelphia: Saunders, 1988:117–135.
111. Cohen LF, di Sant'Agnese PA, Friedlander J. Cystic fibrosis and pregnancy. A national survey. Lancet 1980; 2:842–844.
112. Kotloff RM, FitzSimmons SC, Fiel SB. Fertility and pregnancy in patients with cystic fibrosis. Clin Chest Med 1992;13:623–635.
113. Norris MC, Chan L. Respiratory disease. In: Datta S (ed) Anesthetic and Obstetric Management of High-Risk Pregnancy, 2nd edn. St. Louis: Mosby, 1996:168–199.

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12
Cardiovascular Disease in Pregnancy

Phillip S. Mushlin and Karen M. Davidson

The prevalence of cardiac disease in pregnancy has remained relatively constant over the past several decades, ranging from 0.4% to 4.1%,[1–3] but the demographics have changed considerably. Rheumatic heart disease (RHD) has been declining steadily in the developed world,[4] while an increasing number of patients with congenital heart disease (CHD) have been surviving to adulthood.[5] CHD has recently supplanted RHD as the major cause of cardiac disease in pregnancy. With certain lesions (e.g., pulmonary hypertension and cyanotic disease), the risk of maternal mortality may be as high as 50%.[5]

Other than trauma, cardiovascular disease is the most common nonobstetric cause of maternal death.[6] Although healthy women will occasionally develop myocardial dysfunction during pregnancy (e.g., peripartum cardiomyopathy), most cardiovascular complications arise from interaction between a preexisting heart condition and the physiologic stresses of pregnancy. Adaptations of the circulatory system to pregnancy will exacerbate some cardiac disorders but not others. An understanding of interactions between gestation and pathophysiology is useful for predicting the risk of pregnancy for women with various cardiac diseases, and the stages of gestation in which cardiac decompensation is most likely to occur.

This chapter focuses on mechanisms by which pregnancy-related changes in physiology affect women with a spectrum of cardiovascular disorders (Table 12.1).[7,8] We discuss the preconceptual care of women with moderate-to-severe cardiovascular disease as well as the strategies for the obstetric and anesthetic management of such women during pregnancy (Table 12.2). The chapter also addresses the dilemmas and challenges that confront a woman, her family, and the health care team when her desire for motherhood conflicts with a cardiovascular condition that portends high rates of maternal or perinatal morbidity and mortality.

Cardiovascular Changes of Pregnancy

Discerning Normal Changes from Cardiovascular Disease

An uncomplicated pregnancy causes major cardiovascular changes, which may be misinterpreted as cardiovascular disease on physical examination (Table 12.3), electrocardiography (Table 12.4), echocardiography (Table 12.5), and chest radiography (Table 12.6).[9] Healthy parturients often develop cardiopulmonary symptoms such as fatigue, orthopnea, and presyncope, which are usually benign. These findings must be distinguished from clinical abnormalities such as paroxysmal nocturnal dyspnea, syncope, and diastolic murmurs, which usually signal the development or exacerbation of cardiovascular disease. Diagnostic dilemmas that occur during pregnancy may be difficult to resolve, owing to an understandable reluctance to use techniques that might adversely affect the fetus, especially during the period of fetal organogenesis (Table 12.7).[10] However, the mother's life may be endangered if an essential procedure, such as cardiac catheterization, is delayed in order to prevent fetal exposure to ionizing radiation. In some instances, echocardiographic guidance rather than radiographic imaging can provide satisfactory conditions for performing invasive cardiologic procedures.[11]

Time-Related Cardiovascular Adaptations

Hemodynamics

The circulatory system undergoes dynamic changes throughout pregnancy; by the 40th week of gestation, the values of cardiovascular parameters differ markedly from those of the nonpregnant state (Table 12.8). Blood pressure (BP) starts to decline in the first trimester and descends until midpregnancy, before returning to preconceptual values near term.[12,13] Diastolic BP falls more than systolic BP, so the pulse pressure widens. The decrease in blood pressure is primarily due to less peripheral vascular resistance, which may be attributable to (1) gestational hormones; (2) other hormones, such as prostaglandins, atrial natruretic peptides, endothelial nitric oxide; (3) heat generation by the fetus; and (4) the low resistance circulation of the gravid uterus.

The total increase in cardiac output during gestation is between 40–50%. Cardiac output begins to rise in the 5th gestational week in association with a slight elevation in heart rate. Echocardiographic data indicate that nearly half of the total increase in cardiac output has occurred by the 8th ges-

Table 12.1. Risk stratification for pregnant women with cardiac disease.

Low risk
Mitral valve prolapse (isolated) without significant regurgitation
Valvular regurgitation with normal ventricular systolic function
Mitral valve stenosis (NYHA class I or II)
Pulmonic stenosis, mild to moderate
Bioprosthetic valve (e.g., porcine)
Small left-to-right shunt (e.g., ASD, VSD, PDA)
Tricuspid valve disease
Repaired lesions and no residual cardiac dysfunction
Intermediate risk
Left ventricular dysfunction, moderate to severe
History of peripartum cardiomyopathy with no residual ventricular dysfunction
Mitral or aortic stenosis, moderate to severe
Pulmonic stenosis, severe
Mechanical prosthetic valves
Large left-to-right shunt (unrepaired or palliated noncyanotic congenital heart disease)
Coarctation of the aorta, uncorrected
High risk
History of peripartum cardiomyopathy plus ventricular dysfunction
Aortic stenosis, severe
Eisenmenger's syndrome; unrepaired or palliated cyanotic congenital heart disease
Primary pulmonary hypertension, severe
Marfan syndrome with aortic root or major valvular involvement
NYHA class III or IV symptoms

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; NYHA, New York Heart Association

Source: Data from Siu SC, Colman JM. Congenital heart disease: heart disease and pregnancy. Heart 2001;85:710–715, with modification.

Table 12.2. Guiding principles: providing care to women with cardiovascular disease.

Any type of cardiovascular (CV) disease may be present. The etiology and the patient's functional status should be determined as early as is practical.
Understanding the pathophysiologic impact of the underlying cardiac disease is critical for optimizing the outcome of the mother and fetus.
Complex issues (e.g., obstetric, cardiac, anesthetic, social, ethical) are involved in the management of a high-risk pregnancy. A multidisciplinary team approach is required to ensure the best outcome.
Understanding the CV adaptations of pregnancy, which vary predictably with the stage of gestation, helps the health care team to anticipate and prevent acute clinical deterioration.
Management decisions should focus on minimizing risks to the mother and fetus. When a treatment for one may harm the other, the mother's interests should receive the higher priority.
Prevention of a CV complication is much easier than the treatment of the problem. Early planning and aggressive monitoring help to ensure that the mother's CV system is managed optimally.
Labor and delivery cause major physiologic stress. Effective sedation, anxiolysis, and analgesia are essential to minimize this stress.
Neuraxial techniques (e.g., continuous epidural), when not contraindicated (e.g., coagulopathy, infection, neurologic deficit), can produce analgesia and anesthesia without causing hemodynamic instabilty.
Postoperative pain is a major cardiovascular stress; the focus here should be prevention (e.g., epidural or intrathecal morphine), and failing this, aggressive treatment to ablate the pain.
CV decompensation often occurs postpartum; thus, monitoring in an intensive care setting is often indicated for 24–72 h after delivery.

Table 12.3. Cardiac findings that may be present on history and physical examination during normal pregnancy.

History	
Symptoms	Decreased exercise capacity, fatigue
	Dyspnea, orthopnea
	Palpitations, lightheadedness, syncope
Physical examination	
Inspection and palpation	Hyperventilation
	Peripheral edema
Jugular venous pressures and pulses	Neck vein distension
	Prominent A and V waves; brisk x and y descents
Auscultation	
Lungs	Basilar rales
First heart sound	Increased, exaggerated splitting
Second heart sound	Exaggerated splitting
Systolic murmur	Mid-ejection, at left sternal border, over pulmonary area; radiates to suprasternal notch
Continuous murmurs	Cervical venous hum, mammary soufflé

tational week, owing primarily to an elevated stroke volume (Figures 12.1, 12.2).[14,12] Peripheral resistance falls by 30% during the first trimester and approaches a nadir around the 16th gestational week (Table 12.9), the maximum increases in cardiac output (2.2 L/min) and left ventricular volume by the 24th week of gestation. These increases are greater in parous than nulliparous women.[12] Cardiac output remains fairly stable from midpregnancy until term, with a possible small decline in the final weeks of pregnancy.[15] Beyond the 20th week of pregnancy, cardiac output is increasingly influenced by body position, being higher in the lateral decubitus than in the supine position owing to aortocaval compression (Figure 12.3). Heart rate plateaus around the 32nd week of pregnancy, with an average increase of 10 to 20 beats per minute.[12,15]

Studies using invasive hemodynamic monitoring in healthy women have shown cardiac output (43%) and heart rate (17%) to be higher during late pregnancy than 3 months after delivery (Table 12.10).[13] In addition, late pregnancy induced

Table 12.4. Electrocardiographic changes during normal pregnancies.

Heart rate	Sinus tachycardia is common
Cardiac rhythm	Frequent PACs and PVCs; occasional arrhythmias (paroxysmal supraventricular tachycardia)
QRS axis	Deviated to either the left or right
Lead III	Inverted P-wave and small Q-wave, which disappears during inspiration
Leads V2 and V1	R/S ratio is increased
ST segments and T waves	ST segment depression; flattened or inverted T waves often associated with cesarean delivery and tocolytic therapy tocolysis (especially ritodrine)

PAC, premature atrial contractions; PVC, premature ventricular contractions.

Source: From Ref. 427, with permission.

Table 12.5. Echocardiographic findings during normal pregnancies.

Systolic and diastolic left ventricular dimensions	Minimal increase
Left ventricular function	Unchanged or slight increase
Right atrium, right ventricle, and left atrium	Moderate increase in size
Pulmonary, tricuspid, and mitral valve	Annuli dilatate progressively Mild regurgitation present (functional)
Pericardium	Small effusion

relative reductions in systemic vascular resistance (21%), pulmonary vascular resistance (34%) and colloid oncotic pressure (14%), but it did not significantly affect pulmonary capillary wedge pressure (PCWP), central venous pressure, left ventricular stroke work index, or mean arterial pressure.[13]

Hankins and Clark[16] studied oxygen transport in healthy pregnant women to determine if the physiological increase in cardiac output was associated with the greater oxygen delivery to tissues. They took blood samples from pulmonary and radial artery catheters that were placed in late pregnancy (36–38 weeks of gestation) and again three months after delivery. Their data show that pregnancy is associated with decreases in O_2 contents of both arterial blood (16.0 vs 18.0 ml per dl) and mixed venous blood (12.0 vs 13.5 ml per dl) and that oxygen delivery is not significantly greater in late gestation than in the non-pregnant state (868 vs 806 ml per min; not significant).

Intravascular Volume

Blood volume begins to increase around the 6th gestational week and approaches a peak around midpregnancy. The maximal expansion of blood volume averages 50%, but varies considerably from patient to patient (20% to 100%). Larger increases occur in multigravida and women who have multifetal gestations than in primiparous women with singleton pregnancies.[9,12]

The mechanism of the plasma volume expansion during pregnancy involves an estrogen-mediated stimulation of the renin-aldosterone system,[6] which promotes retention of sodium and water. Other hormones that may contribute to the changes of intravascular volume include deoxycorticosterone, prostaglandins, progesterone, prolactin, placental lactogen, growth hormone, adrenocortical hormone, and atrial natruretic peptides.[9,17]

The erythrocyte mass also increases, but less rapidly than plasma volume. The result is a decrease in the hemoglobin concentration until the 30th gestational week (i.e., "physiologic anemia of pregnancy"). The "normal" hematocrit can be as low as 32%, and often increases with iron therapy.

Table 12.6. Chest radiographic findings during normal pregnancies.

Parameter imaged	Finding
Left upper cardiac border	Straightened
Position of the heart	Horizontal
Lung fields	Increased lung markings
Pleural space	Small effusion

Table 12.7. Maternal exposure to ionizing radiation from diagnostic procedures.

Diagnostic procedure	Radiation exposure[a]
Chest radiograph	20 millirad to the chest
Standard fluoroscopy	1–2 rad/min to the chest
High-level fluoroscopy or cineangiography	2–5 rad/min to the chest
Cardiac catheterization	2–5 rad/min to the chest

[a]The goal is to limit total radiation exposure to less than 5 rads. If the dose exceeds 5 rads, the risk–benefit analysis should be discussed with the patient, including the option of terminating the pregnancy.

Supine Hypotensive Syndrome

Supine hypotensive syndrome (SHS) may affect up to 11% of pregnant women.[9] It typically develops late in pregnancy, and is uncommon after delivery or before the 20th gestational week. The syndrome is characterized by a sudden onset of symptoms when the mother becomes supine and her enlarged uterus compresses the inferior vena cava (Figure 12.3)[18] However, the syndrome can occur with a woman in the pelvic tilt or sitting position.[19] Circulatory manifestations range from minimal to severe syncopal shock. Hypotensive episodes are usually accompanied by an increase in maternal heart rate, a decrease in pulse pressure,[19] and symptoms such as weakness, lightheadedness, nausea, dizziness, and syncope.[19] However, severe supine hypotension has been reported to occur without maternal symptoms.[19]

Cardiovascular Effects of Parturition

Anxiety, pain, and uterine contractions contribute to the large hemodynamic effect of labor and delivery. Maternal hyper-

Table 12.8. Cardiovascular changes in the nonpregnant state compared with 40 weeks gestation.

Variable	Direction of change	Average change
Blood volume	↑	+35%
Plasma volume	↑	+45%
Red blood cell volume	↑	+20%
Cardiac output	↑	+40%
Stroke volume	↑	+30%
Heart rate	↑	+15%
Femoral venous pressure	↑	+15 nm Hg
Total peripheral resistance	↓	−15%
Mean arterial blood pressure	↓	−15 mm Hg
Systolic blood pressure	↓	−0 to 15 mm Hg
Diastolic blood pressure	↓	−10 to 20 mm Hg
Central venous pressure	No change	

Source: From Cheek TG, Gutsche BB. Maternal physiologic alterations during pregnancy. In: Shnider SM, Levinson GL (eds) Anesthesia for Obstetrics. Baltimore: Williams & Wilkins, 1987:6. Used by permission.

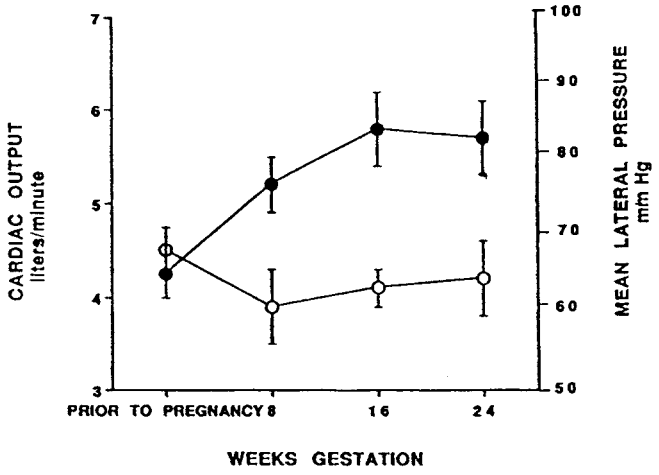

FIGURE 12.1. Time-related effects of pregnancy on cardiac output (*closed circles*) and mean arterial pressure (*open circles*); circles show values before conception and at the 8th, 16th, and 24th weeks of gestation. Data were determined using echocardiography with women in the left lateral position. (From Capeless EL, Clapp JF. Am J Obstet Gynecol 1989;161:1449, with permission.)

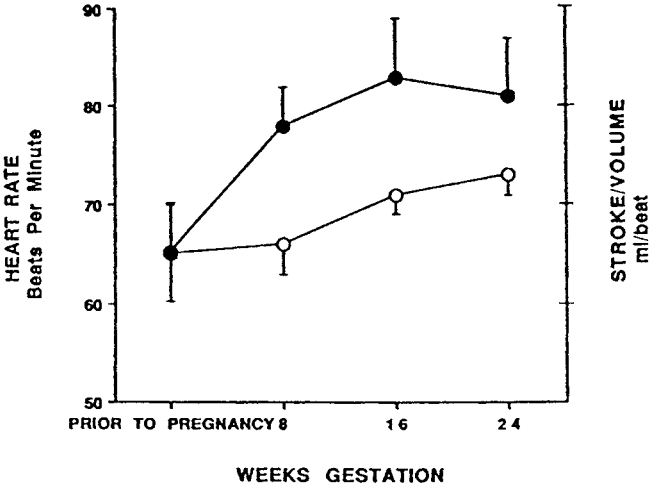

FIGURE 12.2. Time-related effects of pregnancy on stroke volume (*closed circles*) and heart rate (*open circles*); circles show values before conception and at the 8th, 16th, and 24th weeks of gestation, with women in the left lateral position. Elevations of stroke volume (rather than heart rate) are primarily responsible for the increases in cardiac output shown in Figure 12.1. (From Capeless EL, Clapp JF. Am J Obstet Gynecol 1989;161:1449, with permission.)

ventilation is a ubiquitous response to labor pain, which may reduce placental perfusion. Epidural analgesia blunts or eliminates this response.[20,21]

Approximately 200 to 400 mL of uteroplacental blood is translocated into the systemic circulation during each contraction, which causes undulating increases of maternal venous return, stroke volume, cardiac output, and BP.[22] Cardiac output increases progressively from early labor through the second stage of labor and reaches a peak immediately after delivery (Figure 12.4); these increases can be associated with as much as a threefold increase in oxygen consumption.[23,24]

Epidural anesthesia markedly attenuates the decreases in transcutaneous PO_2[25] (Figure 12.5) and hyperkinetic cardiovascular responses to labor contractions.[26] Hagerdal and coworkers[27] compared contraction-related oxygen consumption (VO_2) and minute ventilation (VE) before and after induction of epidural anesthesia (during the first stage of labor). Before epidural anesthesia, contractions led to a 63% increase in VO_2 and a 74% increase in VE; epidural anesthesia completely prevented these increases. In the second stage of labor, epidural anesthesia (versus no epidural) lowered VO_2 by 25% and VE by 31%.[27]

Cardiovascular Changes in the Puerperium

Blood loss averages approximately 500 mL for a vaginal delivery and 800 mL for a cesarean delivery. When the blood loss is minimal, a large transient increase in venous return occurs immediately after delivery, because caval compression is relieved, and blood from the tonically contracted uterus is redistributed to the systemic circulation (autotransfusion). Effective blood volume expands, and there are marked elevations of ventricular filling pressure, stroke volume, heart rate, and cardiac output. The circulatory changes during delivery occur rapidly and can lead to hemodynamic deterioration in women with compensated cardiovascular disease.

Heart rate and cardiac output fall to prelabor values within 1 hr after delivery, and by 24 h, mean blood pressure and

TABLE 12.9. Cardiovascular measurements.

Cardiovascular parameter	Before pregnancy (baseline)	8th week pregnancy	16th week pregnancy	24th week pregnancy	Maximum % change vs. baseline
Heart rate (beats/min)	65 ± 3	68 ± 4	72 ± 3	73 ± 3	+12%
End-diastolic volume (mL)	109 ± 9	122 ± 9	125 ± 8	126 ± 8	+16%
Stroke volume (mL)	65 ± 5	79 ± 5	83 ± 6	81 ± 5	+28%
Ejection fraction (%)	61 ± 2	64 ± 4	66 ± 2	64 ± 2	+8%
Cardiac output (L/min)	4.2 ± 0.4	5.2 ± 0.3	5.9 ± 0.4	5.7 ± 0.3	+40%
Mean arterial pressure (mm Hg)	69 ± 3	62 ± 4	69 ± 2	67 ± 4	−10%
Systemic vascular resistance (dynes sec cm^{-5})	1376 ± 143	969 ± 76	926 ± 68	930 ± 82	−33%

Source: From American Journal of Obstetrics & Gynecology 1989;161:1449 (with modification).

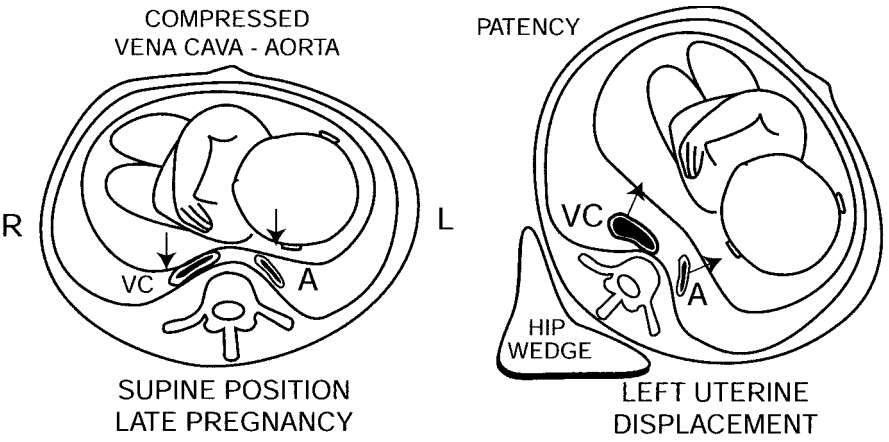

FIGURE 12.3. Compression of the aorta (*A*) and vena cava (*VC*) when the mother is supine (*drawing on left*). When she is in the left lateral recumbent position (*wedge* under her right *hip*), both vessels are *patent* (*drawing on right*). *R*, right; *L*, left. (From Dripps RD, Eckenhoff JE, Vandam LE. Introduction to Anesthesia: The Principles of Safe Practice, 6th ed. Philadelphia: Saunders, 1982: 286, with permission.)

stroke volume have returned to their prelabor values.[9] The cardiovascular changes of pregnancy resolve gradually during the first 3 to 6 months after delivery. However, residual effects due to cardiovascular remodeling can persist for at least a year postpartum and may lead to augmented circulatory changes during a subsequent pregnancy.[13]

Management of Women with Cardiovascular Disease: General Principles

General principles of management for women with cardiovascular disease (CV) are shown in Table 12.11.

Preconceptual Counseling

Women should receive preconceptual counseling about the impact of pregnancy on their underlying disease (see Table 12.1) and their functional cardiac status (Table 12.12). The process should include a thorough medical evaluation and a discussion of cardiac procedures that would be best performed in the nonpregnant state to avoid potential fetal risks. If a woman has a major cardiac lesion that is correctable (e.g., critical aortic stenosis), she should be advised to have it repaired before pregnancy to improve both maternal and fetal prognosis. Similarly, a woman may benefit from an electrophysiologic study, a radiofrequency ablation procedure, or the insertion of a pacemaker or an automatic implantable cardioverter-defibrillator (AICD) before conception.

Special Considerations

Preventing a Crisis

Parturients with significant CV disease should be managed by a multidisciplinary team at a high-risk medical center where around-the-clock coverage is provided by specialists in perinatology, cardiology, cardiac surgery, nursing, and obstetric anesthesiology.[28] If a woman's CV disorder is associated with a high likelihood of maternal morbidity or mortality (see Table 12.1), she should undergo a thorough cardiac evaluation. The cardiologist and obstetrician should discuss their findings with the parturient, so that she can make an informed decision about continuing or terminating the pregnancy.

Pregnancy depletes the CV reserve of such parturients, rendering them vulnerable to stresses that might otherwise be inconsequential. Thus, it may be particularly challenging to manage obstetric complications and emergencies including preeclampsia, placental previa, abruptio placentae, acute fetal distress, uterine atony and postpartum hemorrhage. The

TABLE 12.10. Central hemodynamic changes.

Parameter	Nonpregnant	Pregnant
Cardiac output (L/min)	4.3 ± 0.9	6.2 ± 1.0
Heart rate (beats/min)	71 ± 10.0	83 ± 10.0
Systemic vascular resistance (dyne cm sec^{-5})	1,530 ± 520	1,210 ± 266
Pulmonary vascular resistance (dyne cm sec^{-5})	119 ± 47.0	78 ± 22
Colloid oncotic pressure (mm Hg)	20.8 ± 1.0	18.0 ± 1.5
Colloid oncotic pressure–pulmonary capillary wedge pressure (mm Hg)	14.5 ± 2.5	10.5 ± 2.7
Mean arterial pressure (mm Hg)	86.4 ± 7.5	90.3 ± 5.8
Pulmonary capillary wedge pressure (mm Hg)	6.3 ± 2.1	7.5 ± 1.8
Central venous pressure (mm Hg)	3.7 ± 2.6	3.6 ± 2.5
Left ventricular stroke work index (g m m^{-2})	41 ± 8	48 ± 8

Source: Clark SL, Cotton DB, Lee W, et al. Am J Obstet Gynecol 1989;161:1439. Used by permission.

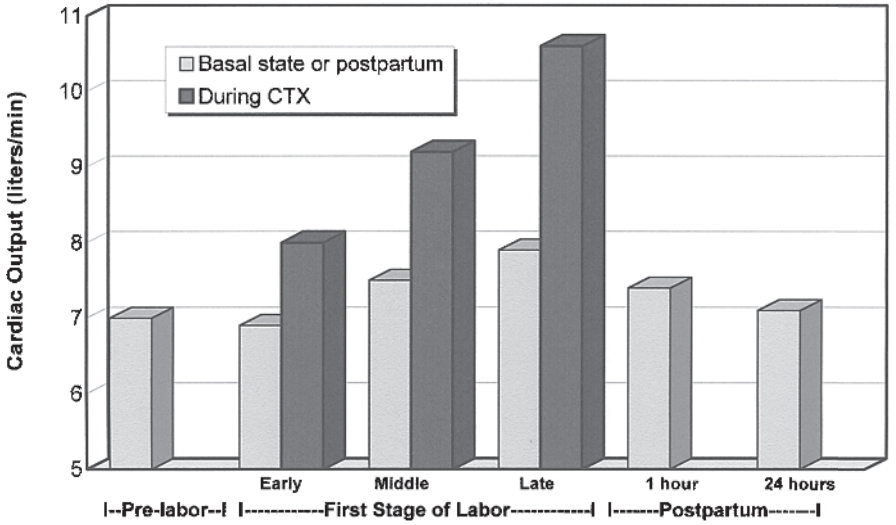

FIGURE 12.4. Cardiac output during the first stage of labor. *Bar heights* show mean values of cardiac output (L/min) determined echocardiographically before labor, as labor progressed (early ≤3 cm; middle 4–7 cm; late ≥8 cm; cervical dilation), and after delivery (at 1 h and 24 h). *CTX*, uterine contraction; *PP*, postpartum. Measurements during labor were taken both in the basal state (between CTX) and at the peak of a CTX. Basal cardiac output increased by 0.9 L/min in the first stage of labor, whereas cardiac output during contractions increased progressively as labor advanced (i.e., from 1.1 to 1.8 to 2.7 L/min in early, middle, and late labor, respectively). Larger stroke volumes accounted for the increases of basal cardiac output, whereas the CTX-related elevations resulted from increases of both stroke volume and heart rate. Women studied (n = 15) received labor analgesia with meperidine, nitrous oxide, and oxygen and had uncomplicated vaginal deliveries. (Data from Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. Br Med J 1987;295:1169.)

obstetric team and parturient should discuss potential maternal–fetal triage scenarios and develop contingency plans for unexpected emergencies, so that life-and-death decisions do not have to be made during a crisis.

Medical Management

Careful medical management is the key to a successful outcome of pregnancy for a woman with severe CV disease. She should be seen weekly, with special consideration given between the 28th and 36th weeks of gestation. The obstetrician should address emotional problems and levels of physical activity. If dyspnea, palpitations, or fatigue occurs, then physical exertion should be restricted. Attention to diet is important. A nutritionally sound diet with supplemental vitamins and iron helps to prevent both anemia and excessive weight gain (whether from overeating or high salt intake). Women who are taking certain diuretics may need potassium supplements. Prevention of infection is paramount and requires careful observation by the obstetric team. Finally, vigilance for manifestations of congestive heart failure is essential during the weekly visit; a woman with CV disease who shows signs of decompensation may need to be hospitalized a few weeks before delivery for closer monitoring.

Anticoagulant Therapy

Women with cardiac disease often require medication to prevent or treat conditions associated with thrombosis and

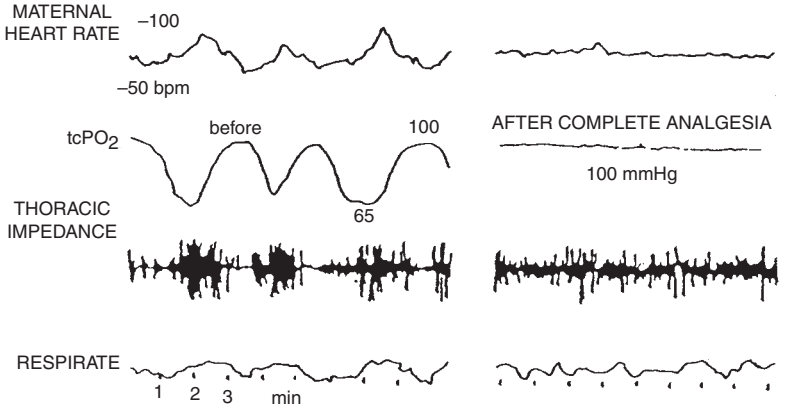

FIGURE 12.5. Epidural analgesia blunts maternal cardiopulmonary responses to labor (i.e., heart rate, ventilation, thoracic impedance, and transcutaneous oxygen tension, [$tcPO_2$] to labor. Painful uterine contractions (*left*) cause maternal hyperventilation; this leads to hypoventilation between contractions; which causes $tcPO_2$ to decrease from 100 to 65 mm Hg. Epidural analgesia (*right*) stabilizes maternal heart rate, pattern of ventilation, and [$tcPO_2$] at 100 mm Hg. (From Huch R, Huch A, Lubbers DW. Transcutaneous PO_2, New York: Thieme-Stratton, 1981:139, with permission.)

TABLE 12.11. General principles of management for women with cardiovascular disease.

Stage	Goals of care
Before conception	Identify CV conditions and functional class. Obtain cardiology evaluation.
	Advise to undergo necessary surgical corrections.
	Counsel about prognosis for successful pregnancy outcome, including risks to maternal health (long term) and of fetal anomalies and fetal wastage.
	Review issues related to future pregnancy (e.g., increased need for maternal and fetal surveillance).
	Review medications and discuss the risk–benefit analysis for each medication with cardiologist and patient.
	Provide birth control counseling to help prevent unwanted pregnancies.
First trimester	Perform multidisciplinary evaluation by cardiology and perinatology.
	Counsel about risks of maternal morbidity and mortality, as well as prognosis for successful pregnancy outcome.
	Reevaluate medications with cardiologist, adjusting as needed to minimize fetal risks without compromising maternal CV status.
	Avoid therapeutic interventions that can safely be postponed until the second trimester (e.g., fluoroscopy).
	Review option of pregnancy termination if maternal morbidity and mortality are significant.
	Discuss transfer of care to a tertiary referral center.
Second trimester	Continue close multidisciplinary evaluation of patient.
	Evaluate for fetal congenital heart disease by level II fetal ultrasound.
	Evaluate fetal growth by serial fetal ultrasound.
	Perform necessary cardiac diagnostic studies, procedures, and operations.
	Adjust medication doses to maintain therapeutic levels.
	Implement restriction of maternal activity as necessary to maintain CV stability.
Third trimester	Continue close multidisciplinary evaluation of patient.
	Institute fetal testing with weekly NSTs.
	Evaluate growth by serial fetal ultrasound.
	Obtain OB anesthesia consultation.
	Have team meeting on labor and delivery to plan delivery management.
	Review risk–benefit of induction, spontaneous labor, and elective cesearean section.
	If anticoagulated, switch to unfractionated heparin.
Labor and delivery	Close monitoring by multidisciplinary team.
	Adequate pain relief.
	Monitoring of maternal cardiovascular condition and fluid status in ICU setting as necessary.
Postpartum phase	Take measures to prevent (and manage) postpartum clinical deterioration typically associated with specific maternal CV diseases.
	Hemodynamic monitoring in ICU setting.

CV, cardiovascular; NST, nonstress test; ICU, intensive care unit.

thromboembolism. Anticoagulant medications must be used with care to minimize risks of fetal malformation and injury while optimally protecting the mother from devastating thrombotic complications. Occasionally, a conflict will occur. If a woman has a first-generation mitral valve prosthesis, then continuous warfarin therapy throughout pregnancy may be safer than discontinuing its use during the period of fetal organogenesis. Such therapy, however, subjects the fetus to increased risks of congenital malformation.

Because heparin does not cross the placenta, it has no direct effects on the fetus. In contrast, warfarin readily traverses the placenta and often causes severe fetal complications. Ginsberg and Hirsch[29] reported that the perinatal death rate was 2.5% when the mother received heparin versus 16.8% when the mother received warfarin. They noted that warfarin was associated with an embryopathy in 4.6% of pregnancies (45 of 970).[29] Iturbe-Alessio et al.[30] reviewed rates of congenital malformations related to first trimester warfarin therapy in women with cardiac valvular disease. Embryopathies occurred in 10 of 35 (29%) infants exposed to warfarin between the 6th and 12th weeks of gestation, but there was not a single embryopathy when heparin was substituted for warfarin during these gestational weeks (19 pregnancies studied). They recommended that once pregnancy is recognized, women should be switched from warfarin to heparin.

TABLE 12.12. New York Heart Association (NYHA) functional classification.

Class I:	Asymptomatic
Class II:	Symptomatic with exertion
Class III:	Symptomatic with normal activity
Class IV:	Symptomatic at rest

To achieve the desired benefits of heparin therapy, the mother must also bear its risks. Unfractionated heparin increases the risk of bleeding complications during pregnancy and osteoporosis. Patients with ischemic heart disease who receive subcutaneous heparin for longer than six months are at increased risk for developing osteoporosis; this concern may be of relevance for pregnant women who require anticoagulant therapy throughout pregnancy. Fortunately, heparin-related bone abnormalities may resolve after the heparin is discontinued.[31]

Infective Endocarditis

Infective endocarditis is a rare but debilitating condition. The incidence has been estimated to be as high as 1 in 8000 de-

liveries.[32] This incidence appears to be decreasing, which may be a result of the extensive use of antibiotics, the decreased prevalence of RHD, improved aseptic technique during obstetric procedures, or aggressive treatment of obstetric infections. Risk factors for endocarditis in patients with preexisting cardiac lesions include dental and urologic procedures, intravenous injections of illicit drugs,[33] and prolonged therapy with intravenous medications. Mothers with infective endocarditis have an overall mortality rate of nearly 30%, and the fetal mortality rate is about 23%.[34] Seaworth and Durack[34] reported that streptococci (usually *Streptococcus viridans*) is the pathogen in 75% of cases; enterococci and group B streptococci are uncommon causes (except after abortion).

Antibiotic Prophylaxis

Controversy still exists about the need for prophylactic antibiotics for a woman who is expected to have an uncomplicated labor and vaginal delivery.[35] There is general agreement, however, that prophylactic antibiotics are indicated for procedures that cause bacteremia when patients are at increased risk for endocarditis due to surgically constructed systemic-pulmonary shunts or conduits, prosthetic valves, RHD, or previous infective endocarditis.[35–37] Prophylactic antibiotics, intravenous ampicillin and gentamicin, are often typically given during labor and again 24 h after delivery. For a penicillin-allergic patient, vancomycin may be substituted.[35] The use of prophylactic antibiotics is not recommended for an uncomplicated elective cesarean delivery in a woman who is not in labor and has intact membranes. The current recommendations are shown in Table 12.13.

Obstetric Considerations

Preparing for Delivery

After establishing that the risk for perinatal morbidity or mortality is increased, consultations with perinatologists and pediatricians should be arranged as early as practical. A pediatrician should attend the delivery because the primary responsibility of the obstetrician and anesthesiologist is to provide maternal care, and they may be unavailable to assist with neonatal resuscitation. Postpartum care of the mother should occur in a setting that is equipped and staffed to monitor and treat women whose CV condition may abruptly deteriorate following delivery.

Vaginal Versus Cesarean Delivery

Cesarean delivery has often been recommended for women with CV disease to circumvent the hyperkinetic circulatory effects of labor and vaginal delivery. However, a cesarean delivery does not eliminate the CV stresses of delivery. Cardiac output may increase up to 50% during and after an elective cesarean delivery, and oxygen consumption shortly after delivery may be 25% higher than the prepregnancy value.[38] Furthermore, a cesarean delivery, especially if emergent, increases the likelihood of major circulatory instability, which may result from the larger blood loss or the greater depth of anesthesia that is required for cesarean delivery. General anesthesia, for example, is usually associated with transient tachycardia, episodes of hypertension or hypotension, and myocardial depression. Neuraxial anesthesia produces an extensive sympathectomy, which lowers BP, alters heart rate, and often requires immediate treatment with vasoactive agents. Profound hypotension and tachycardia are likely to occur when a woman with a sympathectomy hemorrhages or receives a large dose of oxytocin to treat uterine atony. Moreover, a neuraxial anesthetic will occasionally fail to adequately block nociceptive input; this can lead to a stress response and necessitate an emergent general anesthetic, which can further destabilize the circulation.

Anesthesia Considerations

Anesthesia Consultation

The anesthesia consultation should be scheduled far in advance of the anticipated time of delivery. The anesthesiologist gives special attention to the obstetric and cardiac history. The physical examination focuses on the CV and pulmonary systems, as well as on the airway and lumbar spine.

TABLE 12.13. Prophylactic antibiotic regimens for genital urinary and gastrointestinal procedures.

Regimen	Drug	Dosage regimen
Standard regimen	Ampicillin, gentamicin, amoxicillin	Ampicillin 2.0 g, IV or IM, plus gentamicin 1.5 mg/kg (not to exceed 80 mg), IV or IM, 30 min before the procedure; followed by amoxicillin 1.5 g orally, 6 h after the initial dose. Alternatively, the parenteral regimen may be repeated once, 8 h after the initial dose.
Alternative regimen for low-risk patient	Amoxicillin	2.0 g orally 1 h before procedure; then 1.5 g 6 h after the initial dose.
Regimen for patients allergic to ampicillin, amoxicillin, and penicillin	Vancomycin and gentamicin	Vancomycin 1.0 g, IV, over 1 h, plus gentamicin 1.5 mg/kg (not to exceed 80 mg), IV or IM, 1 h before the procedure; may be repeated once, 8 h after the initial dose.

IV, intravenous; IM, intramuscular.

Source: Data from Djena AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations of the American Heart Association. JAMA 1997;277:1794–1801.

Oxygen saturation (SpO_2) is measured while the patient is breathing room air. The electrocardiogram (ECG) with rhythm strip and echocardiographic findings are reviewed. The anesthesiologist, in consultation with the cardiologist, may pursue additional cardiac testing to promote a better understanding of the patient's cardiac disease. The anesthesia team should be made aware of the obstetrician's plan regarding the use of anticoagulant medications, so that neuraxial anesthesia, if desired, will not be withheld because the patient is anticoagulated around the time of delivery. The anesthetic plan highlights the hemodynamic goals for management of the patient's cardiac disease and addresses monitoring requirements, anesthesia techniques, and medical therapy for optimizing both maternal and perinatal outcome.

Monitoring for Labor and Delivery

A baseline 12-lead ECG and rhythm strip should be obtained for all cardiac patients. It is prudent to monitor the ECG during labor and delivery and to display two leads simultaneously (i.e., II and V5) to facilitate the detection of myocardial ischemia and arrhythmias.

Blood Pressure

A standard sphygmomanometer and cuff should be used to measure blood pressure (BP) in both arms to help detect major pathology of the aorta or large arteries. Such measurements are also useful for verifying the accuracy of an automated BP monitor or an arterial line. Continuous BP monitoring should be considered for women with moderate to severe valvular lesions, congenital heart disease, congestive heart failure, ischemic heart disease, or aortic pathology such as occurs with Marfan syndrome. An arterial catheter provides beat-to-beat BP information, allows easy sampling of arterial blood gases, and may be less traumatic to a patient than prolonged use of an automated device that inflates and deflates every 1 to 2 min. The morbidity of a radial artery catheter is extremely low when proper precautions are taken.

Pulse Oximetry

Pulse oximetry is a valuable tool for evaluating the adequacy of oxygenation of arterial blood. Continuous monitoring of SpO_2 is helpful for managing a congenital heart disease that involves an intracardiac shunt. A decrease in SpO_2 may indicate a worsening of the shunt, a greater degree of V/Q mismatching, or a lower cardiac output. Elevations of SpO_2 suggest an improvement in cardiopulmonary function. Thus, SpO_2 may be useful for gauging a patient's response to various therapeutic interventions.

Temperature

Maintaining normothermia helps to prevent undesirable increases in oxygen consumption, deleterious changes in vascular resistance, and cardiac arrhythmias. Several methods provide accurate measurements of core temperature, including the use of a compensated infrared thermometer in the external auditory canal or the thermistor of an indwelling pulmonary artery (PA) catheter.

Central Pressure Monitoring

Decisions about invasively monitoring the central circulation are based on a careful analysis of the potential risks involved versus the anticipated benefits of such monitoring. Before a central catheter is inserted, the patient should receive supplemental oxygen and anxiolytic doses of sedatives. During the procedure, BP, ECG, SpO_2, and fetal heart rate should be monitored. Uterine displacement is important. It is generally advisable to minimize the time that the patient is maintained in the Trendelenburg position.

A central venous pressure (CVP) catheter is useful for parturients with severe CV disease because it provides continuous information about intravascular volume status, as well as a direct conduit for administering drugs into the central circulation. Potential complications of a CVP catheter include hemorrhage, infection, nerve injury, pneumothorax, and air embolism.

Pulmonary Artery Catheter

A pulmonary artery (PA) catheter can provide a wealth of information: (1) direct measurements of CVP and PA pressure; (2) indirect measurement of left atrial pressure via the pulmonary capillary wedge pressure (PCWP); (3) measurement of cardiac output by thermodilution (using the Fick principle); and (4) calculations of systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). In addition, CVP and PA waveforms can be monitored continuously, which may facilitate early detection of, and proper intervention for, tricuspid or mitral regurgitation. Furthermore, mixed venous O_2 saturation (SvO_2) can be measured from blood samples drawn from a PA catheter. An oximetric PA catheter allows continuous monitoring of SvO_2. Finally, a PA catheter that is equipped with multiple electrodes or channels for insertion of a pacer wire can be useful for electrically pacing the heart.

Pulmonary Artery versus Central Venous Pressure Catheter

Although a PA catheter can clearly provide more information than a CVP catheter, it is difficult to know in advance whether the value of the additional information will justify the additional risks of a PA catheter. Because a PA catheter traverses an actively moving valve in the beating heart, it can traumatize both the valve and myocardium. The catheter provides a nidus for clot formation which may occur more often in hypercoagulable states, such as pregnancy. Complications associated with the use of a PA catheter include (1) venous or arterial hemorrhage and hematoma; (2) arrhythmias; (3)

pneumothorax; (4) infection; (5) myocardial or valve injury; (6) pulmonary artery rupture; (7) pulmonary ischemia and infarction; (8) thromboembolism; (9) air embolism; (10) microshock; (11) cerebral ischemia and infarction; and (12) neurovascular trauma. In addition, insertion of a PA catheter occasionally induces a transient right bundle branch block (RBBB), which can cause a complete heart block if the patient has a preexisting left bundle branch block (LBBB). Despite the many potential complications associated with a PA catheter, major problems seldom arise. However, when they do, the effects can be catastrophic, particularly in a patient with minimal CV reserve function.

A pulmonary catheter may help in the management of a pregnant woman who has (1) ischemic heart disease, (2) congestive heart failure, (3) primary pulmonary hypertension, (4) severe valvular disease, (5) hypotension associated with pulmonary edema or renal insufficiency or (6) septic shock. In the setting of acute myocardial infarction (MI), PCWP provides a more accurate reflection of left ventricular filling pressure than does the CVP pressure. Prophylactic insertion of a PA catheter may be warranted in women who are known to have an ejection fraction below 0.4, a left ventricular end-diastolic volume (LVEDV) exceeding 18 torr, or a cardiac index of less than 2.0 liter/min/meter^2. The value of a PA catheter generally increases as cardiovascular reserve function is becoming depleted; that is, when incorrect clinical decisions can have lethal consequences. The benefits of a PA catheter are often best appreciated in retrospect, perhaps after struggling to manage severe hemodynamic instability in a parturient with pulmonary hypertension and right ventricular failure.

The risk–benefit analysis will seldom favor using a PA catheter for parturients who have critical aortic stenosis but no other cardiovascular lesion. An arrhythmia triggered by inserting a PA catheter can cause a marked decrease in cardiac output, resulting in CV collapse. A CVP catheter and an arterial line usually provide the essential hemodynamic information in a parturient with aortic stenosis. Reductions of BP that result from a very carefully titrated neuraxial anesthetic are usually straightforward to correct.

With Eisenmenger syndrome, the risk–benefit analysis will rarely favor the use of a PA catheter; relatively common complications associated with this monitoring device can produce devastating consequences in these patients. In addition, the catheter may pass through the defect between the right and left circulation [e.g., atrial septal defect (ASD), ventricular septal defect (VSD)] and cause cardiac trauma. Finally, cardiac output data are difficult to interpret due to the intracardiac shunt.

Regional and General Anesthesia

The terms regional anesthesia (or analgesia) and neuraxial anesthesia (or analgesia) are used interchangeably in this chapter. Generally, analgesia refers to the desired result of a neuraxial technique that blocks pain (e.g., parturition), whereas anesthesia will refer either to the desired result of a technique used for a woman undergoing a cesarean delivery or be used synonymously with the term analgesia. The techniques for providing analgesia and anesthesia are the same, but anesthesia involves a denser block and a more extensive sympathectomy (i.e., a higher dose of local anesthetic) than analgesia. The preferred neuraxial technique for a woman with CV disease is usually continuous epidural (i.e., standard epidural) or continuous spinal-epidural (CSE), and occasionally continuous spinal anesthesia.

Parturients whose CV reserve function is markedly decreased can benefit greatly from neuraxial anesthesia. The anesthetic not only ablates their pain but also minimizes their stress and hemodynamic responses to labor and delivery. Neuraxial anesthesia is also preferred to general anesthesia for such women who have a cesarean delivery. A very carefully titrated neuraxial anesthetic is less likely than a general anesthetic to cause a sudden or unexpected change in CV and pulmonary parameters.

General anesthesia involves interventions that can cause cardiovascular collapse in a patient whose circulatory status is tenuous. These include (1) laryngoscopy and tracheal intubation, which are very stimulating procedures; (2) positive pressure ventilation, which may abruptly decrease venous return and cardiac output; and (3) use of pharmacologic agents, which may adversely affect the cardiovascular system. A rapid sequence induction with thiopental and succinylcholine is a standard component of a general anesthetic for cesarean delivery, and often causes acute hemodynamic perturbations. Moreover, the standard anesthetic does not effectively block stress responses to noxious stimuli, because the anesthetic depth is intentionally limited to minimize fetal exposure to anesthetic agents and to prevent uterine atony. Pretreatment with a beta-blocker (e.g., labetalol) can reliably blunt the hemodynamic response to laryngoscopy and tracheal intubation, but it may also cause CV decompensation in a patient who has an acutely failing left ventricle.

When general anesthesia is required, an opioid-based technique is preferred for women who cannot tolerate major hemodynamic perturbations. A carefully conducted opioid-based anesthetic typically provides remarkable CV stability throughout anesthesia and surgery. However, the rate of anesthesia induction is slower than with the standard rapid sequence method; this prolongs the time until the airway is secured and theoretically increases the risk of aspiration pneumonitis. To minimize this risk, women should refrain from eating or drinking for 8 h before an elective cesarean delivery or be nourished with clear liquids only during labor. Women may also benefit from medications, such as sodium citrate (30 mL by mouth) and metoclopramide (10 mg IV, 30 min before induction) before anesthesia is induced. During induction, cricoid pressure is applied and maintained until the airway has been secured with a cuffed tracheal tube.

If the induction involves a high-dose of fentanyl, the fetus may become narcotized. This is only a minor problem when

the pediatric team is present for delivery; they can ventilate the newborn and antagonize the fentanyl-induced respiratory depression with naloxone. The mother will often require mechanical ventilation postoperatively, which can favorably affect the dynamics of some cardiac disorders by reducing both preload and afterload. However, for women with a highly preload-dependent circulatory system, the elevated intrathoracic pressures from ventilatory support may be deleterious. Positive pressure ventilation worsens cardiopulmonary dynamics of some congenital heart diseases by altering V/Q matching, venous return, cardiac output, size of the shunt, and even shunt direction. In addition, the timing and techniques of extubation require careful attention to minimize "bucking on the tube," which can cause profound circulatory effects.

Remifentanil, an ultrashort-acting congener of fentanyl, is a useful adjunct for a general anesthetic whose goals include optimal hemodynamic stability and minimal respiratory depression of the newborn and mother postoperatively.[39–41] Remifentanil readily crosses the placenta, is rapidly cleared by the fetus, and does not appear to affect the newborn.[39] Scott et al.[41] described a woman with mitral valve disease, asthma, and preeclampsia who had an emergency caesarean delivery performed under a general anesthetic that included remifentanil; good hemodynamic stability was achieved without neonatal respiratory distress. Infusions of remifentanil and propofol have been reported to provide stable general anesthesia for successful cesarean delivery of women with multivalvular disease and severe pulmonary hypertension[42] and peripartum cardiomyopathy.[40]

Neuraxial anesthesia, unlike general anesthesia, can effectively block afferent nerve transmission and minimize the release of endogenous catecholamines, antidiuretic hormone, and other neuroendocrine transmitters associated with the stress response.[43] Because a "single-shot" spinal anesthetic often produces an abrupt sympathectomy and hypotension, it is contraindicated for women who cannot tolerate circulatory instability. In contrast, continuous neuraxial techniques with proper monitoring will typically provide both effective anesthesia and cardiovascular stability when neuraxial medications are slowly titrated while intravenous agents are carefully administered to prevent hypotension. This approach is usually preferred for a pregnant woman with CV disease, even for one with tight aortic stenosis,[43] hypertrophic obstructive cardiomyopathy (HOCM),[44] mitral stenosis,[45] Eisenmenger's syndrome,[46] or MI.[47] At the end of the operation, the sympathectomy should be allowed to resolve in a timely manner. Some women, such as those with severe mitral stenosis, may develop pulmonary edema when the resolution of the sympathectomy coincides with the postpartum expansion of intravascular volume.

Continuous neuraxial anesthesia offers several potential advantages over general anesthesia. First, the parturient is usually awake, cooperative, and capable of reporting the onset of cardiac symptoms. Second, regional anesthesia avoids the hemodynamic lability associated with tracheal intubation and the potentially adverse effects of positive pressure ventilation on intrathoracic pressure. Third, neuraxial anesthesia provides good CV stability and blunts the stress response. Fourth, a sensory level of T4 or higher blocks sympathetic outflow and may thereby reduce heart rate and prevent coronary artery spasm. Fifth, the associated sympathectomy decreases systemic vascular tone, which reduces cardiac work and may improve forward cardiac output. Sixth, women with arrhythmic disorders may benefit from an epidural infusion of 2% lidocaine, which produces plasma lidocaine levels that have been shown to suppress ventricular arrhythmias.[48] Finally, epidural or spinal morphine provides effective and long-lasting postoperative analgesia.

Treatment of Anesthesia-Induced Sympathectomy

Ephedrine is usually the preferred vasoactive agent of choice for treating hypotension associated with regional anesthesia in parturients.[49–51] Butterworth and coworkers[52] studied the CV effects of ephedrine in a dog model that involved cardiopulmonary bypass and an indwelling spinal catheter. A high level of spinal anesthesia decreases arterial resistance, dilates venous capacitance beds, and lowers heart rate by blocking cardiac sympathetics without altering parasympathetic outflow. In this setting, intravenous ephedrine increases arterial resistance, constricts venous capacitance vessels, and exerts both positive inotropic and chronotropic effects.

Ephedrine and dopamine act on the CV system in a manner almost exactly reciprocal to the effects of sympathectomy associated with high spinal or epidural anesthesia.[52,53] Phenylephrine also increases peripheral vascular resistance and decreases venous capacitance, but unlike ephedrine or dopamine, it has minimal effects on myocardial contractility and heart rate.

The effects of several vasoactive agents on placental perfusion were studied in chronically instrumented pregnant ewes.[54] Each agent was titrated to produce a 25% elevation of maternal BP. Ephedrine best maintained placental perfusion. The relevance of this finding to regional anesthesia-induced hypotension is questionable for two reasons: (1) pregnant women rarely receive intravenous vasopressors with the intent of elevating their BP to a supernormal level; and (2) pressure-flow autoregulation does not occur in placental vessels. Placental vessels are usually maximally dilated, so placental perfusion is highly dependent on maternal BP.[54] In this context, an alpha-agonist may improve placental perfusion by restoring a normal maternal BP. Although phenylephrine can partially constrict placental vessels, this effect is probably not clinically important because of the large vascular reserve in a normal placenta. Clinical studies have confirmed that phenylephrine is a safe and effective drug for treating maternal hypotension associated with regional anesthesia.[55,56] However, in the presence of severe uteroplacental insufficiency, an alpha-agonist could theoretically produce a detrimental effect. At present, there has not been a large randomized clinical study to address this issue.

The proper selection of a vasoactive agent requires consideration of a woman's underlying cardiovascular disease. Phenylephrine would be preferred over ephedrine for treating patients with cardiac conditions exacerbated by (1) tachyarrhythmias, such as those with HOCM, aortic stenosis, or acute MI; (2) increases in heart rate or contractility, including women with ischemic heart disease; or (3) decreases in SVR, including women with Eisenmenger syndrome. If concerns arise that a vasoactive agent might be causing important reductions of uteroplacental perfusion, the status of the fetus can be assessed by continuously monitoring the fetal heart rate (FHR) and intermittently sampling fetal scalp capillary pH.

Termination of Pregnancy

Despite advances in medical technology, pregnancy with certain CV disorders still portends a poor maternal and perinatal outcome. A pregnant woman with Eisenmenger's syndrome, Marfan syndrome with major aortic involvement, or peripartum cardiomyopathy is at relatively high risk of death or of becoming a postdelivery cardiac cripple if the gestation is not terminated.[57,58] In such situations, termination is often offered to protect the mother's life.

Although a termination procedure is usually brief, a complete perioperative plan should still be developed, focusing on the woman's underlying cardiac disease. All patients should receive supplemental oxygen and adequate sedation. Monitoring requirements during and after the procedure are determined by the acuity of the patient's CV disorder. A neuraxial anesthetic (using a low dose of local anesthetic and fentanyl) that is titrated to a level of T9–T10 may be the technique of choice if not contraindicated. This approach provides excellent anesthesia with minimal hemodynamic effects; typically, the patient is comfortable but less sedated than when the procedure is performed using a paracervical block and intravenous sedation. The postoperative management team should be vigilant for signs of bleeding and alterations in coagulation status.

Cardiac Surgery and Cardiopulmonary Bypass

Surgical treatment for acutely decompensated heart disease may be the best, and sometimes the only, effective option even if the patient is pregnant. In 1969, Zitnick et al.[59] reported on a series of 20 cases of cardiopulmonary bypass (CPB) during pregnancy; there was one maternal death (5% mortality rate) and a 33% fetal mortality. In 1983, Becker[60] reviewed 68 open-heart procedures; 98.5% of mothers and 80% of the fetuses survived. Definitive cardiac surgery during pregnancy has become remarkably safe for the mother. The fetal survival rate is respectable, especially when one considers what the fetal outcome would have been if the mother were to die or to have a therapeutic abortion to prevent cardiac decompensation.[61,62] Congenital anomalies associated with CPB have been minimal.

The optimal timing of cardiac surgery is probably during the second trimester before the 30th week of gestation. This approach avoids exposing the fetus to drugs and surgical stress during organogenesis and minimizes the risk of preterm labor that is unresponsive to tocolysis, which becomes increasingly likely as the gestation approaches term.

Perioperative Management

The anesthetic should be tailored to the underlying cardiac disease. General considerations include avoiding aortocaval compression prior to, during, and after CPB and preventing aspiration pneumonitis. Most anesthetic agents have a long record of safety in pregnancy, including fentanyl, morphine, thiopental, scopolamine, succinylcholine, pancuronium, and isoflurane.

Placental perfusion is pressure dependent, so the mother should remain normotensive. Hypotension should be treated immediately, using IV fluids, ephedrine, or phenylephrine, in accordance with the underlying cardiac lesion. Heparin and protamine are well tolerated by the fetus. Pregnancy may increase the likelihood of thrombosis, particularly in women with prosthetic mechanical valves.[30,63,64] Failure to achieve adequate anticoagulation in women with a thrombosed mitral valve prosthesis has necessitated immediate cesarean delivery before and during CPB.[65,66]

The optimal method for protecting the fetus on CPB is unclear. During CPB, it seems prudent to maintain perfusion pressures in the high-normal range (preferably >60 mm Hg) and the maternal PaO_2 between 200 and 300 mm Hg. Maternal blood volume and hematocrit are maintained with IV balanced salt solution and blood, as needed. Surprisingly, the fetus tolerates nonpulsatile CPB well. Farmakides et al.[67] studied uterine artery blood flow on CPB using uterine–umbilical velocimetry and noted that uterine artery flow was pulsatile, despite nonpulsatile pump flow. Hypothermia has been associated with both good and poor fetal outcomes.[68,69] Mild hypothermia ($>32°C$) appears to be well tolerated by the fetus. The risk of a fetal arrhythmia or cardiac arrest is increased at a low core temperature.

When possible, FHR monitoring and maternal tocodynamometry should be used intraoperatively and postoperatively. During CPB, there is minimal beat-to-beat variability, and baseline FHR is reduced[67–72]; occasionally, a sinusoidal FHR pattern occurs.[72] The effects on FHR may be caused by anesthetics such as high-dose opioids, hypothermia, or nonpulsatile blood flow. After rewarming, fetal tachycardia often occurs transiently, and FHR variability returns to normal.

Postpartum Concerns

The mother should be monitored for the onset of premature labor for several days following surgery. If labor begins and tocolysis is indicated, tocolytic agents such as magnesium sulfate or terbutaline should be selected on the basis of the woman's CV condition. Women with a mechanical prosthetic

valve require anticoagulant therapy, whereas those with a bioprosthetic valve do not.

Cardiopulmonary Resuscitation During Pregnancy

Preparations to Manage Cardiac Arrest

Cardiac arrest during pregnancy is rare, occurring in about 1 case per 30,000 deliveries,[73] but the incidence is higher among women with CV disease. Resuscitators must recognize (1) the need to relieve aortocaval compression; (2) the significant physiologic adaptations associated with pregnancy; and (3) the need to perform a cesarean delivery within minutes if the resuscitation is not successful.

For a mother who is rapidly deteriorating hemodynamically, the following simple and potentially lifesaving actions should not be overlooked: (1) laterally displace the gravid uterus; (2) give 100% oxygen; (3) give an IV fluid bolus; and (4) evaluate the need for any medications that are being given.

Uterine Displacement during Resuscitation

When a woman beyond the 20th gestational week is supine, her gravid uterus compresses the iliac and abdominal vessels and can markedly reduce venous return, cardiac output, and BP. The woman must be on a firm surface with uterine displacement for cardiac compressions to be effective. Relieving aortocaval compression requires that the gravid uterus be displaced manually, by placing a wedge under the patient's right hip, or by positioning the patient's back on the rescuer's thighs. The Cardiff wedge, described by Rees and Willis,[73] provides both relief of aortocaval compression and a hard surface for chest compressions. The mother is tilted to an angle of approximately 30°. If a Cardiff wedge is unavailable, a hard surface and a "human wedge" can be used. The individual who is designated as the wedge kneels on the floor, sitting on his or her heels. This person uses one arm to stabilize the woman's shoulders and the other arm to stabilize her pelvis.

Differential Diagnosis

The resuscitation team must be prepared to diagnose and treat pregnancy-related causes of cardiopulmonary arrest. The differential diagnosis includes (1) trauma; (2) drug toxicity; (3) obstetric complications, such as amniotic fluid embolism, peripartum hemorrhage, eclampsia, and peripartum cardiomyopathy; and (4) complications from the spectrum of congenital and acquired cardiac diseases that occur in pregnancy, including MI, valvular thrombosis, pulmonary thromboembolism, and aortic dissection.

Advanced Cardiac Life Support

According to the American Heart Association, standard resuscitative measures and procedures should be followed without modification.[74] There are no changes to the standard advanced cardiac life support (ACLS) algorithms for medications, intubation,[73,75] and defibrillation.[76] The resuscitation should proceed without concerns about the effects of resuscitation medications on uteroplacental blood flow: the key to resuscitation of the child is resuscitation of the mother.[76]

Energy required for defibrillation is not changed by pregnancy. Generally, defibrillatory shocks do not transfer significant amounts of current to the fetus in utero if the electrodes are carefully positioned;[76] the left breast should be displaced superiorly to position the anterior electrode and a wide posterior (back) electrode used if available.[77,78]

If Advanced Cardiac Life Support Fails

If resuscitative measures fail to restore circulation within 5 min of the arrest and the fetus is still viable, an immediate perimortem cesarean delivery should be performed. Even if the fetus is nonviable, however, a cesarean delivery may be needed to improve resuscitative conditions in order to lower metabolic demands.[79–83]

The resuscitation team should realize that prolonged maternal cardiac arrest is not incompatible with infant survival. In one instance, a newborn was delivered by a postmortem cesarean performed 47 min after the mother suffered a fatal gunshot wound (22 min of documented cardiac arrest); the baby was evaluated at 18 months of age and exhibited no evidence of neurologic injury.[84,85]

A neonate delivered by a perimortem cesarean is likely to be hypoxic and acidotic, as well as preterm. A pediatrician should attend the delivery to direct the resuscitation of the newborn. Efforts to resuscitate the mother may be associated with neonatal complications such as cardiac arrhythmias or asystole (from maternal defibrillation and drug therapy), central nervous system toxicity (from antiarrhythmic drugs), and hypoxia because of low maternal cardiac output, uteroplacental vasoconstriction, or maternal hypoxemia acidosis.[84–86]

Thoracotomy and Cardiopulmonary Bypass

If delivery and continued closed-chest cardiopulmonary resuscitation (CPR) do not rapidly restore maternal circulation, more invasive measures may be warranted, including thoracotomy and open-chest cardiac massage. Open-chest CPR provides a higher cardiac output than closed-chest CPR. Moreover, a failure of resuscitation may be caused by maternal complications that have resulted from closed-chest cardiac massage, such as liver laceration,[87] uterine rupture, pneumothorax, and hemopericardium.[88] The risk of cardiac trauma during closed-chest cardiac massage is increased in a patient with a prosthetic heart valve.

The use of CPB has been lifesaving following failed resuscitative measures in women with severe hypothermia,[89] massive pulmonary embolism,[90] and bupivacaine-induced cardiotoxicity.[91]

Diseases of the Cardiac Electrical System

Arrhythmias During Pregnancy

Most types of arrhythmias occur more often during pregnancy, independent of structural heart disease.[92–96] A study involving continuous ECG monitoring of 13 pregnant women without cardiac disease showed all of them to have cardiac arrhythmias during labor. The arrhythmias were usually asymptomatic, including supraventricular tachycardia (SVT), premature atrial contractions (PAC) and premature ventricular contractions (PVC), and sinus tachycardia (ST).[97]

Arrhythmias during pregnancy can produce maternal hypotension and secondary fetal hypoperfusion and bradycardia. This condition must be corrected immediately using IV antiarrhythmic agents or electrical cardioversion. Patients who develop arrhythmias need a thorough medical evaluation to identify precipitating factors that can be treated, such as electrolyte imbalances and thyroid disease, or avoided, such as drugs, cocoa, caffeine, or cigarettes. Because antiarrhythmic drugs cross the placenta and can potentially produce adverse fetal effects (especially during embryogenesis), medical therapy is usually reserved for the treatment or suppression of arrhythmias that cause intolerable symptoms or pose a threat to the mother or fetus. Electrophysiologic evaluations and catheter ablation procedures are usually postponed until after delivery, to avoid exposing the fetus to ionizing radiation (see Table 12.7). However, these procedures can be successfully performed during pregnancy using short fluoroscopy times (e.g., 70 s)[98] or echocardiographic guidance instead of fluoroscopy.[99]

Specific Arrhythmic Disorders

Atrial and Ventricular Premature Beats

Premature atrial and ventricular complexes occur often during pregnancy without affecting the mother or fetus adversely. Drug therapy is generally not required. All that is usually required is reassurance, patient education, and elimination of exacerbating factors such as chemical stimulants, alcohol, stress, and heavy physical activity. Occasionally, therapy with a beta-blocker is needed.[100]

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation and atrial flutter are characteristically associated with rheumatic mitral valve disease or CHD and rarely occur without structural heart disease. Atrial fibrillation has been described in association with magnesium sulfate therapy[101] and preexcitation syndromes.[102]

Specific guidelines for the treatment of atrial fibrillation have been developed by an international collaboration among major cardiology societies.[103] Propranolol or metoprolol and digoxin are the preferred agents for controlling ventricular rate in parturients with atrial fibrillation or flutter. Verapamil is a second-tier agent. Quinidine is often chosen for chemical cardioversion because of its long record of safety in pregnant women. Procainamide is safe for short-term therapy but produces untoward effects that limit its long-term use. Amiodarone is effective for the treatment of atrial fibrillation but is generally avoided during pregnancy owing to its toxicity to the fetus. Urgent situations call for electrical cardioversion, starting at 25 to 50 joules for atrial flutter and 50 to 100 joules for atrial fibrillation.[104]

Atrial Tachycardia

Adenosine is sometimes effective for the treatment of primary atrial tachycardia and should be tried first in a pregnant woman with this condition. A beta-blocker, digoxin, or verapamil may be administered to slow the heart rate. Quinidine and procainamide will occasionally restore and maintain a sinus rhythm. Sotalol is reserved for arrhythmias that are refractory to the commonly used agents (Table 12.14).

Wolff–Parkinson–White and Preexcitation Syndromes

Clinical Features

The Wolff–Parkinson–White (WPW) syndrome, which is the most common of the preexcitation syndromes, has a prevalence of 1 to 3 per 1000 in the general population. This syndrome occurs most often in the absence of preexisting cardiac disease, but it may be associated with disorders such as hypertrophic cardiomyopathy, mitral valve prolapse, tricuspid atresia, transposition of the great arteries, or endocardial fibroelastosis. The clinical hallmark of the preexcitation syndromes is paroxysmal tachycardia at rates of 150 to 300 beats/min. The WPW syndrome, in its classic form, features a triad of ECG findings: short PR interval, prolonged QRS duration, and a delta wave.

Therapy

Determining which therapy is appropriate and which is dangerous for a patient with WPW syndrome requires a rudimentary understanding of impulse conduction through the accessory pathways. The accessory pathway can participate in a reentry circuit that produces or sustains tachycardia. Generally, the atrioventricular (AV) node constitutes one limb of the circuit: the AV node may be used for anterograde (orthodromic) or retrograde (antidromic) conduction to the ventricles. Most WPW patients who are symptomatic have a regular orthodromic tachycardia (narrow QRS complex) and respond to drugs that block AV nodal conduction. Adenosine, for example, has been used successfully during pregnancy to convert symptomatic SVT.[105] However, symptomatic patients with an antidromic (wide QRS complex) tachycardia or an irregular tachycardia (e.g., atrial fibrillation) should not receive drugs that block AV conduction (such as calcium channel

TABLE 12.14. Effects of cardiac medications on the mother and fetus.

Drug	Use in pregnancy	Potential side effects
Aldomet	HTN	Widely used, well studied in pregnancy; no major adverse fetal or maternal effects reported.
Adenosine	Maternal and fetal arrhythmias	No major adverse fetal or maternal effects reported.
Amiodarone	Maternal and fetal arrhythmias	Used only if no safer alternatives exist; can cause IUGR, fetal hypothyroidism, developmental delay.
ACE inhibitors	Cardiomyopathy	Rarely used in pregnancy; associated with IUGR, oligohydramnios, neonatal hypotension, hypothyroidism, renal failure, anemia, skull ossification defects, and fetal death.
Beta-adrenergic blockers	HTN, maternal arrhythmias, MI, mitral stenosis, hyperthyroidism, HOCM, Marfan's syndrome	Widely used in pregnancy; associated with IUGR, fetal bradycardia, and fetal hypoglycemia.
Cardioversion	Maternal arrhythmias	No adverse fetal effects reported.
Digoxin	Maternal and fetal arrhythmias, heart failure	Widely used in pregnancy; no adverse fetal effects noted.
Diltiazem	HTN	Very limited data on use in pregnancy.
Esmolol	Maternal arrhythmias, HTN	Very limited data on use in pregnancy; rapid drops in maternal blood pressure may lead to decreased uteroplacental perfusion.
Hydralazine	HTN	Widely used in pregnancy; maternal hypotension may lead to decreased uteroplacental perfusion.
Lidocaine	HTN	Widely used in pregnancy; no adverse fetal effects reported.
Nifedipine	HTN, tocolysis	Maternal hypotension may lead to decreased uteroplacental perfusion.
Organic nitrates	MI, HTN, pulmonary edema, tocolysis, uterine relaxation for D&E	Very limited data on use in pregnancy; limited reports of FHR decelerations and bradycardia.
Nitroprusside	HTN, aortic dissection	Limited data on use in pregnancy; prolonged use associated with maternal and fetal cyanide toxicity. No teratogenic effects reported.
Procainamide	Maternal and fetal arrhythmias	No adverse fetal or maternal effects reported.
Quinidine	Maternal and fetal arrhythmias	Avoid high doses because of potential oxytocic properties. No adverse fetal effects reported.
Sotalol	Maternal arrhythmias, HTN, fetal tachycardia	No teratogenic effects. Neonatal bradycardia has been reported with use in the third trimester.
Verapamil	Maternal and fetal arrhythmias, HTN, tocolysis	No teratogenic effects. Maternal hypotension may lead to decreased uteroplacental perfusion.

HTN, hypertension; IUGR, intrauterine growth restriction; MI, myocardial infarction; HOCM, hypertrophic obstructive cardiomyopathy; D&E, dilation and evacuation; FHR, fetal heart rate.

blockers, beta-blockers, digoxin, adenosine). These drugs can cause unopposed conduction through an accessory pathway, leading to extremely rapid ventricular rates (e.g., 250–300 beats per minute); in this setting, there is a high risk of degeneration into intractable ventricular fibrillation. For wide complex tachycardia of uncertain mechanism that occurs in hemodynamically stable women, procainamide is the drug of choice. Synchronized cardioversion (with uterine displacement) should be performed immediately for hemodynamically unstable women.

Women with preexcitation syndromes are at increased risk for developing high-grade arrhythmias during pregnancy. Kounis et al.[106] prospectively studied six women with WPW syndrome who had minimal or no symptoms before conception; pregnancy was associated with symptomatic SVT for the first time in three women and an increased frequency of SVT in the other three.[106] As a prophylactic measure, women with preexcitation syndromes should consider radiofrequency ablation procedures before becoming pregnant.

General measures to prevent SVT in women with a preexcitation syndrome include avoiding (1) drugs that stimulate beta-adrenergic receptors, including terbutaline, ephedrine, and epinephrine; (2) situations associated with sympathetic nervous system activation, such as labor and delivery without adequate analgesia; and (3) interventions that produce a sudden sympathectomy, such as single-shot spinal anesthesia for cesarean delivery. Phenylephrine and intravascular volume expansion are preferred treatments for anesthesia-induced decreases in BP. If general anesthesia is required, an opioid-based technique may be preferred because fentanyl congeners do not alter atrial conduction, but they do increase refractoriness and suppress SVT.[107]

Atrioventricular Node-Dependent Tachycardias

The frequency of paroxysmal supraventricular tachycardia (PSVT) is increased during pregnancy. After identifying and eliminating precipitating factors of PSVT, it is appropriate to initiate prophylactic antiarrhythmic therapy with digoxin or a beta-blocker. A breakthrough arrhythmia may respond to a vagal maneuver or to adenosine.[108] Otherwise, treatment with an intravenous beta-blocker or verapamil may be required. Precautions must be taken with verapamil to avoid maternal hypotension and secondary fetal hypoperfusion. If electrical cardioversion is necessary, energies of 50 joules are often adequate.[108] Radiofrequency ablation procedures should be of-

fered to selected women as definitive therapy preconceptually because of the potential for AV node-dependent tachycardias to recur during pregnancy.

Second-Degree and Third-Degree Atrioventricular Block

Most cases of heart block during pregnancy are congenital. A cardiology consultation can help to determine whether a temporary or permanent pacemaker is indicated. A pacemaker is usually indicated for a patient who is symptomatic or who has either prolonged QT interval or left atrial enlargement. Some women with a complete heart block remain asymptomatic during pregnancy and have an uncomplicated labor and delivery without treatment.[109] Occasionally, pregnancy may enhance AV nodal conduction, as suggested by a report of a woman whose heart block improved during two successive uncomplicated pregnancies.[110] On the other hand, a woman who develops a high-grade AV nodal block during pregnancy may require temporary pacing support for labor and delivery.[109]

A pacemaker can be inserted using electrocardiographic and echocardiographic guidance to avoid fetal exposure to ionizing radiation. Successful pregnancies and deliveries have been documented in women with permanent pacemakers placed for symptomatic bradyarrhythmias.[111,112] A maternal pacemaker can produce a spurious fetal bradycardia. One report described fetal scalp electrodes that sensed larger impulses from the mother's pacemaker instead of the fetal ECG.[113] In such cases, ultrasonography will reveal the true FHR.

Ventricular Tachycardia

Pregnancy increases the frequency and severity of ventricular tachycardia (VT), even in young women with structurally normal hearts. VT may occur in association with drugs,[114,115] electrolyte abnormalities,[116] or eclampsia.[117] Idiopathic VT usually derives from abnormalities of the septum or right ventricular outflow tract. The prognosis for women with acquired or congenital cardiac disorders may be worse than for those who have idiopathic VT. Rarely, women with prolonged QT syndromes develop torsade de pointes or have a cardiac arrest during pregnancy. Women with hereditary long QT syndrome are also at increased risk for having a postpartum cardiac event, such as syncope, cardiac arrest, or death.

Clinically stable patients have received lidocaine as the initial therapeutic agent and procainamide as the alternative. When the mother is hemodynamically unstable or the fetus is acutely compromised, immediate electrical cardioversion is required.[108] For prophylactic therapy, a beta-blocker is preferred for women with idiopathic VT. Procainamide and sotalol are second tier medications. Amiodarone is indicated only for emergency use because it is toxic to the fetus. Women who have had episodes of syncopal VT, ventricular fibrillation, or aborted sudden death should be considered candidates for an implantable cardioverter-defibrillator.[108]

Management of Cardiac Arrhythmias During Pregnancy

Pharmacologic Treatment of Maternal Arrhythmias

Use of Antiarrhythmic Drugs

The initial medication should be selected from the reservoir of agents with the best records of safety and efficacy during pregnancy (see Table 12.14). Clinical experience has been greatest with digoxin, quinidine, propranolol, and procainamide; each is well tolerated during pregnancy, and none is associated with adverse fetal effects.

When initiating drug therapy, attempts should be made to find the lowest effective dosages. Monitoring plasma drug levels can help, although they may underestimate the pharmacologically active form of the drug during pregnancy. Clinical responses, instead of drug levels, should be the primary guide for optimizing drug dosages. Periodic reassessments should be made of the indication for antiarrhythmic therapy and of the plasma level of drug needed for a therapeutic response.

Adenosine

Adenosine is a purine nucleoside that modulates conduction through the AV node. It is the drug of choice for PSVT, which is the most common sustained arrhythmia in pregnancy.[96,118] Several features of adenosine make it attractive for use during pregnancy: (1) its onset of action is rapid; (2) its duration of action is brief; and (3) its side effects, although common, are minor and transient.[119]

The efficacy of adenosine to treat acute SVTs has been documented in pregnancy.[105] Physicians should exercise caution when using adenosine for SVT. Narrow complex tachyarrhythmias respond well to adenosine, but wide complex tachycardias can lead to alarmingly high ventricular rates when atrial fibrillation or flutter is present.

Amiodarone

Amiodarone is a class III antiarrhythmic agent that exerts noncompetitive alpha- and beta-adrenergic-blocking effects and can cause marked vasodilation and hypotension which are difficult to correct. Although this agent (and its metabolite, desethylamiodarone) does not readily cross the placenta,[120] its use has been associated with fetal bradycardia, prolongation of the QT interval, preterm delivery, and spontaneous abortion. The high iodine content of amiodarone and its long half-life raise additional concerns about its safety.[121] Iodine traverses the placenta, has a high affinity for fetal thyroid tissue, and may cause fetal goiter, neonatal hypothyroidism (9% incidence), and fetal growth restriction.[122,123] Thus, its use during pregnancy is restricted to the treatment of acute, life-threatening arrhythmias. In some instances, the risk–benefit analysis may favor long-term use of amiodarone to prevent high-grade ventricular arrhythmias or to treat a maternal or fetal arrhythmia that is refractory to other antiarrhythmic

agents.[124–129] Cardiac arrhythmias in the fetus can cause intrauterine congestive heart failure and nonimmune hydrops fetalis, leading to fetal death.

Beta-Blocker Therapy

Beta-blockers have been used extensively in pregnancy for a variety of indications. Labetalol, a relatively nonselective alpha-, beta-1-blocker, preserves placental perfusion and is often the preferred treatment for maternal hypertensive disorders, including preeclampsia.[130] Beta-blockers readily cross the placenta. Continuous FHR monitoring is important for IV beta-blocker therapy, which can cause fetal bradycardia.

However, in gravid ewes, the prolonged administration of the esmolol leads to fetal hypoxia.[131,132] Clinical reports have demonstrated that maternal therapy with esmolol can cause sudden decreases in FHR.[133–135] Based on such reports, it would seem prudent to avoid using esmolol in parturients. Propranolol therapy has been associated with fetal growth restriction.[136] After critically reviewing the literature on this subject, Rubin[137] concluded that propranolol does not adversely affect fetal outcome. Most probably, the observed cases of fetal growth restriction resulted from the maternal disease for which the beta-blocker was prescribed rather than from the beta-blocker per se.

Calcium Antagonists

Calcium antagonists have not been rigorously evaluated in pregnant women. The long-term use of nicardipine for the treatment of severe preeclampsia has been reported to be effective and safe.[138] Calcium channel blockers such as nifedipine increase the risk of uterine atony and postpartum hemorrhage. Verapamil, when given IV, may cause maternal hypotension and secondary fetal hypoperfusion. Although verapamil produces dose-related fetal bradycardia, heart block, and hypotension, it does not appear to be teratogenic.[120] Diltiazem at very high doses has been associated with skeletal abnormalities in animals. A retrospective review of 27 newborns exposed to diltiazem in the first trimester also suggested that this agent might produce congenital anomalies. If a calcium antagonist is needed for antiarrhythmic therapy during the first trimester, verapamil is preferred over diltiazem. However, adenosine or a beta-blocker is generally preferable to a calcium antagonist for the treatment of SVTs during pregnancy.

Digoxin, Quinidine, and Procainamide

These medications have a long record of safe use during pregnancy. Procainamide, if given too rapidly, or at a high dose, can produce hypotension and prolongation of the QT interval. Chronic therapy with procainamide can cause a lupus-like syndrome, which typically resolves after discontinuation of therapy. Procainamide is indicated for women with wide-complex SVT and for transplacental cardioversion of fetal SVT.[139]

Lidocaine

Lidocaine is considered safe for use in pregnancy and is the agent of choice in the emergency management of ventricular arrhythmias.[96] Early reports suggested that fetal exposure to lidocaine during epidural anesthetics can produce subtle, transient neurobehavioral changes in the newborn,[140] but subsequent investigators found no such abnormalities.[141,142]

Phenytoin

Phenytoin, a commonly used anticonvulsant, has unique antiarrhythmic properties. It is used in the treatment of digitalis-induced tachyarrhythmias.[143] It is teratogenic in animals and can cause a constellation of congenital malformations known as fetal hydantoin syndrome.[144] Phenytoin use should be restricted to the acute management of digitalis-induced arrhythmias unresponsive to alternate therapy.

Electrical Cardioversion

Synchronized electrical cardioversion has been performed during all stages of pregnancy and is the treatment of choice for a tachyarrhythmia that is refractory to drug therapy and causes circulatory instability.[145] This procedure is unlikely to harm the fetus, because the current that penetrates the uterus is minimal and the threshold current to induce fetal arrhythmias is high.[76,146] Nonetheless, it is prudent to monitor FHR, because transient fetal arrhythmias occasionally arise during cardioversion procedures.[147,148] The optimal placement of cutaneous electrodes is in an axis that is anterior and posterior to the heart. This approach maximizes current density in the maternal myocardium and reduces the stray current, which could affect the fetus adversely.

Implantable Cardioverter-Defibrillator

On rare occasions, an implantable cardioverter-defibrillator (ICD) is required for a young woman with a conduction abnormality that triggers high-grade ventricular arrhythmias. Such women should be advised to have the device placed preconceptually because the insertion procedure may expose the fetus to a high dose of ionizing radiation (even with proper uterine shielding). When an ICD must be implanted during the period of fetal organogenesis, a radiation safety officer should compute the dose of radiation that the uterus would receive during the procedure. If particularly high doses are needed, it may be prudent to terminate the pregnancy. Favorable outcomes of pregnancy have been reported in women who had devices implanted during the second or third trimester of pregnancy or preconceptually.[149] The ICD delivers a shock of very low energy that does not appear to affect the fetus. If the device is placed through a subpectoral instead of an abdominal route, there is little risk of lead dislodgment as the abdomen expands during pregnancy.[150]

Anesthetic Management of Cardioversion

Tracheal intubation is usually avoided because of its potential to cause severe hemodynamic instability and the short duration of cardioversion procedures. The preferred techniques are monitored anesthetic care (MAC) or a brief intravenous general anesthetic (GA). To prevent aspiration pneumonitis, the patient should not receive any solid food or particulate liquids for 6 to 8 h before the procedure. Many anesthesiologists also administer an inhibitor of gastric acid secretion such as ranitidine or a nonparticulate antacid 30 min before the procedure. Metoclopramide could possibly exacerbate SVT, so the risk–benefit analysis may favor avoiding this agent in a patient with a tachyarrhythmic disorder.[151] Monitoring should be commensurate with the patient's clinical condition. At a minimum, SpO_2, blood pressure, ECG, and end-tidal CO_2 should be monitored. The woman should receive high-flow O_2 by face mask, and uterine displacement should be maintained throughout the procedure. The anesthetic may be accomplished with a low dose of fentanyl and midazolam followed by careful titration of propofol until the patient fails to respond to verbal command. At this point, cardioversion can be performed. The patient usually regains consciousness as soon as the procedure is over.

Diseases of the Myocardium: Cardiomyopathies

Hypertrophic Cardiomyopathy

In this chapter, the term hypertrophic cardiomyopathy (HOCM) includes conditions that may also be called asymmetric septal hypertrophy (ASH) or idiopathic hypertrophic subaortic stenosis (IHSS). HOCM is a primary myocardial disorder with an autosomal dominant pattern of inheritance. Most cases are associated with mutations of genes that code for beta-cardiac myosin heavy chain. HOCM is characterized by asymmetric left ventricular hypertrophy and by myocytes and myofibrils that are in disarray. About 3% of patients with HOCM die each year of progressive heart failure or sudden cardiac death.[152] A minority of patients with HOCM develop a severely hypertrophic left ventricle, diastolic dysfunction, and progressively worsening systolic failure with left ventricular dilation.[153,154] The prognosis is grim, particularly for those who develop atrial fibrillation.[152] In contrast, neither ventricular hypertrophy nor the presence of a pressure gradient is of prognostic significance for the young, asymptomatic, or mildly symptomatic patients who die suddenly. A history of nonsustained VT and syncopal episodes portends a poor prognosis for these individuals.[152]

The clinical presentation of HOCM includes chest pain, palpitations, dizzy spells, syncope, and arrhythmias. Decompensated congestive heart failure may occur in up to 20% of patients. Symptomatic HOCM, unlike peripartum cardiomyopathy (PPCM), rarely develops after delivery.[155] The risk of a fatal ventricular arrhythmia during pregnancy is low. In one instance, a woman in the first trimester developed ventricular fibrillation and was treated successfully with electrical countershock.[156] However, in another case a woman suffered sudden death during moderate exertion at 28 weeks gestation.[157]

Obstetric Management

Preconceptual planning is critical for women with HOCM who have experienced symptoms such as syncope or life-threatening arrhythmias. These women should be considered candidates for insertion of a dual chamber pacemaker or an automatic defibrillator before conception.[158] If HOCM is mild, pregnancy is usually well tolerated.[6] A retrospective study compared pregnancy outcomes of 41 women with HOCM (150 total pregnancies) versus 39 unaffected women from the same families (132 total pregnancies). In this study, there were no maternal deaths, no hospital admissions for cardiac causes, and no deterioration of functional status; 31% of women with HOCM were symptomatic before pregnancy versus 27% during pregnancy. Fetal prematurity was increased only in pregnancies of women who were symptomatic before conception (18% versus 5%), but perinatal outcome was uniformly good.[159] Although HOCM seldom leads to perinatal compromise, 50% of the children of affected mothers have this disorder.

If tocolytic therapy is needed, magnesium sulfate is preferred over a beta-2-agonist (e.g., terbutaline), which decreases systemic vascular tone and may exacerbate left ventricular outflow tract obstruction. Vaginal delivery is the norm for women with HOCM. Induction of labor may increase CV risk, owing to vasodilatory effects of prostaglandins; low doses of oxytocin are better tolerated. Parturients may benefit hemodynamically from augmented ventricular filling during uterine contractions, whereas adverse effects may result from pain-induced stimulation of the sympathetic nervous system. It is advisable to shorten the second stage of labor by using forceps for symptomatic patients. Hypovolemia from perioperative blood loss must be treated promptly. Vasodilators including oxytocin and beta-adrenergic agonists should be used with caution.

Anesthetic Management

Factors that can worsen dynamic outflow obstruction include a low cardiac filling volume, tachycardia, arrhythmias, enhanced contractility, and low vascular tone. Therefore, the major hemodynamic goals in a woman with HOCM are the maintenance of (1) a relative bradycardia and sinus rhythm; (2) a slightly reduced cardiac contractility; (3) a slightly elevated systemic vascular resistance (SVR); and (4) a normal or slight elevation of intravascular volume and venous return (i.e., avoid aortocaval compression).[160–166]

Prevention or aggressive treatment of atrial fibrillation is important, because atrial systole may be needed to maintain

adequate left ventricular (LV) filling. A beta-blocker is first-line therapy for symptomatic elevations of LV pressure, followed by diuretics or calcium antagonists. Women with LV outflow obstruction are at increased risk for infective endocarditis and should receive prophylactic antibiotics for labor and delivery.

Historically, a neuraxial block has been considered dangerous for women with HOCM, especially the obstructive type.[6] However, major hemodynamic perturbations during neuraxial analgesia can be prevented by careful, deliberate titration of analgesic medications and prompt treatment of any associated decrease in BP.[160] Epidural anesthesia and combined spinal epidural anesthesia (CSE) have been used safely for vaginal delivery in parturients with HOCM. Giving an opioid (e.g., fentanyl) either intrathecally or epidurally lowers the analgesic dose of local anesthetic and enforces CV stability. Complete analgesia with stable hemodynamics has been described in a parturient using only intrathecal opioids; she received an infusion of fentanyl and supplemental doses of meperidine through an intrathecal catheter.[167] Close monitoring of blood loss and intravascular volume status and immediate replacement of deficits help maintain CV stability in parturients with HOCM.

An elective cesarean delivery may be managed safely and effectively with epidural anesthesia in women with HOCM.[44,168] A standard spinal anesthetic is avoided because it produces a rapid sympathectomy that often causes BP to decrease precipitously.[164,166] Approximately 70% of women who receive spinal anesthesia for an elective cesarean section develop hypotension unless they receive vasopressor therapy to support their BP.[169] By using a catheter technique (e.g., epidural, CSE, or spinal), anesthesia can be established slowly and vasoactive drugs and intravenous fluids can be carefully titrated to prevent hypotension as the anesthetic-induced sympathectomy is developing. For a woman who has symptomatic HOCM, epinephrine should be excluded from the local anesthetic solution because an accidental intravascular injection of epinephrine (e.g., into an epidural vein) can produce severe, adverse CV effects in such individuals. Phenylephrine is the vasopressor of choice because it increases BP and vascular tone but not heart rate. Ephedrine is potentially riskier because it can cause tachycardia, promote dysrhythmias, and augment cardiac contractility. Intrathecal or epidural morphine (hydrophilic opioid) provides effective analgesia for almost a day after the operation.

When tailored to achieve the desired hemodynamic goals, general anesthesia will usually be well tolerated in women with HOCM. Thiopental and propofol are highly effective induction agents that decrease myocardial contractility, which is desirable in patients with HOCM. Agents for maintaining anesthesia, such as inhaled vapors, opioids, benzodiazepines, propofol, and neuromuscular blockers, can be used in combinations that attenuate neuroendocrine responses to surgery without causing hemodynamic instability.

It is important to maintain useful euvolemia. Postpartum bleeding requires prompt, aggressive treatment. When uterotonic therapy is needed, methylergonovine (Methergine) may be the preferred agent because it increases vascular tone and BP but not heart rate. Oxytocin causes systemic vasodilation, which could exacerbate dynamic outflow obstruction in women with HOCM.

Peripartum Cardiomyopathy

Incidence and Definition

Peripartum cardiomyopathy (PPCM) was first described as a distinct pathological entity in the 1950s.[171–172] It is a rare and potentially fatal form of congestive heart failure,[173] which occurs in one of every 3000 to 4000 live births in the United States.[174,175] The incidence in certain parts of Africa approaches 1 per 1000 deliveries. At a workshop sponsored by the National Heart, Lung, and Blood Institute, PPCM was defined as an idiopathic, dilated cardiomyopathy that has its onset during the final month of pregnancy or within 5 months after delivery.[176] A modified definition that includes strict echocardiographic criteria has recently been proposed (Table 12.15).[177]

Pathogenesis

The etiology of PPCM is still unclear. Viral, autoimmune,[178] and toxic factors and other mechanisms[179–181] have been implicated in the pathogenesis of PPCM.[182,183] Studies involving endocardial biopsies suggest that some women with PPCM have myocarditis,[178] and that its incidence in such women is comparable to that found in an age- and sex-matched nonpregnant control population with idiopathic dilated cardiomyopathy (IDCM). Cardiotropic viruses may play a role in PPCM. Genomic material of such viruses has been identified in 25% to 35% of endomyocardial biopsies from patients with IDCM, suggesting that myocarditis may be a precursor to IDCM.[184] Pregnancy may predispose to injuries from such viruses by exacerbating preexisting immunoregulatory abnormalities. Conceivably, peripartum fluid shifts,[181] excessive salt intake, nutritional factors,[172,181] or toxins could be contributory in women with a pregnancy-related genetic susceptibility to cardiomyopathic processes.[179,185] Emboli in

Table 12.15. Modified criteria for the diagnosis of peripartum cardiomyopathy.

Traditional criteria[176]
Cardiac failure within the last month of pregnancy or initial 5 months postpartum
Absence of preexisting heart disease
No determinable etiology
Strict echocardiographic criteria of left ventricular dysfunction[177]
Left ventricular ejection fraction less than 45% or m-mode fractional shortening less than 30%, or both; and
Left ventricular end-diastolic dimension greater than 2.7 cm/m^2 of body surface area

the cerebral and systemic circulation occur in up to 25% of these cases.[186,187] Postmortem findings include biventricular hypertrophy, a grossly enlarged heart, a pale myocardium with endocardial thickening, and mural thrombi; the heart valves and coronary arteries are normal.[188]

Clinical Course

The clinical manifestations of PPCM resemble those of other types of dilated cardiomyopathies.[189] Women usually present with findings of LV failure such as fatigue, chest pain, dyspnea on exertion, paroxysmal nocturnal dyspnea, palpitations, weight gain, pulmonary embolization, and arrhythmias. Physical examination may reveal peripheral edema, distended neck veins, cardiomegaly, an S3 gallop, and murmurs of mitral and tricuspid regurgitation. The ECG may show tachycardia, ST-T wave changes, T-wave inversion, low voltage, LV hypertrophy (voltage criteria), conduction abnormalities, and arrhythmias. Blood chemistry results are usually normal. The chest radiograph often shows cardiomegaly, pulmonary venous congestion with interstitial or alveolar edema, and occasionally pleural effusions. However, the symptoms, signs, and ECG findings of a mild case of PPCM may be identical to changes associated with a normal pregnancy. Early diagnosis is often difficult without an echocardiographic study. With more advanced disease, echocardiography may reveal four-chamber enlargement, with marked reduction of LV systolic function, pericardial effusions, and regurgitation of the mitral, tricuspid, and pulmonic valves. Rarely will there be high-output heart failure.

About half of those with PPCM experience complete or nearly complete recovery of LV function. The remaining patients either have progressive clinical deterioration, leading to cardiac transplantation or early death,[190] or stabilization of their condition with residual LV dysfunction and chronic heart failure.

Morbidity and Mortality

Early studies indicated that mortality rates for PPCM exceeded 40%, but recent evidence suggests a better outcome, with a mortality or cardiac transplantation rate ranging between 12% and 18%, and a 5-year survival rate of 94%.[191]

Clinical decompensation may be more likely to occur in a woman who develops PPCM than in a woman who has a dilated cardiomyopathy (DCM) that antedates pregnancy.[192] Bernstein and Magriples[192] compared pregnancy-related cardiac outcomes of women with a preconceptual DCM ($n = 8$) versus a PPCM ($n = 23$). In the PPCM group there were three maternal deaths and 4 women required cardiac transplantation. In contrast, 1 woman (prepregnancy EF = 16%) in the DCM group needed cardiac transplantation, but none of the others had a meaningful decline in their cardiac status. The study suggests that the superimposition of pregnancy on preexisting cardiac dysfunction can be well tolerated, and that PPCM may represent an acute, evolving injury in pregnant or postpartum women.

Risk Factors and Subsequent Pregnancies

Peripartum cardiomyopathy (PPCM) occurs more often in high-risk than low-risk pregnancies, including those involving preeclampsia-eclampsia, multiple gestations, and advanced maternal age (greater than 30 years). Familial PPCM has been reported as a complication of molar pregnancy.[193]

The persistence of cardiac dysfunction 6 months after a diagnosis of PPCM places a woman at increased risk for cardiac morbidity and mortality during a subsequent pregnancy.[170] Women with a history of PPCM and normal systolic function preconceptually have a relapse rate of about 20%, whereas nearly 50% of those with residual LV dysfunction before preconception will have a relapse. Mortality rates have been reported to range from 0% to 2% in the former group to 8% to 17% in the latter group.[194] Thus, it seems reasonable to discourage a patient with PPCM from having a future pregnancy, especially if she has persistent cardiac dysfunction.[192,194,195] Women with PPCM who undergo cardiac transplantation may have a successful subsequent pregnancy without evidence of cardiac dysfunction,[196] but the risk of recurrent PPCM in such women is unknown.

Management of Peripartum Heart Failure

Symptomatic patients should receive standard therapy for heart failure and be managed by a multidisciplinary team in an intensive care setting.[103,176] Salt restriction is recommended, and diuretics are used to decrease pulmonary congestion and volume overload. Systolic dysfunction is treated with afterload-reducing medications. Hydralazine is the vasodilator of choice before delivery. Angiotensin-converting enzyme (ACE) inhibitors are reserved for postpartum therapy because these agents can cause fetal malformations and renal injury. Other pharmacologic mainstays for heart failure during pregnancy include inotropic agents such as digitalis glycosides, catecholamines and phosphodiesterase inhibitors. Amrinone has been effective for the short-term treatment of refractory heart failure.[197] Studies in the gravid baboon indicate that positive inotropic effects of amrinone, in contrast to dopamine, occur without any reduction of uterine blood flow.[198] Nitroprusside has been widely used in pregnant women for the short-term treatment of hypertension. However, nitroprusside can cause fetal cyanide toxicity if used at high doses, or for longer than one day. In such settings, maternal cyanide levels must be closely monitored to avert fetal cyanide poisoning.

Anticoagulant therapy is commonly used because PPCM markedly increases the risk of thromboembolic events.[199,200] If such therapy is needed before delivery, unfractionated heparin may be administered with dose adjustments according to the partial thromboplastin time (PTT). A safe and effective alternative is low molecular weight heparin, which has been extensively used in pregnancy for the prevention and treatment of venous thrombosis. Data from a small retrospective study suggest that an intravenous dose of immunoglobulin might improve left ventricular function of women with PCCM.[201] If cardiac failure is severe and refractory to medical therapy, women may require

mechanical support of the heart, using an intra-aortic balloon pump or left ventricular assist device to stabilize their condition. Some women will require cardiac transplantation.[182,190,202]

Obstetric Management

Expeditious delivery of the fetus (cesarean delivery or vaginal delivery with outlet forceps to minimize pushing) may be necessary both to protect the fetus and to limit the CV stress imposed by pregnancy. Anticoagulation therapy with IV heparin during pregnancy and warfarin after delivery of the fetus is often needed because of the high risk of venous stasis and associated thromboembolic events.

Six months after the diagnosis of PPCM, echocardiography should be repeated to assess the recovery of systolic function. The persistence of cardiac dysfunction 6 to 12 months after the initial diagnosis usually indicates an irreversible problem and contraindicates a subsequent pregnancy. Without persistent cardiac dysfunction, however, it is difficult to predict whether a woman will have recurrence of PPCM. If such women become pregnant again, they should have serial echocardiographic evaluations. A finding of ventricular dysfunction would justify consideration of terminating the pregnancy.[194]

Anesthetic Management

The initial management of PPCM should focus on improving congestive heart failure. Invasive monitoring is warranted in the acute phase, until the cardiac function has stabilized. These patients should be maintained in an upright position with uterine displacement. Shortly before delivery, anticoagulants should be withheld and the coagulation status normalized to permit the use of neuraxial anesthetics.

Anesthesia is managed in accordance with the principles appropriate for a patient with severe cardiomyopathy. Both neuraxial and general anesthetics have been used for parturition and cesarean delivery of women with PPCM.[203] Continuous neuraxial anesthesia is usually preferred,[204] as it decreases preload and afterload but not contractility; this improves myocardial performance and reduces myocardial work. The administration of anesthetics, intravenous fluids, and vasoactive medications should be guided by continuous measurements of arterial pressure and central hemodynamic parameters. Intrathecal or epidural morphine can provide effective postoperative analgesia following cesarean delivery. When general anesthesia is needed, agents that depress the myocardium should be used with caution, because they may precipitate cardiac arrest and death.[205] An opioid-based anesthetic (e.g., fentanyl or remifentanil) usually provides excellent hemodynamic stability. Patients with PPCM require prolonged postoperative monitoring in an ICU setting.

Diseases of the Cardiac Valves

Cardiac valvular disease can be congenital or acquired. The prevalence of valvular disease in women of childbearing age has been declining steadily in industrialized nations because of antibiotic therapy, but RHD is still common in many developing countries.

General Principles

National and international committees from major medical societies have established guidelines for the care of patients with cardiac valvular disease. These guidelines address diagnostic testing, physical activity, and therapy during pregnancy,[206] as well as antibiotic prophylaxis[207] and prevention of thromboembolism[208] in women with mechanical heart valves (see later section on Prosthetic Heart Valves).

Rheumatic Fever and Heart Disease

Acute rheumatic fever and RHD are major causes of morbidity and mortality in pregnant women from developing countries. In South Africa, 0.65% of pregnant women have cardiac disease, which is associated with a morbidity and mortality rate of about 9.5%. Most of the deaths are a result of rheumatic mitral stenosis.[4]

Immigrants and visitors from developing nations who seek prenatal care may have rheumatic fever or RHD. Women with acute rheumatic fever require bed rest and treatment of streptococcal pharyngitis and comorbid conditions (such as anemia or nutritional deficiencies). If heart failure develops, it is usually a result of mitral or aortic valve incompetence. It is typically mild and responds to diuretic or vasodilator therapy. Surgical intervention (e.g., mitral valve repair) is rarely needed. RHD is discussed in subsequent sections on cardiac valvular disease.

Regurgitant Valvular Lesions

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the pathologic protrusion of the mitral leaflets into the left atrium during systole. This is the most common congenital heart lesion with a prevalence of 2% to 6% in the general population and 12% to 17% in women of childbearing age.[209] MVP has been classified as primary (idiopathic), which is often associated with characteristic clinical findings (e.g., body habitus, blood pressure, or labile hemodynamics), and secondary, in which the prolapse is a result of a connective tissue disorder or cardiac disease. MVP is often associated with Marfan syndrome.

Pathophysiology

The pathophysiology of MVP involves congenitally oversized, redundant valve leaflets, especially the posterior leaflet, and an increased length of the chordae tendineae. This defect allows the leaflets to prolapse with resultant regurgitation during systole.[210] Chest pain and arrhythmias may be related to,

or associated with coronary artery spasm or compression of the circumflex artery by the posterior leaflet.[211] A decrease in LV end-diastolic volume (LVEDV) permits greater prolapse and may exacerbate symptoms.

Clinical Presentation

The clinical spectrum of MVP ranges from clinically insignificant and unrecognized disease to a condition that is debilitating because of chest pain, dysrhythmia, and mitral regurgitation. MVP is usually associated with nonspecific symptoms (fatigue, dizziness, chest pain, palpitations, and dyspnea), ECG abnormalities, and arrhythmias, and was termed mitral valve prolapse syndrome in the 1960s.[212] The Framingham study revealed that individuals with and without MVP had the same prevalence of symptoms such as atypical chest pain, angina pectoris, dyspnea, and syncope.[209] Thus, a woman should not be assumed to have MVP merely because she has symptoms consistent with this disorder.

Mitral valve prolapse (MVP) has a generally benign course with a prognosis that depends on the absence or presence of coexisting CV disease. Such disorders may include HOCM, Marfan syndrome, an ASD, coronary artery disease, and periarteritis nodosa. Rarely, MVP is complicated by progression of mitral insufficiency, ruptured chordae tendineae, transient ischemic attacks, infectious endocarditis, and sudden death from dysrhythmias.[213]

Women who have MVP without mitral regurgitation do not appear to be at increased risk for sudden death. However, the 2% to 4% with severe mitral regurgitation comprise a group that has been reported to have a rate of sudden death that is 50- to 100-fold greater than the general population and an annual mortality rate of 94 to 188 per 100,000.[214,215] Many patients have a history of dyspnea on exertion, palpitations, chest pain, dizziness, and fainting. Auscultation characteristically reveals a systolic murmur (mitral regurgitation) and a mid-to-late systolic click caused by abrupt deceleration of the prolapsed leaflet.[216] ECG abnormalities are present in up to 70% of patients and may include dysrhythmias, ST-segment changes, T-wave inversion, and QT-interval prolongation.[217,218]

Obstetric Management

Women with MVP generally tolerate pregnancy very well.[219–221] MVP is often discovered incidentally during a routine physical examination; relatively few patients seek medical attention because of chest pain or palpitations. This condition can be difficult to diagnose correctly during pregnancy because the CV changes of a normal pregnancy resemble those of MVP (see Table 12.3). On the other hand, pregnancy-related increases in LVEDV can obscure (i.e., decrease) characteristic auscultatory and echocardiographic abnormalities of MVP.

The initial step in the management of women with MVP is to provide reassurance. Therapy with a beta-adrenergic-blocking agent is usually effective for those who are symptomatic. Beta-blockers also decrease the frequency of arrhythmias associated with MVP including SVT and VT. Older studies had suggested that propranolol might cause intrauterine growth restriction (IUGR) and neonatal depression. However, well-controlled prospective studies have provided reassuring data about the safety of beta-blockers during pregnancy.[215] Thus, these agents should be used as needed for the control of chest pain, palpitations, or arrhythmias in pregnant women with MVP.

The prophylactic use of antibiotics is another important and controversial issue. The committee on rheumatic fever and infective endocarditis of the American Heart Association has recommended use of prophylactic antibiotics only when MVP is complicated by mitral insufficiency. Vaginal hysterectomy is the only gynecologic operation specifically listed in which prophylactic antibiotics are recommended. Uncomplicated vaginal delivery rarely, if ever, precipitates endocarditis.[215] If no infection is suspected, then routine prophylaxis is considered unnecessary for cesarean delivery, uterine dilatation and curettage, and therapeutic abortions.[35] However, because a patient with a thickened mitral valve or mitral regurgitation is at increased risk for developing infective endocarditis, it may be justifiable to give antibiotics routinely, because a seemingly straightforward vaginal delivery may become complicated, with little forewarning.

Anesthetic Management

Goals of anesthetic management include (1) maintaining normal intravascular volume, venous return, and SVR; and (2) preventing arrhythmias, rapid heart rates, and increases in cardiac contractility.

Supplemental oxygen, given by nasal prongs or face mask, is advisable.[222] Maternal antiarrhythmic medications should be continued, and their effects on FHR monitoring should be noted. Prophylactic antibiotics for bacterial endocarditis should be given before anesthetic interventions or delivery. A baseline 12-lead ECG should be obtained, and the ECG should be monitored continuously during labor and delivery.

Effective analgesia or anesthesia is needed to minimize pain and the release of endogenous catecholamines, which can increase MVP and induce arrhythmias. Continuous epidural analgesia is a good choice for labor and vaginal delivery, using a dilute solution of local anesthetic and fentanyl. Anesthetics should be titrated carefully via the catheter to prevent sudden decreases in SVR, which can worsen MVP. Hypotension should be treated aggressively with phenylephrine or IV fluids to restore intravascular volume. Caution should be exercised with medications that exert positive inotropic or chronotropic effects, such as epinephrine, ephedrine, ketamine, atropine, and pancuronium.

Cesarean delivery can be managed with continuous epidural or continuous spinal anesthesia, with care to support the BP and maintain systemic vascular tone. Cardiovascular stability is usually better maintained with a carefully titrated regional anesthetic than with a general anesthetic neuraxial technique.

Thiopental often produces hypotension, which is followed by a hyperdynamic circulatory response during tracheal intubation. This approach may predispose to arrhythmias. In addition, isoflurane, desflurane, and sevoflurane can increase heart rate and decrease peripheral vascular resistance. If a patient has severe MVP, an opioid-based anesthetic technique may be preferred.

Mitral Regurgitation

Etiology

Acute mitral insufficiency or mitral regurgitation (MR) is usually a result of papillary muscle dysfunction or ruptured chordae tendineae. It may arise in the setting of trauma, LV ischemia, infective endocarditis, Marfan syndrome, or a defective prosthetic mitral valve. Chronic MR is rarely an isolated lesion and is usually associated with mitral stenosis.

Common causes of mitral regurgitation include RHD, myxomatous degeneration of the mitral valve, left atrial myxoma, endocarditis, rupture of chordae tendineae, or ischemia of LV papillary muscles.

Pathophysiology

Acute MR can elevate left atrial and pulmonary artery pressures suddenly and cause flash pulmonary edema. In contrast, chronic MR causes volume overloading but not pressure overloading of the left ventricle, because the incompetent mitral valve vents ventricular blood into the more pliable left atrium. Left atrial compliance increases over time, accommodating larger blood volumes without major increases of left atrial or PA pressures. Thus, hemodynamic stresses are more likely to cause pulmonary edema in women with acute, rather than chronic, MR. However, continued volume overloading of the left atrium eventually causes congestion of the pulmonary circuit. When the regurgitant fraction exceeds 0.6, MR is considered severe. Medications and interventions that reduce systemic vascular tone can improve forward cardiac flow.

As MR increases in severity, forward cardiac output declines, and systemic hypotension may result, triggering neuroendocrine reflexes to restore blood pressure. By elevating systemic vascular tone, these reflexes may worsen mitral regurgitation and pulmonary edema.

Medical Management

Patients with acute MR often seek medical attention because of acute dyspnea. Findings on physical examination may include a pansystolic murmur and an S3 gallop. ECG findings vary with the cause of the MR and usually include left atrial enlargement and LV hypertrophy in women with chronic MR.

Symptomatic women should receive supplemental oxygen. Careful monitoring of fluid homeostasis and restriction of fluid input may be needed, along with diuretics or digoxin when LV dysfunction is present. Hydralazine decreases impedance to forward LV ejection and may prevent the isometric exercise of labor from causing hemodynamic deterioration.[223] Arrhythmias require prompt treatment. Women with hemodynamically important MR should receive prophylactic antibiotics because they are at increased risk for endocarditis.

Thromboembolic events are another major concern and may occur in up to 20% of pregnancies complicated by MR. Anticoagulant therapy is indicated for any woman who has had a prior thrombotic event, who is in atrial fibrillation, or who is expected to undergo cardioversion.

Obstetric Management

Mitral valve repair is usually feasible for nonrheumatic prolapsing mitral valves and should be carried out before pregnancy if regurgitation is severe.[224]

Women with MR benefit from the physiologic changes of pregnancy because the decrease in systemic vascular tone helps unload the left ventricle; this may explain the pregnancy-related decrease in the intensity of the murmur of MR. In contrast, both labor and delivery are associated with increases in vascular tone and venous return, which can elevate left atrial pressure and precipitate pulmonary edema. This problem is exacerbated by aggressive IV fluid administration.

Anesthetic Management

Hemodynamic goals include (1) maintaining a sinus rhythm and a slight elevation of heart rate; (2) assuring normal intravascular volume and venous return; (3) maintaining a mild decrease in SVR; (4) preventing an increase in PVR (e.g., by averting pain, hypercarbia, hypoxemia, and acidosis) or a large expansion of central vascular volume; and (5) preventing myocardial cardiac depression.

Invasive monitoring is rarely needed, except for the most severe cases of mitral regurgitation. Then, an arterial catheter is needed to provide continuous information on BP, and a pulmonary artery catheter (PAC) is indicated to measure forward cardiac output. If pulmonary edema and systemic hypotension develop, the information provided by a PAC provided a rational basis for decisions about fluid management and pharmacological therapy.

If the patient is not receiving anticoagulant therapy, epidural anesthesia is an excellent choice for labor and delivery, because it decreases systemic vascular tone and favors anterograde flow of LV blood. The judicious administration of IV fluids is required to maintain cardiac filling pressures. Ephedrine is a preferred vasoactive agent for supporting BP because it produces a mild to moderate increase in heart rate and less vasoconstriction than phenylephrine.

General anesthesia, if necessary, is usually well tolerated in women with MR. Anesthetics should be selected and administered to achieve a slightly elevated heart rate and a mild decreased systemic vascular tone. To be successful in this regard requires that the circulatory depressant effects of the

anesthetic agents be properly timed to offset the CV stimulation that results from anesthetic and surgical interventions.

Tricuspid Regurgitation

Tricuspid regurgitation is usually a functional anomaly caused by right ventricular dilation, which is secondary to pulmonary hypertension. It may also occur in association with rheumatic tricuspid stenosis. Tricuspid regurgitation often causes only a slight elevation of CVP because of the high capacitance of the vena cava and the high compliance of the right atrium.

Management involves treatment of the underlying pulmonary hypertension. Subacute bacterial endocarditis (SBE) prophylaxis is appropriate. One should note that left-to-right shunting is possible in women with a patent foramen ovale, especially in the setting of right heart failure and a sudden decrease in systemic vascular tone.

Aortic Insufficiency

In women of childbearing age, aortic insufficiency (AI) occurs more often than aortic stenosis.[225] AI may be acute or chronic. Acute AI causes rapid hemodynamic deterioration and must be treated promptly with CPB and valve surgery.[225,226] Causes of acute AI include infective endocarditis, retrograde dissection of the aorta, and traumatic rupture of the aortic valve.

Causes of chronic AI include rheumatic disease, ankylosing spondylitis, syphilis, cystic medial necrosis of the aorta, and VSD; 15% of patients with a VSD have prolapse of aortic cusps and chronic AI. The latency period between contracting rheumatic fever until the onset of hemodynamically detectable AI is about 7 years. Women often remain asymptomatic for another 10 to 20 years as their condition insidiously worsens. Most do not develop cardiac complications until after reproductive age.

Pathophysiology

Long-standing AI is characterized by chronic volume overloading and progressive dilation of the left ventricle. Initial compensatory mechanisms to maintain tissue perfusion include increases of heart rate and contractility. The ejection fraction diminishes gradually, and the left ventricle eventually fails. Pulmonary edema develops. Elevations of LV diastolic pressure and wall stress both increases the myocardial oxygen demand and decreases coronary blood flow, which predisposes to cardiac ischemia.

Medical Management

Nifedipine may help to delay the onset of symptoms in women with chronic AI. In the most severe cases of AI, women have manifestations of LV failure: exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), and diaphoresis. A high-pitched decrescendo diastolic murmur can usually be heard along the left sternal border in the third intercostal space, and a diastolic thrill and third heart sound are often present. The ECG may show left ventricular hypertrophy (LVH). A symptomatic woman should undergo aortic valve surgery after delivery, as soon as practical.

Congestive heart failure in women with chronic AI can usually be stabilized with treatments such as oxygen, diuretics, digoxin, and hydralazine. ACE inhibitors, while efficacious, are embryopathic and toxic to the fetus and are best avoided during pregnancy (see Table 12.14). Because a major infection or arrhythmia can cause rapid clinical deterioration in parturients with AI, such conditions require immediate therapy.

Obstetric Management

Most women with chronic AI tolerate pregnancy without major problems. The physiologic adaptations to pregnancy, such as increases in intravascular volume and heart rate and decreases in SVR, favorably affect AI by improving cardiac filling and reducing regurgitant flow.

Anesthetic Management

Hemodynamic goals include (1) a slight elevation of heart rate to minimize LV distension and lower oxygen demand; (2) a slight decrease in peripheral vascular resistance, to lessen the regurgitant fraction and improve cardiac output; and (3) mild increases of intravascular volume and venous return.

Monitoring for a patient with symptomatic AI should include arterial and central venous catheters. Continuous neuraxial anesthesia is well suited for labor and delivery. During labor, early administration of epidural anesthesia prevents pain-associated increases in SVR, which can worsen LV volume overload in women with AI. Hypotension should be treated with volume replacement and ephedrine. Bradycardia is not well tolerated and requires immediate treatment. When general anesthesia is indicated, the techniques and agents used should be selected to avoid unopposed myocardial depression or bradycardia. If either occurs, it should be corrected immediately.

Stenotic Valve Lesions

Aortic Stenosis

Left ventricular outflow obstruction in women of childbearing age is the result of valvular, subvalvular, or supravalvular aortic stenosis. Subvalvular and supravalvular stenoses are typically congenital lesions, whereas valvular stenosis is usually rheumatic in origin. Rheumatic aortic stenosis rarely occurs during pregnancy.

Pathophysiology

Patients become symptomatic when the AV area is reduced by approximately 70% (i.e., from 2.6–3.5 cm^2 to 0.75 cm^2)

or when the gradient between the LV and aortic valve exceeds 50 mm Hg. Because an increased ventricle pressure is needed to eject the stroke volume through the stenotic valve, the left ventricle becomes concentrically hypertrophied and its compliance decreases. The valve area becomes the primary factor that limits forward flow. Stroke volume becomes relatively fixed. Such changes lead to a precarious balance between the oxygen supply and demand of the left ventricle. A reduction in systemic arterial tone cannot increase cardiac output by unloading the left ventricle, but it may reduce coronary blood flow. In this setting, atrial systole is critical for LV filling and cardiac output.

A slow heart rate will decrease cardiac output in women with severe stenosis because the stroke volume is fixed. On the other hand, a rapid rate will decrease diastolic time and coronary perfusion while myocardial oxygen consumption increases. An arrhythmia such as atrial fibrillation can disrupt atrial systole and impair LV filling. An expanded intravascular volume and an ample venous return allow the physiologic demands for an increased cardiac output to be met by optimizing stroke volume instead of by elevating heart rate. A systemic BP that is normal to mildly elevated helps to ensure that the hypertrophied ventricle receives adequate perfusion. An abrupt decrease in peripheral vascular resistance can cause profound hypotension and tachycardia. The neuroendocrine mechanisms that normally correct hypotension by increasing cardiac output will be counterproductive. The stenotic valve limits peak stroke volume, so cardiac output cannot increase without a rise in heart rate; this is poorly tolerated in the presence of severe aortic stenosis.

Clinical Presentation

The clinical presentation usually reflects the severity of stenosis. Dyspnea, angina, or syncope are ominous symptoms and are associated with a life expectancy of less than 5 years if the stenotic lesion is not repaired.[227] Sudden death may occur if an arrhythmia or hypotension develops.

Typical findings on physical examination include a coarse systolic murmur, which reaches its peak intensity at midsystole and characteristically radiates to the apex of the heart and the left neck.[227] The intensity of the murmur, which is related to the outflow obstruction and blood flow across the stenotic valve, begins to decrease when the stenosis is severe enough to reduce cardiac output. The electrocardiogram shows LVH, conduction defects, and diffuse abnormalities of ST segments and T waves. The chest radiograph usually reveals a calcified aortic valve, dilated left ventricle, and poststenotic dilation of the ascending aorta. Echocardiography is the best method for evaluating the severity of aortic stenosis during pregnancy.[228,229]

Medical and Surgical Management

Pregnant women who have symptomatic aortic stenosis should have a cardiology consultation as soon as is practical. Because stroke volume is fixed, these women lack the capacity to meet pregnancy-associated demands for increased cardiac output. When the gradient across the aortic valve exceeds 100 mm Hg, the risk of complications during pregnancy becomes excessive. Management strategies for such women include (1) early termination, valvular replacement, and another attempt to pregnancy versus (2) continuation of pregnancy, formulation of a plan for managing hemodynamic deterioration that is refractory to medical therapy, including provisions for an expeditious cardiac intervention, such as percutaneous balloon valvuloplasty[230] or valvular replacement.[231,232]

Women who develop symptoms during pregnancy usually do so in the second or third trimester. Their risk for major complications and death is increased. A woman with clinical findings suggestive of a life-threatening condition should be considered a candidate for percutaneous balloon valvuloplasty or aortic valve replacement.[233,234] Several reports indicate that good outcomes of pregnancy are achievable for gravid women who undergo percutaneous balloon valvuloplasty to treat symptomatic aortic stenosis.[231,233] Replacement of the aortic valve[235] requires both general anesthesia and cardiopulmonary bypass (CPB), which could adversely affect the outcome of pregnancy. As a rule, invasive interventions are performed only for severe valvular disease that is refractory to medical therapy and are deferred until after the first trimester, whenever possible.

Mild aortic stenosis (valve area >1.0 cm^2) is typically well tolerated during pregnancy.[227] Women who reach 32 to 34 weeks gestation without cardiac symptoms or electrocardiographic evidence of ischemia usually have an uneventful labor and delivery. Women with aortic stenosis are at increased risk for bacterial endocarditis and should receive prophylactic antibiotics as indicated. Bacterial endocarditis, which may be heralded by persistent fevers or sudden aortic insufficiency, requires immediate therapy.

Obstetric Management

Clinically significant aortic stenosis is associated with a very high risk for major complications; maternal and perinatal mortality rates have been reported to be about 17% and 32%, respectively.[228,236] In addition, children of mothers with LV outflow obstruction are at increased risk for cardiac defects. Thus, women of childbearing age with severe aortic stenosis should be counseled about the risks of pregnancy and advised to have valve surgery before conception.

The mode of delivery is usually vaginal, and a cesarean delivery is performed for the usual obstetric indications. A "cardiac delivery" (Table 12.16) is indicated to avert the hemodynamic lability associated with pushing; vaginal delivery is assisted with vacuum or forceps.

Anesthetic Management

The primary hemodynamic goal is to maintain circulatory parameters that are within normal limits.[237–240] Ideally, heart

TABLE 12.16. Cardiac delivery.

Early analgesia for maternal pain control
Close monitoring of fluid status with hemodynamic monitoring
SBE prophylaxis if indicated
Left lateral tilt of mother to improve venous return
Allow fetal vertex to labor through the pelvis in the second stage without maternal expulsive efforts
Operative vaginal delivery with low forceps or vacuum
Cesarean section for the usual obstetric indications
Close hemodynamic monitoring in the postpartum period

SBE, subacute bacterial endocarditis.

rate and rhythm are normal; SVR is normal or elevated slightly; intravascular volume and venous return are normal or elevated slightly; and myocardial contractility is preserved. It is also important to maintain normothermia and prevent shivering to avoid the need for a higher cardiac output.

Invasive monitoring using arterial and central venous catheters is indicated for early detection and prompt treatment of adverse hemodynamic changes. A CVP is usually preferred to a PA catheter, as the latter is more often associated with severe complications including dysrhythmias and PA rupture. It is advisable to have two large-bore IV catheters in place in women at risk for peripartum hemorrhage. Keeping central filling pressures above normal may help to prevent severe circulatory depression if hemorrhage should occur.

Historically, neuraxial anesthesia for patients with severe aortic stenosis was contraindicated. The major concern was that the sympathectomy associated with the neuraxial block would cause cardiovascular collapse. However, it is now clear that a carefully conducted neuraxial anesthetic can be advantageous for parturition or cesarean delivery.[237–240] Incremental injections of local anesthetic solutions provide sufficient time to counteract evolving circulatory changes by administering intravenous vasopressors such as phenylephrine and fluids.

Careful planning and effective communication with the obstetric team is essential to ensure that an emergency cesarean delivery will not be required when a woman lacks adequate anesthesia for the operation. If there is a concern about fetal well-being, the neuraxial anesthetic should be extended slowly to about T6 to prepare for surgical delivery. It is advisable to intensify the block using a local anesthetic solution that does not contain epinephrine (e.g., 2% lidocaine). If bradycardia occurs, it needs to be treated expeditiously yet very cautiously. Agents such as glycopyrrolate, atropine, or ephedrine should be dosed incrementally to avert tachycardia or arrhythmias. Sedatives and anxiolytic medications can prevent anxiety-related tachyarrhythmias.

The safe conduct of general anesthesia for women with severe aortic stenosis requires an anesthetic plan that is well conceived and carefully orchestrated. The anesthesiologist must anticipate and counteract circulatory depressant effects of anesthetics, decreases in venous return from positive pressure ventilation, stress responses to anesthetic and surgical interventions, and peripartum blood losses. The combined use of etomidate and an opioid helps to ensure hemodynamic stability during induction, laryngoscopy, and tracheal intubation. Redfern et al. [241] reported transient maternal hypotension and severe neonatal respiratory depression following an induction with etomidate and alfentanil in a pregnant woman with severe aortic stenosis. Less neonatal depression would be expected with remifentanil, which crosses the placenta but appears to be cleared rapidly by the fetus. Several reports indicate that the administration of a remifentanil-based anesthetic to women with severe cardiac disease can be associated with hemodynamic stability, with little or no ventilatory depression in the newborn.[39–41]

Postoperative monitoring in an ICU setting is essential until the parturient's condition stabilizes (at least 24 h). Epidural or intrathecal morphine without local anesthetics is an excellent way to provide postoperative pain relief.

Mitral Stenosis

Mitral stenosis (MS) is the most common valve lesion in women with RHD.[4] Mitral regurgitation (MR) often accompanies rheumatic MS, but the more serious hemodynamic problem is stenosis.

Pathophysiology

A normal mitral valve has an area of 4 to 6 cm^2. Symptomatic disease occurs as the valve area drops below 2 cm^2; the disease is considered severe when the valve area is less than 1 cm^2. The major hemodynamic impairment is a limitation of LV filling, which results in a reduction in stroke volume and cardiac output and an elevation of left atrial and pulmonary pressures. As the stenosis increases over time, the left atrium dilates (mitral P wave on EKG) and the pulmonary vasculature becomes congested. The lymphatic system of the lungs gradually becomes hypertrophied, which helps to minimize pulmonary edema. Severe and persistent stenosis can cause pulmonary hypertension, right ventricular hypertrophy, and right heart failure.

Some patients develop a low-output state and congestive heart failure. Left atrial dilation predisposes to mural thrombi and atrial fibrillation, which further increase the risk of systemic thromboembolism. Although the LV oxygen supply–demand balance is usually favorable, the situation in the right ventricle may be precarious. Heart rate should be kept slow using interventions such as digitalis, effective analgesia and sedation to maximize LV filling time. Diuretic therapy, which is often indicated to prevent or treat pulmonary congestion, must be used with caution to prevent large decreases of cardiac filling pressures.

Pregnancy decreases plasma oncotic pressure and in women with MS, increases hydrostatic pressure in pulmonary veins and capillaries. These changes alter Starling forces to favor

the transudation of fluid from the pulmonary microvasculature into alveoli.

Clinical Presentation

Mitral stenosis develops slowly during the first two or three decades after an acute bout of rheumatic fever. In about 25% of women, it remains asymptomatic until pregnancy. Some women with undiagnosed MS may be visitors or immigrants from developing countries and are at risk for pulmonary edema during pregnancy. Their condition must be promptly diagnosed and expeditiously treated to prevent major morbidity from pulmonary edema.[224]

Women seek medical attention for concerns such as dyspnea, hemoptysis, chest pain, symptoms of right heart failure, or thromboembolism. Physical examination reveals an accentuated S1, opening snap, diastolic murmur, and presystolic accentuation. The ECG may show left atrial enlargement, atrial fibrillation, and right ventricular hypertrophy (RVH). Echocardiography shows the severity of the stenosis; measurements must be obtained carefully because calculation of mitral valve area by Doppler may be inaccurate during pregnancy.[242]

Medical and Surgical Management

Reductions in heart rate and blood volume are therapeutic mainstays for women with moderate to severe mitral stenosis. Restricting salt intake and administering diuretics will lower blood volume. Excessive use of diuretics, however, may cause hypovolemia and decrease uteroplacental perfusion. Limitation of physical activity and beta-blocker therapy can prevent tachycardia, afford symptomatic relief, and decrease the incidence of pulmonary edema.[243] Atrial fibrillation, if it occurs, must be treated aggressively, using beta-blockers, digoxin, or cardioversion as needed.

When severe MS is unresponsive to medical therapy or afflicts women who cannot be closely monitored during pregnancy, the valve should be repaired or replaced during the second trimester, if practical.[234] Percutaneous balloon mitral valvuloplasty is preferred for women with a pliable valve and no significant MR. The procedure usually improves symptoms and circulatory dynamics dramatically without affecting the mother or fetus adversely.[244–255] Valvuloplasty should be performed with echocardiographic guidance[254,256] or fluoroscopy, using abdominal and pelvic shielding to minimize fetal exposure to ionizing radiation. Complications[254] that may arise include preterm labor, maternal arrhythmias that produce fetal distress,[257] cardiac tamponade that requires surgical intervention, and systemic embolization.[258] Open-heart surgery is well tolerated by the mother but increases the risk of fetal loss. Closed procedures are generally preferred at medical centers that routinely perform them.[234,246]

Pulmonary edema may be inescapable in pregnant women with tight MS. Left ventricular filling is severely limited by the narrowed valve, so cardiac output can increase only if heart rate increases. Higher heart rates, however, allow less time for ventricular filling and cause progressive increases in left atrial volume and pressure. Left atrial distension may lead to arrhythmias such as, atrial flutter and fibrillation, which further increase left atrial pressure. Atrial fibrillation is a major concern; not only does it predispose to pulmonary edema, but it is also associated with 80% of the thromboembolic events that occur during pregnancy. Deaths from MS usually result from pulmonary edema and occur in the postpartum period.

Obstetric Management

Severe MS is dangerous for both the mother and fetus. Thus, a mitral valve repair or replacement is advisable before conception. When valve replacement is needed, and a future pregnancy is desired, a bioprosthetic valve may be preferred to a mechanical valve to avoid anticoagulant therapy.

Pregnancy rarely exacerbates mild MS. However, moderate to severe stenosis (valve area <1.5 cm^2) is associated with clinical worsening of one or two functional classes on the New York Heart Association (NYHA) scale.[9,236,259] The need for hospitalization and cardiac medications increases, and heart failure develops more often. Maternal mortality rate is not increased, but the incidence of fetal growth restriction and preterm births increases markedly.

Labor and vaginal delivery is standard in these women, with cesarean delivery reserved for obstetric indications. Parturients should receive supplemental oxygen from the onset of labor through the early postpartum period to help minimize increases in PVR. Effective analgesia is important because it attenuates the hemodynamic changes of labor and delivery. A cardiac delivery is recommended to moderate the excessive venous return that accompanies maternal expulsive efforts (see Table 12.16).

Anesthetic Management

The general hemodynamic goals include (1) maintaining a sinus bradycardia, (2) maintaining a normal or slight elevation of SVR, (3) maintaining normal or slight elevations of intravascular volume and venous return, (4) preventing large increases in PVR by providing effective analgesia and averting acidosis, hypercarbia, and hypoxemia, and (5) avoiding a decrease in myocardial contractility.[45,260–262]

Invasive Hemodynamic Monitoring

Pulmonary capillary wedge pressure is useful for monitoring hemodynamic trends in parturients with severe MS, unless tachycardia occurs. CVP provides a rough guide to right ventricular function. Clark et al.[261] studied the central circulatory effects of labor and delivery in eight women with NYHA class III or IV mitral stenosis; they used cautious diuresis to optimize preload and propranolol to control heart rate. Immediately after delivery, PCWP was noted to increase by approx-

imately 10 mm Hg, whereas cardiac output did not increase in 75% of the women. The report demonstrates that in parturients with severe MS, the correlation between PCWP and CVP is poor, and that strict hemodynamic control is associated with good maternal and perinatal outcomes.

Invasive monitoring with an arterial catheter, CVP, or PA catheter is advisable for women with severe MS and for those who have been symptomatic during the pregnancy. Monitoring should begin at the onset of labor. Medications such as diuretics, digoxin (for atrial fibrillation), nitroglycerin, and beta-blockers are used as needed to prevent or minimize elevations of left atrial pressure. After delivery and the relief of aortocaval compression, venous return can rise sharply causing marked elevations of PCWP and pulmonary edema.[261] Therefore, invasive monitoring should be continued for at least several hours postpartum.

Anesthetic Techniques

The sympathectomy from an epidural or spinal anesthesia is characterized by dilation of systemic arteries and veins and an increase in venous capacitance. The latter effect, by decreasing the venous return and central filling pressures, may benefit women in congestive heart failure. Thus, epidural anesthesia is an excellent choice for either a vaginal or cesarean delivery. Moreover, maintaining the epidural block during the immediate postpartum period can help to prevent pulmonary edema.

If general anesthesia is needed for a cesarean delivery, then it should be planned to optimize the CV status of a woman with severe MS. The plan must include provisions for maintaining a sinus rhythm, preventing tachycardia, and averting large vacillations in central filling pressures. Administering an opioid such as remifentanil or fentanyl or a beta-blocker before inducing anesthesia can prevent hyperdynamic circulatory responses to laryngoscopy and tracheal intubation. Central pressure monitoring helps guide the timely, judicious replacement of fluids and may be especially valuable if postpartum hemorrhage occurs. Uterotonic agents such as oxytocin, methylergonovine, or prostaglandin $F_{2\alpha}$ should be used with caution, because they can produce adverse circulatory effects. Postoperative care should occur in an ICU setting because the risk of major morbidity and mortality is greatest in the postpartum period.

Pulmonic Stenosis

If pulmonic stenosis is severe, women are advised to undergo a corrective procedure before becoming pregnant. Pregnancy is usually well tolerated by asymptomatic women with isolated pulmonic stenosis. In rare instances, percutaneous balloon valvuloplasty[263] merits consideration during pregnancy in women who (1) develop symptoms as a direct result of the stenotic valve; (2) have progressive right ventricular failure; or (3) become cyanotic and have intracardiac (atrial or ventricular) shunts.

Anticoagulants and Mechanical Valve Prostheses

Prosthetic Heart Valves

Pregnancy in women with a prosthetic valve is associated with an increased risk of maternal and fetal complications.[264] Complications may arise from the pregnancy-related increase in hemodynamic burden across a prosthetic valve or from the hypercoagulable state of pregnancy, which predisposes to major thromboembolic events. Complications may also result from the mother's cardiac disease, requiring pharmacologic therapy (e.g., anticoagulants) that can cause fetal injury.[232,264] The hemodynamic stresses of pregnancy seldom cause cardiac decompensation in women who had been asymptomatic or mildly symptomatic before conception. Occasionally, their functional capacity will decrease during pregnancy, and medical therapy will need to be started or intensified. However, the major threat by far for women with a mechanical prosthetic valve is valve thrombosis and thromboembolic events.[265]

Selecting a prosthetic valve for women of childbearing age is not a simple matter.[224] Bortolotti et al. suggested that a porcine bioprosthetic valve is the best choice for a woman of childbearing age who desires pregnancy.[266] A bioprosthetic valve obviates the need for anticoagulant therapy.[265] However, these valves deteriorate over time, and pregnancy may accelerate the process.[224,232,264] Their hemodynamic profile is inferior (especially small sizes in the aortic position) to mechanical valves,[267] although this may be less problematic when homograft or pericardial bioprosthetic valves are used. New-generation mechanical valves offer a superior hemodynamic profile, excellent stability, and seldom need replacement.[268] Anticoagulant therapy is still required, but the risk of thromboembolism or hemorrhage appears to be low when anticoagulant effects are carefully monitored and tightly regulated. These valves may be the best choice for women of childbearing age who are amenable to close monitoring after valve replacement.[268]

Use of Warfarin in Pregnancy

Salazar et al.[265] compared effects of anticoagulant therapies in a series of 223 pregnancies in women with prosthetic heart valves. The rates of cerebral thromboembolism in women receiving first-trimester therapy with antiplatelet agents, subcutaneous heparin, or warfarin were 25%, 8%, and 2%, respectively. The unacceptably high incidence of major thrombotic complications, including maternal deaths (4%) without warfarin therapy during the first trimester, led to the recommendation that such patients receive oral anticoagulants for the first 35 weeks of pregnancy.[224,265] However, many patients and physicians, especially in the United States, rejected this approach because warfarin crosses the placenta and can cause spontaneous abortion (up to 28%), intracranial bleeding in the fetus (9% when warfarin is used 38th week gesta-

tional), and congenital malformations (5%–30%).[30,265] Warfarin-induced embryopathy includes choanal stenosis and multiple skeletal anomalies including decreased nasal bridge, nasal hypoplasia, small nasal bones, hypoplastic alae nasi, telecanthus, punctate epiphyseal dysplasia of the long bones and the cervical and lumbar vertebral plates. The teratogenic effects of warfarin are limited to the first trimester, and warfarin has been used safely during the second and third trimesters.[30,265] In such cases, heparin is typically substituted for warfarin, usually around the 35th or 36th gestational week, to avoid the onset of labor during warfarin therapy.[265]

Anticoagulant therapy should be most intense for women with the greatest risk of thromboembolism, such as those with a first-generation (e.g., a caged-ball valve) mitral valve, two or more mechanical prostheses, atrial fibrillation, or a history of systemic embolization. When the risk for valve thrombosis is exceedingly high, it may be reasonable to provide thrombotic prophylaxis with warfarin for the first 35 weeks, particularly if therapeutic anticoagulation [international normalized ratio (INR) between 3.0–4.5] is achievable at a low dosage of warfarin (<5 mg/day). Low-dose aspirin (80 mg) is considered safe during pregnancy and may reduce the risk of thrombosis in women receiving a low dose of an oral anticoagulant. High-risk patients who wish to avoid warfarin in early gestation can receive heparin (IV or SQ) during the first trimester, but they require a high-intensity heparin effect [i.e., anti-factor Xa levels of 0.55–0.8 unit/mL or an activated partial thromboplastin time (aPTT) 2.5–3.5 times the control value].[265] It now appears that most women with mechanical valves can be adequately anticoagulated without the use of warfarin during the first trimester.

Women at lower risk for thromboembolism, such as those with a prosthetic aortic valve or second-generation prosthesis in the mitral position, may receive subcutaneous heparin throughout pregnancy maintaining an aPTT 2.0–3.0 times the control. Some women may prefer taking warfarin between weeks 13 through 35 to avoid self-injection of heparin or associated side effects. The intensity of anticoagulation should be monitored frequently and corrected immediately if needed.

Low Molecular Weight Heparin

Although low molecular weight heparin (LMWH) has become a popular anticoagulant for many conditions associated with an increased risk of thromboembolism, LMWH appears to lack the required efficacy as an anticoagulant for women who have a mechanical heart valve. The product labeling includes the warning for enoxaparin, a commonly used LMWH, that this agent " . . . is not recommended for thromboprophylaxis in pregnant patients with prosthetic heart valves, due to reports of valvular thromboses despite adequate anti-coagulation." At present, it seems inadvisable to select a LMWH to provide thromboprophylaxis for pregnant women with a mechanical valve.

Congenital Heart Disease and Intracardiac Shunts

Congenital heart disease is now the predominant cause of cardiac disease in pregnant women in the United States, accounting for 60% to 80% of the cases. A congenital anomaly of the heart or CV system is present in 0.7% to 1% of newborns. Three specific lesions—ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA)—account for over half of the cases (Table 12.17).

Predictors of Outcome

Factors that affect maternal outcome in women with CHD include (1) pathophysiology of the disease, (2) presence or absence of a surgical repair, (3) presence or severity of cyanosis, (4) degree of pulmonary hypertension, (5) maternal functional capacity, (6) degree of myocardial dysfunction, (7) degree of LV outflow obstruction, and (8) history or presence of arrhythmias or other prior cardiac events. A CHD that involves only a small left-to-right shunt (e.g., ASD, VSD, or PDA) is usually well tolerated during pregnancy if appropriate precautions are taken. Generally, women with noncyanotic CHD who are asymptomatic can expect a good outcome, whereas those with cyanosis or an impaired functional status are at increased risk for major complications, including congestive heart failure, arrhythmias, hypertension, myocardial ischemia, infective endocarditis, and thromboembolic phenomena.

Shunt reversals and hypoxemia are more likely to occur in women who have a large ventricular lesion than in those who have a large atrial or a small ventricular defect. During the first two trimesters of pregnancy, these women are at risk for a shunt reversal or an increase in right-to-left shunting because of the physiologic elevation of right ventricular pressure and the decrease in SVR. Cyanotic shunts are associated with a high risk of a poor maternal and fetal outcome.

Congenital heart disease (CHD) affects perinatal outcome adversely, particularly when the mother has an impaired functional status or cyanotic disease. A study of pregnant women

TABLE 12.17. Incidences of congenital heart defects.

Lesions	Incidence (%)
Acyanotic	
Ventricular septal defect	35
Atrial septal defect	9
Patent ductus arteriosus	8
Pulmonary stenosis	8
Aortic stenosis	6
Coarctation of the aorta	6
Atrioventricular septal defect	3
Cyanotic	
Tetralogy of Fallot	5
Transposition of the great arteries	4

Source: From Jordan SC, Scott O. Heart Disease in Paediatrics, 3rd ed. Oxford: Butterworth Heineman, 1989.

with CHD revealed a fetal loss of 45% when the mother was cyanotic and of 20% when the mother was acyanotic. In addition, fetal growth restriction and preterm births occur more often with pregnancies of cyanotic mothers; the frequency of these problems correlates directly with maternal hematocrit values. Furthermore, when the mother has CHD, the risk of CHD in offspring is higher than in the general population.[269] Children born to mothers with CHD are also at increased risk for noncardiac congenital malformations, cognitive dysfunction, and physical impairments.

Good pregnancy outcomes are occasionally reported for women with partially corrected and uncorrected cyanotic heart disease such as pulmonary and tricuspid atresia, transposition of the great vessels, truncus arteriosus, single ventricle, double-outlet right ventricle, and double-inlet left ventricle. However, the risk of a poor outcome is very high. One study described 96 pregnancies in 44 women with cyanotic heart disease without Eisenmenger reaction: 32% of the women developed CV complications, including heart failure, thromboembolic events, SVT, and peripartum bacterial endocarditis resulting in one postpartum maternal death.[270] The presence of a cyanotic shunt was associated with high incidences of fetal loss (57%), fetal growth restriction, preterm deliveries, and both cardiac and noncardiac congenital malformations in offspring.

Management of Intracardiac Shunts: General Principles

Several general principles of management pertain to all women with intracardiac shunts (outlined in Table 12.18): (1) administer prophylactic antibiotics as indicated for vaginal or cesarean delivery; (2) prevent the introduction of air into the venous circulation, which can lead to paradoxical air embolism and severe injury; (3) maintain intravascular volume and venous return; and (4) prevent increases in PVR and decreases in SVR, which can cause a shunt reversal and worsen hypoxemia. Providing supplemental oxygen and monitoring SpO_2 will help optimize oxygen delivery to tissues and allow a shunt reversal to be detected early and corrected promptly. Epidural anesthesia attenuates the cardiovascular changes of labor and delivery. It is preferable to insert the epidural catheter in early labor, before the onset of painful contractions, using incremental dosing of neuraxial medications to achieve the desired clinical effect without inducing hemodynamic instability.

Specific Congenital Heart Lesions

Atrial Septal Defect

The congenital heart defect that is most frequently overlooked in childhood is an ASD of the secundum type (see Table 12.17). It accounts for 9% of the CHD in pregnant women. The effects of pregnancy on a woman with an ASD depend on accompanying lesions, functional status, and pulmonary vascular resistance. Generally, pregnancy is well tolerated in women with an ASD, even with a large left-to-right shunt. Pulmonary hypertension or atrial arrhythmias seldom occur in women of childbearing age. The risk of endocarditis is not increased for a woman with an isolated secundum type of ASD, or who is at least 6 months status post successful re-

TABLE 12.18. Risks related to intracardiac shunts and their management during pregnancy.

Risk factor	Preventative measure
Endocarditis	Give prophylactic antibiotics for delivery (except for a secundum-type ASD)
Paradoxical air embolism	Precautions with IV lines
	Remove air from IV tubing and solutions
	Use special air-extracting filters
	Precautions during epidural catheter placement[428]
	Use loss of resistance to saline (instead of loss of resistance to air)
	Precautions during abdominal delivery
	Maintain uterus in a dependent position (e.g., repair uterine incision in situ, elevate head of OR table)
Increased right-to-left shunting; shunt reversal	Avoid large increases in pulmonary vascular resistance
	Give O_2 via face mask and monitor SpO_2
	Provide early and effective analgesia for labor
	Prevent hypercarbia (respiratory acidosis) through cautious use (or avoidance) of parenteral opioids and sedatives
	Prevent large decreases in systemic vascular resistance
	Ensure that onset of neuraxial anesthesia is slow and controlled
	Promptly treat hypotension induced by neuraxial anesthesia
	Prevent a major decrease in effective blood volume (this decreases right ventricular volume and compromises systemic perfusion)
	Rapidly replace postpartum blood losses with blood and IV fluids
	Avoid large increases in right ventricular volume and pressure (can increase right-to-left-shunting)
	Monitor CVP and give fluids judiciously to prevent overexpansion of blood volume

ASD, atrial septal defect; IV, intravenous; OR, operating room; CVP, central venous pressure; SpO_2, O_2 saturation via pulse oximetry.

pair of a septal defect or surgical ligation and division of a PDA.[35]

Ventricular Septal Defect

A VSD is the most common congenital heart (CH) defect, and accounts for about 35% of the CH lesions that occur in pregnant women. A woman who has had closure of an uncomplicated VSD is at no greater risk during pregnancy than a woman without heart disease. An isolated VSD is usually well tolerated during pregnancy, but it may occasionally be associated with arrhythmias and congestive heart failure. The presence of pulmonary hypertension can markedly increase the risk of pregnancy in women with a VSD. A large reduction in BP, which may occur during or after delivery due to blood loss or anesthesia, can reverse the direction of the shunt. Prompt vasopressor therapy or volume replacement will usually restore BP and corrects the problem. The incidence of VSD in offspring has been reported to be 4% to 11%.[9]

Patent Ductus Arteriosus

A PDA accounts for about 8% of the CH lesions in pregnant women. Pregnancy is usually uncomplicated in women with a PDA and a left-to-right shunt,[9] although some women experience clinical deterioration and congestive heart failure.[9] No maternal deaths occurred in a series of patients with PDA. Surgical intervention is rarely needed during pregnancy.[271] Women with pulmonary hypertension are at increased risk for a shunt reversal from decreases in vascular tone during gestation or early postpartum hypotension. Peripartum hypotension should be corrected promptly, using vasopressor therapy and intravenous fluids.

Ebstein Anomaly

The Ebstein anomaly includes a malformed tricuspid valve, wherein the cusps are displaced downward, the valve tissue is wrinkled, and the chordae tendineae are poorly developed or absent. Ebstein anomaly is less common as an isolated malformation of the tricuspid valve, but this is better tolerated than tricuspid atresia. Many women with this anomaly reach adulthood without surgical intervention.

Pregnancy is well tolerated in women with a noncyanotic Ebstein anomaly. In cyanotic cases, however, there is an increased risk of maternal heart failure, premature births, and fetal loss. The approach to labor and delivery in symptomatic or cyanotic women with Ebstein anomaly includes prophylactic antibiotics, oxygen administration, hemodynamic and blood gas monitoring, and maintenance of systemic BP, intravascular volume, and venous return.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) accounts for 5% of CH lesions in pregnant women and is the most common cause of a cyanotic shunt during pregnancy. TOF consists of a large VSD, an obstructed right ventricular outflow tract (infundibular or valvular, e.g., pulmonic stenosis), and a dilated aorta overriding the interventricular septum. These three lesions, if not corrected shortly after birth, conspire to cause a fourth—right ventricular hypertrophy.

When TOF is mild, surgical closure of the VSD and correction of the outflow obstruction is usually deferred until children are between 2 and 5 years of age. Symptomatic neonates or infants, however, require immediate surgical intervention.[272]

Medical and Surgical Management

The outcome of pregnancy is usually favorable for women with corrected TOF. Occasionally, pregnancy will unmask residual cardiac dysfunction (i.e., present before the surgical correction) or an intracardial lesion in a woman with "corrected" TOF.

Women who have had a palliative procedure for TOF are at high risk for a poor outcome of pregnancy. Those who had a definitive repair of TOF in early childhood have a significantly lower risk of pregnancy than women with residual postsurgical pathology, such as a VSD, pulmonic stenosis or regurgitation, or right ventricular dysfunction.[273] Pulmonary hypertension will often complicate the pregnancies of women who had a shunt procedure to decrease cyanosis.

A poor pregnancy outcome should be anticipated if the mother's SpO_2 is below 80%, her hematocrit exceeds 60%, or she has right ventricular hypertension or syncopal episodes.[9] Cyanotic heart disease portends high rates of spontaneous abortion, preterm deliveries, and fetal growth restriction.[270,271,273–275] It has been recommended that women with the following pathophysiologic findings should undergo surgery before conception: (1) a VSD and a pulmonic-to-systemic flow ratio that exceeds 1.5:1.0; (2) right ventricular outflow obstruction, with a right ventricular systolic pressure exceeding 60 mm Hg; and (3) right ventricular failure because of pulmonary regurgitation.[9]

Obstetric Management

Preconceptually, women with clinically important cardiac disease should have a thorough cardiology evaluation to identify and assess the severity of any cardiac lesions. They should receive counseling about maternal and fetal risks of pregnancy, the effects of pregnancy on their long-term health, and the risks of congenital malformations in their children.

Between the 18th and 20th week of gestation, pregnant women with CHD should undergo a detailed fetal ultrasound and fetal echocardiogram to determine if the fetus has CHD. In addition, serial fetal testing should be performed in the third trimester, especially in women with cyanotic disease. Vaginal delivery is the preferred method for most women with CHD, and cesarean delivery is reserved for obstetric reasons or maternal cardiovascular instability. When an uncomplicated delivery is expected, prophylactic antibiotics are only

required for woman with a prosthetic heart valve or a surgically constructed systemic-to-pulmonary shunt.[35]

Anesthetic Management

Generally, no special measures are required for healthy women with corrected TOF. However, these women may be at increased risk for a cardiac rhythm disturbance because the surgical corrective procedure sometimes disrupts the normal conduction pathways. Thus, they may benefit from continuous ECG monitoring during labor and delivery.

A pregnant woman with uncorrected TOF should be managed in accordance with the following hemodynamic goals: (1) maintain mild elevations of intravascular volume, venous return, and right ventricular filling pressures, which drives pulmonary blood flow; (2) prevent decreases in SVR and increases in PVR, which worsen right-to-left shunting and cyanosis.

The ECG should be monitored continuously to facilitate prompt diagnosis and treatment of cardiac arrhythmias. Women with impaired functional capacity, pulmonary hypertension, or cyanotic disease usually require invasive hemodynamic monitoring with arterial and CVP catheters, as well as periodic measurements of blood gases from the onset of labor through the early postpartum period. Changes in intravascular volume must be anticipated and corrected promptly.

Effective analgesia from the onset of labor through delivery helps avert exacerbations of pulmonary hypertension, right ventricular dysfunction, and cyanotic shunting. For a cesarean delivery, a continuous neuraxial block that is carefully administered generally provides safe and effective anesthesia for a woman with uncorrected TOF. A single-shot spinal anesthetic is relatively contraindicated because it can cause systemic vascular tone and BP to precipitously decrease, inducing a shunt reversal and worsening hypoxemia. Hypovolemia from postpartum hemorrhage is similarly concerning and needs to be treated immediately with a vasoconstrictor and IV fluids. Measures should be taken to prevent an elevation in PVR, impede the ejection of blood into the pulmonary circuit and favor the flow of blood through the cyanotic shunt.

Secondary Pulmonary Hypertension (Eisenmenger's Syndrome)

Victor Eisenmenger originally described the "Eisenmenger complex" in 1897 in an article on congenital defects of the ventricular system.[276] In 1958, Wood redefined the syndrome as "pulmonary hypertension due to high pulmonary vascular resistance with reversed or bidirectional shunt at the aortopulmonary, ventricular, or atrial level."[277]

Pathophysiology

Eisenmenger's syndrome is a complex pathophysiologic state that includes (1) clinical cyanosis; (2) a communication between the right and left circulatory systems (an ASD, a VSD, or an aorticopulmonary anomaly) that allows bidirectional circulatory shunting; and (3) pulmonary hypertension that is relatively fixed at systemic levels, owing to an irreversible elevation of pulmonary vascular resistance (PVR).

Eisenmenger's syndrome is usually the result of an untreated or incompletely treated congenital heart lesion such as ASD, VSD, PDA, TOF. The long-standing left-to-right shunt causes chronic overloading of the right ventricle and excessive pulmonary blood flow. Hypertrophic changes occur in the pulmonary vasculature that lead to a marked elevation in PVR and pulmonary hypertension that is unresponsive to medical therapy or surgical correction.[278] When PA pressure exceeds systemic BP, the flow of blood through the shunt reverses direction (initially it is bidirectional, and later right to left). Adaptive mechanisms that develop over time allow Eisenmenger patients to function at a lower oxygen saturation level than could be tolerated acutely by a healthy person. The mortality rate, without an intervening pregnancy, is highest in the third and fourth decades of life.

In a woman with Eisenmenger's syndrome, pregnancy will not induce the usual reduction in PVR because PVR is pathologically fixed. Therefore, pregnancy-associated increases in cardiac output and pulmonary blood flow cause pulmonary hypertension to worsen. In addition, pregnancy can exacerbate hypoxemia by increasing oxygen consumption, decreasing functional residual capacity, and causing a reduction in SVR, which increases right-to-left shunting. Maternal hypoxemia and circulatory derangements are associated with intrauterine growth restriction and fetal demise.[275,279]

Medical Management

Eisenmenger's syndrome markedly increases the risk for pulmonary thromboembolism. Elkayam[9] recommends prophylactic anticoagulant therapy during the times that women are at the greatest risk for sudden death, which extends from the third trimester until the sixth postpartum week. On the other hand, Kahn[280] has expressed concern that such therapy may lead to, or exacerbate, hemorrhage, which is poorly tolerated in these patients. Hemorrhage can cause severe hypotension, progressively worsening right-to-left shunting and hypoxemia. In a study of seven consecutive women with Eisenmenger's syndrome, all five of the women who had received prophylactic heparin died; three bled excessively during the postoperative or postpartum period. Neither of the two surviving women had received heparin therapy.[281]

Obstetric Management

Eisenmenger's syndrome is associated with a very high maternal mortality rate, ranging from 30% to 50%.[282–284] Because of the grim maternal prognosis and poor overall outcome of pregnancy, women with Eisenmenger's syndrome are strongly advised against pregnancy. Pregnant women

should be counseled regarding the high risks of maternal mortality and offered termination of pregnancy.[285]

Women who choose to remain pregnant need to be very closely monitored by a multidisciplinary team consisting of obstetrician, cardiologist, anesthesiologist, nurses, and other support personnel. Symptoms typically develop in the second trimester[286] and may include fatigue, exertional dyspnea, syncope, chest pain, palpitations, nonproductive cough, hemoptysis, and leg edema. Preterm labor is the rule,[283] so women should be hospitalized, and their physical activity restricted whenever uterine contractions occur.

The maternal mortality rates associated with vaginal delivery and cesarean delivery are 34% and 75%, respectively. An assisted vaginal delivery, which is described as a cardiac delivery in Table 12.6, minimizes the hemodynamic changes associated with the second stage of labor. A planned cesarean delivery may be preferred because of maternal hemodynamic instability, a high risk of fetal distress during vaginal delivery, and the potential need for emergency cesarean delivery. Deaths usually occur in the early postpartum period but may occur as late as 4 to 6 weeks postpartum.[284] The exact cause of death is often unclear, but thromboembolic events appear to play a major role. The mortality rate associated with therapeutic abortion in the series reported by Gleicher et al. was about 7%.[284]

Anesthetic Management

Hemodynamic Goals

The following goals pertain to the anesthetic management of pregnant women with Eisenmenger's syndrome: (1) prevention of increases in PVR by averting pain, anxiety, acidosis, hypercarbia, and hypoxemia; (2) maintenance of mild elevations of intravascular volume, venous return, and cardiac filling pressures; (3) prevention of large or sudden decreases in SVR or systemic BP; and (4) prevention of myocardial depression during general anesthesia.[46,287]

Treatment of Pulmonary Hypertension

Inhaled nitric oxide (iNO) selectively dilates the pulmonary vascular bed without producing systemic hemodynamic effects; this directly improves right ventricular (RV) function and may indirectly improve LV function. In patients with obstructive pulmonary hypertension, iNO can rapidly lower total pulmonary resistance (TPR) without changing systemic blood pressure. A recent study of 23 patients who received graded doses of iNO showed a positive response (TPR decreased $\geq$20%) in 18% of patients at 20 ppm iNO and in 29% at 80 ppm. Patients with predominantly right-to-left shunting, however, did not respond to iNO. Moreover, a rebound increase in TPR ($>$10%) was noted in 35% of patients after cessation of 80 ppm.[288]

Although iNO is easy to administer and may benefit parturients with pulmonary hypertension, the experience with iNO in such women is limited. Goodwin et al.[289] reported that iNO administration to a woman with Eisenmenger's syndrome during the second stage of labor and postpartum was associated with an improvement of progressively refractory hypoxemia and a reduction in PA pressure. It was discontinued after 48 h, but the woman died 2 days later, despite continued vasodilator therapy with an infusion of prostacyclin directly into the pulmonary artery.[289] Another report describes an initial reduction of hypoxemia and pulmonary arterial pressures following iNO administration to a parturient with Eisenmenger's syndrome caused by an ASD. She delivered a live infant at 34 weeks gestation but died of worsening pulmonary hypertension (HTN) and heart failure 21 days later.[290] Recently, some authors have suggested that iNO may lead to good pregnancy outcomes in women with severe primary pulmonary HTN.[291]

Monitoring

Supplemental oxygen should be administered with high-flow masks, and women should receive adequate anxiolytic medication before placing invasive monitors or performing obstetric or anesthesia procedures. Pulse oximetry is an extremely valuable monitor in patients with Eisenmenger's syndrome and can provide useful information about the shunt fraction and direction.[292,293] If the syndrome arises from an uncorrected PDA, then simultaneous monitoring of SpO_2 in preductal (right hand) and postductal (left hand, feet) blood can be used to determine changes in the shunt fraction.[287] An arterial catheter and a CVP catheter yield continuous hemodynamic information, which usually shortens the response time for effectively treating acute hypotension. When CVP decreases, efforts should focus on augmenting venous return by expanding intravascular volume or decreasing venous capacitance.

Spinnato et al.[46] have strongly recommended the use of a PA catheter for patients with Eisenmenger's syndrome, but many clinicians disagree strongly with this advice for several reasons: (1) attempts to insert the catheter may trigger malignant arrhythmias; (2) the catheter may be difficult to position properly owing to RV failure and a large VSD; (3) the catheter provides a nidus for thrombus formation and an entry route for infectious agents or air, which can traverse the shunt and cause paradoxical embolism; (4) severe pulmonary HTN increases the risk of the catheter rupturing a pulmonary artery; (5) PVR is fixed, so the PA pressure is known to be at the systemic level; (6) PCWP may be unreliable owing to the hypertrophic changes in the pulmonary circulation; (7) the cardiac output measurements are spurious and calculations of PVR misleading due to the shunt; and (8) PVR is typically unresponsive to therapy with pulmonary vasodilators.[287,294–297] Thus, the value of data obtained from a PA catheter does not seem to justify the risks of this technique in a patient with Eisenmenger's syndrome.[295]

Anesthetic Techniques

Optimal anesthetic management requires constant and effective communication among the members of the multidisci-

plinary team. In this way, the need for an emergency cesarean delivery under general anesthesia, with its inherent risks, is minimized. Effective analgesia is essential to prevent adverse hemodynamic responses to labor and delivery. Therefore, it is important to manage anticoagulation therapy so that neuraxial analgesia will not incur an excessive risk of an epidural-spinal hematoma. For example, it is advisable to discontinue LMWH at least 3 days before the planned delivery, substituting therapy with unfractionated heparin, which has a more predictable duration of action and an effect that is easier to monitor and reverse. If regional anesthesia is contraindicated, then an intravenous infusion of a potent opioid such as remifentanil, with or without[298] patient-controlled analgesia (PCA), may be the next best option for achieving acceptable pain relief. However, the quality of analgesia typically pales in comparison with that produced by a neuraxial block.[299]

An epidural technique with intrathecal opioids is preferred for labor and delivery.[46] Loss of resistance to saline (instead of air) is the method used to locate the epidural space. A CSE technique may be advantageous. Intrathecal fentanyl can be used during the first stage of labor, supplementing with a dilute solution of local anesthetic, as needed. An epidural infusion of bupivacaine and fentanyl into the epidural space should provide excellent analgesia throughout labor and delivery without producing hemodynamic lability. If fetal distress develops, the epidural block can be intensified and slowly extended to a level of T5 (e.g., 2% lidocaine without epinephrine) to provide a surgical anesthesia within 5 to 10 min. During the second stage of labor, the anesthetic should be dense enough to allow a forceps delivery without discomfort to the patient. When hypotension develops, the adequacy of uterine displacement should be assessed and systemic vascular tone restored with IV phenylephrine.

A neuraxial block using a catheter technique is also the preferred anesthetic for a cesarean delivery.[46,297,300] A single-shot spinal is contraindicated because it can cause a sudden drop in SVR, which increases right-to-left shunting.[284,301] The key to safe use of spinal[300] and epidural anesthesia is the slow, incremental injection of local anesthetic dose while contemporaneously and cautiously correcting any potentially adverse hemodynamic trends. The block can be extended slowly to a level of around T5 using 2% lidocaine (without epinephrine). Epidural or spinal morphine is most useful for postoperative pain management.[302] If this option is not technically feasible, continuous PCA should be considered.

General anesthesia can exacerbate a right-to-left shunt and worsen cyanosis by several mechanisms. First, many anesthetics decrease SVR and lower cardiac output by increasing venous capacitance or causing myocardial depression. Second, anesthetics that are given rapidly in high doses can profoundly depress the circulation and overwhelm the reflex mechanisms that restore circulatory homeostasis. Third, both positive pressure ventilation and volatile anesthetics can decrease the venous return. Finally, volatile anesthetics decrease uterine tone and predispose to uterine atony, which can lead to hypovolemia and hypotension. Blood loss needs to be replaced rapidly while exercising caution to prevent excessive expansion of the intravascular volume.

Lipophilic opioids, such as fentanyl, sufentanil, and remifentanil, are useful components of a general anesthetic because they suppress neuroendocrine stress responses to surgery without causing cardiovascular depression. Except for remifentanil, opioids that are given to the mother in high doses should be expected to cause neonatal respiratory depression. The neonatologist or pediatrician in attendance should be informed that the mother has received a large amount of opioid. Neonates will require ventilatory support until the opioid is either metabolized or antagonized pharmacologically. Additionally, opioids (unlike volatile anesthetics) do not relax uterine smooth muscle or cause uterine atony.

Tay et al.[303] documented a successful GA and pregnancy outcome for a woman with Eisenmenger's syndrome and heart failure (NYHA class IV) in which they flagrantly violated the "don'ts" for managing such patients. An emergency cesarean delivery was required when the woman's functional status deteriorated acutely in the 37th gestational week. Hemodynamic monitoring included a PA catheter. The anesthetic, which included a rapid sequence induction with etomidate, fentanyl and succinylcholine and maintenance with isoflurane and nitrous oxide 50% in O_2, was unremarkable. She received parenteral morphine for analgesia and mechanical ventilation for the first postoperative day. When she returned home after an uneventful recovery, her cardiac functional status was NYHA class II.

Women with Eisenmenger's syndrome require careful monitoring in the early postpartum period, when major complications are most likely to occur.[279] Because hypovolemia will increase pulmonary-to-systemic shunting, it must be corrected expeditiously. If the blood loss has been minimal, however, the rapid expansion of intravascular volume that follows delivery can lead to congestive heart failure, or cause it to worsen.

Primary Pulmonary Hypertension

Primary pulmonary hypertension (primary pulmonary HTN) is associated with a maternal mortality of 30% to 40%[304] and a poor fetal outcome, with high incidences of fetal loss, prematurity, and fetal growth restriction.[304] Unfortunately, women who are at highest risk for CV deterioration during pregnancy are often difficult to identify on the basis of their preconceptual clinical appearance.

Pulmonary Vasodilator Therapy

Primary pulmonary HTN often responds, at least partially, to therapy with pulmonary vasodilators. Supplemental oxygen is a superb pulmonary vasodilator and should be used routinely for these patients. Other agents that have been used to

lower PVR include nitroglycerin, nitric oxide,[291,305,306] calcium antagonists,[305,307] prostaglandins,[307] and endothelin antagonists.[308,309]

Successful short-term use of calcium antagonists has been reported in patients with primary pulmonary HTN during pregnancy[307] and in the postpartum period.[305] Nitric oxide can improve pulmonary HTN that is refractory to other therapy. Prostaglandins have also been documented to lower pulmonary pressure for brief periods during pregnancy.[307,310] Recently, Stewart et al. reported a successful maternal-fetal outcome in a woman with primary pulmonary HTN who received epoprostenol throughout pregnancy.[311]

Additional promising medications for severe pulmonary HTN are on the horizon but have not yet been evaluated in pregnant women. Simonneau et al.[312] reported that treprostinil (a stable prostacyclin analogue) increases exercise capacity and decreases dyspnea, and beraprost (an orally active prostacyclin analogue) produces sustained clinical and hemodynamic improvements. Similarly, bosentan, an endothelin-receptor antagonist, was reported to increase exercise capacity and improve hemodynamics.[308,309] Because primary pulmonary hypertension is associated with a poor outcome of pregnancy, it is likely that pregnant women will be treated with some of these new agents in the near future.

Obstetric Management

Women who have pulmonary HTN should be informed about the high maternal mortality rates associated with this condition and be advised to avoid pregnancy. Estrogen-containing oral contraceptives may exacerbate pulmonary HTN and are not recommended for such women. If conception occurs, women should be offered the option of terminating the pregnancy.[313]

Elevations of intravascular volume and cardiac output during pregnancy increase the workload of the right ventricle and can lead to RV failure and cyanosis. Symptoms typically develop in the second trimester[305] and include fatigue, exertional dyspnea, dependent edema, chest pain, palpitations, nonproductive cough, hemoptysis, and syncope. Maternal deaths typically occur within hours of delivery or several days postpartum.[314] The exact cause of death may be elusive, although the common mechanisms are RV ischemia and failure, arrhythmias, and pulmonary embolism.

During pregnancy, physical activity should be restricted to reduce the circulatory burden. The incidence of preterm delivery is increased in these women. Because of the very high incidence of thromboembolism during pregnancy and postpartum, anticoagulant therapy is recommended throughout gestation, or at least during the third trimester and early postpartum period.[315] The benefit of such therapy, however, remains to be determined.

An assisted vaginal delivery is recommended using the modifications described in Table 12.16.[314] Women with primary pulmonary HTN should be managed in an intensive care setting for several days following delivery because this is when the risk of sudden death is highest.

Anesthetic Management

Conceptually, primary pulmonary HTN is more straightforward to manage than Eisenmenger's syndrome because no pulmonary-to-systemic shunt exists, and the pulmonary vasculature will more often respond to vasodilator therapy. However, severe pulmonary HTN, whether primary or secondary, markedly limits the ability to compensate hemodynamically for decreases in systemic BP. The goals for hemodynamic management of women with primary pulmonary HTN are similar to those for Eisenmenger's syndrome listed earlier.[302,313,314,316–322]

Monitoring typically includes arterial and CVP catheters. A PA catheter can help guide therapy when PVR is not fixed and is responsive to vasodilator therapy.[310] There are no clear guidelines about the use of a PA catheter in these women: some clinicians avoid them,[314] others embrace them.[310]

Continuous neuraxial analgesia is preferred for labor and delivery, using a low dose of local anesthetic and fentanyl.[314] Epidural anesthesia blunts the stress of labor, without hemodynamic compromise.[302,314,316,321,323] Alternatively, effective analgesia can be achieved using intrathecal fentanyl for the first stage of labor,[302] and an early pudendal block for the second stage.

General anesthesia is well tolerated in some cases,[310] but may lead to maternal death in others.[314] Anesthetic agents that elevate pulmonary vascular resistance or cause myocardial depression should be used with caution. Such agents can exacerbate pulmonary HTN and precipitate RV failure. Although positive pressure ventilation reduces the venous return and pulmonary blood flow, it has been used successfully both intraoperatively and postoperatively.[310]

Myocardial Infarction

Katz[324] first described the occurrence of myocardial infarction (MI) during pregnancy in 1922. Subsequently, many reports and reviews on pregnancy-related MI have been published.[325–328] The incidence of MI during pregnancy has been estimated at 1 in 10,000 deliveries and appears to be rising because more women with multiple risk factors are becoming pregnant.

Several risk factors for intrapartum MI have been identified (Table 12.19). Most infarctions during pregnancy affect women over 30 years of age,[329] and multigravidas are at higher risk than primigravidas.[330] Such findings parallel current demographic trends. Average maternal age is increasing, as more women are completing their education or establishing careers before starting a family. More young women are smoking cigarettes, experiencing stress in the workplace, and using cocaine.[331] Diabetes mellitus, recent use of oral con-

Table 12.19. Risk factors for coronary artery disease in pregnant women.

Advanced age (age greater than 35 years)
Multigravidas
Oral contraceptives (use during preceding decade)[332]
Cigarette smoking[334]
Hypercholesterolemia with decreased HDL (prepregnancy)[a]
Diabetes mellitus
Hypertensive disorders (including preeclampsia-eclampsia)[333,334]
Family history of coronary disease

HDL, high density lipoprotein.
[a]Total cholesterol, low-density lipoprotein (LDL), cholesterol, and triglyceride levels are significantly increased during normal pregnancy.

traceptives (OCP),[332] and hypertensive disorders[333,334] increase the risk of an intrapartum MI. However, the presence of multiple concurrent risk factors dramatically increases this risk dramatically: heavy smoking or HTN and concurrent use of OCP (especially with high doses of estrogen) may increase the risk 20-fold.[334]

The impact of a prior MI on a subsequent pregnancy is unclear. Frenkel et al.[335] reviewed 24 pregnancies in women who had a previous MI; none of these women had complications related to the prior infarction. The authors suggest that a good pregnancy outcome can be expected in women who conceive after an MI if they are managed carefully with strict supervision.[335]

Pathophysiology

The etiology of MI in pregnancy is multifactorial. Coronary artery morphology was studied in 54% of patients ($n = 125$) who had an MI during pregnancy.[330] Coronary atherosclerosis with or without intracoronary thrombus, was found in 43% of patients, coronary thrombus without atherosclerotic disease in 21%, coronary dissection in 16%, and normal coronary arteries in 29%.[330]

An MI that is unrelated to atherosclerotic disease may result from coronary spasm or thrombosis, precipitated by factors such as pregnancy-induced HTN or the administration of ergot alkaloids, bromocriptine, oxytocin, and prostaglandins (Table 12.20). Peripartum infarctions are often caused by a dissection of a coronary artery usually in the immediate postpartum phase. About 80% of dissections involve the left anterior descending artery, and nearly 20% are in the right coronary artery. Other potential causes of an intrapartum MI include pheochromocytoma, collagen vascular diseases, Kawasaki disease, sickle cell anemia, hemostatic abnormalities, and use of illicit drugs, especially cocaine. Cocaine can precipitate an MI by inducing tachycardia, coronary artery spasm, coronary thrombosis, HTN, or arrhythmias and by accelerating atherosclerotic disease.[336–340]

Table 12.20. Causes of myocardial ischemia (MI) during pregnancy.

Atherosclerotic coronary artery disease.
Coronary artery injury in the absence of atherosclerotic disease, from vasospasm, dissection, aneurysm, hematoma.
Severe hypertensive disorders, including pheochromocytoma, cocaine abuse.
Marked imbalance of myocardial oxygen supply to demand relationship, especially with coexisting cardiovascular disease, caused by severe tachycardia in association with LVH, hypotension, hypoxemia, or anemia.
Severe aortic stenosis or aortic regurgitation.

LVH, left ventricular hypertrophy.

Morbidity and Mortality from Myocardial Infarction During Pregnancy

A literature review of pregnancy-related myocardial infarctions from 1922 to 1983 identified 68 occurrences, with an overall mortality rate of 37%. The stage of the pregnancy in which the MI occurred was noted to be a significant risk factor. Maternal mortality rate for an MI was 23% in the first or second trimester, 45% in the third trimester, and 50% for an MI that occurred within 2 weeks of delivery. Perinatal and maternal mortality rates were highly correlated.[325] In a more recent study, Badui and Enciso[329] reviewed 109 reports on the subject, involving 136 patients. The average maternal age was 32 years, and 43% of these women had no coronary risk factors. In 47% of the cases studied, there was no significant atherosclerotic disease. Nearly 75% of the infarctions involved the anterior wall. In the series, 26 deaths occurred, constituting an overall maternal mortality rate of 19%; the mortality rate was higher during the third trimester, labor, and puerperium. Eight (31%) had sudden death (5 had coronary thrombosis). The perinatal mortality rate was 16.9%; 52% of fetal deaths were coincidental with that of the mother.[329]

In brief, infarctions typically occur in the third trimester. Most maternal deaths occur at the time of the infarction or around delivery (especially if it occurs soon thereafter).[330] The mortality rate is very high for women with severe preeclampsia who have a postpartum MI.[341] Presently, the overall maternal mortality rate for women having a peripartum MI is about 20%.[329]

Diagnostic Considerations

The diagnosis of ischemic heart disease in pregnant women may be overlooked or delayed for several reasons: (1) MI rarely occurs in pregnant women; (2) diagnostic procedures may present a risk to the fetus; and (3) CV changes of normal pregnancy and ischemic heart disease (IHD) can be similar, so manifestations of IHD may be dismissed as being normal (see Tables 12.3, 12.4). Furthermore, plasma creatinine kinase and myoglobin can increase twofold 30 min after delivery without IHD. In contrast, the plasma level of troponin I provides a useful test for peripartum MI, because it remains within normal limits unless myocardial injury has occurred.

The history and physical examination should focus on risk factors for an intrapartum MI and identify coexisting condi-

tions that unfavorably affect the O_2 supply to demand relationship and prognosis (Figure 12.6). Such conditions include hypertensive disorders, arrhythmias, congenital heart lesions, anemia, medication, and use of illicit drugs. A toxicology screening should be obtained. The diagnostic workup should include serial 12-lead EKG, cardiac enzymes, coagulation profile, electrolyte profile, hematocrit, routine liver enzymes, blood urea nitrogen (BUN), creatinine, glucose, urinalysis, and baseline arterial blood gases. Echocardiography should be performed to evaluate myocardial function and the status of the heart valves. If there is evidence of progressive ischemia or impending infarction, a cardiac catheterization should be performed immediately, using lead shielding that covers, but does not compress, the abdomen.

Medical Management

The key to optimizing the outcome of a pregnancy complicated by an intrapartum MI is careful attention to the needs of both the mother and fetus, using a multidisciplinary team approach. Strict control of maternal hemodynamics will help optimize the balance between myocardial oxygen supply and demand (see Figure 12.6).[342] In general, the medical management for IHD is similar for pregnant and nonpregnant women. There needs to be a search for, and expeditious treatment of, coexisting disorders that can exacerbate IHD (e.g., anemia, untreated hypertension, thyrotoxicosis, drug abuse, infection). The cause of the ischemia needs to be determined because it may affect management decisions.

The initial treatment must be aggressive. The cardiology team should be consulted, and the woman should be evaluated immediately because of the high risk for sudden death. It is important not to overlook the need for uterine displacement, supplemental oxygen (high flow via face mask), intravenous access, and continuous monitoring of the mother and fetus. Women should be managed in a critical care setting until the ischemia resolves and hemodynamically stability is assured. Heparin therapy (low-dose, SC) is usually needed to reduce the risk of deep venous thrombosis secondary to venous stasis and bedrest. Women who have ventricular dyskinesis or hypokinesis, or a ventricular aneurysm, require a higher degree of anticoagulation to prevent mural thrombosis and thromboembolism (e.g., IV heparin, with PTT maintained at twice normal level).[343] Generally, IV heparin is discontinued at least 6 h before surgery, allowing the PTT to return to the normal range before delivery. In an emergency, protamine or fresh-frozen plasma (FFP) may be needed to restore normal coagulation.

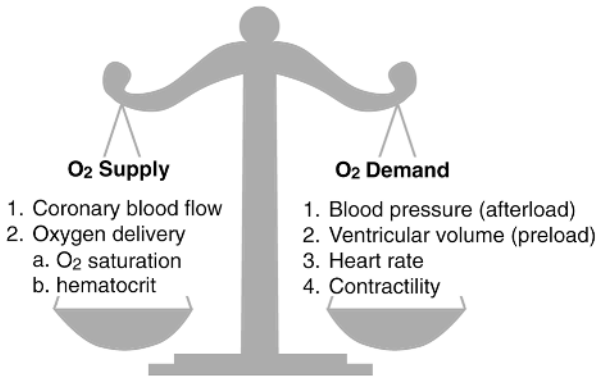

FIGURE 12.6. Factors that affect the balance between myocardial oxygen supply and demand. (From Reich DL, Brooks JL, Kaplan JA. Uncommon cardiac diseases. In: Katz J, Benumof JF, Dadis LB (eds) Anesthesia and Uncommon Diseases. Philadelphia: Saunders, 1990:347, with permission.)

Invasive monitoring and strict control of all CV parameters is essential when hemodynamic instability occurs or is anticipated. Rao et al.[344] reported that intensive postoperative CV care, which included invasive hemodynamic measures, lowers the perioperative mortality rate for individuals with a history of a prior MI. Women who have an intrapartum MI will almost certainly require an operative procedure delivery and anesthesia during the ensuing 3 months, when the risk of reinfarction and perioperative mortality is greatest.[345] Abdominal surgery might further increase this risk.[346]

Efforts should be made to minimize peripartum CV stress. If left ventricular failure develops, it must be aggressively treated. Initial therapy usually includes digitalis and diuretics, proceeding to agents such as dopamine, dobutamine, or norepinephrine if needed, despite their potentially adverse effects on placental perfusion. Tachycardia requires immediate correction. An intraaortic balloon pump (IABP) might help when myocardial deterioration continues unabated despite medical therapy, although an IABP predisposes to thromboembolic risks, which may be especially high during pregnancy. In this setting, interventions such as percutaneous transluminal coronary angioplasty and stent placement, or coronary artery bypass grafting, merit strong consideration.

Refractory congestive heart failure has been reported to improve dramatically shortly after cesarean delivery.[347,348] Listo and Bjorkenheim[347] described a parturient who had an anterior MI complicated by cardiogenic shock and fetal death. The mother's pulmonary edema began to resolve immediately after an abdominal delivery. In another instance, a woman having an intrapartum MI went into preterm labor and subsequently developed heart failure, which required invasive monitoring and inotropic support.[348] Her condition improved rapidly after a cesarean delivery, suggesting that immediate delivery or termination of pregnancy may help protect a stunned but viable myocardium.[348]

Interventional Cardiac Procedures

Percutaneous transluminal coronary angioplasty[341,349,350] with stent placement[351] and CPB surgery[352–355] have been performed successfully during pregnancy.[349,351,353–355]

Thrombolytic therapy has an important role in the management of acute MI; it reduces mortality rates and limits in-

farct size.[356,357] Tissue plasminogen activator (TPA) has a short half-life and is unlikely to cross the placenta because of its high molecular weight (65,000 daltons). Successful intrapartum therapy with TPA in the second trimester has allowed pregnancy to continue, with good maternal and perinatal outcome.[358] Thrombolytic agents are being used in an increasing number of patients, yet, concerns remain about the safety of TPA during pregnancy. Therapy with TPA may be associated with an increased risk of placental abruption, intrauterine hemorrhage, and fetal demise, and its administration near delivery can increase blood loss from an operative procedure.

Obstetric Management

Hankins et al.[325] reviewed 68 cases of MI in pregnancy that occurred between 1925 and 1985 and noted that the survival rate was slightly higher among women who had vaginal delivery instead of a cesarean delivery. At present there is no consensus regarding the optimal method of delivery for a woman who has had an intrapartum MI. In each instance, the pros and cons of a vaginal versus a cesarean delivery should be compared.[359] A scheduled cesarean allows the timing of delivery to be controlled and avoids the stresses of a prolonged labor and maternal expulsive efforts. However, an assisted vaginal delivery (Table 12.16) using continuous neuraxial anesthesia can similarly circumvent the hemodynamic stress of parturition. Disadvantages of a cesarean delivery may include a greater blood loss, higher rate of infection, more pulmonary morbidity, delayed ambulation, and more postpartum pain. However, epidural or intrathecal morphine typically provides excellent postoperative analgesia, and should minimize concerns about pain after a surgical delivery.

Determining the optimal timing of delivery requires a risk–benefit analysis based on maternal CV stability and fetal lung maturity. When possible, it is desirable to maintain the fetus in utero until the lungs are determined to be mature. Then, it seems prudent to deliver the fetus to limit the continued stress of pregnancy on the mother. However, if uncontrolled maternal decompensation precedes fetal maturity, immediate delivery is warranted because maternal considerations take precedence.

In summary, it seems reasonable to reserve cesarean section for obstetric indications unless maternal hemodynamic instability mandates delivery. Synthetic oxytocin is safe to use for the induction of labor and for the treatment of postpartum uterine atony in women with coronary artery disease. However, a large bolus or a rapid infusion of oxytocin may cause hypotension and should be avoided.

Anesthetic Management

Providing anesthesia for women who have suffered an MI during pregnancy requires careful control of CV parameters via invasive monitoring, and the implementation of measures to optimize the myocardial oxygen supply-to-demand relationship (Table 12.21). Tachycardia not only decreases the supply of oxygen to the myocardium, but also increases the oxygen demand of the heart. Therefore, elevations of heart rate should be prevented or treated by ensuring adequate analgesia and using beta-blockers. The oxygen demand also rises when cardiac contractility or wall stress increases, and when metabolic rate increases due to shivering or elevated temperature. Information obtained from a central venous or PA catheter provides a rational basis for administering fluids and CV medication to optimally modulate cardiac filling pressures.

TABLE 12.21. Determinants of myocardial oxygen supply and demand.

Factor	Effect of pregnancy
Determinants of oxygen supply	
Diastolic time	Decreased
Coronary perfusion pressure	May be decreased
Arterial oxygen content	
Arterial oxygen tension	Increased
Hemoglobin concentration	Decreased
Coronary vessel diameter	Unchanged
Determinants of oxygen demand	
Basal oxygen requirements	Increased
Heart rate	Increased
Wall tension	
Preload (LV end-diastolic volume)	May be increased
Afterload (LV wall stress)	Decreased
Contractility	Increased

LV, left ventricle.

When a vaginal delivery is to be attempted, the parturient needs to be in a highly monitored setting throughout labor and delivery, with continuous anesthesia staffing. She should receive supplemental oxygen and intravenous sedatives and anxiolytics as needed to keep her relaxed and calm. Invasive monitoring should be instituted. A continuous neuraxial technique is an excellent choice for labor and delivery[331,360–362] and should be initiated before the onset of painful uterine contractions. A dilute local anesthetic solution with fentanyl can provide effective labor analgesia without hemodynamic compromise. Maintaining a high level of analgesia helps ensure that neuraxial anesthesia can be provided if a cesarean delivery is urgently required because of fetal distress or maternal decompensation. The analgesia should be sufficiently dense during the second stage of labor so that (1) the parturient lacks an urge to push, (2) a forceps delivery can be accomplished painlessly, and (3) the anesthesia level can be rapidly and effectively extended for an emergency cesarean delivery. Postoperatively, the parturient should be monitored intensively in a critical care setting for several days. Postpartum analgesia for an episiotomy or perineal tear may be provided with epidural or intrathecal opioids or with PCA as necessary.

Anesthesia for an elective cesarean delivery is seemingly less complex than for a vaginal delivery. A scheduled ce-

sarean allows necessary personnel and equipment to be present at delivery; it also circumvents the risks of labor, including obstetric emergencies associated with an attempted or failed vaginal delivery. Epidural anesthesia is the preferred technique for cesarean delivery.[361,362] It is probably best to use a local anesthetic solution that does not contain epinephrine (e.g., 2% lidocaine plain, ropivacaine, levo-bupivacaine). An accidental intravascular injection of epinephrine can cause marked tachycardia and HTN, whereas intravascular absorption of epinephrine from the epidural space may simultaneously increase heart rate and decrease BP. The block should be established slowly, while phenylephrine and intravenous fluids are administered to prevent or counteract any adverse hemodynamic effects of the associated sympathetic block. A block to the T3 dermatome interrupts the cardiac sympathetic outflow, which may lower heart rate and prevent coronary spasms that result from intense stimulation of the sympathetic nervous system.[363,364] Adjunctive administration of epidural fentanyl improves the quality of the anesthetic, whereas epidural morphine provides effective and long-lasting postoperative analgesia. Similar benefits can be derived from a CSE technique or a carefully conducted continuous spinal anesthetic. However, a continuous spinal via a standard epidural catheter causes a post dural puncture headache in nearly 70% of women, which would impose an additional CV stress. A single-shot spinal anesthetic is best avoided because it produces a rapid sympathectomy, which can result in severe hypotension.

If regional anesthesia is contraindicated due to coagulopathy or infection, the general anesthetic technique used should minimize the hemodynamic responses to laryngoscopy and tracheal intubation and promote CV stability throughout the perioperative period. Rapid sequence induction with thiopental and succinylcholine, the technique selected for most healthy pregnant women, is usually associated with tachycardia and labile hemodynamics. The preferred method for women with ischemic heart disease is often referred to as a "cardiac anesthetic." This technique uses a high dose of a lipophilic opioid (e.g., remifentanil or fentanyl) to optimize hemodynamic stability in the presence or absence of nociceptive stimulation.

Following delivery, these women remain at high risk for major cardiac complications, including MI and congestive heart failure. They may require monitoring in an intensive care setting for several days after delivery. Keeping the epidural catheter in place may be advantageous for two reasons: (1) effective postoperative analgesia is paramount and may be best achieved by epidural administration of medications; and (2) the epidural-associated sympathectomy may help to prevent, or to treat, pulmonary edema, which occurs in the postpartum period. However, for women who require postpartum anticoagulant therapy, the epidural catheter should be removed before the initiation of such therapy to minimize the likelihood of a spinal-epidural hematoma.

Diseases of the Great Arteries (Aorta)

Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant disorder with a prevalence of 2 to 3 per 10,000 individuals. Women with MFS have a 50% chance of having an offspring who inherits the condition. MFS is a result of mutations in the FBN1 gene (on chromosome 15q) that encodes fibrillin-1, an extracellular matrix component of microfibrils.[365] Prenatal diagnosis has been mainly performed in familial cases by linkage analysis, but mutation detection is now available.[366] Manifestations of MFS range from skeletal overgrowth and cutaneous striae to ectopia lentis and aortic dilatation leading to dissection.[367] MFS may also be responsible for cervical incompetence, abnormal placentation, and postpartum hemorrhagic complications.[368]

The complications of greatest concern during pregnancy include (1) dilation of the ascending aorta, which causes aortic regurgitation and congestive heart failure; and (2) dissection of the proximal and distal aorta with involvement of the iliac and coronary arteries.

Interaction with Pregnancy

The physiologic adaptations to pregnancy, including increases in cardiac output, hormonal effects on connective tissue, and stresses of labor and delivery can lead to CV complications in women with MFS.[369] If major CV abnormalities, such as aortic regurgitation, aortic dilation, and prior aortic dissection, exist before conception, the risk for morbidity and mortality during pregnancy will be very high.[224,370] In contrast, if MFS is not associated with significant CV involvement, pregnancy will generally be well tolerated. In either case, women still require monitoring for evidence of aortic dissection.[369,371–373] Most complications develop in the late phase of pregnancy.

Obstetric Management

Women with MFS should receive preconceptual counseling to discuss potential maternal and fetal risks. Those who become pregnant and have major CV involvement (e.g., aortic dilation, a history of aortic dissection, or a progression of aortic dilatation with cardiac dysfunction)[374] should be made aware of the high risks of maternal mortality and counseled regarding the option of termination. In contrast, women with minor involvement of the CV system and an aortic diameter of less than 4 cm are unlikely to have major CV complications during pregnancy.[371] However, aortic dissection may still occur in women who have a normal size aorta preconceptually.[375]

The aorta and heart (e.g., size of aortic root, status of aortic and mitral valves) should be evaluated before conception and monitored at regular intervals during pregnancy. Trans-

esophageal echocardiography can detect aneurysms and dissections that involve the descending aorta, so this is preferable to a transthoracic examination. Beta-blocker therapy and restriction of vigorous physical activity are advisable to reduce the rate of aortic dilatation and the risk of complications. If substantial aortic dilation occurs during pregnancy, therapeutic abortion or surgical intervention should be considered. A cesarean delivery is generally preferred for women with aortic dilation, aortic dissection, or other cardiac complications, because it circumvents hemodynamic stresses of labor and vaginal delivery.

Pain and anxiety must be controlled during parturition and postpartum, even if this requires significant sedation. Delivery of the fetus should be in accordance with the principles detailed in Table 12.16. The Valsalva maneuver is to be avoided.

Anesthetic Management

Anesthetic management focuses on minimizing aortic root shear forces and wall stress by using invasive monitoring, pharmacologic therapy, and anesthetic techniques to prevent peripartum pain.[376] Uneventful epidural anesthesia[377,378] or general anesthesia[369,379] for cesarean delivery can be achieved even for fetal distress, in the presence of recurrent aortic dissection,[372] with careful preoperative planning and perioperative monitoring.

The key to successful management is strict control of BP and minimization of vascular shear stress. Sudden increases in myocardial contractility BP will increase shear stress. Tachycardia and HTN should be treated aggressively. Invasive hemodynamic monitoring is warranted for women at high risk for aortic dissection. An arterial catheter allows continuous monitoring of BP, and a CVP catheter provides information about the adequacy of intravascular volume status and serves as a conduit for administering vasoactive medications directly into the central circulation.

Some women require expansion of their intravascular volume and beta-blocker therapy before delivery. A continuous neuraxial block is the anesthetic technique of choice. Anesthetic medications should be carefully titrated to effect, and BP should be supported using intravascular volume expansion and incremental doses of phenylephrine as dictated by the clinical situation. Positive inotropic agents, such as ephedrine, epinephrine, calcium, dopamine, or dobutamine, should be used with extreme caution in women who have significant aortic pathology. Methergine should also be used with caution, because it can induce large increases in BP.

Continuous monitoring and control of heart rate and BP should be maintained through the early postpartum period because cardiac output remains elevated during this time. Blood loss should be replaced expeditiously with appropriate crystalloid solutions or blood products.

Coarctation of the Aorta

Coarctation of the aorta is rare, affecting 1 per 2000 to 3000 women.[380] Patients with coarctation of the aorta may present with HTN of unknown etiology.[381–383] When HTN is a result of aortic coarctation, blood pressure in the right upper extremity is usually higher than in the left-sided extremities.[384] The electrocardiogram may show LVH.

Individuals with aortic coarctation have an increased likelihood of having a bicuspid aortic valve, an aortic aneurysm, and a cerebral aneurysm in the circle of Willis. Therefore, they may be at increased risk for aortic rupture or dissection, or cerebral hemorrhage from rupture of a cerebral aneurysm during pregnancy. If aortic coarctation is corrected, and no other congenital anomalies exist, pregnancy is usually uneventful.[384,385] An arm-to-leg BP gradient of less than 20 mm Hg after coarctation repair is correlated with a favorable outcome of pregnancy.[386] The incidence of preeclampsia is similar to that in the general population, and the occurrence of congenital heart disease in the offspring is approximately 3%.[382,386] In contrast, women who have an uncorrected lesion are at increased risk for developing LV failure, aortic rupture or dissection, and endocarditis.[382,384] Fetal mortality may approach 20% because of low uterine arterial pressure.[387] If women have cardiac dysfunction or cyanosis during pregnancy, their offspring have a very high incidence of congenital heart disease. Thus, it is advisable to correct aortic coarctation before pregnancy.[273,386]

Measures to reduce the risk of aortic dissection and rupture of cerebral aneurysms during pregnancy consist of limiting physical activity and controlling BP. However, if BP reduction is excessive, uteroplacental blood flow may be compromised, with adverse consequences. Surgical correction of coarctation has been performed successfully during pregnancy and may be indicated for severe, uncontrolled systolic HTN or heart failure.

Anesthetic Management

The anesthetic goals for uncorrected aortic coarctation include maintaining slight elevations of intravascular volume, heart rate, and arterial BP. Invasive BP monitoring may help during labor and delivery. Postductal pressures (e.g., left radial artery) provide a better indication of uterine perfusion pressure than preductal pressures (e.g., right radial artery).

Neuraxial analgesia is a good choice for labor and delivery, although ephedrine or dopamine administration may be needed to meet the aforementioned hemodynamic goals. The hemodynamic goals for women undergoing cesarean delivery can be achieved easily with general or regional anesthesia. Nonetheless, neuraxial anesthesia is usually preferred to general anesthesia because it produces less circulatory lability and is associated with a lower overall risk (lower potential for airway disasters to occur) of maternal morbidity and mortality. However, an opioid-based general anesthetic is an excellent choice for an urgent cesarean delivery, or in a clinically compromised patient. Remifentanil has been reported to provide hemodynamic stability with minimal neonatal respiratory depression, and it allows immediate postoperative tracheal extubation of the mother.[388]

Takayasu Arteritis

Takayasu arteritis (TA) is an occlusive thromboaortopathy. This uncommon disorder primarily affects young women and may be diagnosed initially during pregnancy.[389,390] A study of C-reactive protein scores and digital plethysmography showed improvements rather than deterioration of TA with pregnancy.[9] Although recent publications have reported favorable maternal outcome, these women occasionally develop large increases in BP,[383,391] heart failure, and massive hemoptysis during pregnancy.[391] Perinatal outcome is usually favorable despite the increased incidence of fetal growth restriction and preterm births associated with TA. The mode of delivery is usually vaginal with forceps to expedite the second stage of labor. Cesarean delivery is performed mainly for obstetric indications or for maternal hypotension and vascular disorders.

Anesthetic Management

Patients with TA should be evaluated to determine the anatomic pattern of the disease and for HTN and its complications. The anesthetic plan should be developed with the recognition that the later stages of pregnancy may be associated with worsening HTN and ischemic symptoms, as well as cardiac failure and cerebral hemorrhage. Noninvasive blood pressure (NIBP) monitoring appears to provide simple and reliable BP measurements, even in patients with pulseless extremities. Blood pressure during anesthesia should be maintained at a level that approximates the preoperative value. Beta-blocker therapy is indicated for HTN, even in women who have severe aortic regurgitation.[392] Neuraxial blockade is preferred for the anesthetic management of labor and delivery. Satisfactory anesthesia for cesarean delivery can be provided using standard epidural[393,394] and CSE techniques,[395] without untoward effects on hemodynamic parameters.[396] If the disease involves the carotid arteries, regional anesthesia is distinctly preferable to general anesthesia because monitoring of consciousness allows neurologic dysfunction to be detected promptly. In one report, a woman with severe bilateral carotid artery stenoses adamantly refused regional anesthesia for a cesarean delivery, so processed electroencephalography was used to monitor for cerebral ischemia. The general anesthetic and operation were conducted without incident.[397]

Hypertensive Disorders in Pregnancy

Hypertension (HTN) during pregnancy is present when systolic BP is 140 mm Hg or higher or diastolic BP is 90 mm Hg or higher. Hypertensive disorders that occur during pregnancy can be divided into four broad categories: gestational HTN, preeclampsia–eclampsia, pregnancy-aggravated HTN, and coincidental HTN (Table 12.22). Such disorders complicate 12% to 22% of pregnancies and are a major source of maternal and perinatal morbidity and mortality; they account for approximately 18% of maternal deaths. Maternal complications include abruptio placentae, pulmonary edema, respiratory failure, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure. Perinatal concerns include prematurity, IUGR, stillbirth, and neonatal death.

TABLE 12.22. Classification of hypertensive disorders in pregnant women.

Classification[a]	Characteristics
Gestational hypertension	Induced by pregnancy and regresses postpartum No proteinuria No pathological edema
Preeclampsia (mild or severe)	Induced by pregnancy and regresses postpartum Proteinuria
Eclampsia	Preeclampsia and the occurrence of a convulsion
Pregnancy-aggravated hypertension	Underlying hypertension that is worsened by superimposed preeclampsia or eclampsia
Coincidental hypertension	Chronic hypertension that either precedes pregnancy or persists postpartum

[a]American College of Obstetricians and Gynecologists. Hypertension in pregnancy. ACOG Tech Bull 1996;219:1.

Chronic Hypertension

Chronic hypertension exists if HTN is present before the 20th gestational week and persists beyond the 6th postpartum week. It occurs in 1% to 5% of pregnancies and is associated with increases in complications (15%) including fetal growth restriction, preterm delivery, abruptio placentae, and hypertensive crisis. Risk factors for complications include maternal age of at least 30 years, long-standing HTN, and superimposed preeclampsia. Medical therapy is recommended for patients with high-risk characteristics (see Table 12.14).

Gestational Hypertension

Gestational hypertension is HTN without proteinuria that develops in a normotensive woman after the 20th week of gestation and resolves by the 6th postpartum week. Up to 25% of women with gestational HTN eventually develop preeclampsia or eclampsia. These two conditions can be difficult to differentiate from one another because proteinuria may not occur until preeclampsia is well established. Antihypertensive therapy is often initiated with labetalol or hydralazine. Pregnancy outcome is usually favorable for women with gestational HTN.

Pheochromocytoma

Although pheochromocytoma is a rare condition, it should be considered in the differential diagnosis of HTN during preg-

nancy. Failure to recognize pheochromocytoma may be lethal to both the mother and the fetus. Early recognition, diagnosis, and management by a multidisciplinary team are essential for a successful outcome.[398]

Harper et al.[399] reviewed 139 cases of pheochromocytoma that occurred in pregnant women between 1980 and 1987. Roughly half the cases were diagnosed before delivery. These authors[399] report that the maternal mortality rate is 17% overall but drops to 1% when the diagnosis is made antepartum. Causes of maternal death in untreated cases have included stroke, cardiac arrhythmia, and pulmonary edema.

Clinical Presentation

Hypertension, which may be paroxysmal or sustained, is the most constant feature of pheochromocytoma. Other manifestations include headaches, palpitations, sweating, blurred vision, anxiety, emesis, dyspnea, and convulsions. The diagnosis of pheochromocytoma is often delayed because of the rarity of this condition and the extensive overlap between the clinical findings in pheochromocytoma and those of preeclampsia or a normal pregnancy. Unlike preeclampsia, a pheochromocytoma will often (1) be present before the 20th week of gestation, (2) produce labile HTN, and (3) produce HTN without proteinuria. If a pheochromocytoma is suspected, the definitive diagnosis is straightforward because maternal catecholamine levels are not normally increased by pregnancy.[400]

Medical and Surgical Management

The immediate goal is pharmacologic control of HTN and tachycardia. Preventing severe hypertensive episodes is probably the single most important factor affecting fetal outcome; such episodes can cause uteroplacental insufficiency, placental abruption, and fetal death.

Initial therapy is with an alpha-adrenergic receptor blocker (e.g., phenoxybenzamine, prazosin), starting at a low dose that is gradually titrated upward until HTN is controlled and the patient experiences mild orthostatic hypotension and nasal congestion. Fluids should be administered liberally during alpha-receptor blockade to fill the expanded intravascular space and to maintain a vigorous urine output. Beta-blocking drugs should be reserved for patients with persistent tachycardia or tachyarrhythmias and those with predominantly epinephrine-secreting tumors. Selective beta-blockade with metoprolol or atenolol is usually preferred.

The timing of surgical resection of the pheochromocytoma must be individualized according to the adequacy of medical control of HTN, tumor size, likelihood of malignancy, and stage of pregnancy. If the situation permits, it is preferable to resect the tumor in the second trimester, when the uterus is relatively quiescent, and the risk of spontaneous abortion during surgery is low.[400–402] If the diagnosis is made in the third trimester, and symptoms and BP can be well controlled medically, surgery should be delayed until after delivery. However, it is imperative to monitor both the mother and fetus because a hypertensive crisis can be triggered by labor contractions, fetal movement, mechanical pressure from the uterus, or hemorrhage into the tumor.

Obstetric Management

The best method of delivery is controversial. A vaginal delivery may be reasonable in multiparous women whose symptoms are well controlled medically. Alternatively, the plan may be elective cesarean delivery after fetal lung maturity has been documented, followed by adrenalectomy using the same general anesthetic.[400,402]

Pregnancy After Maternal Cardiac Transplant

Cardiac transplantation has become standard therapy for many types of end-stage heart disease. The 5-year survival rate exceeds 80%, and modifications of immunosuppressive regimens have led to an improved quality of life for transplant recipients.[403] The most frequent reason for a cardiac allograft in a woman of childbearing age is viral cardiomyopathy.[404] Less common indications include ischemic cardiomyopathy, congenital heart disease,[405] and peripartum cardiomyopathy. Morini et al.[406] reviewed the outcomes of 23 such pregnancies in women with cardiac allografts and noted that many recipients have proceeded to term and delivered a normal healthy infant, either vaginally or by cesarean delivery. Successful pregnancies following heart-lung transplantation have also been reported.[407]

Physiology and Pharmacology of the Transplanted Heart

Unless allograft rejection occurs, the transplanted heart usually maintains excellent ventricular function. It is devoid of autonomic or somatic innervation,[408–412] so individuals with a transplanted heart lack the predominant autonomic tone (i.e., vagal) expressed in healthy young adults. Transplant recipients have a mild sinus tachycardia at rest and do not exhibit bradycardiac reflex responses (e.g., carotid massage) to vagal stimulation or variations of heart rate with respiration (i.e., no sinus arrhythmia). A sympathectomy from a high spinal or epidural anesthetic will not cause bradycardia by blocking cardiac sympathetic fibers because these fibers have already been ablated in transplant recipients. The chronotropic and inotropic responses to stressful stimuli are delayed in these transplant recipients. Interestingly, they regulate their cardiac output in response to exercise, although the response time is slower. This is probably through the Starling mechanism and by modulation of preload and afterload. Thus, maintenance

of adequate preload is particularly important for the maintenance of adequate cardiac output in transplant recipients.

Generally, only medications that directly stimulate receptors in the heart can produce chronotropic, inotropic, or dromotropic effects (e.g., isoproterenol does, atropine does not). Chronic denervation of the heart leads to upregulation of beta-adrenergic receptors and an increased sensitivity to cardiac effects of beta agonists.[196,412]

Medical Management

Numerous successful pregnancies have occurred and apparently normal infants have been delivered by immunosuppressed mothers who had undergone renal,[413–415] hepatic,[416,417] bone marrow,[418] pancreas,[419] and lung transplantation.[420] Such data suggest that immunosuppressive medications can be used during pregnancy without producing teratogenic effects. Immunosuppressive therapy must be continued throughout pregnancy to prevent organ rejection.[421] Strict attention to sterile technique is especially important. Prophylactic antibiotics and immunosuppressive "stress doses" of steroids are indicated before performing anesthetic or surgical procedures.

Periodic transvenous right atrial endomyocardial biopsies are performed in cardiac transplant patients to monitor for evidence of allograft rejection. When carried out during pregnancy (as early as 20 weeks gestation), the patient should receive supplemental oxygen and uterine displacement to prevent aortocaval compression. If fluoroscopy is required, the mother should have a lead shield (not a lead apron) applied directly to her abdomen, to minimize fetal exposure to ionizing radiation.

Obstetric Management

Branch et al.[422] recently evaluated pregnancy outcomes of 47 pregnancies in 35 cardiac transplant recipients. Five pregnancies were terminated because of a short interval between transplantation and conception, and there were 35 (74%) live births. The authors reported that the physiologic changes of gestation are well tolerated and that rejection episodes are rare. However, pregnancy-related complications, such as chronic HTN, preeclampsia, worsening renal failure, premature rupture of membranes, and infections, occur at higher rates in transplant recipients than in women with normal hearts. No maternal deaths occurred during pregnancy, but the rate of late maternal deaths was increased in the recipients compared to age-matched healthy women. Despite higher rates of fetal growth restriction, preterm delivery, and cesarean delivery, fetal loss was not increased in transplant recipients. None of the newborns had congenital malformations.

Most of these women have a vigorous heart and a healthy body and handle the stress of labor and delivery without problems. The mode of delivery, either vaginal or abdominal, should be decided on the basis of obstetric indications.

Anesthetic Management

The preoperative evaluation is important in a patient who has had a cardiac transplant. Frequent cardiology evaluations should be performed to monitor the status of the allograft. These patients often develop accelerated atherosclerosis; but because their heart is denervated, they rarely experience angina during periods of myocardial ischemia. The earliest manifestation of myocardial ischemia may be paroxysmal dyspnea.

A baseline 12-lead EKG should be performed, and the EKG should be continuously monitored throughout labor and delivery. If general anesthesia is required, agents that depress myocardial function should be used with extreme caution or avoided. It is important to maintain an adequate intravascular volume because these women are preload dependent.

Noninvasive monitoring is usually adequate. Invasive monitoring poses a risk of infection and arrhythmias and must be weighed against the value of data to be gained. Maintenance of intravascular volume is important because the patient's cardiac output is preload dependent. Aortocaval compression must be avoided so that venous return is not compromised. The volume changes during labor and delivery are usually well tolerated by women with normal ventricular function and no evidence of rejection.[404,423]

Efforts should be made to minimize the neuroendocrine response to labor. Cardiac transplant recipients have delivered vaginally with[408,424,425] and without[409,426] epidural anesthesia. A continuous neuraxial technique is preferred for women who desire analgesia for labor and delivery. The anesthetic level should be extended slowly, using a dilute solution of local anesthetic; this provides time for compensatory mechanisms to be activated and prevents severe hypotension. If hypotension should occur, it is important to verify uterine displacement and to administer an IV fluid bolus. The effect of ephedrine may be unpredictable because the drug has both direct and indirect effects on the heart. However, ephedrine would be expected to exert its usual effect on the peripheral vasculature. Phenylephrine should help restore BP, although the dose required may be larger than usual because of alpha-1-adrenergic receptor downregulation caused by chronically elevated plasma catecholamine levels. When a heart rate increase is needed, agents that directly stimulate cardiac beta-1-adrenergic receptors such as epinephrine, norepinephrine, or isoproterenol should be selected. The preferred agent depends on the patient's peripheral vascular resistance at the time. Atropine should not be expected to increase heart rate in a cardiac transplant recipient.

If general anesthesia is used, thiopental may have an exaggerated depressant effect on cardiac output. Ketamine may cause excessive tachycardia in these patients because of changes in beta-receptor sensitivity. An opioid-based technique is typically associated with stable hemodynamics.

Summary

As women with cardiac disease live longer and healthier lives, it is increasingly more common to encounter pregnancies in these patients. With proper preconceptual counseling, as well as intensive monitoring during pregnancy, successful pregnancy outcomes are possible. Knowledge of the appropriate obstetric and anesthetic management of each specific cardiovascular complication is essential.

References

1. Tan J, de Swiet M. Prevalence of heart disease diagnosed de novo in pregnancy in a West London population. Br J Obstet Gynaecol 1998; 105(11):1185–1188.
2. Sullivan JM, Ramanathan KB. Management of medical problems in pregnancy—severe cardiac disease. N Engl J Med 1985;313(5):304–309.
3. McFaul PB, Dorman JC, Lamki H, et al. Pregnancy complicated by maternal heart disease. A review of 519 women. Br J Obstet Gynaecol 1988;95(9):861–867.
4. Naidoo DP, Desai DK, Moodley J. Maternal deaths due to pre-existing cardiac disease. Cardiovasc J South Afr 2002;13(1):17–20.
5. Lupton M, Oteng-Ntim E, Ayida G, et al. Cardiac disease in pregnancy. Curr Opin Obstet Gynecol 2002;14(2):137–143.
6. Hess W. Cardiovascular diseases during pregnancy. Considerations for the anesthesiologist. Anaesthesist 1995;44(6):395–404.
7. Clark SL, Phelan JP, Cotton DB. Critical Care Obstetrics. Oradell, NJ: Medical Economics Books, 1987:63.
8. Siu SC, Colman JM. Heart disease and pregnancy. Heart (Br Cardiac Soc) 2001;85(6):710–715.
9. Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald E (ed) Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: Saunders, 2001:2172–2191.
10. Villablanca AC. Heart disease during pregnancy. Which cardiovascular changes are normal or transient? Postgrad Med 1998;104(4):183–184.
11. Meltzer RS, Serruys PW, McGhie J, et al. Cardiac catheterization under echocardiographic control in a pregnant woman. Am J Med 1981; 71(3):481–484.
12. Clapp JF III, Capeless EL. Cardiovascular function before, during, and after the first and subsequent pregnancies. Am J Cardiol 1997;80(11): 1469–1473.
13. Clark SL, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161(6):1439–1442.
14. Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. Am J Obstet Gynecol 1989;161(6):1449–1453.
15. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv 1994;49(12 Suppl):S1–S14.
16. Hankins GD, Clark SL, Uckan E, et al. Maternal oxygen transport variables during the third trimester of normal pregnancy. Am J Obstet Gynecol 1999;180(2):406–409.
17. Thomsen JK, Fogh-Andersen N, Jaszczak P. Atrial natriuretic peptide, blood volume, aldosterone, and sodium excretion during twin pregnancy. Acta Obstet Gynecol Scand 1994;73(1):14–20.
18. Kolibash AJ, Ruiz DE, Lewis RP. Idiopathic hypertrophic subaortic stenosis in pregnancy. Ann Intern Med 1975;82(6):791–794.
19. Kinsella SM, Lohmann G. Supine hypotensive syndrome. Obstet Gynecol 1994;83(5):774–788.
20. Rowe G, Castillo C, Crampton C. Effects of hyperventilation on systemic coronary hemodynamics. Am Heart J 1962;63:67.
21. Rowe GG. Responses of the coronary circulation to physiologic changes and pharmacologic agents. Anesthesiology 1974;41(2):182–196.
22. Lee W, Rokey R, Miller J, et al. Maternal hemodynamic effects of uterine contractions by M-mode and pulsed-Doppler echocardiography. Am J Obstet Gynecol 1989;161(4):974–977.
23. Robson SC, Dunlop W, Boys RJ, et al. Cardiac output during labour. BMJ 1987;295(6607):1169–1172.
24. Robson SC, Boys RJ, Hunter S, et al. Maternal hemodynamics after normal delivery and delivery complicated by postpartum hemorrhage. Obstet Gynecol 1989;74(2):234–239.
25. Huch R, Huch A, Lubbers DW. Transcutaneous PO_2. New York: Thieme-Stratton, 1981:139.
26. Huch R, Huch A. Fetal and maternal $tcPO_2$ monitoring. Crit Care Med 1981;9(10):694–697.
27. Hagerdal M, Morgan CW, Summer AE, et al. Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 1983;59(5):425–427.
28. American Society of Anesthesiologists Committee on Obstetrics. ACOG Committee Opinion. Committee on Obstetric Practice. Optimal goals for anesthesia care in obstetrics. Obstet Gynecol 2001;97(5):1–3.
29. Ginsberg JS, Hirsh J. Use of anticoagulants during pregnancy. Chest 1989;95(2 Suppl):156S–160S.
30. Iturbe-Alessio I, Fonseca MC, Mutchinik O, et al. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med 1986;315(22):1390–1393.
31. Zimran A, Shilo S, Fischer D, et al. Histomorphometric evaluation of reversible heparin-induced osteoporosis in pregnancy. Arch Intern Med 1986;146(2):386–388.
32. Henry DM, Cotton DB. Bacterial endocarditis in pregnancy associated with septic renal embolization. South Med J 1985;78(3):355–356.
33. Cox SM, Leveno KJ. Pregnancy complicated by bacterial endocarditis. Clin Obstet Gynecol 1989;32(1)48–53.
34. Seaworth BJ, Durack DT. Infective endocarditis in obstetric and gynecologic practice. Am J Obstet Gynecol 1986;154(1):180–188.
35. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277(22):1794–1801.
36. Durack DT. Prevention of infective endocarditis. N Engl J Med 1995; 332(1):38–44.
37. Durack DT. Antibiotics for prevention of endocarditis during dentistry: time to scale back? [letter; comment]. Ann Intern Med 1998;129(10): 829–831.
38. Ueland K, Gills RE, Hansen JM. Maternal cardiovascular dynamics. I. Cesarean section under subarachnoid block anesthesia. Am J Obstet Gynecol 1968;100(1):42–54.
39. Kan RE, Hughes SC, Rosen MA, et al. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology 1998; 88(6):1467–1474.
40. McCarroll CP, Paxton LD, Elliott P, et al. Use of remifentanil in a patient with peripartum cardiomyopathy requiring Caesarean section. Br J Anaesth 2001;86(1):135–138.
41. Scott H, Bateman C, Price M. The use of remifentanil in general anaesthesia for caesarean section in a patient with mitral valve disease. Anaesthesia 1998;53(7):695–697.
42. Mertens E, Saldien V, Coppejans H, et al. Target controlled infusion of remifentanil and propofol for cesarean section in a patient with multivalvular disease and severe pulmonary hypertension. Acta Anaesthesiol Belg 2001;52(2):207–209.
43. Yeager MP. Pro: regional anesthesia is preferable to general anesthesia for the patient with heart disease. J Cardiothorac Vasc Anesth 1989;3(6):793–796.
44. Boccio RV, Chung JH, Harrison DM. Anesthetic management of cesarean section in a patient with idiopathic hypertrophic subaortic stenosis. Anesthesiology 1986;65(6):663–665.
45. Hemmings GT, Whalley DG, O'Connor PJ, et al. Invasive monitoring and anaesthetic management of a parturient with mitral stenosis. Can J Anaesth 1987;34(2):182–185.

46. Spinnato JA, Kraynack BJ, Cooper MW. Eisenmenger's syndrome in pregnancy: epidural anesthesia for elective cesarean section. N Engl J Med 1981;304(20):1215–1217.
47. Baron JF, Coriat P, Mundler O, et al. Left ventricular global and regional function during lumbar epidural anesthesia in patients with and without angina pectoris. Influence of volume loading. Anesthesiology 1987;66(5):621–627.
48. Juneja MM, Ackerman WE, Kaczorowski DM, et al. Continuous epidural lidocaine infusion in the parturient with paroxysmal ventricular tachycardia. Anesthesiology 1989;71(2):305–308.
49. Brizgys RV, Dailey PA, Shnider SM, et al. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987;67(5):782–786.
50. Hollmen AI, Jouppila R, Albright GA, et al. Intervillous blood flow during caesarean section with prophylactic ephedrine and epidural anaesthesia. Acta Anaesth Scand 1984;28(4):396–400.
51. Levinson G, Shnider SM. Vasopressors in obstetrics. J Clin Anesth 1974;10(1):77–109.
52. Butterworth JFT, Piccione W, Jr., Berrizbeita LD, et al. Augmentation of venous return by adrenergic agonists during spinal anesthesia. Anesth Analg 1986;65(6):612–616.
53. Butterworth JFT, Austin JC, Johnson MD, et al. Effect of total spinal anesthesia on arterial and venous responses to dopamine and dobutamine. Anesth Analg 1987;66(3):209–214.
54. Ralston DH, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40(4):354–370.
55. Ramanathan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesth Scand 1988; 32(7):559–565.
56. Moran DH, Perillo M, La Porta RF, et al. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. J Clin Anesth 1991;3(4):301–305.
57. Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. Am J Med Genet 1988;29(1): 137–142.
58. German J, Ehlers KH, Engle MA. Familial congenital heart disease. II. Chromosomal studies. Circulation 1966;34(3):517–523.
59. Zitnik RS, Brandenburg RO, Sheldon R, et al. Pregnancy and open-heart surgery. Circulation 1969;39(5 Suppl 1):I257–I262.
60. Becker RM. Intracardiac surgery in pregnant women. Ann Thorac Surg 1983;36(4):453–458.
61. Meffert WG, Stansel HC Jr. Open heart surgery during pregnancy. Am J Obstet Gynecol 1968;102(8):1116–1120.
62. Levy DL, Warriner RA III, Burgess GE III. Fetal response to cardiopulmonary bypass. Obstet Gynecol 1980;56(1):112–115.
63. Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. Anesth Analg 1997;85(4):874–885.
64. Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997; 176(5):1062–1068.
65. Martin MC, Pernoll ML, Boruszak AN, et al. Cesarean section while on cardiac bypass: report of a case. Obstet Gynecol 1981;57(6 Suppl): 41S–45S.
66. Lamarra M, Azzu AA, Kulatilake EN. Cardiopulmonary bypass in the early puerperium: possible new role for aprotinin. Ann Thorac Surg 1992;54(2):361–363.
67. Farmakides G, Shulman H, Mohtashemi M, et al. Uterine-umbilical velocimetry in open heart surgery. Am J Obstet Gynecol 1987;156(5): 1221–1222.
68. Weiss BM, von Segesser LK, Alon E, et al. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984–1996. Am J Obstet Gynecol 1998;179(6):1643–1653.
69. Strickland RA, Oliver WC, Jr., Chantigian RC, et al. Anesthesia, cardiopulmonary bypass, and the pregnant patient. Mayo Clin Proc 1991; 66(4):411–429.
70. Parry AJ, Westaby S. Cardiopulmonary bypass during pregnancy. Ann Thorac Surg 1996;61(6):1865–1869.
71. Khandelwal M, Rasanen J, Ludormirski A, et al. Evaluation of fetal and uterine hemodynamics during maternal cardiopulmonary bypass. Obstet Gynecol 1996;88(4):667–671.
72. Burke AB, Hur D, Bolan JC, et al. Sinusoidal fetal heart rate pattern during cardiopulmonary bypass. Am J Obstet Gynecol 1990;163(1): 17–18.
73. Rees GA, Willis BA. Resuscitation in late pregnancy. Anaesthesia 1988;43(5):347–349.
74. Cummings RO, ed. Advanced Cardiac Life Support. Dallas: American Heart Association, 1997.
75. Oates S, Williams GL, Rees GA. Cardiopulmonary resuscitation in late pregnancy. BMJ 1988;297(6645):404–405.
76. Anonymous. Cardiac arrest associated with pregnancy. Circulation 2000;102(8 suppl I):I247–I249.
77. Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IV. Special resuscitation situations. JAMA 1992;268(16):2242–2250.
78. Curry JJ, Quintana FJ. Myocardial infarction with ventricular fibrillation during pregnancy treated by direct current defibrillation with fetal survival. Chest 1970;58(1):82–84.
79. Kloeck W, Cummins RO, Chamberlain D, et al. Special resuscitation situations: an advisory statement from the International Liaison Committee on Resuscitation. Circulation 1997;95(8):2196–2210.
80. Selden BS, Burke TJ. Complete maternal and fetal recovery after prolonged cardiac arrest. Ann Emerg Med 1988;17(4):346–349.
81. DePace NL, Betesh JS, Kotler MN. 'Postmortem' cesarean section with recovery of both mother and offspring. JAMA 1982;248(8):971–973.
82. Finegold H, Darwich A, Romeo R, et al. Successful resuscitation after maternal cardiac arrest by immediate cesarean section in the labor room. Anesthesiology 2002;96(5):1278.
83. Marx GF. Cardiopulmonary resuscitation of late-pregnant women. Anesthesiology 1982;56(2):156.
84. Lopez-Zeno JA, Carlo WA, O'Grady JP, et al. Infant survival following delayed postmortem cesarean delivery. Obstet Gynecol 1990;76(5): 991–992.
85. Strong TH Jr, Lowe RA. Perimortem cesarean section. Am J Emerg Med 1989;7(5):489–494.
86. Katz VL, Dotters DJ, Droegemueller W. Perimortem cesarean delivery. Obstet Gynecol 1986;68(4):571–576.
87. Lau G. A case of sudden maternal death associated with resuscitative liver injury. Forensic Sci Int 1994;67(2):127–132.
88. Lee RV, Rodgers BD, White LM, et al. Cardiopulmonary resuscitation of pregnant women. Am J Med 1986;81(2):311–318.
89. Litwin MS, Loughlin KR, Benson CB, et al. Placenta percreta invading the urinary bladder. Br J Urol 1989;64(3):283–286.
90. Splinter WM, Dwane PD, Wigle RD, et al. Anaesthetic management of emergency caesarean section followed by pulmonary embolectomy. Can J Anaesth 1989;36(6):689–692.
91. Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass. Anesth Analg 198969(3):403–406.
92. Shotan A, Ostrzega E, Mehra A, et al. Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. Am J Cardiol 1997;79(8):1061–1064.
93. Brodsky M, Doria R, Allen B, et al. New-onset ventricular tachycardia during pregnancy. Am Heart J 1992;123(4):933–941.
94. Widerhorn J, Widerhorn AL, Rahimtoola SH, et al. WPW syndrome during pregnancy: increased incidence of supraventricular arrhythmias. Am Heart J 1992;123(3):796–798.

95. Lee SH, Chen SA, Wu TJ, et al. Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 1995;76(10):675–678.
96. Rotmensch, HH, Rotmensch S, Elkayam U. Management of cardiac arrhythmias during pregnancy. Current concepts. Drugs 1987;33(6):623–633.
97. Upshaw CB Jr. A study of maternal electrocardiograms recorded during labor and delivery. Am J Obstet Gynecol 1970;107(1):17–27.
98. Dominguez A, Iturralde P, Hermosillo AG, et al. Successful radiofrequency ablation of an accessory pathway during pregnancy. Pacing Clin Electrophysiol 1999;22(1):131–134.
99. Lee MS, Evans SJ, Blumberg S, et al. Echocardiographically guided electrophysiologic testing in pregnancy. J Am Soc Echocardiogr 1994; 7(2):182–186.
100. Joglar JA, Page RL. Antiarrhythmic drugs in pregnancy. Curr Opin Cardiol 2001;16(1):40–45.
101. Oettinger M, Perlitz Y. Asymptomatic paroxysmal atrial fibrillation during intravenous magnesium sulfate treatment in preeclampsia. Gynecol Obstet Invest 1993;36(4):244–246.
102. Penkala M, Hancock EW. Wide-complex tachycardia in pregnancy. Hosp Pract (Offic Ed) 1993;28(7):63–64.
103. Fuster V, Ryden LE, Asinger R, et al. ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation: Executive Summary. Circulation 2001;104(17):2118–2150.
104. Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. Drug Saf 1999;20(1):85–94.
105. Afridi I, Moise KJ Jr, Rokey R. Termination of supraventricular tachycardia with intravenous adenosine in a pregnant woman with Wolff-Parkinson-White syndrome. Obstet Gynecol 1992;80(3):481–483.
106. Kounis NG, Zavras GM, Papadaki PJ, et al. Pregnancy-induced increase of supraventricular arrhythmias in Wolff-Parkinson-White syndrome. Clin Cardiol 1995;18(3):137–140.
107. Sharpe MD, Dobkowski WB, Murkin JM, et al. The electrophysiologic effects of volatile anesthetics and sufentanil on the normal atrioventricular conduction system and accessory pathways in Wolff-Parkinson-White syndrome. Anesthesiology 1994;80(1):63–70.
108. Trappe HJ, Pfitzner P. Cardiac arrhythmias in pregnancy. Z Kardiol 2001;90(suppl 4):36–44.
109. Dalvi BV, Chaudhuri A, Kulkarni HL, et al. Therapeutic guidelines for congenital complete heart block presenting in pregnancy. Obstet Gynecol 1992;79(5):802–804.
110. Holdright DR, Sutton GC. Restoration of sinus rhythm during two consecutive pregnancies in a woman with congenital complete heart block. Br Heart J 1990;64(5):338–339.
111. Jaffe R, Gruber A, Fejgin M, et al. Pregnancy with an artificial pacemaker. Obstet Gynecol Surv 1987;42(3):137–139.
112. Gudal M, Kervancioglu C, Oral D, et al. Permanent pacemaker implantation in a pregnant woman with the guidance of ECG and two-dimensional echocardiography. Pacing Clin Electrophysiol 1987;10(3): 543–545.
113. Goodlin RC, Cheatham JP. Electronic fetal monitor paced by maternal implanted pacemaker. Am J Obstet Gynecol 1985;153(5):570–571.
114. Feldman JM. Cardiac arrest after succinylcholine administration in a pregnant patient recovered from Guillain-Barre syndrome. Anesthesiology 1990;72(5):942–944.
115. Swartjes JM, Schutte MF, Bleker OP. Management of eclampsia: cardiopulmonary arrest resulting from magnesium sulfate overdose. Eur J Obstet Gynecol Reprod Biol 1992;47(1):73–75.
116. Varon ME, Sherer DM, Abramowicz JS, et al. Maternal ventricular tachycardia associated with hypomagnesemia. Am J Obstet Gynecol 1992;167(5):1352–1355.
117. Naidoo DP, Bhorat I, Moodley J, et al. Continuous electrocardiographic monitoring in hypertensive crises in pregnancy. Am J Obstet Gynecol 1991;164(2):530–533.
118. Mason BA, Ricci-Goodman J, Koos BJ. Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. Obstet Gynecol 1992;80(3):478–480.
119. Belardinelli L, Linden J, Berne RM. The cardiac effects of adenosine. Prog Cardiovasc Dis 1989;32(1):73–97.
120. Cox JL, Gardner MJ. Treatment of cardiac arrhythmias during pregnancy. Prog Cardiovasc Dis 1993;36(2):137–178.
121. Nademanee K, Piwonka RW, Singh BN, et al. Amiodarone and thyroid function. Prog Cardiovasc Dis 1989;31(6):427–437.
122. Widerhorn J, Bhandari AK, Bughi S, et al. Fetal and neonatal adverse effects profile of amiodarone treatment during pregnancy. Am Heart J 1991;122(4):1162–1166.
123. Laurent M, Betremieux P, Biron Y, et al. Neonatal hypothyroidism after treatment by amiodarone during pregnancy. Am J Cardiol 1987; 60(10):942.
124. McKenna WJ, Harris L, Rowland E, et al. Amiodarone therapy during pregnancy. Am J Cardiol 1983;51(7):1231–1233.
125. Foster CJ, Love HG. Amiodarone in pregnancy. Case report and review of the literature. Int J Cardiol 1988;20(3):307–316.
126. Meijboom EJ, van Engelen AD, van de Beek EW, et al. Fetal arrhythmias. Curr Opin Cardiol 1994;9(1):97–102.
127. Schleich JM, et al. Early prenatal management of a fetal ventricular tachycardia treated in utero by amiodarone with long-term follow-up. Prenat Diagn 2000;20(6):449–452.
128. Fulgencio JP, Hamza J. Anaesthesia for caesarean section in a patient receiving high dose amiodarone for fetal supraventricular tachycardia. Anaesthesia 1994;49(5):406–408.
129. Gembruch U, Manz M, Bald R, et al. Repeated intravascular treatment with amiodarone in a fetus with refractory supraventricular tachycardia and hydrops fetalis. Am Heart J 1989;118(6):1335–1338.
130. Cunningham FG, Lindheimer MD. Hypertension in pregnancy. N Engl J Med 1992;326(14):927–932.
131. Eisenach JC, Castro MI. Maternally administered esmolol produces fetal beta-adrenergic blockade and hypoxemia in sheep. Anesthesiology 1989;71(5):718–722.
132. Ostman PL, Chestnut DH, Robillard JE, et al. Transplacental passage and hemodynamic effects of esmolol in the gravid ewe. Anesthesiology 1988;69(5):738–741.
133. Larson CP Jr, Shuer LM, Cohen SE. Maternally administered esmolol decreases fetal as well as maternal heart rate. J Clin Anesth 1990; 2(6):427–429.
134. Losasso TJ, Muzzi DA, Cucchiara RF. Response of fetal heart rate to maternal administration of esmolol. Anesthesiology 1991;74(4):782–784.
135. Ducey JP, Knape KG. Maternal esmolol administration resulting in fetal distress and cesarean section in a term pregnancy. Anesthesiology 1992;77(4):829–832.
136. Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. Am J Obstet Gynecol 1979; 135(4):485–489.
137. Rubin PC. Current concepts: beta-blockers in pregnancy. N Engl J Med 1981;305(22):1323–1326.
138. Seki H, Takeda S, Kinoshita K. Long-term treatment with nicardipine for severe pre-eclampsia. Int J Gynaecol Obstet 2002;76(2):135–141.
139. Rotmensch HH, Elkayam U, Frishman W. Antiarrhythmic drug therapy during pregnancy. Ann Intern Med 1983;98(4):487–497.
140. Scanlon JW, Brown WU, Jr., Weiss JB, et al. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology 1974;40(2):121–128.
141. Kileff ME, James FM, III, Dewan DM, et al. Neonatal neurobehavioral responses after epidural anesthesia for cesarean section using lidocaine and bupivacaine. Anesth Analg 1984;63(4):413–417.
142. Abboud TK, Khoo SS, Miller F, et al. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. Anesth Analg 1982;61(8):638–644.
143. Atkinson AJ Jr, Davison R. Diphenylhydantoin as an antiarrhythmic drug. Annu Rev Med 1974;25:99–113.
144. Hanson JW, Myrianthopoulos NC, Harvey MA, et al. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976;89(4):662–668.

145. Ogburn PL Jr, Schmidt G, Linman J, et al. Paroxysmal tachycardia and cardioversion during pregnancy. J Reprod Med 1982;27(6):359–362.
146. Page RL. Treatment of arrhythmias during pregnancy. Am Heart J 1995;130(4):871–876.
147. Forgione FN, Acquati F, Caico SI, et al. Incessant ectopic atrial tachycardia in pregnancy: radiofrequency catheter ablation in immediate postpartum with disappearance of tachycardia-related dilated cardiomyopathy. G Ital Cardiol 1994;24(6):755–761.
148. Chow T, Galvin J, McGovern B. Antiarrhythmic drug therapy in pregnancy and lactation. Am J Cardiol 1998;82(4A):58I–62I.
149. Bonini W, Botto GL, Broffoni T, et al. Pregnancy with an ICD and a documented ICD discharge. Europace 2000;2(1):87–90.
150. Natale A, Davidson T, Geiger MJ, et al. Implantable cardioverter-defibrillators and pregnancy: a safe combination? Circulation 1997;96(9): 2808–2812.
151. Bevacqua BK. Supraventricular tachycardia associated with postpartum metoclopramide administration. Anesthesiology 1988;68(1):124–125.
152. Vassalli G, Seiler C, Hess OM, Risk stratification in hypertrophic cardiomyopathy. Curr Opin Cardiol 1994;9(3):330–336.
153. Casali C, d'Amati G, Bernucci P, et al. Maternally inherited cardiomyopathy: clinical and molecular characterization of a large kindred harboring the A4300G point mutation in mitochondrial deoxyribonucleic acid. J Am Coll Cardiol 1999;33(6):1584–1589.
154. Seiler C, Jenni R, Vassalli G, et al. Left ventricular chamber dilatation in hypertrophic cardiomyopathy: related variables and prognosis in patients with medical and surgical therapy. Br Heart J 1995;74(5):508–516.
155. Kazimuddin M, Vashist A, Basher AW, et al. Pregnancy-induced severe left ventricular systolic dysfunction in a patient with hypertrophic cardiomyopathy. Clin Cardiol 1998;21(11):848–850.
156. Mokaddem A, Bachraoui K, Selmi K, et al. Hypertrophic cardiomyopathy and pregnancy. Tunis Med 2000;78(11):682–684.
157. Pelliccia F, Cianfrocca C, Gaudio C, et al. Sudden death during pregnancy in hypertrophic cardiomyopathy. Eur Heart J 1992;13(3):421–423.
158. Piacenza JM, Kirkorian G, Audra PH, et al. Hypertrophic cardiomyopathy and pregnancy. Eur J Obstet Gynecol Reprod Biol 1998;80(1): 17–23.
159. Probst V, Langlard JM, Desnos M, et al. Familial hypertrophic cardiomyopathy. French study of the duration and outcome of pregnancy. Arch Mal Coeur Vaiss 2002;95(2):81–86.
160. Paix B, Cyna A, Belperio P, et al. Epidural analgesia for labour and delivery in a parturient with congenital hypertrophic obstructive cardiomyopathy. Anaesth Intensive Care 1999;27(1):59–62.
161. Ho KM, Kee WD, Poon MC. Combined spinal and epidural anesthesia in a parturient with idiopathic hypertrophic subaortic stenosis. Anesthesiology 1997;87(1):168–169.
162. Chung HM, Kluge R, Schrier RW, et al. Postoperative hyponatremia. A prospective study. Arch Intern Med 1986;146(2):333–336.
163. Haering JM, Communale ME, Parker RA, et al. Cardiac risk of noncardiac surgery in patients with asymmetric septal hypertrophy. Anesthesiology 1996;85(2):254–259.
164. Loubser P, Suh K, Cohen S. Adverse effects of spinal anesthesia in a patient with idiopathic hypertrophic subaortic stenosis. Anesthesiology 1984;60(3):228–230.
165. Minnich ME, Quirk JG, Clark RB. Epidural anesthesia for vaginal delivery in a patient with idiopathic hypertrophic subaortic stenosis. Anesthesiology 1987;67(4):590–592.
166. Baraka A, Jabbour S, Itani I. Severe bradycardia following epidural anesthesia in a patient with idiopathic hypertrophic subaortic stenosis. Anesth Analg 1987;66(12):1337–1338.
167. Okutomi T, Kikuchi S, Amano K, et al. Continuous spinal analgesia for labor and delivery in a parturient with hypertrophic obstructive cardiomyopathy. Acta Anaesth Scand 2002;46(3):329–331.
168. Autore C, Brauneis S, Apponi F, et al. Epidural anesthesia for cesarean section in patients with hypertrophic cardiomyopathy: a report of three cases.Anesthesiology 1999;90(4):1205–1207.
169. Ayorinde BT, Buczkowski P, Brown J, et al. Evaluation of pre-emptive intramuscular phenyl-ephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during caesarean section. Br J Anaesth 2001;86(3):372–376.
170. Demakis JG, Rahimtoola SH, Sutton GC, et al. Natural course of peripartum cardiomyopathy. Circulation 1971;44(6):1053–1061.
171. Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. Circulation 1971;44(5):964–968.
172. Homans DC. Peripartum cardiomyopathy. N Engl J Med 1985;312(22): 1432–1437.
173. Veille JC, Zaccaro D. Peripartum cardiomyopathy: summary of an international survey on peripartum cardiomyopathy. Am J Obstet Gynecol 1999;181(2):315–319.
174. Mehta NJ, Mehta RN, Khan IA. Peripartum cardiomyopathy: clinical and therapeutic aspects. Angiology 2001;52(11):759–762.
175. Brown B, Asaeda G. Prehospital rounds. Hypertension after having a baby. Emerg Med Serv 2002;31(3):74–75.
176. 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(9):1183–1188.
177. Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol 1999;94(2):311–316.
178. Yagoro A, Tada H, Hidaka Y, et al. Postpartum onset of acute heart failure possibly due to postpartum autoimmune myocarditis. A report of three cases. J Intern Med 1999;245(2):199–203.
179. Cenac A, Simonoff M, Moretto P, et al. A low plasma selenium is a risk factor for peripartum cardiomyopathy. A comparative study in Sahelian Africa. Int J Cardiol 1992;36(1):57–59.
180. Irey NS, Norris HJ. Intimal vascular lesions associated with female reproductive steroids. Arch Pathol Lab Med 1973;96(4):227–234.
181. Adesanya CO, Anjorin FI, Sada IA, et al. Atrial natriuretic peptide, aldosterone, and plasma renin activity in peripartum heart failure. Br Heart J 1991;65(3):152–154.
182. Heider AL, Kuller JA, Strauss RA, et al. Peripartum cardiomyopathy: a review of the literature. Obstet Gynecol Surv 1999;54(8):526–531.
183. Brown CS, Bertolet BD. Peripartum cardiomyopathy: a comprehensive review. Am J Obstet Gynecol 1998;178(2):409–414.
184. Jin O, Sole MJ, Butany JW, et al. Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. Circulation 1990;82(1):8–16.
185. Lampert MB, Hibbard J, Weinert L, et al. Peripartum heart failure associated with prolonged tocolytic therapy. Am J Obstet Gynecol 1993; 168(2):493–495.
186. Julian DG, Szekely P. Peripartum cardiomyopathy. Prog Cardiovasc Dis 1985;27(4):223–240.
187. Hodgman MT, Pessin MS, Homans DC, et al. Cerebral embolism as the initial manifestation of peripartum cardiomyopathy. Neurology 1982; 32(6):668–671.
188. Sakakibara S, Sekiguchi M, Konno S, et al. Idiopathic postpartum cardiomyopathy: report of a case with special reference to its ultrastructural changes in the myocardium as studies by endomyocardial biopsy. Am Heart J 1970;80(3):385–395.
189. Van Hoeven KH, Kitsis RN, Katz SD, et al. Peripartum versus idiopathic dilated cardiomyopathy in young women—a comparison of clinical, pathologic and prognostic features. Int J Cardiol 1993;40(1):57–65.
190. Aziz TM, Burgess MI, Acladious NN, et al. Heart transplantation for peripartum cardiomyopathy: a report of three cases and a literature review. J Cardiovasc Surg 1999;7(5):565–567.
191. Felker GM, Jaeger CJ, Klodas E, et al. Myocarditis and long-term survival in peripartum cardiomyopathy. Am Heart J 2000;140(5):785–791.
192. Bernstein PS, Magriples U. Cardiomyopathy in pregnancy: a retrospective study. Am J Perinatol 2001;18(3):163–168.
193. Massad LS, Reiss CK, Mutch DG, et al. Familial peripartum cardiomyopathy after molar pregnancy. Obstet Gynecol 1993;81(5):886–888.

194. Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 2001;344(21):1567–1571.
195. Reimold SC, Rutherford JD. Peripartum cardiomyopathy. N Engl J Med 2001;344(21):1629–1630.
196. Camann WR, Goldman GA, Johnson MD, et al. Cesarean delivery in a patient with a transplanted heart. Anesthesiology 1989;71(4):618–620.
197. Jelsema RD, Bhatia RK, Ganguly S. Use of intravenous amrinone in the short-term management of refractory heart failure in pregnancy. Obstet Gynecol 1991;78(5):935–936.
198. Fishburne JI Jr, Dormer KJ, Payne GG, et al. Effects of amrinone and dopamine on uterine blood flow and vascular responses in the gravid baboon. Am J Obstet Gynecol 1988;158(4):829–837.
199. Futterman LG, Lemberg L. Peripartum cardiomyopathy: an ominous complication of pregnancy. Am J Crit Care 2000;9(5):362–366.
200. Carlson KM, Browning JE, Eggleston MK, et al. Peripartum cardiomyopathy presenting as lower extremity arterial thromboembolism. A case report. J Reprod Med 2000;45(4):351–353.
201. Bozkurt B, Villanueva FS, Holubkov R, et al. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am Coll Cardiol 1999;34(1):177–180.
202. Davies JE, Winokur TS, Aaron MF, et al. Cardiomyopathy in a carrier of Duchenne's muscular dystrophy. J Heart Lung Transplant 2001; 20(7):781–784.
203. Malinow AM, Butterworth JFT, Johnson MD, et al. Peripartum cardiomyopathy presenting at cesarean delivery. Anesthesiology 1985; 63(5):545–547.
204. George LM, Gatt SP, Lowe S. Peripartum cardiomyopathy: four case histories and a commentary on anaesthetic management. Anaesth Intensive Care 1997;25(3):292–296.
205. McIndoe AK, Hammond EJ, Babington PC. Peripartum cardiomyopathy presenting as a cardiac arrest at induction of anaesthesia for emergency caesarean section. Br J Anaesth 1995;75(1):97–101.
206. Bonow RO, Carabello B, de Leon AC, et al. ACC/AHA Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Heart Valve Dis 1998;7(6):672–707.
207. Bonow RO, Carabello B, de Leon AC, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). Circulation 1998;98(18): 1949–1984.
208. Gohlke-Barwolf C, Acar J, Oakley C, et al. Recommendations for prevention of thromboembolism in heart valve diseases. Working group on valvular heart disease, European Society of Cardiology. Z Kardiol 1995; 84(12):1018–1032.
209. Savage DD, Garrison RJ, Devereux RB, et al. Mitral valve prolapse in the general population. 1. Epidemiologic features: the Framingham Study. Am Heart J 1983;106(3):571–576.
210. Barlow JB, Pocock WA. The problem of nonejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. Am Heart J 1975;90(5):636–655.
211. Buda AJ, Levene DL, Myers MG, et al. Coronary artery spasm and mitral valve prolapse. Am Heart J 1978;95(4):457–462.
212. Degani S, Abinader EG, Scharf M. Mitral valve prolapse and pregnancy: a review. Obstet Gynecol Surv 1989;44(9):642–649.
213. Kligfield P, Levy D, Devereux RB, et al. Arrhythmias and sudden death in mitral valve prolapse. Am Heart J 1987;113(5):1298–1307.
214. Devereux RB, Brown WT, Kramer-Fox R, et al. Inheritance of mitral valve prolapse: effect of age and sex on gene expression. Ann Intern Med 1982;97(6):826–832.
215. Cowles T, Gonik B. Mitral valve prolapse in pregnancy. Semin Perinatol 1990;14(1):34–41.
216. Cheitlin MD, Byrd RC. The click-murmur syndrome. A clinical problem in diagnosis and treatment. JAMA 1981;245(13):1357–1361.
217. Jeresaty RM. Mitral valve prolapse—click syndrome. Prog Cardiovasc Dis 1973;15(6):623–652.
218. Gooch AS, Vicencio F, Maranhas V, et al. Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. Am J Cardiol 1972;29(5):611–620.
219. Shapiro EP, Trimble EL, Robinson JC, et al. Safety of labor and delivery in women with mitral valve prolapse. Am J Cardiol 1985;56(12):806–807.
220. Rayburn WF, Fontana ME. Mitral valve prolapse and pregnancy. Am J Obstet Gynecol 1981;141(1):9–11.
221. Tang LC, Chan SY, Wong VC, et al. Pregnancy in patients with mitral valve prolapse. Int J Gynaecol Obstet 1985;23(3):217–221.
222. Thiagarajah S, Frost EA. Anaesthetic considerations in patients with mitral valve prolapse. Anaesthesia 1983;38(6):560–566.
223. Roth A, Shotan A, Elkayam U. A randomized comparison between the hemodynamic effects of hydralazine and nitroglycerin alone and in combination at rest and during isometric exercise in patients with chronic mitral regurgitation. Am Heart J 1993;125(1):155–163.
224. Oakley CM. Valvular disease in pregnancy. Curr Opin Cardiol 1996; 11(2):155–159.
225. Paulus DA, Layon AL, Mayfield WR, et al. Intrauterine pregnancy and aortic valve replacement. J Clin Anesth 1995;7(4):338–346.
226. Tzankis G, Morse DS. Cesarean section and reoperative aortic valve replacement in a 38-week parturient. J Cardiothorac Vasc Anesth 1996; 10(4):516–518.
227. Lao TT, Sermer M, McGee L, et al. Congenital aortic stenosis and pregnancy—a reappraisal. Am J Obstet Gynecol 1993;169(3):540–545.
228. Arias F, Pineda J. Aortic stenosis and pregnancy. J Reprod Med 1978; 20(4):229–232.
229. Hustead ST, Quick A, Gibbs HR, et al. "Pseudo-critical" aortic stenosis during pregnancy: role for Doppler assessment of aortic valve area. Am Heart J 1989;117(6):1383–1385.
230. Bhargava B, Agarwal R, Yadav R, et al. Percutaneous balloon aortic valvuloplasty during pregnancy: use of the Inoue balloon and the physiologic antegrade approach. Catheter Cardiovasc Diagn 1998;45(4): 422–425.
231. Prendergast BD, Banning AP, Hall RJ. Valvular heart disease: recommendations for investigation and management. Summary of guidelines produced by a working group of the British Cardiac Society and the Research Unit of the Royal College of Physicians. J R Coll Physicians Lond 1996;30(4):309–315.
232. Born D, Martinez EE, Almeida PA, et al. Pregnancy in patients with prosthetic heart valves: the effects of anticoagulation on mother, fetus, and neonate. Am Heart J 1992;124(2):413–417.
233. Banning AP, Pearson JF, Hall RJ. Role of balloon dilatation of the aortic valve in pregnant patients with severe aortic stenosis. Br Heart J 1993;70(6):544–545.
234. Chambers CE, Clark SL. Cardiac surgery during pregnancy. Clin Obstet Gynecol 1994;37(2):316–323.
235. Westaby S, Parry AJ, Forfar JC. Reoperation for prosthetic valve endocarditis in the third trimester of pregnancy. Ann Thorac Surg 1992; 53(2):263–265.
236. Hameed A, Karaalp IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. J Am Coll Cardiol 2001;37(3):893–899.
237. Easterling TR, Chadwick HS, Otto CM, et al. Aortic stenosis in pregnancy. Obstet Gynecol 1988;72(1):113–118.
238. Colclough GW, Ackerman WE III, Walmsley PN, et al. Epidural anesthesia for cesarean delivery in a parturient with aortic stenosis. Reg Anesth 1990;15(5):273–274.
239. Brian JE Jr, Seifen AB, Clark RB, et al. Aortic stenosis, cesarean delivery, and epidural anesthesia. J Clin Anesth 19935(2):154–157.
240. Pittard A, Vucevic M. Regional anaesthesia with a subarachnoid microcatheter for caesarean section in a parturient with aortic stenosis. Anaesthesia 1998;53(2):169–173.

241. Redfern N, Bower S, Bullock RE, et al. Alfentanil for caesarean section complicated by severe aortic stenosis. A case report. Br J Anaesth 1987;59(10):1309–1312.
242. Rokey R, Hsu HW, Moise KJ Jr., et al. Inaccurate noninvasive mitral valve area calculation during pregnancy. Obstet Gynecol 1994;84(6):950–955.
243. al-Kasab SM, Sabag T, al-Zaibag M, et al. Beta-adrenergic receptor blockade in the management of pregnant women with mitral stenosis. Am J Obstet Gynecol 1990;163(1):37–40.
244. Baron F, Zottoli E, Hill WC. Percutaneous balloon mitral valvuloplasty during a twin gestation. South Med J 2002;95(3):358–359.
245. Uygur D, Beksac MS. Mitral balloon valvuloplasty during pregnancy in developing countries. Eur J Obstet Gynecol Reprod Biol 2001;96(2): 226–228.
246. de Souza JA, Martinez EE Jr., Ambrose JA, et al. Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. J Am Coll Cardiol 2001; 37(3):900–903.
247. Lee CH, Chow WH, Kwok OH. Percutaneous balloon mitral valvuloplasty during pregnancy: long-term follow-up of infant growth and development. Hong Kong Med J 2001;7(1):85–88.
248. Sajja LR, Mannam GC. Role of closed mitral commissurotomy in mitral stenosis with severe pulmonary hypertension. J Heart Valve Dis 2001;10(3):288–293.
249. Bugliani-Pastalka L, Bugliani G, Suter T, et al. Long-term results after successful mitral valvuloplasty: comparison of Inoue and double balloon technique. Schweiz Med Wochenschr 2000;130(35):1216–1224.
250. Mangione JA, Lourenco RM, dos Santos ES, et al. Long-term follow-up of pregnant women after percutaneous mitral valvuloplasty. Catheter Cardiovasc Diagn 2000;50(4):413–417.
251. Mayer IV, Fischer A, Jakob M, et al. Reversal of increased diastolic stiffness in mitral stenosis after successful balloon valvuloplasty. J Heart Valve Dis 1999;8(1):47–56.
252. Mazur W, Parilak LD, Kaluza G, et al. Balloon valvuloplasty for mitral stenosis. Curr Opin Cardiol 1999;14(2):95–103.
253. Cheng TO, Holmes DR Jr. Percutaneous balloon mitral valvuloplasty by the Inoue balloon technique: the procedure of choice for treatment of mitral stenosis. Am J Cardiol 1998;81(5):624–628.
254. Kultursay H, Turkoglu C, Akin M, et al. Mitral balloon valvuloplasty with transesophageal echocardiography without using fluoroscopy. Catheter Cardiovasc Diagn 1992;27(4):317–321.
255. Bernard Y, Bassand JP, Schiele F, et al. Percutaneous mitral valvulotomy in non-optimal candidates. Eur Heart J 1991;12(suppl B):90–94.
256. Poirier P, Champagne J, Alain P, et al. Mitral balloon valvuloplasty in pregnancy: limiting radiation and procedure time by using transesophageal echocardiography. Can J Cardiol 1997;13(9):843–845.
257. Glantz JC, Pomerantz RM, Cunningham MJ, et al. Percutaneous balloon valvuloplasty for severe mitral stenosis during pregnancy: a review of therapeutic options. Obstet Gynecol Surv 1993;48(7):503–508.
258. Sharma S, Loya YS, Desai DM, et al. Percutaneous mitral valvotomy in 200 patients using Inoue balloon—immediate and early haemodynamic results. Indian Heart J 1993;45(3):169–172.
259. Naidoo DP, Moodley J. Management of the critically ill cardiac patient. Best Practice Res Clin Obstet Gynaecol 2001;15(4):523–544.
260. Vosloo S, Reichart B. The feasibility of closed mitral valvotomy in pregnancy. J Thorac Cardiovasc Surg 1987;93(5):675–679.
261. Clark SL, Phelan JP, Greenspoon J, et al. Labor and delivery in the presence of mitral stenosis: central hemodynamic observations. Am J Obstet Gynecol 1985;152(8):984–988.
262. Ziskind Z, Etchin A, Frenkel Y, et al. Epidural anesthesia with the Trendelenburg position for cesarean section with or without a cardiac surgical procedure in patients with severe mitral stenosis: a hemodynamic study. J Cardiothorac Anesth 1990;4(3):354–359.
263. Cormier B, Vahanian A. Indications and outcome of valvuloplasty. Curr Opin Cardiol 1992;7(2):222–228.
264. Lee CN, Wu CC, Lin PY, et al. Pregnancy following cardiac prosthetic valve replacement. Obstet Gynecol 1994;83(3):353–356.
265. Salazar E, Zajarias A, Gutierrez N, et al. The problem of cardiac valve prostheses, anticoagulants, and pregnancy. Circulation 1984;70(3): I169–I177.
266. Bortolotti U, Milano A, Mazzucco A, et al. Pregnancy in patients with a porcine valve bioprosthesis. Am J Cardiol 1982;50(5):1051–1054.
267. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996;335(6):407–416.
268. Elkayam U. Pregnancy through a prosthetic heart valve. J Am Coll Cardiol 1999;33(6):1642–1645.
269. Whittemore R, Wells JA, Castellsague X. A second-generation study of 427 probands with congenital heart defects and their 837 children. J Am Coll Cardiol 1994;23(6):1459–1467.
270. Presbitero P, Somerville J, Stone S, et al. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. Circulation 1994; 89(6):2673–2676.
271. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 1997;96(9):2789–2794.
272. Kirklin JW, Blackstone EH, Kirklin JK, et al. Surgical results and protocols in the spectrum of tetralogy of Fallot. Ann Surg 1983;198(3):251–265.
273. Whittemore R, Hobbins JC, Engle MA. Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. Am J Cardiol 1982;50(3):641–651.
274. Larsen-Disney P, Price D, Meredith I. Undiagnosed maternal Fallot tetralogy presenting in pregnancy. Aust N Z J Obstet Gynaecol 1992; 32(2):169–171.
275. Shime J, Mocarski EJ, Hastings D, et al. Congenital heart disease in pregnancy: short- and long-term implications. Am J Obstet Gynecol 1987;156(2):313–322.
276. Eisenmenger V. Die Angeborenen Defecte der Kammerscheidewand des Herzens. Z Klin Med 1897;32:1–29.
277. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed control shunt. Br Med J 1958;2:701.
278. Young D, Mark H. Fate of the patient with the Eisenmenger syndrome. Am J Cardiol 1971;28(6):658–669.
279. Heytens L, Alexander JP. Maternal and neonatal death associated with Eisenmenger's syndrome. Acta Anaesthesiol Belg 1986;37(1):45–51.
280. Kahn ML. Eisenmenger's syndrome in pregnancy. N Engl J Med 1993;329(12):887.
281. Pitts JA, Crosby WM, Basta LL. Eisenmenger's syndrome in pregnancy: does heparin prophylaxis improve the maternal mortality rate? Am Heart J 1977;93(3):321–326.
282. Weiss BM, Hess O. Perioperative cardiovascular evaluation for noncardiac surgery: congenital heart diseases and heart diseases in pregnancy deserve better guidelines. Circulation 1997;95(2):530–531.
283. Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. Br J Obstet Gynaecol 1998; 105(8):921–922.
284. Gleicher N, Midwall J, Hochberger D, et al. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34(10):721–741.
285. Su NY, Lin SM, Hseu SS, et al. Anesthetic management of parturients with Eisenmenger's syndrome—report of two cases. Ma Tsui Hsueh Tsa Chi 2001;39(3):139–144.
286. Kandasamy R, Koh KF, Tham SL, et al. Anaesthesia for caesarean section in a patient with Eisenmenger's syndrome. Singapore Med J 2000;41(7):356–358.
287. Pollack KL, Chestnut DH, Wenstrom KD. Anesthetic management of a parturient with Eisenmenger's syndrome. Anesth Analg 1990;70(2): 212–215.
288. Budts W, Van Pelt N, Gillyns H, et al. Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome. Br Heart J 2001;86(5):553–558.
289. Goodwin TM, Gherman RB, Hameed A, et al. Favorable response of Eisenmenger syndrome to inhaled nitric oxide during pregnancy. Am J Obstet Gynecol 1999;180(1):64–67.
290. Lust KM, Boots RJ, Dooris M, et al. Management of labor in Eisen-

menger syndrome with inhaled nitric oxide. Am J Obstet Gynecol 1999;181(2):419–423.
291. Decoene C, Bourzoufi K, Moreau D, et al. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. Can J Anaesth 2001;48(6):584–587.
292. Skinner DH, Tremper KK, Cullen BF. Transcutaneous PO_2 monitoring in the anesthetic management of a patient with Eisenmenger's syndrome. Crit Care Med 1985;13(7):608–609.
293. Panetta C, Schiller N. Evidence of patent ductus arteriosus and right-to-left shunt by finger pulse oxymetry and doppler signals of agitated saline in abdominal aorta. J Am Soc Echocardiogr 1999;12(9):763–765.
294. Devitt JH, Noble WH, Byrick RJ. A Swan-Ganz catheter related complication in a patient with Eisenmenger's syndrome. Anesthesiology 1982;57(4):335–337.
295. Robinson S. Pulmonary artery catheters in Eisenmenger's syndrome: many risks, few benefits. Anesthesiology 1983;58(6):588–590.
296. Schwalbe SS, Deshmukh SM, Marx GF. Use of pulmonary artery catheterization in parturients with Eisenmenger's syndrome. Anesth Analg 1990;71(4):442–443.
297. Atanassoff P, Alon E, Schmid ER, et al. Epidural anesthesia for cesarean section in a patient with severe pulmonary hypertension. Acta Anaesth Scand 1990;34(1):75–77.
298. Owen MD, Poss MJ, Dean LS, et al. Prolonged intravenous remifentanil infusion for labor analgesia. Anesth Analg 2002;94(4):918–919, table of contents.
299. Head BB, Owen J, Vincent RD Jr., et al. A randomized trial of intrapartum analgesia in women with severe preeclampsia. Obstet Gynecol 2002;99(3):452–457.
300. Cole PJ, Cross MH, Dresner M. Incremental spinal anaesthesia for elective caesarean section in a patient with Eisenmenger's syndrome. Br J Anaesth 2001;86(5):723–726.
301. Midwall J, Jaffin H, Herman MV, et al. Shunt flow and pulmonary hemodynamics during labor and delivery in the Eisenmenger syndrome. Am J Cardiol 1978;42(2):299–303.
302. Abboud TK, Raya J, Noueihad R, et al. Intrathecal morphine for relief of labor pain in a parturient with severe pulmonary hypertension. Anesthesiology 1983;59(5):477–479.
303. Tay SM, Ong BC, Tan SA. Cesarean section in a mother with uncorrected congenital coronary to pulmonary artery fistula. Can J Anaesth 1999;46(4):368–371.
304. Weiss BM, Zemp L, Seifert B, et al. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31(7):1650–1657.
305. Monnery L, Nanson J, Charlton G. Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. Br J Anaesth 2001;87(2): 295–298.
306. Lam GK, Stafford RE, Thorp J, et al. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. Obstet Gynecol 2001;98(5):895–898.
307. Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: treatment with pulmonary vasodilators. Obstet Gynecol 1999;93(4):494–498.
308. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346(12):896–903.
309. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001; 358(9288):1119–1123.
310. O'Hare R, McLoughlin C, Milligan K, et al. Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth 1998;81(5):790–792.
311. Stewart R, Tuazon D, Olson G, et al. Pregnancy and primary pulmonary hypertension : successful outcome with epoprostenol therapy. Chest 2001;119(3):973–975.
312. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165(6):800–804.
313. Slomka F, Salmeron S, Zetlaoui P, et al. Primary pulmonary hypertension and pregnancy: anesthetic management for delivery. Anesthesiology 1988;69(6):959–961.
314. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth 1994;41(6):502–512.
315. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336(2): 111–117.
316. Robinson DE, Leicht CH. Epidural analgesia with low-dose bupivacaine and fentanyl for labor and delivery in a parturient with severe pulmonary hypertension. Anesthesiology 1988;68(2):285–288.
317. Penning S, Thomas N, Atwal D, et al. Cardiopulmonary bypass support for emergency cesarean delivery in a patient with severe pulmonary hypertension. Am J Obstet Gynecol 2001;184(2):225–226.
318. Tampakoudis P, Grimbizis G, Chatzinicolaou K, et al. Successful pregnancy in a patient with severe pulmonary hypertension. Gynecol Obstet Invest 1996;42(1):63–65.
319. Power KJ, Avery AF. Extradural analgesia in the intrapartum management of a patient with pulmonary hypertension. Br J Anaesth 1989; 63(1):116–120.
320. Roessler P, Lambert TF. Anaesthesia for caesarean section in the presence of primary pulmonary hypertension. Anaesth Intensive Care 1986; 14(3):317–320.
321. Breen TW, Janzen JA. Pulmonary hypertension and cardiomyopathy: anaesthetic management for caesarean section. Can J Anaesth 1991; 38(7):895–899.
322. Weeks SK, Smith JB. Obstetric anaesthesia in patients with primary pulmonary hypertension. Can J Anaesth 1991;38(7):814–816.
323. Sorensen MB, Korshin JD, Fernandes A, et al. The use of epidural analgesia for delivery in a patient with pulmonary hypertension. Acta Anaesth Scand 1982;26(3):180–182.
324. Katz H. About the sudden natural death in pregnancy: during delivery and puerperium. Arch Gynaekol 1922;115:283.
325. Hankins GD, Wendel GD, Jr., Leveno KJ, et al. Myocardial infarction during pregnancy: a review. Obstet Gynecol 1985;65(1):139–146.
326. Trouton TG, Sidhu H, Adgey AA. Myocardial infarction in pregnancy. Int J Cardiol 1988;18(1):35–39.
327. Lamb MA. Myocardial infarction during pregnancy: a team challenge. Heart Lung 1987;16(6):658–661.
328. Sperry KL. Myocardial infarction in pregnancy. J Forensic Sci 1987; 32(5):1464–1470.
329. Badui E, Enciso R. Acute myocardial infarction during pregnancy and puerperium: a review. Angiology 1996;47(8):739–756.
330. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. Ann Intern Med 1996;125(9):751–762.
331. Hands ME, Johnson MD, Saltzman DH, et al. The cardiac, obstetric, and anesthetic management of pregnancy complicated by acute myocardial infarction. J Clin Anesth 1990;2(4):258–268.
332. Beral V, Hermon C, Kay C, et al. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. BMJ 1999; 318(7176):96–100.
333. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxaemia of pregnancy. Heart 1997;77(2):154–158.
334. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ 1989;298(6667):165–168.
335. Frenkel Y, Barkai G, Reisin L, et al. Pregnancy after myocardial infarction: are we playing safe? Obstet Gynecol 1991;77(6):822–825.
336. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315(17):1046–1051.
337. Schachne JS, Roberts BH, Thompson PD. Coronary-artery spasm and myocardial infarction associated with cocaine use. N Engl J Med 1984; 310(25):1665–1666.
338. Howard RE, Hueter DC, Davis GJ. Acute myocardial infarction following cocaine abuse in a young woman with normal coronary arteries. JAMA 1985;254(1):95–96.

339. Pasternack PF, Colvin SB, Baumann FG. Cocaine-induced angina pectoris and acute myocardial infarction in patients younger than 40 years. Am J Cardiol 1985;55(6):847.
340. Cregler LL, Mark H. Relation of acute myocardial infarction to cocaine abuse. Am J Cardiol 1985;56(12):794.
341. Cowan NC, de Belder MA, Rothman MT. Coronary angioplasty in pregnancy. Br Heart J 1988;59(5):588–592.
342. Reich DL, Brooks JL, Kaplan JA. Uncommon cardiac diseases. In: Katz J, Benumof JF, Dadis LB (eds) Anesthesia and Uncommon Diseases. Philadelphia: Saunders, 1990:347.
343. Davis MJ, Ireland MA. Effect of early anticoagulation on the frequency of left ventricular thrombi after anterior wall acute myocardial infarction. Am J Cardiol 1986;57(15):1244–1247.
344. Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 1983;59b(6):499–505.
345. Topkins MJ, Artusio J. Myocardial infarction and surgery, a five-year study. Anesth Analg 1964;23:716.
346. Tarhan S, et al. Myocardial infarction after general anesthesia. JAMA 1972;220(11):1451–1454.
347. Listo M, Bjorkenheim G. Myocardial infarction during delivery. Acta Obstet Gynecol Scand 1966;45(3):268–278.
348. Mabie WC, Anderson GD, Addington MB, et al. The benefit of cesarean section in acute myocardial infarction complicated by premature labor. Obstet Gynecol 1988;71(3):503–506.
349. Ascarelli MH, Grider AR, Hsu HW. Acute myocardial infarction during pregnancy managed with immediate percutaneous transluminal coronary angioplasty. Obstet Gynecol 1996;88(4):655–657.
350. Webber MD, Halligan RE, Schumacher JA. Acute infarction, intracoronary thrombolysis, and primary PTCA in pregnancy. Catheter Cardiovasc Diagn 1997;42(1):38–43.
351. Sanchez-Ramos L, Chami YG, Bass TA, et al. Myocardial infarction during pregnancy: management with transluminal coronary angioplasty and metallic intracoronary stents. Am J Obstet Gynecol 1994;171(5):1392–1393.
352. Bernal JM, Miralles PJ. Cardiac surgery with cardiopulmonary bypass during pregnancy. Obstet Gynecol Surv 1986;41(1):1–6.
353. Conroy JM, Bailey MK, Hollon MF, et al. Anesthesia for open heart surgery in the pregnant patient. South Med J 1989;82(4):492–495.
354. Majdan JF, Walinsky P, Cowchock SF, et al. Coronary artery bypass surgery during pregnancy. Am J Cardiol 1983;52(8):1145–1146.
355. Garry D, Leikin E, Fleisher AG, et al. Acute myocardial infarction in pregnancy with subsequent medical and surgical management. Obstet Gynecol 1996;87(5):802–804.
356. Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983;308(22):1312–1318.
357. Kennedy JW, Ritchie JL, Davis KB, et al. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983;309(24):1477–1482.
358. Schumacher B, Belfort MA, Card RJ. Successful treatment of acute myocardial infarction during pregnancy with tissue plasminogen activator. Am J Obstet Gynecol 1997;176(3):716–719.
359. Cohen WR, Steinman T, Patsner B, et al. Acute myocardial infarction in a pregnant woman at term. JAMA 1983;250(16):2179–2181.
360. Bembridge M, Lyons G. Myocardial infarction in the third trimester of pregnancy. Anaesthesia 1988;43(3):202–204.
361. Aglio LS, Johnson MD. Anaesthetic management of myocardial infarction in a parturient. Br J Anaesth 1990;65(2):258–261.
362. Soderlin MK, Purhonen S, Haring P, et al. Myocardial infarction in a parturient. A case report with emphasis on medication and management. Anaesthesia 1994;49(10):870–872.
363. Curletta JD, de Leon OA. Epidural anesthesia in patients with coronary artery disease. Anesthesiology 1990;72(1):214.
364. Peters J, Kutkuhn B, Medert HA, et al. Sympathetic blockade by epidural anesthesia attenuates the cardiovascular response to severe hypoxemia. Anesthesiology 1990;72(1):134–144.
365. Milewicz DM. Molecular genetics of Marfan syndrome and Ehlers-Danlos type IV. Curr Opin Cardiol 1998;13(3):198–204.
366. Loeys B, Nuytinck L, van Acker P, et al. Strategies for prenatal and preimplantation genetic diagnosis in Marfan syndrome (MFS). Prenat Diagn 2002;22(1):22–28.
367. Aburawi EH, O'Sullivan J, Hasan A. Marfan's syndrome: a review. Br J Hosp Med 2001;62(3):153–157.
368. Paternoster DM, Santarossa C, Vettore N, et al. Obstetric complications in Marfan's syndrome pregnancy. Minerva Ginecol 1998;50(10):441–443.
369. Ferguson JE II, Ueland K, Stinson EB, et al. Marfan's syndrome: acute aortic dissection during labor, resulting in fetal distress and cesarean section, followed by successful surgical repair. Am J Obstet Gynecol 1983;147(7):759–762.
370. Dalen JE, Alpert JS, Cohn LH, et al. Dissection of the thoracic aorta. Medical or surgical therapy? Am J Cardiol 1974;34(7):803–808.
371. Rossiter JP, Repke JT, Morales AJ, et al. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. Am J Obstet Gynecol 1995;173(5):1599–606.
372. Tritapepe L, Voci P, Pinto G, et al. Anaesthesia for caesarean section in a Marfan patient with recurrent aortic dissection. Can J Anaesth 1996;43(11):1153–1155.
373. Rosenblum NG, Grossman AR, Gabbe SG, et al. Failure of serial echocardiographic studies to predict aortic dissection in a pregnant patient with Marfan's syndrome. Am J Obstet Gynecol 1983;146(4):470–471.
374. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. Eur J Obstet Gynecol Reprod Biol 2001;98(1):28–35.
375. Lipscomb KJ, Smith JC, Clarke B, et al. Outcome of pregnancy in women with Marfan's syndrome. Br J Obstet Gynaecol 1997;104(2):201–206.
376. Gordon CF III, Johnson MD. Anesthetic management of the pregnant patient with Marfan syndrome. J Clin Anesth 1993;5(3):248–251.
377. Cola LM, Lavin JP Jr. Pregnancy complicated by Marfan's syndrome with aortic arch dissection, subsequent aortic arch replacement and triple coronary artery bypass grafts. J Reprod Med 1985;30(9):685–688.
378. Brar HB. Anaesthetic management of a caesarean section in a patient with Marfan's syndrome and aortic dissection. Anaesth Intensive Care 2001;29(1):67–70.
379. Akashi H, Tayama K, Fujino T, et al. Surgical treatment for acute type A aortic dissection in pregnancy: a case of aortic root replacement just after Cesarean section. Jpn Circ J 2000;64(9):729–730.
380. Dizon-Townson D, Magee KP, Twickler DM, et al. Coarctation of the abdominal aorta in pregnancy: diagnosis by magnetic resonance imaging. Obstet Gynecol 1995;85(5):817–819.
381. Lip GY, Singh SP, Beevers DG. Aortic coarctation diagnosed after hypertension in pregnancy. Am J Obstet Gynecol 1998;179(3):814–815.
382. Beauchesne LM, Connolly HM, Ammash NM, et al. Coarctation of the aorta: outcome of pregnancy. J Am Coll Cardiol 2001;38(6):1728–1733.
383. Conti S, Wagner C, Fitpatrick HF. Abdominal aortic coarctation and pregnancy. J Cardiovasc Surg 1980;21(3):379–386.
384. Zeira M, Zohar S. Pregnancy and delivery in women with coarctation of the aorta. Harefuah 1993;124(12):756–758, 795–796.
385. Fadouach S, Azzouzi L, Tahiri A, et al. Aortic coarctation and pregnancy. Apropos of 3 cases followed-up during a period of 10 years. Ann Cardiol Angiol 1994;43(5):262–265.
386. Saidi AS, Bezold LI, Altman CA, et al. Outcome of pregnancy following intervention for coarctation of the aorta. Am J Cardiol 1998;82(6):786–788.
387. Deal K, Wooley CF. Coarctation of the aorta and pregnancy. Ann Intern Med 1973;78(5):706–710.
388. Manullang TR, Chun K, Egan TD. The use of remifentanil for Cesarean section in a parturient with recurrent aortic coarctation. Can J Anaesth 2000;47(5):454–459.
389. Rocha MP, Guntupalli KK, Moise KJ, Jr., et al. Massive hemoptysis in Takayasu's arteritis during pregnancy. Chest 1994;106(5):1619–1622.
390. Wang YM, Mak GY, Lai KN, et al. Treatment of Takayasu's aortitis

with percutaneous transluminal angioplasty and wall stent—a case report. Angiology 1998;49(11):945–949.
391. Ishikawa K, Matsuura S. Occlusive thromboaortopathy (Takayasu's disease) and pregnancy. Clinical course and management of 33 pregnancies and deliveries. Am J Cardiol 1982;50(6):1293–1300.
392. Moncada GA, Hashimoto Y, Kobayashi Y, et al. Usefulness of beta blocker therapy in patients with Takayasu arteritis and moderate or severe aortic regurgitation. Jpn Heart J 2000;41(3):325–337.
393. Beilin Y, Bernstein H. Successful epidural anaesthesia for a patient with Takayasu's arteritis presenting for caesarean section. Can J Anaesth 1993;40(1):64–66.
394. Henderson K, Fludder P. Epidural anaesthesia for caesarean section in a patient with severe Takayasu's disease. Br J Anaesth 1999;83(6):956–959.
395. Liou JT, Sun MS, Lin YH, et al. Combined spinal-epidural anesthesia for cesarean section in a patient with Takayasu's disease. Chung Hua I Hsueh Tsa Chih 2000;63(1):66–70.
396. Kathirvel S, Chavan S, Arya VK, et al. Anesthetic management of patients with Takayasu's arteritis: a case series and review. Anesth Analg 2001; 93(1):60–65.
397. Clark AG, al-Qatari M. Anaesthesia for caesarean section in Takayasu's disease. Can J Anaesth 1998;45(4):377–379.
398. Brunt LM. Phaeochromocytoma in pregnancy. Br J Surg 2001;88(4): 481–483.
399. Harper MA, Murnaghan GA, Kennedy L, et al. Phaeochromocytoma in pregnancy. Five cases and a review of the literature. Br J Obstet Gynaecol 1989;96(5):594–606.
400. Freier DT, Thompson NW. Pheochromocytoma and pregnancy: the epitome of high risk. Surgery (St. Louis) 1993;114(6):1148–1152.
401. Harrington JL, Farley DR, van Heerden JA, et al. Adrenal tumors and pregnancy. World J Surg 1999;23(2):182–186.
402. Botchan A, Hauser R, Kupfermine M, et al. Pheochromocytoma in pregnancy: case report and review of the literature. Obstet Gynecol Surv 1995;50(4):321–327.
403. McGregor CG. Current state of heart transplantation. Br J Hosp Med 1987;37(4):310–313; 316–318.
404. Hosenpud JD, Bennett LE, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: fourteenth official report—1997. J Heart Lung Transplant 1997;16(7):691–712.
405. Dziatkowiak A, Zdebski Z, Tracz W, et al. Successful full-term pregnancy in a patient three and a half years after a heart transplant. Ann Transplant 1996;1(4):65–66.
406. Morini A, Spina V, Aleandri V, et al. Pregnancy after heart transplant: update and case report. Hum Reprod 1998;13(3):749–757.
407. Troche V, Ville Y, Fernandez H. Pregnancy after heart or heart-lung transplantation: a series of 10 pregnancies. Br J Obstet Gynaecol 1998; 105(4):454–458.
408. Kim KM, Sukhani R, Slogoff S, et al. Central hemodynamic changes associated with pregnancy in a long-term cardiac transplant recipient. Am J Obstet Gynecol 1996;174(5):1651–1653.
409. Eskandar M, Gader S, Ong BY. Two successful vaginal deliveries in a heart transplant recipient. Obstet Gynecol 1996;87(5):880.
410. Leachman RD, et al. Response of the transplanted, denervated human heart to cardiovascular drugs. Am J Cardiol 1971;27(3):272–276.
411. Lowenstein BR, Vain NW, Perrone SV, et al. Successful pregnancy and vaginal delivery after heart transplantation. Am J Obstet Gynecol 1988;158(3):589–590.
412. Yusuf S, Theodoropoulos S, Mathias CJ, et al. Increased sensitivity of the denervated transplanted human heart to isoprenaline both before and after beta-adrenergic blockade. Circulation 1987;75(4):696–704.
413. Sgro MD, Barozzino T, Mirghani HM, et al. Pregnancy outcome post renal transplantation. Teratology 2002;65(1):5–9.
414. Pergola PE, Kancharla A, Riley DJ. Kidney transplantation during the first trimester of pregnancy: immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 2001;71(7):994–997.
415. Lau RJ, Scott JR. Pregnancy following renal transplantation. Clin Obstet Gynecol 1985;28(2):339–350.
416. Armenti VT, Herrine SK, Radomski JS, et al. Pregnancy after liver transplantation. Liver Transplant 2000;6(6):671–685.
417. Carr DB, Larson AM, Schmucker BC, et al. Maternal hemodynamics and pregnancy outcome in women with prior orthotopic liver transplantation. Liver Transplant 2000;6(2):213–221.
418. Deeg HJ, Kennedy MS, Sanders JE, et al. Successful pregnancy after marrow transplantation for severe aplastic anemia and immunosuppression with cyclosporine. JAMA 1983;250(5):647.
419. Barrou BM, Gruessner AC, Sutherland DE, et al. Pregnancy after pancreas transplantation in the cyclosporine era: report from the International Pancreas Transplant Registry. Transplantation 1998;65(4):524–527.
420. Kruszka SJ, Gherman RB. Successful pregnancy outcome in a lung transplant recipient with tacrolimus immunosuppression. A case report. J Reprod Med 2002;47(1):60–62.
421. Kossoy LR, Herbert CM III, Wentz AC. Management of heart transplant recipients: guidelines for the obstetrician-gynecologist. Am J Obstet Gynecol 1988;159(2):490–499.
422. Branch KR, Wagoner LE, McGrory CH, et al. Risks of subsequent pregnancies on mother and newborn in female heart transplant recipients. J Heart Lung Transplant 1998;17(7):698–702.
423. Borow KM, Neumann A, Arensman FW, et al. Left ventricular contractility and contractile reserve in humans after cardiac transplantation. Circulation 1985;71(5):866–872.
424. Camann WR, Jarcho JA, Mintz KJ, et al. Uncomplicated vaginal delivery 14 months after cardiac transplantation. Am Heart J 1991;121(3): 939–941.
425. Kirk EP. Organ transplantation and pregnancy. A case report and review. Am J Obstet Gynecol 1991;164(6):1629–1633; discussion 1633–1634.
426. Hedon B, Montoya F, Cabrol A. Twin pregnancy and vaginal birth after heart transplantation. Lancet 1990;335(8687):476–477.
427. Carruth JE, Mivis SB, Brogan DR, et al. The electrocardiogram in normal pregnancy. Am Heart J 1981;102(6):1075–1078.
428. Naulty JS, Ostheimer GW, Datta S, et al. Incidence of venous air embolism during epidural catheter insertion. Anesthesiology 1982;57(5): 410–412.

13
Renal Disease

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This chapter focuses on the obstetric and anesthetic management of gravidas at high risk because of maternal renal disease. To better understand renal disease in pregnancy, one must comprehend the normal changes that occur in the urinary system during gestation. The first section addresses the normal morphologic and physiologic changes in the renal system during pregnancy. Information about acute and chronic renal disease follows. Further discussion includes the essential diagnostic tests as well as antepartum, intrapartum, and postpartum obstetric management recommendations and prognosis. The anesthetic implications of the pathophysiologic changes in parturients with renal dysfunction and the anesthetic management are then discussed.

Changes in the Urinary System During Pregnancy

Anatomic Changes

There is a moderate increase in size and weight as well as change in the radiographic appearance of the kidney during pregnancy. The renal length increases by approximately 1 cm during pregnancy when measured radiographically.[1] The increase in renal mass primarily results from the dilation of the renal pelvis. Other changes include an increase in the renal interstitium.[2] Although the exact cause of urinary system dilation remains elusive, mechanical (the gravid uterus compresses the ureters) and physiologic (relaxation effects of progesterone and estrogen) changes have been speculated. Hormonal effects may predominate in early pregnancy when the ureters appear dilated before the uterus enlarges enough to cause compression. Later, as the uterus enlarges, mechanical effects may predominate.[2] These changes seem to be universal, and up to 97% of all gravidas have relative hydronephrosis.[2]

Physiologic Changes

Renal hemodynamics are altered during pregnancy. Both glomerular filtration rate (GFR) and renal blood flow (RBF) are dramatically increased in pregnancy. The rise in GRF occurs around conception and peaks at 50% above nonpregnant levels by the late second trimester, then decreases slightly by term.[3] The exact etiology of this increase remains unclear. Serum creatinine decreases as clearance increases.[4,5] In addition, there is an increase in proteinuria throughout gestation that results in the relative hypoalbuminemia of pregnancy.[6] Unlike the changes in GFR, most of the increase in proteinuria occurs in the third trimester. Proteinuria increases from 103 ± 49 mg/24 h in the first trimester to 180 ± 50 mg/24 h in late pregnancy.[7,8] The upper limit of normal in pregnancy is considered to be 300 mg protein in a 24-h urine collection. Acid–base metabolism remains a function of renal bicarbonate recovery and hydrogen secretion. There is a relative alkalosis in pregnancy, which appears to be respiratory in origin. Maternal hyperventilation results in a decrease in P_{CO_2} from 36 to 29 mm Hg.[8,9] Compensatory changes for pregnancy-induced respiratory alkalosis include a decrease in serum bicarbonate by 20 mEq/L, base excess by 2 to 3 mEq/L, and total buffer base by approximately 5 mEq/L.[8,9] Thus, in pregnancy a state of mild metabolic alkalosis exists.

In pregnant women, therefore, any further changes such as acute metabolic acidosis induced by renal failure can cause a precipitous decrease in pH due to their inability to compensate.[10] Tubular function is also affected by pregnancy. Glucosuria is more common in gravidas.[11–13] In fact, pregnancy results in up to a 10-fold increase in glucose excretion.[14] The decrease in glucose tubular reabsorption accounts for the common finding of glucosuria in normoglycemic pregnancies. This decrease in tubular reabsorption also results in increased excretion of water-soluble amino acids and vitamins.[15]

Weight gain in pregnancy is largely attributed to increased water retention. The average weight gain in pregnancy is 12 kg, although as much as 20 kg may be physiologic.[16] In fact, body water weight increases to approximately 7 to 8 L during pregnancy.[17] The majority of water retention occurs in the extracellular space, as plasma volume increases by approximately 50% in pregnancy. With increased water retention, there is a decrease in effective osmolality; this decrease in osmolality is primarily a result of altered vasopressin re-

lease.[18,19] The increase in plasma volume and extracellular space represents hypervolemia sensed by the normal sodium and water control mechanisms. Total body sodium increases by 1000 mEq during pregnancy.[20] Serum osmolality decreases by 10 mOsm/kg.[21] The kidney retains its ability to concentrate in the loop of Henle, although hypotonic urine production predominates. Because volume status is regulated by a resetting of the maternal antidiuretic hormone response rather than by the direct effects of sodium on the kidney, sodium restriction in pregnancy is not warranted.

Acute Renal Disease

Acute renal failure (ARF) is defined as a rapid decline in renal function in which GFR approaches zero. Clinical features include an almost linear increase in serum creatinine of at least 0.5 mg/dL/day. Oliguria of less than 400 mL urine output/day is a classic sign found in the majority of patients with ARF. There may be a progressive increase in blood urea nitrogen. If ARF goes untreated, life-threatening metabolic acidosis, uremia, and hyperkalemia soon follow.

Etiology

Etiology for ARF can be classified as prerenal, renal, or postrenal (Table 13.1). Determining the cause of ARF is imperative so actions can be taken to correct it. The distribution of ARF in pregnancy is bimodal. The first peak occurs in the first trimester as a result of miscarriage or abortion complications; the larger peak occurs in the third trimester.

Prerenal Etiology

A common prerenal etiology for ARF implicates hypoperfusion as the causal agent. Most commonly, oliguria results from the normal response of promoting sodium retention and water retention to preserve volume. Obstetric causes of prerenal ARF are shown in Table 13.1. It is often difficult to distinguish prerenal azotemia (volume depletion) from acute tubular necrosis. Laboratory evaluation may include fractional excretion of sodium, urine osmolality, and evaluation of urinary sediment. Fractional excretion of sodium is defined as urine sodium/serum sodium divided by urine creatinine/serum creatinine. Prerenal azotemia characteristics include fractional excretion of sodium usually less than 1%, urine osmolality greater than 500 mOsm/kg H_2O, a bland urinary sediment as opposed to greater than 2% fractional excretion of sodium, urine osmolality of less than 350 mOsm/kg H_2O, and urinary casts or renal tubular epithelial cells seen in urinary sediment in patients with acute tubular necrosis. As a general rule, management of ARF is similar in pregnant and nonpregnant patients. Aggressive management of prerenal ARF is imperative to prevent significant perinatal morbidity or mortality. If volume depletion is the cause, administration of crystalloids, colloids, or blood products should be rapid. The type of intravenous fluid (IVF) that works best for correction of hypovolemia remains controversial. We recommend avoidance of potassium containing IVF.

TABLE 13.1. Prerenal causes of acute renal failure (ARF).

Prerenal azotemia (volume depletion)
Excessive vomiting during pregnancy
Hemorrhage: antepartum, intrapartum, or postpartum ectopic pregnancy, abortion
Preeclampsia[a]
Infection
Pyelonephritis
Septic abortion
Decreased cardiac output
Cardiac failure
Hypotension
Amniotic fluid embolism
Blood transfusion reaction
Drug reaction
Sepsis
Intrinsic renal disease
Acute glomerulonephritis
Acute interstitial nephritis
Acute tubular necrosis
Other
Hemolytic uremic syndrome

[a]Exact pathology unclear.

Renal Etiology

Renal causes of ARF are listed in Table 13.2. Renal causes can be divided into those etiologies that cause acute tubular necrosis (ATN) and those which cause acute interstitial necrosis (AIN). ATN results from a wide variety of renal insults including ischemic insults, pigment-induced ATN from massive hemolysis, aminoglycoside toxicity, heavy metals, or numerous chemotherapeutic agents. The most common cause of ATN is a pharmacologic reaction. Commonly associated drugs include medications often used by obstetricians and anesthesiologists such as beta-lactam antibiotics, sulfa-based

TABLE 13.2. Renal causes of acute renal failure (ARF).

Primary
Minimal change disease
Focal segmental glomerulosclerosis
IgA nephropathy
Membranoproliferative glomerulonephropathy
Membranous nephropathy
Poststreptococcal glomerulonephropathy
Secondary
Systemic lupus erythematosus
Cryoglobulinemia
Polyarteritis nodosa
Wegener's granulomatosis
Goodpasture's syndrome
Henoch–Schonlein purpura
Infection related (endocarditis)

drugs, H_2-blockers, and nonsteroidal antiinflammatory agents. Infectious etiologies such as streptococcus, cyto-megalovirus, and infectious mononucleosis should be investigated. For those who have traveled to endemic areas, malaria and leptospirosis should be considered. The treatment for ATN is supportive and necessitates optimization of electrolyte and fluid balance; occasionally, dialysis is needed. Renal function returns within 7 to 14 days after correction of the causal insult.

Postrenal Etiology

A postrenal cause of ARF implicates an obstructive process. An enlarged uterus from pregnancy may compress either ureter from profound dextro- or levorotation. This problem is more common in cases in which the uterus is enlarged (multifetal gestation, polyhydramnios). Other sources of ureteral obstruction may result from leiomyomata or adnexal masses. A unique pregnancy-related cause of postrenal failure comes from an incarcerated uterus. At 15 weeks gestation, the uterus leaves the true pelvis and rises into the abdomen. If the uterus is extremely retroverted, it may get caught on the sacrum and double back upon itself. The fundus is shifted inferiorly, which causes the uterine cervix to move anteriorly and compress the urethra. Patients present with marked abdominal pain and the inability to void. Treatment should consist of manual decompression. General anesthesia with inhaled anesthestic may be needed to relax the uterus. The patient is then fitted with a Smith–Hodge pessary to keep the uterus anteverted. Pessary use is rarely warranted for more than 2 weeks. After that time, the pregnant uterine fundus will be elevated out of the true pelvis.

Management of ARF from any of these causes requires attention to both volume and metabolic status as well as nutritional support. Volume status should optimize intravascular volume and cardiac filling pressures. Invasive monitoring with central venous pressure (CVP) or pulmonary artery (PA) catheter may be indicated. Attempts should be made to establish a non-oliguric state. Loop diuretics (Furosemide 5–40 mg/kg IV) or Zaroxolyn (5 mg PO) can be used. Fluid intake should be limited to insensible losses (500 mL/24 h) and urine output. Any blood loss should be compensated with appropriate replacement products. Renal dose dopamine (2–3 mg/kg/min) can be used in early ARF but should not be continued if oliguria persists.

Metabolic status may be especially problematic in ARF, and electrolytes should be monitored. If the serum potassium is elevated but less than 6 mEq/L, an exchange resin such as kayexalate in sorbitol can be used. For serum potassium greater than 6 mEq/kg or for those associated with EKG changes, inhaled beta agonists, $NaHCO_3$ 1 mEq/kg, or glucose 50 g with regular insulin 10 units IV can be used. Under these circumstances, hemodialysis is the best therapeutic option. If ECG changes do occur, 10 mL 10% calcium gluconate solution can be administered slowly intravenously to stabilize the cardiac membrane. If faced with hyperphosphatemia, calcium acetate or calcium carbonate can be used three to four times per day. The pH should be maintained at greater than 7.2. The HCO_3 can be calculated as follows: (HCO_3 desired − measured HCO_3) × (0.6 × weight in kg). The purpose of nutrition supplementation in ARF is to facilitate the management of electrolyte imbalance. Daily protein should be restricted to 0.8 g/kg/day + 10 g. Other restrictions should include potassium 1 mEq/kg/day, sodium 4 g/day, calcium intake 1200 mg/day, and phosphate 1 g/day. Iron and folate should be supplemented to balance the decrease in erythropoietin.

Indications for dialysis should include uremic encephalopathy, pericarditis, platelet dysfunction, refractory volume overload, refractory metabolic acidosis, marked hyperkalemia or other severe metabolic abnormalities, and uremic symptoms such as nausea/vomiting or pruritus. Other indications for dialysis are a creatinine greater than 10 mg/dL or a blood urea nitrogen (BUN) greater than 100 mg/dL. Dialysis is indicated before any major anesthetic and surgical interventions to normalize the fluid and electrolyte status.

Chronic Renal Disease

Chronic renal disease patients often desire fertility. However, these are high-risk pregnancies and often have significant maternal or fetal morbidity. Several studies have evaluated parturients with chronic renal insufficiency (serum creatinine >1.4 mg/dL) throughout pregnancy. Hon reported a review of 226 pregnancies in 196 women suggesting that renal disease progresses more rapidly in women who become pregnant than in those who do not.[22] Classification of renal parenchymal disease is shown in Table 13.3. As renal disease progresses, fertility decreases. When pregnancies do occur, miscarriage rates and adverse perinatal outcomes increase. Women with mild renal insufficiency (serum creatinine <1.4 mg/dL) do well with pregnancy and do not progress rapidly

TABLE 13.3. Classification of renal parenchymal disease.

Glomerular
Primary disease
Epithelial disease
Focal glomerulosclerosis
Membranous nephropathy
Proliferative glomerulosclerosis
Chronic glomerulonephritis
Systemic disease
Diabetic glomerulosclerosis
Systemic lupus erythematosus
Systemic vasculitis
Amyloidosis
Interstitial
Acute interstitial nephritis
Chronic interstitial nephritis
Vascular
Arterionephrosclerosis
Arterial emboli
Vasculitis

to end-stage renal disease (ESRD).[23] Prognostic indicators for those with mild renal insufficiency are the control of hypertension and the type of glomerulonephritis. Women with severe renal disease (serum creatinine >3 mg/dL) are often infertile. Those who ovulate and conceive are at high risk for spontaneous fetal loss. In a 1990 review of pregnancies with severe renal disease, 7 of 11 patients were managed successfully (live birth at more than 26 weeks).[24] In addition, patients with moderate or severe disease were likely to develop ESRD more quickly after pregnancy. Prenatal care for patients with chronic renal disease should include baseline studies of a 24-h urine for creatinine clearance and total protein, electrolyte concentrations, and serum albumin. Those with severe renal disease should be educated about the option of elective termination of pregnancy. Parturients should be seen every 2 to 3 weeks until 30 weeks, then weekly. Antenatal fetal testing, including heightened surveillance for growth restriction, should begin at 28 to 32 weeks. Patients with nephrotic range proteinuria should be watched carefully for superimposed preeclampsia. Blood pressure should be controlled to a diastolic blood pressure below 90 mm Hg. In diabetics, calcium channel blockers are the antihypertensive medication of choice. Protein-restricted diets should be stopped at conception because of concerns over abnormal fetal development.

Infectious Renal Disease

The incidence of asymptomatic bacteriuria in pregnancy approaches 10%, which is similar to the incidence of asymptomatic bacteriuria in nonpregnant women of reproductive age.[25,26] Although the incidence of asymptomatic bacteriuria is unchanged in pregnancy, the progression to clinical infection is higher in pregnancy. The progression of asymptomatic bacteriuria to pyelonephritis approaches 25%.[27] Screening in early pregnancy for asymptomatic bacteriuria with midstream urine culture is cost effective.[28] The incidence of pyelonephritis is less than 2% in patients without bacteria upon first trimester screening.[25] The most common cause of bacteriuria is bacteria acquired from the gastrointestinal tract. *Escherichia coli* accounts for approximately 80% of all community-acquired urinary tract infections (UTI) in pregnancy.[25,29] Other organisms include *Klebsiella* sp., *Proteus* sp., and group B streptococci as well as *Enterobacter* sp.. Treatment should be targeted to the specific bacterial sensitivity on urine culture. If no sensitivity report is available, cephalexin or nitrofurantoin are reasonable choices. Treatment should be for 7 days, although the American College of Obstetrics and Gynecology proposes that a 3-day treatment may be sufficient.[30]

Follow-up cultures should be obtained every 4 to 8 weeks for the remainder of gestation. A second positive culture should be retreated, and daily prophylaxis should be instituted with cephalexin 125 mg/day PO or nitrofurantoin 50 mg/day PO. A repeat culture should be done postpartum and be treated accordingly. Cystitis is diagnosed in 1.3% of pregnancies.[31] The clinical syndrome includes dysuria, polyuria, or malodorous urine in the absence of fever or costovertebral angle tenderness confirmed by urinalysis or urine culture. Only about half of patients with clinical cystitis have positive urine cultures.[32] Treatment of cystitis is similar to the foregoing regimens for asymptomatic bacteriuria. Quinalones, although effective, should not be used in pregnancy. Trimethoprim with sulfa is not recommended because of potential fetal adverse effects. After two episodes of urinary tract infection (bacteriuria or cystitis), consideration should be given to routine prophylaxis or routine urine culture. Progression to pyelonephritis is common from asymptomatic bacteriuria but uncommon from cystitis because of early treatment.[31] Pyelonephritis is one of the most common medical complications in pregnancy, with an incidence of about 2%. The diagnosis of pyelonephritis is based on history of fever, flank pain, polyuria, dysuria, or urgency. Physical findings include costovertebral angle tenderness (usually right-sided or bilateral) and, almost uniformly, fever. Laboratory studies reveal leukocytosis, pyuria, and bacteriuria.

Pyelonephritis represents one of the most serious maternal infections and is one of the leading causes of septic shock.[33] Bacteremia occurs in about 10% of parturients with pyelonephritis. Twenty-five percent of parturients with pyelonephritis have evidence of multisystem involvement, most commonly respiratory insufficiency and adult respiratory distress syndrome. Treatment for pyelonephritis includes hospitalization with aggressive hydration and intravenous antibiotics. Antibiotic choices include ampicillin and gentamycin or a first-generation cephalosporin such as cefazolin. Ampicillin alone is inadequate treatment as a result of the high incidence of antimicrobial resistance. With appropriate antibiotic use, the majority of patients become afebrile within 48 h. Parturients who do not respond within 8 h should be evaluated for concomitant urolithiasis. Parturients are treated with parenteral antibiotics until afebrile for 24 h, and then are switched to an oral agent to complete 7 days of therapy. Culture results will dictate the oral antibiotic of choice. When no culture is available, parturients are generally treated with a first-generation cephalosporin or nitrofurantoin for a total of 7 to 10 days of treatment. Readmission rates for recurrent pyelonephritis during the same gestation have been reported to be as high as 60% in the absence of suppressive antibiotics.[34] We recommend suppressive therapy with nitrofurantoin 50 mg or cephalexin 125 mg by mouth each day until 6 weeks postdelivery. Alternatively, urine cultures can be obtained each month to rule out asymptomatic bacteriuria, or parturients may choose to take a daily suppressive dose of antibiotics.

Obstructive Renal Disease

Obstruction of the renal system is a common problem that should be given special consideration during gestation.

Nephrolithiasis is the most common cause of urinary tract obstruction in pregnancy. Although physiologic changes (such as urinary stasis and hypercalciuria in pregnancy) seem to predispose to the formation of stones, the incidence of symptomatic nephrolithiasis is similar to the nonpregnant incidence. The physiologic hydroureter of pregnancy may offer a protective effect, allowing small stones to pass without symptoms. Hendricks et al. reviewed 14 published series and found the incidence to be 1 in 1240 pregnancies.[35] Butler et al. observed that symptoms of nephrolithiasis in 57 pregnancies included gross hematuria (23%), flank and/or abdominal pain (84%), dysuria (20%), and nausea (32%). Common laboratory findings were bacteriuria (81%) and microscopic hematuria (75%).[36] Radiographic imaging is often used to confirm a clinical diagnosis of nephrolithiasis. Renal ultrasonography is the mainstay for diagnosis confirmation. In Butler's review of the Parkland Hospital experience, renal sonogram had a sensitivity of 60%.[36] Renal stones show up as an echodensity with appropriate shadowing within the urinary system. Physiologic ureteral dilation often complicates diagnosis if the stone does not appear hyperechoic. A single-shot or limited intravenous pyelogram is a reasonable alternative when ultrasound or abdominal X-ray studies are normal.

The majority of patients respond well to conservative management consisting of hydration, pain control, and antibiotics if a concomitant infection is present. More severe cases may response to nephrostomy tube, stent placement, or urethroscopy with stone retrieval. Lithotripsy use remains controversial but is usually avoided secondary to fetal safety concerns. Patients with obstructive pyelonephritis may deteriorate quickly and should therefore be treated aggressively to remove the obstruction.

Renal Transplants

The kidney is the most common solid organ allograft transplanted in reproductive-age females. Because transplantation often restores fertility, pretransplant counseling should include discussion of contraception. Pregnancy occurs in approximately 2% of reproductive-age renal transplant patients. Lindheimer et al. have published recommendations for preconceptual counseling.[10] First, patients should wait 2 years before attempting conception and should be in good health. Some suggest a 12-month wait if a living donor transplant was performed. Second, renal function should be stable (creatinine <2 mg/dL and preferably <1.5 mg/dL). There should be no evidence of rejection, minimal proteinuria, and an absence of pelvicaliceal distension on urogram. Third, if hypertension is present, it should be easily managed. Fourth, drug therapy should be reduced to maintenance doses of prednisone (<15 mg/day) and azathioprine (<2 mg/kg/day). Fewer data are available on cyclosporin or Prograf (FK506) doses.[10] In a review of more than 3000 renal transplant pregnancies, the spontaneous abortion rate was 15%. Maternal complications included hypertension, septicemia, allograft rejection, glucose intolerance, and maternal death. Fetal complications included an increased risk of congenital anomalies, iatrogenic prematurity, growth restriction, and sepsis.[37] Pregnancy does not seem to affect long-term allograft function. Sturgiss and Davison conducted a case-controlled trial of 18 renal allograft transplant patients who became pregnant compared to 18 who did not. There was no difference in renal function at a follow-up of 15 years.[21] The same authors recommend that pregnancy be delayed for at least 18 months after transplant surgery to avoid the possibility of higher rates of rejection, infection, and permanent loss of graft function during the early postoperative period. However, a similar study by Salmela et al. (29 patients compared to 22 matched controls) found a higher rate of rejection in patients who became pregnant.[38] In addition, because of increased renal and hepatic function, dosages of immunosuppressant drugs may need to be altered throughout pregnancy.

Pregnancy outcomes in renal transplant patients have been documented in several retrospective studies. Pregnancy does not seem to affect renal allograft function.[39] Pregnancy in dialysis patients is unusual but does occur. Hon reviewed 37 pregnancies in renal dialysis patients; 75% of pregnancies resulted in spontaneous miscarriage, intrauterine fetal demise, or neonatal death, and 42% of live-born neonates were below the tenth percentile for weight.[40] Major problems encountered during pregnancy in dialysis patients are uncontrolled hypertension, abruptio placentae, and anemia.[41]

Anesthetic Management

It is evident from the foregoing discussion that anesthetic management of the parturient with severe renal dysfunction can be a daunting task. To our knowledge, there have been no large-scale prospective or retrospective studies that delineate the effects of any given anesthetic technique in parturients with severe renal dysfunction. Therefore, when relying on data from nonpregnant patients with renal dysfunction to plan the anesthetic management in the parturient, a cautious approach is necessary. Teamwork between the obstetrician, anesthesiologist, and nephrologist is vital for successful management of the parturient with severe renal dysfunction during the peripartum period.

General Considerations

Among the many systemic problems in patients with renal dysfunction, the following are of special interest to the anesthesiologist.

1. In most patients with renal diseases, and especially in those with chronic renal failure and uremia, delayed gastric emptying, vomiting, and nausea are common. Therefore, the

risk of aspiration of gastric contents during induction of general anesthesia is increased.

2. Severe anemia with decreased erythropoietin and 2,3-DPG levels and decreased red cell survival is quite common.[42] Often, patients tolerate this situation well. However, severe maternal anemia can interfere with fetal oxygenation. Therefore, correction with packed red cell transfusion may become necessary, especially before any major surgical intervention. In addition, in some patients, the uremia-induced platelet dysfunction, prolonged Ivy bleeding time, decreased von Willebrand's factor, and factor VIII may preclude the use of regional anesthesia.
3. Severe hypertension and left ventricular hypertrophy are commonly present. Rapid induction of general anesthesia and tracheal intubation can lead to further rise in blood pressure. Uremic pericarditis and pericardial effusion, although rare, are not uncommon. The presence of arteriovenous shunts and chronic anemia can lead to a hyperdynamic circulatory state with low systemic vascular resistance (SVR) and high cardiac output.[42] Hypotension is poorly tolerated, as it can cause myocardial ischemia and cardiac decompensation. On the other hand, with IVF administration, the risk of pulmonary edema is increased in patients with oliguria and anuria. Therefore, accurate monitoring of the hemodynamic parameters with an indwelling arterial line and central venous catheter may become necessary in the peripartum period.[42,43]
4. As mentioned previously, hyperkalemia and metabolic acidosis are commonly present, necessitating hemodialysis before any major anesthetic and surgical interventions. Other electrolyte abnormalities include hypo- or hypermagnesemia. Increased serum magnesium can cause muscle weakness and a heightened sensitivity to all muscle relaxants.[43–45]
5. Albuminuria and low serum albumin levels can alter pharmacokinetics of highly protein bound drugs.[46] The colloid osmotic pressures can be low, leading to pulmonary edema.
6. Pulmonary complications include increased susceptibility to pneumonia, atelectasis, decreased ventilatory reserve, and difficulty in weaning from ventilator.
7. The central nervous system (CNS) is also affected. The symptoms include lethargy, myoclonus, seizures, and uremic encephalopathy. The blood–brain barrier is disrupted, and the CNS effects of sedatives, narcotics, and induction agents such as pentothal are enhanced.[47] In addition, patients with chronic renal failure are often debilitated and are quite sensitive to the respiratory depressant effects of opioids and sedatives. Both autonomic and peripheral neuropathy may be present in these patients. Therefore, these patients are more susceptible to hypotension from sympathetic blockade associated with regional anesthesia. In addition, the presence of motor and sensory changes from peripheral neuropathy can be a problem with regional anesthesia. The implications should be discussed with the patient and documented in the chart.
8. Pharmacology and pharmacodynamics of most intravenous agents are altered in patients with renal dysfunction, especially in those with chronic renal failure. The clearance of drugs may be modified with decreased RBF. The free, unbound fraction of highly protein bound drugs may be increased due to hypoalbuminemia or acidosis with enhanced drug effects.[46] The duration of action of drugs with primary renal elimination may be prolonged because of accumulation of the parent drug or its metabolic compounds. Therefore, all drugs should be titrated to obtain the desired effects. In general, the doses of most anesthetic agents and opioids can be reduced by 25% to 50% in patients with renal dysfunction.
9. Inhalation agents such as methoxyflurane, enflurane, and sevoflurane undergo biotransformation.[48,49] One of the metabolic products is inorganic fluoride ion, which is nephrotoxic. Thus, it would be prudent to avoid such agents in the parturient with renal disease. Isoflurane and halothane are safer, as the release of fluoride ion with these agents is insignificant. Most general anesthetic agents interfere with renal autoregulation.[50,51] In addition, they cause a dose-related reduction in RBF and GFR, renal vasoconstriction, and increased renal vascular resistance.[50,51] Systemic hypotension worsens the situation further. On the other hand, regional anesthesia extending to the T5 level does not seem to interfere with either GFR or RBF provided perfusion pressure is maintained.[52]

Preanesthetic Preparation

A thorough preanesthetic evaluation is necessary. The degree of hemodynamic compromise should be evaluated. Hypertension should be controlled. The presence of congestive failure and pulmonary edema signals the need to optimize the patient's cardiac status before anesthetic interventions.

Laboratory studies should include hemoglobin levels, serum electrolytes, serum creatinine, creatinine clearance, BUN, and uric acid. Coagulation studies should include platelet count, prothrombin time (PT) and partial prothrombin time (PTT). Other baseline investigations include a 12-lead electrocardiogram, chest X-ray, and arterial blood gas values. Blood and blood products should be cross-matched and readily available. Monitoring lines such as CVP and an indwelling arterial line are essential in those with severe renal dysfunction and hypertension. In those patients with pulmonary edema and cardiac compromise, PA catheter placement should be considered for perioperative management.

Patients who are on chronic hemodialysis should undergo dialysis the day before cesarean delivery. All laboratory studies should be repeated after dialysis. In those patients with severe anemia, blood may be transfused during dialysis to avoid pulmonary congestion. Among the blood products, the use of cryoprecipitate is shown to improve renal function while correcting the coagulation deficits.[53]

Analgesia for Labor

For patients with coagulation deficits, intravenous opioids can be used as patient-controlled intravenous analgesia. In the absence of coagulation deficits, a segmental lumbar epidural analgesia should be considered. Optimization of volume status is essential and normal saline can be used for hydration before regional anesthesia. Both amide and ester local anesthetics may be safely used in parturients with renal dysfunction. To avoid the rapid onset of sympathetic block and hypotension, especially in those with autonomic dysfunction, a slow induction of epidural analgesia with dilute local anesthetic solution, such as 0.125% bupivacaine mixed with fentanyl, 1 to 2 μg, is recommended. If hypotension develops despite all these precautions, ephedrine in doses of 2.5 to 5 mg can be given intravenously.

Anesthesia for Cesarean Section

In the absence of coagulation deficits, regional anesthesia is preferred because GFR, RBF, clearance, and other renal function tests are not affected even in the presence of high sensory levels.[52] Hydration before regional anesthesia should be guided by CVP measurements. Normal saline or salt-poor albumin can be used. Routine preanesthetic medications such as oral antacid, cimetidine, and metoclopramide should be administered, as patients with renal diseases are more prone to pulmonary aspiration of gastric contents. The arteriovenous (AV) fistula site should be padded and protected.

Any reduction in renal perfusion pressure from hypotension is poorly tolerated. To minimize any major hemodynamic perturbations, a slow induction of epidural anesthesia is preferable. Uremia is associated with demyelination of nerve fibers. In pregnancy, there is an increased sensitivity to local anesthetics.[54] Therefore, rapid onset and spread of local anesthetics and a higher level of block should be anticipated. In fact, in a study comparing patients with and without chronic renal failure, Orko et al. found that spinal anesthesia with 0.75% bupivacaine resulted in higher sensory and motor levels in parturients with renal disease compared with normal control group.[55] Strangely enough, the duration of block is shortened, presumably the result of hyperdynamic circulation and rapid clearance of the drugs from the subarachnoid space. In addition, autonomic neuropathy increases the risk of hypotension. The presence of metabolic acidosis decreases the seizure threshold for local anesthetics.[43] This factor should be considered when using large doses of local anesthetics epidurally for cesarean section. The dose of local anesthetics should be carefully titrated to obtain the desired level of block. Epinephrine can cause cardiac dysrrhythmias, especially in those patients with hyperkalemia and acidosis. Therefore, when local anesthetic solutions are necessary, those with epinephrine should be avoided.

Two recent case reports indicate that both epidural and spinal anesthesia can be safely used in parturients with chronic renal failure undergoing hemodialysis.[56,57] In the report by Tighe et al., the authors used an epidural anesthesia for cesarean delivery.[56] The parturient underwent hemodialysis on the night before delivery with the input and output in balance. For hydration before block, 1000 mL normal saline was given. Bupivacaine 0.5%, 20 mL, was administered epidurally in increments over 20 min to obtain a T4 block. The parturient had one episode of hypotension after delivery that responded well to intravenous ephedrine and fluids. Afterward, the parturient had a satisfactory recovery. These authors preferred an epidural anesthetic rather than a subarachnoid block, as it is easier to manage blood pressures, height of the block, and fluid maintenance with a slower onset regional anesthetic. On the other hand, Azuma and others describe the successful use of spinal anesthesia with 8 mg tetracaine in a parturient with chronic renal failure undergoing cesarean section.[57] On the morning of surgery, the parturient underwent hemodialysis with elimination-only solute and not water, and received 500 mL of acetated Ringer's solution for hydration before the block. The fluid management was guided by CVP, and blood pressure remained stable during the procedure with an excellent maternal and fetal outcome. The authors concluded that, with careful fluid management, spinal anesthesia can be safely used for cesarean section in parturients undergoing hemodialysis.[57]

For parturients receiving general anesthesia, pentothal may be used for induction but in reduced doses because the blood–brain barrier may be disturbed in patients with severe renal disease.[46] In addition, due to decreased protein binding, the free unbound fraction of the drug may be elevated.[46] For tracheal intubation, the use of succinylcholine is controversial. Serum potassium levels are usually elevated in patients with chronic renal failure. If serum potassium levels are higher than 5.0 mEq/L, the use of succinylcholine is contraindicated. Succinylcholine increases serum potassium levels by 0.5 to 0.7 mEq/L, and in a hyperkalemic patient its use can precipitate severe cardiac dysrhythmias.[45] If the patient has undergone hemodialysis immediately before surgery, and if serum potassium levels are less than 5 mEq/L, succinylcholine may be used cautiously. Tracheal intubation under light general anesthesia can cause an exaggerated hypertensive response. Pretreatment with labetelol or other antihypertensive agents such as hydralazine is necessary. Hydralazine undergoes renal elimination and therefore should be titrated to effect. For muscle relaxation, atracurium is recommended. Low concentrations of halothane and isoflurane can be used for anesthesia maintenance. Opioids such as fentanyl may be safely used, although in reduced doses. Minute ventilation should be increased to compensate for metabolic acidosis. At the end of the procedure, muscle relaxant reversal agents may be used. Because the kidneys excrete these agents, their duration of action may be prolonged. Another

option is to omit the reversal agents altogether, and place the parturient on mechanical ventilation until she fully recovers from the effects of muscle relaxants. All surgical blood loss should be replaced, and the crystalloid infusion should be kept at the minimum maintenance volume. Post operatively, fluid management should be guided by CVP measurement. Intravenous opioids should be used in small incremental doses for postoperative pain relief. Avoidance of opioids with renally excreted metabolites such as morphine 6-glucoronide and normeperidine may be warranted. For those with an epidural catheter in situ, continuous infusion of epidural local anesthetic/opioid mixtures should be considered.

Summary

The successful peripartum management of parturients with severe renal dysfunction is a team effort involving the obstetricians, anesthesiologist, and the urologist.

References

1. Bailey RR, Rolleston GL. Kidney length and ureteric dilation in the puerperium. Br J Obstet Gynaecol 1971;1:55–61.
2. Cietak KA, Newton JR. Serial quantitative nephrosonography in pregnancy. Br J Radiol 1985;58:405–413.
3. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. Clin Obstet Gynaecol 1994;8:209–234.
4. Davison JM, Dunlop W, Ezimokhai M. 24 hour creatinine clearance during the third trimester of pregnancy. Br J Obstet Gynecol 1980;87:106–109.
5. Kuhlback B, Widholm O. Plasma creatinine in normal pregnancy. Scand J Clin Lab Invest 1966;18:654–656.
6. Katz AI, Davison JM, Hayslett JP, et al. Pregnancy in women with renal disease. Kidney Int 1980;18:192–206.
7. Davison JM. The effect of pregnancy on renal function in renal allograft recipients. Kidney Int 1981;27:267–276.
8. Anc RJ, Nicotra MB, Newsom JD, et al. Anterol oxygenation and alveolar arterial gradients in term pregnancy. J Obstet Gynecol 1979;53:183–186.
9. Lucius H, Gahlenbeck H, Kleine HO, et al. Respiratory functions, buffer system, and electrolyte concentrations of blood during human pregnancy. Respir Physiol 1970; 9:311–317.
10. Lindheimer MD, Grunfeld JP, Davison JM. Renal disorders. In: Barron WM, Lindheimer MD (eds) Medical Disorders During Pregnancy, 3rd edn. St. Louis: Mosby, 2000:39–70.
11. Davison JM. Overview: kidney function in pregnant women. Am J Kidney Dis 1987;248–252.
12. Schrier RW, Durr JA. Pregnancy: an overfill or underfill state. Am J Kidney Dis 1987;9:284–289.
13. Davison JM, Hytten FE. The effect of pregnancy on renal handling of glucose. Am J Obstet Gynecol 1975;82:374–382.
14. Davison JM, Dunlop W. Renal hemodynamics and tubular function in normal human pregnancy. Kidney Int 1980;18:152–161.
15. Hytten FE, Cheyne GA. The aminoaciduria of pregnancy. J Obstet Gynaecol Br Commonwealth 1997;79:424–432.
16. Dawes MG, Grundzinkas JG. Patterns of maternal weight gain in pregnancy. Br J Obstet Gynaecol 1999;98:195–291.
17. Chesley LC. Hypertension in Pregnancy. East Norwalk, CT: Appleton-Century-Crofts, 1978:190–228.
18. Davison JM, Sheills EA, Phillips PR, et al. Serial evaluation of vasopressin release and thirst in human pregnancy. Role of human chorionic gonadotrophin in the somoregulatory changes of gestation. J Clin Invest 1988;81:798–806.
19. Lindheimer MD, Davison JM. Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy. Eur J Endocrinol 1995;132:133–143.
20. Davison JM, Vallotton MB, Lindheimer MD. Plasma osmolality and urinary concentration and dilution during and after pregnancy: evidence that lateral recumbency inhibitis urinary concentrating ability. Br J Obstet Gynaecol 1988;88:472–479.
21. Sturgiss SN, Davison JM. Effect of pregnancy on the long term function of renal allografts: an update. Am J Kidney Dis 1995;26:54–56.
22. Hon S. Pregnancy in chronic renal insufficiency and end-stage renal disease. Am J Kidney Dis 1999;23:235–252.
23. Jungers P, Houillier P, Forget D, et al. Influence of pregnancy on the course of primary chronic glomerulonephritis. Lancet 1995;346:1122–1124.
24. Cunningham FG, Cox SM, Harstad TW, et al. Chronic renal disease and pregnancy outcome. Am J Obstet Gynecol 1990;163:453–459.
25. Whalley P. Bacteriuria in pregnancy. Am J Obstet Gynecol 1967;97:723–738.
26. Cunningham FG, Lucas MJ. Urinary tract infections in pregnancy. Clin Obstet Gynecol 1994;8:353–373.
27. Maclean AB. Urinary tract infections in pregnancy. Br J Urol 1997; 80:10–13.
28. Rouse DJ, Andrews WM, Goldenberg RL, et al. Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost-effectiveness and cost-benefit analysis. Obstet Gynecol 1995;86: 119–123.
29. Millar LK, Cox SM. Urinary tract infections complicating pregnancy. Infect Dis Clin N Am 1997;11:13–26.
30. American College of Obstetrics and Gynecology. Antimicrobial therapy for obstetric patients. Educ Bull 1998;245.
31. Harris RE, Gilstrap LC. Cystitis during pregnancy: a distinct clinical entity. Obstet Gynecol 1981;51:578–580.
32. Gallagher DJA. Montgomery JZ, North JDK. Acute infections of the urinary tract and the urethral syndrome in general practice. Br Med J 1965;97:622–626.
33. Mabie WC, Barton JR, Sibai BM. Septic shock in pregnancy. Obstet Gynecol 1997;41:553–561.
34. Harris RE, Gilstrap LC. Prevention of recurrent pyelonephritis during pregnancy. Obstet Gynecol 1974;44:637–641.
35. Hendricks SK, Ross SO, Krieger JN. An algorithm for diagnosis and therapy of management and complications of urolithiasis during pregnancy. Surg Gynecol Obstet 1991;172:49–54.
36. Butler EL, Cox SM, Eberts EG, Cunningham FG. Symptomatic nephrolithiasis complicating pregnancy. Obstet Gynecol 2000;96:753–756.
37. Davison JM. Pregnancy in renal allograft recipients: problems, prognosis, practicalities. Clin Obstet Gynaecol 1994;8:501–525.
38. Salmela KT, Kyllonen LEJ, Holmberg C, et al. Impaired renal function after pregnancy in renal transplant recipients. Transplantation 1993;56: 1372–1375.
39. Crowe AV, Rustom R, Sells RA, et al. Pregnancy does not adversely affect renal transplant function. Q J Med 1999;11:631–636.
40. Hon S. Pregnancy in women requiring dialysis for renal failure. Am J Kidney Dis 1987;9:368–373.
41. Hon S. Pregnancy in chronic renal insufficiency and end stage renal disease. Am J Kidney Dis 1999;33:235–252.
42. Ramanathan S. Obstetric Anesthesia. Philadelphia: Lea & Febiger, 1988: 307–323.
43. Weir PHC, Chung FF. Anesthesia for patients with chronic renal disease. Can Anaesth Soc J 1984;31:468.
44. Madden PJ. Anesthesia for patients with impaired renal function. Anesth Intensive Care 1983;11:468.
45. Miller RD, Way WL, Hamilton WK, et al. Succinylcholine-induced hy-

perkalemeia in patients with renal failure. Anesthesiology 1972;36: 138–141.
46. Ghoniem MM, Pandya H. Plasma protein binding of thiopental in patients with impaired renal and hepatic function. Anesthesiology 1975;42:545–549.
47. Freeman PB, Sheff MF, Haher JF, et al. The blood–cerebrospinal fluid barrier in uremia. Ann Intern Med 1962;56:233–240.
48. Mazze RI, Calverely RK, Smith NT. Inorganic fluoride toxicity: prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 1977;46:265.
49. Conzen PF, Nuscheler M, Melotte A, et al. Renal function and serum fluoride concentration in patients with stable renal insufficiency after anesthesia with sevoflurane and enflurane. Anesth Analg 1995;81:569–575.
50. Cousins MJ, Skowronski G, Plummer JL. Anesthesia and the kidney. Anesth Intensive Care 1983;11:292.
51. Halperin BD, Feeley TW. The effect of anesthesia and surgery on renal function. Int Anesth Clin 1984;22:157.
52. Mather LE, Runciman WB, Ilsley AH. Anesthesia-induced changes in regional blood flow. Implications for drug disposition. Reg Anesth 1982;45:S23.
53. Amnest SJ, Scovill WA, Blumenstock FA, et al. Increased creatinine clearance following cryoprecipitate infusion in trauma and surgical patients with decreased renal function. J Trauma 1980;20:726–732.
54. Flanagan HL, Datta S, Lambert DH, et al. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1977;66:123.
55. Orko R, Pitkanen M, Rosenberg PH. Subarachnoid anesthesia with 0.75% bupivacaine in patients with chronic renal failure. Br J Anaesth 1977;49: 945–949.
56. Tighe KE, Smith ID, Bogod D. Caesarean section in chronic renal failure. Eur J Anaesth 1995;12:185–187.
57. Azuma K, Nakamoto T, Terai T, et al. Cesarean section under spinal anesthesia for a patient with chronic renal failure. Masui 1996;45:880–883.

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14
Endocrine Disorders

John A. Thomas and Jon Rosnes

Human homeostasis is elaborately intertwined with the endocrine system. Every cell within the body requires a stable supply of messages, fuel, and metabolites to perform at its optimum level.[1] Pregnancy induces stress and changes on this system, which will test the limits of its functionality. An underlying endocrine organ dysfunction during pregnancy may require very challenging obstetric and anesthetic management.

The aim of this chapter is to describe the various obstetric and anesthetic implications of endocrine disorders during pregnancy. Specific attention is given to thyroid, parathyroid, and adrenal glands. Chapter 23 discusses diabetes mellitus, the most common endocrine disorder encountered in pregnancy, in detail.

Basic Endocrine Physiology

Hormones and substances travel between cells and act as chemical signals. In general these signals act at one of three sites: (1) on the cell that released it (autocrine), (2) on the adjacent cells (paracrine), or (3) by moving through the blood to distant cells (hemocrine).[1,2] Most hormones discussed here are hemocrine in nature and can be classified chemically as proteins (or polypeptides), steroids, amino acid derivatives, or fatty acid derivatives. Protein or polypeptide hormones include all the anterior pituitary hormones (e.g., follicle-stimulating hormone) as well as glucagons and endorphins. Steroid hormones include those secreted by the gonads and adrenal gland. Examples of amino acid and fatty acid derivatives include catecholamines and prostaglandins, respectively.[1]

Hormones can exert their effects by one of three different actions: (1) direct cell membrane or receptor effects, (2) intracellular second-messenger effects, or (3) intracellular effects on protein synthesis.[1,3–5] Hormonal actions are organized into cascades of messengers, normally under an elaborate and tightly controlled system. This structure includes important feedback loops where a hormone can inhibit its production either directly or indirectly (e.g., at the hypothalamus). Other hormones can exert a positive feedback (under special circumstances) and increase their production. Intracellular function can also directly influence hormone release.[1] Any of these feedback mechanisms can malfunction and result in inappropriate levels of the primary hormone.

Thyroid Disease

Thyroid disease is 5 to 10 times more prevalent in women than in men, affecting 0.2% of all females.[6] Thyroid disorders are the most common endocrinopathy found in women.[6] Therefore, these disorders are not uncommon in the parturient, and several (e.g., gestational trophoblastic disease) are unique to pregnancy. Autoimmune thyroid disease is commonly seen and may improve initially with the immunosuppression seen in pregnancy; however, postpartum flares are not infrequent.[6,7] Thyroid disorders are often first diagnosed during pregnancy because it is frequently the first contact these women have with the health care system. If untreated, both hyper- and hypothyroidism can have profound effects on both the mother and fetus.

Maternal Thyroid Physiology

Identifying thyroid disease during pregnancy can be difficult because symptoms of heat intolerance, tachycardia, fatigue, and appetite changes are relatively common in normal pregnancy.[6–9] The thyroid gland is a vascular organ with two lobes lying adjacent and anterior to the trachea. The recurrent laryngeal and superior laryngeal nerves are closely associated.[10] During pregnancy there is an increase in the volume of the thyroid gland that can be visualized by ultrasonography.[6] However, clinical thyromegaly does not occur and a goiter or nodule is considered abnormal.[6,8] Despite increased blood volume and the dilutional effects during pregnancy, the level of serum thyroxine-binding globulin (TBG) rises. Elevation of TBG is secondary to an estrogen-mediated elevation in hepatic synthesis and prolonged half-life.[8,11,12] Increased TBG, the major thyroid hormone carrier, results in greater amounts

TABLE 14.1. Changes in thyroid physiology that occur with pregnancy.

Increased serum thyroxine-binding globulin (TBG)
Increased total T_4 and T_3
Increased clearance of iodine by kidney
Best overall indicators of thyroid function: free T_4 and thyroid-stimulating hormone (TSH)

Source: Adapted from Drake WM, Wood DF. Thyroid disease in pregnancy. Postgrad Med J 1998;63:583.[12]

of protein-bound thyroxine (T_4) and triiodothyroxine (T_3). However, the free levels of T_3 (FT_3) and T_4 (FT_4) remain within normal nonpregnant ranges.[6,8] FT_3 and FT_4 represent the active form of the hormone. Serum levels of FT_4 rise during the first trimester secondary to a thyrotropin-like effect of human chorionic gonadotropin (hCG), but remain within normal limits. FT_4 levels decline during the second trimester consistent with falling hCG levels.[6,11] Thyroid-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) levels are similar to nonpregnant values. There is a small transient decline in TSH during the first trimester, reflecting the short-lived elevation in FT_4 just discussed.[6] Therefore, TSH levels, especially in the first trimester, may be less useful for diagnosing clinically significant hyperthyroidism compared to nonpregnant individuals.[6] However, most regard the serum levels of FT_4 and TSH as the most useful indicators of thyroid metabolism during pregnancy (Table 14.1).[12]

Fetal Thyroid Physiology

The fetal thyroid gland is inactive for most of the first trimester. At about 10 weeks gestation, FT_4 synthesis and TBG are measurable.[6,12] The placenta is relatively impermeable to thyroid hormones; however, limited amounts of T_3 and T_4 do cross from mother to fetus, as demonstrated in neonates with congenital hypothyroidism. It is thought that thyroid hormones play a significant role in the early development of the central nervous system. Most thyroid medications are transferred in varying degrees to the fetus.[6] Iodine is actively concentrated by the fetus; therefore, the use of radioactive iodine for either diagnosis or treatment during pregnancy is contraindicated (Figure 14.1).[7,9]

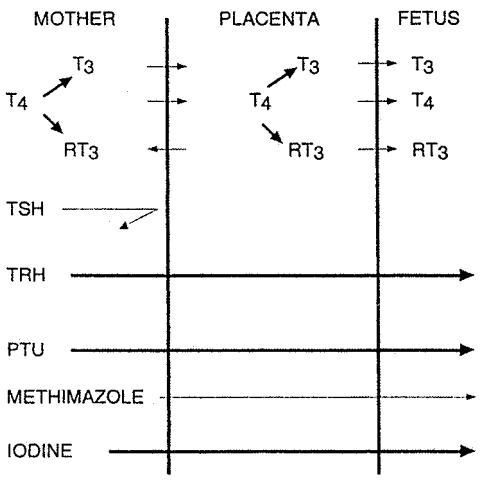

FIGURE 14.1. Use of radioactive iodine during pregnancy. (From Ecker JL, Musci TJ. Treatment of thyroid disease in pregnancy. Obstet Gynecol Clin N Am 1997;24(3):578.)

Hyperthyroidism

Thyrotoxicosis complicates approximately 0.2% of pregnancies and is frequently diagnosed before conception.[6] Newly diagnosed cases occur in about 0.05% of pregnancies.[12] Graves' disease accounts for 95% of hyperthyroidism diagnosed during pregnancy. Thyroid-stimulating antibodies to the TSH receptor produced in Graves's disease cause overproduction of T_3 and T_4. The IgG autoantibodies produced can cross the placenta, causing neonatal disease. These antibodies can be either stimulating or inhibiting in nature. Some authors suggest that the natural immunosuppressive effect of pregnancy can improve autoimmune thyroiditis. However, others question the actual clinical significance of this effect. It does appear that exacerbations often occur postpartum. Other causes of hyperthyroidism in pregnancy include toxic multinodular goiter, other causes of thyroiditis (e.g., Hashimoto's), and trophoblastic disease (Table 14.2).[6,7,12]

Mothers with uncontrolled hyperthyroidism have increased risks of preeclampsia, fetal demise, miscarriage, preterm labor, and low birth weight infants. In addition, severe maternal hyperthyroidism can lead to heart failure or thyroid storm (Table 14.3). In one series, heart failure complicated 12% of hyperthyroid pregnancies and 63% of untreated women presenting in labor.[13]

Diagnosis of hyperthyroidism during pregnancy is difficult. Many classic symptoms such as increased appetite, tachycardia, difficulty sleeping, heat intolerance, and mood swings are associated with normal pregnancy. Physicians have to be astute to discern early symptoms and institute prompt laboratory investigation. A diagnosis is strongly suggested when elevated free T_3 and T_4 levels are accompanied by decreased TSH.[7]

TABLE 14.2. Causes of hyperthyroidism in pregnancy.

Graves' disease
Multinodular goiter
Toxic adenoma
Subacute thyroiditis
Iatrogenic hyperthyroidism
TSH-producing pituitary tumor
Struma ovarii
Transient thyrotoxicosis of hyperemesis gravidarum
Hydatidiform mole

Source: Adapted from Mestman JH. Hyperthyroidism in pregnancy. Clin Obstet Gynecol 1997;40(1):47.

TABLE 14.3. Potential complications of uncontrolled hyperthyroidism in pregnancy.

Maternal	Fetal
Pregnancy-induced hypertension (PIH)	Hyperthyroidism
Preterm delivery	Neonatal hyperthyroidism
Congestive heart failure	Intrauterine growth restriction (IUGR)
Thyroid storm	Small for gestational age (SGA)
Miscarriage	Prematurity
Infection	Stillbirth
Placental abruption	

Source: Adapted from Mestman JH. Hyperthyroidism in pregnancy. Clin Obstet Gynecol 1997;40(1):52.

Obstetric Management

Treatment of hyperthyroidism during pregnancy is primarily by thionamides, which inhibit the synthesis of T_4 (by blocking organification of iodine) and iodination of tyrosine (Figure 14.2). Propylthiouracil (PTU) is frequently the agent chosen to treat thyrotoxicosis in pregnancy. Methimazole is less frequently used in pregnancy because it (1) appears not to inhibit peripheral conversion of T_4 to T_3 (the physiologically active form), (2) is more likely to cross the placenta (see Figure 14.1), and (3) has been associated with a defect in the neonatal scalp (aplasia cutis). More recent studies, however, indicate that both PTU and methimazole are effective in treating hyperthyroid parturients with little difference in risk. Some authors recommend methimazole because (1) it has a longer half-life requiring less frequent dosing and increasing compliance, (2) fewer drug reactions are associated with methimazole, and (3) methimazole costs less than PTU.[6,7]

The typical starting dose of PTU is 100 to 150 mg tid increasing up to 250 to 300 mg tid. Alternatively, methimazole at 20 to 45 mg/day can be used. It takes from 2 to 4 weeks for a clinical response to these drugs. Free thyroxin levels should be monitored and kept in the high normal range. Drug doses are then reduced as tolerated. This regimen carries a relatively low incidence of fetal side effects (e.g., goiter or hypothyroidism). β-Blockers are occasionally utilized to control tachycardia but are usually reserved for cases of thyroid crisis. There is concern over the long-term use of β-blockers because of a possible increased risk of fetal growth retardation and postnatal hypoglycemia. Patients receiving long-term treatment with propranolol may have a higher risk of spontaneous miscarriage.[14] Occasionally, if noncompliance or intolerance to thiomides (agranulocytosis, leukopenia, and increased liver enzymes) develops, a thyroidectomy (total or subtotal) can be indicated. Radioactive iodine is contraindicated in pregnancy, as has been discussed.[6,7,12]

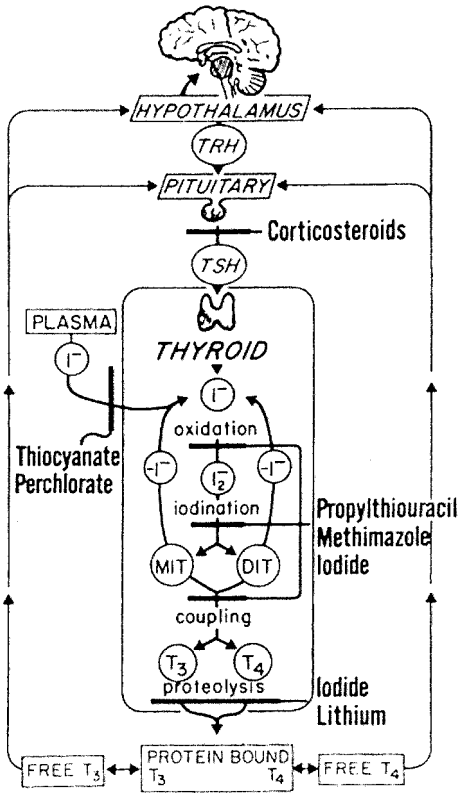

FIGURE 14.2. Treatment of hyperthyroidism during pregnancy. (From Stehling LC. Anesthetic management of the patient with hyperthyroidism. Anesthesiology 1974;41(6):589.)

Thyroid Storm

Thyrotoxic crisis is a severe hypermetabolic state that complicates the medical course in 1% to 2% of parturients with thyrotoxicosis. It can be precipitated by pain of labor, preeclampsia, induction of anesthesia, infection, or surgery. The symptoms of thyroid storm vary from fever and gastrointestinal distress to cardiac decompensation and coma (Table 14.4). Maternal mortality secondary to thyroid storm can be as high as 25%.[6]

Thyroid storm is a medical emergency. The goals are to stop peripheral conversion of T_4 to T_3, decrease the further release of thyroid hormones, and treat the hypermetabolic symptoms. This syndrome should be treated by a multidisciplinary group of physicians (endocrinologist, intensivist, obstetrician, and perinatologist) in an intensive care unit. PTU and potassium iodine (SSKI) are first-line therapies to stop

TABLE 14.4. Clinical features of thyroid storm.

Exaggeration of thyrotoxicosis symptoms
Fever (>38°C)
Disproportionate tachycardia (>130 bpm)
New-onset arrythmia
Jaundice
Profuse diarrhea
Mental confusion (psychosis)
Hyperkinesis → Delirium → Somnolence → Coma

Source: From Gavin LA. The diagnostic dilemmas of hyperthyroxinemia and hypothyroxinemia. Adv Intern Med 1988;33:190.

T_3 and T_4 release as well as the peripheral conversion of T_4 to T_3. PTU may be given by nasogastric tube or rectally in a dose of 400 to 600 mg followed by 150 to 300 mg every 6 h. Sodium iodine should be given intravenously, 0.25 to 0.5 g every 12 h, or as oral Lugol's solution (5% potassium iodine and 10% potassium iodide), 30 to 60 drops/day. For patients unable to take iodine, lithium carbonate can be substituted in a dose of 300 mg by mouth every 6 h. Corticosteroids (dexamethasone, prednisone, or hydrocortisone) can be added to further inhibit peripheral conversion of T_4 to T_3 and prevent development of acute adrenal insufficiency. Propranalol (1 mg/min) intravenously can quickly control heart rate and inhibit peripheral conversion of T_4 to T_3. β-Blockers should be used cautiously, however, because of an increased risk of heart failure in this patient population. Esmolol, a short-acting and easily titratable intravenous β-blocker, is an alternative but has been associated with fetal acidemia. In addition to drug management, it is important to monitor and lower body temperature by active cooling, which can usually be accomplished with acetaminophen, cold crystalloid infusion, or a cooling blanket.[6,9]

Anesthetic Management

The major concerns in the anesthetic management of thyrotoxic patients are the potential for acute activation of adrenergic system and its cardiac effects. Other potential concerns include tracheal compression by an enlarged thyroid gland or goiter, skeletal (respiratory) muscle weakness, and electrolyte abnormalities.[15]

Ideally, those presenting in labor will have been adequately treated and euthyroid before delivery. However, the intense pain of labor and the accompanying anxiety can precipitate sympathetic outflow, which can adversely affect the disease. Early epidural analgesia is the method of choice for pain relief, because it decreases sympathetic outflow and adequately controls labor pain. Epidural, subarachnoid, or general anesthesia may be used safely for cesarean section. Epidural anesthesia may be preferable if time allows, because the level of the sympathetic block can be raised gradually. Concerns have been raised about the use of sypathomimetics in patients with hyperthyroidism because elevated levels of thyroid hormone lead to increased numbers of β-adrenergic receptor sites.[16] Therefore, adequate prehydration should be utilized before regional anesthesia to potentially minimize hemodynamic changes. Phenylephrine has been suggested by some authors to be the drug of choice for managing hypotension in thyrotoxic patients. Bolus doses of 20 to 40 μg phenylephrine appear safe for the fetus.[17] Some authors also suggest omitting epinephrine from local anesthetic solutions[17]; however, one study indicated that the response to exogenous epinephrine in hyperthyroid patients is unaltered.[18] Even if regional anesthesia is successful, anxiety can arise in an awake patient and may cause serious problems for the hyperthyroid parturient. Sedation can be used cautiously to minimize maternal anxiety. Caution must be taken to avoid maternal respiratory depression and excessive neonatal sedation. Midazolam at 0.5 to 2 mg usually achieves this effect.[17] Unfortunately, a frequently unwanted side effect is maternal amnesia.

General anesthesia may be necessary for cesarean section under certain circumstances and can be managed effectively. Careful airway assessment is particularly important because of the potential for tracheal deviation or obstruction in patients with an enlarged thyroid gland.[19] Thiopental remains the induction agent of choice because of its thiocarbamate structure (N−C=S), which appears to have antithyroid activity.[20] Hypercarbia, hypoxia, and light anesthesia may stimulate the sympathoadrenal axis and should be avoided. Similarly, any drugs that precipitate sympathetic stimulation or tachycardia are relatively contraindicated (e.g., atropine and ketamine). Isoflurane is the inhalational agent of choice because of its relative cardiac stability and limited metabolism. Monitoring of neuromuscular blockade is important because subclinical thyroid myopathy may be present. Increased metabolic destruction in hyperthyroid patients can cause relative corticosteroid insufficiency. Perioperative glucocorticoid replacement therapy (hydrocortisone 100 mg IV) can be considered and has the added potential benefit of reducing peripheral T_4 to T_3 conversion.[15,20]

Thyroid storm can be precipitated during labor and delivery or during the induction of anesthesia itself. It is aggressively treated as just described with PTU, iodine, corticosteroids, and temperature control. These patients should be transferred, monitored, and treated in an intensive care unit as soon as possible.

Hypothyroidism

The overall prevalence of hypothyroidism in the general population is similar to hyperthyroidism, ranging from 0.4% to 0.7%.[21] Hypothyroidism is more common in women and the elderly. Recommendations have been made for general screening of women over the age of 50 by serum TSH.[22] Clinical hypothyroidism results in a high incidence of ovulatory dysfunction and infertility. Cases among pregnant women are therefore very rare, with an incidence less than 0.3%.[23] Complications associated with hypothyroidism in pregnancy in-

TABLE 14.5. Pregnancy complications associated with hypothyroidism.

Preeclampsia
Abruptio placentae
Anemia [hematocrit (Hct) <26%)]
Postpartum hemorrhage
Cardiac dysfunction
Low birth weight (<2000 g)
Stillbirths

Source: From Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72:110.

TABLE 14.6. Potential causes of hypothyroidism.

Primary hypothyroidism	Secondary hypothyroidism
Chronic autoimmune thyroiditis	Pituitary dysfunction
Hashimoto's thyroiditis	Irradiation
Atropic hypothyroidism	Surgery
Iatrogenic	Neoplastic
Iodine-131	Sheehan's syndrome
Subtotal thyroidectomy	Idiopathic
Drugs	Hypothalamic dysfunction
Iodine deficiency or excess	Irradiation
Lithium	Granulomatous disease
Amiodarone	Neoplastic
Antithyroid drugs	
Congenital	
Dyshormonogenesis	
Thyroid gland dysgenesis or agenesis	

Source: From Gavin LA. The Diagnostic dilemma of hyperthyroxiemia and hypothyroxiemia. Adv Intern Med 1988;33:196.

clude increased risk of spontaneous abortion and fetal loss, gestational hypertension (preeclampsia), fetal distress, stillbirth, growth retardation, abruption, cardiac dysfunction, anemia, and postpartum hemorrhage (Table 14.5).[6,24]

The etiology of hypothyroidism may be either primary (direct production of thyroid hormone) or secondary (pituitary or hypothalamic problem). Most newly diagnosed cases are primary in nature (Table 14.6).[25] The most common diagnosis encountered is inadequately treated preexisting hypothyroidism. Frequently these patients have undergone medical or surgical treatment for hyperthyroidism (most commonly Graves' disease) that rendered them hypothyroid. These patients account for approximately 65% of the cases observed in pregnancy.[24] Rare causes of hypothyroidism presenting in pregnancy include Hashimoto's disease, idiopathic myxedema, and iodine deficiency. If untreated, maternal hypothyroxemia is associated with increased perinatal mortality and congenital malformations. Severe maternal and fetal hypothyroidism can occur secondary to iodine deficiency, resulting in cretinism (mental retardation, deafness, and spastic diplegia).[12]

Diagnosing hypothyroidism can be difficult in pregnancy because symptoms of tiredness, brawny edema, irritability, dry skin, hair loss, and poor concentration may be dismissed as normal events secondary to pregnancy.[23] Several possible clues are a history of taking thyroid replacement medications, neck irradiation or radioiodine treatment, use of a potentially antithyroid drug (e.g., lithium or amiodarone), or a surgical scar on the anterior neck. TSH level is a sensitive and reliable indicator of primary hypothyroidism in pregnancy. T_4 levels in contrast can be normal secondary to the higher levels of TBG in pregnancy. Therefore, a serum TSH is the recommended initial screening test.[12]

Obstetric Management

An early diagnosis and hormone replacement may improve outcome. The treatment of maternal hypothyroidism typically is thyroxin replacement (100 μg/day). TSH levels are monitored every 3 to 4 weeks.[6] Maternal thyroxine requirements increase as pregnancy progresses, and an increased dosage may be required.[26] Intravenous replacement of thyroid hormone is rarely necessary and is reserved for cases of myxedema coma. There is, however, a significant risk of precipitating coronary ischemia with this method of replacement, and thus it should be reserved for emergency situations.[27]

There do not appear to be any adverse fetal effects from replacement therapy. The potential role of maternal hypothyroidism on fetal cognitive development is unclear. Although the placenta prevents significant amounts of thyroid hormones from being transferred to the fetus, small amounts of T_4 will be transferred, producing T_3 in the fetal brain. It is clear that most infants born to properly treated mothers develop normally.[23]

Anesthetic Management

Parturients should be treated and rendered euthyroid before labor and delivery if possible. Clinical hypothyroidism can be associated with multiple derangements that could contribute to a difficult anesthetic management (Table 14.7). If adequately treated, parturients may safely receive either regional or general anesthesia.

Hypothyroidism can lead to abnormal ventilatory drive with decreasing responses to hypoxia and hypercarbia.[28] Obstructive sleep apnea also occurs more frequently in these parturients. Hypothyroid parturients may be very sensitive to sedatives, particularly opioids, and the risk of significant respiratory depression is elevated.[10] On the other hand, underlying myocardial dysfunction as a result of a cardiomyopathy or coronary disease may become apparent under the stress induced by a painful labor. There is an increased incidence of glucocorticoid deficiency, and therefore a potentially inadequate stress response. Early epidural analgesia effectively blocks the stress response while providing the best labor analgesia and least risk for respiratory depression. Thyroid deficiency is associated with both platelet dysfunction and von Willebrand's

TABLE 14.7. Potential anesthetic implications of hypothyroidism.

Sensitivity to depressant drugs
Decreased cardiac output and heart rate
Decreased drug metabolism
Lack of appropriate baroreceptor response
Alveolar hypoventilation
Impaired respiratory response to hypercarbia/hypoxia
Impaired gastric emptying
Hypothermia
Hypoglycemia
Hyponatremia
Adrenal insufficiency
Anemia

Source: Adapted from Stoelting RK, Dierdorf SF. Endocrine disease. In: Stoelting RK, Dierdorf SF (eds) Anesthesia and Co-Existing Disease. New York: Churchill Livingstone, 1993:353.

disease.[29,30] Therefore, a careful examination of the coagulation status and the patient's bleeding history should be done before the placement of regional analgesia. Regional anesthesia can also be used for cesarean section.

If emergency general anesthesia becomes necessary, there are several anesthetic considerations. In addition to significant airway changes that occur with pregnancy, an enlarged tongue in thyroid-deficient individuals may make direct visual laryngoscope very challenging. It should be appreciated that minimum anesthetic requirements are reduced and that sensitivity to volatile agents, benzodiazepines, and opioids is increased.[31] There is reduced skeletal muscle activity and abnormal response to peripheral nerve stimulation. Small-titrated doses of nondepolarizing agents are recommended. Close monitoring of peripheral nerve stimulation and end-expiratory gas concentrations are crucial.[31] Monitoring of end-tidal CO_2 is invaluable due to a potentially altered response to hypercarbia.[28] Impaired free water clearance can result in hyponatremia; replacement should be with balanced salt solutions. Central venous pressure (CVP) monitoring may become necessary if fluid status is unclear clinically. Myocardial dysfunction, coronary artery ischemia, and bradyarrhythmias are potential cardiac complications of hypothyroidism. Low circulating levels of thyroid hormones are associated with a downregulation in the number of β-receptors, and the responsiveness to agonists may be reduced.

Parathyroid Disease

Parathyroid gland derangements rarely present in women of childbearing age. Diagnosis in pregnancy can be difficult because the physical examination, symptoms, and laboratory findings are unpredictable. However, if unrecognized or improperly managed, either hyperparathyroidism or hypoparathyroidism can lead to both neonatal and maternal complications.[32]

Calcium (Ca^{2+}) homeostasis is maintained by the interaction of parathyroid hormone (PTH), calcitonin (CT), and vitamin D. Normal total serum calcium is in the range of 9.5 to 10.5 mg/dL. Approximately 50% of serum calcium is bound to albumin, 40% is ionized (free), and 10% is attached to chelating agents. Serum calcium therefore fluctuates with the albumin level (1 g albumin decrease = 0.8 mg/dL serum calcium decrease).[32]

Parathyroid hormone (PTH) is secreted by the inferior and superior parathyroid glands, which are usually located adjacent to the upper and low poles of the thyroid gland. It acts directly on the kidney and bone to increase extracellular calcium levels. It also acts indirectly on Ca^{2+} absorption through the gastrointestinal tract by increasing synthesis of $1,25(OH)_2D_3$ in the kidney. Calcitonin is released from parafollicular C cells in the thyroid when serum Ca^{2+} levels are high; it counteracts the effects of PTH. Vitamin D is converted in the kidney to its most active form, $1,25(OH)_2D_3$, and plays a significant role in both bone and intestinal reabsorption of Ca^{2+}.[33]

Maternal Parathyroid Physiology

The goal of Ca^{2+} regulation during pregnancy is to ensure proper transfer to the fetus while protecting the mother from depletion of bone calcium stores. Albumin levels decline, extracellular fluid volume increases, and renal calcium excretion is elevated during pregnancy. The placenta actively concentrates fetal Ca^{2+}.[34] Despite these factors, total serum calcium levels decrease slightly during gestation. The effect of pregnancy on ionized calcium activity is controversial but appears to be minimal.[32] This relative stability is secondary to several changes in homeostasis during pregnancy, including a twofold increase in the intestinal absorption of calcium caused by elevated $1,25(OH)_2D_3$.[32,34] The increased absorption is stimulated by estrogen and an elevated level of PTH-related protein (PTHrP), which has PTH-like activity. Controversy exists about what exactly happens to PTH levels during pregnancy. Several studies have shown increased PTH levels during pregnancy, while others reported decreased levels.[34] These discrepancies may be related to the assays used to measure serum PTH levels. More recent studies indicate that levels remain in a relatively normal range. However, the level of PTHrP is elevated during pregnancy and is not recognized by standard radioimmunoassays for PTH.[34] This protein plays a multifactorial role in pregnancy, including effects on placental Ca transport, lactation, onset of labor, embryogenesis, and fetal growth.[34]

Fetal Parathyroid Physiology

Fetal calcium homeostasis depends on the active concentration of calcium by the placenta, resulting in a relative fetal hypercalcemia.[35] At birth, the continuous supply of calcium stops, leading to a fall in the infant's serum calcium level, which reaches a nadir between 24 and 48 h of age. The levels then slowly increase and stabilize at adult levels by 7 days of life.[35]

Hyperparathyroidism

Hyperparathyroidism is either primary or secondary. Primary causes are intrinsic to the parathyroid gland, whereas secondary hyperparathyroidism occurs after chronically low calcium levels cause the parathyroid glands to release excessive PTH. The majority of women presenting with hypercalcemia have primary hyperparathyroid disease.[32]

Primary hyperparathyroidism has an overall incidence of approximately 0.15%. Only 110 cases occurring during pregnancy have been reported in the literature.[34] Some authors suggest that normal placental shunting of calcium to the fetus and increased urinary excretion during pregnancy may cause underdiagnosis. In addition, hyperparathyroidism is associated with an increase in early fetal loss, which may also contribute to its underdiagnosis.[32,34] Regardless of the reason, if it goes undiagnosed or untreated, serious maternal and

fetal complications may result. Neonatal hypocalcemia and tetany have led to the discovery of undiagnosed maternal hyperparathyroidism.[32]

Approximately 80% of the cases seen in pregnancy are the result of a single parathyroid adenoma. Other etiologies include 15% primary hyperplasia, 3% multiple adenomas, and 2% carcinomas.[32] The majority (50%–80%) of pregnant woman with hyperparathyroidism are asymptomatic.[34] However, a recent review of 70 parturients with hyperparathyroidism, found that 36% had gastrointestinal symptoms, 34% weakness and fatigue, and 26% vague neurologic complaints (headache, lethargy, confusion, and emotional lability).[36] In this series, 24% of the parturients were asymptomatic, and 36% had nephrolithiasis, 19% had bone disease, 13% had acute pancreatitis, 10% had hypertension, and 8% experienced hypercalcemic crisis.[36] Acute pancreatitis, if it occurs during pregnancy, can have significant neonatal and maternal morbidity.[34] Hypercalcemic crisis is a rare and serious complication, usually presenting in patients with serum calcium levels greater than 13 mg/dL.[32] Potential symptoms include vomiting, hypertension, generalized weakness, dehydration, and mental status changes. Associated complications in pregnancy include preeclampsia and hyperemesis gravidarum.[32] Eleven cases of hypercalcemic crisis have been reported during pregnancy; three maternal and four neonatal deaths resulted. Four of these cases occurred in the postpartum period, indicating that the greatest risk may be after the preferential shunting of calcium to the fetus has stopped.[32]

Neonatal complications secondary to maternal hyperparathyroidism include fetal loss, preterm delivery, and neonatal hypocalcemia with or without tetany.[32] Maternal hypercalcemia leads to fetal hypercalcemia and decreased PTH, which in turn can lead to impaired development of the parathyroid glands and neonatal hypocalcemia.[34]

Obstetric Management

Surgical removal of the abnormal parathyroid gland remains the most effective management of primary hyperparathyroidism in pregnancy.[32] Pregnancy is a relative contraindication to treatment with mithramycin and bisphosphonates. Other standard drug therapies such as diuretics, oral phosphates, and calcitonin have been used successfully.[34] However, depending on the situation, studies indicate pharmacologic management in pregnancy may carry a higher risk of complications compared with early parathyroidectomy.[34] Surgery is the treatment of choice when the diagnosis of primary hyperparathyroidism is made early (first or second trimester) and serum calcium is less than 11 mg/dL.[32] If a diagnosis is made in the third trimester, the incidence of surgical complications associated with parathyroidectomy rises (58% in one series).[32]

Medical management is utilized for parturients with persistent hypercalcemia (>11 mg/dL) for whom surgical treatment is deemed unacceptable. Oral phosphate at 1.5 to 2.5 g/day lowers serum calcium levels, but side effects include nausea, vomiting, and hypokalemia. Adequate hydration is critical to avoid dehydration and urinary complications.[32] The goals are to lower serum calcium and prevent further hypercalcemia until delivery. Then, a postpartum parathyroidectomy can be performed.[34]

Hypercalcemic crisis is a medical emergency and warrants an aggressive approach. Immediate rehydration with intravenous normal saline is indicated to restore normal fluid balance and promote renal excretion of calcium.[33] Then, loop diuretics, which depress proximal tubular reabsorption of calcium and promote urinary excretion, are given to induce a forced diuresis. Additional treatment with calcitonin, oral phosphates, or bisphosphates may be indicated.[32] Recently, the calcium receptor has been cloned, and newer drug therapies are targeting this receptor. NPS R-568 is an experimental modulator of this receptor which holds promise in the treatment of hyperparathyroidism.[32]

Anesthetic Management

No evidence indicates one anesthetic technique is superior to another. Lumbar epidural analgesia and anesthesia for either labor or cesarean section is acceptable and has the advantage of minimal side effects. Regardless of the anesthetic chosen, there are several potential concerns. If hypercalcemia is present, the severity and potential side effects of elevated calcium levels should be considered. Levels above 14 mg/dL are considered medical emergencies and should be managed as already outlined. These patients are frequently dehydrated. A key management principle is aggressive hydration with normal saline and ensuring adequate urinary output.[32] Hypertension and cardiac conduction disturbances (prolonged P-R interval, wide QRS complex, or short Q-T interval) may occur, and monitoring an electrocardiogram is indicated. Muscle weakness and mental status changes can be present, making aspiration risks higher and complicating the use of muscle relaxants. Unpredictable responses to succinylcholine, nondepolarizers, and reversal agents should be anticipated. Longstanding disease or lytic bone lesions increase the risk for fractures; careful positioning is prudent.[37,38]

Hypoparathyroidism

Hypoparathyroidism is most commonly a result of thyroidectomy because the parathyroid glands can easily be damaged or removed during this procedure.[32] Other potential causes are surgical (parathyroidectomy), genetic, or autoimmune-related dysfunction. Hypoparathyroidism is a rare disorder during pregnancy that presents with symptoms of hypocalcemia such as numbness, tingling, or carpopedal spasm. More serious complications include dyspnea, laryngeal stridor, larygospasm, and seizures.[34] A diagnosis is strongly suggested by the presence of chronically lower serum calcium levels accompanied by high serum phosphate levels.[32] Physical findings may include Chvostek's sign (spasm of facial muscles when facial nerve is

tapped) and Trousseau sign (carpopedal spasm when a blood pressure cuff is inflated in the arm).[32] Hypocalcemia during gestation can result in serious maternal and neonatal complications. Fetal hyperparathyroidism, bony changes, and intrauterine growth retardation can result secondary to maternal hypoparathyroidism.[32]

Obstetric Management

Maternal treatment does not differ from the nonpregnant treatment, which includes a high-calcium, low-phosphate diet, vitamin D supplementation (50,000–150,000 IU/day), and calcium supplementation (2–5 g/day). More aggressive therapy includes addition of thiazide diuretics and sodium restriction. Serum calcium is monitored regularly with the goal of normocalcemia. Fetal development appears normal if maternal calcium is maintained within normal limits.[32]

Anesthetic Management

Regional analgesia, by preventing hyperventilation or hypoventilation, may provide the advantage of fewer respiratory-related electrolyte shifts in case of labor and vaginal delivery. Both regional and general anesthesia can be used for cesarean section. Electrolytes including calcium, phosphate, and magnesium should be checked before any anesthetic.[37] Symptomatic or severe hypocalcemia (<3.5 mEq/L) should be corrected before anesthesia. In an emergency, intravenous 10% calcium gluconate (7.5 mg/kg) should be administered slowly.[38] Maintenance of adequate calcium levels may require continuous infusion of 10% calcium gluconate (500 mL/6 h).[37] The ECG should be monitored secondary to potential prolongation of the QT/QT_c interval, which may be present in hypocalcemia and precede cardiac dysrhythmias (i.e., 2:1 heart block).[37] Rapid decreases in ionized calcium may precipitate severe hypotension, elevated left ventricular pressures, myocardial dysfunction, and occasionally congestive heart-failure. Respiratory and metabolic alkalosis can abruptly lower ionized calcium levels and should be avoided. Chronically decreased calcium levels can produce muscle weakness (decreased acetylcholine release) whereas rapid decreases may produce muscle spasms (laryngospasm). Therefore, monitoring nondepolarizing muscle relaxation is important and the potential risk of laryngospasm must be appreciated. In symptomatic patients, reviewing coagulation parameters is prudent because an extremely low ionized calcium level can produce abnormal clotting.[38]

Adrenal Gland Disease

The adrenal glands are divided into an adrenal cortex and medulla. The adrenal glands, which lie at the upper pole on the medial aspect of each kidney,[39] mediate important physiologic responses to stress, extracellular fluid and electrolyte shifts, and postural changes.[39,40] These glands produce glucocorticoids, mineralcorticoids, and androgens in their cortex; each is synthesized from cholesterol precursors. The adrenal cortex is subdivided into three zones: the zona glomerulosa, fasciculate, and reticularis.[39] Glucocorticoids (cortisol) are mainly produced in the zona fasciculata. Aldosterone, a mineralcorticoid, is produced in the zona glomerulosa. Cortisol, an essential hormone, is the most important glucocorticoid produced by the adrenal gland.[39] It controls blood pressure and stress responses through regulation of epinephrine production. In addition, cortisol regulates glucose metabolism (increasing glucose), electrolyte balance, and has antiinflammation effects.[39] Aldosterone, produced in the adrenal cortex, also has significant systemic effects. Its production is regulated by the renin-aldosterone system. The main effect of aldosterone is absorption of sodium and secretion of potassium in the kidney. Therefore, aldosterone is important to extracellular fluid volume and electrolyte homeostasis.[39,40]

The adrenal medulla also plays an essential role in the body's physiologic response to stress. Its primary function is production of norepinephrine and epinephrine. Cortisol stimulates phenylethanolamine *N*-methyltransferase, the enzyme responsible for the methylation of norepinephrine to epinephrine.[39] Approximately 75% of the catecholamine released from the adrenal medulla is epinephrine. Catecholamines then have widespread systemic effects.[39,40]

Normal pregnancy is marked by significant changes in the adrenal system, including increased production and decreased breakdown of adrenal steroids.[41] Less understood is the role of fetal and placental steroidogenesis. Cortisol and aldosterone levels increase with pregnancy, as does cortisol binding.[41] Adrenal gland dysfunction is another rare complication of pregnancy; however, adrenal insufficiency, glucocorticoid excess, and adrenal medullary tumors have all been reported in pregnancy.

Addison Disease (Hypoadrenocorticism)

Primary adrenocortical insufficiency (Addison's disease) is rare during pregnancy.[8] Historically, tuberculosis and histoplasmosis were primarily responsible for granulomatous destruction of the adrenal glands.[42] Today, however, the majority of cases are related to autoimmune disease. An acute crisis can occur in patients with chronic secondary adrenal insufficiency, which may occur from any derangement of pituitary or hypothalamic function.[41] Most adequately treated parturients will not have problems with fetal development, labor, or delivery. In fact, the fetus largely maintains its own steroid production and might even help sustain the maternal system. Occasionally, infertility may result from coexisting polyglandular autoimmune disease that involves the ovaries. Some authors have made associations between fetal growth retardation and Addison's disease.[41,43]

Diagnosis in pregnancy is typically made by clinical presentation or a corticotropin stimulation test in which baseline plasma cortisol is measured, intravenous synthetic corticotropin is administered, and the change in plasma cortisol noted.[8] A rise of less than 7 μg/dL indicates an insufficient response and establishes a diagnosis.[39]

Obstetric Management

Pregnancy does not significantly alter the management of adrenal insufficiency. Routine treatment applies, with an emphasis on physiologic steroid replacement, which can be achieved by administering 30 mg hydrocortisone daily.[41] However, during stress (e.g., delivery or surgery), intravenous supplementation with 50 to 100 mg hydrocortisone every 8 h may be indicated.[8,42]

Anesthetic Management

Early application of epidural analgesia may be recommended to decrease the stress response associated with painful labor. Intravenous volume replacement with balanced salt solutions should be instituted, and urine output monitored closely. The decision to prophylactically treat steroid deficiency should be discussed with the obstetric team. For cesarean section, spinal, epidural, or general anesthesia can be instituted without significant complications. The parturient's hemodynamic and fluid status should be closely monitored. If sudden hypotension or an emergency arises, treatment with intravenous hydrocortisone at 100 mg should be instituted. Occasionally, in life-threatening Addison's disease, a continuous infusion of cortisol 10 mg/h may be necessary.[38] Severe cases can present similarly to hemorrhagic shock. Higher doses of intravenous or inhalational anesthetics may produce myocardial depression and hypotension. Invasive monitoring with an arterial line, pulmonary artery catheter, and Foley catheter is very useful in this situation and provides a guide for rapid intravascular volume replacement.[39] Hyponatremia, hyperkalemia, hypoglycemia, hemoconcentration, and decreased renal flow are all potential complications of severe adrenal insufficiency. Therefore, volume replacement should consist of glucose-containing balanced salt solutions, and glucose and electrolyte levels should be monitored closely.[39] Skeletal muscle weakness can accompany severe cortisol deficiency and reduce nondepolarizing muscle relaxant requirements. Monitoring a peripheral nerve stimulator is prudent in these cases. Etomidate may be a poor choice for an induction agent, because it has been associated with adrenal suppression.[40]

Cushing's Disease (Hyperadrenocorticism)

Cushing's syndrome, most frequently associated with long-term corticosteroid use, leads to the characteristic findings of truncal obesity, moon facies, and buffalo hump. Clinical presentation frequently includes hypertension, generalized fatigue, muscle weakness, abnormal skin striae, and amenorrhea.[41] Amenorrhea decreases the number of cases of Cushing's disease presenting in pregnancy. Approximately 70 cases have been reported, and more than half involved benign adrenal tumors,[44–46] in contrast with nonpregnant individuals, in whom pituitary adenoma is the most frequent form of endogenous Cushing's disease.[41] Clinical diagnosis in pregnancy is frequently clear, because symptoms are more pronounced in the parturient. Laboratory diagnosis may be complicated by the fact that estrogen can create inaccuracy in the dexamethasone suppression test, and normal pregnancy values for some tests have not been established.[41]

Maternal complications of Cushing's disease include hypertension, diabetes, wound breakdown, and proximal myopathy. Approximately 10% suffer congestive heart failure associated with severe hypertension.[41] Buescher et al. reported a maternal mortality of approximately 4.6% in 65 parturients.[45] Fetal outcome is also adversely affected. Perinatal mortality ranges from 15% to 25%. Preterm delivery is the leading cause of morbidity, with two thirds of parturients delivering before 38 weeks.[41] Low birth weight is also a frequent complication. Neonatal cortisol withdrawal, also a potential complication of maternal Cushing's syndrome, can occur shortly after birth.[41]

Obstetric Management

Management of Cushing's disease in pregnancy depends on the severity of symptoms and gestational age. If symptoms are mild or occur late in pregnancy, palliatative measures (e.g., management of hypertension) until delivery are frequently the best course.[47] However, if symptoms are severe or diagnosis is made early in pregnancy, surgical intervention remains the definitive treatment. Adrenalectomy and transphenoidal pituitary surgery have both been performed successfully during pregnancy. Unilateral adrenalectomy is performed in the case of an adrenal adenoma, whereas bilateral adrenalectomy is frequently done for adrenal hyperplasia. One review of unilateral adrenalectomy during pregnancy suggested a better neonatal outcome if surgery was not delayed.[46] If adrenalectomy is planned, it should ideally be performed in the early second trimester.

Anesthetic Management

Preanesthetic evaluation of parturients with Cushing's disease should concentrate on management of fluid retention, diabetes, or hypertension if present.[39] Electrolytes and serum glucose level should be reviewed before an anesthetic is used. Bone metabolism is abnormal in hyperadrenocorticism and can cause premature osteoporosis and vertebral body collapse. Bone density may be significantly decreased, and patients should be carefully positioned and manipulated to prevent fractures.[39] Regional analgesia is an acceptable option that

carries the added benefit of blunting the stress response associated with labor.[48] Decreased stress minimizes excess cortisol secretion and can be used for emergency cesarean section. For cesarean section, regional or general anesthesia can be safely administered. The potential for associated skeletal muscle weakness in patients with Cushing's syndrome requires careful monitoring of neuromuscular blockade with a nerve stimulator.[39] Requirement for nondepolarizing muscle relaxants may be significantly reduced.

Pheochromocytoma

Pheochromocytoma, a rare catecholamine-secreting tumor of neural crest origin, arises from chromaffin cells. The overall annual incidence in the general population has been reported as 1.6 to 2.1 per million.[49] Most tumors (90%) are found in the adrenal medulla of one or both adrenal glands. However, they can also occur extraadrenally (paragangliomas) along the sympathetic adrenal axis.[49,50] The majority of adrenal tumors are benign (90%) adrenal adenomas.[50] Overall, approximately 10% are malignant, and it appears the risk is higher when the tumor is extraadrenal in location.[49] These tumors may secrete both adrenaline and noradrenaline in varying amounts. Pheochromocytomas account for approximately 0.1% of hypertension in patients between 40 and 70 years of age.[51] They can occur in association with several multiple endocrine neoplasias and neuroectodermal dysplasias (Table 14.8).[49] There are also associations with diabetes mellitus and thyrotoxicosis.

Encountering pheochromocytoma during pregnancy is a rare event. The incidence in pregnancy is probably less than 1 case per 50,000 term pregnancies.[51] Although it is rare during pregnancy, it can have catastrophic results if unrecognized. Diagnosis can be complicated by the similarities with preeclampsia, including hypertension and occasional proteinuria.[8,41,52] Severe episodes of hypertension and tachycardia can result from labor and delivery, anesthesia, or even fetal movements.[51] Pregnancy does not drastically alter the clinical presentation of pheochromocytoma. Hypertension, either sporadic or sustained, is the most common symptom.[41] Among nonpregnant women with a pheochromocytoma, 98% have hypertension, 80% to 85% headache, 60% to 65% tachycardia, and 65% to 70% experience sweating.[53] A review of parturients with pheochromocytoma reported that more than 80% had hypertension, 60% headaches, and 30% sweating.[54] In nonpregnant patients episodic (paroxysmal) attacks of headache, palpitations, and sweating in association with hypertension have been reported to be 90% reliable for diagnosis.[51] The lack of these symptoms was reported to virtually rule out a diagnosis of pheochromocytoma.[55] Orthostatic hypotension is present in 70% of pheochromocytoma patients secondary to elevated systemic vascular resistance and intravascular volume depletion.[56]

Useful laboratory values used in diagnosis of pheochromocytoma are not altered significantly during pregnancy.[33] The first step is to identify elevated plasma or urine catecholamines. Unfortunately, plasma catecholamines have a serum half-life of 2 min and therefore are ideally measured very near the time symptoms are occurring.[51] Urinary analysis carries less concern for timing, but controversy exists about the best sampling techniques. Screening a 24-h urine for either catecholamines (adrenaline, noradrenaline, and dopamine) or metabolites (metanephrines and vanilmandelic acid) is a good option.[33,51] However, consultation with a clinical pathologist concerning the specific situation is strongly recommended. Recently, testing platelets for catecholamine levels and other tumor markers has been reported to be predictive in diagnosis of pheochromocytoma.[51] Provocative testing with glucagon or histamine is not recommended for fear of precipitating severe symptoms.[33,51] Suppression testing with clonidine or pentolamine, although reported, is unlikely to be used or necessary in pregnancy.[8,33]

Radiographic testing such as ultrasound, computer tomography (CT), magnetic resonance imaging (MRI), and metaiodobenzylguanidine (MIBG) is useful to confirm diagnosis and locate extraadrenal tumors.[53] Ultrasound is frequently the first-line study during pregnancy because of ease and familiarity.[51] It is, however, difficult to visualize many tumors (particularly extraadrenal) with ultrasound. MRI scanning is considered the safest and most definitive study for parturients.[8,41]

Undiagnosed pheochromocytoma during pregnancy results in maternal and fetal mortality rates as high as 58% and 56%, respectively.[49,51,57] On the other hand, when the diagnosis is established and treatment initiated during pregnancy, the maternal and fetal mortality rates decline to approximately 0 and less than 15% respectively.[41] Fetal complications include fetal death, intrauterine growth retardation, and placental abruption.[58] Diagnosis and treatment with α-blockade before delivery significantly reduce fetal mortality.[49,51,59] Even in a patient who has already been surgically treated (i.e., adrenalectomy), a history of pheochromocytoma should raise concern.[41] Long-term follow-up is required because the latency

TABLE 14.8. Pheochromocytoma-associated endocrine syndromes.

MEN (multiple endocrine neoplasias)
Type IIa (Sipple's syndrome)
Medullary carcinoma of the thyroid
Parathyroid hyperplasia or adenoma
Pheochromocytoma
Type IIb/type IIa plus
Mucosal neuromata
Marfanoid habitus
Neuroectodermal dysplasias
Neurofibromatosis
Tuberous sclerosis
Sturge–Weber syndrome
Von Hippel–Lindau syndrome

Source: Adapted from O'Riordan JA. Pheochromocytomas and anesthesia. Int Anesthesiol Clin 1997;35(4):100.

periods for recurrence or malignancy can range from 2 to 12 years. Maintaining a high level of suspicion is imperative for the safe management of these patients.[41,51]

Obstetric Management

Gestational age at the time of presentation may influence the management of pheochromocytoma in pregnancy; therefore, a multidisciplinary approach is essential. However, the initial management remains aimed at control of hypertension and prevention of its adverse effects. A sudden surge in catecholamine levels could be fatal. Therefore, α-adrenergic blockade is the main treatment. Phenoxybenzamine, a noncompetitive irreversible α-blocker, is considered safe during pregnancy and is the most frequently used drug.[30] Phenoxybenzamine appears to decrease the level of catecholamines secreted by tumors, most likely because of α_1-negative feedback on catecholamine synthesis.[30] Unlike pentolamine, phenoxybenzamine has greater α_1-selectivity (100 fold compared to α_2), reducing the risk of rebound hypertension.[53] It is administered orally at 10 mg twice a day; this dose is increased by 10 mg/day until symptoms resolve (50–250 mg/day).[53] Prazocin, a postsynaptic α_1-blocker, is an alternative treatment option.[41,53] Oral metyrosine (250–1000 mg), a drug that interferes with catecholamine synthesis, may be effective, but little is known about its use in pregnancy.[41,60]

β-Blockers are sometimes required to control tachycardia and prevent arrhythmias, but are only instituted after α_1-blockade because their use could eliminate β_2-mediated vasodilatation. This unopposed α_1-stimulation can precipitate profound vasoconstriction, hypertensive crisis, or pulmonary edema.[51,53] Labetalol, a β- and α-blocking agent, is considered safe during pregnancy and has been used successfully to manage pheochromocytoma.[49] However, it should be noted that it has significantly more β-blocking than α-blocking effects. Most α-adrenergic blocking agents cross the placenta but have been safely used throughout pregnancy.[49] β-Blockade has been associated with fetal bradycardia, hypotension, uterine irritability, and impaired fetal recovery from acidosis and hypoxia.[49] Adequate medical treatment of parturients can take 10 to 14 days.

Surgical removal of the catecholamine-secreting tumor is the only definitive therapy for pheochromocytoma.[53] Once a parturient stabilizes with medical management (α_1-blockade), surgical treatment becomes the goal. There is some controversy about timing of surgery for pheochromocytoma in pregnancy.[8,51,53] Management in early pregnancy is more controversial, including pregnancy termination, tumor resection, and, in some cases, medical management until delivery. Most authors divide parturients into those diagnosed before 24 weeks and those diagnosed after.[8,41,53] Before 24 weeks, surgical tumor removal is feasible without significant interference by the gravid uterus. In the second half of pregnancy, the enlarging uterus can make laparotomy and exploration difficult. Cesarean section is the recommended mode of delivery.[51] Therefore, surgery is often postponed until fetal maturity is obtained, and a cesarean section followed by adrenalectomy is done under α-blockade. This course may be altered depending on tumor location and patient stability.

Anesthetic Management

Adequate preanesthetic preparation with α_1-blockade (and β-blocker if necessary) is essential. Once α_1-blockade is initiated, optimal control may require up to 14 days of treatment.[61] To determine if preoperative treatment is adequate, Roizen et al. suggested several criteria (Table 14.9).[61] If these criteria are met, the authors believe the patient's condition has been medically optimized. Adequate α-blockade will help reexpand circulating volume, resulting in a drop in the hematocrit. Once α-blockade is established, β-blockers may be added to control and prevent tachyarrthymias. However, these patients are at risk for catecholamine-induced cardiomyopathy; β-blockade should be undertaken cautiously.[49,61] Rapid intraoperative control of hemodynamics is best undertaken with short-acting agents.

Labor analgesia is not usually a concern because these parturients should not labor. However, it should be intuitive that pain precipitates catecholamine release and should be treated, if it arises, with the safest, most effective means available. Davies and Navaratnarajah described a successful vaginal delivery utilizing epidural analgesia in a parturient with pheochromocytoma.[62] Epidural analgesia effectively blocks the sympathetic response; however, it does not prevent the systemic response to catecholamines produced by the tumor.[49] Concern also exists about potential dangers of sympathetic blockade in inadequately α-blocked and volume-contracted patients.[38]

With regard to anesthetic management for cesarean section, with or without a simultaneous adrenalectomy, there are no prospective randomized studies available. There are reports of successful surgery during pregnancy performed under general, epidural, and combined (regional plus general) anesthesia.[63,64] Spinal and epidural anesthetics have been performed without complications in nonpregnant patients with pheochromocytoma.[65,66] One small study comparing regional with general anesthesia found no difference in outcome. Lumbar epidural anesthesia was reported to provide a cardiovascularly stable anesthetic for cesarean section without adrenalectomy

Table 14.9. Criteria for optimal preoperative condition in pheochromocytoma.

No blood pressure reading higher than 160/90 mm Hg should be evident for 24 h before surgery
Orthostatic hypotension, with readings above 80/45 mm Hg, should be present
EKG free of ST-T changes for at least 1 week
No more than one premature ventricular contraction every 5 min

Source: From Roizen MF, Schreide BD, Hassan SZ. Anesthesia for patient with pheochromocytoma. Anesthesiol Clin N Am 1987;5(2):273.

for two parturients with pheochromocytoma.[66] After an adrenalectomy, patients are prone to develop hemodynamic instability secondary to withdrawal of high circulating catecholamine levels. Some authors express concern over the use of regional anesthesia in this situation because of the sympathectomy.[53]

General anesthesia has been used alone or in combination with epidural anesthesia in the majority of cases.[63,64,67] When general anesthesia is used, the focus should be on preventing serious swings in blood pressure and avoiding drugs that might precipitate hemodynamic instability. Premedication is recommended to prevent anxiety[49] and can safely be achieved with small doses of benzodiazepines (e.g., diazepam or midazolam). When considering induction agents, one must consider and weigh the risks of precipitating a hypertensive crisis versus the increased risk of aspiration in pregnancy. Standard induction with sodium pentathol (4 mg/kg) or etomidate (0.3 mg/kg) followed by succinylcholine (1.5 mg/kg) is acceptable in most situations. Intubation can result in a severe hypertensive response, which might lead to intracranial hemorrhage, pulmonary edema, or decreased placental flow.[49] The response to laryngoscopy can be blunted with intravenous lidocaine (1 mg/kg), labetalol (30 mg), or remifentanil (1 mg/kg). Maintenance of anesthesia is with a volatile agent (isoflurane or sevoflurane) and nitrous oxide. Sevoflurane may have the advantage of being more quickly titratable. Halothane has traditionally been avoided because it may sensitize the heart to catecholamine-induced arrhythmias.[38] Perioperative management consists of optimal preanesthetic treatment, hemodynamically stable induction, preparation for treatment of intraoperative fluctuations in hemodynamics, and careful communication between surgeons and anesthesiologists.

Two large-bore (14- or 16-gauge) intravenous lines should be in place before induction for rapid infusion and volume expansion as needed.[50] A radial arterial line is essential for these patients because of potentially rapid changes in hemodynamics, and it should be placed preoperatively. Standard monitors such as ECG, pulse oximetry, and Foley catheter should be in place. A pulmonary arterial (PA) line or transesophageal echo should be considered for monitoring the fluid status and response to inotropes. Such monitoring may become essential in a patient with catecholamine-induced cardiomyopathy. These authors believe that at least a central access sheath should be placed preoperatively, so that it can provide information on right-sided pressures, and accommodate a PA line intraoperatively if it becomes necessary.

Regardless of the anesthetic chosen, a plan should be made and several drugs prepared for blood pressure management. Choices include nitroprusside, nitroglycerin, magnesium sulfate,[68] trimethaphan, phentolamine, labetalol, and propranolol. Nitroprusside is effective and can rapidly control blood pressure. Doses in the range of 1 μg/kg/min are considered safe for short-term use during pregnancy.[69] Concerns over fetal cyanide toxicity are related more to higher doses and prolonged use, particularly if tachyphylaxis develops. Nitroprusside has been shown to antagonize uterine artery vasoconstriction secondary to norepinephrine.[70] Magnesium sulfate ($MgSO_4$) has been used effectively to manage hemodynamic changes associated with pheochromocytoma.[68,71] It has been reported to be useful in controlling exaggerated blood pressure changes secondary to induction of anesthesia, intubation, and surgical incision. A review by James recommended a loading dose of 40 to 60 mg/kg $MgSO_4$, followed by a 2 g/h infusion until tumor removal.[71,72] Boluses of 20 mg/kg were used to control acute changes in blood pressure. The author reported that, in 23 of 28 cases, $MgSO_4$ was the only agent needed to maintain stable hemodynamics. Total doses in these cases ranged from 8 to 18 g. In another series, James reported reductions in adrenaline and noradrenaline levels during anesthesia and surgery with pheochromocytoma.[71] $MgSO_4$ has several properties that make it a potentially useful agent for these cases, and most obstetric personnel are very familiar with its use. If $MgSO_4$ is utilized, the potential for impaired recovery from muscle relaxation should be anticipated, and appropriate precautions taken.[49] Short-acting antihypertensive agents are preferred intraoperatively, especially if adrenalectomy is performed, because a fall in catecholamines after removal may make hypotension the major problem. It has been suggested, although not studied, that various medications that may cause histamine release or direct release of catecholamines be avoided in patients with pheochromocytoma.[50]

Pituitary Gland Disease

Diagnosis of pituitary gland disorders during pregnancy is not common. Management of a parturient with impairment of the pituitary gland can be complicated and requires involvement of an endocrinologist. The anterior pituitary contains five different cell types: somatotrophs, lactotrophs, corticotrophs, gonadotrophs, and thyrotrophs.[73] These cells are responsible for release of growth hormone, prolactin, adrenocorticotrophic hormone (ACTH), luteinizing and follicle-stimulating hormones, and thyrotropin (TSH), respectively.[8,73] The pituitary gland may increase as much as 70% in size in normal pregnancy, mainly because of hyperplasia of lactotroph cells.[8]

Prolactinomas

Prolactin-secreting pituitary adenomas can result in amenorrhea, galactorrhea, and hyperprolactinemia. They are arbitrarily defined on the basis of size, with microadenomas being less than 10 mm in size and macroadenomas greater then 10 mm in size as measured by CT or MRI.[42] The introduction of bromocriptine (a dopamine-receptor stimulator) has increased the number of parturients presenting with microadenomas.[42] This drug appears to be safe during pregnancy

and free of adverse fetal effects. The majority of cases in pregnancy involve microadenomas. Pregnancy itself can induce enlargement of the pituitary gland and may precipitate symptoms in a previously asymptomatic patient.[42] Symptoms such as headache, visual disturbances, and diabetes insipidus are much more common with macroadenomas, and definitive treatment (surgery or irradiation) is recommended before attempted pregnancy.[74]

Obstetric Management

Most microadenomas presenting during pregnancy are asymptomatic. A review of 250 cases of microadenoma in pregnancy showed symptomatic enlargement in 4 cases and asymptomatic enlargement in the rest of the cases.[74] The incidence of symptoms during pregnancy has been reported to be relatively rare. Parturients presenting with macroadenomas develop symptoms in as many as 15% of the cases.[74] If symptoms develop (visual disturbances or headaches) during pregnancy, the recommendation is to start treatment with bromocriptine immediately. Elevated prolactin levels can confirm diagnosis; however, this is unreliable in pregnancy.[42] Under these circumstances, assessment with CT or MRI is recommended.[42] Surgical interventions are utilized only when a parturient is unresponsive to drug treatment.

Anesthetic Management

In asymptomatic parturients there are no significant anesthetic implications, and these parturients may be managed with either general or regional anesthesia. Parturients should be assessed, particularly those with macroadenomas, for visual disturbances and headaches. In symptomatic cases of microadenomas or macroadenomas, imaging studies can be reviewed, and an assessment of intracranial pressure made. There may be advantages in controlling the pain of labor and pushing that occurs during the second-stage of labor in an attempt to minimize elevations in intracranial pressure. The risk–benefit ratio of regional analgesia and anesthesia can be assessed and, in most cases, these can be safely utilized.

Diabetes Insipidus

Diabetes insipidus rarely complicates pregnancy, and very few cases have been reported. This disease is a result of either the absence of antidiuretic hormone (ADH) secondary to destruction of the posterior pituitary (neurogenic) or lack of response by the renal tubules to ADH (nephrogenic). The underlying cause can be determined by a desmopressin (L-deamino-8-D-arginine vasopressin) response test.[38] Neurogenic diabetes insipidus will result in concentration of the urine after a 5-unit desmopressin (DDAVP) subcutaneous or 20 mg intranasal challenge, whereas nephrogenic diabetes will not.[75,76] This synthetic analogue of vasopressin is also used for treatment of neurogenic diabetes insipidus. Nephrogenic diabetes insipidus has been treated with chloropropamide (an oral hypoglycemic), which increases the responsiveness of renal tubules to ADH.[38] Inadequate release of ADH may be caused by indirect head trauma or direct injury during pituitary surgery. This effect may be transient or partial in nature. Clinical findings include polydypsia, large quantities of dilute urine output, and elevated plasma osmolarity.[38]

Obstetric Management

Desmopressin can be administered intranasally (0.1–0.2 ml once or twice per day), intravenously 5 units over 5 min, or intramuscularly every 2 to 4 days. There is an increased dose requirement in pregnancy secondary to breakdown by placental vasopressinase.[77] Subclinical diabetes insipidus (neurogenic and nephrogenic) can become symptomatic during pregnancy because of this increased metabolism of vasopressin by placental vasopressinase.[78] There may be an association between abnormal labor and diabetes insipidus[79]; it is suggested that insufficient levels of oxytocin are responsible for this. Initial treatment also includes increasing fluid intake either orally or intravenously. Intravenous replacement should be with balanced salt solutions, and electrolytes should be carefully monitored.

Anesthetic Management

The patient should be adequately treated medically (DDAVP) and fluid resuscitated before anesthesia. Parturients with a partial deficiency of ADH do not necessarily need vasopressin replacement unless plasma osmolality rises above 290 mOsm/L.[75] Plasma electrolytes and osmolality should be evaluated and monitored.[75] Monitoring of urine output with a Foley catheter is recommended. For labor and delivery, epidural analgesia can be used. For cesarean section, regional and general anesthesia can be used safely, especially if the parturient has been treated properly beforehand.

Panhypopituitarism

Panhypopituitarism is defined as a generalized deficiency of anterior pituitary hormones. This syndrome may result from autoimmune lymphoid hypophysitis or vascular necrosis.[8] Sheehan suggested that hypotension would cause vasospasm, decreased perfusion, and eventually infarction of the anterior pituitary.[80] Diabetics and vasculopathic patients are more vulnerable. Sheehan's syndrome is often synonymous with the development of anterior pituitary necrosis after massive peripartum hemorrhage. The precipitating event may be hemorrhage, infection, or trauma.[8] Clinical presentation is diverse and broad, reflecting the loss of various endocrine hormones that are under the control of the pituitary gland. Acute neurological sequelae including coma may result.[8] Other clinical

sequelae include hypotension, bradycardia, hypothermia, hypoglycemia, slow respiration, malaise, nausea, vomiting, and hemodynamic collapse.[8] The majority of serious symptoms are the result of sudden hypoadrenalism. The diagnosis of panhypopituitarism will depend on the clinical stability of the parturient. If the parturient is stable, an endocrinologist should be immediately involved because multiple tests may be required to confirm a diagnosis.[8] However, if the parturient is deteriorating, and a diagnosis of panhypopituitarism is suspected, treatment is imperative.

Obstetric and Anesthetic Management

A multidisciplinary approach is required for adequate management in panhypopituitarism. Immediate replacement in the unstable parturient consists of (1) hydrocortisone 100 mg intravenously every 4 to 6 h; (2) thyroxin 0.1 to 0.2 mg intravenously (changing to oral thyroxin); (3) fluid resuscitation with balanced salt solutions; (4) careful monitoring of fluid balance to avoid water intoxication; and (4) prevention of hypothermia.[8] Cases of successful pregnancies in parturients with Sheehan's syndrome have been described.[81] If the parturient has had adequate hormone replacement, outcomes are improved. Parturients must remain on thyroxin and corticosteroid replacement throughout pregnancy. Labor and delivery may require treatment with stress-dose steroids (100 mg hydrocortisone q 8 h). There are no specific anesthetic recommendations other than those already discussed for the specific endocrinopathies. The choice of anesthesia is determined by the stability of the parturient at presentation and could range from an epidural in a parturient with adequate hormonal replacement to general anesthesia in acute hemorrhagic crisis. Careful attention should be given to volume status, electrolytes, reduction of stress response, and adequate hormonal replacement.

Summary

Pregnancy is associated with changes on the normal endocrine system, and these changes may worsen thyroid, parathyroid, adrenal gland, and pituitary gland pathologies. This chapter summarizes obstetric and anesthetic implications of endocrine pathologies during pregnancy.

References

1. Lyons FM, Meeran K. The physiology of the endocrine system. Int Anesthesiol Clin 1997;35(4):1–21.
2. Petraglia F, Florio P, Nappi C, Genazzani AR. Peptide signaling in human placenta and membranes: autocrine, paracrine, and endocrine mechanisms. Endocr Rev 1996;17:156–186.
3. Segal J. Thyroid hormone action at the level of the plasma membrane. Thyroid 1990;1:83–87.
4. Farese RV. Calcium as an intracellular mediator of hormone action: intracellular phospholipid signaling systems. Am J Med Sci 1988;296: 223–230.
5. Miller DS, Sykes DB. Stimulation of protein synthesis by internalized insulin. J Cell Physiol 1991;147:487–494.
6. Ecker JL, Musci TJ. Treatment of thyroid disease in pregnancy. Obstet Gynecol Clin N Am 1997;24(3):575–589.
7. Mestman JH. Hyperthyroidism in pregnancy. Endocrinol Metab Clin N Am 1998;27(1):127–149.
8. Mastrogiannis DS, Whiteman VE, Mamopoulos M, Salameh WA. Acute endocrinopathies during pregnancy. Clin Obstet Gynecol 1994;37(1): 78–92.
9. Mestman JH. Hyperthyroidism in pregnancy. Clin Obstet Gynecol 1997; 40(1):45–64.
10. Edwards R. Thyroid and parathyroid disease. Int Anesthesiol Clin 1997; 35(4):63–83.
11. Hall R. Pregnancy and autoimmune endocrine disease. Baillieres Clin Endocrin Metab 1995;9(1):137–155.
12. Drake WM, Wood DF. Thyroid disease in pregnancy. Postgrad Med J 1998;74(876):583–586.
13. Davis LE, Lucas MJ, Hankins GDV, et al. Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol 1989;160:63.
14. Sherif IH, Oyan WT, Bosairi S, et al. Treatment of hyperthyroidism in pregnancy. Acta Obstet Gynecol Scand 1991;70:461–463.
15. Stehling LC. Anesthetic management of the patient with hyperthyroidism. Anesthesiology 1974;41(6):585–595.
16. Maze M. Clinical implications of membrane receptor function in anesthesia. Anesthesiology 1981;55:160.
17. Gilstrap LC, Wallace DH. Rare endocrine disorders. In: Gambling DR, Douglas MJ (eds) Obstetric Anesthesia and Uncommon Disorders. Philadelphia: Saunders, 1998.
18. Wilson WR, Theilen EO, Hege JH, Valenca MR. Effects of beta-adrenergic receptor blockade in normal subjects before, during, and after triiodothyronine-induced hyper-metabolism. J Clin Invest 1966;45:1159–1169.
19. Farling PA. Thyroid disease. Br J Anaesth 2000;85(1):15–28.
20. Stehling L. Anesthetic implications of hyperthyroidism. Contemp Anesth Pract 1980,3:147–157.
21. Riniker M, Tieche M, Lupi GA, et al. Prevalence of various degrees of hypothyroidism among patients of a general medical department. Clin Endocrinol 1981;14:69–74.
22. American College of Pysicians. Screening for thyroid disease. Ann Intern Med 1998;129:141–143.
23. Montoro MN. Management of hypothyroidism during pregnancy. Clin Obstet Gynecol. 1997;40(1):65–80.
24. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72:108–112.
25. Gavin LA. The diagnostic dilemmas of hyperthyroxinemia and hypothyroxinemia. Adv Intern Med 1988;33:185–204.
26. Mandel SJ, Larsen PR, Seely EW, et al. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. N Engl J Med 1990;323:91–96.
27. Breivik H. Perianaesthetic management of patients with endocrine disease. Acta Anaesth Scand 1996;40:1004–1015.
28. Zwillich CW, Pierson DJ, Hofeldt FD, et al. Ventilatory control in myxedema and hypothyroidism. N Engl J Med 1975;292:662–655.
29. Hofbauer LC, Heufelder AE. Coagulation disorders in thyroid diseases. Eur J Endocrinol 1997;136:1–7.
30. Myrup B, et al. Primary haemostasis in thyroid disease. J Intern Med 1995;238:59–63.
31. Roizen MR, et al. Patients with disorders of thyroid function. Anesth Clin N Am 1987;5(2)277–285.
32. Mestman JH. Parathyroid disorders of pregnancy. Semin Perinatol 1998;22(6):485–496.
33. Mihai R, Farndon JR. Parathyroid disease and calcium metabolism. Br J Anaesth 2000;85(1):29–43.

34. Kohlmeier L, Marcus R. Calcium disorders of pregnancy. Endocrinol Metabol Clin N Am 1995;24(1):15–39.
35. Pitkin RM. Calcium metabolism in pregnancy and the perinatal period: a review. Am J Obstet Gynecol 1985;151:99–109.
36. Carella M, Gossain V. Hyperparathyroidism in pregnancy: a case report and review. J Gen Intern Med 1992;7:448–453.
37. Hensel P, Roizen MF. Patients with disorders of parathyroid function. Anesthesiol Clin N Am 1987;5(2):287–298.
38. Stoelting RK, Dierdorf SF. Endocrine disease. In: Stoelting RK, Dierdorf SF (eds). Anesthesia and Co-Existing Disease, 3rd edn. New York: Churchill Livingstone, 1993:339–374.
39. Sheeran P, O'Leary E. Adrenocortical disorders. Int Anesthesiol Clin 1997;35(4):85–98.
40. Lampe GH, Roizen MF. Anesthesia for patients with abnormal function at the adrenal cortex. Anesthesiol Clin N Am 1987;5(2):245–268.
41. Hadden DR. Adrenal disorders of pregnancy. Endocrinol Metabol Clin N Am 1995;24(1):139–151.
42. In: Cunningham FG, et al (eds). Williams Obstetrics, 20th edn. Stamford: Appleton and Lange, 1997:1232–1233.
43. O'Shaughnessy RW, Hackett KJ. Maternal Addison's disease and fetal growth retardation. J Reprod Med 1984;29:752.
44. Aron DC, Schnall AM, Sheeler LR. Cushing's syndrome and pregnancy. Am J Obstet Gynecol 1990;162:244–252.
45. Buescher MA, McClamrock HD, Adashi EY. Cushing syndrome in pregnancy. Obstet Gynecol 1992;79:130–137.
46. Pricolo VE, Caldwell MD, Mastrofrancesco B, et al. Management of Cushing's syndrome secondary to adrenal adenoma during pregnancy. Surgery (St. Louis) 1990;108(6):1072–1077.
47. Martin RW, Lucas JA, Martin JN, et al. Conservative management of Cushing's syndrome in pregnancy: a case report. J Reprod Med 1989; 34:493.
48. Glassford J, Eagle C, McMorland GH. Caesarean section in a patient with Cushing's syndrome. Can Anaesth Soc J 1984;31:447–450.
49. O'Riordan JA. Pheochromocytomas and anesthesia. Int Anesthesiol Clin 1997;35(4):99–127.
50. Prys-Roberts C. Phaeochromocytoma—recent progress in its management. Br J Anaesth 2000;85:44–57.
51. Potts JM, Larrimer J. Pheochromocytoma in a pregnant patient. J Fam Pract 1994;38(3):289–293.
52. Richart RM, et al. When pheochromocytoma masquerades as preeclampsia. Contemp Obstet Gynecol 1980;15:195–204.
53. Botchan A, et al. Pheochromocytoma in pregnancy: case report and review of the literature. Obstet Gynecol Surv 1995;50(4):321–326.
54. Schenker JG, Granat M. Pheochromocytoma and pregnancy: an updated appraisal. Aust N Z J Obstet Gynaecol 1982;22:1–10.
55. Bravo EL, Gifford RW. Pheochromocytoma: diagnosis, localization and management. N Engl J Med 1984;311:1298–1303.
56. Benowitz NL. Pheochromocytoma. Adv Intern Med 1990;35:195–220.
57. Hart JJ. Pheochromocytoma. Am Fam Physician 1990;42:163–169.
58. Harper MA, Murnaghan GA, Kennedy L, et al. Phaeochromocytoma in pregnancy: five cases and a review of the literature. Br J Obstet Gynaecol 1989;96:594–606.
59. Pestelek B, Kapor M. Pheochromocytoma and abruptio placentae. Am J Obstet Gynecol 1963;85:538–540.
60. Perry RR, Keiser HR, Norton JA, et al. Surgical management of pheochromocytoma with the use of Metyrosine. Ann Surg 1990;212: 621–628.
61. Roizen MF, Schreide BD, Hassan SZ. Anesthesia for patient with pheochromocytoma. Anesthesiol Clin N Am 1987;5(2):269–275.
62. Davies AE, Navarantnarajah M. Vaginal delivery in a patient with a phaeochromocytoma. A case report. Br J Anaesth 1984;56:913–916.
63. Hopkins PM, MacDonald R, Lyons G. Caesarean section at 27 weeks gestation with removal of phaeochromocytoma. Br J Anaesth 1989;63: 121–124.
64. Bakri YN, Ingemansson SE, Ali A, et al. Pheochromocytoma and pregnancy: report of three cases. Acta Obstet Gynecol Scand 1992;71: 301–304.
65. Mitchell SZ, Freilich JD, Brant D, et al. Anesthetic management of pheochromocytoma resection during pregnancy. Anesth Analg 1987;66: 478–480.
66. Stonham J, Wakefield C. Phaeochromocytoma in pregnancy: caesarean section under epidural analgesia. Anaesthesia 1983;38:654–658.
67. Fudge TL, McKinnon WM, Geary WL. Current surgical management of pheochromocytoma during pregnancy. Arch Surg 1980;115:1224–1225.
68. James MF, Huddle KR, Owen AD, et al. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. Can J Anaesth 1988;35:178–182.
69. Shoemaker CT, Meyers M. Sodium nitroprusside for control of severe hypertensive disease of pregnancy: a case report and discussion of potential toxicity. Am J Obstet Gynecol 1984;149:171–173.
70. Lieb SM, et al. Nitroprusside-induced hemodynamic alterations in normotensive and hypertensive pregnant sheep. Am J Obstet Gynecol 1981; 139:925–931.
71. James MFM. Use of magnesium sulphate in the anaesthetic management of pheochromocytoma: a review of 17 anaesthetics. Br J Anaesth 1989; 62:616.
72. James MFM. Clinical use of magnesium infusions in anesthesia. Anesth Analg 1992;74:129–136.
73. Smith M, Hirsch NP. Pituitary disease and anaesthesia. Br J Anaesth 2000;85:3–14.
74. Molitch ME. Pregnancy and the hyperprolactinemic woman. N Engl J Med 1985;312:1364.
75. Malhotra N, Roizen MF. Patients with abnormalities of vasopressin secretion and responsiveness. Anesthesiol Clin N Am 1987;5(2):395–410.
76. Razis PA. Anesthesia for surgery of pituitary tumors. Int Anesthesiol Clin 1997;35(4):23–34.
77. Smith RJ, Dluhy RG, Williams GH. Endocrinology. In: Vandam LD (ed) To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient, 2nd edn. Menlo Park: Addison-Wesley, 1984:145.
78. Lindheimer MD, Barron WM. Water metabolism and vasopressin secretion during pregnancy. Baillieres Clin Obstet Gynaecol 1994;8:311.
79. Hime MC, Richardson JA. Diabetes insipidus and pregnancy: case report, incidence, and review of literature. Obstet Gynecol Surv 1978;3: 375.
80. Sheehan HL. Postpartum necrosis of the anterior pituitary. J Pathol Bacteriol 1936;45:189.
81. Grimes HG, Brooks MH. Pregnancy in Sheehan's syndrome: report of a case and review. Obstet Gynecol 1980;35:481.

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Orthopedic Problems and Maternal Trauma

John P.R. Loughrey and Mehmet R. Genç

Orthopedic Problems

Chronic back problems are common in the general population, and the incidence is increased during pregnancy.[1] Furthermore, the trend toward increasing maternal age at delivery and the development of interventional techniques and spinal surgery has resulted in a greater proportion of parturients with a prior history of lumbar spine problems presenting for regional analgesia and anesthesia. One of the principal concerns among these women is the feasibility of regional analgesia and anesthesia and its effect on preexisting back problems. Consequently, a significant number of parturients referred for antenatal anesthesia assessment require assessment of musculoskeletal problems[2] that may affect the ability to provide reliable, high-quality regional blockade. This section reviews spinal problems in this population and implications for anesthetic and obstetric management.

Backache

Low back pain (LBP) is common, occurring in up to 80% of pregnancies.[1] A number of predisposing factors, including poor socioeconomic status, increased body mass index, lack of exercise, LBP in a prior pregnancy, prepregnancy LBP, and young age have been identified.[3–6] Up to 20% of women may experience moderate to severe incapacitating back pain, which is responsible for prolonged disability in those affected.[7] Progressive lumbar lordosis and increased mobility of the pubic symphysis, sacroiliac, and sacrococcygeal joints are noted to occur during pregnancy. These changes are thought to be partly caused by the effects of the hormone relaxin[8] on the musculoskeletal system in pregnancy. Occasionally, severe pelvic pain results from relaxation or separation of the symphysis pubis. Lumbar disk herniation should also be considered in pregnant women presenting with considerable back or leg pain.

Postpartum back pain (PPBP) has been studied with greater detail because of both the debate regarding the effect of epidural analgesia on its incidence and the relatively common nature of this complaint. MacLeod et al. reported an incidence of new-onset, long-term backache (defined as pain beginning within 3 months after delivery and lasting 6 weeks or more) of 26% at 1 year after delivery in mothers who received epidurals for labor analgesia.[9] In a postal questionnaire study of more than 11,000 deliveries,[10] MacArthur and colleagues found that new-onset backache had a higher incidence at 19% in women who received epidural blockade compared with 10% in those who did not receive epidurals. This study has been criticized, however, for a low response rate of 19% and reliance on voluntary reporting of prior back pain. Furthermore, no increase in the incidence in PPBP following epidural anesthesia for cesarean delivery has been reported, implying that a cause-and-effect relationship between epidurals per se and PPBP does not exist. In a prospective study of more than 1000 women,[11] Breen et al. found the incidence of PPBP to be similar in those who did receive an epidural compared with those who did not (44% versus 45%). A prospective study by Russell et al. showed that when preexisting back pain was considered, the incidence of new-onset PPBP was 7%, irrespective of the method of labor analgesia.[12]

Sacroiliac joint dysfunction is believed to be a common cause of pregnancy-related backache. The sacroiliac joint is a synovial joint that is a complex articulation between the ilium and sacrum. The sacroiliac ligaments promote stability by surrounding the capsule of the joint and are weaker in the anterior portion. When the pregnant woman is standing, the weight of the trunk causes the sacrum to rotate so that the base moves forward and the apex (coccyx) moves backward. The ligaments provide tension against further rotation in the nonpregnant state. With the ligamentous laxity associated with pregnancy this rotation may be excessive. The sacroiliac joints are innervated by the posterior primary divisions of the S1–S3 nerve roots.[13] Pain emanating from the sacroiliac joint is usually experienced in the lumbosacral area but may be referred to the ipsilateral leg. A number of clinical tests such as Patrick's, Gaenslen's, and the pelvic rock tests have been described to stress the joint and identify it as a source of pain. More specific diagnostic tests involving radiation exposure to the fetus, such as radionuclide

bone scanning or fluoroscopically assisted joint injection, are not recommended before delivery. Magnetic resonance imaging is a safe and useful diagnostic tool to rule out lumbar disk herniation in pregnant women.

Obstetric and Anesthetic Management

The mode of delivery does not appear to affect the natural history of antenatal LBP. Regional analgesia is not contraindicated in a pregnant woman with LBP, and analgesia should be expected in the absence of known pathology or neurologic deficit. Nevertheless, the discussion to obtain informed consent for regional anesthesia should include the fact that available data on the association between regional anesthesia and LBP are conflicting. Treatment options for the parturient with moderate to severe LBP should be actively explored in conjunction with a pain medicine specialist and may consist of physical therapy, support braces, TENS (transcutaneous electrical nerve stimulation) units, epidural depot steroid injection,[14] or trigger point injections. Antenatal anesthesia assessment is recommended in parturients with severe LBP to perform and document anatomic and neurologic examination.

Lumbar Disc Herniation

The lifetime prevalence of sciatica is 2%, with 10% of these patients developing persistent radiculopathy.[15] Imaging studies reveal that disc herniations may be present without any symptoms in as many as 21% to 28% of subjects.[16] However, the incidence of acute lumbar disk herniations during pregnancy appears to be low, with a quoted incidence of 1 in 10,000.[17] This figure may underestimate the true incidence, as imaging studies formerly were performed infrequently before the widespread availability of magnetic resonance imaging. Radicular symptoms from intervertebral disk herniation may be present in the absence of neurologic deficit, and other causes of radicular pain including sacroiliac joint referred pain should also be considered. In studying symptomatic patients, tissues in the area of herniated lumbar disks have been analyzed and confirmed to contain increased levels of proinflammatory cytokines including IL-1.[18,19] Phospholipase A2, which is an enzyme that releases arachadonic acid from cell membranes, has been identified and isolated from nucleus pulposis material from patients undergoing diskectomy. The inflammatory nature of the pain associated with lumbar disk herniations partly explains the efficacy of depot epidural injection strategies.[14] Consequently, it is prudent to advise patients that epidural catheter placement may reproduce painful radicular symptoms of sciatica in those with known symptomatic herniations; this may be best avoided by placement of the catheter at a site remote from the pathology, if known. Most patients can be treated conservatively, but those with incapacitating pain, progressive neurologic deficits, or bowel or bladder dysfunction may require surgical treatment. It is important to document preexisting sensory deficits before neuraxial techniques.

Scoliosis

Scoliosis is one of the most common structural spinal disorders encountered in females of childbearing age. The Cobb method of classification is commonly utilized to diagnose and define the extent of the deformity (Figure 15.1). The prevalence of scoliosis defined by a Cobb angle greater than 10° is 2% to 3%.[20,21] The prevalence of uncorrected severe deformity is low, however, as a result of screening programs and active treatment strategies. The underlying anatomic abnormality constitutes an alteration in the anteroposterior alignment of the vertebrae; this is associated with lateral curvature and rotation of the vertebrae, with rib malalignment leading to thoracic deformity. In the area of the apex of the curvature, the spinous processes and vertebrae may rotate away from the convexity. However, rotatory deviation of the vertebrae is not common with curvatures of less than 20°. Most cases are idiopathic, but a number of scoliosis cases are associated with disorders such as muscular dystrophy, spina bi-

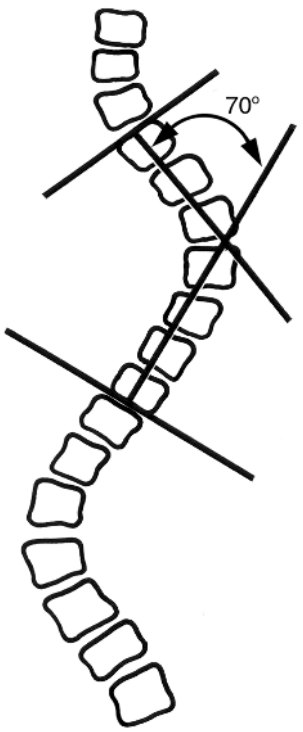

FIGURE 15.1. The Cobb angle estimation to quantify the scoliotic curve. First, lines are drawn along the endplates of the upper and lower vertebrae that are maximally tilted into the concavity of the curve. Next, a perpendicular line is drawn to each of the lines drawn earlier. The angle of intersection is the Cobb angle. (Adapted from Day LJ, et al. Orthopedics. In: Way LW (ed). Current Surgical Diagnosis and Treatment, 9th edn. Norwalk, CT: Appleton & Lange, 1991, with permission.)

fida, and Marfan syndrome. The thoracic spine is the most common site affected, with the majority of curvatures convex to the right. Lumbar involvement usually is associated with the convexity to the left. In those patients with severe scoliosis involving the thoracic spine, a restrictive pulmonary lung function pattern results,[22] with impaired ability to increase minute ventilation in the third trimester and during labor. Pulmonary hypertension may also be observed,[23] with right heart failure occurring in the third trimester from the physiologic increase in cardiac output. Mitral valve prolapse is encountered in 25% of patients with idiopathic scoliosis.[24] There is an inverse relationship between the severity of the curvature and the tests of pulmonary function including forced expiratory volume in 1 s (FEV_1) and vital capacity.

A decision regarding surgical correction for scoliosis is performed based on a combination of factors such as the Cobb angle, the age at presentation, and functional and neurologic assessment. Curvatures of less than 20° generally do not require surgery.[25] Current surgical trends involve preservation of the spinous processes plus instrumentation that extends no further caudad than L3.[26] Anterior and posterior approaches may be combined; the implications of prior abdominal surgery by cesarean section must be considered.

Obstetric Outcome

Overall, the rates of complications of pregnancy and labor as well as the neonatal outcome do not differ in pregnant women with corrected scoliosis from those in the background population.[27] However, LBP during pregnancy is common in women with scoliosis, occurring in about 40%. Pregnancy itself may adversely affect the progression of scoliosis in patients without stabilized scoliotic curves, likely caused by the alteration of weight distribution and ligamentous changes. Thus, women with scoliosis should be advised to undergo an orthopedic evaluation before they become pregnant. In women with preexisting cardiovascular or pulmonary compromise resulting from scoliosis, maternal morbidity may be increased. Preterm delivery and intrauterine growth restriction are possible.

Obstetric and Anesthetic Management

For the parturient with milder degrees of scoliosis and a normal expected obstetric outcome, antenatal anesthesia assessment is helpful. This consultation provides an opportunity for the patient to appreciate the potential technical difficulties that may be encountered in the provision of epidural analgesia and to receive reassurance that neuraxial techniques are not contraindicated. It may also provide an opportunity to review radiographic studies to evaluate the spinal anatomy in conjunction with the physical examination. These women should be advised to receive an epidural catheter early in the course of labor in anticipation of potential technical difficulties in provision of analgesia. The presence of a rotation abnormality may lead to prominence of the transverse processes on palpation that can be mistaken for the spinous processes. The recommended approach for the epidural needle is toward the convex of the curvature, as the interlaminar aperture is greater relative to the concave side. The management of regional analgesia and anesthesia procedures in the presence of corrective spine surgery is discussed below.

The Surgically Corrected Spine

The lifetime prevalence of lumbar surgery in the United States is approximately 3%.[15] One of the most common procedures encountered is diskectomy at one or multiple levels. Minimally invasive diskectomy procedures may have been performed with limited areas of scarring. Following standard diskectomy, the bony anatomy is usually intact, and the lumbar scar restricted to two intervertebral levels. Less commonly, partial or complete laminectomy is performed to decompress a symptomatic nerve root, which may be associated with spinal stenosis. Bone grafting and instrumentation procedures are performed during more extensive surgery such as interbody fusion or correction of scoliosis.

For scoliosis surgery, the Harrington rod,[28] or Wisconsin[29] and Luque[30] instrumentation procedures may be encountered with extension of surgery to below L4 in some cases. Although rod implantation is usually lateral, involving the transverse processes, there may be significant distortion of the bony anatomy that renders the usual landmarks useless for performing regional anesthesia. Despite an absence of spinous processes, laminar hypertrophy or new bone formation often results in narrowed bony windows to the epidural space.

All patients with previous lumbar spine surgery are at an increased risk of dural puncture, unsuccessful identification of the epidural space, and patchy or incomplete epidural analgesia.[31] This latter phenomenon is thought to result from physical impediments to contiguous spread of local anesthetic within the epidural space from scar tissue or adhesions.

Anesthetic Management

In the ideal situation, time will have been allocated in advance to form a management plan for provision of regional analgesia for labor and delivery and to introduce alternative options for the parturient in the event of a technical inability to administer neuraxial blockade. A physical examination in conjunction with operative reports and radiographic films often reveals a potentially smooth approach to the epidural space either above or below the operative site. Assessment of the airway vis-à-vis likely ease of intubation in the event of possible operative delivery must also be a considered factor in planning analgesic technique.

A higher rate of dural puncture may occur in these women as a result of scarring and altered texture of the interspinous ligaments and the ligamentum flavum. If dural puncture is noted, an attempt should be made to pass the catheter intrathecally because of the risk for unpredictable spread of local anesthetic in the epidural space. High-quality analgesia

will result from spinal administration and infusion of opioid and local anesthetic (e.g., fentanyl 25 μg and bupivacaine 2.5 mg, followed by 1–2 mL/h bupivacaine 0.1% with fentanyl 2 μg/mL). Intentional insertion of an intrathecal catheter should not be undertaken routinely, however, as difficulties will also arise if an epidural blood patch (EBP) is required for treatment of a postdural puncture headache. If an EBP is required in the postpartum period, a fluoroscopically guided procedure will likely increase the success and minimize parturient discomfort. If a combined spinal-epidural technique is chosen, and a higher lumbar interspace is selected in these women, care must be taken to avoid the potential for neurologic injury. Ultrasound-guided identification of anatomy in conjunction with a combined spinal-epidural technique has been reported in a parturient with Harrington rods.[32] It may be difficult to achieve good perineal analgesia with an epidural catheter placed at a relatively high level. Therefore, discussion with the obstetrician regarding the likely mode of delivery is helpful. For cesarean delivery under spinal anesthesia, a larger 22-gauge spinal needle should be available if attempts with a 25-gauge needle are unsuccessful because of difficulty passing through calcified ligaments.

A popular alternative to regional analgesia in parturients with previous spine surgery is patient-controlled analgesia. Fentanyl has been associated with fewer neonatal effects than meperidine.[33] The regimens commonly employed are a loading dose of 1 to 2 μg/kg fentanyl, with boluses of 25 to 50 μg every 5 to 10 min. Naloxone must be available at the bedside, and the neonatology service should be informed of the potential for neonatal depression, which is usually not a significant clinical problem at these doses.

The use of implanted devices such as intrathecal infusion pumps and epidurally placed spinal cord stimulater devices is increasing in patients with chronic pain disorders. The potential for opioid tolerance in patients receiving chronic intraspinal opioids and also the risk of infection from neuraxial techniques should be considered, and specialist consultation sought in advance.

Achondroplasia

Achondroplastic dwarfism results from a spontaneous mutation in 80% of cases, with the remainder following an autosomal dominant pattern of inheritance. Several skeletal abnormalities may result from a defect in cartilage formation at the epiphyseal growth plate. Spinal abnormalities include variable reductions in the size of the intrathecal space, with vertebral body abnormalities, disk degeneration, and lumbar hyperlordosis. Short stature, megacephaly, and enlargement of the mandible develop. Tongue enlargement, which is a common feature, can lead to difficulties with airway management under general anesthesia. Kyphoscoliosis often occurs; if severe, this can cause concominant respiratory and cardiac compromise. The pulmonary embarrassment is further exacerbated by an enlarged uterus in the third trimester, causing further reductions in functional residual capacity (FRC). Acquired pulmonary hypertension, leading to cor pulmonale, can occur in achondroplasia, with contributions by restrictive lung disease associated with scoliosis, chronic upper airway obstruction, and sleep apnea.

Obstetric and Anesthetic Management

Cesarean delivery is inevitable for women with achondroplasia because the maternal pelvis is invariably small and contracted resulting in cephalopelvic disproportion. This problem, and other aforementioned problems associated with achondroplasia, should prompt early referral for anesthesia assessment. The choice between regional and general anesthesia for cesarean delivery should be based on individual assessment. As already noted, distorted anatomy may cause difficulties in securing the airway.

Single-shot spinal anesthesia is best avoided for reasons of the potential for unpredictably high spinal levels achieved given the variable size of the intrathecal space in the setting of normal spinal cord dimensions. Placement of an epidural catheter may be difficult because of scoliosis or degenerative changes. Location of the epidural space can be accompanied by needle-through-needle intrathecal localization without dosing intrathecally. This approach may improve the predictive value of epidural catheter function by confirming midline placement and facilitating transdural spread of medication. Of note, the volume of local anesthetic required to achieve an adequate sensory level of anesthesia for cesarean delivery may be reduced by as much as 50%,[34–37] so incremental dosing and assessment are required. In the event of a dural puncture, passage of an intrathecal macrocatheter and incremental dosing as appropriate are recommended.[38]

Osteogenesis Imperfecta

Osteogenesis imperfecta comprises a group of disorders that feature a defect in collagen synthesis and an increased risk of fractures. The prevalence is 1 to 2 in 10,000[39]; of the four types, type 1 is the mildest form, inherited in an autosomal dominant fashion. Musculoskeletal features can include dwarfism, pectus excavatum, and kyphoscoliosis, whereas other organ systems may be affected producing the classic blue sclerae and deafness caused by otosclerosis. Up to 50% of patients may develop hyperthyroidism.

Patients with types 2 and 3 are at higher risk of sustaining intrauterine fetal losses,[40] and all these patients are at risk of postpartum hemorrhage, which is believed to be in part due to uterine collagen abnormalities.[41] Abnormalities of platelet function and capillary fragility have been observed.[42,43] However, a history of clinical bleeding is not a usual feature of the disease, and regional anesthesia is not contraindicated when routine laboratory assessments of coagulation are normal. Several anatomic features may predispose to difficult intubation, including limited cervical spine movement and micrognathia.[44,45]

Spina Bifida

Spina bifida results from a failed fusion of the neural arch, which may (spina bifida cystica) or may not (spina bifida occulta) be accompanied by herniation of the meninges or neural elements. In the latter disorder, which is more common and often asymptomatic, the defect is usually limited to one vertebral level. An underlying problem regarding the presence of spina bifida occulta may be heralded by an overlying skin dimple or tuft of hair. Associated spinal abnormalities, such as scoliosis and neurological disorders such as hydrocephaly with subsequent shunt surgery, are more common in these patients, and therefore patients should be assessed antenatally to allow time for a comprehensive evaluation.

Neurologic deficits should be documented before attempting regional techniques, and care must be taken to chose a low approach to the lumbar spine when performing spinal or combined spinal-epidural techniques in these patients, as an abnormally low position of the spinal cord may exist following corrective surgery. In one report, a low thoracic approach to administration of spinal anesthesia was performed in a patient with preexisting neurologic deficit[46]; this approach should not be practiced. At the site of pathology, attempts to place an epidural needle placement may result in a dural puncture.[47] Epidural spread of local anesthetic may be uneven, resulting in patchy blockade. One case report describes reduced dose requirements for provision of successful analgesia.[48] Placement of an intrathecal catheter has also been described for cesarean section delivery in this setting without adverse sequelae.[49]

Epidural Blood Patch in Cases of Prior Dural Puncture

Unsuccessful central neuraxial blockade with epidural techniques has been observed following dural puncture and epidural blood patch (EBP). One retrospective study noted successful epidurals in only 17 of 29 patients with prior EBP, with prior dural puncture alone also associated with subsequent impairment of epidural analgesia.[50] Anatomic alterations that impede the spread of medication have been hypothesized to be partly responsible. Fibrous organization of the epidural blood clot has been observed in goats up to 3 months following an EBP.[51] By contrast, in a second retrospective study, successful epidural analgesia was achieved in 28 of 29 patients at a mean of 33 months following a prior EBP.[52] Prior dural puncture may signal preexisting anatomic difficulties, and patients with prior dural puncture and EBP may also exhibit increased anxiety concerning regional anesthesia and request antenatal anesthesia evaluation.

Trauma in the Pregnant Woman

Trauma remains one of the primary causes of death in young adults in the Western world. Several unique features of the parturient who has sustained trauma set her apart from other adult trauma victims. When the gestational age of a trauma victim may result in a viable fetus, it is imperative to appreciate that treatment strategies are directed at both mother and fetus. Specific anatomic and physiologic changes that occur with the pregnant state must also be reviewed to assist those who infrequently treat these women in a trauma setting. It is well recognized that an organized multidisciplinary effort is required to achieve optimal maternal and fetal outcomes, and a number of reviews on this topic are available.[53–55]

Anatomic and Physiologic Changes

Genitourinary Changes

During the first trimester, the uterus remains an intrapelvic organ. After the 12th week of gestation, the uterus begins to rise out of the pelvis and encroaches on the abdominal contents and peritoneal cavity. An important clinical landmark is the umbilicus, which is reached at about 20 weeks gestation. Determination of gestational age based on uterine size is not accurate, however, and therefore gestational age must be determined by ultrasonography as soon as it is available. Determination of the gestational age at the time of injury is crucial, because it helps to determine the need for fetal assessment in addition to managing the mother's condition. The possibility of fetal viability in an extrauterine environment (i.e., beyond 24–26 weeks of gestation) can significantly change management decisions if there is evidence of fetal compromise. Placental abruption is the commonest cause of fetal death following trauma.[56] There are several potential mechanisms of abruptio placentae. Trauma-related abruption is thought to be caused by shearing at the tissue interface due to differences in tissue properties between the elastic myometrium and the relatively inelastic placenta. The risk of abruptio placentae appears to be independent of the placental location.[57] Maternal shock or death and rupture of membranes are other consequences of blunt trauma to the abdomen in pregnant women.

Blood and Plasma Changes

Plasma volume increases by 40% to 50% around 34 weeks gestation. This increase is accompanied by an increase of 18% to 30% in red blood cell volume, resulting in a dilutional anemia of pregnancy. Hemoglobin usually remains at 10.5 to 11 g/dL. This increase in blood volume and clotting factors VII, VIII, IX, and X appears to confer a survival benefit in the event of peripartum hemorrhage. Fibrinogen levels increase by 50% to 600 mg/dL in the third trimester; the normal nonpregnant range is 200 to 400 mg/dL. Although the international normalized ratio (INR), activated partial thromboplastin time (aPTT), and bleeding times remain unchanged, the erythrocyte sedimentation rate is elevated, and an increased predisposition to venous thrombosis exists in pregnancy. The white cell count increases to 12,000 to 18,000/mm^3 in the third trimester; further increases to 25,000/mm^3 may be ob-

served in labor. Urea and creatinine levels fall to almost 50% of normal, and glycosuria is common. These changes should be also noted when interpreting laboratory data.

Cardiovascular Changes

The maternal cardiac output increases by 30% to 50% between the 10th and 28th weeks of pregnancy[58] as a result of an increase in both heart rate and stroke volume. Resting venous pressures are unchanged, whereas the second trimester is often associated with a decrease of 5 to 10 mm Hg in mean arterial pressure. These changes should be noted when assessing blood volume status via the hemodyamic response to blood loss in the pregnant state. In general, systolic blood pressure less than 80 mm Hg and tachycardia above 120 beats/min usually indicate a loss of blood volume greater than 30% to 40% (2000 mL in a 60-kg gravida). There may only be subtle hemodynamic responses to blood loss up to 2000 mL. Impaired venous return from caval compression by the gravid uterus may cause a 30% to 40% reduction in cardiac output in the supine position. Therefore, all pregnant women must be placed in a lateral tilted position for assessment and resuscitation.

Electrocardiographic changes, thought to mainly result from the anatomic changes in the position of the heart, may be observed during pregnancy. There is leftward deviation of the axis by 15°; low-voltage QRS complexes and deep Q waves in lead III may also be observed, and flattened T waves and ST segment depression can be seen.

Pulmonary Changes

The diaphragm is elevated, and the anteroposterior diameter of the chest consequently increases; this leads to an apparent widening of the diaphragm and cephalization of the pulmonary vasculature on chest radiography. Pulmonary minute ventilation increases, largely as a result of a progesterone-induced increase in tidal volume; this causes a respiratory alkalosis, with $Paco_2$ levels of 27 to 32 mm Hg. Due to a reduction in the buffering capacity of the blood, the arterial pH remains unchanged. Perhaps the most significant clinical change in pulmonary physiology is the decrease in functional residual capacity, which is reduced by about 20% during the second trimester with 30% of parturients experiencing encroachment of normal tidal ventilation on closing capacity. In turn, this change predisposes to rapid falls in $Paco_2$ during periods of apnea or airway obstruction. At term, the Pao_2 lies between 90 and 100 mm Hg.

Gastrointestinal Tract Changes

The effects of progesterone on the lower esophageal sphincter predispose the parturient to regurgitation of stomach contents and pulmonary aspiration. Therefore, a nasogastric tube and antacids should be used as appropriate in the trauma patient. Gastric emptying per se is not delayed in pregnancy, although trauma and administration of opioid for analgesia will increase the likelihood of a full stomach. The abdominal viscera are displaced in the third trimester, causing unusual pain referral patterns, and alternate patterns of visceral injury following penetrating trauma in particular are frequently seen.

Epidemiology

In countries where maternal mortality from direct obstetric causes continues to fall, trauma as a cause of death rises to prominence.[59,60] Trauma has been observed to occur in 6% to 7% of pregnancies,[55] with hospital admission required in 0.3% to 0.4% of pregnancies.[61] Both national and international variations exist. In the United Kingdom, trauma was the cause of only 4% of all maternal deaths from 1988 to 1990.[62] By contrast, report in the United States from the Cook County medical examiner for a similar period, 1986 to 1989, found trauma to be the leading cause of maternal death, accounting for 43% of all cases.[60] Reported incidences may not reflect the true figures because pregnancy early in the first trimester may be missed in the trauma patient.[63]

In a review by Connolly et al.[64] for the period of 1987 to 1993, a picture of the distribution of the type of trauma cases is instructively typical. In this series, 54.6% of cases were caused by motor vehicle accidents; 22.3% were secondary to assaults and domestic abuse; 21.8% were associated with falls; and 1.3% were associated with burns, puncture wounds, or animal bites. The mean gestational age at the time of trauma was 25.9 weeks.

Fetal Mortality

After maternal death, the most common cause of fetal death is placental abruption. Abruption occurs in 40% to 50% of cases of major trauma and in up to 5% of cases following minor trauma. The fetal mortality associated with traumatic placental abruption is 30% to 68%.[65,66] In a review by Pearlman and Tinatilli, fetal deaths were caused by placental abruption in 69% of cases and direct fetal injury in 27%.[56] Circulatory shock in the mother is associated with 80% fetal mortality, emphasizing the importance of prompt resuscitation.[65,67] In one review of 76 trauma patients, low maternal serum bicarbonate levels associated with hypoperfusion were associated with poor fetal outcomes.[68]

Uterine rupture following major trauma is rare but is associated with nearly 100% fetal mortality. Other causes of fetal mortality and morbidity include direct trauma from blunt or penetrating injury, preterm delivery, and fetomaternal hemorrhage. One recent retrospective study identified the presence of disseminated intravascular coagulation (DIC), with or without placental abruption, as a significant predictor of fetal mortality.[69] In a review of 240 fetal deaths related to maternal injury, the overall maternal mortality rate was 11%.[70] Motor vehicle accidents were the leading mechanism of injury in this review. Although the severity of maternal injuries

usually determines fetal outcome,[71] early obstetric consultation for fetal assessment is essential to ultimately improve fetal outcomes, even in cases without apparent maternal morbidity.

Prehospital Care

Emergency care personnel should possess a knowlege of the basic physiologic changes in pregnancy and avoid aortocaval compression by tilting the patient. The availability of obstetric and neonatal expertise should influence choice of receiving hospital in those cases with a clinical estimation of a fetus greater than 20 weeks or a known gestation greater than 23 weeks. There is a general trend away from using pneumatic antishock garments (PASG) in trauma management, and the use of the PASG in gravid patients has been suggested to be potentially harmful.[72] In patients with uterine contractions, cervical examination must be performed in anticipation of preterm delivery.

Initial Assessment: The Primary Survey

The initial ABC assessment of the mother should be performed before fetal assessment. Securing the airway is a particular concern in pregnant patients beyond 14 weeks gestation who have impaired consciousness, as regurgitation and aspiration risks are increased. Difficulty with intubation is encountered more frequently than in the general population, so difficult intubation aids should be readily available before administration of relaxants. A nasogastric tube should also be inserted following major trauma. Oxygen should be administered from the outset; if a chest tube insertion is required, it should be placed one or two interspaces higher than usual in the midaxillary line, due to elevation of the diaphragm.

The gravid parturient should always be placed in a (left) lateral decubitus position to reduce aortocaval compression by the uterus. If the woman must remain supine (e.g., if a spinal injury is suspected, or if cardiopulmonary resuscitation is being administered), manual displacement of the uterus laterally with a hand or placement of a wedge under a backboard will accomplish this goal. Supplemental oxygen should be administered by nasal cannula, mask, or endotracheal intubation as required to maintain a hemoglobin saturation of 94% or greater. Heated crystalloid solution in the form of lactated Ringer's solution or normal saline should be administered via two large-bore intravenous cannulae (14–16 gauge) over the first 30 to 60 min of acute resuscitation as a 3:1 replacement based on blood loss.

Following stabilization, fetal evaluation should be performed. Electronic fetal cardiac and uterine activity monitoring in pregnant trauma victims beyond 20 weeks gestation may be predictive of fetal distress. Fetal distress may be indicated by tachycardia, late deceleration, and severe variables, caused by abruptio placentae or decreased placental perfusion as a result of blood redistribution in response to acute maternal hemorrhage. At this early stage in the evaluation, an obstetrician can help to optimize care for the mother and viable fetus and to decide whether immediate delivery is warranted.

Radiologic Evaluation and Safety

As in the nonpregnant state, cervical spine, chest, and pelvic radiographs should be obtained following major traumatic injury to the pregnant woman.[54] Omission of these investigations due to concerns over radiation safety for the fetus is unacceptable. Fetal risks of anomalies, growth restriction, or abortions are not increased with radiation exposure of less than 5 rad, a level above the range of exposure for diagnostic procedures. Nevertheless, the uterus must be shielded for nonpelvic procedures. Computed tomographic scanning of the abdomen exposes the fetus to approximately 3.5 rad, depending on the number and thickness of the images and the equipment used. The number of imaging cuts and the area of investigation can be modified to minimize fetal exposure. Exposure can be reduced to approximately 250 mrad (including fetal gonad exposure) by using a low-exposure technique.[73] Magnetic resonance imaging avoids the risks of ionizing radiation, but technical problems with monitoring parturients during the imaging process and visual artifacts originating from metal pieces in stabilizing devices such as cervical collars can limit the usefulness of this technique.

Ultrasound is widely utilized for establishing gestational age, locating the placenta, determining fetal well-being (biophysical profile) and the extent of fetal injury or fetal demise, and estimating amniotic fluid volume. Ultrasonography is rarely useful to detect placental abruption because its sensitivity is relatively low; only 40% to 50% of posttraumatic abruptions are detected by ultrasonography.[74] Ultrasonography may also be used to detect free intraabdominal and pericardial fluid collections or deep vein thrombosis. In a study by Goodwin et al.,[75] the sensitivity for detection of free fluid in the abdomen by ultrasound was found to be 83%. Detection of free intraabdominal fluid obviates the need to perform diagnostic peritoneal lavage (DPL). However, a negative ultrasound does not rule out the possibility of ongoing abdominal bleeding. Therefore, if clinical doubt exists, DPL with subsequent exploratory laparotomy should be performed.

Blunt Trauma

The leading causes of blunt trauma in pregnancy are motor vehicle accidents (MVAs), followed by falls and assaults. Overall mortality from MVAs in the general population has fallen due to improved automotive safety and seatbelts. However, studies confirm that seatbelt use in the pregnant population is not as high as in the general population,[76,77] partly because of perceived risks to the fetus. Under conditions simulating an automobile crash, Pearlman and Viano[78] recorded the lowest force transmission when three-point restraint positioning was used. Crosby and coworkers[79] studied lap belt

versus combination lap and shoulder configuration restraints in baboons, revealing that the rate of fetal death was lower with the combination (12.5% compared to 50%). The American College of Obstetricians and Gynaecologists recommends that lap belts should be placed as low as possible under the abdomen, and that shoulder belts should be off to the side of the uterus between the breasts and over the midportion of the clavicle.

Visceral injury to solid organs should be suspected following major abdominal blunt trauma. Injury to hollow viscera occurs at points of relative fixation such as the cecum, duodenum, and hepatic and splenic flexures. Shoulder pain, a positive DPL, and elevated transaminases should raise the suspicion of hepatic rupture. Surgical procedures for liver rupture include hepatic lobe resection and selective embolization. Splenic rupture should be treated with splenectomy. Neonatal injury following blunt trauma is less frequent than in penetrating trauma because of the protective effect of the muscular uterus and amniotic fluid. Engagement of the head in the pelvis is thought to result in a higher risk of fetal head injury when pelvic fracture occurs. Pelvic fractures may result in significant retroperitoneal bleeding, which is associated with substantial morbidity and mortality. Pelvic fractures are also associated with injuries to the bladder and urethra. Inability to pass a urethral catheter or the presence of hematuria should suggest these injuries. Minor injuries may be managed conservatively. If extravasation of urine has occurred, open exploration via a midline incision is indicated. Uterine rupture in the second trimester is usually associated with pelvic fractures. As the gravid woman is at increased risk of DIC, other blood products should be requested early. Evolving DIC as a result of massive placental abruption necessitates immediate evacuation of the uterus and therefore cesarean delivery.

Penetrating Trauma

Penetrating trauma occurs less frequently than blunt trauma and is mainly associated with stabbing and gunshot injuries. A lower incidence of visceral injury is noted in pregnancy compared with the general population.[80] Thought to be the result of a protective effect of the uterus on other viscera, this applies to later stages of gestation in particular. In a series of 14 women who sustained high-velocity penetrating abdominal injuries, parturients who had entry wounds above the uterine fundus had extrauterine visceral injuries whereas those with wounds below the uterine fundus did not.[81] The two maternal deaths were not secondary to abdominal injury but to other injuries. The patterns of visceral injury with trauma above the fundus are distinct from the nonpregnant state and may involve multiple loops of bowel as these are compressed in the upper abdomen.

The site of penetrating injury is important. Entry wounds below the uterine fundus are associated with a high incidence of fetal injury. The perinatal mortality rate from this type of trauma is high, 47% to 71%, and mortality is frequently caused by direct fetal injury.[53] Management of penetrating trauma is discussed later under Exploratory Laparotomy.

Rhesus Isoimmunization and Fetomaternal Hemorrhage

In addition to standard laboratory tests assayed in trauma victims, a pregnancy test and rhesus antigen typing should be performed on all women of childbearing age. Some degree of bleeding from the fetal to maternal circulation is found in 10% to 30% of trauma cases.[56,82] As little as 0.01 mL RhD-positive blood can cause alloimmunization in RhD-negative patients. A Kleihauer–Betke test may be performed to assess the amount of fetomaternal hemorrhage in RhD-negative patients.[64,83] This test is based on an acid dilution procedure to which adult but not fetal hemoglobin is sensitive. By counting fetal cells on a slide, an estimate of the volume of fetal cells in the maternal circulation is provided. The Kleihauer–Betke test is not sensitive enough to detect small amounts of fetomaternal hemorrhage. Thus, all RhD-negative patients who have experienced abdominal trauma after 14 weeks gestation should receive at least 300 μg anti-D immunoglobulin (RhoGAM); this dose provides coverage for 30 mL fetal whole blood or 15 mL fetal red cells. Additional ampoules (300 μg for every 30 mL whole blood transfused) should be administered if the Kleihauer–Betke test suggests a greater degree of fetomaternal hemorrhage. Administration of anti-D immunoglobulin at any time within the first 72 h following fetomaternal hemorrhage appears to provide protection from alloimmunization. As the sensitivity and specificity of the Kleihauer–Betke test in detecting complications following trauma has been estimated at 56% and 71%, respectively,[84] its use as a screening tool before RhoGAM therapy is not justified.

Head Injury

Brain injury is the cause in 60% to 75% of trauma-related maternal deaths.[85] The management of head injury during pregnancy is the same as in the nonpregnant state. Maternal brain death or massive injury leading to persistent vegetative state during pregnancy is a rare event. Current advances in medicine and critical care enable prolonged life support to avoid premature delivery and maximize the chances for survival in the neonate whose mother is technically brain dead.[86] When assessing the adequacy of ventilation with arterial blood gas analysis, it should be noted that the physiologic respiratory alkalosis of pregnancy results in a bicarbonate serum level of 18 to 31mEq/L.

Burns

Minor burns occur in 1 in 250 pregnancies. The gravid woman with major burns should be resuscitated according to guidelines developed for the nonpregnant patient. Fetal survival

usually parallels the percentage of the burned surface area and survival of the mother. Both maternal and fetal prognosis is poor when the burn area exceeds 50% of the total body surface.[87] In a series of 27 parturients, the fetal loss rate was 56%, and there were no maternal losses when the percentage of the burned surface area was 15% to 25%.[88] In the same series, the fetal and maternal mortality rate rose to 63% in those with 25% to 50% of the surface area burned. In another series of 50 pregnant burn women in the second or third trimester, fetal survival rate did not improve by waiting among those with burns over 50% of their body, because of the poor maternal prognosis.[89] In this series, if the fetus remained undelivered, maternal prognosis was remarkably worse than for a nonpregnant woman suffering otherwise comparable burns. Other studies failed to demonstrate the effect of pregnancy on maternal prognosis.[90] Contributory factors are hypovolemia, pulmonary injury, septicemia, and the intensely catabolic state.

Because large amounts of prostaglandin are released following significant burn injury, women may enter labor spontaneously within several days to a week later. If hemodynamic stability permits and antepartum testing is reassuring, tocolysis with magnesium sulfate or indomethacin may be attempted until a course of antenatal steroids, if indicated, is completed. Beta-sympathomimetic tocolytic agents are associated with increased capillary permeability and therefore should not be preferred in this setting. Because of poor fetal prognosis, after fetal viability is reached, and a course of antenatal steroids, if indicated, is completed, delivery is recommended in those cases with extensive burns. Complications associated with prematurity should be balanced against this strategy. Cesarean delivery is usually reserved for situations in which the gravely ill woman's condition jeopardizes the viable fetus and therefore immediate delivery is indicated.

Obstetric and Anesthetic Management

A multidisciplinary approach is required for the management of the pregnant trauma victim. The emergency room physician should order the initial diagnostic studies and coordinate consultation from appropriate services. Immediate assessment of the pregnant woman by an anesthesiologist for airway management and a trauma surgeon for surgical evaluation is invaluable. The primary goal and initial efforts in managing the injured pregnant woman should be evaluation and stabilization of maternal vital signs. Attention is directed to the fetus after the woman is stabilized. This initial assessment should be followed by a complete, head-to-toe secondary survey; this should start with an obstetric examination and fetal assessment, which should be performed by an obstetrician if available. The presence of vaginal bleeding and pooling of amniotic fluid in the vagina should be noted. A pH greater than 5 or a ferning pattern of dried vaginal secretions seen by microscopy is indicative of amniotic fluid.[91] If a collectable amount of amniotic fluid is present in the vagina, a sample should be sent to test for fetal lung maturity when the gestational age is between 32 and 37 weeks. Immediate delivery can be considered if fetal lung maturity is documented.

Fetal heart sounds may be detected with a conventional stethoscope after 20 weeks gestation. However, a Doppler stethoscope or portable ultrasound is recommended to avoid confusing a normal fetal heart rate (120–160 beats per minute, bpm) and maternal tachycardia. Continuous heart rate monitoring of the fetus with tocodynamometry is indicated for a viable fetus, to assess fetal well-being and uterine contractile activity. Most opioids and anesthetic agents administered to the mother cross the placenta and cause transient reductions in tone and beat-to-beat variability of heart rate in the healthy fetus. Administration of corticosteroid to the mother to promote fetal lung maturity should be considered if preterm delivery is a potential outcome.

Exploratory Laparotomy

The use of DPL to detect intraabdominal bleeding in pregnant patients is well established.[54,92] Common indications for DPL after trauma during pregnancy include abdominal signs or symptoms suggestive of intraperitoneal bleeding, altered sensorium, unexplained shock, major thoracic injuries, and multiple major orthopedic injuries.[93] Open lavage with sharp dissection and opening of the anterior abdominal peritoneum under direct vision, usually periumbilically, is advocated over a blind needle insertion to lessen the likelihood of injury to the enlarged uterus in the third trimester or to other displaced intraabdominal organs. Laparotomy should be performed without attempting DPL if intraperitoneal bleeding is clinically obvious.

For management of gunshot wounds, surgical exploration with laparotomy is usually indicated. Stab wounds that do not appear to penetrate beyond the abdominal wall have been managed nonoperatively.[94] However, evidence of peritoneal penetration requires exploratory laparotomy. When the mother is stabilized, the fetus usually tolerates surgery. Fetal heart rate should be monitored intraoperatively after 24 weeks gestation; this can be achieved by a Doppler device or ultrasound transducer wrapped in a sterile plastic bag. Penetration of the uterus by an object or a projectile often results in fetal injury. Box 15.1 lists the indications for cesarean delivery during an exploratory laparotomy. Cesarean delivery should be performed if the fetus is alive, and if intact fetal survival is deemed probable ex utero. Neither fetal death nor laparotomy itself is an indication for cesarean delivery. The decision to

Box 15.1. Indications for concomitant cesarean delivery during exploratory laparotomy.

- Fetal distress exceeding risks of prematurity
- Uterine rupture with or without fetal extrusion
- Extensive uterine injury requiring hysterectomy
- Maternal instability/evolving disseminated intravascular coagulation (DIC)
- Maternal thoracolumbar spine injury
- Gravid uterus preventing access for exploration or repair of maternal intrabdominal injuries

deliver a live fetus depends on gestational age and fetal condition assessed by antenatal testing.

Other factors that dictate immediate cesarean delivery include extensive uterine injury requiring hysterectomy or the need to gain access to areas of the peritoneal cavity and/or retroperitoneal space for exploration or repair of maternal injuries, including thoracolumbar spine injury. These decisions often are made jointly with the trauma surgeon. If delivery must proceed, a pediatric surgeon and a neonatologist should be available if possible. Antibiotic prophylaxis against streptococcal and clostridial infections should be instituted. Tetanus toxoid (0.5 mL) should also be given to all previously immunized women; in addition; tetanus immunoglobulin should be given to those who are not previously immunized.

Rupture of Membranes, Preterm Labor, and Placental Abruption

Traumatic rupture of the amniotic membranes may occur; this should be ruled out during the pelvic examination. Its consequences are preterm labor, chorioamnionitis, and cord prolapse, which should be considered when treating maternal injuries. Preterm labor is strictly defined as regular uterine contractions associated with progressive cervical dilatation before 37 weeks gestation. Its consequences are morbidity and mortality related to prematurity in the newborn. Tocolysis is relatively contraindicated in parturients with ruptured membranes and when placental abruption is suspected. It is absolutely contraindicated in hemodynamically unstable mothers or in those with nonreassuring fetal status as indicated by intrapartum testing. Preterm contractions often stop after hydration. Thus, in the setting of trauma during pregnancy, tocolysis may be considered only for a selected group of patients under 34 weeks gestation and for 48 h until a course of antepartum steroids is completed. A longer course of tocolysis is often ineffective and may result in additional maternal and neonatal morbidity. The side effects from standard tocolytic agents used in the management of preterm labor have important clinical implications in the setting of trauma. The β-agonist agents cause tachycardia and cardiac arrhythmias and increase oxygen consumption. Such cardiovascular changes may interfere with assessment of hemorrhage. Magnesium sulfate can cause vasodilatation and exacerbate hypotension. Furthermore, it prolongs the action of nondepolarizing muscle relaxants at the neuromuscular junction and it can also prolong the duration of succinylcholine muscle relaxant block. Indomethacin, on the other hand, can impair platelet function and is relatively contraindicated when there is ongoing clinical bleeding.

Because of its low sensitivity to detect placental separation and retroplacental blood clots, ultrasonography is rarely relied upon to detect placental abruption.[75] For this reason, the diagnosis of placental abruption is often based on clinical findings such as vaginal bleeding, uterine tenderness, and contractions. However, these signs are not pathognomonic for placental abruption and may be produced by other injuries. Furthermore, vaginal bleeding is not always present because blood can be retained between a detached placenta and the uterus, leading to concealed hemorrhage. Thus, a high index of suspicion for abruption should be maintained for all trauma patients, and continuous fetal monitoring should be instituted. The optimal length of time for monitoring pregnant patients following trauma is unclear, although a recommended minimum time of observation following minor trauma is 4 h.[57,95,96] However, this recommendation has not been validated by large prospective studies, and delayed presentation of abruption beyond 24 h after trauma may occur.

A large placental abruption can lead to DIC. The diagnosis of evolving DIC is established by demonstration of decreased fibrinogen and elevated fibrin degradation products. Evolving DIC as a result of massive placental abruption necessitates immediate evacuation of the uterus and therefore cesarean delivery.

Anesthesia Techniques

The widespread use of regional anesthesia techniques in pregnant women has contributed to the drop in anesthesia-related maternal mortality. Therefore, for uncomplicated cesarean delivery in the hemodynamically stable parturient with no coagulopathy, spinal or epidural anesthesia is appropriate. Epidural anesthesia is associated with a less precipitous fall in blood pressure and permits the option of extending anesthesia time and provision of postoperative analgesia. However, in the trauma victim with potential airway compromise, hemodynamic instability, or uncertain surgical plans, general anesthesia is the technique of choice. For exploratory laprotomy, general anesthesia is also the technique of choice due to the uncertain nature of subsequent surgical procedure and the potential poor quality anesthesia in such situations with neuraxial techniques alone.

Perimortem Cesarean Section

The clinical scenario of cardiovascular collapse in the parturient, although fortunately uncommon,[97] should be considered, and a strategy for emergent cesarean delivery should be formulated. The rationale for this is that delivery of the fetus improves maternal perfusion during CPR. The improvement in car-

TABLE 15.1. Postmortem cesarean delivery with surviving infants with reports of time from death of the mother to delivery.

Time from maternal death to delivery (min)	Surviving infants	
	Normal/neurologic sequelae	Percentage of births reported
0–5	42/0	70
6–10	7/1	13
11–15	6/1	12
16–20	0/1	1.7
21+	1/2	3.3

Source: Modified from the American College of Obstetricians and Gynecologists, Katz VL, Dotters DJ, Droegemueller W. Perimortem cesarean delivery. Obstet Gynecol 1986;68:571, with permission.

diac output following delivery results from a reduction in aortocaval compression (which is significant after 20 weeks gestation) and removal of the low-resistance uteroplacental vascular unit. Following delivery, lateral tilt to reduce aortocaval compression is no longer needed. Direct chest compression during CPR is more effective when the parturient lies flat on her back. As a result of improved maternal perfusion during CPR, timely delivery by perimortem cesarean section was found to improve neonatal survival and morbidity rates. Katz and coworkers[98] reviewed 61 children who survived perimortem cesarean delivery performed between 1900 and 1985. Approximately 70% of the survivors were delivered with 5 min of their mother's death. The rate of severe neurologic morbidity increases as the delivery is delayed beyond 5 min of maternal death (Table 15.1).

In another series of five parturients who experienced cardiac arrest during induction of anesthesia for elective cesarean section, immediate delivery was associated with good neurologic outcomes whereas delay of 6 to 9 min was associated with adverse neurologic sequelae.[99] Based on these reports, the American College of Obstetricians and Gynecologists recommends that cesarean delivery should be considered for both maternal and fetal benefit 4 min after a woman has experienced cardiopulmonary arrest in the third trimester. Delivery in this situation should be performed without any delay for formal sterility precautions and should be via vertical abdominal wall and uterine incisions.

Summary

Parturients with musculoskeletal pathology as well as pregnant women as a trauma victim can be a complex problem to the anesthesiologists. Physiological changes during pregnancy should be taken into account while taking care of this patient. Close monitoring of both mother and fetus are essential for positive outcome.

References

1. Kristiansson P, Svardsudd K, Schoultz BV. Back pain during pregnancy: a prospective study. Spine 1996;21:702–709.
2. Rosaeg OP, Yarnell RW, Lindsay MP. The obstetrical anaesthesia assessment clinic: a review of six years experience. Can J Anaesth 1993; 40:346–356.
3. Ostgaard HC, Andersson GBJ. Previous back pain and risk of developing back pain in a future pregnancy. Spine 1991;16:432–436.
4. Orvieta R, Achiron A, Ben-Rafael Z, et al. Low back pain of pregnancy. Acta Obstet Gynecol Scand 1994;73:209–214.
5. Fast A, Shapiro D, Ducommun JD, et al. Low back pain in pregnancy. Spine 1987;12:368–371.
6. Mantle MJ, Greenwood RM, Curry HLF. Backache in pregnancy. Rheumatol Rehabil 1977;16:95–101.
7. Ostgaard HC, Andersson GBJ. Postpartum low back pain. Spine 1992;17: 53–55.
8. MacLennan AH, Nicolson R, Green RC. Serum relaxin in pregnancy. Lancet 1986;2:241–243.
9. MacLeod J, Macintyre C, McClure JH, et al. Backache and epidural analgesia. A retrospective survey of mothers 1 year after childbirth. Int J Obstet Anaesth 1995;4:21–25.
10. MacArthur C, Lewis M, Knox EG, Crawford JS. Epidural anaesthesia and long term backache after childbirth. BMJ 1990;301:9–12.
11. Breen TW, Ransil BJ, Groves PA, Oriol NE. Factors associated with back pain after childbirth. Anesthesiology 1994;81:29–34.
12. Russell R, Dundas R, Reynolds F. Long term backache after childbirth: prospective search for causative factors. BMJ 1996;312:1384–1388.
13. Chestnut DH. Obstetric Anesthesia. St. Louis: Mosby-Year Book, 1994.
14. Abram SE. Treatment of lumbosacral radiculopathy with epidural steroids. Anesthesiology 1999;91:1937–1941.
15. Bonica JJ. Bonica's Management of Pain, 3rd edn. Philadelphia: Lippincott/Wiliams & Wilkins, 2001.
16. Jensen MC, Brant-Zawedzki MN, Obuchowski N, et al. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:69–73.
17. LaBan MM, Perrin JC, Latimer FR. Pregnancy and the herniated lumbar disc. Arch Phys Med Rehabil 1983;64:319–321.
18. Takahashi H, Suguro T, Okazima Y, et al. Inflammatory cytokines in the herniated disc of the lumbar spine. Spine 1996;21:218–24.
19. Hunt JL, Winkelstein BA, Rutkowski MD, et al. Repeated injury to the lumbar nerve roots produces enhanced mechanical allodynia and persistent spinal neuroinflammation. Spine 2001;26:2073–2079.
20. Winter RB. Adolescent idiopathic scoliosis. N Engl J Med 1986;314: 1379–1380.
21. Carter OD, Haynes SG. Prevalence rates for scoliosis in US adults: Results from the first National Health and Nutrition examination survey. Int J Epidemiol 1987;16:537–544.
22. Hamilton PP, Byford LJ. Respiratory and cardiovascular functions in musculoskeletal disorders. Probl Anesth 1991;5:91–106.
23. Kafer ER. Respiratory and cardiovascular functions in scoliosis and principles of anesthetic management. Anesthesiology 1980;52:339–351.
24. Hirshfeld SS, Rudner C, Nash CL, et al. The incidence of mitral valve prolapse in adolescent scoliosis and thoracic hypokyphosis. Pediatrics 1982;70:451–454.
25. Lonstein JE, Carlson JM. The prediction of curve progression in untreated idiopathic scoliosis during growth. J Bone Joint Surg 1984;66A:1061–1071.
26. Bridwell KH. Surgical treatment of adolescent idiopathic scoliosis: the basics and controversies. Spine 1994;19:1095–1100.
27. Orvomaa E, Hiilesmaa V, Poussa M, et al. Pregnancy and delivery in patients operated by the Harrington method for idiopathic scoliosis. Eur Spine J 1997;6:304–307.
28. Harrington PR. Treatment of scoliosis: correction and internal fixation by spine instrumentation. J Bone Joint Surg 1962;44A:591–610.
29. Drummond D, Guadagni J, Keene JS, et al. Interspinous process segmental spinal instrumentation. J Pediatr Orthop 1984;4:397–404.
30. Luque ER. Segmental spinal instrumentation for correction of scoliosis. Clin Orthop 1982;163:192–198.
31. Crosby ET, Halpern SH. Obstetric epidural anaesthesia in patients with Harrington instrumentation. Can J Anaesth 1989;36:693–696.
32. Yeo ST, French R. Combined spinal-epidural in the obstetric patient with Harrington rods assisted by ultrasonography. Br J Anaesth 1999;83:670–672.
33. Rayburn WF, Smith CV, Parriot JE, Woods RE. Randomised comparison of meperidine and fentanyl during labor. Obstet Gynecol 1989;74:604–606.
34. Morrow MJ, Black IH. Epidural anaesthesia for caesarean section in an achondroplastic dwarf. Br J Anaesth 1998;81:619–621.
35. Carstoniu J, Yee I, Halpern S. Epidural anaesthesia for caesarean section in an achondroplastic dwarf. Can J Anaesth 1992;39:708–711.
36. Brimacombe JR, Caunt JA. Anaesthesia in a gravid achondroplastic dwarf. Anaesthesia 1990;45:132–134.
37. Ravenscroft A, Rout C. Epidural anaesthesia for caesarean section in an achondroplastic dwarf. Br J Anaesth 1999;82:301–303.
38. Crawford M, Dutton DA. Spinal anaesthesia for caesarean section in an achondroplastic dwarf. Anaesthesia 1992;47:1007.
39. Byers PH, Steiner RD. Osteogenesis imperfecta. Annu Rev Med 1992; 43:269–282.
40. Cole WG, Dalgleish R. Perinatal lethal osteogenesis imperfecta. J Med Genet 1995;32:284–289.

41. Key TC, Horger EO. Osteogenesis imperfecta as a complication of pregnancy. Obstet Gynecol 1978;51:67–71.
42. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984;33:177–179.
43. Hathaway WE, Solomons CC, Ott JE. Platelet function and pyrophosphates in osteogenesis imperfecta. Blood 1972;39:500–509.
44. Cunningham AJ, Donnelly M, Comerford J. Osteogenesis imperfecta: anesthetic management of a patient for cesarean section: a case report. Anesthesiology 1984;61:91–93.
45. Cho E, Dayan SS, Marx GF. Anaesthesia in a parturient with osteogenesis imperfecta. Br J Anaesth 1992;68:422–423.
46. Broome IJ. Spinal anaesthesia for Caesarean section in a patient with spina bifida cystica. Anaesth Intensive Care 1989;17:377–379.
47. McGrady EM, Davis AG. Spina bifida occulta and epidural anaesthesia. Anaesthesia 1988;43:867–869.
48. Vaagenes P, Fjaerestad I. Epidural block during labour in a patient with spina bifida cystica. Anaesthesia 1981;36:299–301.
49. Nuyten F, Gielen M. Spinal catheter anaesthesia for caesarean section in a patient with spina bifida. Anaesthesia 1990;45:846–847.
50. Ong BY, Graham CR, Ringaert KRA, et al. Impaired epidural analgesia after dural puncture with and without subsequent blood patch. Anesth Analg 1990;70:76–79.
51. DiGiovanni AJ, Galbert MW, Wahle WM. Epidural injection of autologous blood for postlumbar-puncture headache. II. Additional clinical experiences and laboratory investigation. Anesth Analg 1972;51:226–232.
52. Hebl JR, Horlocker TT, Chantigian RC, Schroeder DR. Epidural anesthesia and analgesia are not impaired after dural puncture with or without epidural blood patch. Anesth Analg 1999;89:390–394.
53. Stone IK. Trauma in the obstetric patient. Obstet Gynecol Clin North Am 1999;26:459–467, viii.
54. Vaizey CJ, Jaconson MJ, Cross FW. Trauma in pregnancy. Br J Surg 1994;81:1406–1415.
55. Henderson SO, Mallon WK. Trauma in pregnancy. Emerg Med Clin N Am 1998;16:209–228.
56. Pearlman MD, Tintinalli JE. Evaluation and treatment of the gravida and fetus following trauma during pregnancy. Obstet Gynecol Clin N Am 1991;18:371–381.
57. Pearlman MD, Tintinalli JE, Lorenz RP. A prospective controlled study of outcome after trauma in pregnancy. Am J Obstet Gynecol 1990;162: 1502–1507.
58. Ueland K, Novy MJ, Peterson EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 1969;104:856–864.
59. Sachs BP, Brown DA, Driscoll SG, et al. Maternal mortality in Massachusetts. Trends and prevention. N Engl J Med 1987;316:667–672.
60. Fildes J, Reed L, Jones N, et al. Trauma: the leading cause of maternal death. J Trauma 1992;32:643–645.
61. Lavin JP, Polsky SS. Abdominal trauma during pregnancy. Clin Perinatol 1983;10:423–438.
62. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1988–1990. London: HSMO, 1994.
63. Bochicchio GV, Napolitano LM, Haan J, et al. Incidental pregnancy in trauma patients. J Am Coll Surg 2001;192:566–569.
64. Connolly AM, Katz VL, Bash KL, et al. Trauma and pregnancy. Am J Perinatol 1997;14:331–336.
65. Goldman SM, Wagner LK. Radiologic management of abdominal trauma in pregnancy. Am J Radiol 1996;166:763–767.
66. Hill DA, Lense JJ. Abdominal trauma in the pregnant patient. Am Fam Physician 1996;53:1269–1274.
67. Lavery JP, Staten-McCormick M. Management of moderate to severe trauma in pregnancy. Obstet Gynecol Clin N Am 1995;22:69–90.
68. Scorpio RJ, Esposito TJ, Smith LG, Gens DR. Blunt trauma during pregnancy: factors affecting fetal outcome. J Trauma 1992;32:213–216.
69. Ali J, Yeo A, Gana TJ, McLellan B. Predictors of fetal mortality in pregnant trauma patients. J Trauma 1997;42:782–785.
70. Weiss HB, Songer TJ, Fabio A. Fetal deaths related to maternal injury. JAMA 2001;286:1863–1868.
71. Rogers FB, Rozycki GS, Osler TM, et al. A multi-institutional study of factors associated with fetal death in injured pregnant patients. Arch Surg 1999;134:1274–1277.
72. Domeier RM, O'Conner RE, Delbridge TR, et al. Position Paper: Use of pneumatic anti-shock garment (PASG). National Association of EMS Physicians, 1997:33–35.
73. Moore MM, Shearer DR. Fetal dose estimates for CT pelvimetry. Radiology 1989;171:265–267.
74. Harrison SD, Nghiem HV, Shy K. Uterine rupture with fetal death following blunt trauma. Am J Radiol 1995;165:1452.
75. Goodwin H, Holmes JF, Wisner DH. Abdominal ultrasound examination in pregnant blunt trauma patients. J Trauma 2001;50:689–693.
76. Schiff M, Kasnic T, Reiff K, Pathak D. Seatbelt use during pregnancy. West J Med 1992;156:665–667.
77. Chang A, Magwene K, Frand E. Increased safety belt use following education in childbirth classes. Birth 1987;14:148–152.
78. Pearlman MD, Viano D. Automobile crash simulation with the first pregnant crash test dummy. Am J Obstet Gynecol 1996;175:977–981.
79. Crosby WM, King AL, Stout LC. Fetal survival following impact: improvement with shoulder harness restraint. Am J Obstet Gynecol 1972; 112:1101–1106.
80. Feliciano DV, Burch JM, Spjut-Patrinely V, et al. Abdominal gunshot wounds: An urban trauma center's experience with 300 consecutive patients. Ann Surg 1988;208:362–370.
81. Awwad JT, Azar GB, Seoud MA, et al. High-velocity penetrating wounds of the gravid uterus: review of 16 years of civil war. Obstet Gynecol 1994;83:259–264.
82. Rose PG, Strohm PL, Zuspan FP. Fetomaternal hemorrhage following trauma. Am J Obstet Gynecol 1985;153:844–847.
83. Emery CL, Morway LF, Chung-Park M, et al. The Kleihauer-Betke test. Clinical utility, indication, and correlation in patients with placental abruption and cocaine use. Arch Pathol Lab Med 1995;119:1032–1037.
84. Towery R, English TP, Wisner D. Evaluation of pregnant women after blunt injury. J Trauma 1993;35:731–735.
85. Jordan BD. Maternal head trauma during pregnancy. Adv Neurol 1994; 64:131–138.
86. Feldmman DM, Borgida AF, Rodis JF, Campbell WA. Irreversible maternal brain injury during pregnancy. A case report and review of the literature. Obstet Gynecol Surv 2000;55:708–714.
87. Polko LE, McMahon MJ. Burns in pregnancy. Obstet Gynecol Surv 1998; 53:50–56.
88. Mabrouk AR, el-Feky AE. Burns during pregnancy: a gloomy outcome. Burns 1997;23:596–600.
89. Matthews RN. Obstetric implications of burns in pregnancy. Br J Obstet Gynaecol 1982;89:603–609.
90. Amy BW, McManus WF, Goodwin CW, et al. Thermal injury in the pregnant patient. Surg Gynecol Obstet 1985;161:209–212.
91. Esposito TJ. Trauma during pregnancy. Emerg Med Clin N Am 1994;12: 167–199.
92. Rothenberger DA, Quattlebaum FW, Zabel J, Fischer RP. Diagnostic peritoneal lavage for blunt trauma in pregnant women. Am J Obstet Gynecol 1977;102:752–769.
93. Trauma during pregnancy. Technical bulletin no. 161. ACOG, 1991.
94. Grubb DK. Nonsurgical management of penetrating uterine trauma in pregnancy: a case report. Am J Obstet Gynecol 1992;166:583–584.
95. Dahmus MA, Sibai BM. Blunt abdominal trauma: are there any predictive factors for abruptio placentae or maternal-fetal distress? Am J Obstet Gynecol 1993;169:1054–1059.
96. Curet MJ, Schermer CR, Demarest GB, et al. Predictors of outcome in trauma during pregnancy: identification of patients who can be monitored for less than 6 hours. J Trauma 2000;49:18–24.
97. Dildy GA, Clark SL. Cardiac arrest during pregnancy. Obstet Gynecol Clin N Am 1995;22:303–314.
98. Katz VL, Dotters DJ, Droegemueller W. Perimortem cesarean delivery. Obstet Gynecol 1986;68:571–576.
99. Marx GF. Cardiopulmonary resuscitation of late pregnant women. Anesthesiology 1982;56:156.

16
Malignant Hyperthermia

Jordan Tarshis and Janet Bodley

Malignant hyperthermia (MH) was first described by Denborough in 1960. Although mortality was initially high, it has dropped drastically with the widespread use of dantrolene and educational efforts by international anesthesia organizations. All anesthesiologists should be familiar with the syndrome and its basic treatment, and even most medical students are aware of the disease and its association with anesthesia.

There were no reported crises associated with pregnancy before 1972, which prompted Crawford to write a letter to Lancet, eliciting cases.[1] Since that time, case reports and small series have been published, but no maternal or neonatal deaths have been reported. This chapter reviews some of the issues and challenges of MH and pregnancy. For a broader review of MH, the reader is directed to recent reviews in the literature.[2,3]

Pathophysiology

Malignant hyperthermia is an uncommon inherited disorder of skeletal muscle that is triggered by all inhalational anesthetics (with the exception of nitrous oxide) and succinylcholine. The cellular defect involves abnormal calcium release from the sarcoplasmic reticulum of skeletal muscle. It is a potential disease, and those carrying the gene are considered MH susceptible (MHS) because they are usually asymptomatic until exposed to a trigger.

The manifestations of MH are that of a hypermetabolic state emanating from skeletal muscle. An international consensus group has developed a grading scale to predict MH susceptibility.[4] Although this scale is intended for researchers, the diagnostic and pathophysiologic criteria are useful for clinicians (Table 16.1).

Genetics

It has long been known that the transmission of MH is autosomal dominant with variable penetrance, but it was only in 1990 that the putative gene was isolated to the long arm of chromosome 19.[5,6] It was hoped that there would be a single genetic alteration to account for the disease, but in fact there is significant genetic heterogeneity.[7] In only about 50% of MHS patients can an abnormality at this locus be identified. Linkage analysis has demonstrated other loci as being involved, and there is the possibility that in some cases susceptibility may be conferred by the interaction of several genes.[8]

Initial reports pointed to the ryanodine receptor (RYR) as the causative defect of MH. Ryanodine is a plant alkaloid that effects calcium release from the sarcoplasmic reticulum. Although this receptor is involved in many of the genotyped pedigrees,[2] there are more than 20 known genetic mutations at this and other loci,[9] with certainly more to be discovered.

The implication of this genetic heterogeneity is that genetic testing for MH is unlikely to become widespread in the near future. If a well-described genetic defect exists in the family, then other members of that family can be diagnosed by genetic testing. Because in most cases the mutation has not been described, the in vitro contracture test (IVCT) using halothane and caffeine remains the gold standard.

In Vitro Contracture Testing for Malignant Hyperthermia

The current gold standard for diagnosis of MH remains the caffeine halothane contracture test in which a strip of muscle (often the gracilis or vastas lateralis) is incubated in halothane or caffeine. A positive test occurs when there is an exaggerated contraction in response to these drugs. There are two international protocols for performing this test. The North American Malignant Hyperthermia Group protocol has a sensitivity of 97% and specificity of 78%,[10] and the European MH Group protocol has a sensitivity of 99% and specificity of 94%.[11]

One of the major differences between protocols is the presence of a MH equivocal (MHE) category in the European protocol whereas the North American protocol only has positive and negative categories. From a clinical perspective, MHE

TABLE 16.1. Pathophysiology of a malignant hyperthermia (MH) reaction.

Pathophysiologic process	Clinical indicators
Rigidity	Generalized muscular rigidity
	Masseter muscle spasm
Muscle breakdown	Elevated serum creatinine kinase
	Myoglobinuria
	Myoglobinemia
	Increased serum K^+ >6 mEq/L
Respiratory acidosis	Increased end-tidal CO_2
	Increased arterial CO_2
	Inappropriate tachypnea
Temperature increase	Inappropriately rapid increase in temperature
Cardiac involvement	Inappropriate sinus tachycardia
	Ventricular tachycardia or fibrillation
Multifactorial	Arterial pH < 7.25
	Arterial base deficit greater than 8 mEq/L
	Rapid reversal of acidosis with dantrolene

Source: Adapted from Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994;90(4):775,[4] with permission.

patients should be treated as MH susceptible (MHS). Investigators have compared the European and North American protocols and found excellent but not complete concordance.[12,13] Ørding et al. examined variability between centers and found differences between two centers that were using the same protocol.[14]

Overall, centers tend to agree on those individuals whose muscles react strongly to the caffeine halothane test. Disagreement increases as the in vitro response weakens. Considering the known genetic heterogeneity, and hence the variability of the cellular defect, this result is not surprising. The chance of a false positive is much higher than that of a false negative. The negative predictive value of the in vitro test is very high[13,15] and can exclude MH with near certainty. Nevertheless, the astute clinician must always consider the possibility of MH when presented with the typical signs and symptoms.

In an attempt to improve the in vitro sensitivity and specificity of contracture testing, other reagents have been investigated. The most useful of these is ryanodine or its analogue 4-chloro-*m*-cresol, which has been shown to improve the accuracy of in vitro contracture testing.[3,16] There is not yet an international protocol, but many centers have started using ryanodine as a confirmatory test and to categorize equivocal cases.[12] In future in vitro testing, it is hoped, one international protocol will use caffeine, halothane, and ryanodine.[17,18]

Who Is at Risk?

Theoretically, any patient who is exposed to a triggering agent is at risk of manifesting MH. Uneventful prior exposure to a trigger is no guarantee of MH-negative status.[19] Practically, MH is a rare event, and most anesthesiologists never encounter a reaction in their careers. Patient and family history is the best screening method.

Any parturient who has a personal history of a previous reaction or a positive muscle biopsy is considered susceptible. First-degree relatives should also be considered susceptible unless they have had a negative in vitro test. It is worth repeating that even untested first-degree relatives who have been exposed to triggering agents uneventfully in the past should be considered at risk. In a review of 503 published cases, Strazis and Fox reported that 24% of reported adult MH crisis cases had a median of 2 previous uneventful surgeries each, with a range of 1 to 9.[19]

Both parents of a proband should be considered susceptible unless tested otherwise. Islander et al. reported on the in vitro testing of both parents of known cases and found that in 32 of 101 pairs of parents, both would be considered clinically susceptible.[20] Interestingly, for 12 sets of parents, both were found to be MH negative.

Fetal Risks

The fetus/neonate must also be considered to be at risk for MH. At least two case reports have been published that detail possible MH reactions in neonates whose mothers had received general anaesthesia for cesarean delivery.[21,22] In addition, there are several reports about MH reactions in infants,[23–27] but confirmation by IVCT in the proband or in immediate relatives has not been obtained. Chamley et al. recently reported a case of an MH reaction in a 6-month-old child with later confirmation by IVCT as well as evidence of a novel RYR1 mutation.[9] This report shows that although MH in infancy may be rare, it does exist.

Malignant hyperthermia susceptibility can be inherited from either the mother or the father. The chance of inheriting MH is 50% if either the mother or the father is known to be MHS; this risk increases to 75% if both parents are MHS, and may be higher still if either parent is homozygous for the trait. If triggering agents are administered to the mother, the neonate must be observed for signs of MH. From 1987 to 1994, 19 patients who either were MHS or had a family member who was MHS delivered at Women's College Hospital, Toronto. Of these, four parturients were referred because the husband was MHS and there was concern for the neonate. None of these women or their neonates had an MH reaction.[28] Pollock and Langton followed 11 women with MHS and 5 women whose partners (father of the newborn) were MHS.[29] Again, in this series there were no MH reactions when triggering agents were avoided.

Associated Conditions

By definition, MH involves a disorder of muscle cell membranes, and patients may manifest other myopathies.[2] The most common, called MH myopathy or Evans myopathy after the first family in which MH was described, is the most

common autosomal dominant inherited form of MH. The myopathy is usually subclinical, although the serum creatine kinase (CK) may be raised. Measuring the CK is not a useful screening tool.[30]

Central core disease (CCD) is the only other myopathy in which a definite association with MH has been found.[31] The clinical presentation of this disease varies from asymptomatic to disabling as a result of a slow or nonprogressive myopathy. There are diagnostic histochemical and electron microscopic findings. Genetic analysis has shown CCD to be genetically heterogeneous, similar to MH. In some, but not all, families the genetic mutations of CCD and MH coexist in the same ryanodine receptor.[8]

Other myopathies, such as Duchenne's muscular dystrophy and King–Denborough syndromes, are possible but unlikely to be related.[31] Neuroleptic malignant syndrome is a clinically distinct entity although it may be present similarly to MH.[2]

Sudden Infant Death Syndrome

The observation that the father of a child who had died of sudden infant death syndrome (SIDS) had a myopathy that predisposes to MH[32] prompted Denborough et al. to look for further evidence of an association between MH and SIDS.[33] Muscle samples were obtained from 15 parents of 13 children who died of SIDS. Five of these parents had positive IVCTs. Serum CK levels were not elevated in any of the parents. These findings raise the possibility that MH may present as sudden unexpected death in infants. It is interesting that overheating has been given as a possible factor in some unexpected infant deaths.[34] Eight of 33 SIDS cases investigated pathologically showed histologic changes in the small intestine of the kind associated with heat stroke. The metabolic changes associated with MH may contribute to the high temperatures found in some infants who die unexpectedly.

In contrast to this study, Ellis et al. investigated this suggested relationship between SIDS and MH and failed to find an association.[35] This investigation included three components—a questionnaire sent to patients known to be MHS, a questionnaire sent to SIDS parents, and muscle biopsy in 14 SIDS parents. They found the incidence of SIDS in the MHS population to be the same as that in the general population. They concluded that the findings of Denborough et al.[33] were due to methods of case selection in that SIDS families with a family history of an anesthetic complication were preferentially investigated.[35] Further investigation in this area may be helpful to more clearly define the presence or absence of an association between SIDS and MH.

Masseter Muscle Rigidity

Masseter muscle rigidity (MMR), which is defined as a significant and sometimes prolonged increase in masseter muscle tone after succinylcholine, is considered a risk factor and possibly a very early sign of a MH reaction. A retrospective study by Allen and Rosenberg found that 25% of adults referred for muscle biopsy after an episode of MMR tested positive for MH.[36] There is controversy whether, following MMR, the surgery should be canceled or continued with a trigger-free anesthetic. As obstetric cases are not always elective, there is no option but to continue. A trigger-free anesthetic is suggested with appropriate postoperative monitoring as for a known MH patient. The anesthesia machine need not be changed, but replacing the fresh gas outlet hose and using a new disposable circuit with high fresh gas flows should be considered.[37]

Triggers of Malignant Hyperthermia

The known pharmacologic triggers of MH include all halogenated anesthetic vapors (including sevoflurane and desflurane) and succinylcholine. Nitrous oxide and nondepolarizing neuromuscular blocking agents are safe. Older texts considered amide local anesthetics and ketamine to be possible triggering agents, but more recent work suggests these agents are safe.[3]

The question arises regarding fetal risk surrounding the use of succinylcholine for an MH-negative mother when the father is positive. Succinylcholine is a highly charged molecule but can still cross the placenta in very small amounts.[38] If possible, it should be avoided, but because it has unique pharmacologic properties compared to currently available nondepolarizing neuromuscular blocking agents, it still plays a role in airway management. Maternal safety must not be compromised, and if succinylcholine is used, the neonate should be carefully observed for even subtle signs of MH by a pediatrician or neonatologist.

Anticholinergics can exacerbate fever because of their antidiaphoretic action. Although this may complicate the diagnosis or management of a reaction, anticholinergics are not considered triggers. In vitro, ephedrine increased muscle contractions in the presence of halothane, but this occurred at concentrations 1000 to 2000 fold higher than clinically relevant plasma levels.[39] Catecholamines, including epinephrine, norepinephrine, and ephedrine, are also considered safe.

Caffeine is used for the in vitro testing, and there is concern that it or related drugs such as theophylline or phosphodiesterase inhibitors could trigger MH. Although in vitro reactions can be demonstrated, they occur at levels far above clinically relevant concentrations. Phenothiazines can trigger neuroleptic malignant syndrome (NMS) and have intrinsic anticholinergic properties but do not appear to trigger MH at therapeutic concentrations.[3]

An interesting question is whether MH can occur in a susceptible individual in the absence of a pharmacologic trigger. There are a number of reports of MH signs and symptoms occurring in response to heat stress, physical exertion, viral illness,[2] or a nontriggering anesthetic.[40] There are no reports of labor causing an MH reaction. Considering the known genetic heterogeneity and variability in in vitro testing, it is likely that

some individuals may manifest MH signs and symptoms under certain conditions without exposure to known triggers. Fortunately, this appears to be a very rare occurrence and has not yet been reported in the peripartum period.

Drugs Used in the Management of Labor and Delivery

Oxytocin and prostaglandin $F_{2\alpha}$ are considered safe in MHS parturients, whereas ergot preparations are relatively contraindicated.[28,41,42] These latter drugs are of concern because of their sympathomimetic properties and the potential to obscure or exacerbate a MH reaction. There are no reports of either class of these drugs triggering a MH reaction in pregnancy; however, the potential risks of using the drug versus the risks of persistent uterine atony and hemorrhage must be considered if this scenario arises.

Recognizing Malignant Hyperthermia in the Laboring Patient

The diagnosis of an MH crisis in the pregnant patient may be masked by some physiologic changes of pregnancy and by some relatively common problems that can develop during labor and delivery. For example, pulse rates of 100 beats per minute (bpm) or higher depending on the maternal position are regarded as physiologic during rest periods between uterine contractions in the second stage.[29,42] The majority of patients with MH episodes develop a tachycardia above 120 bpm. Maternal tachypnea is also a normal response to pain, physical exertion, and fever. The development of a fever in labor is not uncommon and may be a sign of infection (chorioamnionitis) and/or dehydration.[42] Furthermore, a maternal metabolic acidosis often occurs normally during the second stage of labor, and a base deficit of 4.5 to 6 mmol can develop in a well-managed labor depending on duration.[29] Small increases in CK levels are also normal, secondary to uterine contractions and maternal exertion. Arterial blood gases may help in determining if MH is likely. In the presence of other signs such as muscle rigidity or hyperkalemia, immediate treatment should be initiated.

Monitoring maternal heart rate, blood pressure, and temperature at least hourly during labor will help to identify early manifestations of a MH reaction. Intraarterial blood pressure and ECG monitoring are not mandatory but should be immediately available. Central temperature monitoring is preferable to skin temperature. It is suggested that monitoring continue for 4 h after delivery.

When a MHS parturient is admitted to the labor ward, the anesthesiology staff should be notified immediately. An intravenous line should be established early, and blood samples sent for hematology, biochemistry, and CK. Although a CK level is not prognostic, it can serve as a baseline should the diagnosis of a MH reaction be entertained later. The MH cart should be immediately available on the labor ward, and an operating room should be prepared by flushing the anesthetic machine and taping the vaporizers off in a well-described fashion[37] or by using a dedicated MH machine. Ideally, this room should not be used for other patients until after delivery. If this is not possible, it should be reprepared after each use.

An epidural analgesia for labor and delivery is encouraged. The fetal heart rate should be continuously monitored, and the neonate is monitored with temperature, heart rate, and respiratory rate determined hourly for 4 h.

Management of an Acute Reaction

The most important element in the management of an acute malignant hyperthermia reaction is early recognition and treatment with dantrolene. Every hospital should have a MH cart with the typical contents listed in Table 16.2. This cart usually resides in the main operating room and should be brought to the labor floor when a known MHS patient is present. If the labor ward is remote from the main OR, or the volume of MHS parturients is high, a dedicated MH cart for the labor ward is recommended.

Basic treatment is targeted at metabolic support and intravenous dantrolene. An outline of treatment recommended by the Malignant Hyperthermia Association of the United States (MHAUS) clinical update 2000/2001[43] is shown in Box 16.1.

TABLE 16.2. Suggested contents of a malignant hyperthermia (MH) cart.

Drugs
Dantrolene sodium, 36 vials
Sterile water to mix dantrolene (not NaCl)
Dextrose 50%
Antiarrhythmics including beta-blockers and current ACLS management drugs
Mannitol
Calcium chloride
Sodium bicarbonate
Furosemide
N.B.: Calcium channel blockers should NOT be used.
Equipment
Ice bags
Temperature probes
Nasogastric tubes
Foley catheters
Urine collection containers
Syringes, needles
Catheters for intravenous and intraarterial placement
Arterial and central venous pressure monitoring equipment
Collection tubes for blood gases, electrolytes, blood counts, coagulation profiles
MH protocol with telephone help numbers
List of cart contents so it can be kept complete

Box 16.1. Management of an acute malignant hyperthermia (MH) reaction.

Immediate:
- Call for help. Start dissolving the dantrolene in sterile water (not saline).
- Stop volatile anesthetics and succinylcholine.
- Hyperventilate with 100% oxygen.
- Administer 2.5 mg/kg dantrolene intravenously. Repeat as necessary, titrated to signs of malignant hyperthermia (MH).
- Monitor core temperature, electrocardiogram, arterial blood pressure, and urine output.
- Treat acidosis with bicarbonate if not rapidly improved with dantrolene.
- Treat hyperkalemia with glucose, insulin, and calcium.
- Avoid calcium blockers. Persistent arrhythmias may be treated with any other standard antiarrhythmic and usually respond to correction of hyperkalemia and acidosis.
- If hyperthermic, cool by nasogastric, rectal lavage, and surface cooling, but avoid overcooling.

After initial stabilization:
- Continue intravenous dantrolene for at least 24 h after control of initial episode (approximately 1 mg/kg q 6 h).
- Watch for recrudescence by monitoring in an intensive care unit (ICU) for 36 h. Recrudescence occurs in about 25% of MH cases.
- Avoid parenteral potassium.
- Ensure adequate urine output by hydration and diuretics because myoglobinuria is common.
- Follow coagulation profile watching for the occurrence of disseminated intravascular coagulation (DIC).
- Measure creatine kinase (CK) every 6 h until falling then at least daily until normal. CK may remain elevated for 2 weeks. Recall that baseline CK may be elevated in some patients.
- For further consultation during reaction, call MH hotline at 1-800-MH-HYPER (800-644-9737), or 1-315-464-7079 if outside the U.S.A.
- Report acute MH episodes to the North American MH Registry: 1-412-692-5464.
- Counsel patients and families regarding testing and future anesthetics. (An excellent source of information is the MHAUS website: http://www.mhaus.org.)

Source: Adapted from MHAUS website: http://www.mhaus.org/clinical_update_2000.htm

Dantrolene

Dantrolene sodium is a lipid-soluble hydantoin analogue used in the therapy of MH crises. Three characteristics are unique to pregnancy: possible adverse effects on the fetus and newborn infant, effects on uterine contractility, and secretion of dantrolene into breast milk.

Shime et al.[44] performed a prospective study to evaluate the effects on the fetus and newborn of prophylactic oral dantrolene in pregnant women. These investigators chose a relatively low dosage of oral dantrolene. Minor maternal side effects were reported; however, there were no detectable fetal or neonatal adverse effects. The mean maternal serum dantrolene level (0.99 mg/mL) was lower than that thought to provide malignant hyperthermia prophylaxis. Therefore, fetal/neonatal effects may be encountered with higher levels. As the prophylactic use of dantrolene is now quite rare, the fetus is less likely to have in utero exposure unless a MH crisis is diagnosed early during a cesarean section or occurs during surgery in pregnancy.

Newborns have demonstrated decreased muscle tone after intravenous dantrolene use around delivery, although respiratory or cardiovascular depression has not been observed. It is possible that placental transmission of dantrolene may protect the neonate who has inherited MH.

The effects of dantrolene on uterine contractions must also be considered. There is controversy in the literature regarding the association of dantrolene with uterine atony. In isolated uterine muscle preparations of guinea pigs, dantrolene suppressed the activity of oxytocin-induced contractions.[45] Weingarten et al. have reported a case of a woman who developed postpartum uterine atony after treatment with intravenous dantrolene (prophylactically) for known MH susceptibility.[46] This patient also had preeclampsia and likely chorioamnionitis in labor. She had a cesarean section for failure to progress. After delivery, she developed uterine atony and postpartum hemorrhage that did not respond to intravenous oxytocin, intramuscular methylergonovine, and prostaglandin $F_{2\alpha}$. This patient had a hysterectomy for uterine atony after a D&C also failed to stop the bleeding. The authors note that although a cause-and-effect relationship between dantrolene and atony cannot be proven, the sequence of events suggest that dantrolene may have contributed to its development.

In contrast to this suggestion, Shin et al. studied the effect of dantrolene on contractility of isolated human uterine muscle from eight healthy patients undergoing elective cesarean section at term.[47] This study showed that dantrolene alone has no effect on spontaneous contractility in isolated uterine muscle, but that any observed uterine muscle relaxation is most likely related to the mannitol in the prepared solution. A comprehensive review of dantrolene by Britt details the conflicting information regarding the effects of this drug on intestinal and bladder smooth muscle.[48]

Breast-feeding is an important aspect of the postpartum period, and the presence of dantrolene in breast milk following maternal therapy should be considered and discussed with the patient. Fricker et al. addressed this concern after a case in which a suspected MH crisis at cesarean section was treated with intravenous dantrolene.[49] The patient received decreasing doses of dantrolene for 3 days, and concentrations of this drug in breast milk were determined. They noted that the highest concentration of dantrolene was detected 36 h after the first intravenous bolus, and that the half-life in breast milk is 9 h. Even if 70% of this dose enters neonatal circulation via gastrointestinal absorption, the peak serum levels are still far less than those described as insignificant after placental transfer.

Dantrolene Prophylaxis

Dantrolene prophylaxis has been used in the past but has fallen out of favor. The efficacy has never been proven, and the risk

of a reaction using a trigger-free anesthetic is minimal. There have been no reported cases of a MH reaction that has not responded to treatment with dantrolene. The administration of dantrolene is not benign; in a volunteer study by Wedel et al., all subjects demonstrated side effects (visual symptoms, subjective muscle weakness, dizziness, fatigue) after an intravenous dose of 3 mg/kg.[50]

Recent publications suggest restriction of dantrolene to treatment of acute reactions,[29] and the MHAUS clinical update states that dantrolene prophylaxis is usually not indicated.[43]

Clinical Scenarios

Anticipating patient requirements is a hallmark of excellent clinical care, and for the parturient, several clinical scenarios are now discussed: labor and spontaneous vaginal delivery, nonemergent cesarean section, emergent cesarean section, and postpartum care.

Vaginal Delivery

Ideally, all MHS pregnancies should have an anesthesia consult before the onset of labor. Once the parturient arrives on the labor ward, the preparations already discussed should be undertaken. Epidural analgesia is recommended to minimize the stress of labor and to avoid the risk of general anesthesia should an urgent operative delivery be required. Management of labor is per the obstetrician, and there is no contraindication to oxytocin. A high index of suspicion should be maintained should the patient develop muscle aches/rigidity, tachycardia above 120 bpm, or resting tachypnea. Recall that low-grade intrapartum fever is common and may have several etiologies including chorioamnionitis, dehydration, or prolonged epidural analgesia.[51] Fever is uncommonly a presenting sign of a MH reaction,[52] and there is usually significant metabolic derangement by the time a fever is manifest.

Any combination of local anesthetics or opioids is safe. Epinephrine in the epidural solution is also safe but has no significant benefit for labor analgesia and is therefore falling out of favor.[53] Nitrous oxide is not a trigger, and therefore a N_2O/O_2 mix for labor analgesia (Entonox) is acceptable.

Nonemergent Assisted Delivery

Regional anesthesia, using either a spinal, epidural, or combined technique, is again preferred for an instrumented or operative delivery. Maternal monitoring should include electrocardiogram, pulse oximetry, blood pressure, and core temperature. Continuous rectal temperature monitoring is preferred in the patient under neuraxial block, but if this is technically unfeasible, frequent tympanic membrane temperatures will provide accurate trends. Some centers initially advocated arterial line monitoring, but most now consider non-invasive monitoring acceptable.[29] Arterial line monitoring should be available if clinical conditions warrant its use.

The operating room should be prepared in the usual fashion for an MHS patient; the MH cart should be available, and aspiration prophylaxis provided. Although regional anesthesia should be adequate for the delivery, one must always be prepared to provide a trigger-free general anesthetic should the block prove inadequate or a surgical complication occur.

Emergent Cesarean Section

An emergent cesarean for fetal distress is always a challenging event and is even more so with a MHS parturient. If an epidural is in situ, it can be used to achieve rapid surgical anesthesia, preferably with 3% chloroprocaine, which has a very short serum half-life and is not trapped in an acidotic fetus.

Without an epidural, the anesthesiologist must decide between spinal and general anesthesia. Barring contraindications to neuraxial block, this decision will be based on careful assessment of the airway, the comfort of the anesthesiologist in rapidly siting a needle into the subarachnoid space, and the urgency of the delivery.

If general anesthesia is undertaken, preoxygenation with four vital capacity breaths followed by a rapid sequence induction with rocuronium is an effective alternative to succinylcholine. Good intubating conditions at 80 s and a duration of action of 33 min are achieved after a dose of 0.6 mg/kg rocuronium.[54] Anesthesia can be maintained with any combination of oxygen, nitrous oxide, opioids, propofol, pentothal, ketamine, etomidate, or benzodiazepines. A pure nitrous-narcotic technique is not recommended for reasons of the increased risk of awareness.

Postpartum Care

Postoperative temperature monitoring for 4 h after surgery is recommended by MHAUS. There are no guidelines for duration of monitoring after an uneventful vaginal delivery in MHS parturients, but 2 to 4 hours is recommended by some and seems reasonable.[29] Continuous temperature monitoring may be difficult in this population, and intermittent tempera-

Box 16.2. Differential diagnosis of postpartum fever in a malignant hyperthermia susceptible (MHS) parturient.

Genital tract infection (e.g., endometritis)
Upper or lower respiratory tract infection
Cystitis/pyelonephritis
Mastitis
Thrombophlebitis (superficial or deep)
Wound infection
Adverse drug reaction
Other viral illness
Malignant hyperthermia

ture readings every 30 to 60 min will detect significant changes. Postpartum fever is common; although a high degree of suspicion of MH must be maintained with these women, other causes are also likely. A differential diagnosis of postpartum fever occurring within 48 h of delivery in the MHS parturient is listed in Box 16.2. The parturient should be examined by both the anesthesiologist and obstetrician, and there should be evidence of a hypermetabolic state or some of the clinical indicators listed in Table 16.1 before dantrolene is started.

If a MH reaction occurs intrapartum, the parturient should be in an intensive care unit setting for at least 36 h after delivery. Monitoring should include electrocardiogram, arterial line for blood pressure, frequent bloodwork, central temperature, and urine output. Dantrolene should be started immediately and continued for at least 24 h. Recrudescence after the initial crisis occurs in approximately 25% of cases[52] and may necessitate a second course of dantrolene. Genetic counseling after an acute event is recommended for both the proband and her family.

Summary

In summary, MH is an uncommon but potentially lethal disease. The mainstays of treatment are to avoid triggers in known susceptible patients and to treat rapidly with dantrolene if a crisis occurs. Cooperation and communication between anesthesiologists, obstetricians, and nurses will help manage these parturients. Vigilance and awareness on the part of caregivers and the use of dantrolene have decreased fatality rates during the past 20 years.[19] The Malignant Hyperthermia Association of the United States maintains an excellent website with up-to-date information for both health care providers and the public (www.mhaus.org).

References

1. Crawford JS. Hyperpyrexia during pregnancy. Lancet 1972;1:1244.
2. Denborough M. Malignant hyperthermia. Lancet 1998;352:1131–1136.
3. Hopkins PM. Malignant hyperthermia: advances in clinical management and diagnosis. Br J Anaesth 2000;85:118–128.
4. Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994;80:771–779.
5. McCarthy TV, Healy JMS, Heffron JJA, et al. Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. Nature (Lond) 1990;343:562–564.
6. MacLennan DH, Duff C, Zorzato F, et al. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature (Lond) 1990;343:559–561.
7. Wallace AJ, Wooldridge W, Kingston HM, et al. Malignant hyperthermia—a large kindred linked to the RYR1 gene. Anaesthesia 1996;51:16–23.
8. Curran JL, Hall WJ, Halsall PJ, et al. Segregation of malignant hyperthermia, central core disease and chromosome 19 markers. Br J Anaesth 1999;83:217–222.
9. Chamley D, Pollock NA, Stowell KM, et al. Malignant hyperthermia in infancy and identification of novel RYR1 mutation. Br J Anaesth 2000;84:500–504.
10. Allen GC, Larach MG, Kunselman AR, et al. The sensitivity and specificity of the caffeine-halothane contracture test: a report from the North American malignant hyperthermia registry. Anesthesiology 1998;88:579–588.
11. Ørding H, Brancadoro V, Cozzolino S, et al. In vitro contracture testing for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant MH and unrelated low-risk subjects. Acta Anaesthesiol Scand 1997;41:955–966.
12. Fletcher JE, Rosenberg H, Aggarwal M. Comparison of European and North American malignant hyperthermia diagnostic protocol outcomes for use in genetic studies. Anesthesiology 1999;90:654–661.
13. Islander G, Ranklev-Twetman E. Comparison between the European and North American protocols for diagnosis of malignant hyperthermia susceptibility in humans. Anesth Analg 1999;88:1155–1160.
14. Ørding H, Islander G, Bendixen D, et al. Between-center variability of results of the in vitro contracture test for malignant hyperthermia susceptibility. Anesth Analg 2000;91:452–457.
15. Loke JCP, MacLennan DH. Baysian modeling of muscle biopsy contracture testing for malignant hyperthermia susceptibility. Anesthesiology 1998;88:589–600.
16. Baur CP, Bellon L, Felleiter P, et al. A multicenter study of 4-chloro-*m*-cresol for diagnosing malignant hyperthermia susceptibility. Anesth Analg 2000;90:200–205.
17. Gronert GA. Testing for MH susceptibility. Acta Anaesthesiol Scand 1997;41:953–954.
18. Larach MG, MacLennan DH. How carefully can we phenotype patients suspected of malignant hyperthermia susceptibility. Anesthesiology 1999;90:645–648.
19. Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. Anesth Analg 1993;77:297–304.
20. Islander G, Bendixen D, Ranklev-Twetman E, et al. Results of in vitro contracture testing of both parents of malignant hyperthermia susceptible probands. Acta Anaesthesiol Scand 1996;40:579–584.
21. Sewall K, Flowerdew RM, Bromberger P. Severe muscular rigidity at birth: malignant hyperthermia syndrome? Can Anaesth Soc J 1980;27:279–282.
22. Hinkle AJ, Dorsch JA. Maternal masseter muscle rigidity and neonatal fasciculations after induction for emergency cesarean section. Anesthesiology 1993;79:175–177.
23. Wiswell TE, Bent RC, Solenberger R. Malignant hyperthermia in infancy. South Med J 1989;82:1451–1452.
24. Bailey AG, Bloch EC. Malignant hyperthermia in a three-month-old American Indian infant. Anesth Analg 1987;66:1043–1045.
25. Wilhoit RD, Brown RE, Bauman LA. Possible malignant hyperthermia in a 7-week-old infant. Anesth Analg 1989;68:688–691.
26. Meluch AM, Sibert KS, Bloch EC. Malignant hyperthermia following isoflurane anesthesia in an American Lumbee Indian. N C Med J 1989;50:485–487.
27. Pennington GP, Joeris L. Malignant hyperthermia in a 3-month-old infant: a case report. J Med Assoc Ga 1996;85:162–163.
28. Lucy SJ. Anaesthesia for caesarean delivery of a malignant hyperthermia susceptible parturient. Can J Anaesth 1994;41:1220–1226.
29. Pollock NA, Langton EE. Management of malignant hyperthermia susceptible parturients. Anaesth Intensive Care 1997;25:398–407.
30. Ellis FR, Clarke IMC, Modgill M, et al. Evaluation of creatinine phophokinase in screening patients for malignant hyperthermia. Br Med J 1975;3:511–513.
31. Brownell AKW. Malignant hyperthermia: relationship to other diseases. Br J Anaesth 1988;60:303–308.
32. Denborough MA. Sudden infant death syndrome and malignant hyperpyrexia. Med J Aust 1981;1:649–650.
33. Denborough MA, Galloway GJ, Hopkinson KC. Malignant hyperpyrexia and sudden infant death. Lancet 1982;2:1068–1069.

34. Stanton AN, Scott DJ, Downham MA. Is overheating a factor in some unexpected infant deaths? Lancet 1980;1:1054–1057.
35. Ellis FR, Halsall PJ, Harriman DG. Malignant hyperpyrexia and sudden infant death syndrome. Br J Anaesth 1988;60:28–30.
36. Allen GC, Rosenberg H. Malignant hyperthermia susceptibility in adult patients with masseter muscle rigidity. Can J Anaesth 1990;37:31–35.
37. Beebe JJ, Sessler DI. Preparation of anesthesia machines for patients susceptible to malignant hyperthermia. Anesthesiology 1988;69:395–400.
38. Drabkova J, Crul JF, van der Kleijn E. Placental transfer of 14C labelled succinylcholine in near-term *Macaca mulatta* monkeys. Br J Anaesth 1973;45:1087–1096.
39. Urwyler A, Censier K, Seeberger MK, et al. In vitro effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia. Br J Anaesth 1993;70:76–79.
40. Pollock N, Hodges M, Sendall J. Prolonged malignant hyperthermia in the absence of triggering agents. Anaesth Intensive Care 1992;20:520–523.
41. Willatts SM. Malignant hyperthermia susceptibility: management during pregnancy and labour. Anaesthesia 1979;34:41–46.
42. Douglas MJ, McMorland GH. The anaesthetic management of the malignant hyperthermia susceptible parturient. Can Anaesth Soc J 1986;33:371–378.
43. MHAUS. Clinical update 2000/2001—Managing MH. Malignant Hyperthermia Association of the United States, 2001.
44. Shime J, Gare D, Andrews J, et al. Dantrolene in pregnancy: lack of adverse effects on the fetus and newborn infant. Am J Obstet Gynecol 1988;159:831–834.
45. Conte-Camerino D, Lograno MD, Siro-Brigiani G, et al. Dantrolene sodium: stimulatory and depressant effects on the contractility of guinea-pig uterus in vitro. Eur J Pharmacol 1983;92:291–294.
46. Weingarten AE, Korsh JI, Neuman GG, et al. Postpartum uterine atony after intravenous dantrolene. Anesth Analg 1987;66:269–270.
47. Shin YK, Kim YD, Collea JV, et al. Effect of dantrolene sodium on contractility of isolated human uterine muscle. Int J Obstet Anesth 1995;4:197–200.
48. Britt BA. Dantrolene. Can Anaesth Soc J 1984;31:61–75.
49. Fricker RM, Hoerauf KH, Drewe J, et al. Secretion of dantrolene into breast milk after acute therapy of a suspected malignant hyperthermia crisis during cesarean section. Anesthesiology 1998;89:1023–1025.
50. Wedel DJ, Quinlan JG, Iaizzo PA. Clinical effects of intravenously administered dantrolene. Mayo Clin Proc 1995;70:241–246.
51. Camann WR, Hortvet LA, Hughes N, et al. Maternal temperature regulation during extradural analgesia for labour. Br J Anaesth 1991;67:565–568.
52. Allen GC, Brubaker CL. Human malignant hyperthermia associated with desflurane anesthesia. Anesth Analg 1998;86:1328–1331.
53. Dounas M, O'Kelly BO, Jamali S, et al. Maternal and fetal effects of adrenaline with bupivacaine (0.25%) for epidural analgesia during labour. Eur J Anaesthesiol 1996;13:594–598.
54. Abouleish E, Abboud T, Lechevalier T, et al. Rocuronium (Org 9426) for Caesarean section. Br J Anaesth 1994;73:336–341.

17
Hemoglobin Bart's Hydrops Fetalis Syndrome

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Hydrops fetalis is the final pathway of many conditions that leads to the accumulation of fluid in fetal tissues and body cavities. Hydrops fetalis is diagnosed on ultrasound examination when the skin edema measured at the level of the skull is more than 5 mm,[1] with associated different serous effusions, polyhydramnios, and increased placental thickness. The incidence of hydrops as reported in neonatal series ranges from 1 in 1475[2] to 1 in 3538.[3] Because of the high rate of intrauterine deaths of such fetuses, these figures are underestimations of the actual incidences.

The mechanisms causing hydrops fetalis are either immunologic or nonimmunologic. Erythroblastosis fetalis generally refers to an immune-mediated hemolytic disease of the fetus characterized by the presence of erythroblasts in the fetal circulation. The classical and most common type of erythroblastosis fetalis is caused by rhesus alloimmunization, followed by Kell antigen sensitization. The incidence of erythroblastosis fetalis has been reduced dramatically by the introduction of anti-D immunoglobulin in the 1960s.[4] Alloimmunization of RhD-negative women carrying an RhD-positive fetus has been reduced to less than 1%. With the reduction in cases of erythroblastosis fetalis and improvements in neonatal care, the significance of the contribution of nonimmune hydrops fetalis toward perinatal mortality has decreased from 3% to 1%.[5]

The pathogenesis of nonimmune hydrops fetalis (NIHF) is complex and may include a wide variety of mechanisms resulting from maternal, placental, or fetal disorders. Common causes of NIHF include chromosomal, hematologic, and cardiovascular disorders and fetal infections. Less common causes include fetal malformations of the thorax, disorders of the hepatobiliary, gastrointestinal, and genitourinary systems, and placental disorders such as chorioangiomas. Despite new and aggressive treatments, such as surfactants, steroids, and high-frequency ventilation, the overall outcome of the infant born with hydrops remains poor; the mortality rate ranges from 50% to 100%.[6]

In Southeast Asian countries (such as Taiwan, Singapore, Thailand, and Hong Kong), hemoglobin Bart's hydrops fetalis syndrome is the most common cause of NIHF, accounting for 20% to 80% of such cases.[7–10] With the migration of Asian populations into countries such as the United States,[11] the United Kingdom,[12] and Australia,[13] the syndrome is seen with increasing frequency in these countries.[14] With systematic detection of homozygous α-thalassemia-1 in early pregnancy and termination of such affected pregnancies, the incidence of Hb Bart's hydrops fetalis syndrome can be controlled.[15]

Terminology

Whipple and Bradford first coined the term "thalassa anaemia" or "anaemia by the sea" in 1932 to associate the disease with the Mediterranean area. At that time, most families with the disease were of Greek and Italian descent. It was discovered later that thalassemia occurs in high frequency in Asia and Southeast Asia as well, albeit thalassemia of a different variety.

Hemoglobin (Hb) Bart's hydrops fetalis syndrome was first described in 1960[16] in fetuses that suffered from severe anemia, hypoxia, heart failure, and hydrops fetalis. These fetuses usually died in utero or in the early neonatal period. They were later found to be characterized by the absence of all four α-globin genes on chromosome 16. Deletion of one or two α-globin genes leads to asymptomatic carriers, whereas deletion of three α-globin genes leads to a clinical condition called HbH disease. HbH disease is a phenotypically heterogeneous condition with mild to severe clinical presentation; blood transfusion may be required for improvement in survival and quality of life (Table 17.1).

The phenotypes and genotypes have been used interchangeably in various accounts of this condition. Hb Bart's hydrops fetalis syndrome is a clinical diagnosis made when fetal hydrops is present and Hb Bart's constitutes the major hemoglobin in fetal blood. Homozygous α-thalassemia-1 ($--/--$) is the genotype that causes Hb Bart's hydrops fetalis. With better and earlier prenatal diagnosis of fetuses affected by this condition, homozygous α-thalassemia-1 is often detected when the fetus has not shown any signs of hydrops on ultrasound. To use the term hemoglobin Bart's hydrops fetalis syndrome in such a situation would therefore not be literally correct.

TABLE 17.1. Characteristics of different forms of α-thalassemia.

Phenotype	Number of functional α-globin genes	Clinical presentation	MCV (fL)[17]	MCH (pg)[17]	Genotype	Genetic description
Normal	4	None	85–100	~30	($\alpha\alpha/\alpha\alpha$)	Normal
Alpha-thalassemia trait-2 (α^+)	3	Asymptomatic	75–85	~26	($-\alpha/\alpha\alpha$)	Heterozygous α-thalassemia-2
Alpha-thalassemia trait-1 (α^0)	2	Asymptomatic	65–75	~22	($--/\alpha\alpha$)	*cis*-α-Thalassemia trait 1 (both genes deleted on same chromosome) or heterozygous α-thalassemia-1
					($-\alpha/-\alpha$)	*trans*-α-Thalassemia trait 1 (1 gene deleted on each chromosome) or homozygous α-thalassemia-2
HbH disease	1	A phenotypically heterogeneous disease caused by genetic heterogeneity and characterized by chronic hemolytic anemia with jaundice, hepatosplenomegaly, folate deficiency, increased susceptibility to infection; may required blood transfusion and splenectomy	60–70	~20	($--/-\alpha$)	Compound heterozygous α-thalassemia-2 and α-thalassemia-1
Hb Bart's hydrops fetalis syndrome	0	Fetal hydrops associated with the finding of Hb Bart's as the major hemoglobin (>80%) in fetal blood	110–120	Reduced	($--/--$)	Homozygous (α-thalassemia-1

Hb, hemoglobin; MCV, mean cell volume; MCH, mean corpuscular hemoglobin.

Epidemiology

α-Thalassemia is the most common genetic disease in the world. Although α-thalassemia is commonly seen in Mediterranean countries, Asia, and Southeast Asia (Figure 17.1), cases of Bart's hydrops fetalis are also commonly seen in Southeast Asia and South China. This phenomenon can be explained by an understanding of the population genetics of α-thalassemia.

Populations that have a high prevalence of heterozygous α-thalassemia-1 (e.g., Chinese,[18] Thais,[19] Filipinos[20]) have a higher prevalence of Bart's hydrops fetalis. Those with a high prevalence of only heterozygous α-thalassemia-2 (e.g., Indians,[21] Italians,[22] Africans,[23] Arabs,[24,25] Javanese from Indonesia[26]) do not have a high prevalence of Bart's hydrops fetalis. HbH disease, however, has been reported in Israel,[27] Italy,[28] Cuba,[29] Hong Kong,[30] Taiwan,[31] Thailand,[32,33] India,[34] and Saudi Arabia.[24]

Molecular Basis

The α-globin genes are found on the distal segment (p13.1-pter) of the short arm of chromosome 16. The gene cluster is made up of one embryonic ζ-globin gene, two α-globin genes, and four pseudogenes. Unlike β-thalassemia, which results most frequently from single nucleotide substitutions, α-thalassemia is predominantly caused by large deletions within the α-globin cluster. Common deletional mutations that cause α-thalassemia-1 and α-thalassemia-2 are seen in Figures 17.2 and 17.3, respectively.[17] Nondeletional mutations that manifest as α-thalassemia-2 include Hb Constant Spring and Hb Quong Sze (common in South Asia and Southeast Asia regions),[36] Hb Seal Rock,[37] Hb Westmead,[38] $\alpha^{Hph}\alpha$, $\alpha^{Ncol}\alpha$, $\alpha\alpha^{Ncol}$, $\alpha^{lc}\alpha$, and $\alpha^{TSaudi}\alpha$.[39]

In Southeast Asia, the three common α-thalassemia mutations are the $--$SEA, $--$FIL, and $--$THAI deletions, which are all heterozygous α-thalassemia-1 in the *cis* pattern. The $--$SEA (Southeast Asian type) deletion is 20.5 kb in length; both α-globin genes are deleted, but the embryonic ζ-globin gene is spared. It is commonly found in Hong Kong,[40] Taiwan,[41] Southern China,[42] and Thailand.[43,44] The prevalence rates of heterozygous carriers of $-$SEA deletion in these countries range from 3.5% to 14.0%. About 5% of people of Southeast Asian origin living in the United States were found to be carriers of the $--$SEA deletion.[45] Homozygosity for this deletion is the most common cause of the Hb Bart's hydrops fetalis syndrome[46] and was the first discovery of the molecular basis for a human genetic disease.[47] $--$FIL (Filipino) and $--$Thai mutations are large α-thalassemia deletions in which all the ζ- and α-globin genes are deleted.[48]

In Mediterranean countries such as Cyprus,[49] Greece,[50] Italy,[22] and Turkey,[51] rare cases of Hb Bart's hydrops fetalis

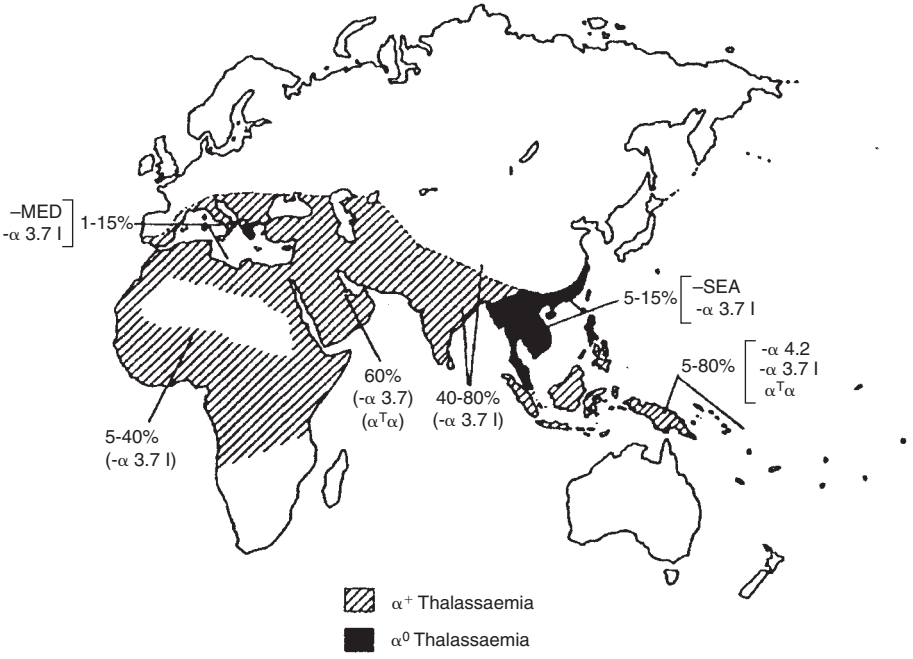

FIGURE 17.1. Worldwide distribution of α-thalassemia. (From Weatherall DJ. Thalassemia in the next millennium. Keynote address. Ann NY Acad Sci 1998;850:1–9,[35] with permission.)

have been reported. These cases are caused by one of two deletional mutations, $--$MED and $-\alpha^{20.5}$. As these mutations are quite rare, Bart's hydrops fetalis syndrome is not common in Mediterranean populations.

Pathophysiology

In normal fetal erythropoiesis (Figure 17.4), three embryonic hemoglobins predominate during embryogenesis: Hb Gower 1 ($\zeta 2\epsilon 2$), Hb Gower 2 ($\alpha 2\epsilon 2$), and Hb Portland 1 ($\zeta 2\gamma 2$). As the production of embryonic ζ- and ϵ-globin chains switches to α-globin chains, the embryonic globin chains become almost undetectable by 6 to 7 weeks, and HbF ($\alpha 2\gamma 2$) predominates as the major hemoglobin in the fetus from then on.

In fetuses with homozygous $--$SEA deletions, Hb Portland 1 ($\zeta 2\gamma 2$) remains the major hemoglobin present; it is expressed at very low levels after the switch to α-globin synthesis in the fetus, with Hb Portland 2 ($\zeta 2\beta 2$) being produced to a much lesser extent later. Although these Hb Portlands 1 and 2 can delivery oxygen to fetal tissues, the amounts of these hemoglobins are insufficient to keep pace with the needs of the fetus. Thus, the fetus is exposed to severe anemia at a very early stage in utero.

In fetuses with homozygous $--$FIL or $--$Thai deletions where the entire ζ- and α-globin gene clusters are lacking, only homotetrameric $\epsilon 4$ and Hb Bart's ($\gamma 4$) are present. As these hemoglobins have very high oxygen affinity, they are incapable of oxygen delivery to tissues in the rapidly growing embryo. These conceptuses generally miscarry after succumbing to severe hypoxia early in gestation. Hence, they do not present with the Hb Bart's hydrops fetalis syndrome.[14] However, fetuses

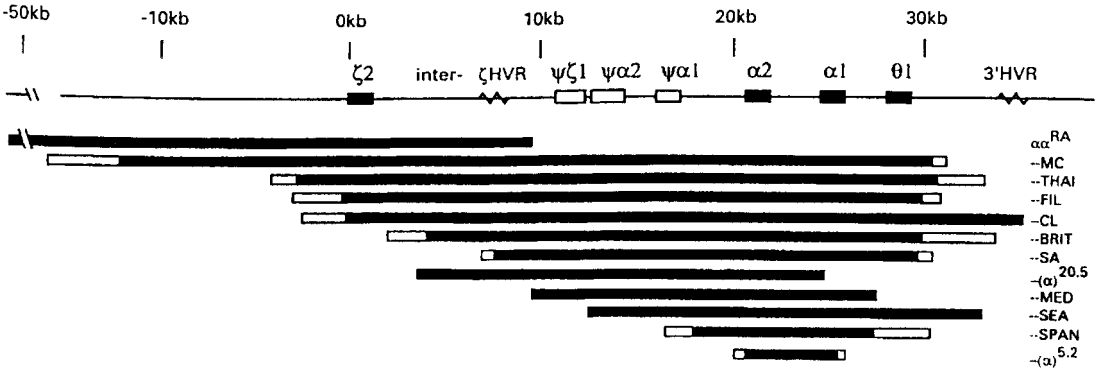

FIGURE 17.2. Mutations causing α-thalassemia-1 (α^0). (From Higgs DR, Vickers MA, Wilkie AO, et al. A review of the molecular genetics of the human alpha-globin gene cluster. Blood 1989;73(5):1081–1084, with permission.)

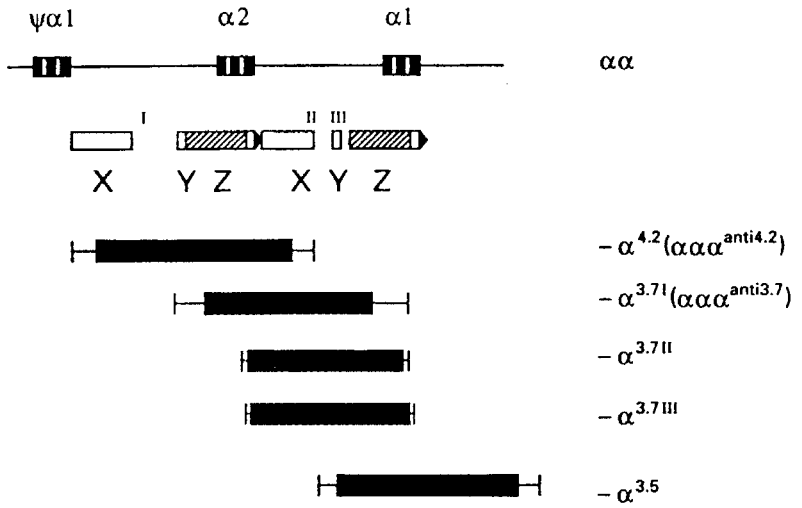

FIGURE 17.3. Mutations causing α-thalassemia-2 (α^+). (From Higgs DR, Vickers MA, Wilkie AO, et al. A review of the molecular genetics of the human alpha-globin gene cluster. Blood 1989;73(5):1081–1084, with permission.)

that are compound heterozygous for −−SEA and −−FIL deletions, or −−SEA and −−Thai deletions may still develop the Hb Bart's hydrops fetalis syndrome.

The situation in homozygous α-thalassemia-1 is thus different from that of β-thalassemia major in a few aspects. The switch to β-globin chain synthesis usually remains incomplete during the first year after birth. Therefore, the fetus with homozygous β-thalassemia is not exposed to intrauterine hypoxia from early gestation, and the clinical manifestations may be ameliorated by the sustained synthesis of fetal hemoglobin during the first 6 months of life.

Strategy to Reduce Problems Associated with Homozygous α-Thalassemia-1

The ultimate goal of prenatal diagnosis for α-thalassemia is the reduction of perinatal mortality and maternal morbidity and mortality resulting from pregnancies with Bart's hydrops fetalis. This goal can be achieved by the following strategy:

a. Identification of carriers on routine antenatal blood tests
b. Genetic counseling of at-risk couples
c. Prenatal diagnosis
d. Counseling for further management: timely termination of affected pregnancies must be offered.

In non-Asian countries such as Canada[53] and the United Kingdom,[54] α-thalassemia carriers are often discovered in the second or third trimester after the diagnosis of fetal hydrops has been made. In these antenatal populations, at-risk couples are not identified before or early in pregnancy. Although hospital-based screening and prenatal diagnosis have been available for many years in Hong Kong, it is estimated that 34.5% of pregnancies that are at risk for homozygous α-thalassemia are not referred for prenatal diagnosis.[40] Thus, there is an urgent need for a community-based program of education, screening, and counseling, especially where the disease is prevalent or within certain ethnic groups in the area.

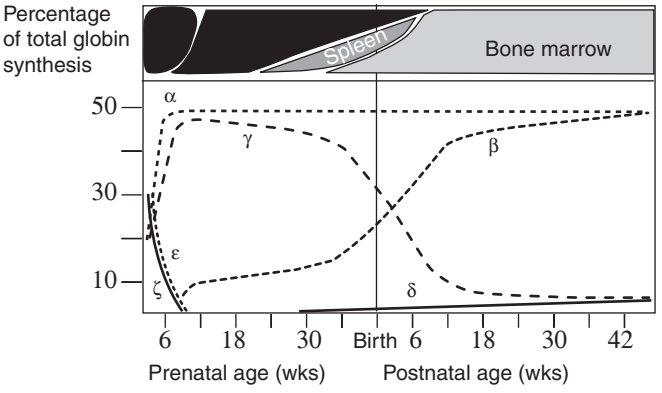

FIGURE 17.4. Normal fetal erythropoiesis. (From Olivieri NF. Fetal erythropoiesis and the diagnosis and treatment of hemoglobin disorders in the fetus and child. Semin Perinatol 1997;21(1):63–69, with permission.)

Identifying the Carrier Parents

The laboratory diagnosis of α-thalassemia carriers is of growing importance,[65] particularly because early prognosis of homozygous α-thalassemia-1 provides an option for safe termination of affected pregnancies that are universally lethal.

Red Cell Indices

Initial screening for the α-thalassemia trait is by red cell indices. Microcytosis can be caused by iron deficiency anemia, α-thalassemia, β-thalassemia, or other structurally abnormal hemoglobinopathies.[56] Most laboratories use mean cell volume (MCV) alone (<75–80 fL), some use mean corpuscular hemoglobin (MCH) alone (<25 pg), and others use both MCV and MCH. More than 99% of α-thalassemia trait-1 has an MCH below 25 pg; in occasional cases of α-thalassemia trait 1, MCH may be between 25 and 26 pg.

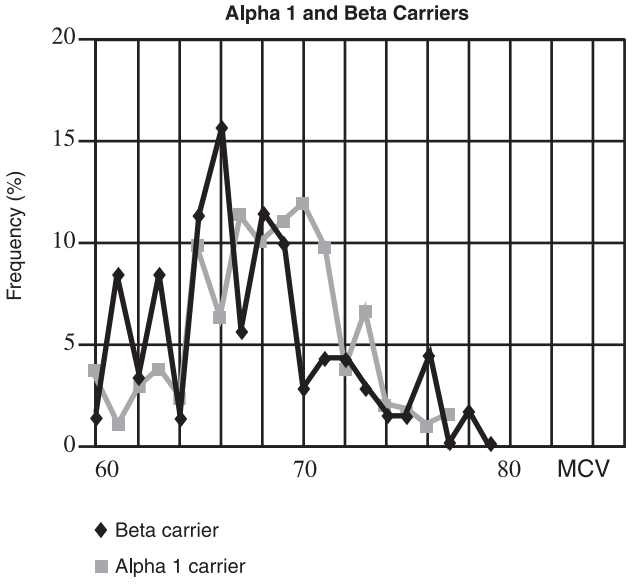

FIGURE 17.5. Mean corpuscular volume (MCV) distribution of α-1 and β-thalassemia carriers.

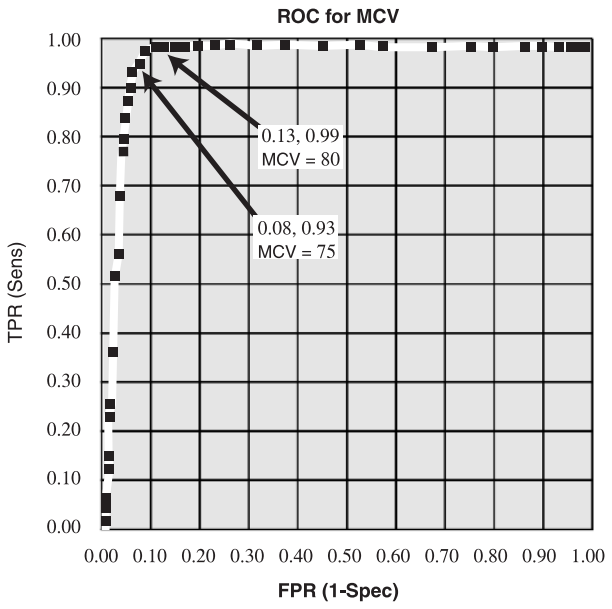

FIGURE 17.6. Receiver operating characteristic (ROC) curve of MCV for β-thalassemia carriers.

In countries such as Singapore,[57] Hong Kong,[58] and Thailand,[15] antenatal screening for both α- and β-thalassemias by MCV has been practiced for more than 10 years and has been found to be simple, effective, and reliable. Remarkably, unpublished data from one of the authors (G.S.H. Yeo) show that the MCV distribution of α-thalassemia-1 carriers and β-thalassemia minor are similar and are almost always less than 75 fL (Figure 17.5). Hence, the ROC (receiver operating characteristic) curve of MCV distribution for α-thalassemia-1 carriers is expected to correlate very closely to that for β-thal-assemia carriers (Figure 17.6).

A simple screening program to detect carriers of thalassemia traits at risk for producing offspring with severe thalassemia can therefore be easily implemented (Figure 17.7). This plan requires that routine complete blood counts with blood indices be done at least once for both partners by the first antenatal booking visit. A cutoff value of MCV below 80 fL would detect almost all cases of α-thalassemia-1 carri-

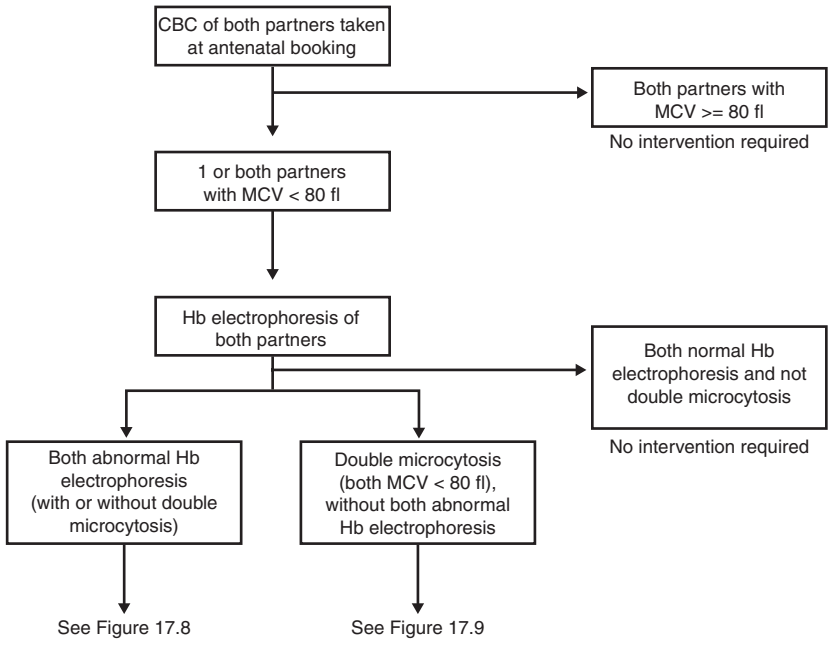

FIGURE 17.7. Screening algorithm for thalassemia in KK Hospital, Singapore.

ers and β-thalassemia minor. This procedure would allow the early detection of pregnancies at risk of producing severe thalassemia in the offspring, which would facilitate prenatal diagnosis of the pregnancy and legal termination of affected pregnancies before 24 weeks of gestation. Such a screening program would not, however, be effective in diagnosing pregnancies at risk of having fetuses with HbH disease because it detects only some carriers of α-thalassemia-2 whose MCV may range from 75 to 85 fL. Utilizing a higher MCV cutoff value to detect all α-thalassemia-2 carriers would, however, result in a higher false-positive rate for the test.

Hemoglobin Electrophoresis

If one or both partners show microcytosis on blood indices, Hb electrophoresis of both partners should be performed urgently to diagnose β-globin chain abnormalities, and the pregnancy should be managed accordingly if both partners were found to have such a condition (Figure 17.8).

Hemoglobin electrophoresis can be done on cellulose acetate at an alkaline pH of 8.2 to 8.6. Electrophoresis on citrate agar or agarose gel at an acidic pH of 6.0 to 6.2 can also be used as a supplement as it can identify some high-affinity hemoglobins that have abnormal mobility at acid pH but normal mobility at alkaline pH. HbA2 can be quantified by microcolumn chromatography or high performance liquid chromatography (HPLC). An elevated HbA2 level is used to diagnose a carrier of the β-thalassemia mutation. A normal Hb electrophoresis result does not exclude the condition of α-thalassemia carrier.

Other Tests of Differentiation

During her reproductive years, the female is at risk of iron deficiency anemia, being exposed to blood losses from menses before pregnancy and the additional demand of the fetus for iron during pregnancy. The laboratory diagnosis of iron deficiency anemia usually requires low plasma ferritin, low serum iron, high serum transferrin, low hemoglobin, and low MCV levels. Plasma ferritin is the earliest biochemical analyte to decrease in iron deficiency anemia. As it is an acute-phase reactant, its levels may rise to normal or even higher values in the presence of inflammation and hence confuse the laboratory picture. It is unusual for the male who consumes a well-balanced diet to suffer from iron deficiency, and thalassemia is therefore a diagnosis to be excluded in the male showing microcytosis.

Differential red cell distribution initially showed promise of segregating iron deficiency anemia from thalassemia. However, with the availability of modern hematology machines, the evaluation of differential red cell distribution is rarely performed as it is unreliable in most laboratories.

HbH inclusion bodies (precipitates of β4 tetramers) can be seen in adult carriers of α-thalassemia mutations when hemoglobin is incubated with a redox agent such as brilliant creosol blue dye. This search is laborious, and the results are highly observer dependent. However, certain laboratories have reported it as a highly accurate method of diagnosing α-thalassemia in the absence of coexisting HbE hemoglobinopathy or β-thalassemia.[59]

Diagnosis of α-Thalassemia (Including DNA Analysis)

In communities with high prevalence rates of α-thalassemia, the need to perform the gold standard investigations of hemoglobin electrophoresis and serum iron or plasma ferritin to differentiate these conditions should not be allowed to delay the diagnosis of α-thalassemia carriers, as it would compromise the window of opportunity for first trimester prenatal diagnosis and early decision for selective termination of affected pregnancies. If a routine complete blood count shows normal

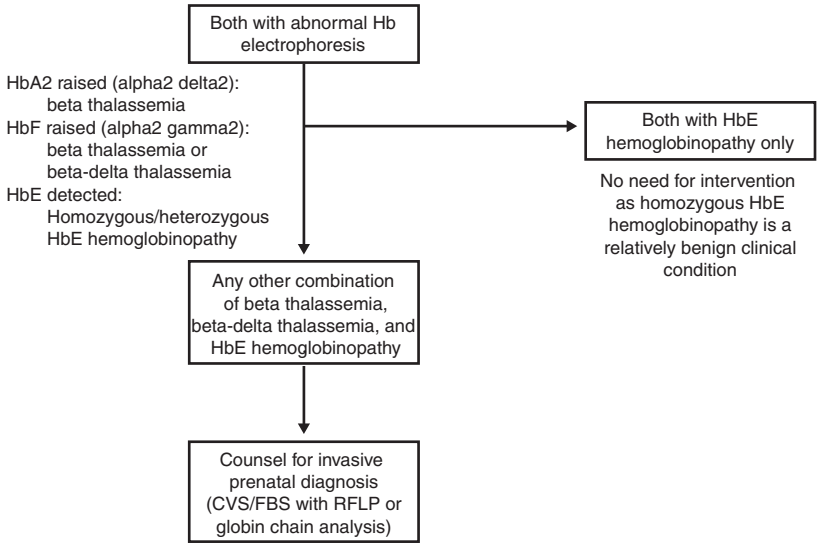

FIGURE 17.8. Management algorithm for β-thalassemia and β-chain hemoglobinopathy.

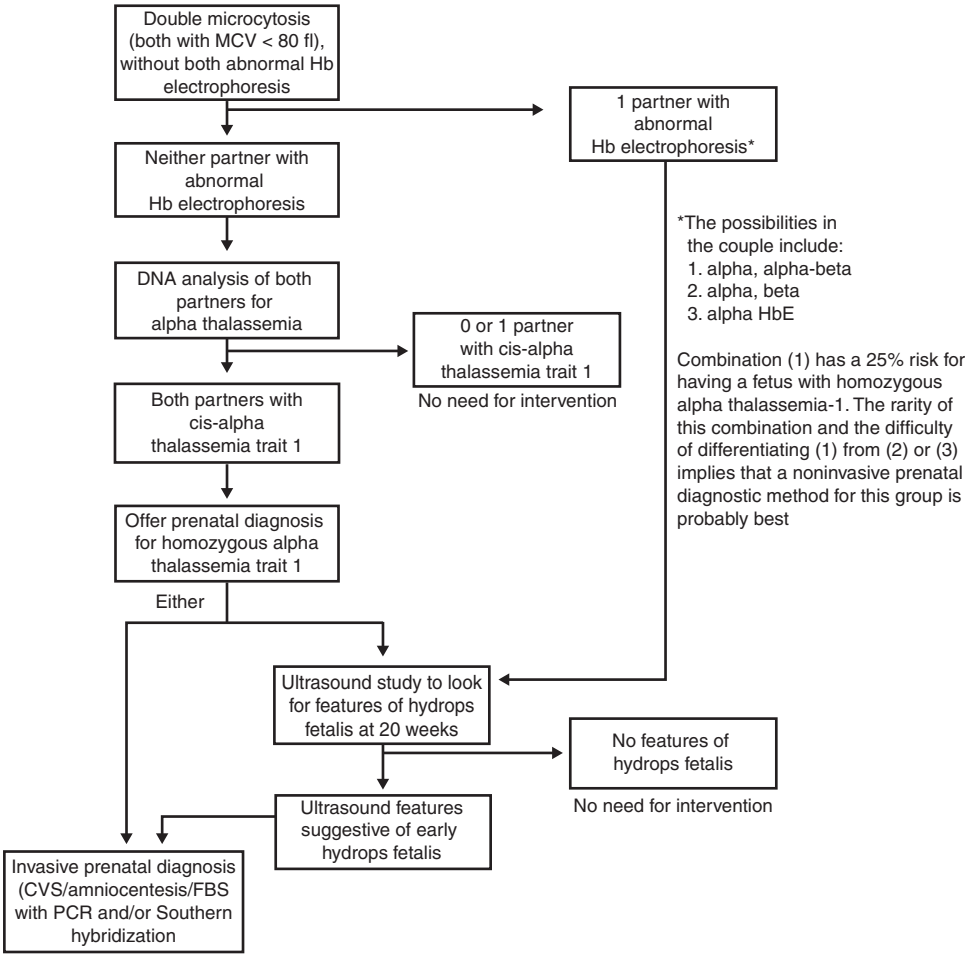

FIGURE 17.9. Management algorithm for α-thalassemia. *CVS*, chorionic villus sampling; *MCV*, mean corpuscular volume; *PCR*, polymerase chain reaction.

or low normal Hb and low MCV and the Hb electrophoresis shows normal HbA2, α-thalassemia is the presumptive diagnosis. The presence of the β-thalassemia trait itself does not exclude the simultaneous presence of the α-thalassemia trait; 7% of β-thalassemia carriers in Hong Kong were subsequently found to be double heterozygous for α-thalassemia-1 and β-thalassemia minor.[60] A DNA study should be done to determine the genotype of the partners with presumptive diagnosis of α-thalassemia-1 (Figure 17.9). Using a new method of polymerase chain reaction technique that utilizes three primers bridging the breakpoints, the antenatal diagnosis of deletional α-thalassemia of the Southeast Asian type ($--$SEA) can be achieved. There is also a rapid method for the detection of the common α-thalassemia deletions by multiplex polymerase chain reactions.[61]

The polymerase chain reaction (PCR) is a very sensitive diagnostic tool, but its specificity may be hampered because of contamination by foreign DNA, and misdiagnosis may occur.[62] Misdiagnosis of affected and normal fetuses as heterozygotes may result from maternal DNA contamination, whereas misdiagnosis of heterozygotes as normal or affected may result from a failed PCR. Although laborious and time consuming, the Southern hybridization analysis should also be done to complement the findings of the PCR to reduce the potential misdiagnoses.

Genetic Counseling

Hemoglobin (Hb) Bart's hydrops fetalis syndrome is characterized by the loss of all four α-globin gene loci ($--/--$) or homozygous α-thalassemia-1. It results from the inheritance of the genes from both parents who are *trans*-α-thalassemia trait 1 or heterozygous α-thalassemia-1 ($--/\alpha\alpha$). Clinically, the fetus is profoundly anemic, and the major component of the hemoglobin is Bart's hemoglobin (γ4), which is functionally useless for oxygen transfer. The endpoint is almost always death in utero or in the early neonatal period; the presence and amount of hemoglobin Portland determines the length of survival of the fetus.

The issue of prenatal diagnosis mainly arises when both parents are heterozygous α-thalassemia-1 ($--/\alpha\alpha$). It should thus be impressed upon the parents that there is a 25% chance of the fetus being homozygous α-thalassemia-1, which would eventually present as Bart's hydrops, and a 75% chance that

the fetus would be clinically asymptomatic (50% chance of being heterozygous α-thalassemia-1 and 25% chance of being normal genotypically). If both parents carry the $--$FIL or $--$Thai deletions, there would be no need for invasive prenatal diagnosis, as affected pregnancies invariably miscarry early in gestation.

Genetic counseling for the pregnancy at risk of producing offspring with HbH disease is fraught with more difficulties. If the parents are carriers of *cis*-α-thalassemia-1 ($--/\alpha\alpha$) and α-thalassemia-2 ($-\alpha/\alpha\alpha$), there is a 25% chance of the fetus being afflicted with HbH disease. If the parents are carriers of *cis*-α-thalassemia-1 ($--/\alpha\alpha$) and *trans*-α-thalassemia-1 ($-\alpha/-\alpha$), there is a 50% chance of the fetus being afflicted with HbH disease. If both parents are carriers of *trans*-α-thalassemia-1 ($-\alpha/-\alpha$), then there is a 100% chance that the fetus would also be trans α-thalassemia-1 ($-\alpha/-\alpha$), which is asymptomatic and of no clinical consequence. The main difficulty in counseling about HbH disease is the phenotypic heterogeneity, a consequence of its genetic heterogeneity[30]; some with HbH disease are symptomatic, whereas others are transfusion dependent. A careful assessment of the family history and counseling by the clinical geneticist is thus invaluable.

Prenatal Diagnosis of Bart's Hydrops

Presentation at Third Trimester (Beyond 24 Weeks of Gestational Age)

Clinical presentation is often that of a hydropic fetus when both parents have low MCV on blood tests. In addition to this, the mother may have problems of preterm labor and preeclampsia with gross edema in excess of that expected for the degree of hypertension.

Sonographic features are typical of fetal anemia.[63] In Bart's hydrops fetalis, findings in most (>90%) cases included hepatosplenomegaly, cardiac enlargement, edematous placenta, and fetal ascites. Common findings include oligohydramnios (82%), subcutaneous edema (75%), decreased fetal movement (74%), cord edema (63%), and enlarged umbilical vessels (62%). Pericardial or pleural effusion was seen in only 15% of cases.

When the presentation is such, chorionic villus sampling (CVS) is usually done for DNA study. Although cordocentesis can be done to obtain fetal blood for evaluation, it is associated with much higher fetal loss rates.

Presentation Before 24 Weeks

At-risk couples who present early in pregnancy should be offered choices of noninvasive or invasive prenatal diagnostic methods.

Ultrasonographic Prediction

Serial ultrasound examinations at 12 to 14 weeks and 20 to 22 weeks (including a fetal anomaly survey) can be performed to measure the cardiothoracic ratio and placental thickness and to detect other ultrasound markers. Once ultrasound findings suggestive of early hydrops fetalis are detected, invasive procedures may then be offered to confirm the diagnosis of Bart's hydrops. Although this option allows a reduction of invasive procedures for the diagnosis of Bart's hydrops (and the laboratory resources and procedural-related fetal losses that accompany them), it often delays the termination for fetuses with homozygous α-thalassemia-1.

Ultrasonographic cardiothoracic ratio measurement has been shown to be reliable at 13 to 14 weeks and at 17 to 18 weeks to predict a fetus with Bart's hydrops fetalis.[64] Using a cardiothoracic ratio cutoff level of 0.5 or more, 75% of affected pregnancies were detected at 13 to 14 weeks, and all cases were detected at 17 to 18 weeks. False-positive rates were 7% and 8%, respectively. Sensitivity and specificity of 100% using a cardiothoracic ratio greater than 0.5 for the disease have also been reported.[65] However, practical difficulties in defining the planes and boundaries of the fetal heart at 12 to 13 weeks limit the usefulness of the test at this time.

Placental thickness has been measured by ultrasound at 10 to 21 weeks gestation to detect Hb Bart's hydrops fetalis.[66] Using a cutoff of mean placental thickness (for the relevant gestational age) plus 2 SD, the sensitivity in detecting affected pregnancies increase with gestation age: 0.72 (before 12 weeks), 0.95 (after 12 weeks), and close to 1.0 (by 18 weeks). The specificity remained unchanged at 0.97.

In addition to cardiothoracic ratio and placental thickness to detect early changes of hydrops, other nonspecific changes of hydrops should also be investigated. Ultrasound markers that are found more frequently in fetuses with Bart's hydrops include increased nuchal translucency, echogenic bowel, limb reduction defects, and increased forward flow through the ductus venosus.

Nuchal translucency (NT) has been investigated as a possible ultrasound marker for fetuses with Bart's hydrops fetalis at 12 to 13 weeks. Although NT of fetuses with Bart's hydrops fetalis was grossly thickened in some fetuses at 13 weeks, as a group, the average increase is 0.3 to 0.4 mm; the overlap of NT was too extensive between cases and controls.[67] Our own experience with the measurement of NT between 10 to 14 weeks using a cutoff of NT greater than 2.5 mm for the diagnosis of fetuses with Bart's hydrops fetalis was dismal. Although the positive predictive value was high (both fetuses with NT >2.5 mm were subsequently diagnosed to have homozygous α-thalassemia-1), the negative predictive value was 73.3% (4 of the 51 with NT $\leq$2.5 mm were subsequently diagnosed to have homozygous α-thalassemia-1). This limitation precludes the use of first trimester NT measurement as an exclusive test to differentiate affected from nonaffected fetuses. Aneuploidy would also have to be considered in cases with thickened NT.

Fetal echogenic bowel has been observed in fetuses with meconium peritonitis, cystic fibrosis, aneuploidy, congenital viral infection, and intrauterine growth restriction. Lam et al.

documented the strong association of echogenic bowel in fetuses with Bart's hydrops fetalis, the finding being present in 31% of such fetuses in the first and second trimesters.[68] Fetal echogenic bowel may therefore serve as a marker for Bart's hydrops fetalis in the first and second trimesters.

Limb reduction defect is rare, but terminal transverse limb reduction defects were found in 8% of Bart's hydrops fetalis.[69] The sonographic identification of limb reduction defects thus may be a specific marker of Hb Bart's disease.[70]

The usefulness of fetal ductus venosus Doppler velocimetry to detect such affected fetuses at 12 to 13 weeks of gestation was also studied.[71] Although the affected fetuses had significantly increased forward flow velocities in the ductus venosus throughout the cardiac cycle, extensive overlap of this index between affected and unaffected fetuses precludes its use in predicting anemia at 12 to 13 weeks.

Invasive Diagnostic Methods

All invasive diagnostic methods are associated with the potential for fetal loss. However, these methods allow early diagnosis of pregnancies with Bart's hydrops fetalis and early termination of such affected pregnancies.

Chorionic villus sampling can be performed from 10 weeks gestation onward. The chorionic villus sample could be analyzed for DNA by PCR with specific probes and Southern hybridization; it can also be analyzed for fetal karyotype. CVS is associated with 1% to 2% procedure-related fetal loss rate with confined placental mosaicism in occasional cases. As CVS can be performed as early as 10 weeks gestation, it has the advantage of allowing for termination of pregnancy by suction curettage in the first trimester.

Amniocentesis is performed from 15 weeks onward; it is associated with a lower procedure-related fetal loss rate, 0.5% to 1%. DNA from amniotic cells can then be amplified with PCR and analyzed with probes and Southern hybridization.

Cordocentesis is usually performed after 18 weeks. It is associated with procedure-related fetal loss rates of 2% to 5% (up to 50% for a hydropic fetus). Fetal blood for hemoglobin level study and hemoglobin electrophoresis can confirm the diagnosis. This diagnostic approach may however be of particular value in areas where resources for molecular studies are limited. DNA-based analysis of the fetal blood can also be undertaken to define the genetic diagnosis.

Counseling for Further Management

Fetal Considerations

Termination of pregnancy is an option, even if the condition is diagnosed in the third trimester, when the fetus is diagnosed to be homozygous α-thalassemia-1. Previously all such fetuses had a uniform prognosis: death in utero or in the early neonatal period.

There have been some cases of homozygous α-thalassemia-1 who survived beyond the neonatal period with in utero fetal blood transfusion or postnatal transfusion. There is much heterogeneity in the presentation of Hb Bart's hydrops fetalis syndrome, but such a degree of prenatal compensation is very rare; survival with such prenatal rescue has been undependable, with high psychosocial consequences. Chui and Waye summarized the outcome for six such children who survived with homozygous α-thalassemia-1.[14] Most of these newborns had severe neonatal complications, and only two were found to have apparently normal development on follow-up at a few years old. Nevertheless, the successful management of β-thalassemia major that has prolonged survival and improved quality of life has given the clinician valuable experience. These patients may potentially enjoy a similar favorable outcomes from a program of regular blood transfusions with effective iron-chelating therapy.

Allogeneic bone marrow transplantation has been performed in some cases, with failures reported in most of these experiments. It may, however, offer a cure for such patients in future.[72–74]

Gene therapy offers little hope of cure in the near future. It has not been used in homozygous α-thalassemia-1 yet, and little progress has been made for its use in patients with β-thalassemia major and sickle cell disease despite 10 years of experience. Shortcomings in all gene transfer vectors and an inadequate understanding of the biological interactions of these vectors with the host remain the major difficulties in gene therapy.[75]

Such heroic measures must remain experimental. These newborns often have serious neonatal complications. Some suffer delays in cognitive and motor functions, and many have associated congenital structural abnormalities. Transverse terminal limb defects are strongly associated with Bart's hydrops. Male survivors have hypospadias: the failure of proper fusion of the urogenital folds may be secondary to the development of the hydrops or to a gene defect located at the chromosome 16p13.3 region. These gross abnormalities must be made known to the parents if such an option is deliberated. Ethical and health cost considerations remain debatable issues in such a treatment program. More benefit would be derived from resources that support an effective thalassemia screening program.

Maternal Complications

In additional to a poor prognosis for the fetus, there are maternal complications secondary to fetal hydrops.

The maternal mirror syndrome is one of the complications. It is a type of preeclampsia characterized by an extremely rapid onset and rapid deterioration, tending to happen only if the placenta is grossly edematous. Other complications include maternal anemia, pregnancy-induced hypertension, and antepartum hemorrhage. Complications such as malpresentation, prematurity, nonreassuring fetal heart rate pattern, and difficult vaginal delivery can lead to a higher cesarean deliv-

ery rate in these women. Retained placenta and postpartum hemorrhage are also more frequent in these parturients.

Anesthetic Management

The anesthesiologist may be involved in the management of a fetus with Bart's hydrops during the delivery process. In the future, when ex utero continuity of quality life is a norm with gene therapy or stem cell transplant, in utero transfusion may be an acceptable prenatal therapeutic procedure. In utero transfusion is sometimes performed with the use of a muscle relaxant for the fetus. Pancuronium, 0.3 mg, has been used, but most currently available relaxants are applicable (e.g., atracurium, *cis*-atracurium, miracurium, rocuronium) if required; this prevents the fetus from making sudden movements that may dislodge the intravascular needle from the umbilical vein or even cause laceration of the vessels. Maternal sedation is seldom needed and can be achieved with benzodiazepines (diazepam, midazolam), short-acting opioids (fentanyl, alfentanil, remifentanil), or propofol. The anesthesiologist has a role in monitoring the mother and providing the sedation (monitored anesthetic care or intravenous sedation).

If a cesarean section is necessary, it is imperative that maternal hypotension is avoided. In addition to general anesthesia, the low-dose, low-concentration combined spinal-epidural (CSE) technique as described by Rawal[76] may be useful in this situation. The author's (E. Thomas) experience with intrathecal bupivacaine 0.125% 4 mL plus fentanyl 10 to 15 μg was excellent in terms of cardiovascular stability.[77]

The patient is first transfused with 0.5 to 1 L Ringer's lactate unless she has cardiac problems or any contraindication to a fluid load. When the procedure is completed, the patient is turned to the supine position with a left uterine displacement. If the sensory level is at T10 or lower, lidocaine 0.5%, 2 to 4 mL, is introduced through the epidural catheter to extend the block. Generally only up to 4 mL 1.5% lidocaine is necessary; 0.25% bupivacaine can also be used. Ephedrine, in 5-mg increments, is used to treat maternal hypotension resulting from sympathetic blockade.

Recently, some interest in this field has been generated by Vercauteren et al. on preloading and small-dose neuraxial block,[78] lending credence to the proposal that the low-dose sequential CSE technique is suited for compromised mothers and fetuses presenting for cesarean section. A sequential CSE will be the anesthesia of choice for the foreseeable future.[79,80] Analgesia for labor can be administered via a lumber epidural/CSE or systemic opioids.

Termination of the pregnancy is the most common management for a Bart's hydrops. Depending on other problems associated with the pregnancy (e.g., placenta previa major, polyhydramnios, severe preeclampsia, postpartum hemorrhage), general or regional anesthesia could be administered for the procedure with the caveat of avoiding hypotension.

Summary

Bart's hydrops fetalis is a common disease in people of Southeast Asian origin. With the increasing migration of these populations to other parts of the world, it is important for all those involved in the care of obstetric population to be familiar with the management of such cases. One must pay particular attention to the blood indices available on the complete blood counts that are performed routinely in all obstetric cases. Choices must be made available to at-risk pregnancies. Timely termination of affected pregnancies would reduce the perinatal mortality and maternal morbidity associated with Bart's hydrops fetalis. Affected pregnancies that progresses to the third trimester may be associated with maternal complications such as preeclampsia-like disease, anemia, and postpartum hemorrhage. With further research into in utero therapy, bone marrow transplantation, stem cell transplant, and gene therapy, in the future, fetuses with Bart's hydrops may survive with a good outcome.

References

1. Fleischer AC, Killam AP, Boehm FH, et al. Hydrops fetalis: sonographic evaluation and clinical implications. Radiology 1981;141(1):163–168.
2. Poeschmann RP, Verheijen RH, Van Dongen PW. Differential diagnosis and causes of non-immunological hydrops fetalis: a review. Obstet Gynecol Surv 1991;46:223–231.
3. Macafee CA, Fortune DW, Beischer NA. Non-immunological hydrops fetalis. J Obstet Gynaecol Br Commonw 1970;77:226–237.
4. Wysowski DK, Flynt JW Jr, Goldberg MF, Connell FA. Rh hemolytic disease. Epidemiologic surveillance in the United States, 1968 to 1975. JAMA 1979;242(13):1376–1379.
5. Andersen HM, Drew JH, Beischer NA, et al. Non-immune hydrops fetalis: changing contribution to perinatal mortality. Br J Obstet Gynaecol 1983;90(7):636–639.
6. Wy Ca, Sajous CH, Loberiza F, Weiss MG. Outcome of infants with a diagnosis of hydrops fetalis in the 1990s. Am J Perinatol 1999;16(10):561–567.
7. Yang YH, Teng RJ, Tang JR, et al. Etiology and outcome of hydrops fetalis. J Formos Med Assoc 1998;97(1):16–20.
8. Anandakumar C, Biswas A, Wong YC, et al. Management of non-immune hydrops: 8 years' experience. Ultrasound Obstet Gynecol 1996;8(3):196–200.
9. Thumasathit B, Nondasuta A, Silpisornkosol S, et al. Hydrops fetalis associated with Bart's hemoglobin in northern Thailand. J Pediatr 1978;73(1):132–138.
10. Liang ST, Wong VC, So WW, et al. Homozygous alpha-thalassaemia: clinical presentation, diagnosis and management. A review of 46 cases. Br J Obstet Gynaecol 1985;92(7):680–684.
11. Heer N, Choy J, Vichinsky EP. The social impact of migration on disease. Cooley's anemia, thalassemia, and new Asian immigrants. Ann NY Acad Sci 1998;850:509–511.
12. Petrou M, Brugiatelli M, Old J, et al. Alpha thalassaemia hydrops fetalis in the UK: the importance of screening pregnant women of Chinese, other South East Asian and Mediterranean extraction for alpha thalassaemia trait. Br J Obstet Gynaecol 1992;99(12):985–989.
13. Prior JF, Jury KL, Erber WN. Alpha thalassaemia in western Australia. Br J Haematol 1999;105(suppl 1):81.
14. Chui DHK, Waye JS. Hydrops fetalis caused by alpha thalassaemia: an emerging health care problem. Blood 1998;91(7):2213–2222.

15. Tongsong T, Wanapirak C, Sirivatanapa P, et al. Prenatal eradication of Hb Bart's hydrops fetalis. J Reprod Med 2001;46(1):18–22.
16. Lie-Injo LE. Alpha-chain thalassemia and hydrops fetalis in Malaya: report of five cases. Blood 1962;20:581.
17. Higgs DR, Vickers MA, Wilkie AO, et al. A review of the molecular genetics of the human alpha-globin gene cluster. Blood 1989;73(5): 1081–1084.
18. Xu XM, Cai XH, Li J. Molecular screening and prenatal diagnosis of the deletional alpha-thalassemia by polymerase chain reaction amplification. Zhonghua Yi Xue Za Zhi 1994;74(8):495–497.
19. Lemmens-Zygulska M, Eigel A, Helbig B, et al. Prevalence of alpha-thalassaemias in northern Thailand. Hum Genet 1996;98(3):345–347.
20. Ko TM, Hwa HL, Liu CW, et al. Prevalence study and molecular characterization of alpha-thalassemia in Filipinos. Ann Hematol 1999;78(8): 355–357.
21. Desai S, Colah R, Gupte S, Mohanty D. Is cellulose acetate electrophoresis a suitable technique for detection of Hb Bart's at birth? Hum Hered 1997;47(4):181–184.
22. Galanello R, Sanna MA, Maccioni L, et al. Fetal hydrops in Sardinia: implications for genetic counselling. Clin Genet 1990;38(5):327–331.
23. Mockenhaupt FP, Falusi AG, May J, et al. The contribution of alpha$^+$-thalassaemia to anaemia in a Nigerian population exposed to intense malaria transmission. Trop Med Int Health 1999;4(4):302–307.
24. Pressley L, Higgs DR, Clegg JB, et al. A new genetic basis for hemoglobin-H disease. N Engl J Med 1980;303(24):1383–1388.
25. El-Kalla S, Baysal E. Alpha-thalassemia in the United Arab Emirates. Acta Haematol 1998;100(1):49–53.
26. Tan JA, Tay JS, Soemantri A, et al. Deletional types of alpha-thalassaemia in Central Java. Hum Hered 1992;42(5):289–292.
27. Tamary H, Klinger G, Shalmon L, et al. The diverse molecular basis and mild clinical picture of HbH disease in Israel. Ann NY Acad Sci 1998;850:432–435.
28. Galanello R, Aru B, Dessi C, et al. HbH disease in Sardinia: molecular, hematological and clinical aspects. Acta Haematol 1992;88(1):1–6.
29. Martinez G, Ferreira R, Hernandez A, et al. Molecular characterization of HbH disease in the Cuban population. Hum Genet 1986;72(4): 318–319.
30. Chen FE, Ooi C, Ha SY, et al. Genetic and clinical features of hemoglobin H disease in Chinese patients. N Engl J Med 2000;343(8):544–550.
31. Yang CP, Hung IJ. Hematological data analysis in children with thalassemia trait or hemoglobin H disease in Taiwan. J Formos Med Assoc 1991;90(6):591–597.
32. Bunyaratvej A, Butthep P, Fucharoen S, Saw D. Erythrocyte volume and haemoglobin concentration in haemoglobin H disease: discrimination between the two genotypes. Acta Haematol 1992;87(1-2):1–5.
33. Wongchanchailert M, Laosombat V, Maipang M. Hemoglobin H disease in children. J Med Assoc Thail 1992;75(11):611–618.
34. Basu D, Singh T, Chopra K, et al. Hemoglobin H disease: a report of five cases. Indian Pediatr 1993;30(6):791–793.
35. Weatherall DJ. Thalassemia in the next millennium. Keynote address. Ann NY Acad Sci 1998;850:1–9.
36. Ko TM, Xu X. Molecular study and prenatal diagnosis of alpha- and beta-thalassemias in Chinese. J Formos Med Assoc 1998;97(1):5–15.
37. Merritt D, Jones RT, Head C, et al. Hb Seal Rock [(alpha 2) 142 term → Glu, codon 142 TAA → GAA]: an extended alpha chain variant associated with anemia, microcytosis, and alpha-thalassemia-2 (−3.7 kb). Hemoglobin 1997;21(4):331–344.
38. Jiang NH, Liang S, Wen XJ, et al. Hb Westmead: an alpha 2-globin gene mutation detected by polymerase chain reaction and Stu I cleavage. Hemoglobin 1991;15(4):291–295.
39. Wenning MR, Kimura EM, Costa FF, et al. Alpha-globin genes: thalassemic and structural alterations in a Brazilian population. Braz J Med Biol Res 2000;33(9):1041–1045.
40. Lau YL, Chan LC, Chan YY, et al. Prevalence and genotypes of alpha and beta thalassaemia carriers in Hong Kong: implications for population screening. N Engl J Med 1997;336:1298–1301.
41. Hsieh FJ, Ko TM, Chen HY. Hydrops fetalis caused by severe alpha thalassaemia. Early Hum Dev 1992;29(1–3):233–236.
42. Modell B, ed. Guidelines for the Control of Haemoglobin Disorders. Geneva: World Health Organization Hereditary Diseases Programme, 1994.
43. Kitsirisakul B, Steger HF, Sanguansermsri T. Frequency of alpha-thalassemia-1 of the Southeast Asian-type among pregnant women in northern Thailand determined by PCR technique. Southeast Asian J Trop Med Public Health 1996;27(2):362–363.
44. Fucharoen S, Winichagoon P. Haemoglobinopathies in Southeast Asia: molecular biology and clinical medicine. Hemoglobin 1997;21(4):299–319.
45. Hofgartner WT, West Keefe SF, Tait JF. Frequency of deletional alpha-thalassemia genotypes in a predominantly Asian-American population. Am J Clin Pathol 1997;107(5):576–581.
46. Taylor JM, Dozy A, Kan YW, et al. Genetic lesion in homozygous alpha thalassaemia (hydrops fetalis). Nature (Lond) 1974;251(5474):392–393.
47. Ottolenghi S, Lanyon WG, Paul J, et al. The severe form of alpha thalassaemia is caused by a hemoglobin gene deletion. Nature (Lond) 1974;251(5474):389–392.
48. Fischel-Ghodsian N, Vickers MA, Seip M, et al. Characterization of two deletions that remove the entire human zeta-alpha globin gene complex (−−Thai and −−FIL). Br J Haematol 1998;70(2):233–238.
49. Sophocleous T, Higgs DR, Aldridge B, et al. The molecular basis for the haemoglobin Bart's hydrops fetalis syndrome in Cyprus. Br J Haematol 1981;47(1):153–156.
50. Kattamis C, Metaxotou-Mavromati A, Tsiarta E, et al. Haemoglobin Bart's hydrops syndrome in Greece. Br Med J 1980;281(6235):268–270.
51. Gurgey A, Altay C, Beksac MS, et al. Hydrops fetalis due to homozygosity for alpha-thalassemia-1, -(alpha)-20.5 kb: the first observation in a Turkish family. Acta Haematol 1989;81(3):169–171.
52. Olivieri NF. Fetal erythropoiesis and the diagnosis and treatment of hemoglobin disorders in the fetus and child. Semin Perinatol 1997;21(1): 63–69.
53. Yong KN, Wadsworth D, Langlois S, et al. Thalassemia carrier screening and prenatal diagnosis among the British Columbia (Canada) population of Chinese descent. Clin Genet 1999;55(1):20–25.
54. Modell B, Petrou M, Layton M, et al. Audit of prenatal diagnosis for haemoglobin disorders in the United Kingdom: the first 20 years. BMJ 1997;315(7111):779–784.
55. Guideline. The laboratory diagnosis of haemoglobinopathies. Br J Haematol 1998;101(4):783–792.
56. Mach-Pascual S, Darbellay R, Pilotto PA, Beris P. Investigation of microcytosis: a comprehensive approach. Eur J Haematol 1996;57(1):54–61.
57. Yeo GS, Tan KH, Liu TC. Screening for beta thalassaemia and HbE traits with the mean red cell volume in pregnant women. Ann Acad Med Singapore 1994;23(3):363–366.
58. Sin SY, Ghosh A, Tang LC, Chan V. Ten years' experience of antenatal mean corpuscular volume screening and prenatal diagnosis for thalassaemias in Hong Kong. J Obstet Gynaecol Res 2000;26(3):203–208.
59. Skogerboe KJ, West SF, Smith C, et al. Screening for alpha-thalassemia. Correlation of hemoglobin H inclusion bodies with DNA-determined genotype. Arch Pathol Lab Med 1992;116(10):1012–1018.
60. Lam YH, Ghosh A, Tang MH, Chan V. The risk of alpha-thalassaemia in offspring of beta-thalassaemia carriers in Hong Kong. Prenatal Diagn 1997;17(8):733–736.
61. Liu YT, Old JM, Miles K, et al. Rapid detection of alpha-thalassaemia deletions and alpha-globin gene triplication by multiplex polymerase chain reactions. Br J Haematol 2000;108(2):295–299.
62. Ko TM, Tseng LH, Hwa HL, et al. Misdiagnosis of homozygous alpha-thalassaemia 1 may occur if polymerase chain reaction alone is used in prenatal diagnosis. Prenatal Diagn 1997;17(6):505–509.
63. Tongsong T, Wanapirak C, Srisomboon J, et al. Antenatal sonographic features of 100 alpha-thalassemia hydrops fetalis fetuses. J Clin Ultrasound 1996;24(2):73–77.
64. Lam YH, Ghosh A, Tang MH, et al. Early ultrasound prediction of preg-

nancies affected by homozygous alpha-thalassaemia-1. Prenatal Diagn 1997;17(4):327–332.
65. Lam YH, Tang MH, Lee CP, Tse HY. Prenatal ultrasonographic prediction of homozygous type 1 alpha-thalassemia at 12 to 13 weeks of gestation. Am J Obstet Gynecol 1999;180(1 pt 1):148–150.
66. Ghosh A, Tang MH, Lam YH, et al. Ultrasound measurement of placental thickness to detect pregnancies affected by homozygous alpha-thalassaemia-1. Lancet 1994;344(8928):988–989.
67. Lam YH, Tang MH, Lee CP, Tse HY. Nuchal translucency in fetuses affected by homozygous alpha-thalassemia-1 at 12–13 weeks of gestation. Ultrasound Obstet Gynecol 1999;13(4):238–240.
68. Lam YH, Tang MH, Lee CP, Tse HY. Echogenic bowel in fetuses with homozygous alpha-thalassemia-1 in the first and second trimesters. Ultrasound Obstet Gynecol 1999;14(3):180–182.
69. Lam YH, Tang MH. Limb reduction defects as the sonographic manifestation of hemoglobin Bart's disease at 10 weeks of gestation. Ultrasound Obstet Gynecol 2000;16(6):587–589.
70. Lam YH, Tang MH. Sonographic diagnosis of limb reduction defects in a fetus with haemoglobin Bart's disease at 12 weeks of gestation. Prenatal Diagn 1999;19(10):983–985.
71. Lam YH, Tang MH, Tse HY. Ductus venosus Doppler study in fetuses with homozygous alpha-thalassemia-1 at 12 to 13 weeks of gestation. Ultrasound Obstet Gynecol 2001;17(1):30–33.
72. Diukman R, Golbus MS. In utero stem cell therapy. J Reprod Med 1992;37(6):515–520.
73. Westgren M, Ringden O, Eik-Nes S, et al. Lack of evidence of permanent engraftment after in utero fetal stem cell transplantation in congenital hemoglobinopathies. Transplantation 1996;61(8):1176–1179.
74. Eddleman K. In utero transfusion and transplantation in alpha thalassemia. In: Migliaccio AR (ed) Stem Cell Therapy of Inherited Disorders. Rome, 1996.
75. Barbour V. The balance of risk and benefit in gene-therapy trials. Lancet 2000;355(9201):384.
76. Rawal N. Single segment combined subarachnoid and epidural block for caesarean section. Can Anaesth Soc J 1986;32(2):254–255.
77. Tay DH, Tay SM, Thomas E. High-volume spinal anaesthesia. A dose-response study of bupivacaine 0.125%. Anaesth Intensive Care 1992;20(4):443–447.
78. Vercauteren MP, Coppejans HC, Hoffmann VH, et al. Prevention of hypotension by a single 5-mg dose of ephedrine during small-dose spinal anesthesia in prehydrated cesarean delivery patients. Anesth Analg 2000; 90(2):324–327.
79. Crowhurst JA, Birnbach DJ. Small-dose neuraxial block: heading toward the new millennium. Anesth Analg 2000;90(2):241–242.
80. Birnbach DJ. Obstetric anesthesiology in the new millennium. Anesth Analg 2000;90(5):1241–1243.

18
Autoimmune Disease

Miriam Harnett and Thomas McElrath

Autoimmune diseases are a group of disorders whose expression is influenced by multiple genes and environmental factors and is also affected by age, gender, and reproductive status. Women of childbearing age have the highest incidence of several autoimmune disorders: the female-to-male ratios are about 3 to 4 to 1 in rheumatoid arthritis (RA) and 9 to 1 in systemic lupus erythematous (SLE). This clinical observation suggests that hormones are involved in the pathogenesis of these various autoimmune diseases, although mechanisms are complex. Because pregnancy is associated with a dramatic physiologic increase in estrogen and other steroids, there is the potential for pregnancy to affect the course of autoimmune diseases. Indeed, some autoimmune conditions, such as RA, often are improved during pregnancy, and others, such as polyarteritis nodosa, often worsen during pregnancy. The effects of pregnancy on autoimmune diseases have been attributed to a relative state of enhanced hormonal immunity and weakened cellular immunity.

This chapter discusses the medical, obstetric, and anesthetic management of the various autoimmune disorders that can occur during pregnancy.

Rheumatoid Arthritis

Etiology

Rheumatoid arthritis is an autoimmune disorder of unknown etiology. The autoantibody rheumatoid factor can be detected in 80% to 90% of patients. RA is relatively common, occurring in 1% to 2% of the population, and implicating 1 in 1000 to 1 in 2000 pregnancies. It occurs three times more commonly in women than in men, and the incidence in women increases with advancing age. Specific subtypes of HLA-DR4 are increased among RA patients and also some subtypes of DR1 and DR14.[1]

Pathophysiology

Rheumatoid arthritis is a systemic, chronic inflammatory disorder characterized by symmetric polyarthritis. The commonly involved joints include the metacarpophalangeal joints, the proximal interphalangeal joints, and the wrists. Forty-five percent of seropositive patients have cervical spine involvement; these patients with cervical spine involvement most commonly complain of a limited range of motion secondary to pain. Extraarticular manifestations including vasculitis, lung disease (systemic granulomas may be found in the lungs and can occasionally cavitate, resulting in a pneumothorax or bronchopleural fistuala), pericarditis, peripheral neuropathies, and subcutaneous nodules occur in 20% of patients with RA. The most serious complication of RA is coronary vasculitis, caused by thrombosis of the small arteries.

Effect of Pregnancy on Rheumatoid Arthritis

In 1938, Hench reported relief of symptoms in 90% of patients during pregnancy.[2] Since then, other retrospective studies that reported 345 pregnancies indicated that 75% of patients experienced improvement in their arthritis.[3] The ability to predict pregnancy experience has not been found to be related to the presence or absence of rheumatoid factor, the duration of the disease, or the degree of disability. However, there is agreement that if a patient undergoes symptomatic improvement during one pregnancy, this is likely to happen again in further pregnancies. Recurrence of symptoms has been found in 36% of parturients during the first postpartum month and in up to 98% of pregnant women by the fourth postpartum month.[4] Pregnancy has not been found to negatively influence the prognosis for RA, with no difference being found in functional capacity or disease activity.

Effect of Rheumatoid Arthritis on Pregnancy

There is no indication for adverse effects of RA on pregnancy, with no increase in premature labor, although intrauterine growth restriction (IUGR) has been associated with vasculitis.

Medications

Patients with active RA are likely to be taking nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination with disease-modifying drugs (DMARD). Salicylates, indomethacin, and the newer NSAIDs have not been shown to be teratogenic in humans. Although prophylactic cessation is not necessary,[5,6] the possibility of abnormal amniotic fluid dynamics and compromised fetal renal perfusion associated with prolonged NSAID use warrants close observation with administration during pregnancy. Additionally, NSAIDs may result in reversible renal impairment in premature infants and have also been implicated in necrotizing enterocolitis.[7] Aspirin is prescribed by some physicians for symptomatic relief during pregnancy, but it should be discontinued in the third trimester because of the increased risk of central nervous system (CNS) hemorrhage and the possibility of closure of the ductus arteriosus.[8,9] There are insufficient data regarding the prophylactic withdrawal of DMARD. Transplacental passage of gold salts is limited because of the high protein binding, but it has been suggested that this therapy should be administered on the first day of the menstrual cycle to withdraw the drug as soon as the pregnancy is recognized.

There have been case reports linking antimalarials to ear and eye damage; however, overall antimalarials are generally considered safe during pregnancy. Penicillamine has been used in pregnancy, but there are case reports of fetal connective tissue abnormalities linked to its use. Sulphsalazine and azathioprine have been used without problems and can be continued during pregnancy and breastfeeding.[10] Cytostatic drugs such as methotrexate, cyclophosphamide, and chlorambucil should be withdrawn at least 3 months before conception.

There is no evidence in humans that corticosteroids lead to any fetal malformations. In fact, the majority of corticosteroids are metabolized by the placenta with comparatively little transfer into the fetal compartment. For parturients taking corticosteroids during pregnancy, stress doses should be administered during labor and delivery.

Obstetric Management

No association has been found between RA and adverse pregnancy outcome, although there is some evidence to suggest that the fetuses of parturients with vasculitis have IUGR.[11] Vaginal delivery may be compromised in some cases by hip involvement or previous hip joint replacement, but this consideration should not preclude normal vaginal delivery so long as adequate care and attention to positioning is maintained during the second stage of labor.

Anesthetic Management

A comprehensive history and physical examination is mandatory predelivery in parturients with RA. Examination of the airway is of vital importance. The following joints, which are involved in airway management, may be involved: the temporomandibular joint (TMJ), the cricoarytenoid joint, and the cervical spine. The TMJ may be ankylosed, so that mouth opening is inadequate and intubation thus is difficult. Cervical spine involvement is common and may result in severe flexion deformity of the neck and atlantoaxial instability, with possible spinal cord damage with neck extension.[12] Other joint involvement of particular interest to the anesthesiologist includes the hip, knee, and lumbar intervertebral joints. Limitation in the movement of these joints may render proper positioning for regional techniques difficult.

Examination of the heart and lungs should focus on evidence of kyphosis of the spine and resulting restrictive lung disease. Predelivery pulmonary function tests may indicate restrictive lung disease with a markedly reduced functional residual capacity; this may result in reduced oxygen reserve and a consequent inability to push during the second stage of labor. Care must be taken in such cases to avoid a high-level regional block that would further compromise the parturient woman's respiratory reserve. Cardiac disease may be detected by the presence of a pericardial effusion, valvular or conduction defects, or cardiomyopathy. All peripheral nerve involvement should be well documented before either general or regional anesthesia, particularly in parturients with Felty's and Sjogren's syndromes.

The parturient's medication may dictate the choice of anesthetic. Bleeding time is no longer considered the test of choice for measuring platelet function in pregnant women on aspirin therapy. More recently, thromboelastography (TEG) has been used. Parturients on steroid therapy must receive stress dose steroids. These women on long-term steroids may have osteoporosis and thus require very careful positioning during labor and delivery. Adverse drug reactions to gold therapy include extensive skin eruptions and oral ulcers, renal damage, and aplastic anemia. Therefore these women need comprehensive examination of their mouth and skin and a complete blood count (CBC), blood urea nitrogen (BUN), and creatinine.[13]

The choice of anesthetic depends on the degree of multiorgan involvement. Epidural analgesia and anesthesia appears to be a good choice; however, limitation of joint movement at the hips and knees may make epidural placement difficult. In parturients with severe rheumatoid disease, spinal anesthesia is probably best avoided due to unpredictable spread of anesthesia. However, early recognition of these parturients and careful planning of their anesthetic management should allow an epidural to be placed for labor and consequent cesarean delivery if necessary. Pregnant women with extensive cardiorespiratory involvement may require invasive monitoring, especially if regional anesthesia is planned. Parturients who have an epidural or spinal for anesthesia will benefit from neuraxial opoids for postoperative pain relief. Those who do not have a regional technique for anesthesia will benefit from patient-controlled intravenous narcotic pain relief. However, it is important to bear in mind the potentially compromised respiratory function in those with severe disease.

Systemic Lupus Erythematous

Etiology

Systemic lupus erythematosus (SLE) is a chronic, inflammatory multiorgan autoimmune disorder characterized by periods of remissions and relapses. SLE is nine to ten times more common in females than males and most commonly affects those in the age group between 15 and 50 years, with a peak incidence at 30 years of age. Its prevalence is 1 in 700 women, and it is two to four times more common in the African-American and Hispanic populations.[14] The most clinically relevant IgG autoantibodies are antinuclear antibodies (ANA), particularly anti-dsDNA, which is present in 80% to 90% of untreated patients with SLE and is diagnostic of the disease. Other clinically relevant autoantibodies include antibodies to RNA–protein conjugates such as Ro/SSA, La/SSB, nuclear riboprotein (nRNP), and Sm as well as antiphospholipid antibodies.[15]

Pathophysiology

Antigen–antibody complexes are formed with a resulting secondary inflammatory response. The combination of the immune complexes and the secondary inflammatory response within the glomerulus leads to irreversible renal damage. Deposits also occur within the skin and other endothelial surfaces. During pregnancy, the most common clinical manifestations include arthralgias, fever, skin lesions and renal disease. The classic malar rash affects fewer than half of patients; however, most have skin lesions at some stage during the course of the disease. More than 90% of patients have joint symptoms, and these symptoms are often the presenting complaint.[16]

Effect of Pregnancy on Systemic Lupus Erythematosus

Studies of the incidence of flare-ups during pregnancy have given conflicting results.[17] Lupus flares during pregnancy do not seem to be exceedingly more serious than those occurring in nonpregnant patients. Flares may occur in any trimester and during the postpartum period. SLE pregnancies should be regarded as high-risk pregnancies, and close monitoring for disease activity is mandatory throughout the pregnancy and puerperieum.

Most pregnant women with SLE do not have severe renal involvement, as renal disease impairs fertility. However, if preexisting renal disease is present, pregnancy may cause permanent renal dysfunction in up to 7% of women.[18] Renal flares may be difficult to differentiate from preeclampsia as there is an increased incidence of preeclampsia in parturients with SLE, and both conditions may present with hypertension, proteinuria, and edema. However, differentiation is possible, as most parturients with a lupus flare during pregnancy tend not to concurrently increase their blood pressure. Furthermore, renal lupus flares will respond to increase in doses of prednisone whereas the renal consequences of preeclampsia do not moderate with steroid exposure. Other useful data include rising levels of anti-dsDNA and typical SLE symptoms such as rash, mucosal ulcers, urinary casts, and polyarthritis. A definite diagnosis of lupus nephritis can be made by renal biopsy, which, although it has been reported during pregnancy, is generally not a first-line diagnostic modality given pregnancy-associated increases in renal perfusion and potential for biopsy-related hematoma formation. Alternative pathway complement activation products C4a, C5b, Ba, and Bb, and C1s–C1 inhibitor complexes are abnormal in active lupus nephritis but not in preeclampsia.[15]

The Effect of Systemic Lupus Erythematosus on Pregnancy

The best predictor of outcome in SLE pregnancies is the absence of disease activity in the 6 to 12 months before conception even if severe renal disease has previously been present.[19] Retrospective studies indicate an overall increased rate of pregnancy loss in patients with SLE.[20,21] The most important factor associated with SLE and pregnancy loss is the presence of antiphospholipid antibodies, but other factors include renal disease, disease activity, and a history of previous pregnancy loss.[22–24] IUGR has been reported in up to 32% of parturients with SLE.[25] Antiphospholipid antibody, renal disease, and preeclampsia are risk factors for IUGR.

Preterm delivery occurs in up to 50% of SLE pregnancies,[26] the most common causes being preeclampsia, fetal compromise, and preterm premature rupture of membranes. The risk factors for preterm delivery are disease activity, chronic hypertension, and antiphospholipid antibody.[24] Transplacental passage of anti-Ro and anti-La antibodies can result in neonatal lupus that is characterized by a more benign transient cutaneous lupus and more morbidly severe congenital heart block.[27] In most instances, the mother is asymptomatic. Treatment of the heart block includes maternal administration of steroids and digitalis, early delivery, and neonatal pacing.

Medications

High doses of both aspirin and NSAIDs should be avoided in the last weeks of pregnancy because of the effects on platelets and physiologic changes such as closure of the ductus.[5–8] Corticosteroids and hydroxychloroquine have been used without associated congenital abnormalities. For parturients in whom immunosuppression is absolutely necessary during pregnancy, azathioprine and cyclosporin A have been used safely under close obstetric supervision.[10] Cyclophosphamide is teratogenic and should be avoided.

Obstetric Management

Because of the increased risk of preterm delivery and IUGR, accurate dating by ultrasound should be obtained at the first

prenatal visit. Maternal blood should be checked for antiphospholipid antibodies, as the presence of such antibodies confers a much higher risk of fetal loss. Baseline platelet count, creatinine clearance, and 24-h urinary protein should also be obtained. The value of complement levels is controversial.[28] In the presence of anti-Ro antibody, fetal echocardiography should be performed in the second trimester. Care must be taken to monitor for preeclampsia, and weekly nonstress tests should be performed after 32 weeks gestation. There are reports of up to 50% of parturients having cesarean delivery, but it should be reserved for obstetric indications.[29]

Anesthetic Management

The anesthetic plan depends on the severity of the disease and the extent of organ involvement. A comprehensive examination of the cardiorespiratory system is mandatory. The most common cardiac manifestation is pericarditis, which may present as acute heart failure. Cardiomyopathy may result from direct muscle involvement or may be secondary to chronic hypertension, coronary artery disease, or uremia, all of which are end results of SLE. On examination, evidence of a friction rub, murmurs, or third heart sound should be sought. The echocardiogram may show evidence of valvular thickening, vegetations, regurgitation and stenosis. Parturients with valvular disease should receive antibiotic prophylaxis. Evidence should be sought of pleural effusion, pulmonary infarcts, pulmonary hypertension, and pulmonary vasculitis by seeking a history of hemoptysis and shortness of breath and the presence of rales and pleural rub on physical examination. Pulmonary function testing usually reveals a restrictive pattern. The parturient with severe renal disease is likely to be on dialysis. Other system involvement includes the peripheral nervous system, presenting as peripheral neuropathies and foot drop, and the central nervous system, with parturients having a history of seizures and psychiatric disorders such as depression, mania, and schizophrenia. Peripheral neuropathies should be well documented before general or regional anesthesia. Evidence of hematologic disorders should be sought, including anemia, thrombocytopenia, and coagulopathy. 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 or true autoantibodies against specific coagulant factors. True coagulation factor autoantibodies may result in a significant bleeding diathesis, which would contraindicate a regional anesthetic. Because of the presence of antibodies, blood crossmatching may be difficult. SLE rarely involves the cervical spine. Parturients receiving steroids should receive stress doses.

Antiphospholipid Syndrome

Etiology

Antiphospholipid syndrome (APS) is defined by recurrent miscarriage and/or late pregnancy loss with the presence of antiphospholipid antibodies (aPL). Defective embryonic implantation is believed to be the underlying pathologic change associated with both APS-mediated pregnancy loss as well as preeclampsia and IUGR. The clinical criteria for obstetric diagnosis of APS are listed in Box 18.1.[30]

Box 18.1. Clinical criteria for diagnosis of antiphospholipid syndrome (APS).

1. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
2. One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency
3. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosome causes excluded

Pathophysiology

Antiphospholipid syndrome affects the process of implantation. Several aPL have been described, but the two most commonly associated with problems in pregnancy are lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). These antibodies have been associated with recurrent pregnancy loss, thromboembolism and thrombocytopenia, and APS. LA and aCL are present in 34% and 44%, respectively, of patients with SLE; however, only 35% of patients with LA have SLE.[31] APS is considered a process distinct from SLE. Placental pathology in these cases has shown placental infarction, necrosis, and thrombosis of the placental and decidual vessels. The mechanism behind these antibodies causing thrombosis is unknown, but theories include decreased plasminogen activity, increased platelet aggregation, inhibition of prostacyclin and protein C, and increased factor VIII activity.[32,33]

Effect of Pregnancy on Antiphospholipid Syndrome

The most serious medical complication in APS is thrombosis; 70% of these are venous in origin, but arterial thromboses also occur. Most thromboses occur in the lower extremities, but cerebral infarction, pulmonary embolism, and myocardial infarction also occur. Thromboses in unusual sites should prompt the suspicion of APS.[34] Up to 69% of patients with APS have been reported to have recurrent thromboses in a relatively short follow-up period.[35] Autoimmune thrombocytopenia and autoimmune anemia have been linked to APS. APS has been linked to severe illness in the postpartum period consisting of fever and cardiopulmonary disease. Multiple thromboses, renal insufficiency, and pulmonary hypertension can also occur and may be fatal.

Obstetric Management

After documentation of APS in a women with recurrent fetal loss (having excluded such causes as anatomic, chromosomal, and hormonal), there are several options that can be considered including aspirin, steroids, heparin, and intravenous gamma globulin (γ-globulin). Steroids, however, are less likely to be used, as they are associated with the development of gestational diabetes, hypertension, and prematurity.[36,37] Presently, consideration should be give to the use of low-dose aspirin and/or heparin, neither of which is associated with teratogenesis. The long-term use of heparin during pregnancy was previously thought to be associated with a significant decrease in maternal bone loss, but this concern has subsequently been refuted. Two randomized, prospective studies have reported a live birth rate of 70% using the combination of aspirin and heparin.[38,39] Aspirin should be started as soon as there is a positive pregnancy test, and heparin as soon as the pregnancy has been proved to be intrauterine. Low molecular weight (LWM) heparin is used at our instition. As with unfractionated heparin, the time to peak and half-life are shortened with LMW heparin in pregnancy, and higher doses and twice-daily dosing are needed.

Anesthetic Management

The parturient should be evaluated for coexisting autoimmune disorders. One of the chief areas of concern is the provision of a regional anesthetic in a parturient on heparin. Aspirin should be discontinued at 36 weeks gestation to prevent closure of the ductus. In our hospital, it is policy to electively change from LMW heparin to unfractionated heparin at 36 weeks gestation; this provides better control over the timing of a regional anesthetic. We check coagulation parameters and advise holding the morning dose of heparin when induction or cesarean section is planned. Ideally, the parturient should have had her last dose of LMW heparin at least 24 h before a regional technique. In the case of a parturient presenting in labor and requesting a regional anesthetic while still taking LMW heparin, we perform a Hep test (anti-factor Xa activity). If this value lies in the normal range, we proceed with the regional anesthetic. If the Hep test lies beyond the normal range, we do not perform a regional anesthetic until it normalizes but instead prescribe a patient-controlled analgesic (PCA) combination of fentanyl and ketamine.

Myasthenia Gravis

Etiology

Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission. It is characterized by muscle weakness and fatigability following repetitive activity. The most common clinical signs and symptoms include difficulty in speaking, ptosis, diplopia, dysphagia, and occasionally respiratory distress. Remissions and exacerbations are unpredictable. The prevalence of MG is 1 in 10,000 to 1 in 50,000. MG occurs twice as commonly in females as males, with onset occurring frequently in the third decade. Women with MG have a higher incidence of other autoimmune diseases such as RA, autoimmune thyroiditis, and SLE. The transplacental passage of autoimmune antibodies leads to neonatal MG in 10% to 20% of neonates born to mothers with MG.[40,41]

Pathophysiology

Serum autoantibodies against acetylcholine receptors at the motor endplate occur in 85% of MG patients. There is no definite correlation between antibody level and disease activity, and 10% to 20% of patients with clinical evidence of MG have no evidence of antibodies. Disease activity is usually well controlled on acetylcholinesterase inhibitors.

Effect of Pregnancy on Myasthenia Gravis

Plauche reported that the clinical course of MG remained stable in 32% of pregnancies, improved in 29% of pregnancies, and was exacerbated in 41% of pregnancies.[40] No correlation has been found between MG severity before conception and exacerbation of symptoms during pregnancy, and the clinical course of the disease during one pregnancy does not predict the course during a subsequent pregnancy. Exacerbations are most likely to happen during the first trimester and during the first month postpartum.[42]

Effect of Myasthenia Gravis on Pregnancy

There is no evidence of an increase in the rate of spontaneous abortion associated with MG. Approximately 85% of pregnancies end in a live birth. A preterm delivery rate between 13% and 41% has been reported.[40,43] Congenital malformations unrelated to medications have also been reported, the most common being fetal akinesia deformation sequence as a result of a number of congenital myopathies and neuropathies.[44] Another form of malformation has also been reported that includes multiple ankyloses, craniofacial dysmorphism, pulmonary hypoplasia, and growth retardation. This form of congenital malformation is believed to be caused by prolonged fetal immobilization.[45]

There is no correlation between the occurrence of neonatal MG and acetylcholine receptor antibody titers.[43] Symptoms of neonatal MG, which include a weak cry, poor sucking, hypotonia, and occasionally respiratory insufficiency, occur between a few hours and a few days after delivery and persist for 3 weeks to 3 months. These symptoms respond well to anticholinesterase therapy. Acetylcholine receptor antibodies pass into breast milk and therefore may enhance neonatal MG, whereas maternal anticholinesterase drugs also pass into breast milk and may cause neonatal gastrointestinal upsets.

Medications

The use of anticholinesterase drugs is safe during pregnancy, but the dosage may need to be altered because of the increase in plasma volume and renal clearance. Corticosteroids, azathioprine, and sometimes cyclosporin A may also be needed if the disease process is not adequately controlled with anticholinesterase drugs. Corticosteroids have been associated with a slightly increased risk of neonatal cleft lip, while there has never been any definite demonstration that azathioprine is teratogenic. A higher incidence of spontaneous abortion and preterm delivery has been reported in parturients taking cyclosporin compared to those taking corticosteroids or azathioprine.[46] Plasmapheresis and high-dose γ-globulins are safe for treatment of myasthenic crisis during pregnancy.[47,48]

Obstetric Management

Frequent ultrasound examinations are advised to detect signs of decreased fetal movement. Parturients should follow fetal kick-counts and seek medical advice if fetal movement is notably reduced. Reduced diaphragmatic motion can occur due to receptor antibodies, and this increases the risk of pulmonary hypoplasia. MG does not affect uterine activity because the uterus is a smooth muscle, and duration of labor does not differ from that of a nonmyasthenic parturient. Forceps delivery has been recommended to reduce maternal fatigue. Cesarean delivery should be reserved for obstetric indications.[43]

A worsening of myasthenic symptoms has been associated with several medications. Most notably, these preparations include tocolytics such as magnesium sulfate, terbutaline, and ritodrine and aminoglycoside antibiotics, as well as the tetracyclines and polymyxin.

Anesthetic Management

These parturients should be assessed during pregnancy with a careful history and examination. A list of medications and dosage should be sought. The most commonly used anticholinesterase medication is neostigimine, which has a duration of action of 2 to 3 h. Intravenous neostigimine 0.5 mg equates to 1.5 mg subcutaneously, 0.7 mg IM, and 15 mg orally. Pyriostigimine has a longer duration of action, 4 to 6 h, and equivalent doses to neostigimine are IV 2 mg, IM 3 mg, and orally 60 mg.

Symptoms of excess cholinergic medication include nausea, vomiting, abdominal cramps, diarrhea, and increased salivary and tear duct secretions. More serious symptoms include muscle weakness and respiratory failure, referred to as "cholinergic crisis." The symptoms may be mistaken for a myasthenic crisis, but the two can be differentiated by the administration of 1 to 2 mg IV edrophonium, a short-acting anticholinesterase. In overmedicated patients, the muscle strength does not change and may even slightly deteriorate, but patients suffering from a myasthenic crisis will have a dramatic improvement in muscle strength. Because the administration of edrophonium may produce respiratory muscle weakness, the testing location should be equipped with airway resuscitation equipment.

The parturient should be examined for evidence of ptosis and be asked about blurred vision, chewing and swallowing difficulty, and shortness of breath during rest and exercise. Symptoms of respiratory compromise warrant further pulmonary function testing, which may predict the need for peripartum ventilatory assistance. Both involved and uninvolved muscle groups have sensory changes, and common complaints include lower backache, headache, ocular pain, and parasthesias of the lip, tongue, face, and extremities that should be carefully documented before anesthesia.

All medications that may cause respiratory depression should be used with caution in parturients with MG. Regional analgesia is usually preferred for pain relief during labor. Because plasma cholinesterase activity may be decreased in parturients with MG, amide-type local anesthetics are thought to be a safer choice when using large quantities such as in epidural anesthesia for cesarean section.

Vital capacity measurement and continued observation for the development of bulbar weakness should be made throughout the course of labor. Additional anticholinesterase medication may be required during labor because of the increased physical and emotional stresses. Stress doses of corticosteroids during labor should be administered to parturients receiving long-term steroid treatment.

If the parturient requires a cesarean section, a regional anesthetic should be administered, provided there is no evidence of bulbar or respiratory muscle weakness. Pregnant women with MG are very sensitive to nondepolarizing muscle relaxants, and even small doses will result in a rapid and exaggerated effect. Therefore, their use should be avoided intraoperatively if possible. Involved muscles are more sensitive to the effects of depolarizing muscle relaxants, but uninvolved muscles are resistant to their effects. Also, the use of anticholinesterase drugs will make the duration of action of muscle relaxant unpredictable. Volatile anesthetic agents will potentate the effect of any muscle relaxant used. Use of a nerve stimulator is essential, and reversal of neuromuscular blockade should be done by using incremental doses of neostigimine 0.5 mg or pyridostigimine 1.0 mg. Factors that predict the need for postoperative ventilation are listed in Box 18.2.[49] Skin in-

Box 18.2. Predictors for the need of postoperative ventilation in myasthenia gravis (MG).

1. Duration of MG $>$ 6 years
2. History of chronic respiratory disease
3. Pyridostigimine dosage greater than 750 mg/day
4. Preoperative vital capacity less than 2.9 L

filtration with local anesthetic should be used to reduce postoperative pain. The mother should be carefully observed for postpartum exacerbation of the disease, and it should be remembered that anticholinesterease requirements can vary also in the postpartum period.

Polymyositis and Dermatomyositis

Polymyositis (PM) is a systemic disease characterized by a nonsuppurative inflammatory myopathy of striated muscle, which is termed dermatomyositis (DM) when it is associated with skin lesions. There are two peaks of onset: childhood/juvenile onset and onset at 45 to 65 years of age; therefore, it is uncommon during pregnancy. The annual incidence is 0.5 to 8.4 per million, with women affected twice as commonly as men.[50]

Pathophysiology

The etiology of DM is unknown. DM may be associated with an underlying malignancy, raising a possible involvement of tumor immunity in the pathogenesis. It has been suggested that the fetus and its complement of foreign antigens might be involved in the development of DM in pregnancy. Viral infections also sometimes precede the onset of DM. Piconaraviruses have surface proteins similar to aminoacyl tRNA synthetases, against which myositis-associated antibody Jo-1 is directed. This evidence suggests a possible role of viral infections in the pathogenesis of the disease.[51,52] The diagnostic criteria for PM and DM are listed in Box 18.3.[53]

Effect of Pregnancy on Polymyositis/Dermatomyositis

Ishii et al. reviewed 12 reports on 29 pregnancies. The initial diagnosis was made in 40% of these parturients during pregnancy or the immediate postpartum period. In those who had been diagnosed before pregnancy, the disease remained inactive in 61% and was exacerbated in 11%.[54]

Box 18.3. Diagnostic criteria for polymyositis.

1. Symmetric weakness of proximal muscles
2. Histologic evidence of muscle inflammation and necrosis
3. Elevation of serum skeletal muscle enzymes (the most reliable indicator of disease activity)
4. Electromyographic evidence of myopathy

Diagnostic criteria for dermatomyositis include three of the above four plus:

1. Heliotrope eruption (blue-purple discoloration of the upper eyelids) or
2. Gottron's papules (raised, scaly, violet eruptions over the knuckles)

Effect of Polymyositis/Dermatomyositis on Pregnancy

Fertility has been reported to be decreased in parturients who have been diagnosed with this disease. In parturients with inactive disease, most pregnancies not ending in spontaneous abortion will proceed to term. Ishii et al. reported that 32% of pregnancies ended in fetal death or abortion, and that 26% of infants were delivered prematurely if the disease was active. Postpartum onset is very rare and, as with onset during pregnancy, the disease tends to improve after delivery. Neonates have not been reported to be affected by the disease.[54]

Medications

The first-line treatment for DM and PM is oral corticosteroids, with treatment over a period of months often necessary to acquire remission. High doses, up to 1 mg/kg/day, are continued until serum creatinine kinase has fallen to normal range; this is usually followed by an improvement in muscle strength. A reducing dose of steroid over many months is recommended. In about 25% of patients, steroids will be either ineffective or poorly tolerated, and the use of cytotoxic agents must be considered.

Obstetric Management

For parturients with known disease, pregnancy should be planned at the time of remission to maximize the chances of a favorable outcome. Serum creatinine kinase can guide this decision. Frequent monitoring of the disease activity and serial assessments of growth for viable fetuses should be offered, as the mechanism of fetal loss is unknown. Operative delivery should be reserved for obstetric indications.

Anesthetic Management

As for all chronic disease processes, the anesthetic management of these parturients begins with evaluation during the antenatal period, paying particular attention to the cardiorespiratory status of the parturient. Spirometry should be obtained to see if there is respiratory muscle involvement. Ten percent to 15% of parturients have dysphagia and reflux, and chronic aspiration pneumonitis is the most common respiratory problem in these women. Ten percent to 15% of individuals may have interstitial fibrosis. These parturients should have an EKG to rule out an arrhythmia, and they should be questioned and examined for evidence of cariomyopathy. Evidence of muscle weakness should be carefully documented preoperatively. Women taking steroids should be administered intravenous stress-dose steroids. Care should be taken to avoid an excessively high level if a regional block is used in a parturient with already compromised respiratory function. An atypical response to suxamethonium has been re-

ported, with a short-lived thumb contracture that resolved in 3 min, and prolonged paralysis (50 min) in another woman who was homozygous for atypical pseudocholinesterase.[55,56] An atypical response to vecuronium has also been reported, with neuromuscular blockade lasting 9.5 h, but other reports have indicated a normal response to nondepolarizing muscle relaxants.[57]

Scleroderma

Etiology

Scleroderma is a chronic connective tissue disease that occurs in women three to five times more frequently than in men. It is characterized by connective tissue overproduction and fibrosis of the skin and visceral organs. The annual incidence is 2 to 10 per million, with a prevalence of 28 to 130 per million.[58] Features of the disease include sclerosis, atrophy, contractors, and skin breakdown and ulceration, as well as myositis, gastrointestinal, renal, and lung involvement. The disease process can be either limited or diffuse.

Pathophysiology

The etiology of the disease is unknown, but the disease process involves excess production of collagen and other matrix constituents by fibroblasts, leading to microvascular obliteration and fibrosis within the skin and other organs. Parturients with these disease have antinuclear and anticentromere antibodies. Fetal cells are known to persist in the maternal blood for decades after pregnancy. There is a suggestion that fetal cells remain unrecognized by the host because of HLA incompatibility, and that later activation of the fetal cells by an unknown stimulus results in development of the disease.[59]

The diagnosis includes the presence of Raynaud's phenomenon, nonpitting edema, and hidebound skin. CREST syndrome (limited cutaneous scleroderma) involves calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. Diffuse scleroderma also involves the pulmonary, renal, cardiac, and musculoskeletal systems.

Effect of Pregnancy on Scleroderma

One report found the disease symptoms to be unchanged or improved during pregnancy, with no significant deterioration found in lung or other organ function. The changes in pregnancy such as edema, arthralgias, and gastointestinal reflux are similar to scleroderma symptoms. Symptoms of Raynaud's phenomenon usually improve. However, the report did find several episodes of renal crisis in their patients during and after pregnancy.[60] Renal crisis is difficult to diagnose and treat during pregnancy. It usually presents during the third trimester. It can mimic preeclampsia with an acute onset of severe hypertension, thrombocytopenia, and increases in serum creatinine. There are no reliable means to differentiate between preeclampsia and a scleroderma flare beyond a measure of clinical intuition and experience. Parturients with scleroderma need to monitor their blood pressure carefully at home three to five times per week. The only medication that sucessfully controls the associated hypertension in renal crisis is an angiotensive-converting enzyme (ACE) inhibitor, and despite an association with fetal renal defects, their use should be considered during pregnancy. Women with scleroderma should be encouraged to delay pregnancy until 3 to 5 years after the onset of the symptoms, because at this stage the disease process should have stabilized and the risk of renal crisis is reduced.[60] Patients with silent myocardial disease could potentially develop difficulties given the cardiovascular changes of pregnancy, particularly if β-agonists are used.

Effect of Scleroderma on Pregnancy

There is no increase in spontaneous abortion in parturients with scleroderma; however, preterm delivery is more likely. The general belief now is that the disease should not be assumed to be the cause of infertility. If these women consider the timing of their pregnancy and are closely monitored, they can have a successful pregnancy without excessive risk to the mother or baby. However, parturients with scleroderma are more likely to have small full-term infants.[61]

Medications

D-Penicillamine is used to modulate skin, renal, and pulmonary involvement by interfering with collagen cross-linking. The fetal risks are probably not high enough to warrant stopping it during pregnancy.[62] Glucocorticoids are used to help with inflammatory myositis, but these have no effect on disease progression and have been reported to be associated with the induction of renal crisis. Immunosuppressive agents are of no benefit.[63] Stanazolol and prostacyclin analogues help with the vasospastic component of Raynaud's phenomenon.[64] ACE inhibitors are the agent of choice for treating hypertensive crisis of scleroderma in pregnancy, and they have been used safely during pregnancy.[65] NSAIDs can be used to treat joint pain, but in a limited and controlled fashion.

Obstetric Management

Women with scleroderma symptoms for less than 4 years and those with diffuse cutaneous scleroderma are at greater risk to have more aggressive disease than those with long-standing disease.[66] Parturients with scleroderma should be evaluated for the presence of renal, cardiac, and respiratory function; some recommend termination if advanced disease is present.[58] Intensive antenatal monitoring for renal disease, hypertension, cardiac disease, and fetal growth and well-being is necessary.

Uterine and cervical wall thickening may lead to ineffective uterine contractions or cervical dystocia at delivery.[67] A vaginal delivery at term should be anticipated, but there should be no hesitation to do a cesarean section given there is no association between scleroderma and delayed wound healing. Postpartum care should include continued monitoring of the disease and recognition of new-onset hypertension.[66]

Anesthetic Management

The pregnant woman with scleroderma is an anesthetic challenge. These parturients must be seen during the antenatal period, and a comprehensive history and physical examination should be carried out. Blood testing should include a full blood count, coagulation screen, urea and electrolytes, and urinalysis. An EKG and pulmonary function test should also be carried out. Regional analgesia should be encouraged, as it allows analgesia during labor; it will allow anesthesia for cesarean section, if necessary, and also causes vasodilation and increased skin perfusion of the lower extremities. Lower doses of local anesthetic may be required as longer than normal blocks have been described in parturients with scleroderma. Epidural anesthesia is to be preferred to spinal anesthesia, as the dose of the local anesthetic can be titrated and an excessively high level can be avoided. A thorough examination of the airway is necessary and should include mouth opening, visualization of the oropharyngeal structures, and the extent of neck extension. General anesthesia is best avoided, as these women are at increased risk of difficult intubation and are also at a higher risk of aspiration. Venous access may be difficult but should be obtained early in labor, and central venous access may be necessary. Noninvasive blood pressure monitoring may be difficult because of extensive skin involvement, and invasive blood pressure monitoring may be necessary. Efforts to preserve warmth, including warming the delivery room and intravenous fluid and the use of thermal socks, should be made in parturients with Raynaud's disease.

Ankylosing Spondylitis

Etiology

Ankylosing spondylitis (AS) is a chronic progressive disease of the sacroiliac and the synovial joints of the spine. Bony ridges develop along the vertebrae, giving rise to the characteristic "bamboo spine" X-ray appearance. AS differs from RA in that it is generally confined to the hips and spine. The peak age of onset is between 15 and 29 years of age. It is found more commonly in Caucasians, and the male-to-female ratio in adulthood is 3 to 1.[68]

Effect of Ankylosing Spondylitis on Pregnancy

The fertility rate and pregnancy outcome have been found to be similar to normal controls, and the rate of spontaneous abortion, stillbirth, frequency of assisted delivery, and duration of labor are also with in normal limits. The fetuses have generally been delivered at term and have been of normal birth weight,[69,70] most likely because these parturients have very few systemic features associated with the disease. However, the incidence of cesarean delivery is higher in parturients with AS compared to healthy women, and in 58% the reason cited was the presence of AS.[70]

Effect of Pregnancy on Ankylosing Spondylitis

Unlike RA, pregnancy has been found to ameliorate the disease in only 25% of women.[70] Those that improve during pregnancy generally have an accompanying disease such as psoriasis or inflammatory bowel disease.[71] Overall, no changes and improvement have been reported with equal frequency; therefore, one can assume that pregnancy has no effect on AS.[72] Pregnancy did however influence the extraspinal manifestations such as anterior uveitis and peripheral arthritis, both of which have been described as increasing in the postpartum period.[73] The frequency of postpartum flare has been found to be significantly increased in women with active AS at conception.[70] Disease activity generally returns to normal during the year following delivery. Preconditions for improvement during pregnancy have been found to be a history of peripheral arthritis and female sex of the fetus.[70]

Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the main medication used in the management of patients with AS. Although there is no evidence of teratogenicity associated with their use, the noted reduction in fetal renal perfusion accompanying prolonged exposure should limit their use during pregnancy. Parturients who require NSAIDs during pregnancy should have the lowest effective dose prescribed, which should be discontinued 6 to 8 weeks before delivery. NSAIDs do pass into breast milk but can still be taken provided they are administered at or shortly after breast feeding. Sulphsalazine has been compared to the use of corticosteroids, and no difference in fetal outcome has been reported. No increases in birth defects, pathologic jaundice, or small-for-date babies were detected.[74] There is no demonstrated benefit from the use of corticosteroids in the management of spinal disease in AS.

Obstetric Management

A vaginal delivery at term should be anticipated unless other medical or obstetric problems become apparent. As mentioned previously, cesarean delivery has more frequently been performed in parturients with AS, and in 58% of the cases AS was reported to be the reason.[70] Severity of AS could be one possible explanation or, more likely, the inclination of the obstetrician to do a primary surgical delivery in a woman with inflammatory joint disease. Inflammation of the sacroil-

iac joints, although painful, is not a mechanical hindrance for the progress of labor.

Anesthetic Management

These parturients must be seen during the antenatal period, and particular attention should be paid to the cardiorespiratory system, airway, and anatomy of the back and hip joints. With regard to the cardiac system, a small number develop aortic insufficiency due to proximal aortitis. The mitral valve may also be involved, but most of these cardiac complications are seen in patients who have had the disease for more than 15 years.[75] A baseline EKG should also be performed.

Involvement of the costovertebral angle may produce fixation of the thoracic cage, and diffuse pulmonary fibrosis may also be present. In association with the reduced lung volumes associated with pregnancy, this may cause severe restrictive lung disease, and pulmonary function testing should be performed in all parturients. If severe respiratory disease is present, care must be taken to avoid a high block with a regional anesthetic technique for either analgesia or anesthesia.

Limitation of cervical spine movement may occur in these parturients, and complete neck fusion may be present, with the neck usually in the flexed position. If the disease has been present more than 16 years, 75% of patients have cervical ankylosis and a high risk of cervical fractures.[76] All parturients with AS should have cervical spine X-rays to rule out the presence of a fracture. Parturients with cervical spine disease requiring general anesthesia should have an awake fiboptic intubation. Mouth opening may also be limited in these women because of TMJ involvement, and the presence of the disease in the cricoarytenoid joints may make them more prone to trauma of the vocal cords.[75,76] Therefore early involvement of the anesthesiologist in the care of these women in labor is to be advocated, preferably with the placement of an early epidural that can be used for labor and cesarean delivery if necessary. The placement of a regional block may be difficult due to ossification of the interspinous ligaments and limitation of flexion of the lumbar vertebrae. Cauda equina syndrome and peripheral nerve lesions have been described in these patients, and the presence of these problems must be noted before any anesthetic involvement.[75]

Idiopathic Thrombocytopenic Purpura

Etiology

Idiopathic thrombocytopenic purpura (ITP) is the most common autoimmune bleeding disorder of pregnancy. The female-to-male ratio is almost 3 to 1, and more than 70% of females are less than 40 years of age.[77] ITP is not infrequently diagnosed during pregnancy and accounts for 3% of all cases of thrombocytopenia at the time of delivery.[78] There is no single reliable confirmatory test, and in milder forms (platelets 80–100 $\times$ 10^{-9}/L), it may be indistinguishable from gestational thrombocytopenia. ITP is a diagnosis of exclusion. Gestational thrombocytopenia is asymptomatic and usually diagnosed during pregnancy at the time of the routine CBC. Women with gestational thrombocytopenia have no previous history of bleeding disorders and are not at increased risk for bleeding complications; therefore, parturients with gestational thrombocytopenia do not require additional testing or specialized care. Other causes of thrombocytopenia during pregnancy include preeclampsia, SLE, human immunodeficiency virus (HIV) infection, APS, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation. These disorders can be excluded with a medical history and examination, assessment of blood pressure, HIV serology, and other laboratory studies such as liver function tests. ITP is diagnosed by CBC and a peripheral blood smear. The CBC is normal except for the thrombocytopenia and an increased proportion of slightly enlarged platelets seen on the peripheral smear.[79]

Pathophysiology

Idiopathic (immune) thrombocytopenic purpura (ITP) is a syndrome characterized by immunologically mediated thrombocytopenia. The disorder is caused primarily by autoantibodies to platelet membrane glycoproteins, leading to increased platelet destruction and a lack of an appropriate increase in marrow production of platelets.[77,80] The most common signs and symptoms, if any, include petechiae, ecchymoses, easy bruising, epistaxis, gingival bleeding, and menorrhagia. Severe bleeding complications are rare even in severely thrombocytopenic patients.

Medical Management

Treatment is considered appropriate for parturients with a platelet count less than 10,000/μL or a platelet count 10,000 to 30,000/μL during the second or third trimester or for parturients with bleeding. It is controversial as to whether women with platelet counts between 30,000 and 50,000/μL should be treated during the third trimester, but more aggressive treatment should be pursued in anticipation of delivery.[81]

Glucocorticoids are the first line of treatment and are usually initiated at a dose of 1 to 2 mg/kg/day for 3 to 5 days; the dose is then tapered to the lowest effective dose. Intravenous immunoglobulin (IVIG) is an appropriate initial treatment for pregnant women with a platelet count below 10,000/μL in the third trimester and for a woman with a platelet count between 10,000 and 30,000/μL who are bleeding, as it is generally perceived that IVIG can increase platelet count more rapidly and to a greater degree than glucocorticoids. There are no known adverse fetal effects from IVIG.

In pregnant women who are refractory to both glucocorticoids and IVIG and who have symptomatic severe thrombocytopenia (platelet count $<$10,000/μL), splenectomy is an ap-

propriate consideration in the second trimester, as it will lead to a 70% to 80% immediate and sustained response. In those unresponsive to splenectomy, cytotoxic agents are considered. Cytotoxic agents have been used in the second and third trimesters and are associated with a very low risk of teratogenicity but are also associated with prematurity and low birth weight. Azathioprine has been used extensively in renal transplant parturients, but response to azathrioprine can take 3 to 6 months. Dapsone has been used as a treatment for ITP; adverse effects on pregnancy have not been noted, although it can be excreted into the breast milk and cause hemolysis in the infant.[82]

Obstetric Management

Immunoglobulin G (IgG) antiplatelet antibodies cross the placenta, placing the fetus and neonate at risk for thrombocytopenia. Occasionally, this results in minor clinical bleeding such as purpura, hematuria, or rarely, intracranial hemorrhage, which can result in severe neurologic impairment. This possibility has led to the advocation of cesarean section for parturients with maternal platelet counts below 50,000/μL.[83,84] A neonatologist should be present to care for the potential bleeding complications and the anticipated decrease in platelet count during the first several days after birth. Even though there is a theoretical risk of thrombocytopenia in the neonate, breast-feeding should not be discouraged.[85] Platelets, fresh-frozen plasma, and IVIG should be available for the mother at delivery.

Anesthetic Management

Parturients on steroids should have stress doses during labor. The anesthetic management of these parturients depends on the severity of the disease. In our hospital, the decision whether to perform an epidural for labor is based on the bleeding history of the parturient and platelet count in labor. We usually place an epidural in patients with platelet counts as low as 70,000 to 75,000/μL. If the platelet count is lower than this, we prescribe patient-controlled analgesia (PCA) with a combination of intravenous fentanyl and ketamine. Bleeding time is no longer used as an assessment tool for platelet function, but TEG has recently become popular as a global method of assessing clotting function.[86] Of course, the decision whether to provide regional analgesia for labor must be made in light of the maternal risk of general anesthesia should this be necessary. If a platelet transfusion is necessary, administration should be as close to the time of surgery as possible, because platelet survival is reduced in these parturients and has been reported to be as short as 48 min.

Autoimmune Hemolytic Anemia

Autoimmune hemolysis (AIH), whether clinically associated with anemia or not, occurs at a rate of approximately 1 in 200,000 in the age group of 20 to 50 years old.[87] In pregnant women, the incidence rises to 1 in 50,000. It is unclear why AIH occurs more frequently during pregnancy.[88]

Pathophysiology

The autoimmune antibodies are mainly IgG warm-reacting autoantibodies, which can cross the placenta and can cause hemolysis in the fetus. The breakdown of the erythrocytes carrying the antibodies occurs via antibody-dependent cell-mediated cytotoxicity (ADCC), and phagocytosis and destruction take place in the spleen.[87] Corticosteroids are particularly effective against ADCC. IgM antibodies may also be found with AIH during pregnancy.[88] Although these antibodies do not cross the placental barrier, they can bind complement. When hemolysis occurs, this takes place intravascularly and is entirely or almost entirely unaffected by corticosteroids. Both antibodies can cause severe hemolysis. In cases involving IgG warm autoantibodies with an idiopathic form of AIH emerging only during pregnancy, treatment with prednisone (initial dosage, 40–60 mg) should prove effective. The hemolysis generally disappears spontaneously after the pregnancy has ended. Relevant hemolysis is rarely seen in the newborn. On the other hand, an AIH that was clinically relevant before pregnancy or secondary to an associated disease is generally more severe, because when IgG autoimmune antibodies are responsible, therapy is often not successful. The pregnancy more often ends in a spontaneous abortion or miscarriage.[88,89]

Obstetric Management

A positive direct Coomb's test is the most commonly used test to detect an antibody. Complete serologic tests including characterization of autoantibodies and detection of any concurrent alloantibody should be performed so that the least incompatible blood can be transfused if necessary. Blood transfusion involves a risk but needs to be given if the parturient exhibits life-threatening manifestations of anemia such as angina, cardiac decompensation, and neurologic signs such as lethargy.

Chaplin et al. reported that autoimmune hemolytic anemia in pregnancy provoked life-threatening anemia in 40% to 50% of the mothers and stillbirths or severe postpartum hemolytic anemia in 35% to 40% of their infants.[90] However, it has also been reported that autoimmune hemolytic anemia in pregnancy is usually mild and does not require treatment, and that the risks to the infant are less than previously thought if the mother is promptly treated. There is an increased risk to the infant when other collagen conditions are present. With early diagnosis and appropriate treatment, the outlook for mother and child is good.[87] Because of the risk of fetal hemolysis, serial ultrasonographic examinations of the fetus should be

performed, and tests of fetal well-being such as biophysical testing should also be carried out. In the postpartum period, the parturient should be observed closely for potential exacerbations of the disease, and the neonate should be monitored for hemolysis and for the persistence of antibodies.

Anesthetic Management

Transfusion therapy may be complicated in these individuals. In an emergency situation, the least incompatible cells available should be used for transfusion. In parturients with severe cold agglutinin disease, the cool operating room may cause agglutination to occur with resultant acrocyanosis, Raynaud's phenomenon, or immune complex nephritis. This situation may lead to hemolysis and may cause severe anemia, hemoglobinuria, and renal failure. Perioperative plasmapheresis, intraoperative forced-air surface warming, and warming of all intravenous solutions are effective techniques to prevent this cascade of events.

Summary

When pregnancy occurs in women with autoimmune diseases many problems related to obstetrics and anesthesia may occur. In addition, pregnancy itself my alter the course of the autoimmune disease.

References

1. Ostensen M. Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Ann N Y Acad Sci 1999;876:131–143.
2. Hench PS. The ameliorating effect of pregnancy on chronic atropic (infectious rheumatoid) arthritis, fibrosis, and intermittent hydrarthrosis. Mayo Clin Proc 1938;13:161–167, 138.
3. Ostensen M, Aune B, Husby G. Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. Scand J Rheumatol 1983;12:69–72.
4. Oka M. Effect of pregnancy on the onset and course of rheumatoid arthritis. Ann Rheum Dis 1953;12:227–229.
5. Brooks PM, Needs CJ. The use of antirheumatic medication during pregnancy and in the puerperium. Rheum Dis Clin N Am 1989;15:789–806.
6. Ostensen M. Safety of nonsteroidal anti-inflammatory drugs during pregnancy and lactation. Immunopharmacology 1996;4:31–41.
7. Wiggins DA, Elliott J. Oligohydramnios in each sac of a triplet gestation caused by Motrin: fulfilling Kock's postulates. Am J Obstet Gynecol 1990;162:460–461.
8. Rumack CM, Guggemheim MA, Rumack BH, et al. Neonatal intracranial hemmorhage and maternal use of aspirin. Obstet Gynecol 1981; 58(suppl 5):52–56.
9. Stuart MJ, Gorss SJ, Elrad H, et al. Effects of acetylsalicylic acid ingestion on maternal and neonatal hemostasis. N Engl J Med 1982;307: 909–912.
10. Ostensen M. Optimization of anti-rheumatic drug treatment in pregnancy. Clin Pharmacokinet 1994;27:486–503.
11. Dhring JL. Pregnancy, rheumatoid arthritis, and intrauterine growth retardation. Am J Obstet Gynecol 1970;108:325–326.
12. Keenan MA, Stiles CM, Kaufman RL. Acquired laryngeal deviation associated with cervical spine disease in erosive polyarticular arthritis. Anesthesiology 1983;58:441–449.
13. Ruddy S, Roberts WN. Rheumatoid arthritis. In: Lichtenstein LM, Fauci AS (eds) Current Therapy in Allergy, Immunology, and Rheumatology, 3rd edn. Toronto: Dekker, 1988:110.
14. Steinberg AD. Systemic lupus erythematosus. In: Wyngaarden JB, Smith LH, Bennett JC (eds). Cecil Textbook of Medicne, 19th edn. Philadelphia: Saunders, 1992:1522–1530.
15. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol 1989;44:93–151.
16. Duerbeck N, Coney PJ. Systemic lupus erythematosus in pregnancy. Comp Ther 1998;24:123–128.
17. Lockshin MD. Does lupus flare during pregnancy? [Editorial]. Lupus 1993;2:1–2.
18. Ramsey-Goldman R. Pregnancy in systemic lupus erythematosus. Rheum Dis Clin N Am 1988;14:130–138.
19. Urowitz MB, Gladman DD, Farewell VT, et al. Lupus and pregnancy studies. Arthritis Rheum 1993;36:1392–1397.
20. McHugh NJ, Reilly PA, McHugh LA. Pregnancy outcome and autoantibodies in connective tissue disease. J Rheumatol 1989;16:42–46.
21. Meehan RT, Dorsey JK. Pregnancy among patients with systemic lupus erythematosus receiving immunosuppressive therapy. J Rheumatol 1987;14:252–258.
22. Lockshin MD, Druzin ML, Goei S, et al. Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. N Engl J Med 1985;313:152–156.
23. Ramsey-Goldman R, Kutzer JE, Kuller LH, et al. Previous pregnancy outcome is an important determinant of subsquent pregnancy outcome in women with systemic lupus erythematosus. Am J Reprod Immunol 1992;28:195–198.
24. Englert HJ, Derue GM, Loizou S, et al. Pregnancy and lupus: prognostic indicators and response to treatment. Q J Med 1988;250:125–136.
25. Mintz R, Niz J, Gutierrez G, et al. Prospective study of pregnancy in systemic lupus erythematosus: results of a multidisciplinary approach. J Rheumatol 1986;13:732–739.
26. Johnson MJ, Petri M, Witter FR, et al. Evaluation of preterm delivery in a systemic lupus erythematosus pregnancy clinic. Obstet Gynecol 1995; 86:396–399.
27. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained form a national neonatal lupus registry. J Am Coll Cardiol 1998;31: 1658–1666.
28. Samuels P, Pfeifer SM. Autoimmune disease in pregnancy: the obstetrician's view. Rheum Dis Clin N Am 1989;15:307–322.
29. Lockshin MD. Pregnancy associated with systemic lupus erythematosus. Semin Perinatol 1990;14:130–138.
30. Wilson WA, Gharavi AE, Koike T, et al. International statement on preliminary classifaication criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–1311.
31. Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticogulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Ann Intern Med 1990;112:682–698.
32. Derksen RHWM, Hasselaar P, Oosting JD, et al. The antiphospholipid antibody dilemma [Review]. Clin Rheumatol 1990;9(1 suppl 1):39–44.
33. Espinoza LR, Hartmann RC. Significance of the lupus anticoagulant. Am J Hematol 1986;22:331–337.
34. Chandramouli NB, Rodgers GM. Management of thrombosis in women with antiphospholipid syndrome. Clin Obstet Gynecol 2001;44:36–47.
35. Edwards MH, Pierangeli S, Liu X, et al. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. Circulation 1997;96:4380–4384.
36. Al-Sayegh FA, Ensworht S, Huang S, et al. Hemorrhagic complications of long-term anticoagulant therapy in 7 patients with systemic lupus erythematosus and antiphospholipid syndrome. J Rheumatol 1997;24:1716–1718.

37. Asherson RA, Morgan SH, Harris EN, et al. Anticardiolipin antibody, recurrent thrombosis and warfarin withdrawal. Ann Rheum Dis 1985;44; 823–825.
38. Babikian VL, Levine SR. Theraueutic considerations for stroke patients with antiphospholipid antibodies. Stroke 1992;23(suppl 1):33–37.
39. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. Am J Med 1992;92:217.
40. Plauche WC. Myasthenia gravis. Clin Obstet Gynecol 1983;26:592–604.
41. Donaldson JO, Penn AS, Lisak RP, et al. Acetylcholine receptor antibody in neonatal myasthenia gravis. Am J Dis Child 1981;135:222–225.
42. Batocchi AP, Majolini L, Evoli A, et al. Course and treatment of myasthenia gravis during pregnancy. Neurology 1999;52:447–452.
43. Eden RD, Gall SA. Myasthenia gravis and pregnancy: a reappraisal of thymectomy. Obstet Gynecol 1983;62:328–333.
44. Dulitzky F, Sirota L, Landman J, et al. An infant with multiple deformities born to a myasthenic mother. Helv Paediatr Acta 1987;42:173–176.
45. Pena SDJ, Shokeir MHK. Syndrome of camptodactyly, multiple ankyloses, facial anomalies and pulmonary hypoplasia: a lethal condition. J Pediatr 1974;85:373–374.
46. Haugen G, Fauchald P, Sodal G, et al. Preganacy outcome in renal allograft recipients: influence of cyclosporin A. Eur J Obstet Gynecol Reprod Biol 1991;39:25–29.
47. Watson WJ, Katz VL, Bowes WA, et al. Plasmapheresis during pregnancy. Obstet Gynecol 1984;76:451–457.
48. Kaaja R, Julkunen A, Ammala P, et al. Intravenous immunoglobulin treatment of pregnant patients with recurrent pregnancy losses associated with antiphospholipid antibodies. Acta Obstet Gynecol Scand 1993;72:63–66.
49. Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis. Anesthesiology 1980;53:26–30.
50. Wortmann RL. Polymyositis. In: Wyngaarden JB, Smith LH, Bennett JC (eds). Cecil Textbook of Medicine, 19th edn. Philadelphia: Saunders, 1992:1546–1549.
51. Bernard P, Bonnetblanc J-M. Dermatomyositis and malignancy. J Invest Dermatol 1993;100:128S–132S.
52. Rosenberg NL, Rotbart HA, Abzug MJ, et al. Evidence for a novel picornavirus in human dermatomyositis. Ann Neurol 1989;26:204–209.
53. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344–347, 403–407.
54. Ishii N, Ono H, Kawaguchi T, et al. Dermatomyositis and pregnancy: case report and review of the literature. Dermatologica 1991;183:146–149.
55. Johns RA, Finholt DA, Stirt JA. Anaesthetic management of a child with dermatomyositis. Can Anaesth Soc J 1978;33:71–74.
56. Eielsen O, Stovner J. Dermatomyositis, suxamethonium action and atypical pseudocholinsterase. Can Anaesth J Soc 1978;25:63–64.
57. Flusche G, Unger-Sargon J, Lambert DH. Prolonged neuromuscular paralysis with vecuronium in a patient with polymyositis. Anesth Anal 1987;66:188–190.
58. Black CM. Systemic sclerosis and pregnancy [Review]. Balliere Clin Rheumatol 1990;4:105–124.
59. Artlett CM, Welsh KI, Black CM, et al. Fetal–maternal HLA compatibility confers susceptibility to systemic sclerosis. Immunogenetics 1998; 47:17–22.
60. Steen VD. Pregnancy in women with systemic sclerosis. Obstet Gynecol 1999;94:15–20.
61. Steen VD, Medsger TA. Fertility and pregnancy outcome in women with systemic sclerosis. Arthritis Rheum 1999;42:763–768.
62. Steen VD, Medsger TA, Rodnan GP. D-Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. Ann Intern Med 1982;97:652–659.
63. Tuffanelli DL. Systemic scleroderma. Med Clin N Am 1989;73:1167–1180.
64. Muller-Lander U, Benning K, Lang B. Current therapy of systemic sclerosis (scleroderma). Clin Invest 1993;71:257–263.
65. Lopez-Ovejero JA, Saal SD, D'Angelo WA, et al. Reversal of vascular and renal crises of scleroderma by oral angiotensin-converting-enzyme blockade. N Engl J Med 1979;300:1417–1419.
66. Steen VD. Connective tissue disease and pregnancy. Scand J Rheumatol 1998;27(suppl 107):72–75.
67. Steen VD, Conte C, Day N, et al. Pregnancy in women with systemic sclerosis. Arthitis Rheum 1989;32:151–157.
68. Gran JT, Husby G. The epidemiology of ankylosing spondylitis. Semin Arthritis Rheum 1993;22:319–334.
69. Gran JT, Ostensen M. Spondyloarthrides in females. Ballieres Clin Rheum 1998;12:695–715.
70. Ostensen M, Ostensen H. Ankylosing spondylitis—the female aspect. J Rheum 1998;25:120–124.
71. Ostensen M, Husby G. A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. Arthritis Rheum 1983;26:1155–1159.
72. Ostensen M, Husby G. Ankylosing spondylitis and pregnancy. Rheum Dis Clin N Am 1989;15:241–254.
73. Ostensen M, Husby G, Romberg O. Ankylosing spondylitis and motherhood. Arthritis Rheum 1982;25:140–143.
74. Mogadam M, Dobbins WO, Korelitz BI, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981;80:72–76.
75. Sinclair JR, Mason RA. Ankylosing spondylitis: the case for awake intubation. Anaesthesia 1984;39:3–11.
76. Salathe M, Johr M. Unsuspected cervical fractures: a common problem in ankylosing spondylitis. Anesthesiology 1989;70:869–870.
77. George JN, El-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. N Engl J Med 1994;331:1207–1211.
78. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Engl J Med 1993;329:1463–1466.
79. Silver RM. Management of idiopathic thrombocytopenic purpura in pregnancy. Clin Obstet Gynecol 1998;41:436–448.
80. Ballem PJ, Segal GM, Statton JR, et al. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura: evidence for both impaired platelet production and increased platelet clearance. J Clin Invest 1987;80:33–40.
81. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura; a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;174:1014–1018.
82. Godeau B, Durand JM, Roudot-Thoraval F, et al. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. Br J Haematol 1997;97;336–339.
83. Scott JR, Rote NS, Cruikshank DP. Antiplatelet antibodies and platelets counts in pregnancies complicated by autoimmune thrombocytopenic purpura. Am J Obstet Gynecol 1983;145:932–939.
84. Ayromlooi J. A new approach to the management of immunologic thrombocytopenic purpura in pregnancy. Am J Obstet Gynecol 1990;163:1147–1150.
85. The American Society Hematology ITP practice guideline panel. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hemalology. Ann Intern Med 1997;126:319–326.
86. Sharma SK, Philip J, Whitten C, et al. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastography. Anesthesiology 1999;90:385–390.
87. Sokol R, Hewitt S. Autoimmune hemolysis: a critical review. Crit Rev Oncol Hematol 1985;4:125–154.
88. Sokol R, Hewitt S, Stamps B. Erythrocyte autoantibodies, autoimmune hemolysis and pregnancy. Vox Sang 1982;43:169–176.
89. Issaragrisil S, Krautrachue M. An association of pregnancy and autoimmune hemolytic anaemia. Scand J Haematol 1983;31:63–68.
90. Chaplin H, Cohen R, Bloomberg G, et al. Pregnancy and idiopathic autoimmune haemolytic anaemia: a prospective study during 6 months gestation and 3 months post-partum. Br J Haemtol 1973;24:219–229.

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19
Preeclampsia and Eclampsia

Stephen P. Gatt and David Elliott

Risk of Developing Preeclampsia and Eclampsia

The risk of developing gestational hypertension is 6% to 7% and that of developing preeclampsia (PE) is 5% to 6%. In 3% to 5% of all pregnancies, there is preexisting hypertension.[1–5] Eclampsia occurs in 0.05% of pregnancies.[4,5]

Genetic factors, that is, both fetal (maternal and paternal) and maternal genes and their interaction, are the main determinants of the likelihood of preeclampsia.[1,6–9] In a Swedish cohort, the "nonshared environmental" effects contributed 0.46 [95% confidence interval (CI), 0.29–0.67) and the hereditary factors 0.54 (95% CI, 0–0.71).[7] Several genetic and environmental factors interact to determine the predisposition and severity of PE.[10,11] There are several genetic variants that determine the level of this predisposition as shown in Table 19.1. There is also evidence that PE is a syndrome of sympathetic overactivity.[12] This is most obvious when postganglionic sympathetic nerve activity in skeletal muscle blood vessels is measured.[12] Women with elevated cardiac output in early pregnancy are more likely to develop PE.[13]

There are several risk factors for increased maternal morbidity in PE. The commonest maternal complications following eclampsia are listed in Table 19.2.[21]

Early Diagnosis of Preeclampsia

It is becoming increasingly possible to predict which high-risk women are likely to progress to PE. The most promising screening tests are currently the following:

1. Fetal DNA in maternal plasma[15]
2. Cold pressor test at 16 to 20 weeks showing arterial pressure rise greater than 10 mm Hg during and after placement of an icebag on the forehead for 3 min
3. Quantitative assessment of the diastolic notch in uterine artery velocity waveforms[16,17]
4. Elevation in the erythroblast count in maternal blood[18]
5. Elevation of cardiac output (later, crossing over to low cardiac output as vascular resistance increases) measured using Doppler echocardiography[19]

The mortality and morbidity from PE continues to decline in the developed world (see Table 19.2).[4,11,13,14,20]

Definition of Hypertension in Pregnancy

The normal pattern of arterial blood pressure during the course of pregnancy is a fall in both systolic and diastolic pressures, especially during the second trimester. By way of contrast, hypertension in pregnancy is defined as systolic arterial pressure (SAP) $\geq$ 140 mmHg and/or diastolic arterial pressure (DAP) $\geq$ 90 mmHg. Measurements should be taken with the patient sitting comfortably, using an appropriately sized cuff and a mercury sphygmomanometer. Korotkoff phase V (K5) point of disappearance should be used to record the diastolic pressure, as it is detected more reliably than K4 during pregnancy and more closely reflects the true diastolic pressure.[10] In addition, the blood pressure should be measured on the same arm throughout pregnancy to reduce interobserver error.

Of significance is that a blood pressure of 140/90 mm Hg or higher is outside 2 SD of the mean[21] in the normal pregnant population and is associated with a clinically significant increase in perinatal mortality.[2]

Classification of Hypertension in Pregnancy

Many classifications of hypertension in pregnancy (e.g., the 2000 Australasian Society for the Study of Hypertension in Pregnancy [ASSHP] classification) exist. The European classification is shown in Table 19.3.[5,11] It can be seen that preeclampsia is one of a number of the hypertensive disorders of pregnancy, its significance lying in the multisystem nature of the disease rather than being an isolated finding.

Table 19.1. Genetic and environmental factors that may predispose to preeclampsia (PE).

Gene variants	Environmental contributors
Angiotensin T-235	Chronic renal disease
Tumor necrosis factor-α	Antiphospholipid (anticardiolipin) syndrome
Human leukocyte antigen G	Chronic hypertension
Endothelial NO synthetase at 298	Family history of PE
Factor V Leiden	Twin gestation
Methylene tetrahydrofolate reductase	Nulliparity
β_2-Adrenergic receptor	Age >40 years, <18 years
	Diabetes
	Ethnicity
	Period of exposure to paternal seminal fluid (including oral intercourse, period of cohabitation)
	Socioeconomic factors
	Use of condoms and barrier methods
	Previous autologous blood transfusion

Source: Compiled from Schneider MM, Landau R, Mörtl MM. New insights in hypertensive disorders of pregnancy. In: Obstetric & Gynecologic Anaesthesia: Baillere's Best Practice & Research. London: Lippincott Williams & Wilkins and Epidemiological Study of Contraception. American College of Obstetricians & Gynecologists Technical Bulletin. Int J Gynecol Obstet 1996;53:175–183, with permission.

Definition of Preeclampsia

At present, there is no diagnostic test specific for preeclampsia. It is a clinical entity defined as hypertension that arises after 20 weeks gestation or in the early postpartum period and returns to normal within 3 months postpartum. In addition one or more of the following must be present:

- Proteinuria ≥300 mg/24h or a spot urine protein/creatinine ratio ≥30 mg/mmol
- Renal insufficiency evidenced by oliguria or serum/plasma creatinine ≥0.09 mmol/L
- Liver disease with elevated serum transaminases and/or severe epigastric and/or right upper quadrant pain
- Neurologic manifestations such as severe headaches, hyperreflexia, clonus, visual disturbances, or eclamptic convulsions (by definition)
- Hematologic disturbances such as thrombocytopenia, disseminated intravascular coagulation, or hemolysis
- Fetal growth retardation

Table 19.2. Major maternal complications following eclampsia.

HELLP syndrome	11%
Abruptio placentae	10%
Neurologic deficit	7%
Aspiration pneumonitis	7%
Disseminated intravascular coagulation (DIC)	6%
Pulmonary edema	5%
Cardiac arrest	4%
Renal failure	4%
Maternal death	1%

HELLP (syndrome), hemolysis/elevated liver enzymes/and low platelets.
Source: Adapted from Mattar F, Sibai BM. Eclampsia: risk factors for maternal morbidity. Am J Obstet Gynecol 2000;182:307–312, with permission.

Table 19.3. Classification of hypertensive disorders of pregnancy.

Pregnancy-associated hypertension
Gestational hypertension
Preeclampsia
Preexisting hypertension
Preexisting hypertension complicated by superimposed preeclampsia
Eclampsia

Source: Modified from Schneider MM, Landau R, Mörtl MM. New insights in hypertensive disorders of pregnancy. In: Obstetric & Gynecologic Anaesthesia: Baillere's Best Practice & Research. London: Lippincott Williams & Wilkins, 2001:291–297, with permission.

It is worth noting that, although common, proteinuria is not mandatory to the diagnosis of preeclampsia. Additionally, edema is no longer included in the diagnosis of preeclampsia as it is too nonspecific a finding to be of value.

Classification of Preeclampsia

Preeclampsia is classified as either mild or severe; there is no moderate category. Preeclampsia is severe when the SAP is 160 mm Hg or more or the DAP is 110 mm Hg or higher. Additional features of severe preeclampsia include the following:

- Proteinuria ≥5 g/24 h
- Pulmonary edema or cyanosis
- Hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP)

The differentiating features between mild and severe disease are shown in Table 19.4.

Table 19.4. Factors that differentiate mild from severe preeclampsia.

Factor	Mild PE	Severe PE
Systolic arterial pressure	<160 mm Hg	≥160 mm Hg
Diastolic arterial pressure	<110 mm Hg	≥110 mm Hg
Urinary protein	<5 g/24 h; Dipstick + or ++	≥5 g/24 h; Dipstick +++ or ++++
Urine output	>500 mL/24 h	≤500 mL/24 h
Headache	No	Yes
Visual disturbances	No	Yes
Epigastric pain	No	Yes
Right upper quadrant abdominal pain	No	Yes
Pulmonary edema	No	Yes
Cyanosis	No	Yes
HELLP	No	Yes
Platelet count	>100,000/mm^3	<100,000/mm^3

Some but not necessarily all features need be present in the same patient. HELLP, hemolysis/elevated liver enzymes/and low platelets.

Hemolysis, Elevated Liver Enzymes, and Low Platelet, Hemolytic Uremic, and Thrombotic Thrombocytopenic Purpura, Syndromes

The hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome is simply a form of severe PE in which the systemic arterial blood pressure may not be markedly elevated.[22] Although an aggressive, multidisciplinary approach has improved the morbidity and mortality, HELLP still has a substantial mortality.[14,23,24] HELLP and its complications (hepatic rupture, subcapsular hematoma, hepatic hemorrhage, acute renal failure, disseminated intravascular coagulation, pericardial and pleural effusions, ascites)[24] require prompt recognition and aggressive management.[24,25]

Although lactate dehydrogenase (LDH) and platelet count are still the two best tests to monitor disease progress in HELLP, a number of others are useful to secure the diagnosis: full blood count, LDH, serum transaminases (SGOT, SGPT), urinalysis, haptoglobin, blood film, monoclonal D-dimer, LDH isoenzymes, bilirubin, prothrombin time (PT), and activated partial thromboplastin time (aPPT).[26] Other complications (or, perhaps, variants) of severe PE are hemolytic uremic (HUS)/thrombotic trombocytopenic purpura (TTP) and acute fatty liver of pregnancy (AFLP).[27]

In some severe cases of HELLP and HUS/TTP, plasmapharesis, plasma exchange, and steroids may help,[22,25–27] but in most cases early delivery allows the disease process to resolve.[27,28]

The Clinical Picture of Severe Preeclampsia

Although most parturients presenting to our Obstetric Acute Care Centre do seem to conform to a particular pattern, there are so many potential variables that it is not unusual to come across an atypical case. Indeed, PE is the disease with more exceptions than strict conformists.

The physiologic and hemodynamic changes produced by normal pregnancy are shown in Table 19.5.[6] The most notable are the 43% increase in cardiac output (CO) and the 21% decrease in systemic arterial vascular resistance (SVR).[13,29] In a woman with severe PE, onto these changes of pregnancy must be superimposed the features of severe PE as shown in Table 19.6. The main differences in mean arterial pressures between normal and PE women throughout gestation and in the postpartum period are shown in Figure 19.1.[13] The progression of cardiac output increase throughout pregancy in preeclamptic and nonpreeclamptic women is shown in Figure 19.2.[13] The lack of correlation between central venous pressure and pulmonary capillary wedge pressure in preeclamptics is shown in Figure 19.3. Once the severe preeclamptic receives a regional block, either for blood pressure control or pain relief in labor, or as anesthesia for cesarean section or instrumental delivery, the changes imposed by regional anesthesia must be added to this already complex clinical picture (Figure 19.4). To add insult to injury, the clinical picture of severe PE is not always "typical." In a small but significant number of PE women, the picture is atypical.[13,29–35] HELLP women are one such subgroup, but there are others. For example, although SVR index (SVRI) is often more than 2200 dynes cm^{-5} m^2, it is normal (1500–2200) in many and low (<1500) in a few. Likewise, although the cardiac index is normal (>3 L/min/m^2) or high (>5) in most severe preeclamptics, in a small minority it is low (<3). The large hemodynamic alterations that occur intrapartum and immediately postpartum can make the clinical picture and hemodynamic measurements difficult to interpret. Nevertheless, a feature that bears remembering (Figure 19.5)[36] is that myocardial function in the untreated preeclamptic is normal or "hyperdynamic."[36]

The differential diagnosis of PE includes acute cocaine intoxication, essential hypertension, renal disease, idiopathic thrombocytopenic purpura, gallbladder disease, systemic lupus, acute fatty liver of pregnancy (AFLP), pheochromocytoma, cardiomyopathy, dissecting aortic aneurysm, glomerulonephritis, and ruptured bile duct.

TABLE 19.5. Hemodynamic changes in late pregnancy in nonpreeclamptic women.

Cardiac output, up 43%
Heart rate, up 17%
Systemic vascular resistance, down 21%
Pulmonary vascular resistance, down 34%
Colloid osmotic pressure (COP), down 14%
COP-pulmonary capillary wedge pressure gradient, down 28%
Indices that are either unaltered or not affected to an appreciable degree in normal pregnancy:
Mean arterial pressure
Pulmonary capillary wedge pressure (PCWP)
Central venous pressure
Pulmonary artery pressure
Left ventricular stroke work index (LVSWI)
LVSWI/PCWP

TABLE 19.6. Classical clinical picture of severe, untreated PE.

Factor	Change
Left ventricular function	Marked elevation
Cardiac output	Moderate elevation
Systemic vascular resistance	Marked elevation
Colloid osmotic pressure	Usually decreased
Mean arterial pressure	Marked elevation
Central venous pressure	Modest decrease
Plasma volume	Modest decrease
Blood viscosity	Small elevation
Red blood cell (RBC) deformability	Mild increase
Pulmonary vascular resistance	Unaffected
Urine output	Moderate decrease

Source: From Gatt S. Clinical management of established pre-eclampsia/gestational hypertension: perspectives of the midwife, neonatologist and anaesthetist. In: Brown M (ed) Baillière's Clinical Obstetrics and Gynecology. Pregnancy and Hypertension Edition, vol 1. Baillère's Best Practice and Research. London: Baillère Tindall 1999:95–105, with permission.

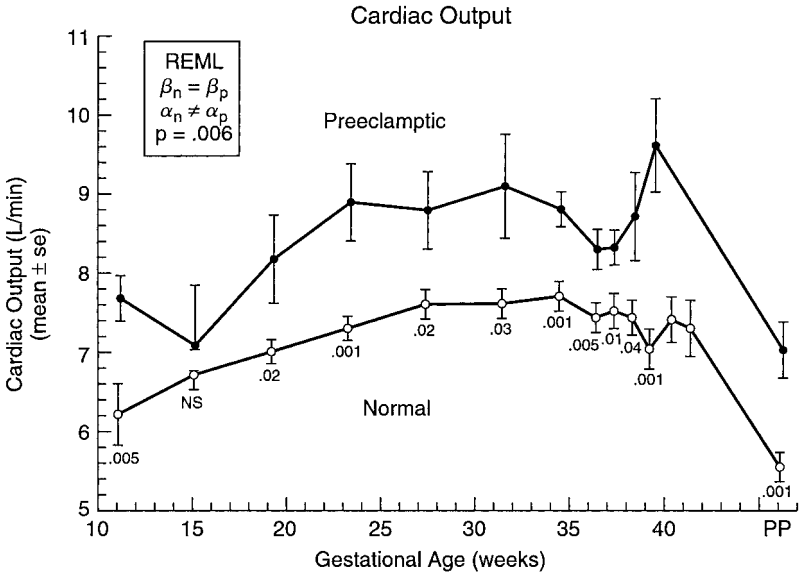

FIGURE 19.1. Mean blood pressure in preeclamptic (*filled circles*) and normal (*open circles*) throughout and after pregnancy. (Modified with permission from Easterling TR, Benedetti TJ. Maternal hemodynamics in normal and preeclamptic pregnancies. A longitudinal study. Obstet Gynecol 1990;76:1061–1069.)

Medical Treatment of Hypertension in Nonpregnant Women of Childbearing Age

The main groups of drugs used in the management of hypertension preexisting before pregnancy are the β_1 selective (e.g., metoprolol) and nonselective (e.g., propranolol) β-blockers; the α-blockers (e.g., prazosin); the combined α- and β-blockers (e.g., labetalol); the thiazide (e.g., hydrochlorothiazide); thiazide-like (e.g., indapamide); and potassium-sparing (e.g., triamterene with hydrochlorothiazide) diuretics; other diuretics (e.g., frusemide); the centrally acting antihypertensives (e.g., methyldopa, clonidine); the vasodilators (e.g., hydralazine); the angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril); the dihydropyridine (e.g., nifedipine) and nondihydropyridine (e.g., verapamil) calcium channel blockers; and the angiotensin II receptor antagonists (e.g., irbesartan).[36–38]

The agents used for treatment of hypertension in nonpregnant women of childbearing age are summarized in Table 19.7, and the thiazide and thiazide-like diuretics are classified in Table 19.8.[36,39] Not all these agents are appropriate for use in pregnancy or delivery.[39,41]

Suitability of Hypertension Medications in Pregnancy

The ACE inhibitors are contraindicated in pregnancy as they are associated with fetal renal dysfunction and oligohydramnios.[38] They are also a cause of fetal wastage.[40] The angiotensin II receptor antagonists are similarly associated with adverse fetal renal development and should not be used in pregnancy.

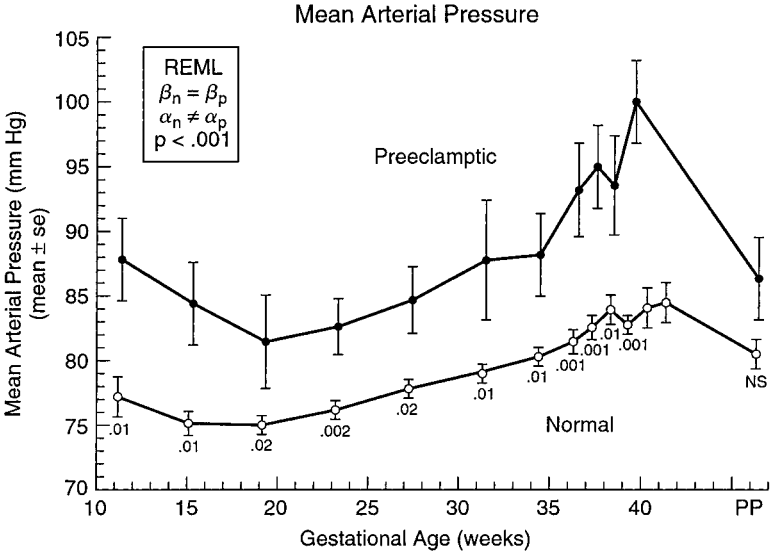

FIGURE 19.2. Cardiac output in preeclampsia (PE) (*full circles*) and non-PE (*open circles*): women at each week of gestation (*x*-axis) and in the postpartum period. (Modified with permission from Easterling TR, Benedetti TJ. Maternal hemodynamics in normal and preeclamptic pregnancies. A longitudinal study. Obstet Gynecol 1990; 76:1061–1069.)

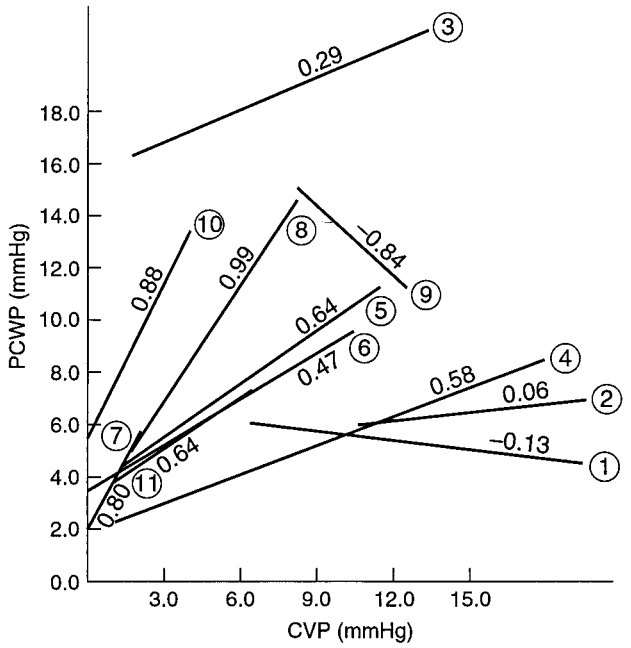

FIGURE 19.3. Correlation between central venous pressure (*CVP*) and pulmonary capillary wedge pressure (*PCWP*) in severe PE. The correlation is poor, and it is worst when CVP is less than 6 cm H_2O. (Reproduced with permission from Newsome LR, Bramwell RS, Curling PE. Hemodynamics in severe preeclamptics. Anesth Analg 1986;65:33.)

Atenolol is associated with intrauterine growth retardation.[42] Esmolol may be useful in the acute management of hypertensive crises but has been associated with profound fetal bradycardia.[43] Diuretics can cause further contraction of an already depleted intravascular volume in the mother and may result in fetal electrolyte imbalance. The thiazide and related diuretics have been reported to cause fetal thrombocytopenia.

The calcium channel blockers do not have any direct adverse neonatal effects but can cause fetal hypoxia secondary to maternal hypotension.[38] They may also potentiate respiratory embarrassment when used in combination with magnesium sulfate.

Labetalol, oxprenolol, hydralazine, methyldopa, prazosin, and clonidine are all efficacious and relatively safe.[1,44,45] Nifedipine, nitroglycerine, nitroprusside, and trimetaphan are used in those with severe disease during labor, cesarean section, and immediately postpartum (vide infra).[40]

Hypertension Management Immediately Before Delivery

The antihypertensive agent or techniques that may be needed immediately before delivery in cases of severe hypertension when SAP is 160 mm Hg or higher and DAP is 110 mm Hg or higher[46] may have to be different from those used for routine management of hypertension in the antenatal period. The main requirements are that these agents are sufficiently short acting that their effect is transient in the event that hypotension supervenes, that they are extremely potent so that they can be

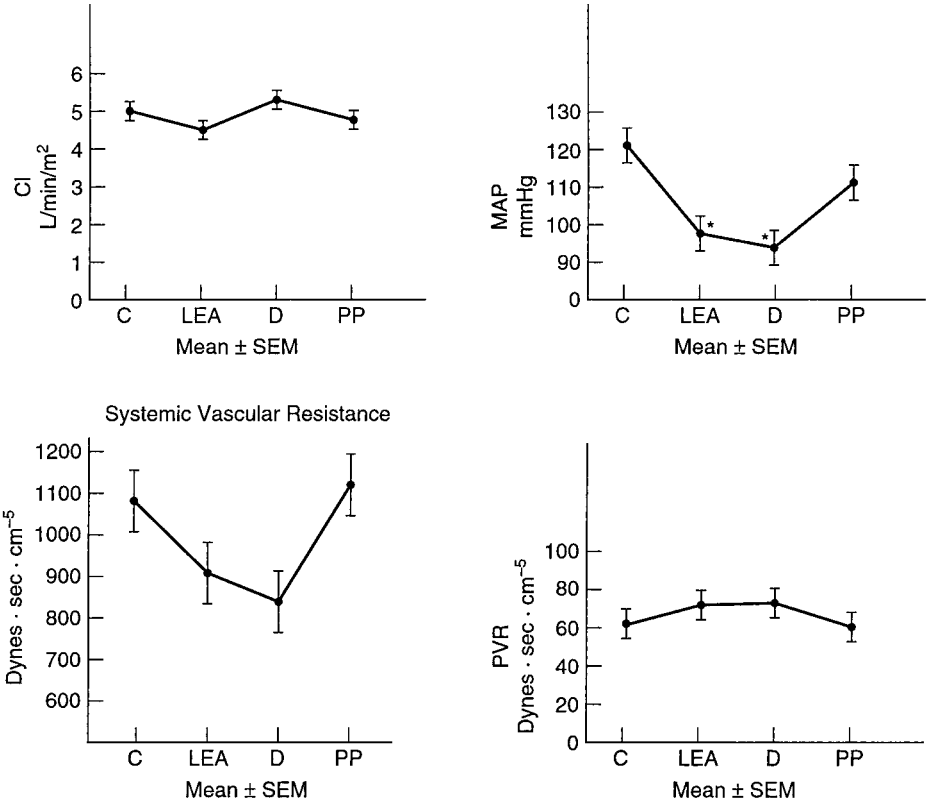

FIGURE 19.4. Cardiac index (*CI*), mean systemic arterial pressure (*MAP*), systemic vascular resistance (*SVR*) and pulmonary vascular resistance (*PVR*) in severely preeclamptic patients at control (*C*), after lumbar epidural anesthesia (*LEA*), at delivery (*D*), and 2 h postpartum (*PP*). (Reproduced with permission from Newsome LR, Bramwell RS, Curling PE. Hemodynamics in severe preeclamptics. Anesth Analg 1986;65:33.)

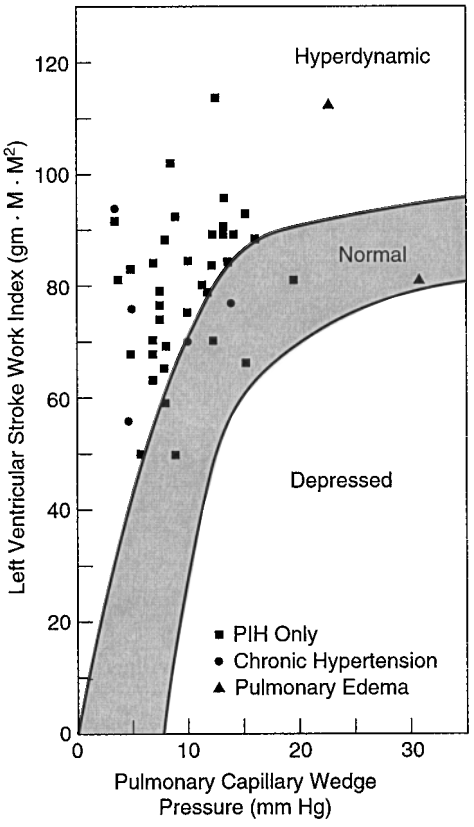

FIGURE 19.5. Left ventricular curves in women with severe untreated PE, chronic hypertension, and pulmonary edema. *PIH*, pregnancy-induced hypertension. (Reproduced with permission from Cotton DB, Lee W, Huhta JC, et al. Hemodynamic profile of severe pregnancy induced hypertension. Am J Obstet Gynecol 1988;158:523–529.)

titrated to effect, and that they produce their effect (preferably) by arteriolar dilatation. They should have minimal or no effect on the fetus when they are used in the short term.

Although the antihypertensive drugs used most commonly in pregnancy are labetalol, methyldopa, oxprenolol, and hydralazine[47] [but not the ACE inhibitors and (some) Ca^{2+} channel blockers], if more rapid control of hypertensive crises is required, sodium nitroprusside (SNP),[48] nitroglycerine (TNG), trimetaphan (Arfonad), bolus hydralazine, minibolus diazoxide, and β- or α-adrenoreceptor blockers (e.g., labetalol) may be necessary.[1,49–51]

TABLE 19.8. Thiazide and thiazide-like diuretics.

Class of thiazide	Agent
Thiazide	Bendrofluazide
	Chlorothiazide
	Chlorthalidone
	Hydrochlorothiazide
Thiazide-like	Indapamide
Potassium-sparing combinations	Triamterene + hydrochlorothiazide
	Amiloride + hydrochlorothiazide

Source: From Drug and Therapeutics Information Service. National Prescribing Service (NPS) News 1999;6:3, with permission.

Obstetric Management

The aim of treating preeclampsia is to prolong the pregnancy to a stage that maximizes fetal viability but does not endanger the mother's well-being.

Drug Treatment of Hypertension

There is no evidence of improved fetal well-being from the control of maternal blood pressure, but arterial pressure control may protect the mother from adverse effects associated with uncontrolled hypertension, especially intracerebral hemorrhage. Although a causal link remains unproven, the evidence for this comes from noting the increase in use of antihypertensive agents in PE in association with a reduction in maternal deaths from intracerebral hemorrhage over the past

TABLE 19.7. Agents for treatment of hypertension.

Class of drug	Subclass	Drug
β-Blockers	β_1 selective	Atenolol, metoprolol, timolol
	Nonselective	Propranolol, oxprenolol, pindolol
α-Blockers		Prazosin
α- and β-Blockers		Labetalol, carvedilol
Centrally acting antihypertensives		Methyldopa, clonidine
Vasodilators		Hydralazine, minoxidil
Diuretics	Thiazide	Bendrofluazide, chlorothiazide, chlorthalidone, hydrochlorothiazide
Thiazide-like diuretics		Indapamide
Potassium-sparing diuretic combinations		Amiloride/hydrochlorothiazide
		Triamterene/hydrochlorothiazide
Angiotensin-converting enzyme (ACE) inhibitors		Captopril, enalapril, fosinopril, isinopril, perindopril, quinapril, ramipril, trandolapril
Ca^{2+} channel blockers	Dihydropyridines	Amlodipine, felodipine, nifedipine
	Nondihydropyridines	Verapamil, diltiazem
Angiotensin II receptor antagonists		Irbesartan, candesartan

Source: From 1999 World Health Organization. International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999;17:151–183, with permission.

decade.[6,20] It is important that blood pressure is reduced to a safe level rather than attempting to achieve "normal" pregnancy levels. Too aggressive blood pressure control may actually lead to a reduction in placental blood flow and fetal compromise.

Agents to lower blood pressure are divided into those used for the longer-term home or hospital management of PE and those used for acute hypertensive episodes, usually in the delivery suite or operating theater environment. Orally administered agents are the mainstay of treatment of the former (methyldopa, oxprenolol, labetalol, clonidine, hydralazine, nifedipine). Acute hypertensive episodes usually require parenterally administered drugs (hydralazine, labetalol, diazoxide, or, for more severe pressure rises, SNP, glyceryl trinitrate, or trimetaphan). The potent intravenous agents require invasive arterial blood pressure monitoring during their use.

Bedrest

Although traditionally prescribed, bedrest appears to be of minimal or no benefit in the management of PE.

Aspirin

Low-dose aspirin (50–100 mg) has been suggested as an agent to prevent or modify the severity of PE by correcting the prostacyclin/thromboxane A_2 imbalance. The large multicenter CLASP study failed to demonstrate a reduction in PE incidence with the nonselective use of low-dose aspirin.[52] However, the most recent Cochrane Collaboration systematic review of effectiveness and safety of antiplatelet agents showed a 15% decrease in the risk of PE and a 7% decrease in risk of delivery before 37 completed weeks when low-dose aspirin is used. The reviewers concluded, however, that there are insufficient data available to make clear recommendations as to which women are most likely to benefit, when treatment should be started, and at what dose.[53,54] Current obstetric practice generally uses low-dose aspirin in those mothers identified as being at high risk of developing PE. The use of aspirin is not a contraindication to the use of regional anesthesia.

Calcium

Early observational studies suggested that a high-calcium diet and calcium supplementation might reduce the likelihood of developing PE. Subsequent work indicated calcium supplements result in a modest decrease in the risk of PE. The effect is greatest for those women at high risk of developing PE and those with low baseline calcium intake. To date, there is no evidence that perinatal outcome is improved if women with established PE add calcium supplements to their diet.[55]

Fish Oils and Salt Restriction Diets

Fish oils are high in ω-3 fatty acids which compete with arachidonic acid and inhibit the production of thromboxane A_2. For this reason, diets high in fish oils have been suggested to reduce the risk of developing PE. The large European Multicentre Fish Oil Supplementation trial has proved this to be a false hope. Likewise, there appears to be no benefit from any other dietary manipulation including salt restriction.

Plasma Volume Expansion

Plasma volume is reduced in women with PE. There is no benefit for mother or fetus in plasma volume expansion in mild PE. Volume expansion can be beneficial if central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP) is low; if the woman has oliguria or deteriorating renal function; before placement of epidural, spinal, or combined spinal-epidural (CSE) block; or before initiating vasodilator therapy.[53,54,56]

Delivery of the Fetus

The only "cure" for PE is delivery of the fetus. The timing of delivery depends on the gestational age of the fetus and the severity of the mother's condition. The aim is to maximize fetal age and viability without endangering the mother's well-being. Preeclampsia occurring at term (≥37 weeks) is an indication for delivery. Before 32 weeks gestation, conservative management with careful monitoring of the mother and fetus is recommended. Between 32 and 37 weeks, every case needs individual assessment and a decision made on the relative maternal versus fetal condition.[57,58] The absolute and relative maternal and fetal indications for delivery are shown in Table 19.9.[37]

Volume Manipulation

Volume Restriction

Although women with PE are often edematous, they also have a reduced plasma volume.[33,50,53,56,59] Consequently, fluid restriction, sodium restriction, or the use of diuretics poses a

TABLE 19.9. Absolute and relative maternal and fetal indications for delivery in severe preeclampsia (PE).

Absolute	Relative
Maternal	Maternal
Convulsion	Severe hypertension
Cerebral irritability	Right upper quadrant abdominal pain
Heart failure	Heavy proteinuria
Oliguria with urine output <20 ml/hr	
Uncontrollable hypertension	
Rising serum creatinine (>50%)	
Thrombocytopenia	
Disseminated Intravascular coagulation	
Clinical placental abruption	
Fetal	Fetal
Fetal distress	Intrauterine growth retardation

Source: From Gallery EDM. Hypertension in pregnancy. Practical management recommendations. Drugs 1995;49(4):561, with permission.

great risk to them, and these treatments should not be used.[58] The only exceptions are those women with pulmonary edema[13,30,33,58,59] (which is usually iatrogenic) or with severe cerebral edema with raised intracranial pressure.

Volume Expansion

The contraction of central plasma volume in those with severe PE is usually in excess of 500 mL,[53] although this is not always the case.[56] The induction of vasodilatation without judicious volume preloading[50] or fluid administration *pari passu* with the imposition of vasodilatation (sometimes guided by central pressure monitoring)[60] in those with severe disease can pose a risk of precipitous, life-threatening blood pressure falls.[50,61]

Fluid preloading is recommended in preeclamptics having epidural anesthesia,[54,58] spinal or combined spinal anesthesia,[54] parenteral antihypertensive medication,[53] or intravenous magnesium therapy,[62] and in those who are oliguric,[58,63] or who have signs of central dehydration,[53] or in those whose central pressures (CVP and/or PCWP) are low.[63]

Because most women with severe PE are oliguric and have low plasma volume,[64] the majority will benefit from modest and gradual plasma volume expansion.[51] Volume expansion before anesthesia in the severe preeclamptic or eclamptic parturient reduces maternal hypotension and fetal heart rate abnormalties.[54]

Successful volume replacement is a matter of timing and balance; that is, treatment of several parameters simultaneously. Preferably, volume repletion and increasing vasodilatation should be achieved at the same time if pulmonary and cerebral edema on the one hand and blood pressure drops on the other are to be avoided.[51] Parallel adjustments should be made to relieve the vasospasm, oliguria, hypertension, and hypovolemia.[57,61,65] Also, it should be remembered that the hemodynamic balance is continuously changing as treatment proceeds.[33,57]

Magnesium

Although there is little doubt that magnesium sulfate is efficacious in the management of those with eclampsia and severe PE, there is little evidence that it is of use in those with mild PE and gestational hypertension; if one agent is to be used, magnesium sulfate appears to be the best choice.[66,67]

Magnesium is superior to antihypertensive agents in preventing seizures in those with severe PE.[67] In randomized controlled trials, in those who received antihypertensives, the seizure rate was 2.8% (22/793) as compared to a rate of 0.9% (7/815) in those who received magnesium.[66] Table 19.10. offers a therapeutic plan for the prevention of convulsions in those who either have severe PE or have already experienced a convulsion.[65]

TABLE 19.10. Prevention of convulsions in those with severe preeclampsia (PE) or prior convulsion.

Previous seizure:
Magnesium sulfate
Diazpam
Phenytoin (less commonly)
Both phenytoin and magnesium (rarely)
Severe preeclampsia
Control of blood pressure
Lumbar epidural block
Magnesium
Diazpam/phenytoin

Source: Modified from Gatt S. Hypertensive disorders and renal disease in pregnancy and labour. In: Birnbach D, Gatt S, Datta S (eds) Obstetric Anesthesia. New York: Harcourt, 2000, with permission.

Anesthetic Management

There is mounting evidence that spinal and CSE anesthesia is as safe as epidural anesthesia for the severe preeclamptic.[68,69] There is even a suggestion that a continuous spinal technique can be of benefit.[70] A randomized comparison of anesthetic techniques in those with severe PE shows that, during anesthesia for cesarean section, the mean arterial pressure (MAP) rises at intubation in the general anesthesia (GA) group. Also, MAP is considerably lower in the spinal group than in both the GA and epidural groups.[71] Although the number of women in each subgroup (epidural, 27; CSE, 27; GA, 26) was small, it seems that, in severe PE, both general and regional techniques are equally acceptable for cesarean delivery if steps are taken to ensure a careful approach to either method.[68]

The traditional wisdom has been that epidural anesthesia would seem to be superior to GA for cesarean section and that, in labor and delivery, epidural analgesia has the added advantage of improved blood pressure control, increased renal and uteroplacental blood flow, and decreased potential for seizures. Nevertheless, in some, a regional block is contraindicated if there is concurrent coagulopathy or active bleeding. Table 19.11 shows that the systemic arterial pressures during cesarean section under GA, epidural block, and CSE are not very different.[71] The risks of GA in severe PE include hemodynamic instability at induction and intubation and again at extubation. Hypertension and tachycardia can lead to raised intracranial pressure.[35]

Level of Platelet Count and Regional Anesthesia

Major epidural bleeding with subsequent neurologic deficit is a very rare complication of obstetric anesthesia.[69] It would seem that epidural and CSE anesthesia are safe in those preeclamptics with platelet counts greater than 100×10^9/L, perhaps even in those with counts greater than 75×10^9/L. Justifiably, there is significant reluctance amongst obstetric anesthesiologists to undertake epidural or CSE in those parturients with platelet counts below 50×10^9/L. Between 50 and 100×10^9/L lies a gray zone in which the clinician has to weigh the risk of epidural/CSE anesthesia against a host of other competing risks (e.g., difficult airway, platelet function defects, respiratory depression in the neonate, other markers of disseminated intravascular coagulation).

TABLE 19.11. Systemic arterial pressure during cesarean section under general anesthesia (GA), epidural anesthesia (EDB), and combined spinal-epidural anesthesia (CSE).

Arterial pressure	GA	EDB	CSE
Highest SAP	170	163	158
Highest DAP	108	103	102
Lowest SAP	112	110	110
Lowest DAP	60	59	61

SAP, systolic arterial systemic pressure; DAP, diastolic arterial systemic pressure.

Source: From Wallace DH, Leveno KJ, Cunningham FG, et al. Randomised comparison of general & regional anesthesia for cesarean delivery in pregnancies complicated by severe PE. Obstet Gynecol 1995;86:2, with permission.

In the absence of an absolute test that can define this risk, an arbitrary point of platelet count needs to be selected below which there is a theoretical risk of bleeding of sufficient magnitude as to produce nerve root, cauda equina, or spinal cord compression. There is still controversy as to whether the remaining platelets are normal in PE. There are those who have demonstrated that, in all but the most severe preeclamptics/eclamptics with disseminated intravascular coagulation or evidence of hemolysis, the platelets are normal[34]; others have found some platelet function abnormalities.[72]

It should be remembered that, in the presence of severe thrombocytopenia, once bleeding in the epidural or subdural spaces commences, it can be very hard to monitor, to investigate, or to control. Very few patients with PE or eclampsia have a platelet count well below 90×10^9/L.[73] Also, neurologic damage is rare. In a review of 23,287 parturients, the incidence of neurologic damage was 36.2 per 10,000 for epidural block, 34.7 per 10,000 following general anesthesia, and 18.9 per 10,000 following vaginal delivery without anesthesia/analgesia. None of these women had a platelet count below 69×10^9/L, none had clinical evidence of bleeding, and in none was the platelet count falling. Only 30 had platelet counts below 100×10^9/L.[74] On the other hand, denying epidural anesthesia to a woman may be detrimental to her health, especially if she requires GA and has an anticipated difficult airway.[75]

From reviews of the case reports to date, it would seem that a platelet count of 54×10^9/L (95% confidence limits, 40–75×10^9/L) is associated with adequate clot formation.[72,74] As the upper limit of the 95% confidence interval for the relationship is a platelet count of 75×10^9/L, regional anesthesia should not be denied to PE patients with platelet counts greater than this.[65,72,74]

Thromboelastographic studies show that clot strength declines rapidly with decreasing platelet count below 80×10^9/L.[61,76] Figures 19.6. and 19.7 show the thromboelastographic evidence for the assertion that there may be increasing risk from regional blockade as the platelet count falls below 75 to 80×10^9/L.[72,76]

Both clinical experience and laboratory evidence suggest that a safety cutoff point of 75 to 80×10^9/L is justified. For most institutions, the consensus position at which, if all other hazards balance out, the obstetric anesthesiologist would not use a major neuraxial regional technique as the method of choice to produce anesthesia for cesarean section or other operative delivery, analgesia for vaginal delivery, or blood pressure control in PE revolves around this platelet value. In 1996, a survey of anesthesiologists showed that 66% of academic anesthesiologists and 55% of private practice anesthesiologists will place an epidural when platelet count is between 80×10^9/L and 100×10^9/L.[75]

Bleeding Time Test

Although thrombocytopenia is not rare, there are relatively few patients who have a very low platelet count that will contraindicate the placement of an epidural (Table 19.12). In the gray zone between 50×10^9/L and 100×10^9/L, can the bleeding time (BT) be of assistance in deciding whether there is an increased probability of epidural hematoma? There is no evidence that BT can predict the magnitude of bleeding, or that it changes sufficiently in advance to allow for successful intervention, and it does not correlate with degree of epidural bleeding.[77]

Management and Prophylaxis of Convulsions

Convulsions should be treated promptly using IV thiopentone or diazepam. It is also important to maintain a patent airway, to administer oxygen by face mask, and to apply

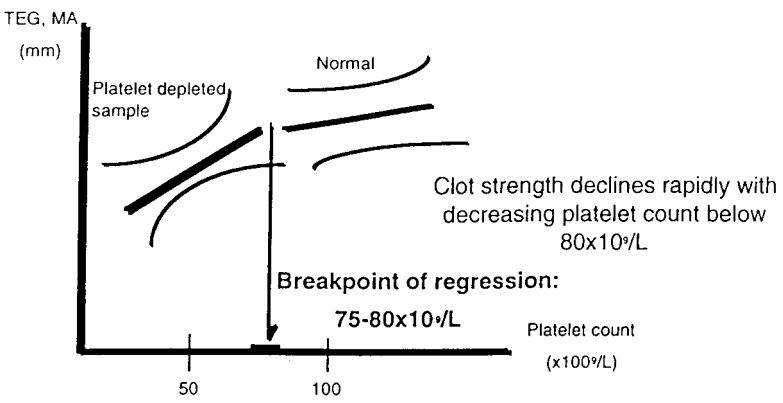

FIGURE 19.6. Clot strength as measured by maximum amplitude (*MA*) of thromboelastograph (*TEG*) as platelet count is progressively decreased. As the platelet count falls below 75–80×10^9/L, the clot strength declines rapidly. (Modified with permission from Warren E, Lyons G, Columb MO, Gorton H. Thrombocytopenia, regional blockade, and thromboelastography. Eur Soc Meet Abstracts 2000;A498.)

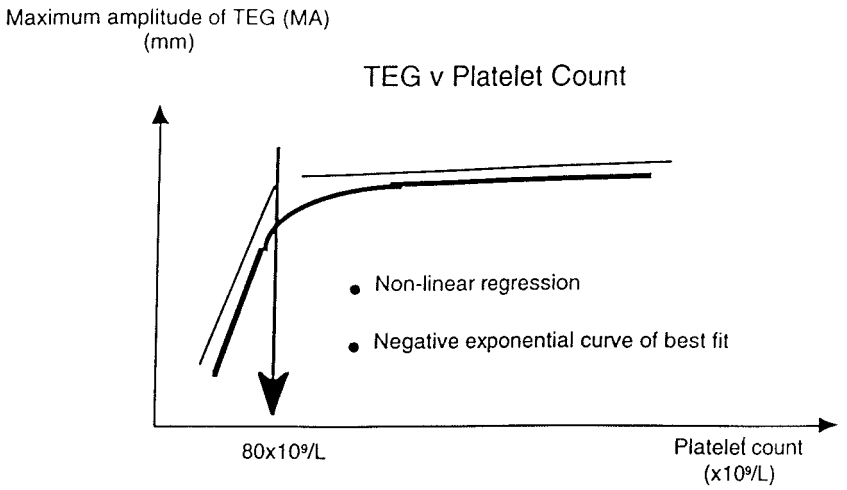

FIGURE 19.7. Maximum amplitude of thromboelastograph (*MA*) in millimeters as a function of platelet count. At a platelet count of around 80×10^9/L, the negative exponential curve of best fit shows a dramatic change of slope. TEG, thromboelastograph. (Modified with permission from Orlikowski CEP, Rocke DA, Murray WB, et al. Thromboelastography changes in pre-eclampsia and eclampsia. Br J Anaesth 1996;77:157–161.)

left lateral pelvic tilt. Recurrence of convulsions can be reduced by placement of effective sympathetic block (epidural anesthesia), by strict control of hypertension, and by prophylactic administration of magnesium sulfate (or, in a limited number of situations, phenytoin)[6,62,78,79] (see Table 19.10).

Magnesium is superior to both diazepam and phenytoin for the control of seizures.[80] In those who had already had a seizure, those receiving magnesium had a 52% lower risk of recurrence than those receiving diazepam and a 67% lower risk than those given phenytoin.[78] Recurrent seizures occured in 23.1% (216/935) of those receiving phenytoin and 9.4% (88/932) of those who received magnesium in a summary of randomized, controlled studies in eclamptics.[66] Magnesium is also superior to diazepam or phenytoin for the treatment of eclampsia[66,78,80] (See Table 19.10).

TABLE 19.12. Incidence of thrombocytopenia in the mild and severe preeclamptic pregnant and normal pregnant patient.

	Thrombocytopenia		
	$<150 \times 10^9$/L	$<100 \times 10^9$/L	$<50 \times 10^9$/L
Severe preeclampsia (PE)			
Pritchard et al. (1976)	25.0%		
Gibson et al. (1982)	20.0%		
Kelton et al. (1985)	34.0%		
Gatt et al. (1988)	22.5%	7.5%	2.5%
Orlikowski et al. (1996)[72]	37.0%	14.0%	
Mild and severe preeclampsia			
Ramanathan et al. (1980)	30.0%		
Normal pregnancy			
Rolbin et al. (1988)	6.4%		

Postdelivery Care

Although PE invariably resolves following delivery, there is a period of several days postpartum when the mother remains at risk from the disease. Forty percent (40%) of eclamptic seizures occur after delivery. Pulmonary edema resulting from fluid overload and deteriorating renal function also often occur postpartum. The nadir of platelet count and function occurs 24 to 36 h postpartum, gradually improving thereafter. It is important not to be complacent in the postpartum management of the disease. Antihypertensives usually need to be continued and only weaned once the hypertension has resolved. Continuation of a continuous epidural infusion will give good analgesia and, as a useful adjunct, will help with blood pressure control. Magnesium infusions should be continued at least 24 h after the most recent seizure in the case of eclampsia. Daily platelet count, hemoglobin, and renal function tests are indicated in severe PE.

Follow-Up

Long-term follow-up of women who have had PE is usually undertaken by the obstetrician to ensure that blood pressure and renal function have returned to normal by 3 months postpartum.

Admission to the Intensive Therapy Unit

Severe preeclamptics and eclamptics should be admitted to the ITU when (1) invasive monitoring needs to be instituted because pulmonary edema or intractable hypertension or anuria supervene, (2) severe hypertension needs immediate management, especially if neurologic symptoms supervene, (3) severe oliguria or anuria needs aggressive management (e.g., invasive monitoring and dialysis),[81,82] (4) repeat convulsions need to be controlled (and prophylaxis instituted), (5) massive blood loss (from disseminated intravascular coagulation, abruptio placentae, or postpartum hemorrhage) or

HELLP occur,[22,26] or (6) the dire sequelae of PE—intracerebral (pontine hemorrhage,[83] cerebral edema, choroidal ischemia[84]) or intraabdominal (liver rupture, hepatic subcapsular hematoma) catastrophes—supervene.[1,61,65]

Summary

From the anesthesiologist's point of view, the first contact with the parturient is usually during labor or cesarean section and delivery. In this situation, the time spent in volume preloading, blood pressure control, stabilization of the mother's condition, and choice of anesthetic or analgesia technique is time well spent.[3,41] Such preparation will often reduce fetal and maternal morbidity.[6] Consequently, it is imperative that the anesthetist be warned early of such women presenting for delivery.

References

1. Magee LA, Ornstein MP, von Dadelszen P. Management of hypertension in pregnancy. BMJ 1999;318:1332–1336.
2. Paruk F, Moodley J. Maternal and neonatal outcome in early- and late-onset preeclampsia. Semin Neonatol 2000;5:3:197–207.
3. Gatt S. Pre-eclampsia. In: Birnbach DJ (ed) Ostheimer's Manual of Obstetric Anesthesia, 3rd edn. New York: Saunders/Harcourt Brace, 1999.
4. Walker JJ. Pre-eclampsia. Lancet 2000;356:1260–1295.
5. Mörtl MG, Schneider MC. Key issues in assessing, managing and treating patients presenting with severe preeclampsia. Int J Obstet Anesth 2000;9:39–44.
6. Gatt S. Clinical management of established pre-eclampsia/ gestational hypertension: perspectives of the midwife, neonatologist and anesthetist. In: Brown M (ed) Baillière's Clinical Obstetrics and Gynaecology, Pregnancy and Hypertension Edition: Baillère's Best Practice and Research, vol 13. London: Baillère Tindall, 1999;95–105.
7. Salonen-Ros H, Lichtenstein P, Lipworth L, Cnattingius S. Genetic effects on the liability of developing pre-eclampsia and gestational hypertension. Am J Med Genet 2000;91:256–260.
8. Broughton-Pipkin F. What is the place of genetics in the pathogenesis of preeclampsia? Biol Neonate 2000;76:325–330.
9. Lie R, Rasmussen S, Brunborg H, et al. Fetal and maternal contributions to risk of preeclampsia: population-based study. BMJ 1998;316:1343–1347.
10. Higgins JR, de Swiet M. Blood-pressure measurement and classification in pregnancy. Lancet 2001;357:131–135.
11. Schneider MM, Landau R, Mörtl MM. New insights in hypertensive disorders of pregnancy. In: Obstetric & Gynecologic Anaesthesia: Baillere's Best Practice & Research. London: Lippincott Williams & Wilkins, 2001:291–297.
12. Schobel H, Fischer T, Geiger H, Schmieder R. Preeclampsia: a state of sympathetic overactivity. N Engl J Med 1996;335(20):1480–1485.
13. Easterling TR, Benedetti TJ, Schmucker BC, et al. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstet Gynecol 1990;76:1061.
14. Mattar F, Sibai BM. Eclampsia: risk factors for maternal morbidity. Am J Obstet Gynecol 2000;182:307–312.
15. Lo YM. Fetal DNA in maternal plasma. Ann NY Acad Sci. 2000;46: 1903–1906.
16. Ohkuchi A, Minakami H, Sato I, et al. Predicting the risk of pre-eclampsia and small for gestational age infant by quantitative assessment of the diastolic notch in uterine artery flow velocity waveforms in unselected women. Ultrasound Obstet Gynecol 2000;16:171–178.
17. Aquilina J, Barnett A, Thompson O, Harrington K. Comprehensive analysis of uterine artery flow velocity waveforms for the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2000;16:163–170.
18. Holzgreve W, Li JC, Steinborn A, et al. Elevation in erythroblast count in maternal blood before the onset of pre-eclampsia. Am J Obstet Gynecol 2001;184:165–168.
19. Bosio P, McKenna P, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstet Gynecol 1999; 94:978–984.
20. United Kingdom Health Department. Why Mothers Die. A Report on the Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996 CEMD Triennium. London: Stationery Office, 1999.
21. Stone P, Cook D, Hutton J, et al. Measurements of blood pressure, oedema and proteinuria in a pregnant population of New Zealand. Aust N Z J Obstet Gynecol 1995;35:32–37.
22. Saphier CJ, Repke JT. Hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome: a review of diagnosis and management. Semin Perinatol 1998;22(2):118–133.
23. Onrust S, Santema JG, Aarnoudse JG. Pre-eclampsia and the HELLP syndrome still cause maternal mortality in the Netherlands and other developed countries; can we reduce it? Eur J Obstet Gynecol Reprod Biol 1999;82(1):41–46.
24. Sheikh RA, Yasmeen S, Pauly MP, Riegler JL. Spontaneous intrahepatic hemorrhage and hepatic rupture in HELLP syndrome: four cases and a review. J Clin Gastroenterol 1999;28(4):323–328.
25. Anumba DO, Robson SC. Management of pre-eclampsia and haemolysis, elevated liver enzymes, and low platelets syndrome. Curr Opin Obstet Gynecol 1999;11:2:149–156.
26. Jones SL. HELLP: a cry for laboratory assistance: a comprehensive review of the HELLP syndrome highlighting the role of the laboratory. Hematopathol Mol Hematol 1998;11(3):147–171.
27. Maalati K, Dawson RB, Collins JO, et al. Persistent preeclampsia post partum with elevated liver enzymes and hemolytic uremic syndrome. J Clin Apheresis 1999;14:(2):69–78.
28. Curtin WM, Weinstein L. A review of HELLP syndrome. J Perinatol 1999;19(2):138–143.
29. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal pregnancy. Am J Obstet Gynecol 1989;161(6):1439–1442.
30. Wasserstrum N, Cotton DB. Hemodynamic monitoring in severe pregnancy-induced hypertension. Clin Perinatol 1986;13:781.
31. Cotton DB, Gonik B, Doman KF, et al. Cardiovascular alterations in severe pregnancy induced hypertension: relationship of central venous pressure to pulmonary capillary wedge pressure. Am J Obstet Gynecol 1985; 151:762.
32. Newsome LR, Bramwell RS, Curling PE. Hemodynamics in severe preeclamptics. Anesth Analg 1986;65:33.
33. Cotton DB, Lee W, Huhta JC, et al. Hemodynamic profile of severe pregnancy induced hypertension. Am J Obstet Gynecol 1988;158:523–529.
34. Schindler M, Gatt S, Isert P, et al. Thrombocytopenia and platelet functional defects in preeclampsia: implications for regional anaesthesia. Anaesth Intensive Care 1990;18:169.
35. Williams K. Hypertension in pregnancy. Can Family Physician 1995;41: 626–632.
36. World Health Organisation. International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999;17:151–183.
37. Gallery ED. Hypertension in pregnancy. Practical management recommendations. Drugs 1995;49(4):555–562.
38. Mastrobattista JM. Angiotensin converting enzyme inhibitors in pregnancy. Semin Perinatol 1997;21(2):124–134.
39. Drug and Therapeutics Information Service. National Prescribing Service (NPS) News 1999;6:3.
40. Burrows RF, Burrows EA. Assessing the teratogenic potential of angiotensin-converting enzyme inhibitors in pregnancy. Aust N Z J Obstet Gynecol 1998;38:306–309.
41. Gatt SP. Gestational proteinuric hypertension. Curr Opin Anesthesiol 1991;5:354–359.

42. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999;12: 541–547.
43. Australian Drug Evaluation Committee, Government Department of Health and Family Services. Australian Categorization of Risk of Drug Use in Pregnancy: Prescribing Medicines in Pregnancy, 4th edn. Canberra: Australian Government Publishing Service, 1999:1–59.
44. Walters BNJ, Redman CWG. Treatment of severe pregnancy-associated hypertension with the calcium antagonist nifedipine. Br J Obstet Gynecol 1981;21:11–15.
45. Gallery EDM, Ross M, György AZ. Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. Br Med J 1985;291:563–566.
46. Chadwick HS, Easterling T. Anesthetic concerns in the patient with preeclampsia. Semin Perinatol 1991;15(5):397–409.
47. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for the treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 1984;148:951.
48. Naulty S, Cefalo RC, Lewis PE. Fetal toxicity of nitroprusside in the pregnant ewe. Am J Obstet Gynecol 1981;139:708.
49. CDC Surveillance Summary. Maternal mortality in pregnancy in the USA from 1980 to 1985: US maternal mortality surveillance, 1980–85. MMWR 1988.
50. Guidelines Clearing House Statement "Hypertension." Summary and recommendations for a rational hypertension guideline in Germany. Z Arzt Fortbd Qualitatssich 2000;94:5:341–349.
51. Van Hook JW. Management of complicated preeclampsia. Semin Perinatol 1999;23(1):79–90.
52. CLASP: a randomised trial of low dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994; 343:619–629.
53. Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of women with pre-eclampsia. Cochrane Database Syst Rev 2000;2:CD001805.
54. Hofmeyr GJ. Prophylactic intravenous preloading for regional analgesia in labour. Cochrane Database Syst Rev 2000;2:CD000175.
55. Van den Elzen HJ, Wladimiroff JW, Overbeek TE, et al. Calcium metabolism, calcium supplementation and hypertensive disorders of pregnancy. Eur J Obstet Gynecol Reprod Biol 1995;59(1):5–16.
56. Brown MA, Zammit VC, Mitar DM. Extracellular fluid volumes in pregnancy-induced hypertension. J Hypertens 1992;10:61–68.
57. Brown MA, Gallery EDM, Gatt SP, et al. Consensus statement. Management of hypertension in pregnancy, consensus statement of the Australasian Society for the Study of Hypertension in Pregnancy. Executive summary. Med J Aust 1993;158:700–702.
58. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy. Executive summary and full consensus statement. Aust NZ J Obstet Gynecol 2000;40(2):133–155.
59. Clark SL, Horenstein JM, Phelan JP, et al. Experiences with the pulmonary artery catheter in obstetrics and gynecology. Am J Obstet Gynecol 1985;152:374.
60. Gilbert WM, Towner DR, Field NT, Anthony J. The safety and utility of pulmonary artery catheterisation in severe pre-eclampsia and eclampsia. Am J Obstet Gynecol 2000;182:(6):1397–1403.
61. Gatt S. What has been happening on the pre-eclampsia front in the last few years? In: Abstract Book. Continuing Education Conference Australian and New Zealand College of Anaesthetists, New Zealand Society of Anaesthetists and Australian Society of Anaesthetists, 1999, p 41.
62. Appleton MP, Kuehl TJ, Raebel MA, et al. Magnesium sulfate versus phenytoin for seizure prophylaxis in pregnancy-induced hypertension. Am J Obstet Gynecol 1991;165:907–913.
63. Clark SL, Greenspoon JS, Aldahl D, et al. Severe pre-eclampsia with persistent oliguria: management of hemodynamic subsets. Am J Obstet Gynecol 1986;154:490.
64. Lyall F, Greer IA. Pre-eclampsia: a multifaceted vascular disorder of pregnancy. J Hypertens 1994;13:1339–1345.
65. Gatt S. Hypertensive disorders and renal disease in pregnancy and labour. In: Birnbach D, Gatt S, Datta S (eds) Obstetric Anesthesia New York: Harcourt, 2000.
66. Witlin AG, Sibai BM. Magnesium sulfate therapy in preeclampsia and eclampsia. Obstet Gynecol 1998;92:5:883–889.
67. Duley L, Gulmezoglu AM, Henderson-Smart DJ. Anticonvulsants in women with pre-eclampsia. Cochrane Database Syst Rev 2000;2: CD000025.
68. Hood D, Curry R. Spinal versus epidural anesthesia for cesarean section in severely preeclamptic patients. Anaesthesia 1999;9(5):1276–1283.
69. Lao TT, Halpern SH, MacDonald D, Huh C. Spinal subdural haematoma in a parturient after attempted epidural anaesthesia. Can J Anaesth 1993;40:340–345.
70. Overdyk FJ, Harvey SC. Continuous spinal anesthesia for cesarean section in a parturient with severe preeclampsia. J Clin Anesth 1998;10: 510–513.
71. Wallace DH, Leveno KJ, et al. Randomised comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. Obstet Gynecol 1995;86:2.
72. Orlikowski CEP, Rocke DA, Murray WB, et al. Thromboelastography changes in pre-eclampsia and eclampsia. Br J Anaesth 1996;77:157–161.
73. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Engl J Med 1993;329:1463–1466.
74. Gatt S. A platelet count of less than 75×10^9/L is a contraindication to lumbar epidural anesthesia—how low can you, go? [Abstract]. Anesthesiology 2000.
75. Beilin Y, Bodian CA, Haddad EM, Leibowitz AB. Practice patterns of anesthesiologists regarding situations in obstetric anesthesia where clinical mangement is controversial. Anesth Analg 1996;83:735–741.
76. Warren E, Lyons G, Columb MO, Gorton H. Thrombocytopenia, regional blockade and thromboelastography. Eur Soc Meet Abstr 2000;A498.
77. Channing Rodgers RP, Levin J. A critical reappraisal of the bleeding time. Semin Thromb Hemostasis 1990;16:1.
78. Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995;345:1455–1463.
79. Idama TO, Lindow SW. Magnesium sulphate: a review of clinical pharmacology applied to obstetrics. Br J Obstet Gynecol 1998;105(3):260–268.
80. Lucas MJ, Leveno KJ, Cunningham FG, et al. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995;333(4):201–251.
81. Sibai BM, Kustermann L, Velasco J. Current understanding of severe preeclampsia, pregnancy-associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and postpartum acute renal failure: different clinical syndromes or just different names? Curr Opin Nephrol Hypertens 1994;3(4):436–445.
82. Gartner HV, Sammoun A, Wehrmann M, et al. Preeclamptic nephropathy—an endothelial lesion. A morphological study with a review of the literature. Eur J Obstet Gynecol & Reprod Biol 1998;77(1):11–27.
83. Aguglia U, Tinuper P, Farnarier G, et al. Electroencephalographic and anatomoclinical evidence of posterior cerebral damage in hypertensive encephalopathy. Clin Electroencephalogr 1984;15:53–60.
84. Saito Y, Tano Y. Retinal pigment epithelial lesions associated with choroidal ischemia in preeclampsia. Retina 1998;19:(3):262–263.

20
Preterm Labor

Scott Segal and Errol R. Norwitz

The mean duration of singleton pregnancy is 40 weeks (280 days) dated from the first day of the last menstrual period. Term is defined as 2 SD from the mean or, more precisely, 37 to 42 completed weeks (266–294 days) of gestation. Preterm (premature) labor is defined as labor occurring before 37 completed weeks of gestation. Preterm birth occurs in 7% to 12% of all deliveries but accounts for more than 85% of all perinatal morbidity and mortality.[1,2] Although the ability of physicians to identify women at risk for preterm delivery has improved, the overall incidence of preterm birth has remained unchanged for the past 30 years. During this same period, improvements in perinatal outcome have resulted from antepartum steroid administration and advances in neonatal care. Solving the problem of premature delivery remains the single greatest challenge to maternal–fetal medicine in the twenty-first century.

Etiology

Preterm labor likely represents a syndrome rather than a diagnosis because the causes are varied. Indeed, several investigators have suggested replacing the term preterm labor with preterm birth syndrome. Approximately 20% of preterm deliveries are iatrogenic and are performed for maternal or fetal indications, including intrauterine growth restriction, preeclampsia, placenta previa, and nonreassuring fetal testing.[3] Of the remaining cases of preterm birth, around 30% occur in the setting of preterm premature rupture of the membranes, 20% to 25% result from intraamniotic infection, and the remaining 25% to 30% are caused by spontaneous (unexplained) preterm labor. The various etiologies of preterm labor are listed in Table 20.1.

Prediction and Prevention

Identification of those women most likely to experience preterm labor is an important goal of modern obstetric management because of the dramatic consequences of preterm birth and the relatively ineffective treatments for preterm labor once it occurs. Screening tests for prediction of preterm birth can be divided into four general categories: risk factor scoring, home uterine monitoring, assessment of cervical maturation, and measurements of endocrine/biochemical markers. Numerous risk factors for preterm birth have been identified (see Table 20.1), some of which are modifiable (cigarette smoking, illicit drug use), whereas others are not (African-American race, maternal age). Several risk factor-based scoring protocols based primarily on historical factors, epidemiologic factors, and daily habits, have been developed in an attempt to identify women at risk. Reliance on risk factor-based screening protocols alone, however, will fail to identify more than 50% of pregnancies that deliver preterm (low sensitivity), and the majority of women who screen positive will ultimately deliver at term (low positive predictive value).[4,5] As such, risk factor-based screening protocols have largely fallen out of favor. Similarly, although an increase in uterine activity is a prerequisite for preterm labor, home uterine monitoring of women at high risk of preterm delivery has not been shown to reduce the incidence of preterm birth.[6] However, such an approach has been shown to increase visits to the labor and delivery floor, increase obstetric intervention, and increase the cost of antepartum care.[6]

Cervical effacement is a prerequisite for preterm birth. Serial digital evaluation of the cervix in women at risk for preterm delivery is useful if the examination remains normal. However, an abnormal cervical finding (shortening or dilatation) is associated with preterm delivery in only 4% of low-risk women and 12% to 20% of high-risk women.[7] Real-time sonographic evaluation of the cervix, on the other hand, has demonstrated a strong inverse correlation between cervical length and preterm delivery.[8,9] If the cervical length is below the 10th percentile for gestational age, the pregnancy is at a sixfold increased risk of delivery before 35 weeks' gestation.[8] A cervical length of 15 mm or less at 23 weeks occurs in less than 2% of low-risk women but is predictive of delivery before 28 and 32 weeks in 60% and 90% of cases, respectively.[9] Whether obstetric interventions such as cervical cerclage or

TABLE 20.1. Risk factors for preterm delivery.

Nonmodifiable risk factors	Modifiable risk factors
Prior preterm birth	Cigarette smoking
African-American race	Illicit drug use
Age <18 or >40 years	Anemia
Poor nutrition	Bacteriuria/urinary tract infection
Low prepregnancy weight	Genital infection
Low socioeconomic status	?? Strenuous work
Absent prenatal care	?? High personal stress
Cervical injury or anomaly	
Uterine anomaly or fibroid	
Excessive uterine activity	
Premature cervical dilatation (>2 cm) or effacement (>80%)	
Overdistended uterus (twins, polyhydramnios)	
? Vaginal bleeding	

prophylactic tocolysis can modify the risk of preterm delivery associated with cervical shortening remains controversial.

A number of biochemical markers have been associated with preterm birth, including, but not limited to, activin, inhibin, follistatin,[10,11] fetal fibronectin,[12–14] collagenase,[15] and tissue inhibitors of metalloproteinases.[16] To date, fetal fibronectin is the only established biochemical screening test for preterm delivery. Elevated levels of fetal fibronectin in cervicovaginal secretions, which may reflect separation of the fetal membranes from the maternal decidua,[12] are associated with premature delivery. However, in a low-risk population, the positive predictive value of a positive fibronectin test at 22 to 24 weeks gestation for spontaneous preterm delivery before 28 weeks and 37 weeks was only 13% and 36%, respectively.[13] The value of this test may lie in its negative predictive value (99% of patients with a negative fetal fibronectin test will not deliver within 7 days),[14] which may prevent unnecessary hospitalization.

Although numerous risk factors for preterm delivery have been identified (see Table 20.1), it remains unclear whether modification or treatment of these risk factors will affect the overall incidence of preterm birth. It is generally accepted that regular prenatal care is associated with a decrease in the incidence of preterm birth. In 1993, the March of Dimes Multicenter Prematurity Prevention Trial conducted a randomized, controlled trial of 2395 women at high risk for preterm birth in which women were randomized to either standard of care or enhanced care intervention (which included more frequent prenatal visits, improved patient education regarding signs of preterm labor, and weekly pelvic examinations after 20–24 weeks).[17] There was no significant difference in spontaneous preterm birth rates between the two groups. The authors concluded that the "studied interventions are not recommended for similar populations." Bedrest is often recommended for women at high risk for preterm birth at an estimated cost of more than $250 million per year. Although bedrest has been shown to improve uteroplacental blood flow, leading to a slight increase in birth weight, it has not been shown to decrease the incidence of preterm delivery.[18]

Box 20.1. Guidelines for the prevention of preterm delivery.

- Prevention and early diagnosis of sexually transmitted diseases and genitourinary infections
- Cessation of smoking and substance abuse
- Cervical cerclage, if indicated
- Prevention of multifetal pregnancies
- Workforce policies for select women (such as flexible schedules, rest breaks)

The most contentious issue involves screening and treatment of genital infections. Lower genital tract infections have been associated with preterm delivery. Such infections may serve as a marker of upper genital tract infection or may lead to direct migration of organisms to the decidua, fetal membranes, and amniotic fluid. Bacterial vaginosis, for example, complicates 12% to 22% of all pregnancies and is strongly associated with preterm delivery.[19] There is a 40% increased incidence of very low birth weight infants born to women with untreated bacterial vaginosis,[19] and antibiotic treatment has been shown to decrease the rate of preterm labor and premature birth by 33% to 70%.[20,21] It is clear from these studies that women with symptomatic bacterial vaginosis should be treated (Box 20.1). Whether to screen all asymptomatic women for bacterial vaginosis, however, remains unclear. Indeed, several recent large prospective randomized controlled trials have suggested that screening and treating asymptomatic women for bacterial vaginosis may be associated with a paradoxical increased risk of preterm birth.[22] As such, this approach has recently been abandoned.

Obstetric Management

The last decade has seen a remarkable transformation in the obstetric care of the parturient experiencing preterm labor. Through the early 1990s, most authors (including those of the previous edition of this text) advocated aggressive short- and long-term tocolysis, maternal bedrest, hydration, and antibiotics, combined with corticosteroid therapy for fetal lung maturation. On the basis of several large randomized trials, many of these therapies have now been found to be of little benefit but associated with substantial cost and maternal morbidity. For this reason, the standard of care is now considered to be a more limited approach in which short-term tocolysis (<48 h) is used to facilitate corticosteroid therapy and possible transfer of the mother to a tertiary care center before delivery.[23]

Guidelines for the management of preterm labor are summarized in Box 20.2. A definitive diagnosis of preterm labor is mandatory before any treatment is initiated. Preterm labor remains a clinical diagnosis. The classical diagnosis of preterm labor includes regular phasic uterine contractions with progressive cervical effacement and/or dilatation before 37 weeks gestation. Cervical dilatation in the absence of uter-

Box 20.2. Guidelines for the management of preterm delivery.

- Confirm diagnosis of preterm labor
- Exclude contraindications to expectant management and/or tocolysis
- Administer corticosteroids, if indicated
- Group B *Streptococcus* chemoprophylaxis, if indicated
- Pharmacologic tocolysis
- Consider transfer to tertiary care center

ine contractions is seen most commonly in the second trimester and is suggestive of cervical incompetence. In this setting, cervical cerclage is the treatment of choice. Similarly, the presence of uterine contractions in the absence of cervical change should be referred to as premature uterine contractions or false labor but does not meet criteria for the diagnosis of preterm labor. As such, treating such women for preterm labor is likely to be effective, irrespective of the therapeutic regimen selected. The argument that treatment should be initiated before there is evidence of cervical change, to prevent the cervix from effacing and dilating, is not supported by the literature and likely represents recollection bias by practitioners who have had great success in "treating" women with premature uterine contractions.

In many instances, premature labor represents a necessary escape of the fetus from a hostile intrauterine environment, and, as such, aggressive intervention to stop labor may be counterproductive. Every effort should be made to exclude contraindications to expectant management and/or tocolysis, including, among others, intrauterine infection, unexplained vaginal bleeding, nonreassuring fetal testing, and intrauterine fetal demise. Indeed, evidence of nonreassuring fetal testing may prompt emergent cesarean delivery rather than tocolysis. Intraamniotic fluid infection is a clinical diagnosis with evidence of fetal tachycardia, uterine tenderness and contractions, maternal tachycardia, or maternal fever, usually in the setting of an elevated white cell count. Amniocentesis with culture-proven amniotic fluid infection remains the gold standard for the diagnosis but is of little clinical value, because a few days are usually needed to obtain the results. Amniotic fluid Gram stain may be useful, but it has a sensitivity of only about 50%.[24]

Bedrest and hydration are commonly recommended for the treatment of preterm labor but are without proven efficacy.[25] Although there are substantial data indicating that broad-spectrum antibiotic therapy can prolong latency in the setting of preterm premature rupture of the membranes remote from term, there is no consistent evidence that such an approach can delay delivery in women with preterm labor and intact membranes.[26,27]

Pharmacologic therapy of limited duration remains the cornerstone of modern management. Ethanol (which inhibits oxytocin release from the posterior pituitary) was the first effective tocolytic agent,[28] but adverse maternal side effects have severely limited its use. Although a number of alternative agents are now available (Table 20.2), no reliable data suggest that any of these agents are able to delay premature delivery for longer than 48 h. Because no single agent has a clear therapeutic advantage, the side-effect profile of each of the drugs will often determine which to use in a given clinical setting.[29–32] Magnesium sulfate (which acts both to suppress nerve transmission to uterine smooth muscle and to lower the concentration of intracellular calcium within myometrial cells, which is necessary for activation of the myosin–actin contractile unit) has a wide margin of safety and has become the first-line agent for use in preterm labor in North America.[33] β-Adrenergic agonists (which reduce intracellular calcium levels and decrease the sensitivity of the myosin–actin contractile unit to available calcium through an adenyl cyclase/cAMP-dependent mechanism) are also commonly used. Indeed, ritodrine hydrochloride is the only agent that has received approval from the U.S. Food and Drug Administration for the treatment of preterm labor. However, such agents have a higher incidence of major adverse effects compared with magnesium.[34]

Nifedipine (a dihydropyridone calcium entry blocker) is as effective as magnesium and β-adrenergic agonists in delaying preterm delivery and is associated with fewer maternal side effects.[35,36] The major concern limiting the use of calcium channel-blocking agents, however, is the reported adverse effect on uteroplacental blood flow. Prostaglandin synthesis inhibitors such as indomethacin, although capable of delaying premature birth,[37] have been associated with a number of serious neonatal complications, especially if given shortly before delivery.[38] Promising newer agents include potassium channel openers[39] and oxytocin receptor antagonists,[40] although recent reports on the efficacy of the oxytocin receptor antagonist 1-deamino-2-D-tyr-(OEt)-4-thr-8-orn-vasotocin/oxytocin (Atosiban) in the treatment of preterm labor have been disappointing, showing it to be no more effective than other tocolytics.[41,42]

Maintenance tocolytic therapy beyond 48 h has not been shown to confer any therapeutic benefit but does pose a significant risk of adverse side effects.[43,44] In a meta-analysis of 16 randomized trials conducted through the mid-1980s, King et al. found only modest prolongation of labor (24–48 h) and no improvement in neonatal outcome.[45] More recent trials including aggressive adjunctive therapies (including preterm labor education, weekly clinic visits, home uterine contraction assessment, daily phone contact, and 24-h perinatal nurse access) also failed to demonstrate efficacy of long-term oral or subcutaneous tocolytic therapy.[43,44] As such, maintenance therapy is not generally recommended. Oral β-agonist therapy may have a role in decreasing uterine irritability and thereby diminishing patient anxiety, physician telephone consults, and visits to labor and delivery. This effect should not be confused with the use of maintenance β-agonist therapy to "treat" preterm labor. Similarly, the concurrent use of two or more tocolytic agents has not been shown to be more effective than a single agent alone, and the cumulative risk of side effects generally pre-

TABLE 20.2. Management of preterm labor.

Tocolytic agent	Route of administration (dosage)	Efficacy[a]	Major maternal side effects	Major fetal side effects
Magnesium sulfate	IV (4–6 g bolus, then 2–3 g/h infusion)	Effective	Nausea, ileus, headache, weakness	Decreased beat-to-beat variability
	Oral maintenance (100–120 mg q 4 h)	Not effective	Hypotension Pulmonary edema Cardiorespiratory arrest ? Hypocalcemia	Neonatal drowsiness, hypotonia ? Ileus ? Congenital ricketic syndrome (with treatment >3 weeks)
β-Adrenergic agonists				
Terbutaline sulfate	IV (2 μg/min infusion, maximum 80 μg/min)	Effective Efective	Jitteriness, anxiety, restlessness, nausea, vomiting, rash	Fetal tachycardia Hypotension
	SC (0.25 mg q 20 min)	Not effective		Ileus
Ritodrine hydrochloride[b]	Oral maintenance (2.5–5 mg q 4–6 h)	Not effective Effective	Cardiac dysrythmias, myocardial ischemia, palpitations, chest pain	Hyperinsulinemia, hypoglycemia (more common with isoxsuprine)
	IV pump (0.05 mL/h)	Effective		Hyperbilirubinemia, hypocalcemia
Isoxsuprine hydrochloride	IV (50 μg/min infusion, maximum 350 μg/min)	Effective Not effective	Hypotension, tachycardia (more common with isoxsuprine)	? Hydrops fetalis
Salbutamol	IM (5–10 mg q 2–4 h)	? Effective		
	Oral maintenance (10–20 mg q 3–4 h)	Unproven Unproven	Pulmonary edema Paralytic ileus	
	IV (0.05–0.5 mg/min)		Hypokalemia	
	Oral (10 mg q 8–12 h)		Hyperglycemia, acidosis	
	IV (6–30 μg/min)			
	Oral (4 mg q 4–6 h)			
Prostaglandin inhibitors				
Indomethacin	Oral (25–50 mg q 4–6 h)	Effective	Gastrointestinal effects (nausea, heartburn), headache, rash Interstitial nephritis	Transient oliguria, oligohydramnios Premature closure of the neonatal, ductus arteriosus and persistent pulmonary hypertension
Naproxen	Rectal (100 mg q 12 h)	Effective		
Fenoprofen	Oral (375–500 mg q 6 h)	Effective		
Aspirin	Oral (200–300 mg q 6 h)	Effective		
Meloxicam	Oral (375–500 mg q 6–12 h) (investigational)	Unproven Unproven	Increased bleeding time (most common with aspirin)	? Necrotizing enterocolitis, intraventricular hemorrhage
Calcium channel blockers				
Nifedipine	Oral (20–30 mg q 4–8 h)	Effective	Hypotension, reflex tachycardia (especially with verapamil) Headache, nausea, flushing Potentiates the cardiac depressive effect of magnesium sulfate Hepatotoxicity	—
Nicardipine	Oral (20–40 mg q 8 h)	Unproven		
Verapamil	Oral (80–120 mg q 8 h)	Unproven		
Potassium channel openers				
Levcromakalin	(Investigational)	? Effective	?	?
Oxytocin antagonists				
Atosiban	IV (1 μM/min infusion, maximum 32 μM/min)	Effective	Nausea, vomiting, headache, chest pain, arthralgias	? Inhibit lactation
Phosphodiesterase inhibitor				
Aminophylline	Oral (200 mg q 6–8 h)	? Effective	Tachycardia	Fetal tachycardia
	IV (0.5–0.7 mg/kg/h)	? Effective		
Others				
Ethanol	(Historical interest)	Effective	Alcoholic intoxication	? Alcohol toxicity (theoretically)
Nitroglycerine	TD (10–50 mg q day)	Unproven	Hypotension, headache	Fetal tachycardia
	IV (100 μg bolus, 1–10 μg/kg/min infusion)	Unproven	Profound hypotension	Uteroplacental insufficiency
Diazoxide	IV (1–3 mg/kg infusion)	Unproven		

IM, intramuscular; IV, intravenous; SC, subcutaneous; TD, transdermal.

[a]Efficacy is defined as proven benefit in delaying delivery by 24–48 h as compared with placebo or standard control.

[b]The only tocolytic agent approved by the U.S. Food and Drug Administration.

cludes this course of management.[46] The use of sequential therapy, however, may be beneficial.[47] Cyclic therapy, such as treatment with oxytocin receptor antagonists at night and β-agonists during the day, is currently being considered, but there is as yet no evidence that this approach is any more effective than standard tocolytic therapy. In the setting of preterm premature rupture of the fetal membranes, tocolysis has not been shown to be effective and is best avoided.[48]

Anesthetic Management

The evolution in modern obstetric management of parturients with preterm labor has led to changing priorities for the anesthesiologist in the management of these patients. In particular, the lessened popularity of long-term treatment with β-agonists has diminished the importance of the interactions of these agents with anesthetics. However, there are several important issues to consider when planning the anesthetic care of the woman with preterm labor, and indeed the anesthesiologist fills an important role in the successful outcome for both the mother and infant. The anesthetic goals in preterm labor are summarized in Box 20.3.

Early Consultation

An important facet of the care of the parturient in preterm labor is the unpredictable nature of the delivery process. Most obstetricians will attempt at least short-term tocolysis of infants who may benefit from steroid therapy. The early care of these women, therefore, will likely be expectant, with no immediate plans for delivery. If the parturient does proceed to active labor, delivery may be imminent, the fetus may be compromised by rapid progression and descent, and emergency vaginal or cesarean delivery may be required. The situation may demand immediate anesthetic care. Only by careful early consultation with the woman and obstetrician can the anesthesiologist deliver a safe and appropriate anesthetic. Although some parturients and obstetricians may be reluctant to initiate regional anesthesia for a woman in whom delivery is hopefully to be avoided, it is our practice to advise early epidural placement if only to avoid the need for emergency general anesthesia should the situation rapidly deteriorate. In some cases we place an epidural catheter, test it for appropriate position, and then allow the block to subside during the period of expectant management.

Box 20.3. Anesthetic goals for the management of preterm delivery.

- Early consultation with patient and obstetrician
- Preparation for precipitous vaginal delivery or emergency cesarean section
- Vaginal delivery: slow and controlled
- Cesarean section: emergencies common
- Minimize fetal effects of anesthetic drugs
- Avoid interactions with tocolytic drugs

Mode and Timing of Delivery

The obstetric literature is equivocal on the preferred mode of delivery for the preterm infant. The immature fetus, particularly one with very low birth weight or extreme prematurity, may poorly tolerate trauma during vaginal delivery. Preterm infants have less oxygen-carrying capacity due to their lower hemoglobin concentration and are therefore more susceptible to asphyxia during labor and birth. Softer cranial bones and less well developed dura mater, germinal matrix, and subependymal veins, combined with a lower concentration of circulating clotting factors, may render the premature infant more prone to intraventricular hemorrhage and neurologic impairment. Although it would therefore seem logical that cesarean section should be the preferred mode of delivery, performing an emergency operative delivery on a mother when the fetus is marginally viable is controversial. Moreover, the data supporting abdominal delivery are generally retrospective and poorly controlled.

Barrett and colleagues retrospectively examined the outcome in 109 infants with birth weights under 1000 g and found no difference in neonatal morbidity or mortality in the 750- to 1000-g infants.[49] There was a nonsignificant trend toward less intraventricular hemorrhage in the 500- to 750-g group. Conversely, Anderson and colleagues, in a prospective but nonrandomized study of 89 infants less than 1750 g, appeared to show a reduction in intraventricular hemorrhage with cesarean delivery before active-phase labor in the first hour after birth.[50] Interestingly, the incidence of this complication later in life and overall incidence did not differ with mode of delivery. However, there was a reduction in severe (grade III or IV) hemorrhage when active labor was avoided, regardless of mode of delivery. Similarly, Malloy et al. noted an increase in cesarean births from 24% to 44% in the early 1980s in Missouri for infants with birth weights of 500 to 1499 g.[51] There was a reduction in first-day death associated with cesarean delivery (10% versus 22% in the vaginal delivery group), attributable to a reduction of deaths, in the extremely low birth weight group (500–740 g). Death in the succeeding 6 days was higher in the cesarean group, however, so that the overall death rate did not differ between modes of delivery. Taken together, these studies suggest that severe morbidity and mortality is slightly and transiently reduced for extremely low birth weight infants but that no clear long-term advantage is realized. Meta-analysis of six small, randomized trials (total $n = 122$) confirmed no clear advantage of elective versus selective cesarean delivery of premature infants but showed a significant increase in maternal morbidity.[52]

When the premature infant is in the breech presentation, the decision to deliver abdominally is less controversial; vaginal breech delivery is not popular in the United States even for term infants. Some data however more definitively sup-

port cesarean delivery. For example, Main et al. showed a reduction in mortality from 58% to 29% with cesarean delivery in breech presentation infants less than 1500 g in a retrospective study in the early 1980s.[53] Conversely, in the one randomized trial attempted to date, Penn et al. were forced to close the trial due to low enrollment and the reluctance of many clinicians to attempt vaginal delivery of the premature breech infant.[54]

The anesthesiologist must therefore be prepared in many cases for cesarean delivery should signs of active labor or nonvertex position be present. Obstetricians may pursue aggressive tocolytic measures for a brief period to allow time for maternal steroid administration, followed by cesarean delivery. Awareness of the time course for completion of this therapy will assist the anesthesiologist in planning for the availability of appropriate resources when delivery must occur.

Type of Anesthesia

The anesthetic goals for delivery of the preterm infant are similar to those of other compromised fetuses. When vaginal delivery is contemplated, the timing may be uncertain (e.g., a long period of expectant management or attempted tocolysis may be followed by precipitous delivery). Cesarean delivery may either be planned or emergent, depending on the clinical situation. As is the case with most obstetric cases, regional anesthesia is generally preferred to general or no anesthesia. No prospective or high-quality retrospective studies exist addressing the choice of type of anesthesia. The limited data that have been reported favor regional anesthesia.[55] Early placement of an epidural catheter offers flexibility in providing labor analgesia, facilitating a slow, controlled vaginal delivery (which may reduce the possibility neonatal trauma), or producing surgical anesthesia for cesarean delivery should the fetal condition deteriorate. When cesarean delivery is certain, and no epidural catheter is in place, we prefer spinal anesthesia for its rapid onset of action, reliability, technical ease, minimal exposure of the mother and fetus to local anesthetic and other drugs, and avoidance of general anesthesia with its attendant risks to both mother and fetus.

Minimizing Effects of Anesthetics on the Fetus

The choice of local anesthetic for regional block may influence the condition of the preterm infant at delivery. Several factors render the preterm fetus more susceptible than the term fetus to the depressant or toxic effects of local anesthetics. Protein binding capacity is reduced because of less total protein[56] and reduced binding of local anesthetic to available protein.[57] Furthermore, high serum bilirubin in the fetus competes with local anesthetic for protein-binding sites.[58–60] The fetal blood–brain barrier is less well developed in the premature fetus, theoretically leading to toxicity at a lower total drug concentration.[61] Finally, asphyxia is more common in these fragile fetuses, and asphyxia alone contributes to toxicity because of ion trapping of local anesthetic in the fetal circulation, further reduction in protein affinity for local anesthetic, increased blood–brain barrier permeability, and increased sensitivity to the myocardial depressant effects of local anesthetic.[62–65] Formerly, the preterm human fetus was thought to have an immature ability to metabolize drugs, but this does not appear to be the case, as it is in some other species.[66–70]

The toxic effect of local anesthetic on the preterm fetus is a matter of common misconception. Most anesthesiologists are aware of the phenomenon of ion trapping, in which the weak base forms of local anesthetics become protonated and charged in the acidemic fetus leading to their accumulation in the fetus as a result of poor back-diffusion into the maternal circulation of the polar ionized form of the anesthetic. This trapping may lead to a positive umbilical vein/maternal vein (UV/MV) ratio[71] but should not result in high enough concentrations to be directly toxic to the fetus unless the maternal concentration is extremely high, a situation that would undoubtedly lead to signs of maternal toxicity as well. In fact, studies in fetal lambs suggest that the preterm fetus is actually less likely to experience toxicity from lidocaine than older fetuses. Teramo et al.[72] administered lidocaine via the femoral vein to preterm and term fetal lambs. Only when bolus doses of greater than 20 mg kg^{-1} were given directly intravenously to the fetus did signs of cardiovascular depression (as well as convulsions) appear. The fetal cardiovascular response was less pronounced and occurred at higher plasma levels in preterm versus term lambs.[72,73] Doses this large would result in a fetal plasma concentration more than 10 times that expected in the maternal circulation during epidural analgesia, which is unlikely to be observed even with extremes of ion trapping.

However, the preterm fetus may indeed be harmed by lidocaine. In several experiments also performed with the fetal lamb preparation, Morishima et al.[74,75] studied the effect of lidocaine on the fetal adaptive response to asphyxia. Fetal lambs were exposed to moderate asphyxia by umbilical cord clamping. The usual response to this stimulus is bradycardia and a shift in blood flow preferentially to vital organs (heart, brain, adrenal). Maternally administered lidocaine, but not saline control, impaired this compensatory response, resulting in fetal acidemia, hypotension, and reduced vital organ blood flow. This impairment was not seen in term fetal lambs[75] and was less pronounced when bupivacaine rather than lidocaine was administered.[76]

Although outcome studies in preterm humans have not been reported, chloroprocaine is associated with the lowest incidence of transient fetal heart rate abnormalities when compared to bupivacaine or lidocaine.[77] It would therefore seem reasonable to use chloroprocaine when the preterm fetus is compromised, especially if rapid induction of epidural anesthesia is required. Lidocaine and bupivacaine remain good choices in nonemergent situations. Of course, spinal anesthesia for cesarean section exposes the mother, and in turn the fetus, to minimal amounts of local anesthetic and is an ex-

cellent choice when operative delivery is certain. When general anesthesia is required, all the usual precautions in protecting the mother and fetus are indicated. In addition, the possible reduction in the capacity of the fetus to bind or eliminate maternally administered depressant drugs should be borne in mind.

Interactions of Tocolytic Drugs with Anesthetics

Although the popularity of long-term tocolysis is likely to continue to wane, parturients in preterm labor are still commonly treated with these agents for brief periods to allow for transfer to an appropriate facility or for corticosteroid therapy. Anesthesiologists must be aware of the anesthetic implications of therapy with these drugs, particularly because anesthesia may be required under emergency conditions for women receiving them. In addition, anesthesiologists may administer some of these drugs themselves in the setting of various obstetric emergencies.

β-Adrenergic Agonists: Ritodrine and Terbutaline

β_2-Adrenergic agonists activate adenylate cyclase and increase cytoplasmic cAMP, which in turn causes activation of a cAMP-dependent kinase that inactivates myosin light chain kinase (MLCK) (Figure 20.1) β_2-Agonists also may decrease intracellular calcium through a variety of mechanisms. Ritodrine and terbutaline are β_2 selective, but both possess significant β_1 activity as well, which explains some of their side effects. β-Adrenergic agonists cause substantial maternal side effects, leading to discontinuation in 10% to 25% of mothers. Cardiovascular and pulmonary effects are of particular importance to the anesthesiologist.

Tachycardia occurs because of direct β_1 and β_2 effects on the myocardium, as well as a reflex response to β_2-mediated vasodilatation and diastolic hypotension. This effect is dose related and may be minimized or treated by reducing the dose of the tocolytic. Chest pain and palpitations are common symptoms, and rarely, dysrhythmias (supraventricular tachycardia) and myocardial ischemia may occur. Changes in the ECG include ST-segment depression and T-wave flattening or inversion.

Pulmonary edema occurs in approximately 1% to 5% of patients treated with parenteral β-agonists and may be life threatening. Most reports have suggested that this complication occurs 24 to 72 h after beginning therapy and is more common in parturients receiving larger doses or multiple tocolytic drugs, in those with multiple gestations, in infected mothers, and possibly in women receiving large doses of crys-

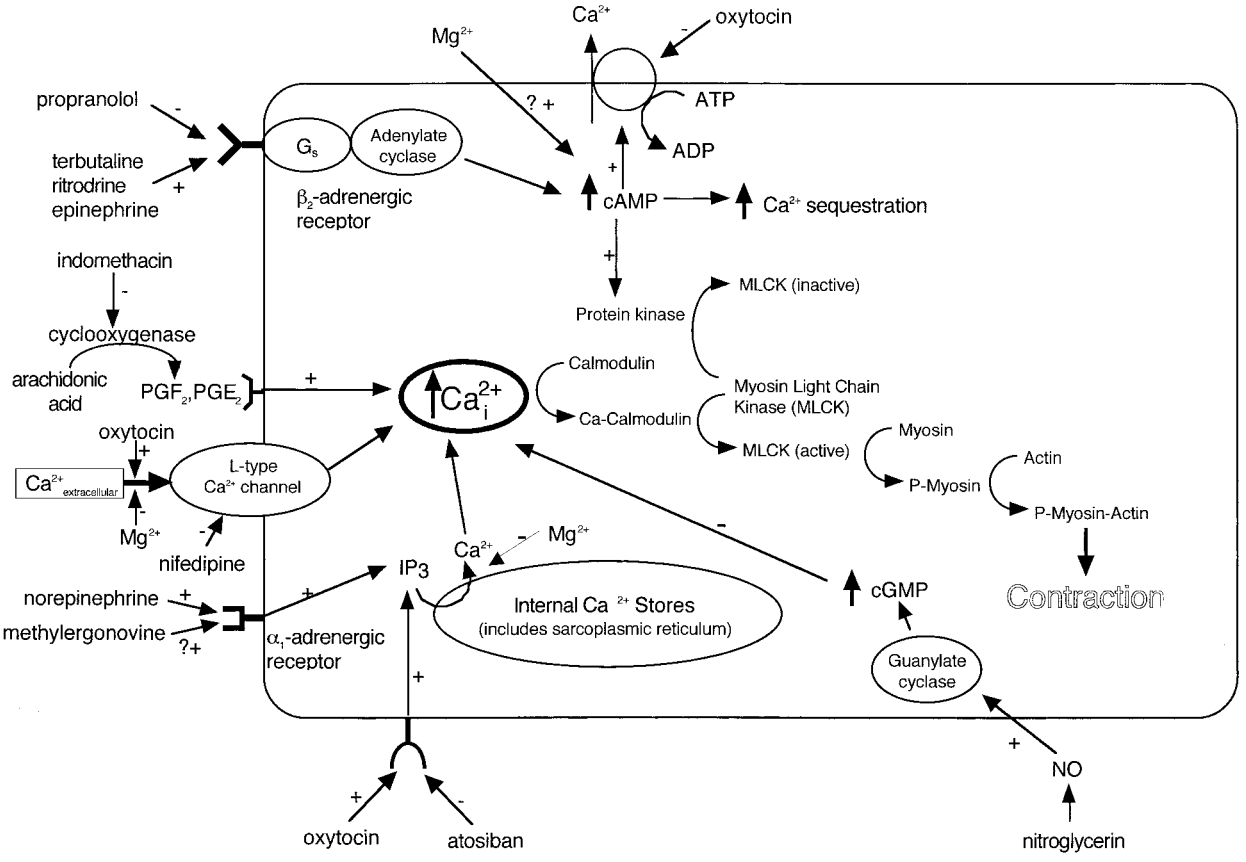

FIGURE 20.1. Schematic diagram of various mechanisms of pharmacologic manipulation of uterine contraction.

talloid solutions.[78] Several theories have been advanced to explain this complication, including fluid overload,[79] low colloid oncotic pressure,[80] and direct myocardial failure. The best data support a noncardiogenic mechanism; the strong correlation between infection and pulmonary edema suggests that capillary leak, not ventricular dysfunction, is the primary cause.[81] Furthermore, normal pulmonary capillary wedge pressure (PCWP) and the absence of myocardial failure detected by echocardiography in patients with pulmonary edema in the setting of β-agonist therapy support this hypothesis.[82] Pulmonary edema induced by β-agonists should be managed by fluid restriction (which reduces fluid translocation to the lung even in capillary leak syndromes), oxygen therapy, and discontinuation of the β-agonist. Only in rare cases is diuretic therapy, intubation, or mechanical ventilation required.

Hyperglycemia may occur due to β-receptor-mediated stimulation of pancreatic glucagon release and hepatic glycogenolysis. Hyperglycemia is usually self-limited except in diabetic mothers, and the latter may usually be managed with careful blood sugar monitoring and insulin therapy.

Hypokalemia occurs because of the insulin-mediated cotransport of glucose and potassium into the intracellular space. Total body potassium is normal, however, and potassium supplementation is not indicated.

Fetal and neonatal effects include increased heart rate, neonatal hypoglycemia caused by maternal hyperglycemia, and neonatal hyperinsulinemia. The possibility that long-term exposure to β-agonists could cause permanent myocardial injury to the neonate remains very controversial.

Tachycardia associated with β-agonist therapy may complicate treatment of maternal hypotension during regional anesthesia. A few case reports of exaggerated tachycardia or tachydysrhythmias have appeared, and many authorities have recommended that induction of anesthesia be delayed for 15 to 30 min after discontinuing parenteral β-agonist therapy. Hypotension has also been reported to be more common in patients receiving regional anesthesia in the setting of β-agonist therapy[83]. In experimental animals, however, hypotension was no more common after induction of epidural analgesia in sheep receiving ritodrine than in those receiving saline.[84]

The choice of vasopressor used to treat hypotension during regional anesthesia in the setting of β-agonist therapy must be individualized. Animal studies support the safety and effectiveness of ephedrine in restoring uterine blood flow, even in the setting of tachycardia.[85] Phenylephrine may also be used cautiously in these cases, in doses of 40 to 80 μg.[86] It should be noted, however, that the safety of phenylephrine has been established only in term, healthy fetuses, and not in the setting of the premature, possibly compromised fetus. Our practice is to begin with ephedrine in doses of 5 to 10 mg, closely monitoring for excessive tachycardia. If the heart rate exceeds 150, if dysrhythmias develop, or if the drug is ineffective in restoring maternal blood pressure, phenylephrine is used.

If general anesthesia is required, drugs causing further tachycardia should be avoided (e.g., pancuronium, atropine). Halothane should be avoided because of its ability to sensitize the myocardium to the dysrhythmic effects of maternal catecholamines. Hyperventilation should be avoided, because it may exacerbate hypokalemia.

Magnesium Sulfate

Magnesium sulfate ($MgSO_4$) inhibits calcium influx into the myometrial cell, inhibits calcium mobilization from the sarcoplasmic reticulum, and increases intracellular cAMP, all of which decrease the activity of MLCK and reduce contractile function of the cell (see Figure 20.1).

Magnesium sulfate ($MgSO_4$) is administered as an intravenous infusion. The usual loading dose is 4 g over 15 min, followed by 1 to 4 g/h. Serum levels and clinical examination are used to monitor the effect of magnesium therapy. Therapeutic concentrations are 4 to 6 mEq/L (5–7 mg/100 mL). Electrocardiographic changes, including QRS widening and prolonged P-R interval, can occur at 5 to 10 mEq/L but do not progress to sinoatrial (SA) or atrioventricular (AV) block until 15 mEq/L, and cardiac arrest occurs at still higher concentrations, approximately 25 mEq/L. Respiratory depression occurs at approximately 10 to 15 mEq/L. Deep tendon reflexes are suppressed at 10 mEq/L, so clinical examination can be an effective screening monitor for toxicity.

Magnesium sulfate ($MgSO_4$) is eliminated by the kidney, and caution must be exercised in the setting of renal insufficiency. Serum levels decrease rapidly after discontinuation of the drug in patients with normal renal function. Side effects of $MgSO_4$ are generally less severe than those of β-adrenergic drugs. Chest pain, palpitations, hypotension, nausea, sedation, blurred vision, and, rarely, muscle weakness and pulmonary edema have been reported. Modest vasodilatation occurs after bolus administration of $MgSO_4$, but the hypotension that may occur is short lived and does not persist with continued infusion.[87]

Some data suggest hypotension is more likely in parturients given regional anesthetics while receiving intravenous $MgSO_4$.[88] However, vasopressors including ephedrine have been shown to effectively normalize maternal blood pressure and uteroplacental blood flow in this setting. Phenylephrine may also be used, but the modest vasodilatation induced by magnesium does not prevent α-adrenergic mediated uterine vasoconstriction after large doses.[89]

Magnesium interferes with normal neuromuscular transmission.[90] Patients requiring general anesthesia may have reduced requirements for neuromuscular blocking drugs, because Mg ions can compete with acetylcholine at the postjunctional receptor as well as inhibit the release of acetylcholine from the prejunctional membrance. Defasiculating doses of nondepolarizing muscle relaxants should not be used, because complete paralysis may occur. Although $MgSO_4$ can also potentiate depolarizing drugs, a normal intubating dose of succinylcholine should be given, because the response is variable. Subsequent

doses of muscle relaxants of either class should be guided by use of a peripheral nerve stimulator.

Hypermagnesemic women may be sedated, and therapeutic $MgSO_4$ levels will decrease the minimal alveolar concentration (MAC) for volatile agents in experimental animals by approximately 20%.[91]

Inhibitors of Prostaglandin Synthesis

Indomethacin and related drugs inhibit cyclooxygenase and decrease production of the prostaglandins PGE_2 and PGF_2. Through mechanisms that remain incompletely understood, this effect decreases intracellular calcium and uterine contraction (see Figure 20.1).

Indomethacin can be given orally or rectally. The usual dose is 50 mg, followed by 25 mg every 4 to 6 h. Serum half-life is approximately 2 h in the mother but 11 to 19 h in the fetus. Furthermore, clinical effects may persist for some time after serum levels have decreased.

Maternal side effects are minimal and include gastrointestinal upset. Because cyclooxygenase inhibition also reduces thromboxane A_2 production, platelet aggregation is reduced as well. Unlike aspirin-induced platelet dysfunction, the effect of indomethacin is reversible.[92]

Fetal effects of indomethacin have limited the popularity of this drug, at least in the United States. Prostaglandins of the E class maintain patency of the fetal ductus arteriosus, and cyclooxygenase inhibitors can cause reversible ductal constriction. The risk appears to be related to gestational age; short courses of indomethacin (24–48 h) are tolerated well by fetuses under 32 to 34 weeks gestation. Longer courses and use closer to term are associated with a greater risk of ductal constriction and persistent fetal circulation at birth.[93]

Indomethacin also reduces fetal urine production, either by direct action on the fetal renal circulation or by increasing antidiuretic hormone action in the fetus. Amniotic fluid (primarily composed of fetal urine) is reduced by prolonged indomethacin use, and indeed, prostaglandin synthesis inhibitors are sometimes used to treat polyhydramnios. The effect is reversible after discontinuing the drug.[94]

Indomethacin is devoid of hemodynamic effects on the mother. There is a theoretical risk of increased bleeding, including epidural hematoma, in mothers taking prostaglandin synthesis inhibitors. However, the increased risk appears very small, and only a few case reports of such complications in women receiving these drugs exist.[95] A review of minor hemorrhagic complications during epidural placement also found no association with the use of nonsteroidal antiinflammatory drugs.[96] We do not routinely order tests of coagulation or bleeding time in otherwise asymptomatic patients receiving prostaglandin synthesis inhibitors.

Calcium Channel Blockers

Nifedipine and the other calcium entry-blocking drugs inhibit the L-type (voltage-dependent) calcium channel on the myometrial cell and decrease intracellular calcium (Figure 20.1). Nifedipine has been the most widely studied of the drugs in this class for use in tocolysis. Several nonrandomized studies have demonstrated excellent efficacy in short-term arrest of preterm labor with minimal fetal side effects. Maternal side effects include headache, nausea, and facial flushing; most studies have found that these side effects are mild and that the calcium channel blockers are better tolerated than β-agonists. Some animal data suggest decreased uteroplacental blood flow during nifedipine therapy, but this effect has not been observed in the clinical reports to date.[97]

Nifedipine is administered orally or sublingually in doses of 10 mg which may initially be repeated hourly until effective tocolysis has been observed or maternal side effects intervene (usually 40 mg is the maximum dose). Maintenance therapy is 10 to 20 mg orally every 4 to 6 h.

Used alone, nifedipine has minimal conduction, chronotropic, or hypotensive effects in normal subjects. However, in the presence of potent inhalational anesthetics, it can cause hypotension and atrioventricular conduction defects, vasodilation, and hypotension. Refractory uterine atony, unresponsive to both oxytocin and prostaglandin therapy, has also been reported.[98]

Nitroglycerin

Nitroglycerin (TNG) is a donor of nitric oxide, which, in vascular smooth muscle, stimulates guanylate cyclase increasing cyclic GMP and reducing intracellular calcium. In uterine muscle, the mechanism of the effect of TNG has not been firmly established, and there is some evidence that mechanisms other than NO-cGMP may operate, at least at supraphysiologic doses (see Figure 20.1).

Nitroglycerin has recently been introduced into clinical practice for short-term reduction in uterine activity, particularly in the treatment of tetanic contractions of the uterus that inhibit delivery of the infant or the placenta.[99,100] More recently, controlled trials have shown it to be as effective as β_2-agonists in short-term tocolysis, with a better side-effect profile.[101] Side effects of TNG have been mild. Headache and modest hypotension have occasionally been reported. A recent retrospective review of pulmonary edema in obstetric patients identified exposure to tocolytic TNG during open fetal surgery as a risk factor for more severe and longer-duration pulmonary dysfunction.[102]

Anesthesiologists usually administer TNG in obstetric emergencies, and care must be taken to dilute stock solutions of the drug appropriately. We dilute 10 mg of 5 mg/mL TNG in 250 mL saline to achieve a 40 μg/mL solution. Because TNG can adhere to plastic containers, it is necessary to dilute the drug immediately before use or to use commercially prepared infusions in glass bottles. Obstetricians and anesthesiologists must realize that the effect of bolus administration the drug is very brief, and all personnel must be immediately ready to perform the required obstetric intervention immediately after the uterus relaxes.

Postdelivery Considerations

The preterm neonate is at higher risk for a variety of complications, including acidosis, respiratory distress, hypovolemia and anemia, persistent fetal circulation, hypoglycemia, hypothermia, hypotonia, and hyperbilirubinemia. Ideally neonatologists and a well-equipped newborn intensive care unit should be available. However, as the second-line provider of neonatal resuscitation, the anesthesiologist must be prepared to assist in the immediate postdelivery care of these fragile neonates.

Summary

Although the ability of obstetric care providers to identify women at risk for preterm birth has improved during the past three decades, there are as yet no effective strategies available for the prevention or treatment of women at risk for preterm labor. Evolution of obstetric care of preterm labor over the past two decades has resulted in less emphasis on pharmacologic prolongation of gestation and a greater emphasis on optimal preparation for delivery should short-term tocolysis fail. The anesthesiologist can contribute to a better outcome for both the infant and mother by early consultation with the pregnant women and obstetric care team, by devising a flexible anesthetic plan to accommodate an uncertain timing and mode of delivery, and by appreciating the interactions between anesthetic and tocolytic drugs and their effects on both individuals.

References

1. Rush RW, Keirse MJNC, Howat P, et al. Contribution of preterm delivery to perinatal mortality. Br Med J 1976;2:965–968.
2. Villar J, Ezcurra EJ, de la Fuente VG, Canpodonico L. Pre-term delivery syndrome: the unmet need. Res Clin Forums 1994;16:9–33.
3. Tucker JM, Goldenberg RL, Davis RO, et al. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? Obstet Gynecol 1991;77:343–347.
4. Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Am J Obstet Gynecol 1980;55:692–695.
5. Mercer BM, Goldenberg RL, Das A, et al. The preterm prediction study: a clinical risk assessment system. Am J Obstet Gynecol 1996;174: 1885–1893.
6. Iams JD, Johnson FF, O'Shaughnessy RW. A prospective random trial of home uterine activity monitoring in pregnancies at increased risk of preterm labor. Am J Obstet Gynecol 1988;159:595–603.
7. Mortensen OA, Franklin J, Lofstrand T, et al. Prediction of preterm birth. Acta Obstet Gynecol Scand 1987;66:507–511.
8. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334: 567–572.
9. Heath VCF, Southall TR, Souka AP, et al. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynaecol 1998;12:312–317.
10. Petraglia F, De Vita D, Gallinelli A, et al. Abnormal concentration of maternal serum activin A in gestational diseases. J Clin Endocrinol Metab 1995;80:558–561.
11. Petraglia F. Inhibin, activin, and follistatin in the placenta: a new family of regulatory proteins. Placenta 1997;18:3–8.
12. Lockwood CJ, Senyei AE Dische MR, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325:669–674.
13. Goldenberg RL, Mercer BM, Meis PJ, et al. The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth. Obstet Gynecol 1996;87:643–648.
14. Iams JD, Casal D, McGregor JA, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. Am J Obstet Gynecol 1995; 173:141–145.
15. Rajabi M, Dean DD, Woessner JF. High levels of serum collagenase in preterm labor: a potential biochemical marker. Obstet Gynecol 1987;69: 179–186.
16. Clark IM, Morrison JJ, Hackett GA, et al. Tissue inhibitor of metalloproteinases: serum levels during pregnancy and labor, term and preterm. Obstet Gynecol 1994;83:532–537.
17. Collaborate Group on Preterm Birth Prevention. Multicenter randomized, controlled trial of a preterm birth prevention program. Am J Obstet Gynecol 1993;169:352–366.
18. Goldenberg RL, Cliver SP, Bronstein J, et al. Bed rest in pregnancy. Obstet Gynecol 1994;84:131–136.
19. Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med 1995;333:1737–1742.
20. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med 1995;333:1732–1736.
21. McGregor JA, French JI, Parker R, et al. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation. Am J Obstet Gynecol 1995;173: 157–167.
22. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500–1507.
23. American College of Obstetricians and Gynecologists. Preterm labor. ACOG Tech Bull 1995;206:710–719.
24. Romero R, Yoon BH, Mazor M, et al. A comparative study of the diagnostic performance of amniotic fluid glucose, white blood cell count, interleukin-6 and Gram stain in the detection of microbial invasion in patients with preterm premature rupture of membranes. Am J Obstet Gynecol 1993;169:839–851.
25. Guinn DA, Goepfert AR, Owen J, et al. Management options in women with preterm uterine contractions: a randomized clinical trial. Am J Obstet Gynecol 1997;177:814–818.
26. Gibbs RS, Romero R, Hillier SH, et al. A review of premature birth and sub-clinical infection. Am J Obstet Gynecol 1992;166:1515–1528.
27. Romero R, Sibai B, Caritis S, et al. Antibiotic treatment of preterm labor with intact membranes: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 1993;169:764–774.
28. Fuchs A-R, Fuchs F. Ethanol for prevention of preterm birth. Semin Perinatol 1981;5:236–251.
29. Norwitz ER, Robinson JN, Challis JRG. The control of labor. N Engl J Med 1999;341:660–666.
30. Besinger RE, Niebyl JR. The safety and efficacy of tocolytic agents for the treatment of preterm labor. Obstet Gynecol Surv 1990;45:415–440.
31. Higby K, Xenakis EM-J, Pauerstein CJ. Do tocolytic agents stop preterm labor? A critical and comprehensive review of efficacy and safety. Am J Obstet Gynecol 1993;168:1247–1259.
32. Hill WC. Risks and complications of tocolysis. Clin Obstet Gynecol 1995;38:725–745.
33. Norwitz ER, Robinson JN. The control of labor [Letter]. N Engl J Med 1999;341:2098–2099.
34. The Canadian Preterm Labor Investigation Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med 1992; 327:308–312.

35. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulfate in the management of preterm labor: a randomized study. Am J Obstet Gynecol 1993;169:960–964.
36. Papatsonis DNM, Van Geijn HP, Adär HJ, et al. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol 1997;90:230–234.
37. Zuckerman H, Shalev E, Gilad G, Katzuni E. Further study of the inhibition of preterm labor by indomethacin. Part II. Double-blind study. J Perinat Med 1984;12:25–29.
38. Norton ME, Merril J, Cooper BAB, et al. Neonatal complications after the administration of indomethacin for preterm labor. N Engl Med J 1993;329:1602–1607.
39. Morrison JJ, Ashford MLJ, Khan RN, Smith SK. The effects of potassium channel openers on the isolated human pregnant myometrium before and after the onset of labor: potential for tocolysis. Am J Obstet Gynecol 1993;169:1277–1285.
40. Anderson LF, Lyndrup J, Akerlund M, et al. Oxytocin receptor blockade: a new principle in the treatment of preterm labor? Am J Perinatol 1989;6:196–199.
41. Goodwin TM, Valenzuela G, Silver H, et al. Treatment of preterm labor with the oxytocin antagonist atosiban. Am J Perinatol 1996;13:143–146.
42. Goodwin TM, Zograbyan A. Oxytocin receptor antagonists: update. Clin Perinatol 1998;25:859–871.
43. Rust OA, Bofill JA, Arriola RM, et al. The clinical efficacy of oral tocolytic therapy. Am J Obstet Gynecol 1996;175:838–842.
44. Guinn DA, Goepfert AR, Owen J, et al. Terbutaline pump maintenance therapy for prevention of preterm delivery: a double-blind trial. Am J Obstet Gynecol 1998;179:874–878.
45. King JF, Grant AM, Keirse M, Chalmers I. Beta-mimetics in preterm labour: an overview of the randomized controlled trails. Br J Obstet Gynaecol 1988;95:211–222.
46. Ferguson JE, Hensleigh PA, Kredenster D. Adjunctive use of magnesium sulfate with ritodrine for preterm labor tocolysis. Am J Obstet Gynecol 1984;148:166–171.
47. Valenzuela G, Cline S. Use of magnesium sulfate in premature labor that fails to respond to beta-mimetic drugs. Am J Obstet Gynecol 1982; 143:718–719.
48. Allen SR. Tocolytic therapy in preterm premature rupture of membranes. Clin Obstet Gynecol 1998;41:842–848.
49. Barrett JM, Boechm FH, Vaughn WK. The effect of type of delivery on neonatal outcome in singleton infants of birth weight of 1,000 g or less. JAMA 1983;250:625–629.
50. Anderson GD, Bada HS, Sibai BM, et al. The relationship between labor and route of delivery in the preterm infant. Am J Obstet Gynecol 1988;158:1382–1390.
51. Malloy MH, Rhoads GG, Schramm W, Land G. Increasing cesarean section rates in very low-birth weight infants. Effect on outcome. JAMA 1989;262:1475–1478.
52. Grant A, Penn ZJ, Steer PJ. Elective or selective caesarean delivery of the small baby? A systematic review of the controlled trials. Br J Obstet Gynaecol 1996;103:1197–1200.
53. Main DM, Main EK, Maurer MM. Cesarean section versus vaginal delivery for the breech fetus weighing less than 1,500 grams. Am J Obstet Gynecol 1983;146:580–584.
54. Penn ZJ, Steer PJ, Grant A. A multicenter randomised controlled trial comparing elective and selective caesarean section for the delivery of the preterm breech infant. Br J Obstet Gynaecol 1996;103:684–689.
55. Wright RG, Shnider SM, Thirion A-V, et al. Regional anesthesia for preterm labor and vaginal delivery: effects on the fetus and neonate. Anesthesiology 1988;69:A654.
56. Cook LN. Intrauterine and extrauterine recognition and management of deviant fetal growth. Pediatr Clin N Am 1977;24:431–454.
57. Mather LE, Long GJ, Thomas J. The binding of bupivacaine to maternal and foetal plasma proteins. J Pharm Pharmacol 1971;23:359–365.
58. Boggs TR, Hardy JB, Frazier FM. Correlation of neonatal serum total bilirubin concentration and development status at age eight months. J Pediatr 1967;71:553–560.
59. Chez RA, Fleischman AR. Fetal therapeutics: challenges and responsibilities. Clin Pharmacol Ther 1973;14:754–761.
60. Cashore WJ, Stern L. Neonatal hyperbilirubinemia. Pediatr Clin N Am 1977;24:509–527.
61. Low JA, Wood Sl, Killen HL, et al. Intrapartum asphyxia in the preterm fetus <2000 gm. Am J Obstet Gynecol 1990;162:378–382.
62. Asling JH, Shnider SM, Margolis AJ, et al. Paracervical block anesthesia in obstetrics. II. Etiology of fetal bradycardia following paracervical block anesthesia. Am J Obstet Gynecol 1970;107:626–634.
63. Rosefsky JB, Petersiel ME. Perinatal deaths associated with mepivacaine paracervical block in labor. N Engl J Med 1968;278:530–533.
64. Anderson KE, Gennser G, Nilsson E. Influence of mepivacaine on isologated human foetal hearts at normal or low pH. Acta Physiol Scand 1970;353:34–47.
65. Morishima HO, Heyman MA, Rudolph AM, et al. Transfer of lidocaine across the sheep placenta to the fetus: hemodynamic and acid-base responses of the fetal lamb. Am J Obstet Gynecol 1975;122:581–588.
66. Rane A, Sjoqvist F, Orrenius S. Cytochrome P-450 in human fetal liver microsomes. Chem Biol Interact 1971;3:305.
67. Yaffe SJ, Juchau MR. Perinatal pharmacology. Annu Rev Pharmacol 1974;14:219–238.
68. Alvares AP, Shilling G, Levin W, et al. Cytochromes P-450 and b5 in human fetal liver microsomes. Clin Pharmacol Ther 1969;10:655–659.
69. Pelkonen O, Vorne M, Arvela P, et al. Drug metabolizing enzymes in human fetal liver and placenta in early pregnancy. Scand J Clin Lab Invest 1971;27(suppl):S116–S117.
70. Rane A, Sjoqvist F, Orrenius S. Drugs and fetal metabolism. Clin Pharmacol Ther 1973;14:666–672.
71. Biehl D, Schnider SM, Levinson G, Callender K. Placental transfer of lidocaine: efffects of fetal acidosis. Anesthesiology 1978;48:409–412.
72. Teramo K, Benowitz N, Heymann MA, et al. Effects of lidocaine on heart rate, blood pressure, and electrocorticogram in fetal sheep. Am J Obstet Gynecol 1974;118:935–949.
73. Teramo K, Benowitz N, Heymann MA, et al. Gestational differences in lidocaine toxicity in the fetal lamb. Anesthesiology 1976;44:133–138.
74. Morishima HO, Pedersen H, Santos SM, et al. Adverse effects of maternally administered lidocaine on the asphyxiated preterm fetal lamb. Anesthesiology 1989;71:110–115.
75. Morishima HO, Santos AC, Pedersen H, et al. Effect of lidocaine on the asphyxial responses in the mature fetal lamb. Anesthesiology 1987;66:502–507.
76. Santos AC, Yun EM, Bobby PD, et al. The effects of bupivacaine, L-nitro-L-arginine-methyl ester, and phenylephrine on cardiovascular adaptations to asphyxia in the preterm fetal lamb. Anesth Analg 1997; 85(6):1299–1306.
77. Abboud TK, Khoo SS, Miller F, et al. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. Anesth Analg 1982;61:638–644.
78. Katz M, Robertson PA, Creasy RK. Cardiovascular complications associated with terbutaline treatment for preterm labor. Am J Obstet Gynecol 1981;139:605–608.
79. Philipsen T, Eriksen PS, Lynggard F. Pulmonary edema following ritodrine-saline infusion in premature labor. Obstet Gynecol 1981;58: 304–308.
80. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. Ann Intern Med 1989;110:714–718.
81. Hatjis CG, Swain M. Systemic tocolysis for premature labor is associated with an increased incidence of pulmonary edema in the presence of maternal infection. Am J Obstet Gynecol 1988;159:723–728.
82. Finley J, Katz M, Rojas-Perez M, et al. Cardiovascular consequences of β-agonist tocolysis: an echocardiographic study. Obstet Gynecol 1984;64:787–791.

83. Shin YK, Kim YD. Anesthetic considerations in patients receiving ritodrine therapy for preterm labor (abstract). Anesth Analg 1986;65: S140.
84. Chestnut DH, Pollack KL, Thompson CS, et al. Does ritodrine worsen maternal hypotension during epidural anesthesia in gravid ewes? Anesthesiology 1990;72:315–321.
85. Chestnut DH, Ostman LG, Weiner CP, et al. The effect of vasopressor agents upon uterine artery blood flow velocity in the gravid guinea pig subjected to ritodrine infusion. Anesthesiology 1988;68:363–366.
86. Moran DH, Perillo M, LaPorta RF, et al. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean section. J Clin Anesth 1991;3:301–305.
87. Elliott JP. Magnesium sulfate as a tocolytic agent. Am J Obstet Gynecol 1983;147:277–284.
88. Vincent RD, Chestnut DH, Sipes SL, et al. Magnesium sulfate decreases maternal blood pressure but not uterine blood flow during epidural anesthesia in gravid ewes. Anesthesiology 1991;74:77–82.
89. Sipes SL, Chestnut DH, Vincent RD, et al. Which vasopressor should be used to treat hypotension during magnesium sulfate infusion and epidural anesthesia? Anesthesiology 1992;77:101–108.
90. Ramanathan J, Sibai BM, Pillai R, et al. Neuromuscular transmission studies in preeclamptic women receiving magnesium sulfate. Am J Obstet Gynecol 1988;158:40–46.
91. Thompson SW, Moscicki JC, DiFazio CA. The anesthetic contribution of magnesium sulfate and ritodrine hydrochloride in rats. Anesth Analg 1988;67:31–34.
92. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (eds). The Pharmacological Basis of Therapeutics, 9th edn. X: X, 1996:617–657.
93. Moise KJ. Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. Am J Obstet Gynecol 1993;168:1350–1353.
94. Kirshon B, Moise KH, Mari G, et al. Long-term indomethacin therapy decreases fetal urine output and results in oligohydramnios. Am J Perinatol 1991;8:86–88.
95. Williams KN, Jackowski A, Evans PJD. Epidural hematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. Pain 1990;42:197–199.
96. Horlocker TT, Wedel DJ, Schroeder DR, et al. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesth Analg 1995;80:303–309.
97. Murray C, Haverkamp AD, Orleans M, et al. Nifedipine for treatment of preterm labor: a historic prospective study. Am J Obstet Gynecol 1992;167:52–56.
98. Csapo AI, Puri CP, Tarro S. Deactivation of the uterus during normal and premature labor by the calcium antagonist nicardipine. Am J Obstet Gynecol 1982;142:483–491.
99. Peng AT, Gorman RS, Shulman SM, et al. Intravenous nitroglycerin for uterine relaxation in the postpartum patient with retained placenta. Anesthesiology 1989;71:172–173.
100. DeSimone CA, Norris MC, Leighton BL. Intravenous nitroglycerin aids manual extraction of a retained placenta. Anesthesiology 1990;73:787.
101. Lees CC, Lojacono A, Thompson C, et al. Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. GTN Preterm Labour Investigation Group. Obstet Gynecol 1999;94:403–408.
102. DiFederico EM, Burlingame JM, Kilpatrick SJ, et al. Pulmonary edema in obstetric patients is rapidly resolved except in the presence of infection or of nitroglycerin tocolysis after open fetal surgery. Am J Obstet Gynecol 1998;179:925–933.

21
Postdate Pregnancy

Pamela Jane Morgan and Fay Weisberg

Pregnancy commonly ends 280 days after the first day of the last menstrual period. Traditionally, a pregnancy that has completed 294 days from the last period has been associated with an increased risk of adverse fetal and neonatal outcomes. It is now believed that the risk of adverse perinatal events may be increased as early as 40 to 41 completed weeks.[1]

Pregnancy that extends beyond expected dates has been described in the literature for centuries. In 130 A.D. Gellius Aulus noted in his "collection of incongruous matter" called *Noctes Atticoe* that "the Emperor Hadrian, having consulted with the physicians and wise men, decreed that in cases in which the women was of chaste manners and irreproachable conduct, the child born eleven months after the death of a husband was legitimate."[2]

Obstetric Management

Accurate dating of the pregnancy is essential so that unnecessary and perhaps harmful intervention in a pregnancy that is not truly postterm can be avoided. Accurate dating also allows for the provision of effective care if the pregnancy is indeed postterm.

Dating of the pregnancy begins with the first day of the last menstrual period. Unfortunately, this may not be very precise, as it relies on the parturient's recollection of the date and may be further hampered by irregular cycles, the use of oral contraceptives, or long periods of amenorrhea before conception. Various other criteria have been used to help date the pregnancy, but their use in modern obstetrics is limited. These methods include early estimation of uterine size by bimanual examination, level of serum beta-human chorionic gonadotropin (βhCG), date of quickening, and abdominal palpation.

An ultrasound examination before 20 weeks of gestation is an excellent method of confirming or establishing the true gestational age of the fetus. Randomized controlled trials of routine versus indicated ultrasound have shown a decrease in induction of labor "for postterm pregnancy" among women having routine ultrasound scans.[3]

Incidence

An estimated 5% to 10% of all pregnancies are postterm.[3] This rate varies depending on the accuracy of pregnancy dating, the population studied, the frequency with which labor was induced, the frequency of elective cesarean section, the use of ultrasound, and the definition of postterm pregnancy. Studies undertaken within the last 15 years indicate that the incidence of postterm pregnancy has decreased, probably because of the increased use of ultrasound to date pregnancies. This decreasing incidence may also have an effect on the risk of perinatal mortality and morbidity.

Complications

The risks to the fetus and mother of continuing pregnancy beyond 42 weeks are well known (Table 21.1). In pregnancies complicated by hypertension, diabetes, or other risks for uteroplacental insufficiency, the risks to the neonate are even higher.[4]

Obstetric Management Strategies

Induction of labor has seemed an obvious approach to the postterm pregnancy with its attendant potential increase in complications. Inducing labor, however, is not always easy or uneventful when the cervix is unfavorable. In addition, not all patients elect to undergo induction, and terminating the pregnancy may not always be necessary. Given all the confounding variables associated with the problem of the postterm pregnancy, it is not surprising that there is no consistent approach to the management of this condition.

In general, labor induction is indicated when the benefits of delivery outweigh the risks to the mother or fetus of continuing the pregnancy. In low-risk pregnancies, there appears to be no indication to induce labor before 41 weeks. At 41 weeks, pregnant women can be managed by either antenatal serial monitoring, induction, or cesarean section. Management will depend

TABLE 21.1. Complications of postdate pregnancy.

Complication	Incidence in postdate pregnancy[a]
Fetal	
Perinatal death	4–7/1000 deliveries (2–3/1000 at 40 weeks)*[5]
Fetal macrosomia	
Meconium	2.5%—10% (0.8%–1% at 40 weeks)[6]
Fetal distress	37.7% (17.5% at 40 weeks)[7]
Uteroplacental insufficiency	8.4% (5% at 40 weeks)[6] 20%–40%[1]
Maternal	
Labor dystocia	9.5%–11.9% (2.4%–9.5% at 40 weeks)**[6]
Cesarean delivery	8.2% (5.4 at 40 weeks)***[8]
Severe perineal trauma	3.3% (2.6% at 40 weeks)[8]
Postpartum hemorrhage	10% (9.1% at 40 weeks)****[8]

[a]Superscripted numbers refer to reference list.
*Relative risk (RR) 1.68, confidence interval (CI) 1.02,1.76; **relative risk (RR) 1.26, confidence interval (CI) 1.23,1,29; ***relative risk (RR) 1.25, confidence interval (CI) 1.26,1.31; ****relative risk (RR) 1.09, confidence interval (CI) 1.06,1.12.

on the wishes of the expectant mother and physician and the condition of the cervix or the Bishop score (Table 21.2). This score is used as a predictor for the ease of labor induction.

Antepartum Assessment

If antenatal monitoring is chosen as a means of monitoring a postterm pregnancy, it should be commenced at 41 weeks gestation.[10] Many methods of antepartum fetal testing have been described; however, the biophysical profile has been shown to be the most predictive for both a normal pregnancy and one at risk for intrauterine hypoxia. When the score has been normal, waiting for spontaneous labor resulted in healthy neonates and a much lower cesarean section rate in postterm infants.[11] Currently, it is recommended that the biophysical profile be performed twice weekly at 41 weeks gestation, with immediate delivery if there is evidence of fetal compromise or oligohydramnios.[10]

Fetal heart rate decelerations observed during nonstress testing are predictive of increased fetal and neonatal morbidity and mortality in postterm pregnancies.[12] Induction is recommended in these instances, regardless of whether there are accompanying normal fetal heart accelerations. These decelerations are likely the result of decreased amniotic fluid volume.

Several studies have suggested that the identification of oligohydramnios determined by ultrasound may be used alone, with the nonstress test, or in conjunction with the biophysical profile to identify those postterm fetuses most at risk.[12]

TABLE 21.2. Bishop score

Score	Position of cervix	Consistency	Station	Effacement (%)	Dilatation (cm)
0	Posterior	Firm	−3	0–30	Closed
1	Midposition	Medium	−2	40–50	1–2
2	Anterior	Soft	−1,0	60–70	3–4
3			+1,+2	>80	>5

Source: Adapted from O'Brien W, Cefalo R. Labor and delivery. In: Gabbe S, Niebyl J, Simpson J (eds). Obstetrics: Normal and Problem Pregnancies. New York: Churchill Livingstone, 1986:351–378.

Labor Induction

Once the decision to induce labor is made, the route and management of the induction depends on the presenting part of the fetus, the Bishop score, and the presence or absence of conditions that do not allow for a vaginal delivery.

If the cervix is favorable, and the presenting part of the fetus engaged and well applied to the cervix, labor may be most easily induced by amniotomy with or without intravenous oxytocin. When the Bishop score is greater than 8, induction appears to be most successful.[13] If the cervix is unfavorable, and induction must be carried out, an attempt should be made to "ripen" the cervix using any of the accepted methods available, including prostaglandin gel, prostaglandin vaginal inserts, or mechanical methods. Once the cervix is more favorable, an amniotomy may be carried out, and labor managed accordingly.

There are few studies on the risk of labor induction in postterm pregnancies. The largest trial, the Canadian Multicenter Postterm Pregnancy Trial,[10] concluded that induction of labor resulted in a lower rate of cesarean section than serial antenatal monitoring, and that the rates of perinatal mortality and neonatal morbidity were similar with the two approaches to management.

Intrapartum Management

Labor is a particularly dangerous time for the postterm fetus. An early amniotomy will help identify the presence of meconium and allow for a scalp electrode if needed for continuous fetal monitoring. In labors that are accompanied by oligohydramnios or meconium staining, intraamniotic infusions have recently been shown to be effective for both reversing abnormal fetal heart rate tracings and decreasing the incidence of meconium aspiration in newborns.[14]

Anesthetic Management

The postterm parturient provides some challenges for the obstetric anesthesiologist. The higher incidence of cesarean section, instrumental delivery, and shoulder dystocia in this population increases the likelihood for the urgent or emergent need for an anesthesiologist. Nulliparous postterm parturients who present in spontaneous labor have been noted to have an increased incidence of cesarean section due to an increased incidence of uterine dysfunction.[8] Labor induction is not uncommon, especially if fetal surveillance methods have demonstrated abnormalities in measured parameters.[13] Many women request labor analgesia because induction or augmentation with oxytocin, long labor, and fatigue all contribute

to the severity of pain and the maternal ability to cope. The use of multimodal pain management strategies can be used to help ease pain following instrumental or operative delivery.

Obesity

Obesity has been demonstrated to be a risk factor for postdatism.[15] In a longitudinal retrospective study of 7407 term pregnancies, Johnson et al. found the frequency of fetal macrosomia and unscheduled cesarean section to rise almost simultaneously in relationship to increasing maternal body mass index (BMI) and to increasing gestational weight gain.[15] There was evidence on trend analysis that risk of postdatism increased with weight gain and with BMI. The obese patient presents multiple challenges to the anesthesiologist. Of significant importance is the task of managing a difficult airway in an obese parturient for emergency cesarean section. The insertion of an epidural catheter in early labor, therefore, is well advised. Should the epidural or combined spinal-epidural technique prove to be challenging, there is sufficient time to site the catheter and ensure adequate analgesia is obtained. As well, anesthesia for cesarean section or forceps delivery is facilitated by an indwelling epidural catheter, thereby avoiding either manipulation of the airway or surgical delay while a technically difficult regional block is attempted. This delay becomes especially important when fetal well-being is compromised.

Labor Induction

Labor induction is common practice in the postterm parturient. Induction protocols vary by institution but often include the administration of vaginal intracervical or oral medications or intravenous oxytocin. Prostaglandin E_2 (PGE_2) gel and vaginal tablets are given to ripen the cervix for labor induction.[16] Side effects from prostaglandins used for this purpose are rare but include gastrointestinal disturbances, fetal heart rate abnormalities, uterine hyperstimulation, and uterine rupture.[16–18] Uterine hyperstimulation with sustained contractions can also occur with intravenous oxytocin but usually resolves with discontinuation of the infusion.

Fetal Macrosomia

Fetal macrosomia becomes increasingly more likely as gestational age increases.[8] A retrospective case-control study in a large tertiary care center in Pakistan demonstrated an increased incidence of operative delivery, shoulder dystocia, birth trauma, fetal distress, neonatal intensive care unit (NICU) admissions, and perinatal loss in macrosomic babies.[6] In a study comparing primigravid to multigravid women, Mocanu and colleagues noted the incidence of shoulder dystocia to be low in both groups, and thus the authors did not advocate the elective delivery of macrosomic infants by cesarean section.[19] This study was a prospective computerized outcome of labor over a 5-year period and included 198 primigravid and 630 multigravid women with macrosomic babies as defined by birth weight greater than 4.5 kg. There was an increased incidence of prolonged labor, operative vaginal delivery, and emergency section in primigravid women compared to multigravid women and a higher incidence of these factors when compared to primigravid women with normal birth weight infants.[19]

Fetal macrosomia is a significant risk factor for the development of shoulder dystocia, with the incidence increasing in direct relationship to increasing fetal weight.[20–22] In one study of infants born in California, shoulder dystocia was noted to be 5.2% for infants 4000 to 4250 g, 9.1% for those 4250 to 4500 g, 14.3% for 4500 to 4750 g, and 21.1% for those 4750 to 5000g.[21] Major risk factors for shoulder dystocia include: postmaturity, maternal obesity, excessive maternal weight gain, diabetes, prolonged second stage of labor, midpelvic delivery, and previous shoulder dystocia.[20] Odds ratios for these risk factors were determined by Nesbitt and coworkers, who found that, after controlling for other parameters, the increased risk was significant with diabetes [odds ratio (OR), 1.7], assisted delivery (OR, 1.9), and induction of labor (OR, 1.3).[21] Nocon et al. reported that the risk of shoulder dystocia with assisted delivery and diabetes was only increased in the presence of fetal macrosomia.[22]

There are two important points to be made related to the development of shoulder dystocia. Maternal pushing efforts are important in assisting the obstetrician in the delivery process. However, if these efforts are unsuccessful, the situation may require extension of an existing regional blockade or the induction for general anesthesia for emergency cesarean section.[23] Equally important as the maternal considerations are the attendant fetal complications related to asphyxia and the required obstetric maneuvers. The presence of a neonatologist or qualified individual capable of neonatal resuscitation is mandatory when this situation arises. In any case, the obstetric anesthesiologist should be aware of the increased risk of shoulder dystocia with fetal macrosomia. Early epidural analgesia designed to limit the degree of motor blockade for second stage may have a dual advantage in that it allows effective maternal expulsive efforts as well as a conduit for extension of regional blockade should cesarean section become necessary.

Fetal macrosomia (>4000 g) has been determined to be an independent predictor of episiotomy, with a quoted increase greater than 50% [OR, 1.6; confidence intervals (CI), 1.1, 2.5].[24] Perineal trauma and subsequent postpartum pain constitute an important issue that requires attention and treatment in the postterm parturient.

Pain in the immediate postpartum period can be related to uterine contractions or incisional pain from either episiotomy or cesarean section. Uterine cramping can be attributed to the action of prostaglandins as intrinsic myometrial stimulants.[25] Nonsteroidal antiinflammatory drugs (NSAIDs) have been used effectively to treat postpartum pain related to uterine ac-

tivity.[25,26] As well, NSAIDs have been found useful when given prophylactically in the prevention of pain from perineal injury.[26] In some institutions, ketorolac is not used. Another modality of postpartum pain relief in parturients with severe lacerations is use of duramorph if an epidural catheter is already present. The use of self-medication packages, which included dibucaine ointment 1%, ibuprofen, acetaminophen, and docusate sodium, has been shown to significantly decrease narcotic usage in the postpartum period.[27]

Fetal macrosomia is associated with increased perinatal morbidity and mortality.[28] Vaginal delivery carries a much greater risk of injury to the fetus than cesarean section.[28] Brachial plexus palsy, an extremely serious injury, is often due to shoulder dystocia. A 5-year review of perinatal factors associated with birth trauma indicated that, to varying degrees, occurrences of clavicular fracture, facial nerve injury, and brachial plexus injury were associated significantly more often with prolonged gestation, macrosomia, and shoulder dystocia.[26] The ability to predict these injuries, however, appeared limited.

Postpartum Pain

In a prospective study of 93 women, it was found that, on average, women required 1 month to return to perineal comfort after delivery.[30] When the data were examined for cause of an extended period of perineal discomfort, delivery by forceps was associated with a significantly longer time to recovery ($p < 0.005$) irrespective of the damage to the perineum.[30] Unfortunately, relief of pain in the delayed postpartum period is beyond the scope of the obstetric anesthesiologist.

The use of neuraxial opioids for pain relief following cesarean section is a well-accepted analgesic technique. The side effects related to the use of these drugs include pruritus, urinary retention, sedation, and, rarely, respiratory depression. Decreasing the dose of neuraxial opioids may decrease the side effects such as pruritus with adequate pain relief.[31] Maternal satisfaction may be improved as a result.[32] In situations where general anesthesia was used for abdominal delivery, the use of patient-controlled analgesia is extremely effective for postoperative analgesia.

The inclusion of NSAIDs in the pain management regimen following cesarean section has been shown to significantly potentiate spinal narcotics and to decrease postoperative analgesic requirements.[33] A multimodal approach to postcesarean analgesia in our institution includes a combination of neuraxial opioids, oral acetaminophen with codeine, and rectal NSAIDs.

Summary

The management of the postterm pregnancy remains controversial. An accurate estimation of the gestational age of the patient is essential. A policy of ultrasound before 20 weeks gestational age will help decrease the incidence of uncertain dates at term. Once a pregnant woman has reached term and there are no medical or obstetric reasons to induce labor, the parturient may continue her pregnancy. At 41 weeks an assessment of the cervix should be done, and if the Bishop score is greater than 8, induction should be considered. If the Bishop score is unfavorable, or if the individual chooses not to be induced, then she should undergo serial antenatal testing with biophysical profile or amniotic fluid volume estimation with ultrasound. Although the management of the postterm pregnancy remains somewhat controversial, it seem prudent to recommend delivery of all pregnancies by 42 weeks gestation.

If at all possible, an early consultation by an obstetric anesthesiologist is useful in that it provides information regarding the patient's airway and ease of intubation should an emergency cesarean section be required. This consultation also allows the anesthesiologist and the patient to discuss the advantages of regional analgesia and perhaps will result in its early institution in a controlled situation. Low-dose analgesic techniques designed to minimize motor block allow excellent maternal expulsive efforts and perhaps decrease the need for instrumental delivery. In turn, perineal trauma may be limited, and postpartum pain minimized, allowing an optimum outcome for mother and baby.

References

1. The Society of Obstetrics and Gynaecology of Canada. Maternal-Fetal Medicine Committee. Management of post-term pregnancy; committee opinion. J Soc Obstet Gynaecol Can 1994;16:1581–1586.
2. Browne FJ, McClure Browne JC. Antenatal and Postnatal Care, 8th edn. London: Churchill, 1955.
3. Neilson JP. Routine ultrasonography in early pregnancy. In: Chalmers I (ed). Oxford Database of Perinatal Trials, version 1.3, disk issue 7, record 3872. Oxford: Cochrane Database, 1992.
4. Lucas W, Anctil A, Callagan D. The problem of postterm pregnancy. Am J Obstet Gynecol 1963;91:241–250.
5. Feldman GB. Prospective risk of stillbirth. Obstet Gynecol 1992;79: 547–553.
6. Karim S, Mastoor M, Ahmed AJ, et al. Macrosomia: maternal and fetal outcomes. Obstet Gynecol 1994;20:73–76.
7. Usher R, Boyd M, McLean F, et al. Assessment of fetal risk in postdate pregnancies. Am J Obstet Gynecol 1988;158:259–264.
8. Boyd ME, Usher R, McLean FH, et al. Obstetric consequences of postmaturity. Am J Obstet Gynecol 1988;158:334–338.
9. O'Brien W, Cefalo R. Labor and delivery. In: Gabbe S, Niebyl J, Simpson J (eds). Obstetrics: Normal and Problem Pregnancies. New York: Churchill Livingstone, 1986:351–378.
10. Hannah ME, Hannah WJ, Hellmann J, et al. Induction of labor as compared with serial antenatal monitoring in postterm pregnancy. A randomized controlled trial. The Canadian Multicenter Postterm Pregnancy Trial Group. N Engl J Med 1992;326:1587–1592.
11. Johnson JM, Haran CR, Lange IR, et al. Biophysical profile scoring in the management of the postterm pregnancy: an analysis of 307 patients. Am J Obstet Gynecol 1986;154:269–273.
12. Cunningham FG, MacDonald PC, Gant NF. Williams Obstetrics, 18th edn. Norwalk, CT: Appleton & Lange, 1988.
13. Shaw KJ, Medearis AL, Horenstein J, et al. Selective labor induction in postterm patients: observations and outcomes. J Reprod Med 1992;37: 157–161.

14. Hofmeyr G, Gulmezoglu A, Buchmann E, et al. The collaborative randomized amnioinfusion for meconium project. Br J Obstet Gynaecol 1998;10:304–308.
15. Johnson JWC, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. Am J Obstet Gynecol 1992;167:353–372.
16. Winkler M, Rath W. A risk-benefit assessment of oxytocics in obstetric practice. Drug Saf 1999;20:324–345.
17. Wing DA, Park MR, Paul RH. A randomized comparison of oral and intravaginal misoprostol for labor induction. Obstet Gynecol 2000;95:905–908.
18. Chua S, Arulkumaran S, Vanaja K, et al. Preinduction cervical ripening: prostaglandin E_2 gel vs hygroscopic mechanical dilator. J Obstet Gynaecol Res 1997;23:171–177.
19. Mocanu EV, Greene RA, Byrne BM, Turner MJ. Obstetric and neonatal outcome of babies weighing more than 4.5 kg: an analysis by parity. Eur J Obstet Gynecol Reprod Biol 2000;92:229–233.
20. Bennett BB. Shoulder dystocia: an obstetric emergency. Obstet Gynecol Clin N Am 1999;26:445–458.
21. Nesbitt TS, Gilbert WM, Herrchen B. Shoulder dystocia and associated risk factors with macrosomic infants born in California. Am J Obstet Gynecol 1998;179:476–480.
22. Nocon JJ, McKenzie DK, Thomas LJ, et al. Shoulder dystocia: an analysis of risks and obstetric maneuvers. Am J Obstet Gynecol 1993;168:1732–1739.
23. O'Shaughnessy MJ. Hysterotomy facilitation of the vaginal delivery of the posterior arm in a case of severe shoulder dystocia. Obstet Gynecol 1998;92:693–695.
24. Robinson JN, Norwitz ER, Cohen AP, et al. Predictors of episiotomy use at first spontaneous vaginal delivery. Obstet Gynecol 2000;96:214–218.
25. Windle ML, Booker LA, Rayburn WF. Postpartum pain after vaginal delivery: a review of comparative analgesic trials. J Reprod Med 1989;34:891–895.
26. Searles JA, Pring DW. Effective analgesia following perineal injury during childbirth: a placebo controlled trial of prophylactic rectal diclofenac. Br J Obstet Gynaecol 1998;105:627–631.
27. Greene JF, Juiper O, Morosky M, et al. A postpartum self-medication program: effect on narcotic use. J Womens Health Gend Based Med 1999;8:1073–1076.
28. American College of Obstetricians and Gynecologists. Fetal macrosomia. Bulletin 159. Int J Gynecol Obstet 1991;39:341–345.
29. Perlow JH, Wigton T, Hart J, et al. Birth trauma: a five-year review of incidence and associated perinatal factors. J Reprod Med 1996;41:754–760.
30. Abraham S, Child A, Ferry J, et al. Recovery after childbirth: a preliminary prospective study. Med J Aust 1990;152:9–12.
31. Palmer CM, Emerson S, Voulgaropoulos D, et al. Dose-response relationship of intrathecal morphine for post-cesarean analgesia. Anesthesiology 1999;90:437–444.
32. Morgan PJ, Halpern S, Lam-McCulloch J. Comparison of maternal satisfaction between epidural and spinal anesthesia for elective cesarean section. Can J Anesth 2000;47:956–961.
33. Pavy TJ, Gambling DR, Merrick PM, et al. Rectal indomethacin potentiates spinal morphine analgesia after cesarean delivery. Anaesth Intensive Care 1995;23:555–559.

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22
Hematologic Disease

David L. Hepner, Louise Wilkins-Haug, and Peter W. Marks

Blood Loss in Pregnancy

Normal spontaneous vaginal delivery is usually associated with a blood loss of 500 mL, whereas an uncomplicated cesarean section is often associated with a blood loss of 800 mL.[1] Uncorrected abnormalities of the coagulation system, whether present before the pregnancy or caused by the pregnancy itself, may lead to a marked increase in blood loss that may be difficult to control and may precipitate obstetric hemorrhage. Obstetric hemorrhage remains the most common cause of maternal mortality in the United States.[2] Coagulopathies are the fourth most common reason for pregnancy-related deaths due to hemorrhage, accounting for 14% of cases.[2] Early consultation with a hematologist is recommended for parturients with coagulopathies, and a treatment plan should be developed in the antepartum period. However, some conditions that are acquired during pregnancy may present in the peripartum period. Knowledge of these conditions and of their recommended treatment is essential for a practitioner of obstetric anesthesia.

Pregnancy leads to an engorgement of the epidural venous plexus, and the incidence of intravascular epidural catheters has been reported to be as high as 8.5% in parturients.[3,4] Uncorrected abnormalities of the coagulation pathway, either inherited or acquired, may augment the bleeding that occurs after an intravascular epidural catheter cannulation. This bleeding may create a hematoma in the epidural space, which is a closed space with the potential for spinal cord compression. Permanent neurologic damage is the most feared complication of neuraxial anesthetic techniques, and these techniques are relatively contraindicated in parturients with coagulopathies. However, the cause, severity, and treatment of coagulopathies vary. In some instances, neuraxial anesthetic techniques are utilized in parturients with minor or corrected coagulation abnormalities after a careful risk–benefit analysis is performed.

The incidence of epidural hematoma in the general population is very low; it has been reported to be 1 in 150,000 after an epidural technique and 1 in 220,000 after a subarachnoid block.[5] The incidence of epidural hematoma in patients who are anticoagulated or who have clotting abnormalities and have received neuraxial techniques is not known. A retrospective analysis of case reports of epidural hematoma and neuraxial techniques demonstrated that most cases (68%) occurred in patients with impaired coagulation.[5] Seventy-five percent of cases occurred with an epidural technique, and 25% occurred after a subarachnoid block. Forty-seven percent of cases that utilized an epidural catheter occurred at the time of catheter removal. Only 8% of all the cases occurred in parturients. It is not known if the reason for this low number in parturients is because of the hypercoagulable state of pregnancy or because anesthesiologists avoided neuraxial techniques in parturients with impaired coagulation.

An understanding of normal primary and secondary hemostasis and of pregnancy-related changes is essential to understand congenital or acquired coagulation abnormalities that may occur in the peripartum period. Primary hemostasis is initiated when injury to a vessel wall leads to denudation of the endothelium. Platelets then bind to the surface, in part through von Willebrand's factor, a large multimeric protein that, when activated by collagen binding, serves as a latch between the platelet and the vessel wall. Platelet activation releases adenosine diphosphate (ADP) and other mediators that lead to further activation and the formation of a platelet plug (Figure 22.1). The activated platelets also provide the membrane surface upon which activation of the clotting cascade occurs (Figure 22.2). Binding to exposed tissue factor in conjunction with small amounts of factor Xa leads to activation of factor VIIa; this subsequently leads to the production of thrombin from prothrombin, which then can activate the contact arm of the coagulation cascade as well as convert fibrinogen to fibrin leading to the formation of a clot. Subsequently, factor XIII cross-links the clot into a mature state that is relatively resistant to fibrinolysis.

Pregnancy is associated with an expansion of the intravascular volume that is larger than the expansion of the red cell volume; this is responsible for the physiologic anemia of pregnancy (mean hemoglobin, 12.3 g/dL).[1] Pregnancy is also associated with a hypercoagulable state characterized by increased platelet hemostatic capacity despite a decreased platelet count. All clotting factors, except factors XI and XIII, increase during pregnancy. Fibrinogen increases by as much

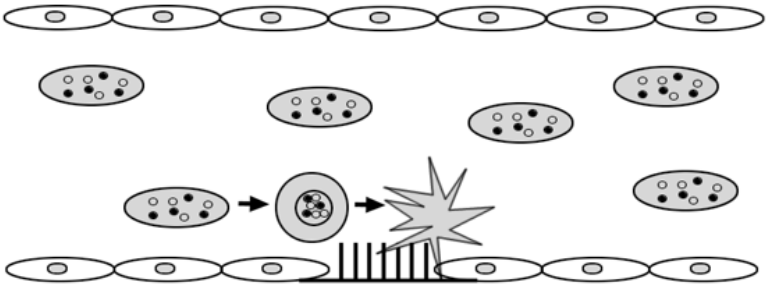

FIGURE 22.1. Schematic diagram of primary hemostasis. Platelets rolling on the vascular surface encounter denuded endothelium and activated von Willebrand's factor. The platelets then become activated themselves, releasing adenosine diphosphate (ADP) and other mediators that attract additional platelets and lead to the formation of a platelet plug, which serves as a scaffold for deposition of the clotting cascade.

as 50%.[1] Prothrombin and the thrombin–antithrombin complex are also elevated in normal pregnancies, while fibrinolysis is diminished, as is demonstrated by elevated levels of plasminogen activator inhibitor 1 and 2.[6]

Disorders of Platelets in Pregnancy

Pregnancy is associated with normal platelet function but often with a decreased platelet number. However, there are also some disorders of pregnancy that are associated with a more severe thrombocytopenia. The main reasons for pregnancy-associated thrombocytopenia include incidental thrombocytopenia of pregnancy (gestational thrombocytopenia) (74%), hypertensive diseases of pregnancy (21%), and immune thrombocytopenic disorders of pregnancy (idiopathic thrombocytopenic purpura and systemic lupus erythematosus) (4%). The remaining rare cases of thrombocytopenia include disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), fatty liver of pregnancy, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and antiphospholipid syndrome.[7]

The cardinal sign of bleeding due to thrombocytopenia is the presence of petechiae and purpura. Petechiae are tiny red dots in the dependent regions of the body or where the blood pressure cuff is inflated, whereas purpura are larger and can be the result of a convergence of petechiae.

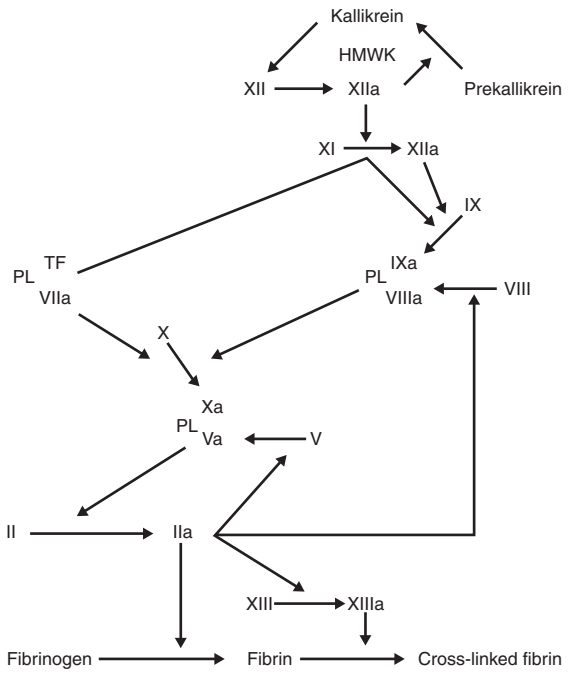

FIGURE 22.2. The coagulation cascade. Coagulation is initiated when factor VII binds to exposed tissue factor at a site of injury. Small amounts of factor Xa in the circulation activate VII to VIIa. This activity then leads to the conversion of further factor X to Xa, generation of thrombin, and initial deposition of fibrin strands. Thrombin is a key regulator, activating a number of proteins including the nonenzymatic cofactors V and VIII. In addition, activation of factors IX and XI leads to amplification of coagulation. Factor XIII serves to cross-link fibrin and produce a stable clot. The role of factor XII in coagulation is not clear. *PL*, phospholipid; *HMWK*, high molecular weight kininogen; *TF*, tissue factor.

Gestational Thrombocytopenia

Gestational thrombocytopenia, which presents during pregnancy in women without a prior history of thrombocytopenia, is usually mild (from 70–100 to 150 $\times$ 10^3/mm^3), tends to occur during the third trimester of an uncomplicated pregnancy, and resolves postpartum. It occurs in up to 8.3% of parturients. Platelet function is normal, and the disorder has no adverse effects on parturients or neonates.[8] Parturients are without clinical signs of bleeding, and neonates have normal platelet counts.[9] Postulated reasons for gestational thrombocytopenia include hemodilution, mild DIC, and increased destruction.[10]

Obstetric Management

Gestational thrombocytopenia is a benign condition associated with a normal history and physical examination. Therefore, once other abnormal conditions that may cause pregnancy-related thrombocytopenia are ruled out, there should not be any special considerations in the obstetric management of parturients with gestational thrombocytopenia.

Anesthetic Management

Gestational thrombocytopenia is not a contraindication to regional anesthesia, as it is rarely associated with a platelet count below 70 $\times$ 10^3/mm^3. Platelet function is normal, and it is usually an incidental laboratory finding. Most anes-

thesiologists are not usually aware of gestational thrombocytopenia, as a majority of practitioners do not require any laboratory testing before placing a regional anesthetic in a healthy parturient.[11,12] Furthermore, most anesthesiologists in the United States would place an epidural in an otherwise healthy parturient with platelet count between 80,000 and 100,000/mm^3.[12] In a series of 30 parturients with platelet counts between 69,000 and 98,000/mm^3, the majority of parturients who received epidural analgesia with platelets below 100,000/mm^3 had gestational thrombocytopenia.[13]

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura, which is caused by increased platelet destruction by maternal autoantibodies, represents the majority of cases of immunologically mediated thrombocytopenia during pregnancy. These antibodies are specific for distinct epitopes on platelet membrane glycoproteins, especially IIb/IIIa and Ib/IX/V.[14] It is also referred to as immune thrombocytopenic purpura (ITP), occurs in 0.1% to 0.2% of parturients, and accounts for 3% of cases of pregnancy-associated thrombocytopenia.[7,8] The platelet function is not affected, and most parturients do not bleed until the platelet count is below 20×10^3/mm^3. This disease is not specific to pregnancy, and some patients are identified before the pregnancy. The risk of ITP is not increased in pregnancy but ITP tends to occur coincidentally, as it is more common in females (3:1 ratio), and in the second and third decades of life. ITP persists in the postpartum period.

The diagnosis of ITP is a clinical diagnosis based on a platelet count less than 100×10^3/mm^3 early in the pregnancy, exclusion of other causes of pregnancy-related thrombocytopenia, and the absence of splenomegaly. Confirmation of the diagnosis may be obtained with a bone marrow biopsy that demonstrates an increased size and number of megakaryocytes. This change occurs in response to the increased platelet destruction by autoimmune antibodies against platelet surface antigens.[15] Antiplatelet antibodies against platelet glycoproteins IIb/IIIa and Ib/IX are available via antigen capture assays and are found in 75% to 80% of parturients with ITP.[16] However, these antibodies are not routinely measured, as the management is the same regardless of the presence or absence of these antibodies. In addition, the absence of antiplatelet antibodies does not rule out ITP.

The platelet function is normal in parturients with ITP, and bleeding tendencies are usually related to the platelet number. Most cases present with easy bruising in parturients with a long history of mild hemostatic impairment. Other parturients are asymptomatic, and the diagnosis is made on routine blood monitoring. Platelet counts in the range of 40 to 60×10^3/mm^3 early in the pregnancy should be considered indicative of ITP until proven otherwise. A minority of the cases present with a sudden onset of severe thrombocytopenia and evidence of hemostatic impairment.[16]

Obstetric Management

Expectant management is utilized in most parturients, as the majority have a platelet count greater than 50×10^3/mm^3 in the absence of spontaneous bleeding. Treatment with corticosteroids is recommended in parturients with spontaneous bleeding or with platelet counts below 50×10^3/mm^3. The dose is intravenous methylprednisone 1 mg/kg or oral prednisone 1 mg/kg, and most parturients respond to this treatment. Other authorities recommend intravenous gammaglobulin (IVIgG) 1 g/kg, which raises the platelet count to acceptable levels ($>50 \times 10^3$/mm^3) in 50% of parturients. A second dose may be repeated 1 week later and leads to acceptable levels in 75% of parturients.[16] Splenectomy is reserved for parturients not responsive to glucocorticoids after several weeks of treatment or for those requiring a prolonged high dose of steroids.

IgG antibodies present in ITP cross the placenta and may lead to fetal and neonatal thrombocytopenia. The level of maternal thrombocytopenia does not predict fetal thrombocytopenia, and there are reports of neonatal platelet counts below 50,000/mm^3 in mothers with platelet counts above 50,000/mm^3.[7] Moderate to severe fetal thrombocytopenia ($<$50,000/mm^3) is present in 9% to 15% of all cases but rarely leads to severely affected neonates with morbidity or mortality.[9] The natural history of ITP-associated neonatal thrombocytopenia is for platelets to nadir at 24 to 48 h after delivery. Although mild fetal thrombocytopenia is common, it is rarely associated with intracranial hemorrhage.[14]

The mode of delivery depends on the status of the mother or neonate. Cesarean section is reserved for the usual obstetric indications, or if the fetal platelet count is below 20×10^3/mm^3. However, some have advocated a cesarean section for maternal reasons only, as routine determination of fetal platelet counts is not warranted.[14] Even though fetal platelet counts can be determined, it is not without a risk, and there is no specific treatment for the fetus.[14] Vaginal delivery is safe in the setting of ITP, and some authorities recommend it for a majority of parturients.[17] Precautions during vaginal delivery such as restricted use of vacuum and forcep-assisted delivery are reasonable. Maternal platelet transfusion is reserved for those with clinical evidence of impaired hemostasis (petechiae and purpura), and for those with platelet counts below 20×10^3/mm^3.[15] This intervention is usually a temporizing measure, as the transfused platelets will also be destroyed by the antiplatelet antibodies.

Anesthetic Management

Most parturients with ITP have platelets above 50×10^3/mm^3 with normal function. It is of note that ITP is characterized by increased platelet destruction of old platelets, leaving younger and larger platelets in the circulation. These remaining platelets have an increased number of platelet granules that enhance platelet function.[16] Therefore, some experts have suggested that it may be prudent to perform a regional anes-

thetic on parturients with ITP, provided that the platelet count is above $50 \times 10^3/mm^3$, there is no clinical evidence of bleeding, and there is no other associated comorbid condition.[10] It is important to document the absence of a prior history of bleeding and the platelet number at the time of the regional technique. Other laboratory tests of coagulation, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), are usually normal.

As platelets are removed from the circulation via binding to Fc receptors on the surface of the spleen, splenectomy may be of benefit for parturients with severe thrombocytopenia refractory to steroids.[14] Splenectomy is usually performed during the second trimester of pregnancy to minimize the risks of miscarriage and preterm labor. Parturients in the second trimester have a normal gastric pH and volume but a lower esophageal sphincter tone. Aspiration prophylaxis, with sodium citrate and metoclopramide, is currently recommended. Left uterine displacement must be utilized to minimize aortocaval compression by the gravid uterus. The incision is usually midline abdominal or left subcostal, and the preferred anesthetic technique is general anesthesia. Rapid sequence induction should be performed, and gentle attempts at laryngoscopy should be used to minimize laryngeal bleeding. It is also recommended that well-lubricated endotracheal ($<$7.0 mm) and nasogastric tubes be used to avoid airway hematoma and epistaxis. There is the potential for major blood loss, and it is important to have rapid transfusion equipment available as well as large-caliber intravenous catheters (at least two 16-gauge intravenous catheters). Platelets and red blood cells should be available in the operating room. Platelet transfusions are usually given after ligation of the splenic vessels, as this leads to decreased platelet sequestration.

von Willenbrand's Disease

von Willenbrand's disease is a disorder of platelet adhesion with defective platelet aggregation and is the most common inherited bleeding disorder in humans. It is inherited in an autosomal dominant fashion and has been reported in 3 to 4 of 100,000 to 1.3% of the population.[18] It is characterized by mucosal bleeding, despite normal platelet counts and normal clot retraction. Classical manifestations of mucosal bleeding include epistaxis, gingival bleeding, easy bruising, and menorrhagia. The bleeding time is increased, and the plasma factor VIII (FVIII) activity is often decreased.

von Willenbrand's factor (vWF) is synthesized and stored in megakaryocytes and endothelial cells. It is stored within the alpha granules of the platelets and provides an adhesive link between platelets and the vessel wall at the site of vascular injury (primary hemostasis). vWF also participates in secondary hemostasis by stabilizing and carrying FVIII in plasma. vWF carries FVIII to the sites of platelet plug and fibrin clot formation.[18] vWF is modified by estrogens, and the production is increased during pregnancy.[18,19] Therefore, bleeding complications are unusual in the antepartum period. In addition, FVIII:C levels are increased in the antepartum period.

Most parturients will already have a diagnosis of vWD, as this is an inherited disease. However, some cases may present in pregnancy with excessive gingival bleeding or menorrhagia or in the postpartum period with hemorrhage. It is recommended that thrombocytopenia and coagulation pathway abnormalities first be ruled out by obtaining a platelet count, PT, and aPTT.[19] Parturients with vWD have normal platelet count and coagulation parameters (PT, aPTT). There are different laboratory tests for vWD, and it is important to perform a panel of them as they help to differentiate between the different types of vWD (Table 22.1). Furthermore, the treatment may vary from type to type. For example, 1-deamino-D-Arg-8-vasopressin (DDAVP) is beneficial for parturients with type 1 disease but may exacerbate thrombocytopenia in parturients with type 2B disease. The ristocetin cofactor activity assay (vWF:RCo) measures vWF binding to platelet GpIb or vWF activity. Plasma vWF antigen (vWF:Ag) is then done to quantify the deficiency of vWF, and FVIII activity is measured in a functional assay. The ristocetin-induced platelet aggregation test (RIPA) assesses the ability of the platelet-associated vWF to support aggregation. Gel electrophoresis can also be performed to determine the vWF multimer structure.

The platelet function analyzer (PFA-100) is an in vitro bleeding time device that measures blood flow through a small cut in a collagen-epinephrine or collagen-ADP-coated membrane and is a crude measurement of platelet function.[20] The time required for occlusion (closure time, CT) is indicative of platelet function and primary hemostasis; it measures platelet plug formation and is strongly dependent on plasma vWF.[21] Recently, it has been used in clinical settings for assessment of platelet dysfunction, and it might also be useful for monitoring antiplatelet therapy.[22] It has a high specificity for normal platelet function and high sensitivity for platelet dysfunction. It is also dependent on glycoprotein Ib and IIb-IIIa, platelet count, and hematocrit.

There are three main different types of vWD (Table 22.2). Type 1 disease is the most common and accounts for 70% of all cases. It is characterized by a quantitative decrease in vWF that results in mild to moderate bleeding. It has a decreased vWF:RCo, vWF:Ag, and FVIII but normal multimeric distribution. Most mild to moderate cases respond well to desmopressin (DDAVP). DDAVP is a synthetic analogue of argi-

TABLE 22.1. von Willenbrand's disease laboratory testing.

Laboratory testing	Significance
vWF:Ag	Measures the amount of plasma vWF
vWF:RCo	Measures vWF activity in plasma
Factor VIII	Measures plasma factor VIII
Gel electrophoresis	Measures vWF multimer structure
RIPA	Measures ability of vWF on the platelet surface to support aggregation

vWF, von Willenbrand factor; vWF:Ag, vWF antigen; vWF:RCo, ristocetin cofactor activity assay; RIPA, ristocetin-induced platelet aggregation test.

TABLE 22.2. Classification of von Willenbrand's disease.

Type	vWF:Ag	vWF:RCo	Factor VIII	vWF multimer structure	DDAVP response	Bleeding
Type 1	Decreased	Decreased	Decreased	Normal	Good in most cases	Mild–moderate
Type 2A	Decreased	Decreased(more than any other test)	Decreased	Abnormal	Variable	Variable
Type 2B	Low to normal	Decreased	Low to normal	Abnormal	May worsen thrombocytopenia	Thrombocytopenia may worsen bleeding
Type 2M	Low to normal	Decreased	Low to normal	Abnormal	Variable	Variable
Type 2N	Low to normal	Low to normal	Decreased	Normal	Variable	Variable
Type 3	Markedly reduced or absent	Markedly reduced	Markedly reduced	Normal	No response	Severe

vWF, von Willenbrand factor; vWF:Ag, vWF antigen; vWF:RCo, ristocetin; DDVAP, 1-deamino-D-Arg-8 vasopressin.

nine vasopressin that causes an indirect release of vWF and FVIII from endothelial cells.

Type 2 disease is divided into four subtypes: A, B, M, and N. Type 2A has a decreased vWF:RCo, vWF:Ag, and FVIII. In type 2A, vWF:RCo has the lowest level of the three tests. High molecular weight multimeres (HMWM) are decreased or absent on analysis. Type 2B has decreased vWF:RCo and a low normal vWF:Ag and FVIII. HMWM are also decreased. The RIPA reveals hyperaggregability to ristocetin. A unique characteristic of this type of vWD is that thrombocytopenia is common and may be exacerbated by pregnancy. Infants of parturients with type 2B disease may also experience neonatal thrombocytopenia. Type 2M disease is characterized by abnormal multimer distribution on gel analysis and an abnormal vWF:RCo. Type 2N is characterized by decreased FVIII activity, but normal vWF multimers, vWF:Ag, and vWF:RCo. Response to DDAVP is variable in most of these subtypes of vWD. As mentioned earlier, some authorities consider DDAVP to be contraindicated in parturients with type 2B disease. Other available treatment options for these parturients include cryoprecipitate and plasma concentrates containing FVIII and vWF. The most frequently used concentrate is Humate P as it contains 2.5 IU ristocetin cofactor activity to 1 IU of FVIII:C, and has a multimeric content that is near normal.[23]

Type 3 disease is the least common but the most severe type of vWD. It is characterized by markedly reduced or absent vWF:Ag. In addition, vWF:RCo and FVIII activity are markedly reduced. This type is refractory to DDAVP treatment and usually presents with moderate to severe bleeding. Cryoprecipitate or preferably plasma concentrates containing FVIII and vWF are the treatment options.

Obstetric Management

Most parturients will have a diagnosis before presentation for labor and delivery. Parturients with type I vWD often improve during the antepartum period, as vWF and its activity and factor VIII increase as the pregnancy progresses. Parturients with type 2 vWD also experience an increase in vWF and its activity, but the abnormal morphology persists. These parturients do not improve with pregnancy and are at an increased risk of postpartum hemorrhage, a risk which remains for as long as 6 weeks postpartum. Women with type 2B may experience increased bleeding throughout the pregnancy, as there is increased production of abnormal multimers that bind to platelets. Spontaneous platelet aggregation then leads to a worsening of the thrombocytopenia.[24] Parturients with type 3 vWD have very little to no vWF and thus experience minimal to no changes with the pregnancy. It is imperative to understand that the hemostatic changes of pregnancy in parturients with vWD vary between individuals and between different pregnancies in the same individual.

Of clinical importance is the understanding that although vWD may be corrected with the pregnancy, as in some cases of type 1 disease, the level of vWF decreases after the delivery of the placenta; this may precipitate postpartum hemorrhage. Kadir and colleagues[24] reported an 18.5% incidence of primary postpartum hemorrhage. However, most cases occurred in parturients with uncorrected vWD during pregnancy and without prophylaxis. The incidence of secondary postpartum hemorrhage was 20%. Others have reported a 25% to 28% incidence of secondary postpartum hemorrhage.[25,26] Therefore, it is recommended that type 1 parturients have a DDAVP trial before the time of delivery and preferably before the pregnancy. If a response to DDAVP is observed during the trial period, then a dose of 0.2 to 0.4 μg/kg over 15 to 30 min before a vaginal delivery, or 60 to 90 min before a cesarean section, is used if necessary. Parturients who do not respond to DDAVP and those with types 2B and 3 need to be treated with factor VIII/vWF plasma concentrate before a procedure.[19] It has been recommended that FVIII and vWF:RCo be kept above 50 IU/dL at the time of delivery and for 72 to 96 h after an uncomplicated vaginal delivery and 96 to 120 h after a cesarean section.[24,27]

Antenatal testing for fetal vWD is possible, but it is not necessarily recommended as it is associated with fetal mortality and is not always predictive of neonatal bleeding. It may be wiser to collect cord blood at the time of delivery and perform tests for vWD at this time. Cesarean section should not

be chosen on the basis of the possibility of neonatal vWD, as it may lead to increased maternal bleeding in parturients with vWD. Most experts recommend vaginal delivery with the avoidance of episiotomy and instrumental delivery if possible.[19] Intramuscular injections should be avoided in offspring of parturients with vWD, and a circumcision should be postponed until a diagnosis of vWD is excluded.

Anesthetic Management

Although the bleeding time is increased in parturients with vWD, its determination is not currently recommended as it is operator dependent and difficult to standardize. There are reports of the use of regional anesthesia in parturients with mild type 1 vWD.[28–30] Kadir and colleagues[24] reported a series of eight parturients with vWD who received regional analgesia or anesthesia for labor and delivery. All except one parturient had clotting factors and coagulation screen that had normalized during the pregnancy. One parturient received prophylactic treatment before the regional technique. The type of vWD and whether DDAVP was part of the prophylaxis are not clear from the available information. Regional anesthesia is contraindicated if the coagulation screen is abnormal; this is especially true in parturients with more severe types of vWD such as type 3, where the vWF is markedly reduced and does not normalize with pregnancy.

DDAVP causes a rapid but transient increase in vWF and FVIII and can facilitate the performance of procedures. Spinal anesthesia is preferred for a cesarean section, as it avoids further manipulation to the epidural space. In addition, it leads to less trauma to the epidural venous plexus. However, the anesthesiologist must be ready to convert to general anesthesia, as the delivery of the placenta may precipitate postpartum hemorrhage. The epidural catheter, placed with combined spinal epidural or epidural techniques, should also be removed as soon as possible after the removal of the placenta. Side effects of DDAVP include tachycardia, hypertension, and facial flushing. Fluid retention may be a result of the antidiuretic properties of this peptide, and it is essential to avoid excessive administration of intravenous fluids to these parturients.

The PFA-100 is able to differentiate medication-induced platelet dysfunction from that caused by disorders such as vWD. A decreased CT correlates with qualitative platelet defects and with decreased vWF levels.[31] The CT can also differentiate DDAVP responders from nonresponders, as the PFA-100 is very sensitive to platelet vWF and to the large vWF multimeres.[32] However, further work is necessary before using the PFA-100 in making decisions concerning whether to use neuraxial techniques in parturients with vWD.

Labor and delivery analgesia for a parturient with type 3 disease can be provided by a fentanyl patient-controlled analgesia. At our institution, parturients receive a 13-μg bolus with a 7-min lockout and a 4-h limit of 300 μg. Ketamine can be added if necessary to improve the analgesia in doses of 15 to 30 mg/h. If a cesarean section is performed in a parturient with type 3 disease, a general anesthetic is preferred. It should be conducted in a manner similar to that described for a parturient with ITP, where extreme caution should be exerted to minimize laryngeal bleeding and airway hematoma. Adequate intravenous access and reserved blood products are of utmost importance before proceeding with a scheduled case.

Bernard–Soulier Syndrome

Bernard–Soulier syndrome is a less common disorder of platelet adhesion with defective platelet aggregation. It is usually transmitted as an autosomal recessive trait, and family history is rare.[19] It is a result of a quantitative or qualitative defect in platelet membrane glycoproteins. Glycoprotein Ib-V-IX is an active receptor for vWF that is required for platelet adhesion to subendothelial tissue and is also essential for platelet aggregation into hemostatic plugs.[33] The clinical presentation of this disorder, with mucous membrane bleeding, is similar to that of vWD as vWF depends on platelet membrane glycoproteins.

Peripheral smear demonstrates an overall decreased number of platelets that are larger than usual. Although the RIPA is markedly abnormal, other tests for vWD are normal. In addition, this disorder is distinguished from vWF by the failure of its platelets to aggregate in response to bovine plasma.[19]

Obstetric Management

Most parturients will have a diagnosis before the pregnancy, but there are reported cases in which the diagnosis was made because of late postpartum hemorrhage.[34,35] It can also present with antepartum or early postpartum hemorrhage.[34] Although the route of delivery is controversial, most experts recommend allowing a trial of labor.[19] Prophylactic platelet transfusion before delivery has been recommended, as most of these parturients bleed in the immediate postpartum period.[19,36] It has been recommended that platelets be leukocyte depleted to decrease the risk of neonatal alloimmunization.[19] Maternal immunization to glycoprotein Ib/IX during pregnancy can produce antibodies against it and lead to neonatal alloimmune thrombocytopenia[37,38]; this can cause maternal resistance to platelet transfusion and severe fetal thrombocytopenia and massive intracranial bleeding. Management of active bleeding episodes includes platelet transfusions, desmopressin (DDAVP), antifibrinolytic therapy, and uterotonic agents for postpartum hemorrhage.[34] There is one report of a parturient who had to undergo a gravid hysterectomy because of uncontrollable hemorrhage.[39]

Anesthetic Management

The literature regarding the anesthetic management is very limited, as this is a very rare disorder. There is a report in the nonobstetric literature of a 20-year-old woman scheduled for

a sagittal osteotomy of the mandibular rami under general anesthesia.[40] The authors caution against using halothane in these patients, as it may inhibit the aggregation of platelets and prolong the bleeding time.[40] Analgesic and anesthetic considerations for labor and delivery, and for a cesarean section, should not differ from those of a parturient with type 3 vWD.

Disorders of Platelet Secretion

These rare disorders, which include gray platelet syndrome and storage pool disease, are characterized by a deficiency in platelet granules or their contents. Because platelet granules and their contents are involved in platelet adhesion, these present similarly to disorders of platelet adhesion. For example, gray platelet syndrome is characterized by a deficiency of platelet alpha granules whereas storage pool disease is characterized by a deficiency of platelet dense granules.[19] Although alpha granules contain vWF and platelet factor 4, dense granules contain ADP and prevent its degradation. ADP is essential for platelet activation and aggregation.

Obstetric Management

The recommendation for the obstetric management of these parturients is limited, as these are rare disorders. Vaginal delivery is not contraindicated and is preferred by some.[41] Platelet transfusions are recommended before delivery.

Anesthetic Management

There is little published information in the anesthetic literature, or for that matter in the obstetric literature, on the anesthetic or obstetric management of these conditions. Common sense indicates that regional techniques be avoided in these parturients and that caution be taken during laryngoscopy and intubation during general anesthesia. It has been recommend to avoid medications that may adversely affect platelet function such as some antibiotics, phenothiazines, and hydroxyethyl starch.[42]

Glanzmann's Thrombasthenia

Glanzmann's thrombasthenia is an autosomal recessive disorder of platelet aggregation that is characterized by a qualitative or quantitative defect in platelet glycoprotein IIb-IIIa. Glycoprotein IIb-IIIa is the most abundant surface protein involved in platelet aggregation. It undergoes a conformational change during platelet activation to express its receptor function for fibrinogen.[33] It is this binding of fibrinogen and glycoprotein IIb-IIIa that mediates platelet aggregation.

There are two types of Glanzmann's thrombasthenia. Type 1 is more severe and is characterized by absent glycoprotein IIb-IIIa, and by low levels of fibrinogen; type 2 is milder with a quantitative deficit in glycoprotein IIb-IIIa but normal levels of fibrinogen. Although both types are associated with mucous membrane bleeding, this is more severe with type 1 disease. Other platelet receptors can compensate for the decreased GIIb-IIIa receptor in type 2 disease.

Mucocutaneous bleeding confirms a disorder of platelet function, and final diagnosis is by laboratory tests. These tests reveal normal platelet counts, prolonged bleeding times, and platelets that fail to aggregate in the presence of platelet activators such as ADP and collagen.[19]

Obstetric Management

Although the maternal condition is not a contraindication to a trial of labor, the fetal condition may warrant a cesarean section. Many of these parturients have had platelet transfusions and may develop antibodies against one of the deficient glycoproteins. These alloantibodies may cross the placenta and may result in fetal alloimmune thrombocytopenia.[43] The intrapartum treatment is similar to that of parturients with disorders of platelet adhesion and secretion, consisting of platelet transfusions and aggressive use of uterotonic agents.[44]

Anesthetic Management

There are no reports of regional techniques in these parturients, and it is safer to avoid these techniques. It is also better to avoid pudendal nerve blocks, as these may lead to a pelvic hematoma.

Alloimmune Thrombocytopenia

Alloimmune thrombocytopenia (AIT) is unique in that it only affects the neonate. It is caused by maternal antiplatelet alloantibodies or autoantibodies (IgG) that cross the placenta and are directed against a specific platelet antigen lacking in the mother. These alloantibodies have a high affinity for the platelet membrane glycoproteins; platelet destruction is severe, causing fetal thrombocytopenia.[14] Neonatal thrombocytopenia in the absence of maternal thrombocytopenia is almost always AIT. The HPA platelet alloantigen system accounts for most cases, and HPA-1a (PI^{A1}) is the most common antigen[45,46] AIT has a high fetal and neonatal morbidity and mortality, and up to 30% of fetuses or neonates may suffer intracranial hemorrhage.[14] This fetal or neonatal disorder can be associated with severe thrombocytopenia ($<20 \times 10^3/mm^3$), and almost all fetuses or neonates with such a low platelet count have AIT.[7] The incidence of AIT is 1 in 5,000 to 1 in 10,000, and almost all cases are discovered after the onset of neonatal thrombocytopenia.

Obstetric Management

Risk factors for this disorder include a sibling with AIT or a more distant family history. The fetal thrombocytopenia worsens as the pregnancy progresses. Although 50% of cases occur in the first pregnancy, it has a recurrence rate of 97% in future pregnancies. Genotyping of the relevant platelet anti-

gen system in the father allows for the determination of whether all, or only one half, of subsequent pregnancies will be affected. However, as PL^{A1} is relatively common in the Caucasian population, many fathers will be homozygotic PL^{A1}/PL^{A1}. Thus, all subsequent pregnancies will have only PL^{A1} + fetuses. In cases in which the father is identified as a heterozygote (PL^{A1}/PL^{A2}), amniocentesis and genotyping of the fetal platelet antigen can differentiate PL^{A1} from PL^{A2} fetuses.

For at-risk PL^{A1} fetuses, it is essential to diagnose this condition antenatally and to start treatment immediately. Treatment plans are individualized based upon the status of prior affected offspring. Maternal intravenous immunoglobulin (IVIg) is recommended in the setting where the diagnosis is made following a sibling with thrombocytopenia, but without clinical bleeding. Maternal IVIg has been reported to have a 70% efficacy. Assessment of fetal platelets is generally reserved for those families with evidence of a prior in utero or neonatal bleeding episode, as the complication rate of percutaneous umbilical sampling (PUBS) is as high as 10%. PUBS is often used to assess the efficacy of IVIg treatment. Intrauterine antigen-negative platelet transfusion can be given if the fetal platelet count is below $30 \times 10^3/mm^3$.[47,48] Alternatively, some advocate empiric administration of IVIg for parturients with a history of AIT. Some have recommended high-dose maternal prednisone (60 mg/day) if there is no response to IVIg.[45] The mode of delivery is also dependent on the fetal platelet count. An elective cesarean section before labor is performed if the platelet count is less than $50 \times 10^3/mm^3$ or if it is unknown.[49]

Anesthetic Management

It is important to emphasize that this is a fetal/neonatal disorder, and that the mother is not affected. It is always important to rule out other maternal conditions, such as ITP, that may cause neonatal thrombocytopenia. We recommend mea-surement of the maternal platelet count and will administer regional anesthesia provided that it is greater than $70 \times 10^3/mm^3$ or greater than $50 \times 10^3/mm^3$ in the presence of ITP.

Microangiopathy in Pregnancy

Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome

The new guidelines from the National High Blood Pressure Education Program define preeclampsia as a pregnancy-specific disorder that develops after 20 weeks gestation with a blood pressure greater than or equal to 140/90 mm Hg, and 24-h urinary protein greater than or equal to 300 mg.[50] Severe preeclampsia is characterized by any of the following: urinary protein greater than or equal to 5 g/24 h, epigastric or right upper quadrant pain, diastolic blood pressure of 110 mm Hg or higher, headache or visual disturbances, oliguria, creatinine above 1.2 mg/dL, elevated liver function tests, pulmonary edema, thrombocytopenia, or HELLP syndrome.[50] The latter condition deserves special attention, and we discuss it here.

The HELLP syndrome, which was originally described by Weinstein,[51] consists of hemolysis, elevated liver enzymes, and low platelet count. The hemolysis and low platelets are caused by microangiopathic red cell and platelet destruction, whereas the elevated liver enzymes are a result of fibrin obstructing hepatic sinusoids.[52] It occurs in up to 10% of pregnancies complicated by severe preeclampsia and may be life threatening.[52] It is more common in older parturients, in multiparae, and in Caucasians. It usually presents in the second or third trimester and may also occur in the postpartum period in parturients with a previous diagnosis of preeclampsia. It could occur in parturients with a normal blood pressure and with no proteinuria.[53] Parturients may have one or all of the components of the HELLP syndrome, and the maternal morbidity increases as the components increase.

Obstetric Management

Treatment for HELLP syndrome includes magnesium sulfate for seizure prophylaxis and a plan for an early delivery of the neonate. Magnesium sulfate is continued through labor and delivery and for 24 h postpartum. Although delivery of the fetus is the definitive treatment for HELLP syndrome, up to 30% of parturients have manifestations of the HELLP syndrome within 48 h after delivery. Furthermore, higher liver enzymes and lower platelet counts may occur postpartum.

The mode of delivery depends on the gestational age and on the severity of the maternal and fetal condition. Antenatal maternal administration of glucocorticoids (two doses of bethamethasone 12 mg intramuscularly, 24 h apart) is given before delivery if the gestational age is less than 34 weeks. It is best to wait 48 h after the first dose of bethamethasone and to give a total of two doses, but only if both maternal condition and fetal condition are stable. Corticosteroids accelerate the appearance of pulmonary surfactant, hasten pulmonary maturity, and reduce the incidence of respiratory distress syndrome, intraventricular hemorrhage, and mortality in premature infants.[54] Maternal indications for delivery include a gestational age of 38 weeks or more, platelet count below $100 \times 10^3/ mm^3$, progressive deterioration in hepatic or renal function, suspected placental abruption, persistent severe headaches or visual changes, or persistent severe epigastric pain.[50] Fetal indications for delivery include severe fetal growth restriction, nonreassuring fetal testing results, or oligohydramnios.[50] Fetal thrombocytopenia has the same prevalence in preeclamptics as in the general obstetric population, and there are no data that correlate maternal thrombocytopenia with fetal thrombocytopenia.[55] HELLP syndrome per se is not a contraindication for a vaginal delivery, and in the stable parturient, most obstetricians would attempt an induction of labor. Worsening liver enzymes or a continued drop in the platelet

count mandate an urgent delivery that is more expeditiously accomplished via a cesarean section.

Transfusion of platelets has been recommended if the platelet count is less than $50 \times 10^3/mm^3$ before a cesarean section and if it is less than $20 \times 10^3/mm^3$ before a vaginal delivery.[52] Aggressive postpartum use of uterotonic agents is indicated, as uterine atony may be exacerbated by magnesium sulfate. However, methylergonovine is relatively contraindicated with maternal hypertension because it causes generalized vasoconstriction.

Anesthetic Management

Although the HELLP syndrome is not a contraindication to regional anesthesia, a low platelet count or the presence of a coagulopathy may preclude the use of regional anesthesia. Our practice consists of checking the platelet count in any parturient with preeclampsia. We do not obtain any other coagulation test if the platelet count is greater than $100 \times 10^3/mm^3$, because thrombocytopenia is the first and most common coagulation parameter to be affected with microangiopathy.[11,56–58] It has been recommended that the PT, aPTT, and fibrinogen levels be monitored if the platelet count is less than $100 \times 10^3/mm^3$.[59] Circulating levels of fibrin degradation products are occasionally elevated, antithrombin III levels are lower, and plasma fibrinogen levels are unaffected unless the disease has coexisting placental abruption.[50] Disseminated intravascular coagulation (DIC), although uncommon with the HELLP syndrome, could result secondary to endothelial cell damage. Placental abruption is commonly associated with the HELLP syndrome and is also likely to lead to DIC.

A decade ago two studies demonstrated a prolonged bleeding time in parturients with preeclampsia and a platelet count below $100{,}000/mm^3$, and some anesthesiologists refused to administer a regional technique to these parturients.[60,61] However, more recent publications have noted that the bleeding time is operator dependent and may not be predictive of surgical bleeding.[62,63] Recently, thromboelastography (TEG) has been utilized to evaluate the platelet function and coagulation status of parturients with preeclampsia.[64,65] TEG is a sensitive test for the global assessment of coagulation.[66] TEG can determine the clot strength (maximum amplitude), the rate of clot formation/strengthening (K time and alpha angle), and fibrinolysis. In addition, it is a test of platelet function, plasma factor activity, and activators and inhibitors of coagulation.[66] Changes in TEG are related to changes in aPTT (reaction time or R-time), platelet function (maximum amplitude or MA), and activity of coagulation factors VIII and XIII (MA).[67] Orlikowski et al.[64] and Sharma et al.,[65] independently, demonstrated a strong correlation between the MA and the platelet count in preeclamptics with a platelet count less than $100 \times 10^3/mm^3$. Both studies demonstrated a normal MA (54–80 mm Hg range in normal pregnancy) when the platelet count was above $75 \times 10^3/mm^3$. However, Sharma[65] demonstrated that severely preeclamptic parturients with a platelet count below $100 \times 10^3/mm^3$ were hypocoagulable. These parturients had prolonged R- and K-times and decreased MA and alpha angle.

More recently, the PFA-100 has been used to measure platelet function in preeclamptics.[68] Preliminary reports comparing the PFA-100 to the TEG have suggested that primary hemostatic function impairment as a result of preeclampsia is demonstrated by an elevated CT (PFA-100) but not by the MA (TEG). Furthermore, in another study, the same authors demonstrated that thrombocytopenia (platelets $<80{,}000/mm^3$) is better reflected by the CT than by the MA.[69] In addition, parturients with preeclampsia have a longer CT when compared to controls, reflecting a decrease in platelet function.[70] Further work is recommended before making a decision whether to provide neuraxial anesthesia based on the PFA-100.

Our practice consists of providing a regional technique in parturients with a stable platelet count above $75 \times 10^3/mm^3$, provided that no other abnormal coagulation parameters are present. It is very important to follow the downward trend of the platelet count, as it may continue to decrease even further. We review the PT, aPTT, and fibrinogen in parturients with platelet counts between $75 \times 10^3/mm^3$ and $100 \times 10^3/mm^3$ and provide a regional technique if these coagulation parameters are normal. We perform a TEG in the absence of these additional coagulation parameters and provide a regional technique if the TEG parameters are normal.

We prefer to perform a spinal anesthetic for the parturient undergoing a cesarean section and without an epidural catheter in situ. Spinal anesthesia is less likely to cause trauma to the epidural venous plexus and provides more reliable and rapid anesthesia than the epidural technique. Although some experts still recommend the epidural technique because of a slower and more controlled onset of a sympathectomy,[71] two recent studies have demonstrated that spinal anesthesia is safe in severely preeclamptic parturients.[72,73] Spinal anesthesia, when compared to epidural anesthesia, led to a similar drop in the blood pressure and to similar ephedrine requirements. Furthermore, laryngoscopy, intubation, and emergence from general anesthesia after a failed or patchy epidural, may cause significant hypertension. Airway swelling may result from preeclampsia and may lead to a failed intubation. We prefer a subarachnoid technique for a preeclamptic parturient undergoing a cesarean section.

Special attention is of utmost important in the thrombocytopenic parturient with right upper quadrant or abdominal pain. These parturients are at risk for rupture of a liver hematoma and could bleed profusely.[52] A call for emergent assistance is recommended, as control of the airway and rapid transfusion of blood products is essential. Rapid transfusion of crystalloids, colloids, and blood products could lead to more airway swelling. Therefore, it has been recommended to convert to a general anesthetic via a rapid sequence induction as early as possible before a worsening of the airway. Rapid transfusion of platelets and red blood cells is necessary, whereas fresh-frozen plasma and fibrinogen should be transfused based on clinical and laboratory findings. Management of these parturients is difficult, as pulmonary edema,

hypotension, hypertension, or coagulopathy may present at any time during the resuscitation.

Thrombotic Microangiopathy

Thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS) belong to the group of disorders labeled thrombotic microangiopathies. These disorders are characterized by thrombocytopenia, hemolytic anemia, and multiorgan failure.[74] Intravascular platelet aggregation leads to thrombocytopenia, occludes perfusion to vital organs, and causes erythrocyte fragmentation.[74] Although central nervous system manifestations are more common with TTP, renal failure is more common with HUS. The classic presentation of TTP consists of thrombocytopenia, microangiopathic hemolysis, neurologic symptoms, renal impairment, and fever.[75] HUS is associated with platelet and erythrocyte destruction and renal failure. A complete blood count with peripheral blood smear and liver function tests complement the clinical diagnosis. Erythrocyte fragmentation leads to hemolytic anemia and schistocytes on peripheral blood smear, and serum lactic dehydrogenase is elevated as a result of the hemolysis.[74] A urine analysis may reveal proteinuria and hematuria, and serum creatinine and blood urea nitrogen may be elevated as a result of an ischemic insult to the kidneys.

A recent review of TTP-HUS in pregnancy found that it occurs in 1 in 25,000 births, occurs mostly in the peripartum period, occasionally is confused with severe preeclampsia, tends to reoccur, and may lead to life-threatening complications.[76] Unlike preeclampsia, these disorders are associated with hemolytic anemia and do not improve after delivery. HUS is more likely to appear in childhood, and the adult syndrome may occur in the postpartum period. Although TTP is a rare disorder, it may be associated with pregnancy, as it is more common in females and has a peak incidence during the third and fourth decades of life.[75]

Obstetric Management

Immediate treatment is essential, as these disorders are associated with significant morbidity and mortality. Treatment consists of plasmapheresis and transfusion with fresh-frozen plasma.[74] Glucocorticoids are recommended for parturients who fail to respond to plasma exchange and transfusion of packed red blood cells for those who are anemic. Platelet transfusions are not routinely recommended as they may cause thrombosis and worsen the disease process.[75] However, platelets should be used if life-threatening bleeding is present. Induction of labor or immediate delivery by cesarean section is not recommended unless there is coexisting worsening preeclampsia or if the fetal condition worsens. TTP-HUS does not improve after delivery and may occur early in pregnancy. Preterm delivery and intrauterine fetal death are frequent complications as a result of endothelial injury leading to vascular obstruction.[75]

Anesthetic Management

There are very few reports in the literature about the management of patients with TTP-HUS. This is a very rare disorder, and the commonly accepted treatments are nonsurgical. Splenectomy has been used as a last effort in patients who have failed medical intervention.[77,78] It is of note that the patients from the last two reports were young females (ages 21 and 22), and one was pregnant at 20 weeks gestation.[77,78] Although it is a very rare disorder, it is likely to be associated with pregnancy. Regional anesthesia is relatively contraindicated for these parturients, as all of them have a platelet count below $100 \times 10^3/mm^3$. In addition, functional platelet defects, prolonged PT, and decreased coagulation factors may be present.[79] DIC is rarely associated with TTP-HUS.

Continued steroid replacement is necessary in parturients receiving glucocorticoids, as is the avoidance of intramuscular medications in the setting of thrombocytopenia and the avoidance of medications that cause prolonged central nervous system (CNS) dysfunction.[78] In addition, adequate intravascular access and replacement of blood products in the setting of hemorrhage are mandated. It is best to save platelet transfusions for life-threatening bleeding. Gentle insertion of laryngoscopy blades and of endotracheal and nasogastric tubes is essential to avoid epistaxis and laryngeal hematoma. It has also been recommended that the mean arterial pressure be kept very close to normal levels to avoid further compromise of cerebral and other vital organ perfusion.[78,79] It is also important to avoid renally excreted agents, as renal failure is common with this disease process.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the widespread activation of coagulation leading to intravascular deposition of fibrin and depletion of platelets and coagulation factors.[80] In addition, there is a suppression of native anticoagulants such as antithrombin III, proteins C and S, and tissue factor-pathway inhibitor. Furthermore, an impaired fibrinolytic system contributes to the clinical manifestation of DIC.[80] The end result is severe bleeding and the thrombosis of small and midsize vessels that may result in multiorgan failure.

DIC is usually a result of a disease process that triggers the coagulation pathway. Common causes of DIC in pregnancy include placental abruption, amniotic fluid embolism, acute fatty liver of pregnancy, HELLP syndrome, sepsis, saline-induced abortion, massive hemorrhage, and intrauterine fetal death at greater than 4 weeks (Box 22.1). DIC was an associated condition in one half of deaths caused by spontaneous abortion (less than 20 weeks gestation).[81] Precipitating events include placental tissue thromboplastin in placental abruption

Box 22.1. Obstetric conditions associated with disseminated intravascular coagulation (DIC).

Placental abruption
Amniotic fluid embolism
Acute fatty liver of pregnancy
HELLP syndrome
Sepsis
Saline induced abortion
Massive transfusion
Intrauterine fetal death after 4 weeks
Spontaneous abortion

and amniotic fluid embolism, endothelial cell damage in HELLP syndrome, the cell-specific membrane component of the microorganism in sepsis, and massive transfusion with hemorrhage.

The diagnosis is based on generalized bleeding in the presence of a disorder known to be associated with DIC or in the presence of massive blood transfusion. There is no single laboratory test that alone makes the diagnosis of DIC. However, a combination of laboratory tests in the presence of a clinical condition known to be associated with DIC makes the diagnosis.[82] Common laboratory results in DIC include a platelet count below $100 \times 10^3/mm^3$, prolonged PT and aPTT, the presence of fibrin degradation products or D-dimers in plasma, and low levels of antithrombin III (AT III).[80] Although the plasma fibrinogen may be low with DIC, this is not necessary for the diagnosis as it is often in the normal range.

Obstetric Management

The most important concept when dealing with parturients with DIC is to treat the underlying cause. Otherwise, whatever treatment is provided may only help to temporize the coagulopathy, and the underlying cause will continue to release the substance causing the DIC. The treatment of the underlying cause, almost always, consists of the delivery of the fetus and placenta. Other recommended treatments include fresh-frozen plasma (FFP), cryoprecipitate, platelet transfusions, and AT III. Fresh-frozen plasma is given to replace coagulation factor consumption and is needed for an operative vaginal delivery or cesarean section in a parturient with DIC. Platelet depletion may necessitate replacement, and most obstetricians prefer a platelet count above $50 \times 10^3/mm^3$ before a cesarean section.

There are reported cases of DIC secondary to placental abruption with a previable pregnancy that have resolved with either replacement of clotting factors or with conservative management.[83–85] The goal here is to assure maternal safety first, as uterine evacuation almost always improves the coagulopathy. However, if the parturient is hemodynamically stable, pertinent laboratory values are monitored closely and are increasing, and adequate clotting factor deficiencies are replaced, then it may be helpful for the fetus to gain more intrauterine life.

Anesthetic Management

Regional anesthesia is contraindicated in the setting of frank DIC. However, the problem that may arise is that a parturient may develop DIC after an epidural catheter is sited. It has been recommended that the epidural catheter be removed in a parturient with DIC, provided that there is no evidence of bleeding around the epidural catheter insertion site.[86] These authors state that epidural catheters could migrate into epidural veins and increase the risk of bleeding into the epidural space.[86] Others have recommended that the epidural catheter be kept in situ until the coagulopathy has resolved.[5,87] Epidural hematomas have been reported to occur in anticoagulated parturients at the time of epidural catheter withdrawal.[88] Some experts recommend that it is important to have normal coagulation values before needle placement as well as before epidural catheter removal.[5,87] It is our practice to keep epidural catheters in situ until the coagulopathy is corrected. We aggressively correct the coagulopathy with blood products (see following), perform a thorough neurologic check to rule out neurologic changes that may occur from cord compression, and do not give any local anesthetic through the epidural catheter as this may blunt early clinical signs of cord compression. We remove the epidural catheters after the coagulation parameters have normalized.

The main role of the anesthesiologist in a parturient with DIC is to have adequate intravenous access and to assist in providing supportive blood product replacement. At least two 18-gauge intravenous catheters are necessary for this purpose. Management of DIC consists of treating the underlying cause, maintenance of blood volume, and replacement of depleted clotting factors. Platelet and FFP transfusions are the first line of treatment and should be utilized in the setting of active bleeding, or in a parturient with a coagulopathy scheduled for an operative procedure. Further therapeutic options include the transfusion of AT III concentrate and fibrinogen. It is recommended that a plasma fibrinogen level be checked before replacing this blood product. There are reported cases of treatment with recombinant activated factor VII, but the mechanism is unknown.[90] However, caution should be employed before the routine use of this product for DIC as it can cause thrombogenecity. Other controversial therapeutic options include the transfusion of AT III-independent inhibitors of thrombin such as desuridin and anticoagulants such as heparin. The problem with these options is that even though they may inhibit thrombin and fibrin deposition, they may also worsen the coagulopathy.

Factor Deficiencies

Hemophilia A

Hemophilia A is a deficiency of factor VIII activity, associated with deep intramuscular hematomas or hemarthrosis. It is an X-linked recessive disease that is almost exclusively

present in males (1/10,000 men). Females are carriers of the disease and are rarely affected. Affected females may be a result of the normal gene not functioning properly or being inactivated.[91] Most female carriers are free of bleeding manifestations, and pregnancy is associated with an increase in the concentration of factor VIII; this may account for the reported cases of parturients who have mild or moderate variants of the disease (homozygous) and that are free of bleeding complications.[92]

The disease is first suspected when there is persistent bleeding after dental extractions, heavy menorrhagia, or hemarthrosis. It is then confirmed by laboratory testing including a prolonged aPTT, a normal PT, and a low factor VIII activity. Carriers are identified by a low factor VIII clotting activity (VIII:C). Factor VIII is located on the X chromosome. Factor VIII is carried by vWF, which is located on chromosome 12 and is under separate autosomal control.[92] Therefore, vWF is unaffected by hemophilia A.

Obstetric Management

Carrier females are much more common that homozygous parturients. Prior bleeding complications in carriers are likely to improve with pregnancy as a result of the elevated levels of factor VIII. Homozygous parturients with mild disease may improve but, depending on factor VIII levels and clinical manifestations of bleeding, may require factor VIII or cryoprecipitate transfusions before the delivery. The goal is to have a factor VIII level greater than 50% of normal, especially if a cesarean section is planned.

Intrauterine detection of hemophilia is possible by DNA analysis provided that a recognized mutation of the factor VIII gene has been identified in the carrier.[92] Alternatively, fetal blood can be obtained via cordocentesis. Some experts have recommended avoiding fetal scalp electrodes in affected infants as there are reports of large hematomas following the placement of these electrodes.[92] Intrauterine fetal transfusions are not currently recommended, and vaginal delivery has been reported to be safe for affected infants. Furthermore, cesarean section will increase maternal bleeding complications.

Anesthetic Management

It is important to obtain a thorough family history, a hematology consult, and a full workup of the affected individual. Intramuscular administration of medications is avoided in parturients with hemophilia, as this may cause intramuscular bleeds. Regional anesthesia may be acceptable in parturients who are carriers of the disease, have normal levels of factor VIII, and are free of bleeding complications. Some female carriers of hemophilia can have variable levels of factor VIII, and there are reports of postpartum hemorrhage in parturients with presumed low levels of FVIII.[93] Regional anesthetic techniques are best avoided in homozygous parturients, as bleeding in the epidural space is always a potential complication. Furthermore, factor VIII levels decrease postpartum, presenting potential bleeding complications for the homozygous parturient and for the carrier with low levels of factor VIII before the pregnancy. For this reason, nonsteroidal antiinflammatory agents should be avoided in the postpartum period.

If the risk of a general anesthetic is greater than the risk of an epidural hematoma for a cesarean section, then a single shot spinal is preferred. Ideally, factor VIII levels should be increased to 100% of normal, or to a number close to it. A spinal carries a lower likelihood of epidural vessel trauma, and there is no need to instrument the epidural space after delivery. There is a report in the nonobstetric population of 46 hemophiliacs given spinal or epidural anesthesia without complications.[94] All these patients had hemophilia without any coexisting hematologic disease and had normal levels of factors VIII and IX after replacement therapy. In addition, all relevant coagulation parameters were closely watched during the entire period in cooperation with the Hemophilia Center.[94]

Hemophilia B (Christmas Disease)

Christmas disease is a deficiency of factor IX activity and is also an X-linked recessive disease almost exclusively present in males. The clinical features are very similar to those of hemophilia A, and the aPTT is also prolonged. The diagnosis is based on a low plasma factor IX level in the presence of a normal level of factor VIII.

Obstetric Management

The obstetric and fetal/neonatal management is similar to that of hemophilia A. Factor IX levels increase with pregnancy, and most females are carriers of the disease. Carriers are usually free of bleeding complications. However, there is a report of a parturient who had two postpartum hemorrhages requiring transfusion and was later found to be a female carrier with a factor IX level of 24%.[93] It is recommended that factor IX levels be greater than 40% of normal before delivery in affected parturients. Although FFP contains factor IX and has been used in the past, current recommended treatment consist of factor IX concentrate.

Anesthetic Management

The anesthetic management is similar to that of parturients who are carriers or have hemophilia A. Regional anesthetic techniques can be offered to carrier females who have normal levels and are free of bleeding complications. Although it is best to avoid regional techniques in homozygous patients, there is a case series of 46 epidural and spinal anesthetics performed in patients with hemophilia A and B with corrected factors VIII and IX.[94]

Other Factor Deficiencies

Factor XI (FXI) deficiency is inherited as an autosomal recessive disorder and is prevalent in Ashkenazi Jews. Although

it has an equal prevalence in males and females, some bleeding complications are specific to women; these include menorrhagia and postpartum hemorrhage.[95]

Obstetric Management

The risk of postpartum hemorrhage can be high in parturients with factor XI deficiency, because factor XI levels do not increase with pregnancy. Kadir et al.[96] demonstrated a 16% incidence of primary postpartum hemorrhage and a 24% incidence of secondary postpartum hemorrhage among parturients with factor XI (FXI) deficiency. Most cases of hemorrhage occurred when the levels of FXI were less than 50 IU/dL, and no parturient who received prophylactic FXI transfusion during labor had a bleeding complication.[96] An antenatal hematology consultation is recommended in these parturients. Fresh-frozen plasma and FXI concentrate have been utilized in the treatment of these parturients, with the goal being to maintain a FXI level greater than 30%. However, others have demonstrated that the level of FXI does not correlate with bleeding tendencies in the general population.[97]

Anesthetic Management

Factor XI deficiency leads to a prolongation of the aPTT, and most anesthesiologists would avoid regional techniques in these parturients. There is a report of two parturients with mild to moderate FXI deficiency (levels >50 IU/dL) and normal coagulation screen who received regional anesthesia for labor and delivery.[96] However, it is unclear from the information given whether spinal or epidural techniques were used, or the exact meaning of a normal coagulation screen. Although the minimum FXI level before a regional technique is unknown, a true normalization of FXI before a cesarean section may allow for a one-shot spinal.

Connelly and Brull[98] described the anesthetic management of a parturient with inherited FXI deficiency as well as acquired factor XI inhibitor. FXI inhibitor may form in response to repeated transfusions with FXI. The transfusion of FXI and FFP may not be effective, as it may result in an increase of FXI inhibitor. An alternative in such cases includes the transfusion of activated factors that are further down in the coagulation cascade. This parturient received activated FIX before excision of a giant cell tumor and a coagulant complex with activated FVII before a cesarean delivery.[98] Other anesthetic considerations are very similar to those of parturients with hemophilia, including the avoidance of intramuscular medication and use of gentle laryngoscopy and intubation.

The discussion of other factor deficiencies is beyond the scope of this chapter, as they are very uncommon and the obstetric and anesthetic management is similar to the factor deficiencies already mentioned. Factor XII deficiency is an exception. Although the aPTT is significantly prolonged, it is not associated with any bleeding tendencies. These parturients may even be more prone to thrombosis, and this condition per se is not a contraindication to regional anesthesia. Parturients with inherited factor deficiencies are usually followed by hematologists, who should be involved in their management early in the pregnancy.

Acquired Factor Inhibitors

Acquired inhibitors to FVIII may develop in previously healthy parturients with no prior history of a bleeding disorder. It is thought that elevated levels of FVIII in pregnancy may trigger this phenomenon. These inhibitors should be suspected when an isolated elevated aPTT is detected in a parturient who is bleeding in the postpartum period. A FVIII assay may reveal undetectable levels of factor VIII.[99]

Management of such inhibitors involves factor concentrates and depends on the titer of the inhibitor. Fortunately, most of these inhibitors resolve spontaneously within several months after delivery. An antepartum hematology consult is essential to develop a treatment plan in the setting of bleeding complications that may occur in the peripartum period. A full discussion of acquired factor inhibitors is beyond the scope of this chapter.

Other Hematologic Complications Affecting Pregnancy

A number of other hematologic disorders are encountered in parturients that may affect their peripartum management, including iron deficiency anemia and hemoglobinopathies. Such disorders can have adverse effects on both maternal and fetal outcome.

Iron Deficiency Anemia

Iron deficiency anemia is relatively common in menstruating females, and the prevalence is approximately 5% in the United States. Individuals who are particularly at risk include those with excessive or repeated blood loss, such as multiparous women, and those with low oral intake of heme-bound iron, such as vegetarians. In addition, given the increased iron requirement in pregnancy, individuals who have marginal iron stores or who are iron deficient may become frankly anemic.

Obstetric Management

Red cell indices may be useful early in pregnancy to help detect individuals at risk for becoming significantly anemic. In particular, a hematocrit early in pregnancy of less than 32% with a mean corpuscular volume (MCV) less than 80 fL should provoke investigation of the iron status. In healthy women, the ferritin level is the most reliable indicator of iron stores and if low (<10 ng/mL) should suggest supplementation with an iron preparation. Which preparation to use (iron sulfate, iron dextran, iron gluconate) is a matter of choice, although iron gluconate and iron dextran are sometimes asso-

ciated with fewer gastrointestinal side effects. The most important feature of management in this regard is to begin iron supplementation early in pregnancy, as it can take several months to adequately replete iron stores.

There may be a benefit from the administration of intravenous iron if severe iron deficiency is detected late in the pregnancy. A repletion occurs very rapidly, and a reticulocytosis can occur within a week when iron is administered by this route. The hematocrit can increase by several points in less than a month. The two iron preparations approved for parenteral use in the United States are iron dextran (InFed) and iron gluconate (Ferrlecit). Iron dextran has the advantage that a full repletion can be given in one sitting but the disadvantage that there is a 0.7% risk of an anaphylactic reaction. Iron gluconate is associated with fewer allergic reactions, but generally requires several infusions to fully replete iron stores. Appropriate administration of IV iron late in pregnancy may help avoid the need for postpartum transfusion.

Anesthetic Management

There is no minimal hematocrit at which a blood transfusion is necessary. Appropriate supplementation with iron, as already stated, is essential. It is also important to maximize oxygen delivery to the fetus. Supplemental oxygen and maintenance of the left uterine displacement position are helpful. Maternal hyperventilation secondary to painful uterine contractions may lead to respiratory alkalosis with a leftward shift of the oxyhemoglobin dissociation curve.[100] Hypothermia may also compromise oxygen delivery to the fetus. The avoidance of hypothermia and early epidural analgesia are recommended to blunt this decreased oxygen delivery.

Hemoglobinopathies

The hemoglobinopathies include the thalassemias and the structural mutations, such as sickle cell anemia. Parturients with alpha- or beta-thalassemia trait, or sickle cell trait, are for the most part asymptomatic. There are no special recommendations for their management in pregnancy, except recognition of these conditions. In the case of alpha- or beta-thalassemia trait this recognition is not only important for genetic counseling (for instance, to avoid hydrops fetalis), but also to prevent possibly deleterious empiric iron supplementation on the basis of a low MCV.

Sickle Cell Disease

Sickle cell disease (SSD) occurs when valine replaces glutamic acid in the sixth position of the β-chain and results in hemoglobin S (Hgb S).[101] This Hgb S may account for more than 50% of hemoglobin in patients with SSD.[102] SSD occurs in 1 in 600 African American people, and as many as 8% of African-Americans are heterozygous carriers of SSD (40% Hgb S).[102] Carriers of SSD are free of clinical manifestations, and the condition is benign. Homozygous patients have a Hgb S solution that polymerizes, causing cell sickling. Cell sickling usually leads to vasoocclusion as some sickle cells adhere to the endothelium.[102] Vasoocclusion can affect most organ systems and often leads to painful episodes, stroke, acute chest syndrome, liver disease, splenic sequestration, and renal insufficiency. Women with SSD may experience recurrent spontaneous abortions as a result of this vasoocclusion.

Obstetric Management

Parturients with SSD have increased maternal and fetal morbidity and mortality.[103] It is believed that sickle cells adhere to the endothelium of the uterine blood vessels and may compromise their flow; this may lead to preterm labor and intrauterine fetal growth restriction. Maternal and fetal complications may also be a result of higher endogenous catecholamines that may worsen a vasoocclusive crisis and cause decreased uterine blood flow. Sickling is also triggered by hypoxia, acidosis, or dehydration. Therefore, it is recommended that supplemental oxygen, left uterine displacement, and intravenous hydration be provided during labor and delivery. Vaginal delivery is the mode of delivery of choice, unless there is a maternal or fetal indication for a cesarean section.

Routine transfusion of parturients with SSD does not appear to be necessary or indicated.[104] Maternal and neonatal outcomes were similar in parturients who had prophylactic transfusions and in those who did not. However, consideration should be given to transfusion in sickle cell parturients with repeated crises during pregnancy to try to minimize their occurrence. Blood transfusion should also be considered for medical and obstetric complications such as worsening hypoxemia or anemia, acute chest syndrome, splenic sequestration, or septicemia.[105] Parturients may also be predisposed to peripartum infections, such as pneumonia, or hypercoagulable events, so appropriate vigilance for these complications should be maintained, and early intervention instituted.[102]

Anesthetic Management

Early epidural placement is recommended for parturients with SSD because increased endogenous catecholamines may lead to vasoconstriction.[103] Generous hydration, a warm environment, supplemental oxygen, and maintenance of left uterine displacement are essential for these parturients. There is a report of an intraoperative death during cesarean section in a parturient with sickle cell trait that was believed to be caused by a severe form of concealed aortocaval compression despite the use of left uterine displacement.[101] The authors of this report recommend that, in parturients with sickle cell trait or SSD, a pulse oximeter be used in the lower extremity to assure adequate oxygenation below the level of the uterus. They further recommend avoiding local ischemia or stagnation, because parturients with SSD or sickle cell trait may be difficult to resuscitate if they become severely hypoxic or

cyanotic.[101] Shivering should be treated immediately, as it increases oxygen consumption and may precipitate hypoxia.

Other issues that may arise in parturients with SSD include management of pain crises in the peripartum setting. In general, opioids may be administered safely as needed to control pain. For women who are maintained on chronic opioids throughout pregnancy, a withdrawal plan for the newborn needs to be coordinated with the neonatologists. Epidural analgesia has been used for the management of labor pain and sickle cell crisis with excellent results.[103] Not only do epidural local anesthetics provide analgesia, but they also may act as vasodilators enhancing blood flow.

Postpartum neuropathies may occur in the postpartum period as a result of vasoocclusion. Sickle cell-induced neuropathies are usually bilateral but may also be unilateral. There is a recent report from our institution of a sickle cell-induced peripheral neuropathy after spinal anesthesia.[106] The authors pointed out that it is necessary to rule out other causes such as obstetric complications. Anesthetic complication is very unusual, difficult labor may compress the lumbosacral plexus and result in lower extremity peripheral neuropathies.

Thalassemia

Thalassemic syndromes are inherited disorders produced by a quantitative defect in the synthesis of globin chains of hemoglobin. They are classified according to the type of globin chain that is affected. Homozygous forms result in thalassemia major, whereas heterozygous forms result in thalassemia trait. Alpha-thalassemia results in hydrops fetalis and spontaneous abortion and is incompatible with life.

Obstetric Management

Thalassemia minor does not usually create obstetric or anesthetic problems. Although most females are sterile and do not usually survive to adulthood, recent advances in transfusion therapy and iron chelation have resulted in successful pregnancies of patients with beta-thalassemia major.[107,108] Aggressive management with blood transfusion, iron chelation, and serial echocardiograms is recommended. Beta-thalassemia intermedia is characterized by hemolytic anemia, and the condition usually worsens in pregnancy. Thalassemia intermedia may require blood transfusion support during pregnancy, depending on the severity of the anemia.

Anesthetic Management

In cases of thalassemia major, one should consider not only problems derived from the severity of the anemia but also those related to transfusion therapy and to facial bony malformations.[109] For example, iron loading of the myocardium is common after multiple transfusions and may lead to cardiomyopathies and congestive heart failure. Facial bony malformations may contribute to difficulty with mask ventilation and tracheal intubation. A "cardiac delivery," early epidural placement, and an assisted delivery is recommended in parturients with thalassemia major or intermedia. Most of these parturients have compromised cardiac function that may worsen with the physiologic changes of pregnancy or with the changes associated with labor and delivery.

Thrombophilias

Prevention of both acute and chronic blood loss requires a complex balance between the opposing forces of thrombosis and antithrombosis. Primary hemostasis is achieved by platelets at the site of injury while secondary hemostasis relies on a multistep sequence of protein activation. Viewed as four sequential steps, the clotting cascade of secondary hemostasis ultimately results in the production of thrombin. Thrombin is an essential component of clot formation required for the conversion of fibrinogen to fibrin. Deficiency or impaired functioning of any one of the proteins of this clotting cascade markedly alters this thrombotic–antithrombotic balance. Many of the causes of increased thrombosis occur within this secondary phase of hemostasis, the "clotting cascade."

Regulation of the activation of clotting cascade proteins underlies the stringent control of the clotting system. Without such regulation, a single milliliter of blood has the capacity to trigger conversion of the total body volume of fibrinogen to fibrin, and thus clot formation, in an estimated 10 to 15 s.[110] The major inhibitors of activation of clotting cascade proteins are antithrombin, protein S, and protein C. A complex of antithrombin III (AT III) with proteins S and C primarily inhibits factors V and VIII, which drive the critical fourth step of the clotting cascade. Without inhibition of this fourth step, progressive clot formation ensues. AT III is also an inhibitor of many other clotting cascade proteins, functioning as a natural regulator of overly aggressive thrombosis.

Without balance between the opposing prothrombotic and antithrombotic forces of the clotting cascade, excess thrombosis results. The primary hypercoagulable states are often inherited abnormalities of the prothrombotic proteins (factor V), and antithrombotic proteins (protein C, protein S, and AT III) (Table 22.3). Abnormalities of other antithrombotic systems exist but are rarely seen clinically. In contrast, the secondary hypercoagulable states are a heterogeneous collection of clinical conditions associated with thrombosis, but often with diverse etiologies. Although the secondary hypercoagulable states are generally considered acquired, some are now recognized to have an inherited component. Antiphospholipid antibody syndrome represents the most commonly encountered of the acquired secondary hypercoagulable states.

Pregnancy-Related Changes

Physiologic change is intrinsic to pregnancy, and it increases the forward drive of the hemostatic pathway toward thrombo-

Table 22.3. Maternal thrombotic complications of primary hypercoagulable states.

Hypercoagulable state	Incidence in the general population	Antepartum risk of thrombosis	Postpartum risk of thrombosis
AT III deficiency	1/350	32%–44%	Less common
Protein C deficiency	1/200–500	3%–10%	7%–19%
Protein S deficiency	1/140	0%–6%	7%–22%
APC resistance (primarily secondary to factor V Leiden)	3–7/100	14%	May be higher

AT III, antithrombin III; APC, activated protein C.

sis formation. Although the etiology of such a mechanism is unclear, the evolutionary need for aggressive thrombosis during pregnancy to prevent maternal death due to hemorrhage likely played a role. Prothrombotic alterations of pregnancy include both anatomic as well as physiologic factors. The increasing size of the gravid uterus plays a significant role in increased venous congestion of the lower extremities. Structural impediments to venous return from the lower extremities are further exacerbated by the 50% or more increase in maternal vascular volume during pregnancy. Additionally, intrinsic mechanical mechanisms to aid venous return from the lower extremities are often further limited by restriction of exercise and lower leg muscular movement in conditions such as preterm labor, placenta previa, or preterm premature rupture of membranes. Nephrotic syndrome, a recognized cause of secondary hypercoagulable states, can occur with severe preeclamspia. However, the contribution of such a nephrotic-induced hypercoagulability to maternal thrombotic disease is rare.

Hormonally, the physiologically appropriate, altered levels of various steroids alone are recognized as risk factors for thrombosis. Estrogen in particular, whether during pregnancy or in the form of oral contraceptives or estrogen replacement therapy, is associated with an increased risk of thrombosis. Users of estrogen containing oral contraceptives have as much as a fourfold increase in thromboembolism over nonusers.[111] This risk follows a fairly linear relationship, with the lower-dose estrogen oral contraceptives associated with the least increase in thromboembolic disease. In addition, changes in the coagulation system during pregnancy predispose to thrombosis; these include increases in clotting factors (I, VII, VIII, IX, X) and decreases in clot inhibitors (protein S).

Hypercoagulable Syndromes

Lupus Anticoagulant

Autoantibodies against phospholipid–protein complexes are a major contributor to thrombosis and represent a secondary hypercoagulable state. When lupus anticoagulant (LAC) or anticardiolipin antibodies (ACA) are present, their interaction with platelet function may play a role. In addition, ACA have an affinity for many of the important phospholipids involved in hemostasis. LAC inhibits binding of the phospholipids needed for the conversion of prothrombin to thrombin.[112]

Antiphospholipid antibodies (APA) are noted in 3% to 5% of the general population, presenting a risk of a thrombotic event of approximately 1% per year. This risk reaches 4% to 6% per year with a coexisting diagnosis of systemic lupus, a history of thrombosis, or high IgG anticardiolipin titers.[113] Although both ACA and LAC are associated with venous as well as arterial thrombosis, ACA are five times more prevalent than LAC.[114] In addition to the development of antiphospholipids with systemic lupus and other autoimmune disorders, other conditions such as malignancy, human immunodeficiency viral infection, and drug ingestion can also be precipitators.[114] Drugs of concern include phenytoin, fansidor, quinidine, quinine, hydralazine, procainamide, phenothiazines, alpha-interferon, and cocaine. In most cases, however, APAs appear in otherwise healthy individuals.

Testing can be complex as well as variable from one laboratory to another. APA syndrome requires specialized testing of all three idiotypes of ACA (IgG, IgM, and IgA), the completeness of which can vary by laboratory.[115] The clinical utility of further specific testing for phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidyllinositol, and phosphatidylglycerol is currently being debated in the clinically suspicious but APA-negative individual.

Obstetric Management

Although arterial thrombosis is noted in one third of cases, APA syndrome most commonly presents with venous thrombosis (two thirds of cases). Cerebrovascular events predominate among those with arterial thromboses (stroke, transient ischemic attacks, multiinfarct dementia, and retinal arterial occlusion).[116] The action of these antibodies with the phospholipids of the platelet membranes may contribute to placental thrombosis. Placental thrombosis accounts for the association of this syndrome with maternal thrombocytopenia and adverse pregnancy outcomes.[117]

The impact on pregnancy outcomes is unpredictable in women without prior thrombotic events but with the finding of ACA. High rates of fetal loss in all three trimesters, placental vasculitis, and maternal thrombocytopenia have been noted with increased frequency. A 50% to 70% chance of recurrent fetal loss has been reported in the setting of a prior history of fetal loss and in the presence of ACA. Although the optimal therapy has not been clear, a combination of one baby aspirin per day and low-dose heparin appears most effective. The use of baby aspirin is initiated preconception, and

heparin is added following the documentation of pregnancy, with both being continued to near term.[118] APAs have not been consistently associated with preeclampsia.[119]

Anesthesia Management

Prostaglandin synthesis is dependent on platelet phospholipid and is essential for platelet activation and aggregation. Therefore, APA syndrome may be associated with maternal thrombocytopenia. This thrombocytopenia may be quantitative as well as qualitative. Quantitative thrombocytopenia is usually a result of platelet aggregation.[120] Therefore, a careful history to elicit mucous membrane bleeding, as well as a platelet count, is mandatory before performing a regional anesthetic on these parturients.

APA syndrome may also be associated with a prolongation of the PT or aPTT or, more likely, an in vitro prolongation of the aPTT. Such findings are rarely a result of antibodies against various coagulation factors and are more commonly a result of the presence of lupus anticoagulant.[121,122] A careful history and physical examination and a thorough workup are necessary to rule out a factor deficiency, as this represents a potential contraindication to neuraxial techniques. Lupus anticoagulant may lead to an elevation of the aPTT without a factor deficiency or a history of a bleeding diathesis and is not a contraindication to neuraxial techniques. This elevation occurs as a result of an abnormal phospholipid and is confirmed by measuring ACA with an enzyme-linked immunosorbent assay (ELISA).[121]

ACA syndrome is often associated with systemic lupus erythematosus. Cardiac complications, including left ventricular dysfunction, occur more often when both conditions coexist.[120] Other noncardiac complications are also more common when these two disorders coexist, including transient ischemic attacks, strokes, vascular occlusions resulting in end-organ damage, and DIC. An arterial catheter, central venous catheter, or pulmonary artery catheter may be necessary in these parturients during labor and delivery.[120]

Measures to prevent thrombosis during labor and delivery include the avoidance of dehydration and hypothermia. It has been recommended to warm intravenous fluids and to use antithrombotic stockings.[120,121] Although hydralazine may lead to thrombosis,[121] the use of this medication may be necessary in parturients with concomitant preeclampsia and elevated blood pressures refractory to labetalol. Routine prophylactic antibiotics prevent an infection, a known thrombotic trigger.

The main difference between ACA syndrome and other prothrombotic disorders is the elevated in vitro aPTT that is not necessarily associated with a bleeding tendency. Parturients with prothrombotic disorders, including APA syndrome, may need to be anticoagulated. Anesthetic considerations for anticoagulated parturients are discussed next. The anticoagulation status during unfractionated heparin therapy and its resolution may be difficult to follow. Alternative coagulation tests that have been used include a blood heparin assay, an activated clotting test, and a thrombin time.[122] It has been recommended to perform antenatal measurement of one of these tests to have a baseline that can be followed.[122]

Factor V Leiden and Prothrombin G20210A Mutations

Activation of protein C is responsible for the degradation of factors V and VIII and, as such, provides control of factor-initiated thrombosis. Resistance to APC can be acquired but is more commonly due to a specific mutation of factor V known as Leiden. Factor V Leiden (FVL), a point mutation of the DNA coding for factor V, renders factor V resistant to the activated protein C (APC). FVL accounts for more than 95% of the inherited forms of APC resistance among the primary hypercoagulable states.[123]

Approximately 1 in 20 Caucasians are heterozygous for FVL, carrying one copy of the mutation; this places them at a 5- to 10-fold increased risk for a venous thrombotic event. Individuals who carry two copies of FVL (homozygotes) face a 90-fold-increased lifetime risk for a thrombotic event.[124] Associations with arterial thrombotic events are unclear and such events may only occur in the setting of other risk factors.

Obstetric Management

The association of FVL with recurrent late (second trimester or later) fetal loss or stillbirth provides the strongest evidence of a relationship between factor V Leiden and pregnancy outcome. The association of factor V Leiden with early first trimester fetal loss may be present but is not so robust.[125] Among carriers of FVL, infertility or miscarriage is 1.5 times greater [95% confidence interval (CI), 1.2–2.7] than in noncarriers, and with two or more losses, 2.5 times greater (95% CI, 1.2–5.13) than expected.[126] The majority of women with FVL have successful pregnancies because of the relatively rare occurrence of late fetal loss.[124] Similarly, limited evaluations of the prothrombin gene polymorphism both support and refute an association with early or late fetal loss.[127]

The association of APC resistance with preeclampsia has been confirmed in several studies.[128,129] When severe preeclampsia is defined according to American College of Gynecologists (ACOG) standards, a 2.4-fold increase in FVL is noted among affected women.[130] Analysis in non-Caucasian populations has not identified this polymorphism as a risk factor for preeclampsia.[128,129] The association of the prothrombin G20210A polymorphism with severe preeclampsia has been variable and is not confirmed in all populations; this may be a result of the lower background frequency of this polymorphism, as sufficient sample size is necessary for the detection of a significant association.

Anesthetic Management

Parturients with FVL have an increased risk of deep venous thrombosis and are likely to be anticoagulated through preg-

nancy. Anesthetic considerations for anticoagulated parturients are discussed next. In addition, these parturients are at an increased risk to develop severe preeclampsia. Anesthetic considerations for HELLP syndrome are discussed in the thrombotic microangiopathy section of this chapter.

Protein S, C, and Antithrombin III Deficiencies

Both quantitative (type I) and qualitative (type II) deficiencies of protein S, protein C, and AT III result in hypercoagulability because of decreased inhibition of factors V and VIII.[131] In addition, with protein S deficiency there is a type III deficiency characterized by normal plasma levels but decreased free protein S. Determination of these protein deficiencies requires special care, as recognized decreases in acute-phase reaction proteins at the onset of a thrombotic event can result in lowered initial levels of these proteins. AT III levels are normally reduced by both acute thrombosis and heparin therapy, and therefore an adequate level at the time of presentation can rule out a deficiency. However, low levels require repeat testing. Similarly, as both protein C and S are vitamin K dependent, and warfarin is an inhibitor of vitamin K, lowered levels of these proteins while on oral anticoagulants may not be due to inherited deficiencies. Protein C may also be deficient in any of several clinical conditions related to the disease state, and a low level is not necessarily an inherited deficiency. These conditions include DIC, liver disease, acute respiratory distress syndrome, and asparaginase treatment.[132] Further testing may require both functional and immunologic assessments to precisely determine the deficiency state, as both qualitative and quantitative deficiencies can exist and are clinically significant.

Deficiencies of protein S, protein C, and AT III are identified in only a minority of parturients with thrombotic disease. Protein S deficiency occurs in less than 1.0% of the general population, and the magnitude of the risk of thrombosis with this inherited deficiency is unclear. Although protein S deficiency is noted in only 2% of first time thrombotic events, heterozygotic carriers face a lifetime risk of thrombosis of 19% to 47% in symptomatic families.[133,134] Protein C deficiency is encountered in only 0.5% of the general population but is seven times more common in patients with a first episode of thrombosis and is especially common in individuals with familial thrombosis (9%).[134] Heterozygosity for protein C deficiency increases the lifelong risk for thrombosis sevenfold. Homozygosity results in severe neonatal presentation and has been associated with increased fetal loss. Neonatal purpura fulminans is one such condition known to be secondary to homozygosity for protein S or C deficiency. It is characterized by thrombosis of cutaneous and subcutaneous vessels, may lead to ischemic necrosis, and can be fatal. Other factors may be contributory among symptomatic heterozygote carriers for protein C deficiency, as these familial carriers have a 50% risk of developing thrombosis.[135] AT III deficiency rarely occurs in the general population (0.17%) and is found in only 1% to 7% of individuals with thrombotic disease.[136] However, similar to the epidemiology of protein S and C deficiencies, individuals in symptomatic families have a markedly increased rate of thrombotic disease (50%).[137] Arterial thrombotic events seem to be much less likely to be associated with antithrombotic protein deficiencies in the absence of a patent foramen ovale, and controversy remains as to whether to screen individuals with arterial thrombosis for antithrombotic protein deficiencies.

Obstetric Management

Deficiencies of proteins S, C, and AT III, despite their relatively rare occurrence in the general population (<1%), have been associated with a variety of pregnancy-related complications associated with placental thrombosis. In pregnancies with adverse outcomes, placental vascular lesions are significantly clustered among those cases in which a maternal inherited thrombophilia deficiency has been established.[138] Maternal deficiencies of proteins S, C, and AT III occur with significantly greater frequency than expected in pregnancies complicated by abruption, intrauterine fetal demise, and intrauterine growth retardation.[139] Likewise, the relative risk of stillbirth is greatest among those individuals with combined thrombophilias.

Anesthetic Management

Some authors have suggested that hypovolemia, decreased cardiac output, hypotension, and hypothermia be avoided in parturients prone to thrombosis, as these may increase the risk of thrombosis.[140,141] Hypothermia can be prevented by warming all intravenous fluids and by using forced-heat blankets during a cesarean section. It has also been suggested that a combined spinal-epidural, with intrathecal opioids and a low-concentration local anesthetic-opioid mixture epidural infusion, be used to minimize major hemodynamic changes.[140] Another possibility is to use a low-concentration local anesthetic-opioid mixture for the initial epidural bolus as well as for the continuous epidural infusion. Both analgesic regimens allow for minimal motor and sensory changes in parturients who are likely to be anticoagulated. Any major change in motor or sensory function, or a sudden onset of back pain, should raise the suspicion of an epidural hematoma. The deep venous thrombosis rate has been shown to be significantly reduced with regional anesthetic techniques when compared to general anesthesia in the nonobstetric population.[142] Anesthetic implications of anticoagulant therapy during pregnancy are discussed next.

Anticoagulation

Treatment

Heparinization schedules should follow general medical guidelines for an acute thrombotic event during pregnancy.

Low molecular weight heparin (LMWH) has gained in popularity, given its once or twice a day dosing and the lack of a need for close serial blood level testing. Efficacy appears to be similar to standard heparin in individuals with primary or secondary hypercoagulable states. In a systematic review of randomized controlled studies for venous thrombosis in particular, LMWH was associated with lower rates of clinically significant bleeding and lower mortality than unfractionated heparin (UH).[143]

Neither UH nor LMWH crosses the placenta. Although oral anticoagulants can be utilized in the nonbreast-feeding mother postpartum, the continued use of heparin during a pregnancy is critical, as its large molecular size prohibits movement across the placenta. Oral anticoagulants, in particular warfarin, readily cross the placenta and are associated with teratogenicity during the first trimester and increased fetal bleeding such as intracranial hemorrhage during the latter stage of pregnancy.

Although treatment in the acute event and through 3 to 6 months for the prevention of recurrence is recommended when thrombotic events occur in individuals with either primary or secondary hypercoagulable states, which parturients to maintain on lifelong anticoagulation is less clear. Currently, individuals identified with AT III deficiency, in particular those from high-risk families, are considered for lifelong anticoagulation. Less clear is the need for lifelong anticoagulation in individuals with deficiencies of proteins S and C. Treatment should be individualized, taking into consideration the woman's age and the family history. Further consideration is often given to lifelong anticoagulation in the presence of an inherited thrombophilia, particularly if the initial event was life threatening or at an unusual site. Lifelong anticoagulation may also be considered if an individual has more than one inherited thrombophilia identified.

Prophylaxis

Women with an inherited thrombophilia and a prior thrombotic event should receive heparin prophylaxis during pregnancy and 4 to 6 weeks postpartum. The risk of thrombosis with AT III deficiency during pregnancy is estimated at 30% to 44% if it goes untreated.[144] Table 22.3 outlines the relative antepartum and postpartum risks of maternal thrombosis associated with each hypercoagulable state. Among symptomatic families, the presence of FVL mutation carries a 14% risk of pregnancy-related thrombosis, a risk which may be even greater postpartum.[145] Postpartum thrombosis occurs more commonly in women with protein C or S deficiencies.[146]

Some individualization of anticoagulant therapies may need to be considered. For those with AT III deficiency, sufficient AT III is generally present to enable adequate anticoagulation with IV heparin. Occasionally, AT III-deficient patients have "resistance" to heparin, requiring larger doses for an anticoagulant effect. Prophylactic anticoagulation for parturients who have been identified to have a thrombophilia but have not had a thrombotic event remains individualized. Factors to consider in this setting include the specific abnormality (AT III deficiency has a much greater risk of thrombosis than FVL), the presence of a familial thrombotic disease, and the existence of comorbid factors such as obesity, prolonged immobilization, and operative delivery.

Obstetric Management

The actions of the inherited thrombophilias on placental compromise and adverse pregnancy outcomes are potentially amenable to treatment by several modalities including baby aspirin, heparin, folic acid, IVIgG, and factor concentrates. However, no randomized controlled trials of interventions currently exist. First-time occurrences of adverse pregnancy outcomes rarely occur among those individuals with inherited thrombophilias. Studies are just now emerging with regard to recurrences of adverse pregnancy outcomes among known thrombophilia carriers.

Recent exploration of LMWH to improve pregnancy outcome among women with thrombophilia and recurrent fetal loss appears promising.[147] One study enrolled women meeting strict criteria for recurrent pregnancy loss and with identified thrombophilia. Subsequent pregnancies were treated with enoxaparin (40 mg/day or 80 mg/day for combined abnormalities) and resulted in significantly better outcomes when compared to historical controls.

Similar results have been obtained with preconception aspirin (81 mg/day) and postconception UH among women with three or more miscarriages and various procoagulant defects. Less than 1% failed therapy, experiencing a fetal loss during a subsequently treated pregnancy.[148] In another study, parturients with known thrombophilia were referred to a high-risk center, and treatment started with postconception heparin. Even though there was a decreased fetal loss rate, other obstetric complications were not altered.[149] Dramatic results were obtained in another study among women with a combination of infertility, miscarriage, and thrombophilia. Early pregnancy loss rate was decreased from 85% to 15% with either preconception enoxaparin (history of infertility) or postconception enoxaparin (miscarriage alone).[150]

Anesthetic Management

Therapeutic anticoagulation with LMWH is a contraindication to regional anesthesia. Discontinuation of prophylactic doses of LMWH at least 10 to 12 h before a regional anesthetic and of therapeutic doses at least 24 h before a regional anesthetic has been recommended.[151] In addition, the utilization of dilute solutions of local anesthetic with opioid mixture allows for monitoring the parturient's neurologic status after the neuraxial block. It is also recommended to wait at least 2 h after the removal of an epidural catheter before giving a dose of LMWH.[151]

The heparin test, an anti-Xa chromogenic assay that is often used to follow the activity of LMWH, takes 15 min to

perform at our institution. Although the American Society of Regional Anaesthesia and Pain Medicine (ASRA) guidelines do not recommend following the anti-Xa level, it is our practice to perform this test in parturients that are taking therapeutic doses (>1 mg/kg enoxaparin) of anticoagulants even if the last dose was given more than 24 h before the test. Our target is a heparin test of less than 0.2 U/mL, as this value is associated with minimal anticoagulation. It is our practice to have more experienced anesthetists perform neuraxial techniques in parturients who have received LMWH recently, even if their heparin test is less than 0.2 U/mL. Midline neuraxial techniques, rather than paramedian techniques, are less likely to encounter epidural vessels and have been recommended.[141] Even though there are no data to support the hypothesis that this heparin test level is predictive of fewer complications, levels of 0.1 to 0.2 U/mL and 0.4 to 1.0 U/mL work well for prophylaxis and for treatment of active thrombosis, respectively.[152]

A recent study demonstrated a correlation between the thromboelastograph (TEG) R-time and the heparin test.[153] This study demonstrated that prophylactic doses of LMWH (enoxaparin 30 mg bid) produced a significant prolongation of the R-time in some patients (6/25), even when measured immediately before the fifth dose (third day). An activated clotting time was also measured and progressively increased with each dose of LMWH but did not correlate with anti-Xa activity.[153] It is premature at this time to use TEG to guide a decision of whether to perform a neuraxial technique in parturients receiving LMWH. Future studies may provide additional useful clinical information.

In the case of recent thrombosis, a change to intravenous UH before delivery may allow for greater flexibility.[154] However, it translates into a longer hospital admission for the parturient. This therapy is not done as an outpatient, as it necessitates frequent laboratory monitoring to adjust the UH infusion rate. It is recommended to discontinue UH at least 2 to 4 h and to check a partial thromboplastin time before the removal of a sited epidural catheter.[155] Although there are no recommendations regarding the placement of neuraxial techniques in patients receiving UH, we have extrapolated from these data, and it is our practice to discontinue UH at least 4 to 6 h and wait until a normalization of the aPTT before a neuraxial block.

Some parturients at risk to develop venous thrombosis are maintained at a high dose of subcutaneous (SC) UH (≥7500 U bid), and these doses may cause an elevation of the aPTT. Although ASRA guidelines state that during minidose prophylaxis there is no contraindication to the use of neuraxial techniques, there are no specific recommendations for these higher doses.[155] It is our policy to discontinue SC UH upon arrival to the labor floor or to skip at least one dose before a planned admission and to wait until a normalization of the aPTT before a neuraxial technique.

Baby aspirin (81 mg/day) is often used to improve pregnancy outcome in parturients with a history of thrombosis and recurrent fetal loss. Antiplatelet medications alone, when used in patients receiving neuraxial techniques, have not been associated with epidural hematomas. It is considered to be appropriate to perform neuraxial techniques in the presence of these medications alone.[156] However, there are reports of spinal-epidural hematoma following epidural anesthesia in the presence of antiplatelet medications and other medications that affect coagulation.[157] Therefore, antiplatelet medications may augment the anticoagulant effect of other medications, and caution should be taken when considering a neuraxial technique on parturients receiving more than one medication that affects coagulation.

Summary

Maternal hemorrhage is one of the leading causes of maternal mortality in the United States and abroad and is often a result of a coagulopathy. In addition, abnormalities of the coagulation pathway, inherited or acquired, are a relative contraindication to regional anesthesia. Hence, we see a very close relationship between the fields of hematology, obstetrics, and anesthesiology. Close communication with our colleagues in the fields of obstetrics and hematology is essential because much of what they do or do not do may have a direct affect on anesthesia plans.

Pregnancy in itself is associated with many physiologic changes, including altered (increased) coagulation. All factors except factors XI and XIII increase with pregnancy. In addition, there is a decrease in fibrinolysis. The decrease in some of the natural anticoagulants, such as protein S, further contributes to the hypercoagulable state of pregnancy. There are some advantages of these changes, such as the increase of factor VIII and von Willebrand's factor that may correct mild forms of von Willebrand's disease during pregnancy. These changes, if confirmed by laboratory findings and the absence of clinical bleeding, may allow for the performance of neuraxial anesthesia techniques.

Parturients are also more prone to arterial and, more commonly, venous thrombosis and are likely to be anticoagulated. The timing of a neuraxial technique or the removal of the epidural catheter in relation to the dosing of an anticoagulant is very important. Knowledge of maternal physiology, pharmacology of anticoagulants, the coagulation pathway, and coagulation abnormalities assists the practitioner in the safe practice of obstetric anesthesia.

References

1. Cunningham FG, Gant NF, Leveno KJ, et al. Obstetrical hemorrhage. In: Williams Obstetrics, 21st edn. New York: McGraw-Hill, 2001:619–669.
2. Chichakli LO, Atrash HK, MacKay AP, et al. Pregnancy-related mortality in the United States due to hemorrhage: 1979–1992. Obstet Gynecol 1999;94:721–725.
3. Griffin RM, Scott RPF. A comparison between the midline and para-

median approaches to the extradural space. Anaesthesia 1984;39:584–586.
4. Norris MC, Ferrenbach D, Dalman H, et al. Does epinephrine improve the diagnostic accuracy of aspiration during labor epidural analgesia? Anesth Analg 1999;88:1073–1076.
5. Vandermeulen EP, Van Anken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg 1994;79:1165–1177.
6. Suzuki S, Morishita S. Platelet hemostatic capacity (PHC) and fibrinolytic inhibitors during pregnancy. Semin Thromb Hemost 1998;24: 449–451.
7. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Engl J Med 1993;329:1463–1466.
8. Burrows RF, Kelton JG. Incidentally detected thrombocytopenia in healthy mothers and their infants. N Engl J Med 1988;319:142–145.
9. Lescale KB, Eddleman KA, Cines DB, et al. Antiplatelet antibody testing in thrombocytopenic pregnant women. Am J Obstet Gynecol 1996; 174:1014–1018.
10. Douglas MJ. Platelets, the parturient and regional anesthesia. Int J Obstet Anesth 2001;10:113–120.
11. Breen TW, McNeil T, Dierenfeld L. Obstetric anesthesia practice in Canada. Can J Anesth 2000;47:1230–1242.
12. Beilin Y, Bodian CA, Haddad EM, Leibowitz AB. Practice patterns of anesthesiologists regarding situations in obstetrical anesthesia where clinical management is controversial. Anesth Analg 1996;83:735–741.
13. Beilin Y, Zahn J, Comerford M. Safe epidural analgesia in thirty parturients with platelet counts between 69,000 and 98,000 mm^{-3}. Anesth Analg 1997;85:385–388.
14. Cohen DL, Baglin TP. Assessment and management of immune thrombocytopenia in pregnancy and in neonates. Arch Dis Child Fetal Neonatal Ed 1995;72:71–76.
15. Johnson JR, Samuels P. Review of autoimmune thrombocytopenia: pathogenesis, diagnosis, and management in pregnancy. Clin Obstet Gynecol 1999;42:317–326.
16. Shehata N, Burrows R, Kelton JG. Gestational thrombocytopenia. Clin Obstet Gynecol 1999;42:327–334.
17. Silver RM, Branch DW, Scott JR. Maternal thrombocytopenia in pregnancy: time for a reassessment. Am J Obstet Gynecol 1995;173:479–482.
18. Nichols WC, Ginsburg D. von Willebrand disease. Medicine. 1997;76: 1–20.
19. Fausett B, Silver RM. Congenital disorders of platelet function. Clin Obstet Gynecol 1999;42:390–405.
20. Cox D. Methods for monitoring platelet function. Am Heart J 1998;135: S160–S169.
21. Homoncik M, Blann AD, Hollenstein U, et al. Systemic inflammation increases shear stress-induced platelet plug formation measured by the PFA-100. Br J Haematol 2000;111:1250–1252.
22. Bock M, De Haan J, Beck KH, et al. Standardization of the PFA-100(R) platelet function test in 105 mmol/l buffered citrate: effect of gender, smoking, and oral contraceptives. Br J Haematol 1999;106:898–904.
23. Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001;66:280–284.
24. Kadir RA, Lee CA, Sabin CA, et al. Pregnancy in women with von Willebrand's disease or factor XI deficiency. Br J Obstet Gynaecol 1998;105:314–321.
25. Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol 1991;98:909–918.
26. Ramsahoye BH, Davies SV, Dasani H, Pearson JS. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review of the literature. Haemophilia 1995;1:140–144.
27. Walker ID, Walker JJ, Colvin BT, et al. Investigation and management of haemorrhagic disorders in pregnancy. J Clin Pathol 1994;47:100–108.
28. Sage DJ. Epidurals, spinals, and bleeding disorders in pregnancy: a review. Anesth Intensive Care 1990;18:319–326.
29. Milaskiewicz RM, Holdcroft A, Letsky E. Epidural anesthesia and von Willebrand's disease. Anaesthesia 1990;45:462–464.
30. Cohen S, Daitch JS, Amar D, Goldiner PL. Epidural analgesia for labor and delivery in a patient with von Willebrand's disease. Reg Anesth 1989;14:95–97.
31. Ortel TL, James AH, Thames EH, et al. Assessment of primary hemostasis by PFA-100 analysis in a tertiary care center. Thromb Haemostasis 2000;84:93–97.
32. Fressinaud E, Veyradier A, Sigaud M, et al. Therapeutic monitoring of von Willebrand disease: interest and limits of a platelet function analyser at high shear rates. Br J Haematol 1999;106:777–783.
33. George JN. Platelets. Lancet 2000;355:1531–1539.
34. Saade G, Homsi R, Seoud M. Bernard-Soulier syndrome in pregnancy; a report of four pregnancies in one patient, and review of the literature. Eur J Obstet Gynecol 1991;40:149–152.
35. Peaceman AH, Katz AR, Laville M. Bernard-Soulier syndrome complicating pregnancy: a case report. Obstet Gynecol 1989;73:457–459.
36. Khalil A, Seoud M, Tannous R, et al. Bernard-Soulier syndrome in pregnancy: case report and review of the literature. Clin Lab Hematol 1998; 20:125–128.
37. Peng TC, Kickler TS, Bell WR, Haller E. Obstetric complications in a patient with Bernard-Soulier syndrome. Am J Obstet Gynecol 1991;165: 425–426.
38. Fujimori K, Ohto H, Honda A, Sato A. Antepartum diagnosis of fetal intracranial hemorrhage due to maternal Bernard-Soulier syndrome. Obstet Gynecol 1999;94:817–819.
39. Michalas S, Malamitsi-Puchner A, Tsevrenis H. Pregnancy and delivery in Bernard-Soulier syndrome. Acta Obstet Gynecol Scand 1984;63: 185–186.
40. Nomura K, Harioka T, Itoh T, et al. Anesthetic management of a patient with Bernard-Soulier syndrome. Masui 1993;42:1521–1523.
41. Edozien LC, Jip J, Mayers FN. Platelet storage pool deficiency in pregnancy. Br J Clin Pract 1995;49:220.
42. Laskey AL, Tobias JD. Anesthetic implications of the grey platelet syndrome. Can J Anaesth 2000;47:1224–1229.
43. Sundqvist SB, Nilsson IM, Svanberg L, Cronberg S. Pregnancy and parturition in a patient with severe Glanzmann's thrombasthenia. Scand J Haematol 1981;27:159–164.
44. Sherer DM, Lerner R. Glanzmann's thrombasthenia in pregnancy: a case and review of the literature. Am J Perinatol 1999;16:297–301.
45. Skupski DW, Bussel JB. Alloimmune thrombocytopenia. Clin Obstet Gynecol 1999;42:335–348.
46. Roberts IA, Murray NA. Management of thrombocytopenia in neonates. Br J Haematol 1999;105:864–870.
47. Cohen DL, Baglin TP. Assessment and management of immune thrombocytopenia in pregnancy and in neonates. Arch Dis Child Fetal Neonatal Ed 1995;72:71–76.
48. Clark AL. Clinical uses of intravenous immunoglobulin in pregnancy. Clin Obstet Gynecol 1999;42:368–380.
49. Flug F, Karpatkin M, Karpatkin S. Should all pregnant women be tested for their platelet PLA (Zw,HPA-1) phenotype? Br J Haematol 1994;86: 1–5.
50. Anonymous. 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.
51. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982;142:159–167.
52. Egerman RS, Sibai BM. HELLP syndrome. Clin Obstet Gynecol 1999; 42:381–389.
53. Okada S, Okada K, Nishitani K. HELLP syndrome in triplet pregnancy complicated by DIC and transient diabetes insipidus. Masui 1998;47: 195–199.

54. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of randomized trials. Am J Obstet Gynecol 1995;173:322–335.
55. Pritchard JA, Cunningham FG, Pritchard SA, Mason RA. How often does maternal preeclampsia-eclampsia incite thrombocytopenia in the fetus? Obstet Gynecol 1987;69:292–295.
56. Prieto JA, Mastrobattista JM, Blanco JD. Coagulation studies in patients with marked thrombocytopenia due to severe preeclampsia. Am J Perinatol 1995;12:220–222.
57. Barron WM, Heckerling P, Hibbard JU, Fisher S. Reducing unnecesary coagulation testing in hypertensive disorders of pregnancy. Obstet Gynecol 1999;94:364–370.
58. Voulgaropoulos DS, Palmer CM. Coagulation studies in the preeclamptic parturient: a survey. J Clin Anesth 1993;5:99–104.
59. Leduc L, Wheeler JM, Kirshon B, et al. Coagulation profile in severe preeclampsia. Obstet Gynecol 1992;79:14–18.
60. Schindler M, Gatt S, Isert P, et al. Thrombocytopenia and platelet functional defects in preeclampsia: implications for regional anesthesia. Anaesth Intensive Care 1990;18:169–174.
61. Ramanathan J, Sibai BM, Vu T, Chauhan D. Correlation between bleeding times and platelet counts in women with preeclampsia undergoing cesarean section. Anesthesiology 1989;71:188–191.
62. Rogers RPC, Levin J. A critical reappraisal of the bleeding time. Semin Thromb Hemost 1990;16:1–20.
63. Lind SE. The bleeding time does not predict surgical bleeding. Blood 1991;77:2547–2552.
64. Orlikowski CEP, Rocke DA, Murray WB, et al. Thromboelastography changes in pre-eclampsia and eclampsia. Br J Anaesth 1996;77:157–160.
65. Sharma SK, Philip J, Whitten CW, et al. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastography. Anesthesiology 1999;90:385–390.
66. Srinivasa V, Gilbertson L, Bhavani-Shankar K. Thromboelastography: where is it and where is it heading? Int Anesthesiol Clin 2001;39:35–49.
67. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thromboelastography. Anesth Analg 1987;66:856–863.
68. Davies J, Fernando R, Hallworth S. Platelet function in preeclampsia: platelet function analyzer (PFA-100) vs, TEG (abstract). Anesthesiology 2001;94:A1.
69. Davies J, Fernando R, Hallworth S. Thrombocytopenia in pregnancy: platelet function analyzer (PFA-100) vs thromboelastogram (TEG) (abstract). Anesthesiology 2001;94:A23.
70. Marietta M, Castelli I, Piccinini F, et al. The PFA-100 system for the assessment of platelet function in normotensive and hypertensive pregnancies. Clin Lab Haematol 2001;23:131–134.
71. Malinow AM. Spinal anesthesia in preeclamptic patients-"supportive" evidence [letter]. Anesthesiology 2000;92:622.
72. Wallace DH, Leveno KJ, Cunningham FG, et al. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. Obstet Gynecol 1995;86:193–199.
73. Hood DD, Curry R. Spinal versus epidural for cesarean section in severely preeclamptic patients: a retrospective survey. Anesthesiology 1999;90:1276–1282.
74. Esplin MS, Branch DW. Diagnosis and management of thrombotic microangiopathies during pregnancy. Clin Obstet Gynecol 1999;42:360–367.
75. Egerman RS, Witlin AG, Friedman SA, Sibai BM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy: review of 11 cases. Am J Obstet Gynecol 1996;175:950–956.
76. Dashe JS, Ramin SM, Cunningham FG. The long-term consequences of thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) in pregnancy. Obstet Gynecol 1998;91:662–668.
77. Dalal FY, Bennett EJ, Grundy EM, et al. Anesthetic considerations in diffuse bleeding diathesis of uncertain origin. Anesth Analg 1976;55:173–176.
78. Pivalizza EG. Anesthetic management of a patient with thrombotic thrombocytopenic purpura. Anesth Analg 1994;79:1203–1205.
79. Johnson GD, Rosales JK. The haemolytic uraemic syndrome and anaesthesia. Can J Anesth 1987;34:196–199.
80. Levi M, Ten Cate H. Current concepts: disseminated intravascular coagulation. N Engl J Med 1999;341:586–592.
81. Saraiya M, Green CA, Berg CJ, et al. Spontaneous abortion-related deaths among women in the United States—1981–1991. Obstet Gynecol 1999;94:172–176.
82. Bick RL. Disseminated intravascular coagulation: objective clinical and laboratory diagnosis, treatment and assessment of therapeutic response. Semin Thromb Hemost 1996;22:69–88.
83. Monteiro MA, Inocencio AC, Jorge CS. "Placental abruption" with disseminated intravascular coagulopathy in the second trimester of pregnancy with fetal survival: case report. Br J Obstet Gynaecol 1987;94:811–812.
84. Olah KS, Gee H, Needham PG. The management of severe disseminated intravascular coagulopathy complicating placental abruption in the second trimester of pregnancy. Br J Obstet Gynaecol 1988;95:419–420.
85. Marinoff DN, Honegger MM, Girard JB. Spontaneous resolution of disseminated intravascular coagulopathy in the second trimester. Am J Obstet Gynecol 1999;181:759–760.
86. Sprung J, Cheng EY, Patel S. When to remove an epidural catheter in a parturient with disseminated intravascular coagulation. Reg Anesth 1992;17:351–354.
87. Horlocker TT. When to remove a spinal or epidural catheter in an anticoagulated patient [letter]. Reg Anesth 1993;18:264–265.
88. Okuda Y, Kitajima T. Epidural hematoma in a parturient who developed disseminated intravascular coagulation after epidural anesthesia. Reg Anesth Pain Med 2001;26:383–384.
89. Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. Br J Haematol 2001;114:174–176.
90. Duerbeck NB, Chaffin DJ, PonJola C. Platelet and hemorrhagic disorders associated with pregnancy: a review. Part I. Obstet Gynecol Surv 1997;52:575–584.
91. Duerbeck NB, Chaffin DG, PonJola C. Platelet and hemorrhagic disorders associated with pregnancy: a review. Part II. Obstet Gynecol Surv 1997;52:585–596.
92. Inwood MJ, Meltzer DB. The female carrier of haemophilia—a problem for the anaesthetist. Can Anaesth Soc J 1978;25:266–269.
93. Hack G, Hofmann P, Brackmann HH, et al. Regional anaesthesia in haemophiliacs. Anaesth Intensive Care 1980;15:45–51.
94. Bolton-Maggs PH. Bleeding problems in factor XI deficient women. Haemophilia 1999;5:155–159.
95. Kadir RA, Aledort LM. Obstetrical and gynaecological bleeding: a common presenting symptom. Clin Lab Haematol 2000;22:12–16.
96. Ragni MV, Seaman SF, Lewis JH. Comparison of bleeding tendency, factor XI coagulant activity, and factor XI antigen in 25 factor XI-deficient kindreds. Blood 1985;65:719–724.
97. Connelly RC, Brull SJ. Anesthetic management of a patient with factor XI deficiency and factor XI inhibitor undergoing a cesarean section. Anesth Analg 1993;76:1365–1366.
98. Michiels JJ, Hamulvak K, Nieuwenhuis HK, et al. Acquired haemophilia A in women postpartum, management of bleeding episodes and natural history of the factor VIII inhibitor. Eur J Haematol 1997;59:105–109.
99. Stoelting RK, Dierdorf SF. Diseases due to altered hemoglobin concentration or structures. In Anesthesia and Co-existing Disease, 3rd edn. New York: Churchill Livingstone, 2002:471–488.
100. Dunn A, Eckert G, King P, Matthews R. Intraoperative death during caesarean section in a patient with sickle-cell trait. Can J Anaesth 1987;34:67–70.
101. Steinberg MH. Management of sickle cell disease. N Engl J Med 1999;340:1021–1030.

102. Finer P, Blair J, Rowe P. Epidural analgesia in the management of labor pain and sickle cell crisis-a case report. Anesthesiology 1988;68: 799–800.
103. Koshy M, Burd L, Wallace D, et al. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease: a randomized cooperative study. N Engl J Med 1988;319:1447–1452.
104. Koshy M, Chisum D, Burd L, et al. Management of sickle cell anemia and pregnancy. J Clin Apheresis 1991;6:230–233.
105. Tsen LC, Cherayil G. Sickle cell-induced peripheral neuropathy following spinal anesthesia for cesarean delivery. Anesthesiology 2001;95: 1298–1299.
106. Aessopos A, Karabatsos F, Farmakis D, et al. Pregnancy in patients with well-treated beta-thalassemia: outcome for mothers and newborn infants. Am J Obstet Gynecol 1999;180:360–365.
107. Jensen CE, Tuck SM, Wonke B. Fertility in beta thalassaemia major: a report of 16 pregnancies, preconceptual evaluation and a review of the literature. Br J Obstet Gynaecol 1995;102:625–629.
108. Olive M, Mora A, Ballve M, et al. Thalassemic syndromes and anesthesia. Rev Esp Anestesiol Reanim 1992;39:166–169.
109. Handin RI. Disorders of coagulation and thrombosis. In Harrison's Principles of Internal Medicine, 14th edn. Fauci AS, Braunwald E, Isselbacher KJ, et al. (eds) New York: McGraw-Hill, 1998:736–743.
110. Carr BR, Ory H. Estrogen and progestin components of oral contraceptives: relationship to vascular disease. Contraception 1997;55:267–272.
111. Gharavi AE, Harris EN, Asherson RA, Hughes GR. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. Ann Rheum Dis 1987;46:1–6.
112. Finazzi G, Brancaccio V, Moia M, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. Am J Med 1996; 100:530–536.
113. Bick RL, Ancypa D. Blood protein defects associated with thrombosis. Laboratory assessment. Clin Lab Med 1995;15:125–163.
114. Bick RL, Haas SK. International consensus recommendations. Summary statement and additional suggested guidelines. European Consensus Conference, November 1991. American College of Chest Physicians consensus statement of 1995. International Consensus Statement, 1997. Med Clin N Am 1998;82:613–633.
115. Schafer AI. Genetic polymorphisms in arterial thrombosis and vascular disease. J Endovasc Ther 2001;8:441–443.
116. Arnout J. The pathogenesis of the antiphospholipid syndrome: a hypothesis based on parallelisms with heparin-induced thrombocytopenia. Thromb Haemostasis 1996;75:536–541.
117. Bick RL, Laughlin HR, Cohen BM. Fetal wastage syndrome due to blood protein/platelet defects: results of prevalence studies and treatment outcomes with low-dose heparin and low-dose aspirin. Clin Appl Thromb Hemost 1995;1:286–292.
118. Dreyfus M, Hedelin G, Kutnahorsky R, et al. Antiphospholipid antibodies and preeclampsia: a case-control study. Obstet Gynecol 2001;97:29–34.
119. Menon G, Allt-Graham J. Anaesthetic implications of the anticardiolipin antibody syndrome. Br J Anaesth 1993;70:587–590.
120. Madan R, Khoursheed M, Kukla R, et al. The anaesthetist and the antiphospholipid syndrome. Anaesthesia 1997;52:72–76.
121. Fahy BG, Malinow AM. Anesthesia with antiphospholipid antibodies: anesthetic management of a parturient with lupus anticoagulant and anticardiolipin antibody. J Clin Anesth 1996;8:49–53.
122. Heijboer H, Brandjes DP, Buller HR, et al. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med 1990;323:1512–1516.
123. Ridker PM, Miletich JP, Buring JE, et al. Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. Ann Intern Med 1998;128: 1000–1003.
124. Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. Placenta 1999;20:519–529.
125. Bare SN, Poka R, Balogh I, Ajzner E. Factor V Leiden as a risk factor for miscarriage and reduced fertility. Aust N Z J Obstet Gynaecol 2000;40:186–190.
126. Pihusch R, Buchholz T, Lohse P, et al. Thrombophilic gene mutations and recurrent spontaneous abortion: prothrombin mutation increases the risk in the first trimester. Am J Reprod Immunol 2001;46:124–131.
127. Zusterzeel PL, Visser W, Blom HJ, et al. Methylenetetrahydrofolate reductase polymorphisms in preeclampsia and the HELLP syndrome. Hypertens Pregnancy 2000;19:299–307.
128. Kim YJ, Williamson RA, Murray JC, et al. Genetic susceptibility to preeclampsia: roles of cytosineto-thymine substitution at nucleotide 677 of the gene for methylenetetrahydrofolate reductase, 68-base pair insertion at nucleotide 844 of the gene for cystathionine beta-synthase, and factor V Leiden mutation. Am J Obstet Gynecol 2001;184:1211–1217.
129. Dizon-Townson DS, Nelson LM, Easton K, Ward K. The factor V Leiden mutation may predispose women to severe preeclampsia. Am J Obstet Gynecol 1996;175:902–905.
130. Van Cott EM, Laposata M. Laboratory evaluation of hypercoagulable states. Hematol Oncol Clin N Am 1998;12:1141–1166.
131. Jorquera JI, Montoro JM, Fernandez MA, et al. Modified test for activated protein C resistance. Lancet 1994;344:1162–1163.
132. Zoller B, Norlund L, Leksell H, et al. High prevalence of the FVR506Q mutation causing APC resistance in a region of southern Sweden with a high incidence of venous thrombosis. Thromb Res 1996;83:475–477.
133. Melissari E, Monte G, Lindo VS, et al. Congenital thrombophilia among patients with venous thromboembolism. Blood Coagul Fibrinolysis 1992;3:749–758.
134. Allaart CF, Poort SR, Rosendaal FR, et al. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. Lancet 1993;341:134–138.
135. Rodeghiero F, Tosetto A. The epidemiology of inherited thrombophilia: the VITA Project. Vicenza Thrombophilia and Atherosclerosis Project. Thromb Haemostasis 1997;78:636–640.
136. Demers C, Ginsberg JS, Hirsh J, et al. Thrombosis in antithrombin-III-deficient persons. Report of a large kindred and literature review. Ann Intern Med 1992;116:754–761.
137. Many A, Schreiber L, Rosner S, et al. Pathologic features of the placenta in women with severe pregnancy complications and thrombophilia. Obstet Gynecol 2001;98:1041–1044.
138. de Vries JI, Dekker GA, Huijgens PC, et al. Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies. Br J Obstet Gynaecol 1997;104:1248–1254.
139. Abramovitz SE, Beilin Y. Anesthetic management of the parturient with protein S deficiency and ischemic heart disease. Anesth Analg 1999;89: 709–710.
140. Fan SZ, Yeh M, Tsay W. Caesarean section in a patient with protein S deficiency. Anaesthesia 1995;50:251–253.
141. Paech M. Anticoagulants and regional anesthesia. Anesth Analg 2000; 90S:47–51.
142. Lensing AW, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular weight heparins: a metaanalysis. Arch Intern Med 1995;155:601–607.
143. Walker ID. Congenital thrombophilia. Baillieres Clin Obstet Gynecol 1997;11:431–445.
144. Martinelli I, Legnani C, Bucciarelli P, et al. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001;86:800–803.
145. Conard J, Horellou MH, Van Dreden P, et al. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. Thromb Haemost 1990;63:319–320.
146. Brenner B, Hoffman R, Blumenfeld Z, et al. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemostasis 2000;83:693–697.
147. Bick RL. Recurrent miscarriage syndrome due to blood coagulation pro-

tein/platelet defects: prevalence, treatment and outcome results. DRW Metroplex Recurrent Miscarriage Syndrome Cooperative Group. Clin Appl Thromb Hemost 2000;6:115–125.
148. Ogueh O, Chen MF, Spurll G, Benjamin A. Outcome of pregnancy in women with hereditary thrombophilia. Int J Gynaecol Obstet 2001;74: 247–253.
149. Sarto A, Rocha M, Geller M, et al. Treatment with enoxaparin adapted to the fertility programs in women with recurrent abortion and thrombophilia. Medicina 2001;61:406–412.
150. Horlocker TT, Wedel DJ. Neuraxial block and low molecular weight heparin: balancing perioperative analgesia and thromboprophylaxis. Reg Anesth Pain Med 1998;23S:164–177.
151. Aguilar D, Goldhaber SZ. Clinical uses of low-molecular-weight heparins. Chest 1999;115:1418–1423.
152. Klein SM, Slaughter TF, Vail PT. Thromboelastography as a perioperative measure of anticoagulation resulting from low molecular weight heparin: a comparison with anti-Xa concentrations. Anesth Analg 2000; 91:1091–1095.
153. Hague WM, North RA, Gallus AS, et al. Anticoagulation in pregnancy and the puerperium. Med J Aust 2001;175:258–263.
154. Liu SS, Mulroy MF. Neuraxial anesthesia and analgesia in the presence of standard heparin. Reg Anesth Pain Med 1998;23S:157–163.
155. Urmey WF, Rowlingson JC. Do antiplatelet agents contribute to the development of perioperative spinal hematoma? Reg Anesth Pain Med 1998;23S:146–151.
156. Litz RJ, Hubler M, Koch T, Albrecht M. Spinal-epidural hematoma following epidural anesthesia in the presence of antiplatelet and heparin therapy. Anesthesiology 2001;95:1031–1033.

23
The Diabetic Parturient

May C.M. Pian-Smith, Sanjay Datta, and Michael F. Greene

The prognosis for diabetic women and their offspring has improved steadily and dramatically since the introduction of insulin. In the first two decades of this century, half the diabetic women attempting to carry pregnancies to term died, and half the offspring of the surviving women died. The incidence of maternal mortality is now so small that it is difficult to measure. However, substantial morbidity such as hypoglycemia, diabetic ketoacidosis, hypertension, and exacerbations of nephropathy and retinopathy still occur with greater frequency during pregnancy. Perinatal mortality is now less than one tenth of what it was when insulin was introduced but is still twice that for the general population. As the absolute magnitudes of the risks fall, it is important not to become complacent and to understand the pathophysiology of the potential complications that await the unwary. Optimizing outcome furthermore requires close communication among internist, obstetrician, anesthesiologist, and pediatrician.

Pathophysiology

Several pathophysiologic processes that affect both mother and fetus govern the obstetric and anesthetic management of the diabetic parturient and are discussed in this section.

Uteroplacental Insufficiency

Placental insufficiency is one of the most important pathophysiologic changes that can be influenced by the anesthetic technique and can directly impact neonatal well-being.

Placental Perfusion

Placental abnormalities have been observed even in association with mild, well-controlled gestational diabetes. Nylund et al. compared uteroplacental blood flow in the last trimester of pregnancy in 26 diabetic gravidas to that of 41 healthy nondiabetic pregnant women.[1] Using intravenous indium-113, they recorded the radiation over the placentas with a computer-linked gamma camera; they found a 35% to 45% decrease in uteroplacental blood flow index in diabetic women. Although the blood flow index further decreased with higher blood glucose, there was no statistically significant difference in the flow between the gestational diabetic parturients and the parturients whose diabetes antedated their pregnancies. Bjork and Persson[2] observed enlarged villi with a concomitant reduction of the intervillous space, which may help to explain the increased density of the placenta of diabetic women and decreased placental blood flow.

Respiratory Physiology

Hemoglobin A_{1c} (Hb A_{1c}) is a glycosylated hemoglobin species. Its concentration is proportional to the level of blood glucose for the 6 weeks before its measurement. Determinations of levels of Hb A_{1c} have been used clinically for some time to assess the degree of glycemic control among diabetic parturients. Concentrations among diabetic women may be two to three times higher than nondiabetic individuals. Beyond being a useful clinical tool, the glycosylation of hemoglobin has physiologic implications for oxygen transport. Madsen and Ditzel[3] have shown that as the percentage of glycosylated hemoglobin rises, the amount of oxygen, molecule for molecule, carried by hemoglobin falls (Figure 23.1). The avidity with which the oxygen is bound is also changed. The affinity of hemoglobin for oxygen is normally modulated by binding with 2,3-diphosphoglycerate (2,3-DPG) so that in the presence of 2,3-DPG the P_{50} rises (i.e., the oxygen is less firmly bound). Bunn et al.[4] demonstrated that Hb A_{1c} changes its P_{50} only minimally in the presence of 2,3-DPG. Madsen and Ditzel[3] have also observed that the P_{50} is inversely correlated with the concentration of Hb A_{1c} (Figure 23.2). The displacement of oxygen from native hemoglobin that is facilitated by 2,3-DPG binding is also associated with the acceptance of a proton (H^+) by the deoxygenated hemoglobin (the Bohr effect) and thus contributes to the buffering capacity of blood. Hemoglobin A_{1c}, with its more tightly bound oxygen, will release the oxygen less well at areas of reduced

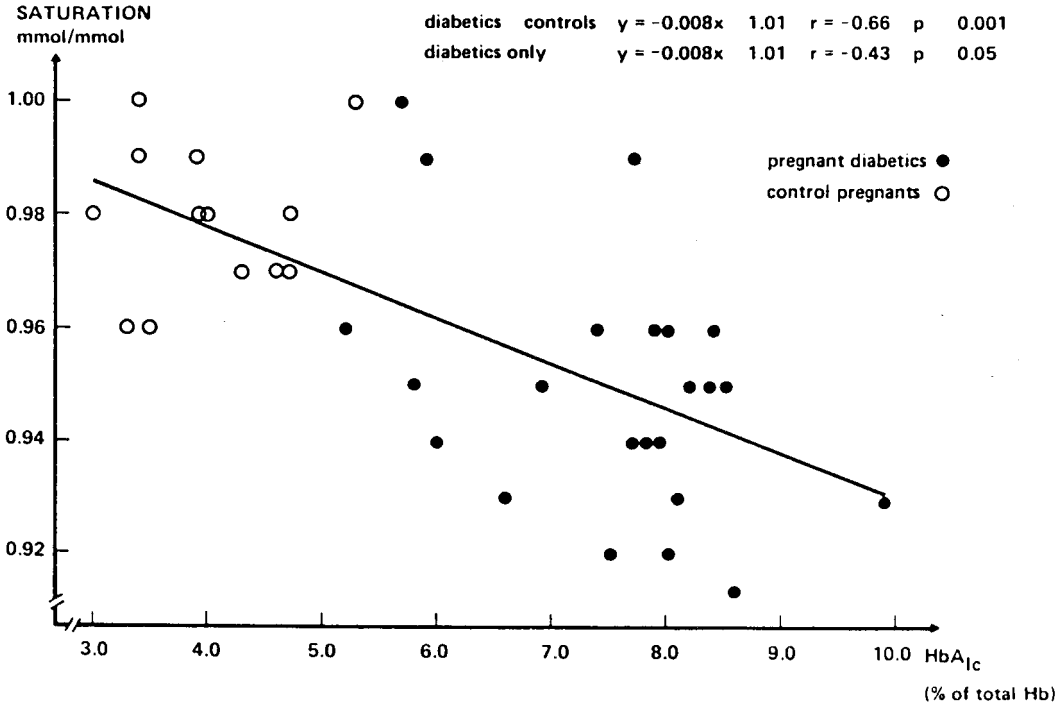

FIGURE 23.1. Correlation between hemoglobin A_{1c} (HbA_{1c}) and arterial oxygen saturation in diabetic women. (From Madsen H, Ditzel J. Changes in red blood cell oxygen transport in diabetic pregnancy. Am J Obstet Gynecol 1982;143:421–424, with permission.)

oxygen tension, such as the placental bed. Diabetic patients who are chronically poorly controlled have high levels of Hb A_{1c} that carry less oxygen and release it less well in the periphery.

The effects of chronic hyperglycemia on the oxygen-carrying properties of maternal hemoglobin just discussed are exacerbated by the fetal effects of acute maternal hyperglycemia. Fetal hyperinsulinemia increases the oxygen requirement of the fetus, regardless of how the fetus is rendered hyperinsulinemic. Fetal hyperinsulinemia can be induced experimentally through maternal administration of sulfonylureas[5] or by direct infusion of insulin in chronically catheterized fetuses.[6,7] Fetal hyperglycemia occurs most commonly in routine clinical care as the result of maternal hyperglycemia. Although the diabetic mother may be relatively insulin deficient, her fetus is endocrinologically intact. Maternal hyperglycemia is noticed promptly by the fetus, because glucose rapidly crosses the placenta to reach concentrations approximately equal to those in the mother. The fetus responds by pouring out insulin from its pancreas. Fetal oxygen consumption rises in direct proportion to the insulin concentration, resulting in falls in both venous and arterial oxygen content (Figure 23.3A,B). Oxygen supply is unable to keep pace with demand, resulting in a progressive rise in the arteriovenous oxygen difference between the umbilical artery and vein (Figure 23.3C). Thus, through several mechanisms, acute and chronic hyperglycemia contribute to fetal hypoxia and acidosis.

Diabetic Ketoacidosis

One of the major causes of fetal mortality and morbidity in diabetic parturients is diabetic ketoacidosis (DKA). Fetal loss has been reported to be as high as 50%. With modern management, however, maternal mortality is so rare that the rate of mortality from DKA is impossible to estimate accurately. Several circumstances can induce DKA: (1) inadequate insulin therapy in the face of a stress such as a bacterial infection; (2) omission of insulin doses in the presence of gastroenteritis because of the parturient's concern about the possibility of an insulin reaction due to anorexia, nausea, and vomiting; (3) pump malfunction in patients receiving continuous subcutaneous insulin infusion therapy; and (4) tocolytic therapy with β-sympathomimetic agents, with or without concomitant glucocorticoid therapy.

Pathophysiology

Diabetic ketoacidosis occurs in the presence of both a relative or absolute deficiency of insulin and a relative or absolute increase in the major counterregulatory hormone, glucagon. The combined state of hypoinsulinemia and hyperglucagonemia is associated with increased hepatic glucose production and decreased peripheral glucose utilization, ultimately causing severe hyperglycemia. In addition, β-stimulation, either through exogenous β-mimetic agents or endogenous epinephrine release due to stress, inhibits insulin-induced glucose transport into peripheral tissues. The resulting hyperglycemia can cause osmotic diuresis and dehydration, characteristic of

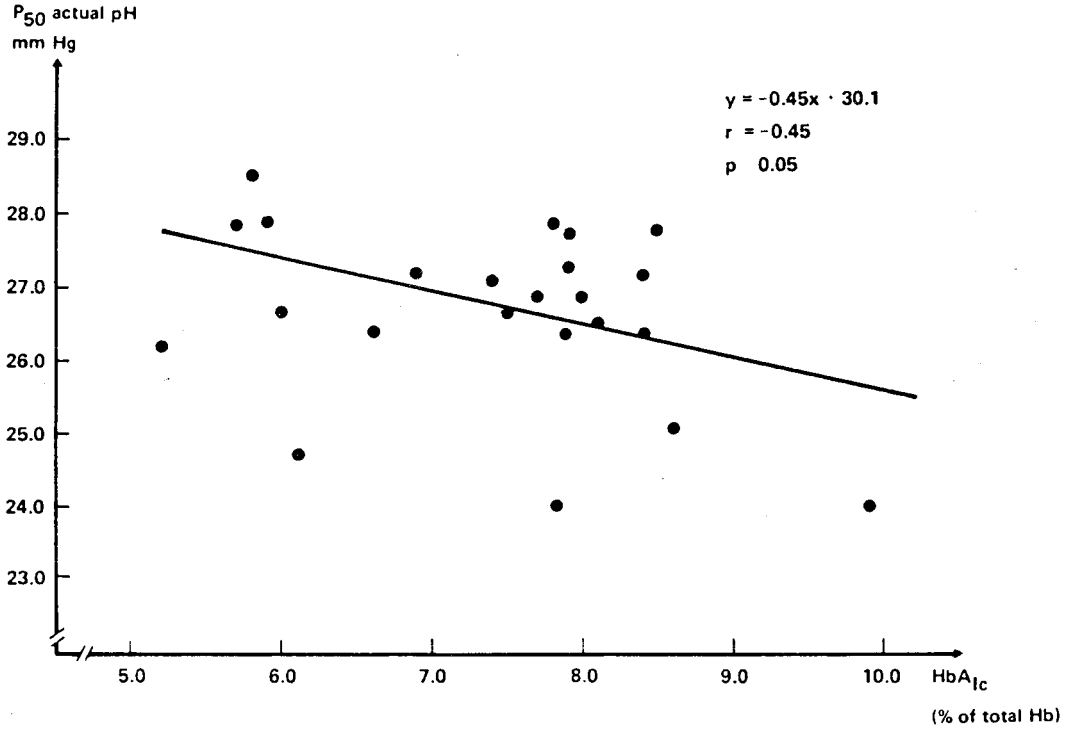

FIGURE 23.2. Correlation of Hb A_{1c} and P_{50} of oxygen. (From Madsen H, Ditzel J. Changes in red blood cell oxygen transport in diabetic pregnancy. Am J Obstet Gynecol 1982;143:421–424, with permission.)

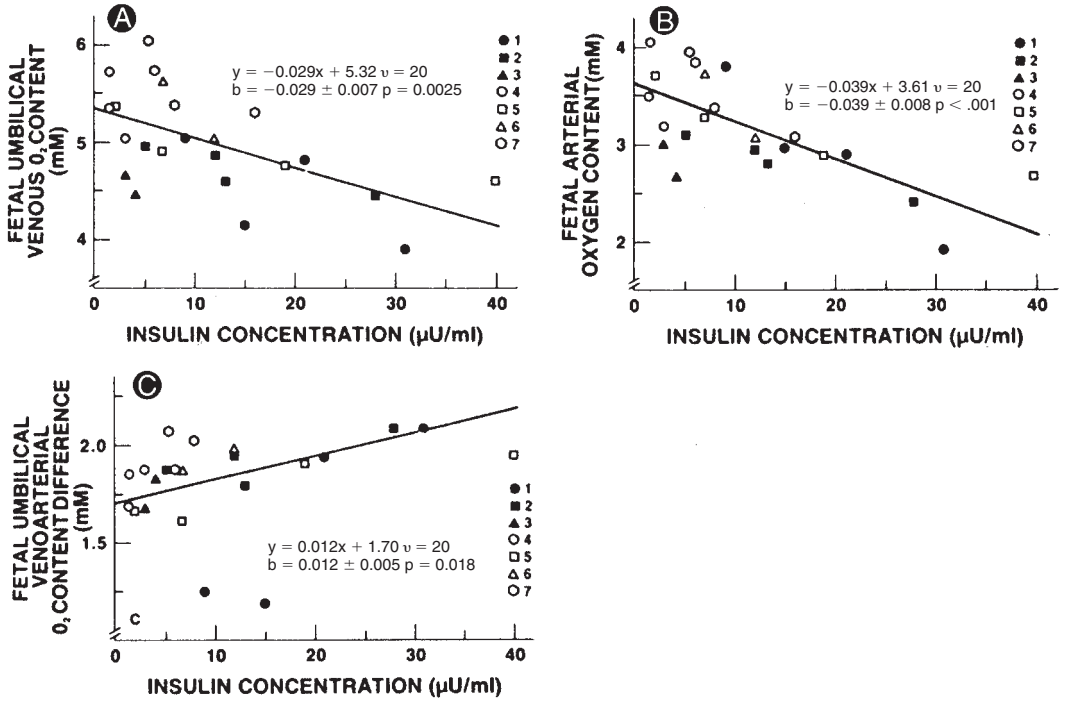

FIGURE 23.3. The association between fetal plasma insulin concentration and fetal arterial oxygen content (**A**), fetal venous oxygen content (**B**), and fetal umbilical venoarterial oxygen content difference (**C**). Shown is the regression line as determined by analysis of covariance. Also shown are the regression equations and the slopes with their standard errors and *p* values. Data from seven animals are represented by the symbols shown in the figure. (From Milley JR, Rosenberg AA, Philipps AF, et al. Am J Obstet Gynecol 1984;149:673. Used by permission.)

DKA. Potassium and sodium concentrations are decreased because of osmotic diuresis.

Uncontrolled diabetes activates oxidative enzymes in the liver, which metabolize free fatty acids to ketone bodies. β-Hydroxybutyrate and acetoacetate will decrease maternal pH and stimulate the respiratory center. Acidosis decreases intracellular potassium by replacing potassium ions with hydrogen ions. Severe hyperglycemia induces an osmotic diuresis. The kidneys waste potassium into the urine in an attempt to retain sodium as intravascular volume falls. Total body potassium is thus depleted. Loss of maternal fluid volume will decrease cardiac output and blood pressure and may ultimately lead to cardiovascular collapse and shock.

Effect on the Fetus

Maternal DKA is frequently associated with the development of nonreassuring fetal heart rate patterns. These patterns, however, usually resolve with treatment of the maternal metabolic disorder without obvious neonatal sequelae. Most obstetricians suggest delaying fetal intervention until the mother is metabolically stabilized.

Clinical Features

Classical presentations include (1) anorexia, (2) nausea, (3) vomiting, (4) polyuria, (5) polydipsia, (6) tachycardia, and (7) abdominal pain or muscle cramps. If severe, the picture could include (1) Kussmaul hyperventilation, (2) signs of volume depletion (e.g., hypotension and oliguria), (3) lethargy to coma, (4) normal-to-cold body temperature, and (5) a fruity odor noticeable on the patient's breath.

Diabetic parturients can develop ketoacidosis with remarkably low blood glucose values (as low as 200 mg/dL). The presence of ketones, maternal arterial pH of less than 7.30, depressed serum bicarbonate, and elevated anion gap confirm the diagnosis.

Treatment

Volume Replacement

Volume replacement management should include two intravenous lines, one for rapid fluid infusion and a second for insulin therapy. Initial treatment should be with normal saline at a rate of 15 to 20 mL/kg/h, 400 mL/m^2/h, or approximately 1 L/h for the first 2 h of the resuscitation. This intervention will rapidly replete the intravascular volume, improving general tissue perfusion, permitting excretion of glucose in the urine, and slowing potassium wasting in the urine. A Foley catheter should be placed early in the resuscitation to accurately monitor urine output. Fluid therapy should be reduced in the third and subsequent hours to 7.5 mL/kg/h according to the clinical situation and urine output. As the blood glucose level comes down to 300 to 250 mg/dL, the intravenous fluid solution should be changed to 5% glucose in water; this will prevent hypoglycemia and provide substrate to suppress lipolysis and ketogenesis. Bicarbonate is only indicated if the maternal pH is less than 7.10. Serum potassium concentrations should be measured frequently because potassium may need to be replaced due to excessive losses. Potassium replacement should not be initiated, however, until adequate urine output has been established. Intravenous fluids should be continued until all nausea and vomiting have resolved, bowel sounds are present, and the patient is able to tolerate adequate quantities of fluids by mouth.

Management of a patient with severe DKA does require a setting in which the patient can be closely monitored with a 1:1 nurse to patient ratio.

Hypertension

Hypertension and preeclampsia are common problems among diabetic gravidas. We reported the incidence and impact of this problem among our patient population at Brigham and Women's Hospital.[8] We observed that 29.8% of all pregnancies were associated with a hypertensive disorder. Because only 6% of the women were known to have hypertensive disorders antedating pregnancy, the majority of these parturients had pregnancy-induced hypertension. Hypertension was the major cause of premature delivery, accounting for one third of all premature deliveries (Table 23.1). Caritis et al. [9] found a 20% overall incidence of preeclampsia in a similar group of diabetic parturients with nulliparity and higher mean arterial pressure early in pregnancy predictive of higher risk.

In addition to the usual degree of hemodynamic fragility associated with severe preeclampsia, women with nephropathy (White class F) may have low serum albumin levels and very low colloid oncotic pressures, making them particularly vulnerable to pulmonary edema if they are vigorously volume loaded in preparation for regional anesthesia.

Hypoglycemia

Compared with the nonpregnant state, normal pregnancy is associated with a fall in fasting blood glucose levels but a rise in postprandial glucose levels. The net result of these changes is a modest rise in mean daily blood glucose levels throughout later pregnancy.[10] Early pregnancy frequently is associated with some degree of anorexia, nausea, and vomiting. In diabetic

TABLE 23.1. Prematurity and hypertensive complications by White's class.

White's class	Prematurity (<37 weeks)	Hypertensive complications
B	20.4	17.5
C	17.4	23.1
D	25.7	30.7
F	52.5	66.1
R	30.5	25.0
All classes combined	26.2	29.8

women taking a fixed daily dose of insulin, these changes often result in an increased frequency of insulin reactions in early pregnancy. Intensively treated nonpregnant diabetic patients often have a diminished awareness of and response to hypoglycemia, which may be exacerbated in parturients with long-standing diabetes with some degree of autonomic neuropathy. Diamond et al.[11] demonstrated a blunted response of counterregulatory hormones to hypoglycemia in pregnant diabetic women. They compared the response to hypoglycemia in nine intensively treated diabetic women and seven nonpregnant nondiabetic age-matched women using a hypoglycemic insulin clamp technique. They found that the counterregulatory hormonal responses of glucagon, epinephrine, and growth hormone did not begin to rise until lower levels of blood glucose were reached; they rose more slowly; and they did not reach the same maximum levels of response in the diabetic pregnant women as compared with the control subjects. One must be vigilant about the possibility of hypoglycemia in diabetic parturients undergoing cesarean section, particularly if the parturient has been placed npo before surgery and is under general anesthesia.

The elevated progesterone levels of pregnancy are associated with delayed gastric emptying. In women with some degree of gastroparesis before pregnancy, this effect can be exacerbated. Delayed and unpredictable gastric emptying can make glycemic control difficult and result in wide swings in postprandial glucose values. At its worst in late pregnancy, it can lead to frequent vomiting, poor weight gain, and frequent hypoglycemia. Frequent vomiting of undigested meals 2 to 3 h after eating is characteristic in these cases. Metoclopramide therapy may be quite helpful for these parturients.

Severe hypoglycemia in the latter half of pregnancy may be associated with a modest degree of fetal bradycardia, as low as 100 beats/min. This decrease reverses slowly as maternal blood glucose levels return to normal, with no obvious adverse consequences to the fetus.

Impaired Cardiac Adjustment

Airaksinen and colleagues made an interesting observation by using echocardiography to assess, in diabetic parturients, the adaptation of the heart to an increase of blood volume during pregnancy.[12] The mean duration of diabetes was 14 years, and 6 of these 17 parturients had microvascular complications. The authors observed a slightly smaller left ventricle in diabetic parturients compared with the control group in the basal state. The pregnancy-induced increase in left ventricular size, stroke volume, and heart rate were observed to be less in diabetic parturients. The authors suggested that normal hemodynamic adjustments to pregnancy were impaired in diabetic parturients. The blunted increases of stroke volume and heart rate were associated with the reduced resting cardiac output in diabetic pregnant women. The mechanisms of these changes are not well understood; however, the factors that might be involved are preclinical diabetic cardiomyopathy and subclinical autonomic neuropathy. Anesthetic implications of these changes might be important. Judicious volume expansion and use of epidural anesthesia for cesarean section might be preferred.

Stiff Joint Syndrome

Stiff joint syndrome is a rare condition consisting of juvenile-onset diabetes, nonfamilial short stature, and joint contractures.[12] If there is a suggestion of stiff joint syndrome, the parturient should have flexion-extension radiographs taken of the cervical spine. Limited atlanto-occipital extension might make intubation difficult, and awake tracheal intubation with or without fiberoptic bronchoscopy may be necessary. A "prayer sign," which is defined by the parturient's inability to approximate the palmar surfaces of the phalangeal joints despite maximal effort, secondary to diabetic stiff joint syndrome, may be beneficial for the anesthesiologist (Figure 23.4)

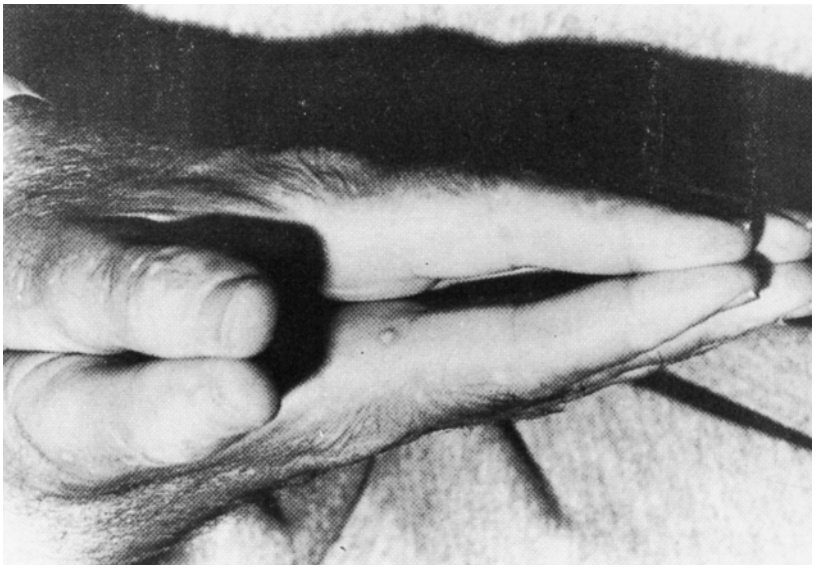

FIGURE 23.4. The "prayer sign." (From Hogan K, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988;67:1162–1165, with permission.[53])

to detect patients with associated involvement of the atlanto-occipital joint.

Diabetic Scleredema

Diabetic scleredema is synonymous with stiff joint syndrome. Eastwood reported a case of anterior spinal artery syndrome after administration of epidural anesthesia for cesarean section in a parturient with stiff joint syndrome. The cause of the complication was unclear; however, the possible mechanisms, as suggested by the authors, were (1) rigid epidural space because of pathologic changes in the connective tissues and ligaments, which made the epidural space less compliant; (2) diminished arterial supply to the spinal cord due to the increased pressure in the noncompliant epidural space because of the high volume of the local anesthetic agent (35 mL) used in this case; and (3) preexisting microvascular disease.

Obstetric Management

It is clear that no single medical or obstetric intervention for diabetic gravidas has been as important in improving their prognosis as improved metabolic control. As pregnancy progresses through the second trimester, placental production of human placental lactogen, which antagonizes the action of insulin, rises; this causes a dramatic increase in insulin requirements to levels 150% and 200% of the prepregnancy requirements. Requirements frequently are noted to peak around 36 weeks and decrease slightly toward term. Trying to adjust to the constantly changing insulin requirement during pregnancy can be a difficult and frustrating experience for a parturient. Just when she thinks she has the right dose, it changes. Parturients should be seen frequently during pregnancy to help them with their glycemic control.

Insulin Therapy

A variety of insulins are now available including rapid-, short-, intermediate-, and long-acting types. Some are the result of genetic engineering of human insulin and are produced by recombinant DNA technology. All are injectable alone or in combination with other varieties. Some mixing combinations may alter the pharmacokinetics of some types of insulins. There has been considerable discussion regarding the best insulin regimen for achieving optimal glycemic control in pregnancy. The majority of women will achieve adequate control with a conventional regimen of two or three injections of short- and intermediate-acting insulin daily. Continuous subcutaneous insulin infusion (CSII) via pump is a labor-intensive method of insulin therapy that requires a very motivated woman. Pump infusion sets are expensive, pumps can malfunction, and it is not clear that this method offers significant advantages for large numbers of parturients.[13,14] None of these regimens is clearly superior to any other. Some women do better with one method than another, and experimentation is helpful.

Oral hypoglycemic agents have been avoided during pregnancy because of fears of potential induction of congenital malformations due to first trimester exposure and neonatal hypoglycemia due to exposure later in pregnancy. Relatively mild hyperglycemia of gestational diabetes later in pregnancy has been treated with glyburide, a sulfonylurea with minimal transplacental passage. Metabolic control obtained and short-term complications observed were comparable to those with insulin treatment.[15]

Blood Glucose Monitoring

More important than the precise regimen according to which the insulin is administered is monitoring the results of treatment. Any serious effort at achieving euglycemia must include self-monitoring of capillary blood glucose. It is very unusual to have a woman who cannot be taught to test her own blood sugar level. We ask parturients to test their glucose levels four times daily: fasting and 2 h after each meal. Women are given forms to record their glucose values, which are reviewed at regularly scheduled visits. We aim for fasting values below 105 mg/dL and 2-h postprandial values of 120 mg/dL or less. We obtain a Hb A_{1c} determination at the first prenatal visit and monthly thereafter.

Congenital Anomalies

The first published documentation that poor glycemic control in the first trimester could lead to an increased incidence of congenital anomalies came from the Joslin Clinic. Miller et al.[16] demonstrated that women with Hb A_{1c} concentrations greater than 8.5% in the first trimester had a 22% risk of having a fetus with a major congenital anomaly, whereas this risk was only 3.3% when Hb A_{1c} was less than 8.5%. Subsequently, numerous studies have confirmed the relationship between poor metabolic control during organogenesis and major malformations (Table 23.2). [17] The multicentered National Institute of Child Health and Human Development (NICHD) Diabetes in Early Pregnancy (DIEP) project, designed to determine precisely which biochemical abnormalities associated with poor metabolic control cause major congenital malformations,[18] found an increased risk of major anomalies among infants of diabetic mothers as compared with nondiabetic controls. They were unable, however, to document any increase in the incidence of major anomalies associated with increasing levels of glycosylated hemoglobin in the first trimester among the infants of the 350 diabetic parturients. Women were recruited into the study before conception or within 21 days of conception. Only 7% of that self-selected group had first trimester glycosylated hemoglobin values greater than 7 SD above the nondiabetic mean. The failure of the project to find a relationship between degree of control and anomalies is undoubtedly because the study population was rather ho-

TABLE 23.2. Major malformations according to first trimester Hb A_1 level, Joslin Diabetes Center, January 1, 1984–December 31, 1992.

SD above mean	Percentage[a]	Major malformations	No major malformations	Percentage[b]	Risk ratio (95% confidence interval)
≤6	≤9.3	10	256	3.7	1.0
6.1–9.0	9.4–11.0	10	183	5.2	1.4 (0.6–3.2)
9.1–12.0	11.1–12.7	8	89	8.2	2.2 (0.9–5.3)
12.1–15.0	12.8–14.4	10	21	32.2	8.6 (4.2–17.3)
≥15.0	≥14.4	5	7	41.7	11.1 (4.8–25.4)

[a]HbA_1as a percentage of total hemoglobin.
[b]Major malformations as a percentage of all pregnancies progressing beyond the first trimester.

mogeneous, with few women in poor metabolic control at increased risk for major malformations.

It appears from the very carefully done DIEP study, with its own nondiabetic concurrent controls, that even well-controlled diabetic women have a greater incidence of malformed infants than do nondiabetic women. The risk for major malformation, however, does not vary over a broad range of glycemic control but rises sharply with very poor control.

Spontaneous Abortion

There has been considerable debate as to whether diabetic women in general have an increased incidence of spontaneous abortion. Several studies have indicated that diabetic women with high Hb A_{1c} values in the first trimester are at increased risk for spontaneous abortion.[19] Data from the DIEP confirm the increased risk of spontaneous abortion associated with poor first trimester metabolic control. [20] Data from the Joslin Clinic also show a significant relationship between first trimester Hb A_{lc} and the risk for spontaneous abortion (Table 23.3).[17]

Macrosomia

Excessive fetal growth (macrosomia) has long been recognized as an important complication of maternal diabetes. According to the classic Pedersen hypothesis, maternal hyperglycemia produces fetal hyperglycemia and thus fetal hyperinsulinemia. Fetal hyperinsulinemia acts as an anabolic stimulus leading to enhanced accretion of fat, bone, and muscle mass. In support of this hypothesis, Sosenko et al. have documented that macrosomic fetuses of diabetic women have high C peptide levels and are at increased risk for neonatal hypoglycemia.[21] Attempts to correlate a variety of indices of glycemic control (e.g., mean daily glucose levels, Hb A_{1c} levels) with risk for macrosomia have had limited success.[22–25] Furthermore, case reports abound documenting the fact that some women can be in excellent glycemic control by all known parameters and yet deliver remarkably macrosomic fetuses.[26] A potential explanation for these apparently conflicting observations was provided by the finding of Menon et al. that insulin could cross the placenta from the maternal to the fetal circulation as insulin–antiinsulin antibody complexes.[27] The level of these antigen–antibody complexes was proportional to fetal weight at birth. An increasing body of evidence indicates that there is a relationship between fetal size at birth and maternal glycemia that extends down through the normal, nondiabetic range with no "threshold" for excessive growth.[10,28,29] Macrosomic fetuses are at increased risk for birth trauma,[30] which has implications for the route and timing of delivery, as discussed next.

Classification

In 1949, Priscilla White proposed the classification of diabetes in pregnancy that later came to bear her name.[31] It was based on criteria that could be identified at the time of the parturient's first prenatal visit, including age of onset, dura-

TABLE 23.3. Spontaneous abortions according to first trimester Hb A_1 level, Joslin Diabetes Center, January 1, 1984–December 31, 1992.

SD above mean	Percentage[a]	Spontaneous abortions	Continuing pregnancies	Percentage[b]	Risk ratio (95% confidence interval)
≤6	≤9.3	38	266	12	1.0
6.1–9.0	9.4–11.0	27	193	12	1.0 (0.6–1.6)
9.1–12.0	11.1–12.7	26	97	21	1.7 (1.1–2.7)
12.1–15.0	12.8–14.4	14	31	31	2.5 (1.4–4.3)
≥15.0	≥14.4	11	12	48	3.8 (2.1–6.8)

[a]HbA_1 as a percentage of total hemoglobin.
[b]Spontaneous abortions as a percentage of all registered pregnancies.

Box 23.1. Modified White's classification of diabetes in pregnancy.

Gestational diabetes mellitus noninsulin requiring (GDMNI): abnormal carbohydrate tolerance with onset or first diagnosis during pregnancy, not requiring insulin.

Gestational diabetes mellitus insulin requiring (GDMI): abnormal carbohydrate tolerance with onset or first diagnosis during pregnancy, requiring insulin.

- Class A: Abnormal carbohydrate tolerance in the nonpregnant state identified prior to the present pregnancy that does not require insulin either prior to or during the pregnancy.
- Class B: Onset of insulin-requiring diabetes after 20 years of age, with duration of less than 10 years.
- Class C: Onset of insulin-requiring diabetes between ages 10 and 20 with duration of less than 20 years, or duration 10 to 20 years regardless of age of onset.
- Class D: Onset of insulin-requiring diabetes prior to age 10 years, or duration greater than 20 years regardless of age of onset, or insulin-requiring diabetes with chronic hypertension, or insulin-requiring diabetes with benign retinopathy.
- Class F: Insulin-requiring diabetes with diabetic nephropathy (proteinuria of greater than 500 mg in a 24-h urine collection).
- Class R: Insulin-requiring diabetes with proliferative retinopathy.
- Class T: Insulin-requiring diabetes with renal transplant.
- Class H: Insulin-requiring diabetes with coronary artery disease.

tion of diabetes, and presence or absence of microvascular or macrovascular complications. She attempted to correlate these classes with pregnancy outcome, hoping to provide guidelines for the management of the pregnancy and a basis for counseling the parturient regarding her prognosis. The system has been modified to add gestational diabetes, which White did not specifically recognize, and renal transplants, which did not exist when she developed the scheme. Other classes have been dropped, such as class E with calcified pelvic vessels on X-ray studies. Several of the classes are not substantially different from one another in many respects, but the modified White's classification system is still useful both for patient counseling and for comparing reports of results from different treatment centers (Box 23.1).

Gestational Diabetes

The hormonal changes of advancing gestation antagonize insulin action. It should not be a surprise then that some women who begin pregnancy with marginal carbohydrate tolerance become frankly intolerant as pregnancy advances. Because undiagnosed and untreated gestational diabetes of a significant degree can result in obstetric complications, women should be screened for gestational diabetes. The method of screening has become a controversial issue. There are several historic risk factors that are associated with increased risk for gestational diabetes (Box 23.2). Anyone with any of these risk factors or anyone who spills glucose into the urine at any time should be screened biochemically.

Box 23.2. Risk factors for gestational diabetes.

- Maternal age 30 years or greater
- Family history of diabetes mellitus
- Obesity
- Previous delivery of macrosomic infant
- Previous near-term stillbirth

Controversy exists as to whether screening by historic risk factors is adequate or whether all pregnant women should be screened biochemically. It has been shown that if a large population is screened biochemically, only one half the parturients with abnormal carbohydrate tolerance would have been detected through screening by history. Would this 50% detection rate identify essentially all the people with significant disease and therefore be adequate? Approximately half of all deliveries in the United States now involve women having their first babies. These women are not eligible for two of the five criteria listed in the box. Some argue that 50% detection is inadequate, and that the only way to deal with the problem is through universal biochemical screening. There is evidence that universal screening coupled with an aggressive approach to insulin therapy in gestational diabetes can reduce the incidence of macrosomia and the necessity for operative delivery due to that macrosomia.[32] However, there has not been a series to date that demonstrates universal screening can reduce the perinatal mortality rate, partly because the perinatal mortality rate is so low that a huge study would be necessary. Such a study is currently underway in multiple centers in several countries. Currently, the position of the American College of Obstetricians and Gynecologists (ACOG) is that initial screening by history followed up with biochemical testing is appropriate. The American Diabetes Association has changed its position several times in recent years but currently recommends biochemical screening only for women who fail to meet rigorous criteria for low risk.[33]

The issues of how and when to screen are less controversial, but the precise values to be used for abnormal results are still debated. Acceptable values for these tests are quoted here. A 50-g oral glucose load followed by a single blood glucose test 1 h after the load should be done at 24 to 28 weeks gestation. A glucose loading test (GLT) value of 140 mg/dL or more should be followed with a 100-g 3-h oral glucose tolerance test (GTT). The upper limits of normal for the GTT are fasting, 105 mg/dL; 1 h, 190 mg/dL; 2 h, 165 mg/dL; and 3 hours, 145 mg/dl. Two or more abnormal values define gestational diabetes.

Parturients with abnormal glucose tolerance should be placed on appropriate diets and have their blood glucose levels checked regularly. If they normalize their glucose levels on diet alone, then they can be managed as normal parturients. If the fasting glucose levels are in excess of 105 mg/dL or the postprandial levels are greater than 120 mg/dL, the

parturient should start insulin therapy and be managed as a diabetic parturient.

Antenatal Monitoring for Fetal Well-Being

The incidence of unexpected near-term demise has been reduced dramatically in the past two decades, undoubtedly mostly as a result of vastly improved metabolic control but possibly at least partly attributable to routine assessment of fetal well-being. The nonstress test (NST) has been the standard, with the oxytocin challenge test (OCT) or contraction stress test (CST) used to evaluate nonreactive NST results in diabetic parturients. We routinely begin weekly NST at 32 weeks and perform them twice weekly from 36 weeks until delivery. Although some authors have reported an unacceptable incidence of loss using this scheme, we have had only two losses of nonmalformed singletons in the third trimester among our last 578 consecutive patients with diabetes antedating pregnancy. It has been proposed that the biophysical profile (BPP)[34] and Doppler umbilical artery flow velocity analysis[35] be integrated into the care of these patients. The BPP is helpful, but given the tendency to polyhydramnios in diabetes, an adequate amniotic fluid volume may not have the same reassurance value that it would have in a nondiabetic patient. The value of Doppler remains to be proven. The NST is inexpensive to perform, relatively fast, and reliable.

Lung Maturity Testing

It has been known for some time that the lungs of infants of diabetic mothers (IDM) mature less rapidly than those of nondiabetic women. Furthermore, these infants tend to develop respiratory distress syndrome (RDS) at lecithin/sphingomyelin (L/S) ratios that would indicate maturity for infants of nondiabetic women. To avoid RDS in these neonates, a variety of strategies have been tried. Bringing more of the parturients closer to term before elective delivery is most important. Before electively delivering a diabetic parturient at less than 39 weeks gestation, fetal lung maturity should be assessed. The presence of a relatively high concentration of phosphatidylglycerol (PG) in the amniotic fluid, as demonstrated by thin-layer chromatography in the standard assay, is a reliable indicator of maturity. Unfortunately, it is a very conservative estimator, and only 50% of PG-negative fetuses will develop RDS. We prefer to use a combination of the L/S ratio and quantitation of saturated phosphatidylcholine (SPC) to predict lung maturity. In practice, any IDM with an SPC greater than 1000 μg/dL and/or an L/S ratio of 3.5 or greater is extremely unlikely (risk, $<1/260$) to develop RDS.

Route and Timing of Delivery

The route and timing of delivery for diabetic gravidas have always been matters of concern. Before the early 1970s, the major concern was to avoid late intrauterine demise. Early deliveries, however, were associated with neonatal morbidity and mortality from RDS. Improved glycemic control and routine assessment of fetal well-being reduced the risk of late demise. Fetal lung maturity testing methods permitted obstetricians to assure lung maturity before elective delivery. The decline in perinatal mortality due to late demise and RDS has permitted attention to be focused on remaining sources of morbidity and mortality. Chief among these concerns are macrosomia and its associated high incidence of operative delivery and birth trauma. Although the risks for shoulder dystocia and subsequent birth injury increase with increasing birth weight in the general population, these risks are magnified[30] among IDM. It has been suggested that this may be due to the body habitus of the IDM with unusually broad shoulders in relation to the head size.[36] Some have proposed elective cesarean delivery for fetuses estimated to be macrosomic by ultrasound examination late in pregnancy.[37] The limits of ultrasound examination to accurately predict macrosomia, the low incidence of permanent injury resulting from traumatic delivery, and the expense and morbidity associated with cesarean delivery make such a proposal controversial.[38]

The major challenges, then, in planning the deliveries of diabetic women are to (1) minimize exposure to risk of a late intrauterine demise; (2) minimize intrapartum fetal hypoxemia and acidosis and recognize and treat it promptly if it occurs; (3) minimize the risks of traumatic birth injury, RDS, and other sources of neonatal morbidity and mortality; (4) minimize the cesarean section rate; and (5) attempt to meet the parents' expectations for the birthing experience to the greatest possible extent. Early delivery is associated with an increased risk for multiple minor morbidities in the nursery, including hyperbilirubinemia and feeding difficulties even after lung maturity has been assured. Attempts to induce labor earlier in pregnancy will also encounter less favorable cervical conditions and result in a higher than necessary cesarean section rate.

Elective deliveries are generally planned between 38 and 40 weeks gestation for all women with insulin-requiring diabetes antedating pregnancy. An ultrasound examination is performed before delivery to estimate the fetal weight. If the fetal weight is estimated to be less than 4000 g, a pelvic delivery is planned. If the fetus is estimated to weigh more than 4000 g, a cesarean delivery is planned, unless the patient has a history of a previous uncomplicated pelvic delivery of a baby of more than 4000 g. Every effort is made to await a favorable cervical examination before the induction of labor.

Anesthetic Management

Management of Labor and Delivery

A parturient scheduled for induction of labor is given approximately one third of her usual morning dose of intermediate-acting insulin and no regular insulin. Capillary blood glucose levels are monitored hourly during labor via finger sticks with

a reflectance meter on the labor floor. If the blood glucose goes above 120 mg/dL, an IV infusion of regular insulin is used to bring the blood glucose level within normal limits. It is particularly important during labor to maintain a normal blood glucose level because hyperglycemia will magnify the degree of acidosis caused by any degree of hypoxemia that may occur. To avoid the accidental infusion of a large volume of glucose-containing IV fluid, the main line is always a nonglucose-containing solution. A 5% glucose-containing solution can be "piggybacked" into the main line via an infusion pump at 125 mL/h. Immediately postpartum, the insulin requirement drops dramatically, so that for a brief period it is usually less than the prepregnancy dose. On the first postpartum day, the patient should be given approximately one half the prepregnancy dose of intermediate-acting insulin with regular insulin as necessary.

Despite the lack of rigorous evidence of efficacy, laboring parturients are continuously monitored electronically with liberal use of scalp pH sampling when necessary. Prophylactic antibiotics are routinely used for women undergoing cesarean section. A single dose of IV antibiotic given at the time of cord clamping has been shown to be effective in series of nondiabetic patients with no demonstrable efficacy to further doses postpartum.

Minimizing Anesthetic Contribution to Fetal Acidosis

The potential contribution of different anesthetic techniques to exacerbate fetal acidosis has been studied. Datta and Brown compared the effects of spinal versus general anesthesia on babies born to healthy and diabetic parturients.[39] Babies born to diabetic parturients receiving spinal anesthesia were more acidotic than those born to mothers receiving general anesthesia. In a follow-up study, Datta et al. measured maternal and fetal blood gas values after epidural anesthesia in diabetics and found a 60% incidence of neonatal acidosis ($pH \leq 7.20$).[40] The acidosis related to both the severity of maternal diabetes and to the presence of maternal hypotension (Table 23.4). Of note, the IV fluid used in both studies was lactated Ringer's with 5% dextrose, and fluid boluses were given to treat maternal hypotension defined as systolic blood pressure less than 100 mm Hg. A subsequent study compared the blood gas results obtained from diabetic and healthy patients undergoing cesarean section: when the IV fluid was dextrose-free lactated Ringer's solution and hypotension was aggressively treated with ephedrine, no differences in blood gas values could be determined between the two groups[41] (Table 23.5).

Table 23.4. Effect of maternal hypotension during cesarean section under epidural on neonatal acid–base status in diabetic parturients.

Umbilical artery	No hypotension	Hypotension
pH	7.24 ± 0.02	7.15 ± 0.03*
P_{O_2} (mm Hg)	19 ± 2	16 + 2
P_{CO_2} (mm Hg)	65 ± 3	71 ± 4
Base deficit (mEq/L)	4.35 ± 0.88	8.25 ± 1.74*

Values reported as mean ± SE.
*$p < 0.05$.

Table 23.5. Effect of strict control of maternal glucose and blood pressure during cesarean section under spinal on neonatal acid–base status in diabetic parturients.

Umbilical artery	Diabetic/no hypotension	Diabetic/hypotension
pH	7.27 + 0.01	7.30 + 0.01
P_{O_2} (mm Hg)	20 + 2	22 + 2
P_{CO_2} (mm Hg)	56 + 2	50 + 2.5
Base deficit (mEq/L)	4 + 1	3 + 0.7

Values reported as mean ± SE.

The mechanisms contributing to fetal acidosis in diabetes are multifactorial: (1) human placenta produces lactate in vitro, especially in the setting of hypoxia, and lactate further increases in the presence of excess glycogen, and (2) fetal hyperglycemia has been associated with fetal acidosis.[42] Kenepp et al. determined that umbilical artery pH was significantly lower when mothers received glucose infusions.[43] Kitzmiller et al.[44] explored the possibility that hypoxia following maternal hypotension produces fetal lactic acidemia in the presence of hyperglycemia after volume expansion with dextrose-containing fluids. Monkey fetuses were exposed to acute hyperglycemia and maternal hypoxia. Although the fetuses were exposed to the same volume of IV fluids and the same duration of maternal hypoxia, the hyperglycemic fetuses (1) had lower arterial oxygen tension and content than the controls despite similar maternal arterial oxygen partial pressures, and (2) had severe metabolic acidosis (pH 7.06 versus 7.23). Other studies have supported the concept that hyperinsulinemia increases oxygen consumption, and that fetal hyperglycemia and hyperinsulinemia can reduce fetal oxygenation in diabetes.[45]

Anesthetic Management for Labor and Vaginal Delivery

Moderate pain of early labor can be relieved with small doses of narcotic drugs (e.g., butorphanol or nalbuphine). The main problem with larger doses of systemic medication is maternal and neonatal respiratory depression. Prolonged labor and decreased uteroplacental perfusion associated with maternal hemodynamic changes due to IV narcotics may result in fetal acidosis. Fetal acidosis subsequently can alter the placental transfer of the drugs, affect perinatal homeostasis, and ultimately potentiate the depressant effects of these drugs. Pain and anxiety associated with natural childbirth or with inadequate labor analgesia may further decrease placental perfusion as a result of increased catecholamine concentrations.[46] Paracervical block can also cause fetal hypoxia because of umbilical and uterine arterial vasoconstriction.[47]

Epidural analgesia is associated with a few obvious advantages: (1) it reduces maternal endogenous catecholamine release and indirectly will increase placental blood flow; (2) it reduces the maternal lactic acid production and hence fetal acidosis; (3) it provides excellent pain relief during the first stage as well as during the second stage, especially if forceps delivery is necessary; and (4) an indwelling epidural catheter can be used should a cesarean delivery become necessary.

At Brigham and Women's Hospital, induction of epidural analgesia is started with 0.25% bupivacaine, and maintenance analgesia is obtained with a continuous infusion of 0.0625% to 0.125% bupivacaine with 2 μg/ml fentanyl (8–10 mL/h). At the Massachusetts General Hospital, the epidural test dose (1.5% lidocaine with 1:200K epinephrine) contributes to the labor analgesia; a T10 sensory level is obtained with 15 mL 0.04% bupivacaine with 1.66 μg/mL fentanyl, and the maintenance analgesia is obtained with the same mixture infused at 15 mL/h.

For forceps delivery, dense perineal anesthesia is necessary; this can be provided by 8 to 10 mL 3% 2-chloroprocaine or 2% lidocaine with bicarbonate added. In the absence of an indwelling epidural catheter, spinal anesthesia in the sitting position (hyperbaric bupivacaine with dextrose) can provide good perineal anesthesia. This technique will provide perineal relaxation and hence less chance of birth trauma; this is especially important for delivery of a large baby. It may be prudent to consider placing an epidural catheter at the time of spinal placement (combined spinal-epidural technique), which can be used if there is urgent operative delivery.

Anesthetic Management for Cesarean Section

Diabetic parturients are at significantly higher risk of needing a cesarean section. A prospective cohort of more than 3700 pregnancies demonstrated a relative risk for cesarean delivery of 2.1 after adjustment for multiple maternal risk factors.[48]

Anesthesia for cesarean section requires special attention for diabetic parturients. Although all parturients are considered "full stomachs," the diabetic parturient has additional risks associated with autonomic neuropathy and gastroparesis. Aspiration prophylaxis should consist of a nonparticulate antacid immediately before surgery; metoclopramide administration is useful, and the addition of a histamine-2-receptor antagonist should be considered for this population.

Hemodynamic alterations are more dramatic during cesarean section compared with vaginal delivery because (1) there is a higher sympathetic blockade, and sympathetic tone might also be abnormal in long-standing diabetic patients; and (2) aortocaval compression by the gravid uterus accentuates the problem of hypotension, especially when associated with high sympathetic block. Hemodynamic control is further hampered by comorbidity, which is common in diabetics. Preclinical diabetic cardiomyopathy, autonomic neuropathy, and low colloid osmotic pressure from renal protein wasting may exacerbate hemodynamic instability and also put the parturient at risk for pulmonary edema in the setting of overzealous hydration.

Either spinal or epidural anesthesia may be appropriate for the diabetic parturient, so long as hypotension is minimized and aggressively treated with ephedrine or, if necessary, phenylephrine. In severe diabetics, epidural anesthesia may be preferred because the sensory block can be brought up more slowly. Spinal anesthesia can be obtained with 12 mg hyperbaric bupivacaine (0.75%) with 10 μg fentanyl added. Epidural anesthesia can be obtained with 15 to 25 mL 2% lidocaine with 1:200K epinephrine and 50 μg fentanyl added. For an urgent cesarean section where fetal acidosis is assumed and an indwelling epidural catheter is present, 3% 2-chloroprocaine is the anesthetic of choice.

Diabetic parturients undergo general anesthesia either because of operative urgency or because of other factors that preclude regional anesthesia. General anesthesia can be problematic because of (1) gastroparesis, (2) limited atlanto-occipital joint extension, (3) increased hemodynamic response to intubation, and (4) impaired counterregulatory hormone responses to hypoglycemia during sleep. When the general anesthetic can be anticipated, metoclopramide (10 mg) should be administered 30 to 45 min beforehand to enhance forward gastric emptying and to increase lower esophageal sphincter tone. Although rare, stiff joint syndrome may affect the airway and atlanto-occipital joint, making intubation difficult. Medications and equipment needed for managing a difficult airway, including those for fiberoptic intubation, should be readily available. Vohra and colleagues[49] observed greater hemodynamic variations in response to intubation in diabetics, including more variability in heart rates, mean arterial pressure, and vascular resistance in the diabetic group. Finally, under regional anesthesia, patients are able to verbalize sensations that may be consistent with hypoglycemia; in contrast, cardiovascular responses to hypoglycemia may be blunted under general anesthesia.

Postoperative analgesia is important for pain control and to help avoid catecholamine and glucose swings after delivery. Analgesia can be achieved many ways. Neuraxial preservative-free morphine offers excellent analgesia for up to 24 h with minimal sedation and occasional pruritus. Morphine can be given intrathecally at the time of spinal placement (0.2 mg) or epidurally (3 mg). Nonsteroidal antiinflammatory medications can be used as rescue drugs for breakthrough discomfort. Pruritus can be treated with small doses of naloxone, or the partial agonist-antagonist, nalbuphine (5 mg intravenously). For patients who have undergone general anesthesia or who were otherwise not a candidate for neuraxial morphine, an effective alternative is patient-controlled analgesia with intravenous morphine, dilaudid, or demoral.

Special Anesthetic Considerations

Diabetic parturients with severe preeclampsia or parturients with diabetic nephropathy with superimposed hypertension

warrant special attention. At the very least, these individuals require pulse oximetry and monitoring of urine output. More invasive monitoring occasionally is needed to assess the fluid status and cardiovascular function. Coagulation status needs to be assessed before induction of regional anesthesia, and the airway assessment should include an evaluation of airway edema.

Renal transplant recipients need determination of baseline renal function. They are usually on immunosuppressive medications and can be glucocorticoid dependent. Proper aseptic technique is particularly important in these parturients, who are prone to infection. Many of the immunosuppressive medications will need to be given in parenteral form because of npo status, nausea, and unreliable enteral absorption during labor. Coordination of care with the transplant team is appropriate.

Postpartum Considerations

After either vaginal or abdominal delivery, insulin management must be carefully regulated. Lev-Ran[50] noted a drop in insulin requirement to zero for 1 to 2 days in 11 of 12 patients undergoing cesarean section. Hypoglycemia appeared in 3 of these 45 patients. A steep rise in blood glucose levels followed this temporary drop in insulin requirement. Insulin needs are sometimes determined on an individual basis.

Parturients who are a risk for developing pulmonary edema often do so after delivery.[51] Invasive monitoring measures that are undertaken before delivery may be most useful when continued into the immediate postpartum period.

Neonatal Resuscitation

Despite the best efforts of obstetricians and anesthesiologists, active neonatal resuscitation is sometimes necessary. Therefore, a neonatologist should attend both vaginal and abdominal deliveries of infants of diabetic parturients, and birth should take place in a hospital with access to facilities for neonatal intensive care. Infants of diabetic mothers have an increased risk of RDS. Serious RDS must be differentiated from milder and more transient (48 h) tachypnea of the newborn, which may be caused by retained fetal lung fluid. The diagnosis of RDS will be made by (1) clinical signs including grunting, chest wall retractions, and a respiratory rate of more than 60 breaths per minute; (2) radiographic findings of diffuse reticulogranular patterns; and (3) an increased oxygen requirement to maintain Pa_{O_2} at 50 to 70 mm Hg for more than 48 h without other causes of respiratory problems. With the advent of modern ventilatory support, including high-frequency ventilation and surfactant therapy, the survival rate of RDS infants has increased dramatically.

The presence of a high hematocrit can also be a major problem in these infants; in its extreme, this condition can produce thrombosis, especially in the renal veins, and may necessitate therapeutic phlebotomy. Hyperbilirubinemia and hypocalcemia can also develop more frequently in these infants.[52] Finally, a high incidence of complex congenital cardiac anomalies still remains a major problem, and these defects may make resuscitative measures more difficult.

Summary

Management of diabetic parturients and their babies poses special challenges to the perinatal team. An understanding of the physiologic changes of pregnancy, of diabetes, and of possible relationships among these changes is key to providing proper care of these patients. Close communication between the perinatologist, anesthesiologist, and neonatologist is essential for good maternal and neonatal outcome.

References

1. Nylund L, Lunell NO, Lewander R, et al. Uteroplacental blood flow in diabetic pregnancy: measurements with indium-I 13m and a computer linked gamma camera. Am J Obstet Gynecol 1982;144:298–302.
2. Bjork O, Persson B. Placental changes in relation to the degree of metabolic control in diabetes mellitus. Placenta 1982;3:367–378.
3. Madsen H, Ditzel J. Changes in red blood cell oxygen transport in diabetic pregnancy. Am J Obstet Gynecol 1982;143:421–424.
4. Bunn HF, Briehl RW, Larrabee P, et al. The interaction of 2,3-diphosphoglycerate with various human hemoglobins. J Clin Invest 1970;49: 1088–1095.
5. Phillipps AF, Dubin JW, Raye JR. Fetal metabolic response to endogenous insulin release. Am J Obstet Gynecol 1981;139:441–445.
6. Milley JR, Rosenberg AA, Philipps AF, et al. The effect of insulin on ovine fetal oxygen extraction. Am J Obstet Gynecol 1984;149:673–678.
7. Carson BS, Philipps AF, Simmons MA, et al. Effects of sustained insulin infusion upon glucose uptake and oxygenation of ovine fetus. Pediatr Res 1980;14:147–152.
8. Greene MF, Hare JW, Krache M, et al. Prematurity among insulin-requiring diabetic gravid women. Am J Obstet Gynecol 1989;161:106–111.
9. Caritis S, Sibai B, Hauth J, et al. Predictors of pre-eclampsia in women at high risk. Am J Obstet Gynecol 1998;179:946–951.
10. Parretti E, Mecacci F, Papini M, et al. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies. Diabetes Care 2001;24:1319–1323.
11. Diamond MP, Reece EA, Caprio S, et al. Impairment of counter regulatory hormone responses to hypoglycemia in pregnant women with insulin-dependent diabetes mellitus, Am J Obstet Gynecol 1992;166:70–77.
12. Airaksinen KEJ, Ekaheimo MJ, Slmea PI, et al. Impaired cardiac adjustment to pregnancy in type I diabetes. Diabetes Care 1986;9:376–383.
13. Kitzmiller JL, Younger NM, Hare JW, et al. Continuous subcutaneous insulin therapy during early pregnancy. Obstet Gynecol 1985;66:606–611.
14. Coustan DR, Reece EA, Sherwin RS, et al. A randomized clinical trial of the insulin pump vs. intensive conventional therapy in diabetic pregnancies. JAMA 1986;255:631–636.
15. Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134–1138.
16. Miller E, Hare JW, Cloherty JP, et al. Elevated maternal hemoglobin A_{1c} in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med 1981;304:1331–1334.
17. Greene MF. Spontaneous abortions and major malformations in women with diabetes mellitus. Semin Reprod Endocrinol 1999;17:127–136.
18. Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. N Engl J Med 1988;318:671–676.

19. Miodovnik M, Lavin JP, Knowles JC, et al. Spontaneous abortion among insulin-dependent diabetic women. Am J Obstet Gynecol 1984;150:372.
20. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med 1988;319:1617.
21. Sosenko IR, Kitzmiller JL, Loo SW, et al. The infant of the diabetic mother: correlation of increased cord C peptide levels with macrosomia and hypoglycemia. N Engl J Med 1979;301:859.
22. Widness JA, Schwartz HC, Thompson D, et al. Glycohemoglobin (HbA_{1c}): a predictor of birth weight in infants of diabetic mothers. J Pediatr 1978;92:8.
23. Adashi EY, Pinto H, Tyson JE. Impact of maternal euglycemia on fetal outcome in diabetic pregnancy. Am J Obstet Gynecol 1979;133:268.
24. O'Shaughnessy R, Russ J, Zuspan FP. Glycosylated hemoglobins and diabetes mellitus in pregnancy. Am J Obstet Gynecol 1979;135:783.
25. Miller JM. A reappraisal of "tight control" in diabetic pregnancies. Am J Obstet Gynecol 1983;148:158.
26. Knight G, Worth RC, Ward JD. Macrosomy despite a well controlled diabetic pregnancy. Lancet 1983;2:1431.
27. Menon R, Cohen R, Sperling MA, et al. Transplacental passage of insulin in pregnant women with insulin dependent diabetes mellitus. N Engl J Med 1990;323:309–315.
28. Schwartz R, Teramo KA. What is the significance of macrosomia? Diabetes Care 1999;22:1201–1205.
29. Mello G, Parretti E, Mecacci F, et al. What degree of maternal metabolic control in women with type I diabetes is associated with normal body size and proportions in full-term infants. Diabetes Care 2000;23:1494–1498.
30. Acker DB, Sachs BP, Friedman EA. Risk factors for shoulder dystocia. Obstet Gynecol 1985;66:762.
31. White P. Pregnancy complicating diabetes. Am J Med 1949;7:609.
32. Coustan DR, Imarah J. Prophylactic insulin treatment of gestational diabetes reduces the incidence of macrosomia, operative delivery, and birth trauma. Am J Obstet Gynecol 1984;150:836.
33. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2002;25:S94–S96.
34. Golde SH, Montoro M, Good-Anderson B, et al. The role of nonstress tests, fetal biophysical profile, and contraction stress tests in the outpatient management of insulin requiring diabetic pregnancies. Am J Obstet Gynecol 1984;148:269.
35. Landon MB, Gabbe SG, Bruner JP, et al. Doppler umbilical artery velocimetry in pregnancy complicated by insulin dependent diabetes mellitus. Obstet Gynecol 1989;73:961.
36. Modanlou HD, Komatsu G, Dorchester W, et al. Large for-gestational-age neonates: Anthropometric reasons for shoulder dystocia. Obstet Gynecol 1982;60:417.
37. Langer O, Berkus MD, Huff RW, Samueloff A. Shoulder dystocia: should the fetus weighing ≥4000 grams be delivered by cesarean section? Am J Obstet Gynecol 1991;165:831–837.
38. Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. JAMA 1996;276:1480–1486.
39. Datta S, Brown WU. Acid-base status in diabetic mothers and their infants following general or spinal anesthesia for cesarean section. Anesthesiology 1977;47:272–276.
40. Datta S, Brown WU, Ostheimer GW, et al. Epidural anesthesia for cesarean section in diabetic parturients: maternal and neonatal acid-base status and bupivacaine concentration. Anesth Analg 1981;60:574–580.
41. Datta S, Kitzmiller JL, Naulty JS, et al. Acid-base status of diabetic mothers and their infants following spinal anesthesia for cesarean section. Anesth Analg 1982;61:662–665.
42. Robillard JE, Sessions C, Kennedy RL et al. Metabolic effects of constant hypertonic glucose infusion in well-oxygenated fetuses. Obstet Gynecol 1978;130:199–203.
43. Kenepp NB, Shelley WC, Kuman S, et al. Effects on newborn of hydration with glucose in patients undergoing cesarean section with regional anesthesia. Lancet 1980;1:645.
44. Kitzmiller JL, Phillippe M, VonOeyen P, et al. Effect of glucose on fetal acidosis in rhesus monkeys. In: XI European Congress of Perinatal Medicine, Rome, 1988.
45. Carson BS, Phillips AF, Simmon MA, et al. Effects of sustained insulin infusion upon glucose uptake and oxygenation of the ovine fetus. Pediatr Res 1980;13:147–152.
46. Schnider SM, Abboud T, Artal R, et al. Maternal endogenous catecholamines decrease during labor after epidural anesthesia. Am J Obstet Gynecol 1983;147:13–15.
47. Ralston DH, Shnider MSS. The fetal and neonatal effects of regional anesthesia in obstetrics. Anesthesiology 1978;48:34–64.
48. Naylor CD, Sermer M, Chen E, et al. Cesarean delivery in relation to birth weight and gestational glucose tolerance. Pathophysiology or practice style? JAMA 1996;275:1165–1170.
49. Vohra A, Kumar S, Charlton AJ, et al. Effect of diabetes mellitus on the cardiovascular responses to induction of anesthesia and tracheal intubation. Br J Anaesth 1993;71:258–261.
50. Lev-Ran A. Sharp temporary drop in insulin requirement after cesarean section in diabetic patients. Am J Obstet Gynecol 1974;120:905–908.
51. Sibai BM, Mabie BC, Harvey CJ, et al. Pulmonary edema in severe preeclampsia-eclampsia: analysis of thirty-seven consecutive cases. Am J Obstet Gynecol 1987;156:1174–1179.
52. Rosenn B, Miodovnik M, Tsang R. Common clinical manifestations of maternal diabetes in newborn infants: implications for the practicing pediatrician. Pediatr Annu 1996;25:215–222.
53. Hogan K, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988;67:1162.

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Emboli in Pregnancy

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Embolic phenomena, whether thrombotic, amniotic, or air emboli, are still one of the leading causes of maternal mortality in the developed and the majority of developing countries.[1–7] Embolic episodes can occur during pregnancy, vaginal delivery, cesarean section, or in puerperium. The most common variety is air embolism, followed by thromboembolism; amniotic fluid embolism is the rarest. Amniotic and air emboli are usually complications that occur in delivery. Thrombotic emboli can occur during pregnancy as well as delivery and occur with an equal incidence in each of the three trimesters of pregnancy. The incidence of thrombotic emboli increases four to five times in the puerperium. The pulmonary tree is the most common target organ for these emboli, but if a right-to-left shunt exists, any organ may be affected.

This chapter discusses the three types of emboli that may complicate pregnancy, their obstetric significance, and their anesthetic management.

Thromboembolic Disease

Thromboembolic conditions have been well documented since the early nineteenth century. Dark red patches in the lung or clots in branches of the pulmonary artery were described before Virchow's classic studies were published in 1858.[8] Estimation of the size of the problem during pregnancy has been clouded by difficulties in making the correct diagnosis.[9] There is also a considerable morbidity among the nonfatal cases such as postthrombotic venous insufficiency, recurrence of thrombosis, and to a lesser extent, pulmonary hypertension.

Incidence

There is a wide range in the reported incidence of deep venous thrombosis during pregnancy.[10] It has been reported as frequently as 0.018 per delivery[11] to 0.00052 per delivery.[12] Other recent reports indicate an incidence of deep venous thrombosis in 0.7 per 1000 pregnancies.[13,14] This variation is further complicated by the reported incidence for fatal pulmonary embolism. In the report on confidential enquiries in maternal death in England and Wales, pulmonary embolism was responsible for the deaths of 12 women per year before or immediately after delivery, or 9.4 per million pregnancies.[15] Even with this rare occurrence, it was second only to abortion as the leading cause of maternal death. However, pulmonary embolism and deep venous thrombosis are not easily diagnosed in nonfatal cases, particularly in pregnancy. It is therefore difficult to obtain accurate data for the incidence of nonfatal deep vein thrombosis and pulmonary embolus.

Risk factors include increased maternal age and parity, obesity, cesarean section, prolonged bedrest, surgical procedures during pregnancy, previous history of venous thrombosis, inherited and acquired thrombophilia, sickle cell disease, antiphospholipid antibodies, and blood type other than O.[16,17]

Etiology

The cause of thrombosis is best described in terms of Virchow's classic triad: vessel wall trauma, venous stasis, and alterations in the coagulation mechanism.[8,18] These factors may contribute to the increased risk of thromboembolism in the pregnant or postpartum patient.

Although vessel injury does not seem to be necessary to initiate thrombosis in the calf veins, it may contribute to the increased incidence of some forms of thrombosis, that is, increased risk of pelvic thrombophlebitis following cesarean section.[19]

Venous stasis is certainly a risk factor during pregnancy. Venous distensibility increases during the first trimester of pregnancy. Varicose veins, hormonal changes, anemia, toxemia, and the hypercoagulable state have also been implicated. Mechanical compression by the gravid uterus on the inferior vena cava causes venous stasis and is uniformly considered a major factor contributing to deep venous thrombosis. This mechanical obstruction is known to result in increased femoral venous pressure, beginning in the early part of the second trimester and continuing until term. Leg vein

obstruction was found by Ikard et al.,[20] using Doppler ultrasound, to be almost universal in the standing position in the third trimester and to be partly present in the lateral position as well. The most common sites of deep venous thrombosis are the venous sinuses within the soleus muscles and the valve sinuses in the left iliofemoral segment, which likewise are the most common sites of venous stasis. The left lower extremity is most often involved, with antepartum deep venous thrombosis secondary to probable compression of the left common iliac vein where it is crossed by the common iliac artery.[21]

Thrombophlebitis has been described in each trimester; it is more common in women who are bedridden for complications of pregnancy, such as threatened abortion, premature rupture of the membranes, and pregnancy-induced hypertension.

The physiology of normal pregnancy is also known to result in a number of significant alterations in coagulation and fibrinolytic mechanisms, which include increased concentrations of coagulation factors, a decrease in coagulation inhibitors, and reduced fibrinolytic capacity. There is also evidence that the concentration of soluble fibrin–fibrinogen complexes is increased. The increased factor VIII activity contributes to the stabilization of these complexes. The role played by platelets in the formation of the thrombus is somewhat equivocal; neither the platelet count nor platelet adhesiveness is increased during pregnancy. The decreased number of circulating platelets after delivery is probably related to normal thrombus formation at the placental site. Venous thrombi contain relatively few platelets, and platelets are not believed to be the instigators of the thrombotic process.

The effect of these physiologic changes is a state of hypercoagulability and increased thrombotic potential that is most marked in late pregnancy and the immediate puerperium. Thrombophilia accounts for approximately 50% of the cases of venous thromboembolism in pregnant and postpartum women. The term thrombophilia is applied to genetic conditions that increase the risk of thrombotic disease in general and during pregnancy in particular.[22] The hypercoagulable state of pregnancy presents special problems for the woman with the inherited or acquired form of this condition. The main causes identified for the inherited thrombophilias are deficiencies of antithrombin, protein C, protein S, activated protein C resistance, and mutant factor II (Table 24.1). Hyperhomocysteinemia is also a risk factor for venous and arterial thrombosis and may result from inherited enzyme defects, with the most common being a thrombolabile mutant of methylenetetrahydrofolate reductase (C677T MTHFR) that leads to hyperhomocysteinemia. These disorders underlie about 50% of the episodes of venous thromboembolism in pregnant and postpartum women but collectively are present in at least 15% of Western populations.[23] From 4% to 10% of these populations carry factor V Leiden, 2% carry the G20210A prothrombin gene mutation, and 10% have homozygosity for the C677T MTHFR mutation. Acquired thrombophilia occurs among patients with antiphospholipid syndrome and lupus anticoagulant and also among patients with essential thrombocythemia.[24,25]

Pathophysiology

The most common embolism is pulmonary thromboembolism, which produces complex alterations in pulmonary mechanics and circulatory function. These changes depend on the quantity and size of the embolus, the site of obstruction, and the presence of preexisting cardiopulmonary disease. A single small embolus may have no effect, whereas a large thrombus may break and shower the lungs with multiple emboli, producing life-threatening bilateral pulmonary dysfunction. With a unilateral pulmonary thromboembolus, the right lower lobe is the most frequently affected area. A large embolus may cause fatal obstruction of the pulmonary circulation. Pulmonary embolism in patients with cardiac disease is

Table 24.1. Factors predisposing to venous thromboembolism (VTE).

Increased hemostatic activity		Decreased venous flow
		Venous obstruction
		Limited venous pump activity
Increased activation	Decreased inhibition	High blood/plasma viscosity
Trauma	Antithrombin deficiency	Previous VTE
Surgery	Protein C deficiency	Other venous obstruction
Delivery and postpartum	Protein S deficiency	Vascular anomalies, e.g., atresia
Prevenous inflammation	Factor V Leiden	Limb paresis
Radioactive radiation	Prothrombin G20210A	Immobilization
Intravenous catheters	Elevated factor II, VII, or IX	Long-haul or air travel
Malignant disease	Lupus anticoagulant	Venous valve insufficiency
	Anticardiolipin antibody	Varicose veins
	Low fibrinolytic activity	Obesity
	Homocysteinemia	Pregnancy
	Nephrotic syndrome	Heart failure
	Inflammatory bowel disease	Dehydration
	Estrogen treatment	Myeloproliferative disease
		Increasing age

often regarded as synonymous with pulmonary infarction. However, this is not always the case. The ratio of infarct to emboli is about 1 in 10. Recurrent pulmonary emboli often result in pulmonary hypertension. Amniotic fluid embolism or fat embolism may present as adult respiratory distress syndrome. Very small emboli pass through to the periphery of the lung. If they do not obstruct a branch of the pulmonary artery, rapid lysis occurs, and there are no hemodynamic disturbances and no clinical symptoms. With large or multiple emboli, occlusion of the pulmonary artery affects the performance of the cardiac and respiratory systems, secondary to both mechanical alterations and reflex changes.

Because the pulmonary arteries receive the right ventricular output, an embolus in the main pulmonary artery or in its major branches can significantly lower left ventricular output. In patients with limited cardiac reserve, the reduction in coronary artery blood flow is poorly tolerated. The right ventricle is comparatively thin walled and becomes an early target for increased right ventricular pressures. Right coronary blood flow does not seem to decrease during embolization; it may increase secondary to local autoregulation. It may take a longer time to develop right ventricular failure, depending upon the preexisting cardiovascular status. With a massive pulmonary embolism of any type, cardiovascular collapse, hypotension, and refractory shock may occur.

Some of the reflex changes from microembolization result in bronchoconstriction and vasoconstriction, but the hemodynamic changes always seem to include an elevation of the right atrial pressure and a lowered cardiac output.[26] These abnormalities are directly related to the extent of embolic obstruction both in patients with previously normal cardiopulmonary systems and in those with prior cardiopulmonary disease.

Respiratory changes include the presence of hypoxemia from an increase in dead space ventilation. The mismatched ventilation/perfusion, bronchoalveolar constriction of terminal airways, and loss of surfactant lead to alveolar atelectasis and the development of regional pulmonary edema, which further contributes to the hypoxemia. Venoarterial shunting and the reduction in cardiac output will augment intrapulmonary shunting and also cause a fall in the Pa_{O_2}. Bronchoalveolar constriction has been attributed to released humoral factors, including serotonin or histamine, and decreased Pa_{CO_2}. The hypoxemia is not fully corrected by oxygen administration, indicating an intrapulmonary shunt.

Clinical and Laboratory Diagnosis

Clinical manifestations of pulmonary embolism are nonspecific, and the diagnosis is frequently missed even in patients with segmental or larger vessel occlusion. The presenting signs and symptoms include shortness of breath, chest pain (sometimes described as a dull substernal tightness), apprehension, altered sensorium, cough, hemoptysis, sweating, syncope, and tachycardia. A sudden gasping attempt of the patient to breathe during ventilation may be the first indication of an intraoperative pulmonary embolus. If the patients are grouped by severity, small emboli are associated with a higher incidence of syncope, whereas sudden massive emboli are associated with a higher incidence of pleural pain. The most common physical findings include tachypnea at a rate of 30 to 40 shallow breaths per minute, decreased breath sounds, rales, tachycardia, and pyrexia. Pain, tenderness, swelling, and warmth of the affected limb, including Homan's sign, are also highly significant. A chest X-ray may offer confirmatory evidence: diminished vascular markings, diaphragmatic elevation, and pleural effusion. Arterial blood gases (which may differ by as much as 15 mm Hg in the third trimester depending on whether the patient is sitting or supine) together with chest X-ray remain the important tests in the initial evaluation of pulmonary embolism. These tests are nonspecific, however, and some form of diagnostic imaging is required. Moser[25] stated that the main value of a chest X-ray is to rule out other causes of chest pain, such as pneumothorax, rib fracture, tumor, infection, or primary cardiac disease.

Ascending venography is the most accurate test for deep venous thrombi. In this technique, radiographic contrast dye is injected into a distal dorsal vein of the foot. During examination, the leg must be relaxed and nonweight-bearing, with the patient in approximately a 40° incline, which allows gradual filling of the leg veins and prevents layering of the dye. Diagnosis of a venous thrombus requires visualization of a well-defined filling defect in more than one radiographic view. Suggestive evidence includes abrupt termination, absence of opacification, or diversion of flow. False-positive studies can occur as a result of poor technique, poor choice of injection site, leg muscle contraction, or a pathologic condition such as external compression by a popliteal cyst, hematoma, local cellulitis and edema, or muscle rupture. Ascending venography is suboptimal for examining the deep femoral and pelvic veins because large nonobstructive thrombi can go undetected.[27]

There are well-known systemic side effects of radiologic contrast dye; however, up to 24% of patients experience muscle pain, leg swelling, tenderness, and erythema.[28] Lowering the concentration of the contrast medium reduces such complications by 70%.[29] Heparinized saline flushing after injection can prevent the uncommon occurrence of clot formation following venography.

Many symptoms mimic those of deep venous thrombosis; in particular, edema and evidence of stasis can occur in normal pregnancy. The benefit of a definitive diagnosis outweighs the side effects and possible complications of venography. Patients with negative studies can thus avoid the significant hazards of anticoagulation as well as the long-term stigma of a diagnosis of deep venous thrombosis.

Noninvasive tests such as Doppler ultrasound and impedance plethysmography are without risks or complications but are much less sensitive for thrombi below the knee. Changes in Doppler shift occur when normal venous blood flow varies

with respiration and with maneuvers such as the Valsalva, release of pressure over a distal vein, or squeezing of the muscles. A decrease in amplitude of these shifts can indicate partial venous obstruction, whereas complete occlusion gives no Doppler shift. Doppler ultrasound is most useful in the detection of popliteal, femoral, or iliac thromboses, and it has a sensitivity of 90%.[30] Thrombi that completely occlude proximal veins and those not large enough to obstruct blood flow can escape detection. Because of collateral venous channels, at least 50% of small calf thrombi are missed with Doppler ultrasound.[31] Results can vary with technique, experience, and patient positioning.

Impedance plethysmography uses changes in electrical resistance to measure changes in blood volume within a limb. With inflation of a thigh cuff, blood is retained in the leg. In the absence of venous obstruction, sudden deflation results in an immediate outflow of blood and a concomitant sudden increase in electrical resistance. A much slower change is associated with impaired outflow, which indirectly implies venous thrombosis. A sensitivity of 95% and specificity of 98% can be achieved with proximal vein thrombi.[32] As in Doppler ultrasound, detection of calf vein thrombi with impedance plethysmography is unreliable. In pregnancy, compression of the inferior vena cava by the gravid uterus can yield falsely positive results,[33] and confirmation by venography may be necessary.

Although infrequently used, thermography detects deep venous thrombosis by an increase in skin temperature. Infrared radiation emission is increased when blood flow is diverted to superficial collaterals or when inflammation is present. These changes are more likely to occur with extensive disease. False-negative results can occur with early or limited thrombosis.

Fibrinogen scanning with ^{125}I is contraindicated during pregnancy because unbound ^{125}I crosses the placental barrier and enters the fetal circulation. It can collect in the fetal thyroid, which becomes theoretically functional at 10 weeks gestation, and can produce thyroid damage. It is also contraindicated in lactating women because radioactivity has been detected in breast milk. Because ^{125}I has a half-life of 60.2 days,[34] temporary interruption of lactation is impractical. In nonlactating postpartum women, ^{125}I-labeled fibrinogen can be used to identify deep venous thrombosis. It has a longer half-life and gives a smaller radiation dose than did the previously used ^{131}I. After intravenous injection, ^{125}I-labeled fibrinogen is incorporated like normal fibrinogen into developing thrombi. Sequential scintillation scanning is performed from 4 h to 7 days later, but usually at 24, 48, and 72 h. With each scan, radioactivity is compared to background precordial values in search of a hot spot. For the lower thigh and calf, accuracy can be as high as 92%.[35] Higher background counts in the femoral artery, bladder, and the overlying muscle mass make detection of thrombi in the common femoral and pelvic veins difficult.

Radionuclide venography using ^{99m}Tc particles is of low risk to the fetus but requires a rapid-sequence gamma camera, which may not be available in many institutions. This technique is more than 90% accurate for deep venous thrombosis above the knee.

More accurate for the diagnosis of pulmonary embolus is a combined ventilation/perfusion scan. A mismatch between ventilation and perfusion defects is sufficiently diagnostic of pulmonary vascular occlusion to begin therapy. If the ventilation defects match those seen on the perfusion scan, pulmonary angiography may not be necessary for the absolute diagnosis. The ventilation/perfusion scan can be performed safely during pregnancy, although technetium should be used rather than iodine, and uterine shielding is necessary. Pulmonary angiography is usually avoided because of the danger of radiation exposure to the fetus.[36,37] Serious morbidity can occur in 2% to 4% of patients undergoing arteriography.[38]

Recent advances have led to the development of contrast enhanced spiral CT angiography (SCTA) and gadolinium-enhanced magnetic resonance angiography (MRA) of the pulmonary artery for diagnosing pulmonary embolism.[39,40] These new techniques have high sensitivity and specificity for clots in the central and segmental pulmonary arteries and have the additional advantages of being noninvasive, free from radiation (for magnetic resonance imaging although not from gadolinium), and providing images of the lung, pleura, and mediastinum. The main limitation of SCTA is its poor sensitivity in detecting emboli in the segmental vessels. In any case, the clinical significance of segmental emboli is uncertain, and pulmonary angiography has similarly been shown to be less accurate than SCTA and MRA in detecting such emboli.

Obstetric and Anesthetic Management

Treatment of pulmonary embolism is designed to support cardiopulmonary function and to prevent extension or recurrence of the pulmonary embolism by institution of systemic anticoagulant therapy.[41] Surgical intervention may be indicated in a very few selected cases. Oxygen therapy is essential; intubation is usually necessary. The levels of Pa_{O_2} should be maintained at 70 mm Hg or above to prevent fetal hypoxia. Morphine is sometimes necessary to relieve pain and anxiety. Fluid status must be monitored closely, and pulmonary edema, cardiac failure, or shock must be treated with the necessary drugs as indicated.

The cornerstone of therapy is anticoagulation.[42–44] After one thromboembolic event, there is a 12% risk of repeat thrombosis during the same pregnancy and a 5% to 10% risk of recurrent thromboembolism with subsequent pregnancies. The initial anticoagulation should always be induced with intravenous heparin because its effect is immediate.[45–50] Heparin is a large mucopolysaccharide molecule (molecular weight, approximately 20,000 daltons). It acts by combining with antithrombin III (heparin cofactor) to inhibit the formation of thrombin. The lack of thrombin prevents the conversion of fibrinogen to fibrin. Heparin also increases the level

of activated factor X inhibitor that again interferes with the production of thrombin from prothrombin. Heparin also inhibits the activation of factor IX (Christmas factor). Heparin prevents the formation of further thrombi but does not act to lyse clots already present. Heparin has a relatively short half-life of 1.5 h; for this reason, continuous intravenous administration is the preferred method for heparin therapy. A suggested protocol is shown in Box 24.1. Heparin is not absorbed from the gastrointestinal tract, and intramuscular injection is not advisable because of the risk of hematoma formation at the injection site. In fact, intramuscular injection of any drug should be avoided in a patient on heparin therapy.

Some groups have used low molecular weight heparins, which are fragments of conventional heparins produced by enzymatic or chemical breakdown, for treatment as well as for prophylaxis of thromboembolism in preganancy.[51,52] Low molecular weight heparin (e.g., enoxaparin 40 mg/day) has the advantage for the patient of once-a-day self-administration and may possibly be associated with fewer hemorrhagic complications.[53,54] This advantage has considerable implications for patient acceptability because pregnant women considered to be at high risk of recurrent thromboembolism are taught to inject themselves and may be given thromboprophylaxis for up to 10 months to cover pregnancy and the puerperium. Low molecular weight heparins have fewer hemorrhagic risks, which may encourage greater use of heparin for thromboprophylaxis if the risk of hemorrhagic complications is perceived to be minimized.[55,56]

Nelson-Piercy et al. found no cases of epidural hematoma or other complications related to the use of regional anesthesia in the presence of low molecular weight heparin.[57] However, epidural hematoma has been described in general surgical cases, especially when large doses were used. Hence, the parturients should be changed to regular heparin if they are on low molecular weight heparin. Other advantages include a lower risk of heparin-induced thrombocytopenia because low molecular weight heparins are less likely to activate resting platelets to release platelet factor 4 and also bind less well to platelet factor 4; their increased bioavailability (85%–90% compared to 10% for conventional heparin) and longer half-life (3–18 h) permit once-daily administration.

Box 24.1. Suggested protocol for continuous heparin therapy.

1. Baseline CBC, prothrombin time (PT), a partial thromboplastin time (PTT), and platelet count.
2. Loading dose of 5000 U heparin by intravenous bolus.
3. a. Heparin solution (concentration 100 U/mL; add 50,000 units of heparin to 500 mL normal saline).
   b. Start therapy at 1000 U/h. Alternatively, 5–20 U/kg/h may be used for initial dose.
   c. Adjust infusion rate to achieve a PTT two to three times the control. Check the PTT after any change in infusion rate and once or twice daily after dosage stabilized.
   d. Control flow of heparin solution with an electronic infusion pump.
4. Check CBC and urinalysis every other day to monitor for occult hemorrhage.

Source: Adapted from Bolan JC. Thromboembolic disease in pregnancy. Clin Obstet Gynecol 1983;26:913–922.

The greatest risk with unfractionated heparin therapy is hemorrhage, the risk of which has been noted to be between 4% and 33%.[58] In addition, heparin can result in allergic reactions, alopecia, osteoporosis, and thrombocytopenia. The etiology of the thrombocytopenia is unknown, but it may be related to platelet consumption as reported in the "white clot syndrome."[46,59] Opinions differ regarding the duration of anticoagulant therapy advisable following an acute episode of thromboembolic disease.[60–66] de Swiet[61] advocates continuing full anticoagulation until 6 weeks after delivery for all parturients who had either deep venous thrombosis or pulmonary embolus during pregnancy. Nelson-Piercy[62] would also continue anticoagulation for the woman with pulmonary embolus, as would Hirsh and Fuster[63] and others.[64]

Considerable controversy also exists as to which therapeutic agent or regimen is preferable for long-term therapy. The standard method in a nonpregnant patient is to initiate anticoagulation with heparin, then to convert gradually to oral anticoagulants.[65] The oral agent most commonly used is sodium warfarin, which acts as a competitive inhibitor of vitamin K in the liver. Warfarin is a small molecule (molecular weight, 1000 daltons) that crosses the placenta readily. In fact, the oral anticoagulants appear to affect the fetus more profoundly than they do the mother because of immature liver enzyme systems in the fetus. Adverse effects from the use of warfarin agents during the first trimester include significant teratogenic potential. Continued warfarin therapy in the late third trimester can cause fetal bleeding either before or after delivery. Other effects secondary to fetal hemorrhage have reportedly resulted from exposure to warfarin during the second and third trimesters. Bonnar et al.[53] reported an overall fetal mortality rate between 15% and 30% in women taking oral anticoagulants during their pregnancy. Because of these adverse effects, most investigators no longer recommend the use of warfarin at any point during pregnancy. Warfarin embryopathy results when Coumadin is administered in the first trimester in 15% to 25% of cases. The most consistent anomalies are degrees of nasal hypoplasia and epiphyseal stapling. Exposure in the second trimester results in a 3% or higher incidence of severe central nervous system anomalies.[67]

If the parturient is receiving heparin therapy at the time of labor and delivery, the situation is much less hazardous. First, the fetus is not affected by the heparin, so fetal hemorrhage is not a risk factor. Second, the half-life of heparin is short; if delivery is anticipated more than 4 to 6 h after the last heparin injection, there is no need to reverse the anticoagulant activity. The usual recommendation is simply to stop the heparin as soon as the patient goes into labor or to omit the heparin dose on the morning of induction or elective cesarean section. If an emergency delivery or cesarean section is needed while the heparin is still active, protamine, a heparin antago-

nist, may be given. Protamine forms a stable salt with heparin, with the result that both drugs lose their intrinsic anticoagulant activity. Each milligram of protamine neutralizes 100 U heparin. The calculated dose of protamine, up to 50 mg, should be slowly administered intravenously over a 3-min period. Protamine can also be used if the patient develops hemorrhagic complications from heparin therapy, but it must be used with care and caution, as protamine sulfate excess may cause anticoagulation. Needless to say, strict attention to circulatory homeostasis during surgery or delivery is essential if anticoagulation is to be resumed in the postpartum period.

Because of the failure of heparin to cross the placenta and its easy reversibility, a number of investigators advocate maintaining the patient on heparin therapy throughout the pregnancy.[68,69] Others use 150 to 250 U/kg every 12 h administered subcutaneously.[70] A continuous infusion pump has been used in an effort to increase patient compliance with subcutaneous heparin therapy. Although early reports are conflicting, it appears that infusion pump delivery of subcutaneous heparin helps maintain therapeutic levels of anticoagulation in the ambulatory or noncompliant patient.[71]

To manage a heparinized patient at onset of labor, one should reduce the dose of subcutaneous unfractionated heparin to 7500 U twice daily in anticipation of the contraction and to counter any bleeding risk. This reduction seems unnecessary in patients taking low molecular weight heparin in daily doses of enoxaparine 40 mg[72] or fragmin 5000 U. Providing the thrombin and activated partial thromoplastin times are not prolonged by more than 5 s, the patients do not bleed excessively, nor is epidural hematoma a problem.

Thrombolytic therapy must be considered in patients with a massive pulmonary embolus.[73,74] Both urokinase and streptokinase have been used in pregnancy. Urokinase is less antigenic and, in theory, should have fewer side effects.[75] Although an increase in the partial thromboplastin time (PTT) and fibrin degradation products can be used to follow thrombolytic therapy, the most sensitive measure is the thrombin time.[76] The thrombin time should be no greater than five times normal. Nonetheless, the risk of bleeding is always present.

Recombinant tissue plasminogen activator (rtPA) has a theoretical advantage over streptokinase and urokinase in that it does not induce systemic fibrinolysis. Instead, rtPA is active when bound to thrombin and is therefore clot specific.[77] Recombinant tissue plasminogen factor has been used successfully in pregnant women suffering massive pulmonary embolism.[78,79] In pregnancy, however, bleeding is the major side effect, usually from the genital tract and often severe; the overall incidence of bleeding as a result from thrombolysis is about 8%. Because of the risk of bleeding, thrombolysis should not be used routinely in pregnancy but reserved for those who are hemodynamically unstable, particularly with regard to systemic hypertension. It would not be appropriate to extrapolate directly from studies in nonpregnant patients[72] using echocardiographic variables as criteria from thrombolic treatment. Because of the risk of bleeding, thrombolytic treatment should not be used at the time of delivery unless it appears that the woman is likely to die.

The role of surgery in the treatment of thromboembolic disease during pregnancy is also limited. Procedures that have been used include femoral vein or vena cava interruption, and thrombectomy or embolectomy. Femoral vein interruption has been used since 1934, and recently the use of an internal saphenous graft to bypass a thromboembolic region has been reported. Interruption of the vena cava is used to prevent recurrent emboli rising in the lower extremities from reaching the lungs. A number of different procedures have been used for this purpose, including ligation, clipping, plication, and placement of a variety of filters or intraluminal grids,[80] but vena cava interruption is associated with a postoperative mortality between 1% and 10% with a significant risk of long-term morbidity secondary to venous obstruction.

Pulmonary embolectomy is a dangerous procedure but may be lifesaving in some parturients. The location and extent of the embolus must be confirmed with angiography before surgery; in fact, it has been stated this is the only indication for angiography during pregnancy.[81] Embolectomy should be reserved to one obvious situation, when massive pulmonary embolism occurs immediately after delivery when thrombolysis should not be used. Criteria for intervention, according to one investigator, include a systolic blood pressure less than 90 mm Hg, urine output less than 20 mL/h, and Pa_{O_2} less than 60 mm Hg after 1 h of nonoperative management. The mortality from embolectomy is high (about 80%), and a minimum success during pregnancy has been described.[82]

Other modalities of treatment include the use of inferior vena caval filters to prevent pulmonary embolization in women with extensive deep vein thrombosis.[83] Other situations in which their use may be indicated include the following: (1) patients in whom anticoagulation is contraindicated; and (2) those who develop serious complications from anticoagulations, such as heparin-induced thrombocytopenia or bleeding, or recurrent pulmonary embolism despite adequate anticoagulation.[84–86]

Thromboprophylaxis

The incidence and prognosis of thromboembolism in pregnancy can be improved or prevented by careful screening of patients for known risk factors such as family or personal history of thrombosis, and hereditary and acquired thrombophilia. The degree of risk is assessed in the antenatal period and allocated to one of two categories:

1. Low-risk patients who had a single episode of previous thromboembolism with no other factors
2. High-risk patients who have had multiple episodes or at least one previous episode or have documented thrombophilia or a family history of thromboembolism

One should treat low-risk parturients with aspirin 75 mg once daily from the time when pregnancy is confirmed to delivery,

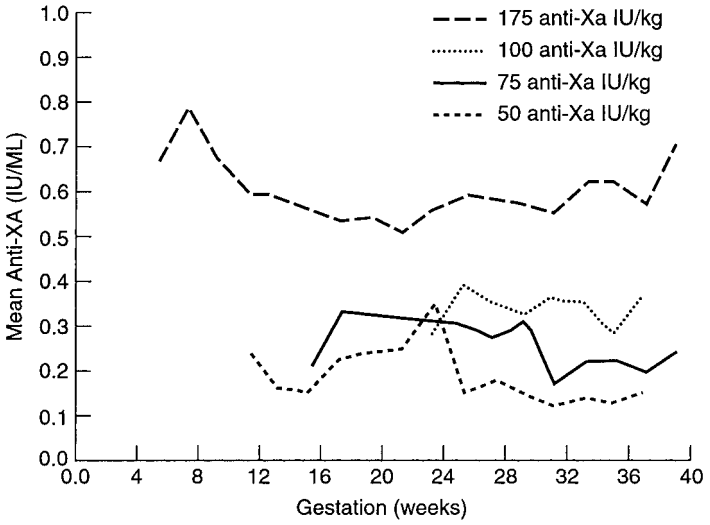

FIGURE 24.1. Peak (4 h) anti-Xa levels throughout pregnancy according to tinzaparin dose (low molecular weight heparin). (Adapted from a Symposium on Venous Thromboembolism held in Dublin, Ireland, on March 2, 2000, with permission. Norris LA. Thrombosis: A threat to pregnancy. Thrombus Embolus 2000;2:5–11.)

then switch to subcutaneous heparin, either unfractionated heparin 7500 U twice daily or low molecular weight heparin, such as enoxaparine, 40 mg once daily. After delivery, one should consider switching to warfarin. Treatment of high-risk parturients should be the same as low-risk patients except that high-risk patients should start taking subcutaneous heparin as soon as pregnancy is diagnosed[87–90] (Figure 24.1). The parturients receiving low molecular weight heparin should be changed to regular heparin at 36 weeks of gestation.

Anesthetic Management

Anesthetic management depends upon when the patient develops her thromboembolism: in the perinatal period, during labor and delivery or cesarean delivery, or postpartum. When thromboembolism has occurred before the time of delivery, the primary problem is providing anesthesia for an anticoagulated patient. When it occurs during labor and delivery the goal is to provide resuscitation, including ventilation and oxygenation (frequently necessitating endotracheal intubation), inotropic support, rapid delivery if indicated, and anticoagulation. The goal of anticoagulation is to prolong the partial thromplastin time (PTT) 1.5 to 2.5 times normal control. Many fear this significantly increases the risk of regional anesthesia and consider epidural and spinal anesthetics to be contraindicated in anticoagulated patients.[91] Epidural, subdural, and subarachnoid bleeding resulting in spinal cord compression and neurologic dysfunction has been reported with regional anesthetics in anticoagulated patients. Owens et al.[92] reported 33 cases of spinal hematoma following lumbar puncture or spinal anesthesia. Six of the cases were in association with the administration of a regional anesthetic, and 27 of the cases involved lumbar puncture for diagnostic or therapeutic purposes. Forty percent (13 patients) had received anticoagulant therapy (heparin, 6; Coumadin, 1; both, 6).

However, regional techniques have been administered to anticoagulated patients without complications. Odoom and Sih[93] reported the results of more than 1000 lumbar epidural blocks in 950 patients undergoing vascular surgery. All patients received oral anticoagulants preoperatively, and the majority also received intravenous heparin intraoperatively. Ten percent of patients experienced postoperative backache, but no side effects were observed that indicated epidural hemorrhage or hematoma, and no patient developed neurologic complications. They concluded that with adequate precautions epidural anesthesia can be safely used.

When thromboembolism occurs during labor and delivery in a parturient for whom epidural anesthesia has already been initiated, can the epidural be safely continued? Rao and El-Etr[94] reported their results on 3164 epidural and 847 subarachnoid catheterizations in which all patients received intravenous heparin 1 hour after the institution of the regional anesthetic. The activated clotting time (ACT) was maintained at twice the baseline. They reported no incidence of peridural hematoma. Matthews and Abrams[95] also reported similar findings on patients receiving intrathecal morphine before heparinization for cardiac surgery.

As with any anesthetic, the risks must be balanced by the benefits to the patient. Although neurologic symptoms associated with regional anesthetics may be rare, the effect of a spinal or epidural hematoma can be catastrophic. There is always the possibility of vascular trauma secondary to needle placement. Phillips et al.[96] reported a 3% incidence of trauma (bloody tap) with epidural and spinal procedures and noted a 6% incidence when multiple attempts were required. The incidence of epidural vein cannulation has been estimated to be about 1% during epidural procedures.[97] Even among patients receiving low-dose (minidose) heparin, there are no case reports or prospective studies that provide assurance that spinal and epidural techniques are safe.[98]

There are some advantages of regional anesthetics in patients with a high risk for thromboembolism. The high incidence of thromboembolism following surgery has been related to blood flow stasis during anesthesia and may therefore be modified by anesthetic technique. Several studies have compared the risk of thromboembolism following general

anesthesia with that following epidural or spinal anesthesia in patients undergoing procedures with a high risk of postoperative deep venous thrombosis.[98–102] In a randomized study by Modig et al.,[98] 67% of patients developed proximal deep venous thrombosis, and 33% of patients developed pulmonary embolism when total hip replacement was performed with general anesthesia. When epidural anesthesia (continued for 24 h postoperatively) was used, these incidences were reduced to 13% and 10%, respectively. Similarly, McKenzie et al.[100] reported a reduction in the incidence of deep venous thrombosis from 76% to 40% by the use of spinal anesthesia in patients undergoing repair of femoral neck fractures. A similar effect with epidural anesthesia has been reported in patients undergoing open prostatectomy.[101] The benefit of regional anesthesia for thoracic or general surgical procedures has not been conclusively demonstrated.[102] It is also not known if spinal-epidural anesthesia has a protective effect that is additive to other methods such as heparin or dextran prophylaxis.

Several mechanisms have been proposed by which spinal or epidural anesthesia may decrease the incidence of deep venous thrombosis. The major effect is probably reversal of blood flow stasis in the lower limbs due to a reduction in vascular resistance as a result of sympathetic block; there may also be a decrease in blood viscosity caused by hemodilution. In contrast to spinal and epidural anesthesia, general anesthesia definitely reduces lower limb blood flow. The second mechanism for the protective effect of spinal-epidural anesthesia is prevention of the hypercoagulable state that may follow general anesthesia.

The recommendations for regional anesthesia techniques in "minidose" anticoagulated parturients are shown in Box 24.2.[99] Further recommendations include letting the epidural block wear off at intervals to allow for neurologic assessment. Should anticoagulation be instituted following epidural placement, the catheter should be left in place until all systemic anticoagulation is reversed or normalized. After catheter removal, frequent neurologic examinations are necessary to detect early changes indicating hematoma formation. Hematoma diagnosis depends on physical examination, electromyogram, computer myography, and magnetic resonance imaging studies. Should an epidural hematoma occur, recovery is unlikely without surgical intervention.[103]

Box 24.2. Recommendations for regional anesthesia in "minidose" anticoagulated parturients.

1. Restrict regional techniques to mothers receiving heparin no more frequently than every 12 h.
2. Before the initiation of the block, the bleeding profile (ACT or aPTT) must be normal.
3. Utilize the left lateral position during block placement to reduce aortocaval compression and distention of the epidural veins.
4. Use a midline approach because lateral techniques are more likely to lacerate epidural vessels.
5. Abandon the procedure and proceed with an alternate anesthetic if a traumatic tap occurs.

Source: Adapted from Writer WDR. Hematologic disease: In: James FM, Wheeler AS, Dewan DM (eds) Obstetric Anesthesia: The Complicated Patient. Philadelphia: Davis, 1998: 267.

Considerations for general anesthesia include careful manipulation of the oral mucosa and gentle endotracheal intubation, avoidance of any type of nasal tube placement, avoidance of neck lines unless absolutely necessary, and close observation of intraoperative and postoperative bleeding.

Summary

Physiologic changes in clotting factors and venous flow during pregnancy increase the likelihood of deep venous thrombosis. Factors placing the pregnant woman at a higher risk include previous history of thromboembolic disease, surgery, or bedrest for any reason during the pregnancy. In the high-risk parturient (prior pregnancy-associated thromboembolic event that is well documented), prophylactic therapy with low-dose heparin is advised throughout pregnancy and continued for 2 weeks after delivery. Clinical diagnosis of thrombophlebitis or pulmonary embolus is unreliable and should be confirmed objectively before therapy is started. The preferred method of therapy is full anticoagulation followed by subcutaneous heparin for the remainder of the pregnancy and the puerperium, although there is considerable controversy regarding long-term therapy. Fibrinolytic agents have no place in pregnancy, and surgical therapy should be reserved for the severely ill patient. If surgery is indicated for a pulmonary embolus in a pregnant woman, anesthetic technique is based on understanding the pathophysiology of pulmonary hypertension. Anesthetic choice must include a careful consideration of the risks of peridural hematoma formation with regional anesthetics in anticoagulated patients.

Should a pulmonary thromboembolism occur during labor and delivery, severe maternal pulmonary and cardiovascular dysfunction may result, with concomitant fetal distress. Immediate treatment includes tracheal intubation, ventilation with 100% oxygen, establishment of large-bore intravenous lines, arterial line placement for both blood pressure monitoring and arterial blood gas analysis, rapid infusion of intravenous fluids to maintain a high venous pressure and augment venous return, administration of sodium bicarbonate to treat acidosis, and inotropic support. Massive embolism with shock, hypotension, and hypoxemia may require cardiopulmonary bypass[104] and pulmonary embolectomy.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare, unpredictable, and unpreventable obstetric catastrophe. It is initiated by entry of amniotic fluid into the maternal circulation and is characterized by the sudden onset of severe dyspnea, tachypnea, and cyanosis during labor, delivery, or the early puerperium.

Amniotic fluid embolism was first reported by Meyer[105] in 1926. It was reported again in an experiment on laboratory animals by Warden in 1927.[106] The importance of this condition and these early studies was not established until 1941, when Steiner and Lushbaugh[107] noted the clinical and pathologic findings of eight women who died suddenly during or just after labor. They performed experimental studies on laboratory animals that produced the same severe disturbances of cardiopulmonary function following the entry of amniotic fluid into maternal circulation. Their study was documented with pathologic findings of pulmonary embolism caused by amniotic fluid particulate matter. Schneider et al.[108] in 1968 showed that lethal qualities of human amniotic fluid infused intravenously into dogs was greatly magnified by the addition of meconium.

Locksmith[109] analyzed the clinical course of 46 cases of amniotic fluid embolism and investigated possible underlying pathophysiologic mechanisms of this condition. Hypotension, pulmonary edema, and adult respiratory distress syndrome (ARDS) were the most frequent maternal findings. Furthermore, there was evidence of fetal distress in all 30 cases in which amniotic fluid embolism occurred with a live fetus in utero at the time of the event.

Incidence

The incidence of amniotic fluid embolism (AFE) has been reported to be between 1 in 8,000 to 1 in 80,000 pregnancies; a more realistic figure is likely between these two extremes.[110–113] The mortality rate is very high. Although it is a rare occurrence, it still remains a leading cause of maternal and fetal death. Morgan[114] in 1979 reviewed 272 cases documented in the British medical literature and reported a mortality rate of 86%. From the same study, 25% of the deaths occurred within the first hour of the onset of symptoms, indicating that even with optimum critical care management a high mortality rate persists. Not all sudden deaths in late pregnancy are due to AFE.

Maternal survival following AFE is rare. Data from Clark[115] suggest that only 15% of patients survive AFE without consequences, which means that 85% of women either died or sustained permanent neurologic damage following documented AFE. Recent studies have suggested a lower incidence of neurologic deficit in survivors, and recurrent nonfatal cases are currently being reported. More recent reports suggest only 36% of these patients died in the first 2 h, which may reflect improved care of the critically ill pregnant woman.

Etiology

Predisposing factors for AFE include advanced maternal age, multiple pregnancies, macrosomic fetuses, short duration of labor, and intense contractions often augmented with an uterine muscle stimulant such as oxytocin.[116] Others suggest that fetal demise, meconium staining of amniotic fluid, amniotomy, pregnancy-induced hypertension (PIH), cesarean section delivery, abruptio placenta, placenta previa, ruptured uterus, amniocentesis, insertion of an intrauterine pressure catheter, pregnancy at term with the presence of an intrauterine device, and direct trauma to the uterus as in road traffic accidents[117] are also causative factors. A significant association of AFE with advanced maternal age has been documented.[114] AFE has also been reported with obstetric procedures in all trimesters of pregnancy as well as in the postpartum period[118] (Table 24.2).

Table 24.2. Obstetric procedures reported with amniotic fluid embolism.

First trimester suction abortion
Second trimester abortion by saline, prostaglandin, urea, or hysterotomy
Amniocentesis
Amnioinfusion
Normal vaginal delivery
Cesarean section

Amniotic fluid embolus syndrome has been reported in association with a myriad of conditions, including first and second trimester abortion with saline, prostaglandins, and urea, and hysterotomy. It has occurred during labor, at delivery, and just after delivery, and one case even developed 32 h postpartum. Most reported cases of AFE occur during labor; a pattern of vigorous labor or hypertonic uterine contractions or labor further stimulated by use of oxytocin often has been implicated in the pathogenesis.[116] Evidence for this association (use of an oxytocic) is primarily anecdotal and must be regarded with skepticism. In a review of this subject, Morgan[114] concluded: "In view of the very wide use of accelerated labour and the rarity of amniotic fluid embolism, it must be concluded that there is no direct association between the two." Placental abruption is present in up to 50% of cases and may contribute to the pattern of uterine hypertonus associated with AFE. In 40% of cases, fetal death is reported before the acute clinical presentation.

In an analysis of data collected in other studies,[119–122] the age range was from 18 to 43 years, with 22 patients 30 years old or older and 12 patients over 35 years of age. The parity of patients ranged from one to eight; the majority of patients were greater than three; however, there were four cases documented in primaparas. The gestational ages of the pregnancies in the patients who subsequently died ranged from 38 to 44 weeks. These data, of course, are excluding those patients who died of AFE secondary to saline or other fluids injected intraamniotically to induce abortion.

The characteristics of the labor pattern varied. However, it is of interest to note that four patients developed amniotic emboli without evidence of labor occurring. The majority of patients were in various stages of labor either spontaneously or augmented (in 22% labor had been induced, and in 11% labor had been augmented with an oxytocic agent). The augmentation or induction of labor was instituted for the usual reasons: ruptured membranes without consistent uterine con-

tractions or postmaturity, in one woman due to PIH and in one case who was electively induced. In 10%, labor was augmented because of poor progress. Of parturients who labored spontaneously, 44% had tumultuous and unusually short labors averaging less than 1 h in duration. No comparably short labors or precipitous deliveries were identified in the parturients who received oxytocin stimulation, nor were tetanic contractions reported.

The membranes were documented to be intact in three cases at the time the embolism or onset of symptoms occurred. In most cases studied, the membranes had ruptured either spontaneously or by amniotomy before the onset of symptoms. There is, however, documentation indicating that simultaneous rupture of membranes with onset of symptoms of AFE and meconium fluid was present in approximately 75% of these women.[107]

Concerning fetal factors, no clear pattern of fetal presentation, position, or engagement could be ascertained; most cases documented indicate a vertex presentation. There was generally a lack of documentation associating station of the presenting part with onset of symptoms. It could be assumed, because the onset of symptoms occurred just before or during delivery, that the fetal presenting part was engaged.

The size of the infants varied from 5 to 11 pounds, but the data particular to exact weight of all infants were not available. There is a high incidence of fetal deaths and intrapartum death of infants, and of those few infants born alive, a very high percentage die in the neonatal period. In one study of 21 infants for whom information was available, 9 died, 5 intrapartum. Ten live births were recorded in this particular study, but only 2 infants were documented to have survived. There is a disproportionately large number of stillbirths, and some researchers believe that the presence of a dead fetus reduces the strength of the membranes and greatly increases the quantity of particulate matter in the amniotic fluid.[123]

For AFE to occur, the fluid must enter into the maternal circulation. Currently, there are three recognized conditions that must exist for this to result: amniotomy, laceration of endocervical or uterine vessels, and a pressure gradient sufficient to force the fluid into the maternal circulation.

A tear or rent in the membranes, such as occurs with amniotomy, has been associated with proven embolism.[124] Various sites of entry of amniotic fluid into maternal circulation have been suggested. Laceration of the endocervical veins can occur during the normal process of cervical dilation and effacement, although more severe lacerations may occur with a very rapid and tumultuous labor or vigorous cervical manipulation associated with vaginal examination. Uterine vessels can be damaged through surgical procedures such as cesarean section or amniocentesis. Trauma is also responsible for causing damage of the uterine vessels. According to Landing,[125] an abnormal opening of the uterine vessels, either decidual or myometrial, that occurs with uterine rupture, placenta accreta, cesarean section, or retained placenta may provide a portal of entry for amniotic fluid. Abruptio placentae, whether marginal or complete, as well as any degree of placenta previa, could also provide a route of entry. If amniotic fluid finds an open maternal venous sinus, it could be pumped by a vigorous contraction through the disrupted amniotic membrane, with resultant embolization.

Intraamniotic injection of fluid (e.g., hypertonic saline, saline solution, or urea) causes a rise in intrauterine pressure that may be greater than that associated with normal labor. Frost[126] in 1967 reported a woman with a hydatidiform mole who died of trophoblastic embolization of the lungs following injection of intraamniotic hypertonic saline. A review of deaths following legal abortions in the United States from 1972 to 1978 revealed that 15 (12%) were due to AFE; all of these followed intraamniotic injections, and none followed uterine curettage.[127] The clinical symptoms in these women were the same as in those with embolism occurring at term. This study also revealed gestational age to be a significant factor. No deaths occurred below 12 weeks of gestation, but the mortality was 7.2 in 100,000 at 21 weeks or more, representing a risk factor 24 times greater after 21 weeks gestation.[127]

Due to the rarity of the condition combined with the fact that diagnosis is most often made during the postmortem examination, it is difficult to determine a definite cause and effect with this catastrophic obstetric event.

Pathophysiology

The two life-threatening consequences of AFE, cardiopulmonary collapse and disseminated intravascular coagulation, may occur in sequence or together. The physiology of AFE results in pulmonary hypertension with a sudden reduction of blood flow to the left heart, decreased left ventricular output, and subsequent peripheral vascular collapse. The sudden development of pulmonary hypertension precipitates acute cor pulmonale and congestive heart failure that thereby cause pulmonary edema. The derangement of the ventilation/perfusion ratio of the lungs produces hypoxemia and tissue hypoxia. Multiple emboli are usually necessary to cause this acute onset of symptoms.

The toxicity of intravenously infused fluid appears to vary remarkably. Although mechanical obstruction of the pulmonary vessels occurs from plugging by fetal squamae and hairs, the severity of the clinical symptoms does not necessarily correlate with the amount of debris.[128–133] Interestingly, multiple authors have described the appearance of squamous cells in the uterine and pulmonary vessels of asymptomatic pregnant women but also among patients who have had coronary bypass surgery.[133–136]

Meconium includes shed fetal squamous cells (squames), fetal hairs, vernix caseosa, and mucin. If the severe pulmonary vascular obstruction and cor pulmonale that develop are not immediately fatal, hemorrhage from disseminated intravascular coagulopathy is soon evident. The cause of disseminated intravascular coagulopathy is controversial. Evidence sug-

gests a potent thromboplastic action of amniotic fluid that causes disseminated deposition of fibrin clots and activation of the lysis system. These hemodynamic processes defibrinate the blood,[131] resulting in afibrinogenemia, coagulopathy, and subsequent hemorrhage.[132] The powerful thromboplastin effects of trophoblasts are well established; systemic release of trophoblastic material may play an even greater role in the coagulopathy of AFE than has been appreciated.

Kitzmiller and Lucas have shown that amniotic fluid collected during labor as compared to fluid collected before labor has greater toxicity when infused into rabbits.[132] The particular substance mediating this reaction is still unknown. Prostaglandins and leukotrienes produce many of the hemodynamic and hematologic effects present in patients with AFE and have been implicated by some researchers.[133] These metabolites of arachidonic acid are present in increased quantities during labor.[134]

Some researchers postulate that an acute anaphylactoid reaction may play a part in the development of the cardiovascular collapse.[135] For a true anaphylactic reaction to occur, sensitization is required, but evidence for this is inconclusive. Stefanini and Turpini[136] noted that an intravenous injection of 15 mL homologous amniotic fluid in dogs produced no effect, but 1 month later, further administration of a 15-mL aliquot, which had been kept frozen, resulted in hypotension, hypofibrinogenemia, and thrombocytopenia. It was therefore suggested that the animal had become sensitized to amniotic fluid and that this might occur in humans. It is possible that penetration of amniotic fluid into the systemic circulation during the antepartum period causes a state of sensitization in humans, and subsequent entry into the circulation during labor and delivery induces an acute anaphylactic reaction. However, the absence or rarity of pruritus, urticaria, laryngospasm, or wheezing in case reports indicates that this is not a mast cell-mediated mechanism.

The most significant pathologic findings at autopsy are limited to the lungs. The lungs show gross evidence of pulmonary edema (in 70% of cases).[137] Alveolar hemorrhage and pulmonary embolism of amniotic fluid materials are present; the presence of embolic particles is essential for diagnosis, but on histologic search, they may be missed because of their small size.[138] The particles are composed of amorphous debris, epithelial squames, and mucin (from meconium); they tend to lodge in small arteries, arterioles, and capillaries of the lungs.[131] Because uterine trauma is a significant factor in the pathogenesis, signs of uterine laceration or uterine rupture may be evident.[138] Acute right ventricular dilation is usually present. From recent experiences with hemodynamic monitoring during the resuscitation of parturients with AFE, Clark[115] described a biphasic response to amniotic fluid embolism. The early phase consists of transient (but perhaps intense) pulmonary vasospasm, which probably results from the release of vasoactive substances; this may account for the right heart dysfunction that is often fatal. This phase probably has a duration of less than 30 min.[139,140] Low cardiac output leads to increased ventilation/perfusion mismatch, hypoxemia, and hypotension. Of interest, right heart function and pulmonary artery pressures are usually close to "normal" by the time that hemodynamic monitoring is begun in humans during resuscitation from AFE.[141–144] A second phase of left ventricular failure and pulmonary edema often occurs in those women who survive the initial insult.[115,139]

A common link among these investigations is the suggestion that the lung injury patterns of AFE are multifactorial. Disseminated intravascular coagulation, commonly observed as late sequelae, may be attributed to antithrombin or thromboplastin-type effects of amniotic fluid or even complement activators.[145] The enormous number of compounds present in human amniotic fluid make all these proposals quite plausible.

Clinical and Laboratory Diagnosis

In a small percentage of parturients, the onset of symptoms has begun before labor was clinically evident. The majority of women develop symptoms during the latter part of the first stage of labor, and a lesser number become acute during birth. Two cases have been documented that were associated with delivery of the placenta, and only one case has been documented to occur as late as 32 h postpartum. In one series, 45% of cases were associated with placental abruption of varying degrees. Many writers believe this to be one of the primary catalysts in the development of an AFE.

In a review of obstetric cases who had developed amniotic embolism,[146] the most common complications that were already present or developed during delivery are listed in order of frequency of occurrence: severe amnionitis, moderate to severe PIH, cephalopelvic disproportion, and traumatic midforceps delivery.

Prodromal symptoms in AFE are sudden chills, shivering, sweating, anxiety, and coughing followed by signs of respiratory distress, convulsions, shock, and cardiovascular collapse. All women were conscious during the onset of symptoms. Respiratory difficulty, evidenced by cyanosis, tachypnea, and bronchospasm, frequently culminates in fulminate pulmonary edema. Hypoxemia explains the cyanosis and likely accounts for the restlessness, convulsions, and coma. Reflex tachypnea results from the decreased arterial oxygen saturation, and cardiovascular collapse, heralded by hypotension, tachycardia, and arrhythmia, may end in cardiac arrest.

Convulsions may be an early manifestation of involvement, combined with cerebral ischemia, and eventually may lead to coma and death. If the parturient survives this initial episode, bleeding occurs secondary to disseminated intravascular coagulopathy and uterine atony. In all cases studied, bleeding was never documented as one of the first indications. A definitive diagnosis is usually made at postmortem examination by demonstration of amniotic fluid material in the maternal circulation and the small arteries, arterioles, and capillaries of the pulmonary vessels. In the living woman, diagnosis can be made

by identification of lanugo or fetal hair and fetal squames in an aspirate of blood from the right heart. Fetal squames have been recovered in the maternal sputum in some cases. In the past, physicians thought that detection of fetal squamous cells in the pulmonary circulation was pathognomonic of AFE.[147,148] However, obstetricians have detected fetal squames in the pulmonary circulation of both antepartum and postpartum women with no clinical evidence of AFE. Recently, Kobayashi et al.[149] described the use of a monoclonal antibody for detection of an amniotic fluid-specific antigen in the maternal circulation of parturients with signs and symptoms of AFE.

Additional diagnostic tools for confirmation of AFE suspected by the classic clinical picture include (1) chest X-ray, which may show enlarged right atrium and ventricle and prominent proximal pulmonary artery (in massive pulmonary embolism) and pulmonary edema; (2) lung scan, which may demonstrate some areas of reduced radioactivity in the lung field; (3) central venous pressure (CVP), with an initial rise due to pulmonary hypertension and eventually a profound drop due to severe hemorrhage; and (4) measurement of blood coagulation factors. In pregnancy, blood coagulation factors are normally increased. However, with AFE, evidence of disseminated intravascular coagulopathy ensues with failure of blood to clot, decreased platelet count, decreased fibrinogen and afibrinogenemia, prolonged prothrombin time (PT) and aPTT, and presence of fibrin degradation products.

In the differential diagnosis of AEF, the following entities are to be considered[150]:

1. Thrombotic pulmonary embolism, which is usually caused by a thrombus originating from the lower extremities or pelvic veins, is usually associated with chest pain. However, it generally occurs later in the postpartum period and may occur with evidence of venous thrombosis.[151]
2. Air embolism, which may follow a ruptured uterus, blood transfusion under pressure, or manipulation of placenta previa, can occur during labor or cesarean section. It is associated with chest pain, but an important differentiating factor from AFE is the auscultation of a typical water-wheel murmur over the pericardium.[152]
3. Aspiration of gastric contents into the lungs causes cyanosis, tachycardia, hypotension, and pulmonary edema (similar to AFE). However, acid aspiration is usually seen in an unconscious patient with loss of the cough reflex,[151] or during induction or emergence from general anesthesia.
4. Eclamptic convulsions and coma in a pregnant patient may resemble this syndrome, but the state of shock in AFE, as well as the presence of hypertension, proteinuria, and edema[152] in the eclamptic patient, differentiate these two conditions.
5. Convulsions from toxic reaction to local anesthetic drugs may be confused with this syndrome. However, the close temporal relationship between the onset of symptoms and administration of the drug[153] is an important differentiating factor. Also, hypertension is usually present in the clinical picture of drug toxicity.
6. Acute left heart failure (seen most commonly in pregnant patients with rheumatic heart disease) may simulate an AFE, but the history of previous disease with ECG changes and other clinical symptoms, for example, cardiac murmur, helps in the diagnosis.
7. A cerebrovascular accident may be considered in the differential diagnosis, but it is distinguished from AFE by the absence of cyanosis, hypotension, and pulmonary edema. Also, examination of cerebrospinal fluid should help in the diagnosis.
8. Finally, hemorrhagic shock in an obstetric case, which is usually associated with ruptured uterus, uterine inversion, abruptio placentae, and placenta previa, may lead to the erroneous diagnosis of AFE. A careful history and physical examination, absence of cyanosis, and presence of low CVP with hemorrhagic shock should lead to the correct diagnosis.

A search from serologic evidence to confirm the diagnosis of AFE has been carried out by Oi et al.[128] These investigators used monoclonal antibodies assay of the mucin-like glycoprotein, sialyl Tn (STN). Significantly higher serum STN levels were found in patients with clinically apparent AFE than in controls. In an additional experiment, the same investigators used immunohistochemical staining with a monoclonal antibody, TKH-2 (directed to STN), to show the presence of STN-containing mucin in lung tissue obtained from parturients who died of apparent AFE.[154]

When correlated with clinical signs and symptoms, other diagnostic tools may be employed to support the presumptive diagnosis of AFE. Shechtman et al.[155] recently used transophageal echocardiography to demonstrate acute right ventricular failure, severe tricuspid regurgatation, and markly elevated right side heart pressure occurring during an acute episode.

Chest radiography is a helpful tool, but, similar to echocardiography, it is limited by a lack of specificity. The chest film frequently reveals only diffuse pulmonary edema.[156] However, cystic-appearing lung masses have been observed.[145] Kanayama et al.[157] have also reported maternal plasma levels of zinc coproporphyrn-1 as a characteristic component of meconium. Lunetta and Penttila[158] proposed an immunohistochemical analysis for identification of syncytiotrophoblastic cells and megakaryocytes to provide more precise data on the incidence and distribution in physiologic and pathologic conditions of AFE. Other investigations including electrocardiography and pulmonary arteriography have not been shown to be particularly helpful in the diagnosis of AFE. Today, there is no single clinical or laboratory finding that by itself can either prove or exclude AFE syndrome.

Obstetric and Anesthetic Management

To prevent AFE, trauma to the uterus must be avoided during maneuvers such as insertion of a pressure catheter or rupture of membranes. Incision of the placenta during cesarean

delivery should also be avoided if possible.[114] Because one of the most frequent predisposing factors is considered to be tumultuous labor, excessively strong and frequent uterine contractions should be controlled by administration of intravenous beta-adrenergic drugs or magnesium sulfate.[114] Also, oxytocic drugs, which might precipitate tetanic uterine contractions, should be used appropriately and judiciously.

In most cases, no therapy has proven effective. Whenever unexplained cyanosis and shock develops during labor, a diagnosis of AFE should be considered.[159] Assuming a diagnosis could be made before death, supportive measures should be focused at cardiopulmonary resuscitation, blood volume replacement, and treatment of coagulopathy.

Resuscitation should begin with endotracheal intubation and mechanical ventilation using inspired oxygen concentrations of 50% to 100% delivered by positive pressure and positive end-expiratory pressure (PEEP). With the use of PEEP, functional residual capacity may increase, and if oxygenation improves, as evidenced by pulse oximetry or arterial blood gases, a lowered PEEP setting may be tried. However, high PEEP may produce a decrease in cardiac output, due to the effect on the increased intrathoracic pressure, and subsequently decrease tissue perfusion. Improved oxygenation may reduce pulmonary capillary fragility and thereby decrease the severity of pulmonary edema. To date, there has been no documentation in the use of hyperbaric oxygen, and some authors think it would be worthwhile in treating the severe tissue hypoxia. To prevent or recognize further deterioration, careful monitoring is essential. Placement of an arterial line to monitor arterial blood gases and other pertinent chemistries, as well as a central venous or Swan–Ganz catheter to monitor cardiac status and state of hydration, are of enormous value.

The causes of pulmonary edema have been variably ascribed to vigorous fluid resuscitation, increased pulmonary capillary permeability, and cardiac decompensation due to hypoxia and tachycardia. The severity of pulmonary edema certainly plays an important role in the initial gas exchange abnormality and duration of the aberration.

Currently, there is no clear regimen of drug therapy to reverse the symptoms and complications of AFE. Drug therapy and other treatment have been supportive and aimed at improving the ventilation/perfusion ratio, maintaining adequate blood pressure, and treating disseminated intravascular coagulopathy.

The drug used to treat pulmonary complications such as bronchospasm and vasoconstriction of pulmonary arterioles is terbutaline, especially if the patient is undelivered with a live fetus. Isoproterenol also relieves pulmonary vasoconstriction and improves cardiac function, although it can cause peripheral vasodilation, which will exacerbate the hypotension. Dopamine may be preferable to isoproterenol, as it improves cardiac function and increases peripheral and renal perfusion unless given in too large a dose, which would decrease renal perfusion. Administration of aminophylline for its bronchodilation and cardiac stimulation effects is controversial, especially because of the tachycardia it produces.

Hydrocortisone in pharmacologic doses up to 2 g/24 h reduces pulmonary vasospasm and pulmonary edema and potentiates the cardiac response to catecholamines. In the event of heart failure, digitalization with a rapid-acting agent is recommended.[160] Diuretics can be used if pulmonary wedge pressure is elevated. Indomethacin has been effective in treating severe pulmonary hypertension in laboratory animals and should be considered. In a condition with such a high rate of mortality, there would be nothing to lose.

Hypotension should be treated first by left uterine displacement if the parturient is undelivered; this can be accomplished easily by insertion of a wedge under the right hip. The vasopressor of choice is ephedrine because it does not decrease uterine perfusion. However, if the fetus has expired or perhaps is already delivered, isoproterenol or dobutamine can be used. The fluid of choice should be lactated Ringer's because its pH is closest to that of blood; the rate of infusion depends on the CVP values or filling pressures if a Swan–Ganz catheter is in place. If acidosis is present, as evidenced by blood gas values, sodium bicarbonate should be administered.

Treatment of the bleeding diathesis requires blood replacement using fresh whole blood, when available, so that the clotting factors so badly needed are intact. Cryoprecipitate and platelet infusions are also required to help combat the coagulopathy. Heparin therapy is controversial; some patients have been documented to survive with its use, but there is documentation of survival without using heparin.

Uterine bleeding in a woman already delivered should be controlled by massage and use of intravenous oxytocin. If uterine bleeding is unresponsive to these methods, one should consider exploration for retained placenta or membranes or a search for cervical or uterine lacerations. Methylergonovine is also a strong uterine stimulant and can be given very slowly by intravenous push. The use of prostaglandins (Hemabat) to control hemorrhage is controversial and may cause bronchospasm or pulmonary hypertension. The use of aminocaproic acid and aprotinin is not well documented in treatment of amniotic embolus, but they can be used when rapid reversal of the lytic state is needed before delivery. Aprotinin (Trasylol) should be the drug of choice if the fetus is still viable, because it does not cross the placenta; aminocaproic acid does cross the placenta, and it is teratogenic as well.

When AFE occurs, the accompanying respiratory distress, cardiovascular collapse, and hemorrhagic tendency are contraindications to any regional techniques. If severe shock develops, general anesthetics must be administered with extreme caution. Because immediate delivery is indicated, emergency cesarean section is usually required. These women are young and typically healthy before the onset of AFE. Resuscitative measures must be aggressive. Alon et al.[161] reported the successful use of cardiopulmonary bypass and pulmonary artery thromboembolectomy for treatment of postpartum shock caused by AFE. Large-volume, rapid intravenous infusion devices may be invaluable during resuscitation. The choice of anesthetic agents will depend on the expectant mother's con-

dition, and aggressive cardiopulmonary resuscitation may be all that the anesthesiologist can provide. Anesthetic agents that produce myocardial depression must be avoided.

Summary

Amniotic fluid embolism, although fortunately rare, is one of the most catastrophic situations in obstetrics. The clinical events in this syndrome include cardiopulmonary collapse and disturbances of the clotting mechanism. Although maternal and fetal prognosis is grave, death need not be the inevitable outcome if early diagnosis is followed by prompt and aggressive management. Recently, there have been several published cases of patients who survived AFE.[104,161] Also, Clark has reported two cases of successful pregnancy outcomes in women who survived AFE in earlier pregnancies.[115]

Venous Air Embolism

Venous air embolism can occur in any surgical patient in whom the operative field is 5 cm or more above the right heart. In obstetrics, there are numerous situations in which venous air embolism can develop, including vaginal delivery, cesarean section, manual extraction of the placenta, and after the insertion, disconnection, or removal of central venous catheters. In addition, several reports have suggested that the injection of air, as part of the loss of resistance technique, during insertion of an epidural anesthetic may also precipitate air embolism.[162–164]

The phenomenon of air embolism has been recognized as a pathophysiologic condition at least since the time of the Napoleonic wars, when Baron Larre first observed that cavalry officers suffering saber wounds of the head and neck frequently died not as a result of blood loss but as a result of air bubbles in the right heart and pulmonary circulation.[165] Although the first diagnosed intraoperative air embolus occurred in 1818 during the excision of a supraclavicular tumor,[166] it was not until 1839 that the concept of the "dangerous region" for surgery was promulgated.[167] In those times, when surgery was performed on conscious patients in the sitting position, it was noted that air embolism could occur whenever the surgical site was "above the level of the venous pulsations." Typically, these events were described as an audible hissing sound in the surgical field, followed by the patient's crying out expressing a sense of impending doom.[168] Often, a "lapping" or "murmuring" sound could be heard in the patient's chest just as the vital signs deteriorated and the patient died.[162] By 1885, Senn[169] had described the pathophysiology of air entrainment from cranial veins in great detail. It has been suggested that 100 mL air can enter the circulation through a 14-gauge catheter in 1 s.[170]

During an episode of venous air embolism, the cardiovascular, pulmonary, and central nervous systems may all be affected, with severity ranging from no symptoms to immediate cardiovascular collapse and death. According to Matjasko et al.,[171] the incidence of severe morbidity or mortality from venous air embolism, even as a consequence of neurosurgery, is only about 1% when patients are treated adequately and in a timely fashion.

Incidence

Until perhaps the past 20 years, it was considered highly unlikely that venous air embolism could occur during a cesarean or vaginal delivery. Venous air embolism had been a well-recognized potential complication in abdominal, orthopedic, plastic, urologic, thoracic, and head and neck procedures, and had also been noted to develop in neurosurgical cases in the lateral, prone, and supine positions.[172] Legallois first proposed it as a potential danger in pregnancy in 1829,[173] and later in 1845 the first case of a fatal air embolism in association with pregnancy was reported. Since that time, similar reports from others have followed.[170–178]

The incidence of venous air embolism in pregnancy has not been accurately known,[176] in part because of the difficulty encountered in making the diagnosis. In fatal cases, the reports and autopsy evidence may not be of sufficient detail to allow the diagnosis to be made with certainty. In nonfatal cases, there are no clinical signs and symptoms that are specific only for venous air embolism. Previous attempts at determining the incidence were based on reports of maternal deaths. Klein et al. reported 2 deaths in 254,249 live births.[156] Barno and Freeman reported 6 deaths in 559,843 live births.[177] Similar data from England and Wales indicate 7 deaths in approximately 750,000 live births.[178] It might be concluded that the incidence of maternal mortality from venous air embolism is approximately 1 per 100,000 live births. In the most recently published statistics for maternal deaths in the United States,[179] 25 cases (about 1%) were thought to be caused by venous air embolism, although the circumstances of these deaths were not disclosed in detail.

But what is the true incidence of venous air embolic events? Studies by Malinow et al.[180] and Fong et al.[181] indicate that although maternal death from venous air embolism may be a rare event, the occurrence of venous air embolism during cesarean section may be more common than previously appreciated. Using a precordial Doppler signal change as evidence of an embolic event, Malinow noted positive Doppler change in 52% (46 of 89) of the women undergoing cesarean section.[180] Fong et al.[181] monitored patients with both precordial Doppler and precordial two-dimensional echocardiography and noted a 71% incidence of changes indicating venous air embolism during general anesthesia for cesarean section and a 39% incidence during epidural anesthesia for cesarean section. Only 1 of 129 parturients (0.78%) in Fong's study experienced chest pain, dyspnea, ventricular tachycardia, and hypotension. A 100% correlation between the two detection modes was also demonstrated. Lew et al.,[182] however, em-

ploying more sophisticated monitors such as expired nitrogen concentrations as well as precordial Doppler, detected an incidence of venous air embolism of 97% in patients undergoing cesarean delivery.

Etiology

For venous air embolism to occur, certain conditions must exist. As noted by early experimentation, there must be vascular access and a gradient between the incisional area and the right heart to promote the movement of air.[183] Gradients as small as 5 cm have been shown capable of entraining large amounts of air (up to 200 mL).[184] Nelson provides the following summary of the physiologic defects that singly or in combination are required for a venous air embolic event[176]:

1. Fixation of the traumatized vein, which prevents normal vascular retraction. The uterine veins, because of their position, course, and fixation, have been assessed to be the most vulnerable to air embolism.
2. Gravity, as venous drainage secondary to gravitational effects creates a high negative pressure. Such veins, when opened, will forcibly entrain air.
3. Suction effect of respiration and circulation: the negative intrathoracic pressures generated with inspiration augment venous return to the heart through increased venous negative pressure.
4. Introduction of gas under pressure into the body.

Certain features of pregnancy and parturition make venous air embolism possible[176]:

1. The availability of the uterine sinuses to the entrance of air. Air forced into the vagina during pregnancy, as may occur with douching, abortion, or insufflation, can result in venous air embolism. In addition, these sinuses can be exposed during low-segment cesarean sections, uterine rupture, and placenta previa.
2. Manipulation of the uterus in labor and the puerperium. Uterine manipulation, manual extraction of the placenta, and incision of the uterus may all result in the opening of uterine venous sinuses and possible entrance of air. Malinow et al.[180] noted positive Doppler changes occurring 74% at the time of hysterotomy, 2% with the delivery of the infant, 13% with the delivery of the placenta, and 11% during hysterotomy repair. Fong et al.[181] noted a 20% occurrence of venous air embolism by precordial two-dimensional echocardiography with uterine incision, 6% with delivery of the infant, 26% with placental removal, and 34% with uterine closure under epidural anesthesia. Under general anesthesia, there was a 10% incidence with uterine incision, 30% with placental removal, and 90% with uterine closure.[181]
3. Negative intraabdominal and uterine venous pressure secondary to positional change. The knee-chest and Trendelenburg positions can create significant negative intraabdominal pressure and increase the gravitational gradient draining the uterine venous sinuses.
4. Douching during pregnancy, although well recognized as a hazard, continues to be a popular practice. It creates a situation where air can be forcibly introduced into the vagina with subsequent risk of venous air embolism. Recently, a case of a venous air embolism following orogenital sex during pregnancy was also reported.[183]

In a review of 45 fatal cases and 2 nonfatal cases, the following etiologic factors were noted.[184] The average age was 32 years. Seven of the parturients (17%) were delivered by cesarean section with either no labor or incomplete labor. Among the laboring women, when venous air embolism developed, it occurred in 12 cases in the first stage, 12 in the second stage, and 14 in the third stage. The most frequently associated finding was placenta previa, which occurred in 24% of women. Manual extraction of the placenta was performed eight times.

Venous air embolism has also been reported in the puerperium. A review of 25 cases occurring within the first day after delivery revealed the following details.[176] The average age of the women was 32 years. The venous air embolism was delayed from 1 to 6 h after delivery; 6 patients collapsed following uterine irrigation, 3 with packing of the uterus, and 1 with manual exploration of the uterus. In 7 of the cases, no specific factor could be determined as the precipitating event. There have also been 10 reported cases occurring after 24 h. Five of these 10 cases occurred as a result of the knee-chest position, a therapy at that time for retroversion and subinvolution of the uterus in the puerperium. The feature common to most of the cases of air embolism related to abortion is the introduction into the uterus of a mixture of air and a solution under pressure, with the resultant separation of the membranes and entry of air into the dilated uterine sinuses.[185] Other factors believed to be associated with the embolic event include "violent jumping in bed" and uterine douching.

Pathophysiology

When air enters the venous system, pulmonary embolism, coronary embolism, and cerebral embolism may all occur, resulting in significant maternal morbidity or mortality. The severity of the air embolism depends upon the size of the subject, the patient's general condition, the rate of entrainment of the gas, the type of gas, and the total volume of gas introduced. Wolffe and Robertson[186] demonstrated that the severity of gas embolism is proportional to body weight and pulmonary artery size. The prolonged continuous entrainment of about 1 to 3 mL/kg/min for as long as 1 to 2 min could result in a fatal embolism.[184–187] In the presence of nitrous oxide during general anesthesia, a smaller volume of air could be rapidly doubled and produce a fatal embolism.

It has been proposed that when massive air embolism occurs, the introduced air is collected in the right ventricle, cre-

ating an "air trap" between the right ventricle and the pulmonary artery.[188] This air trap results in foaming of the blood, loss of valve function, and loss of blood propulsion into the pulmonary inflow tract. Central venous pressures increase, and pulmonary artery pressures decrease. Because pulmonary blood flow has ceased, oxygenation is impaired, and anoxia results. Left ventricular filling is severely diminished, and cardiac output drops to zero. Without immediate intervention, cardiac arrest is inevitable. Boyer and Curry have shown that bronchospasm also accompanies these circulatory changes.[189]

In nonfatal cases, small emboli do not produce the air trap but enter the pulmonary circulation and may result in ventilation/perfusion defects. "Paradoxical" embolism has also been described, with patency of the foramen ovale.[190] Once in the left side of the heart, air emboli to the coronary or cerebral circulation are possible.

Clinical and Laboratory Diagnosis

Signs of venous air embolism may include gasping (spontaneous) respiration, chest pain, increases in CVP, ECG changes, hypotension, changes in heart sounds, cyanosis, and cardiac arrest.[191] Venous air embolism may or may not be present with complaints of chest pain or dyspnea, perhaps depending on the venous air volume. Malinow found a significant relationship between unsolicited complaints of chest pain or dyspnea during cesarean section and the occurrence of positive Doppler changes. The chest pain was described as retrosternal, heavy, nonradiating, and lasting 5 to 10 min. In addition, 20% of the women with Doppler changes complained of dyspnea and eight women complained of both chest pain and dyspnea. Chest pain is not associated with the type of anesthesia given nor with surgical exteriorization of the uterus for hysterotomy repair.[180]

In some operative procedures, however, veins remain open, supported by surrounding tissues so that even if venous pressure is very low, the vein cannot collapse.[192] Once in the venous system, air travels rapidly though the heart to the lungs. Having arrived in the lungs, air in the pulmonary circulation obstructs precapillary arterioles, thereby decreasing pulmonary blood flow. The predominant pathophysiologic changes induced by the majority of episodes of air venous embolism occur in the pulmonary vasculature. The presence of nitrogen in the air bubble (because nitrogen is the principal component of air) plays a major role in the evolution of an air embolism. Because nitrogen is a relatively insoluble gas, the consequences of a nitrogen embolus are more severe than when soluble gases such as CO_2 and N_2O produce the embolism.[193] In a limited number of cases, some of them after cesarean section for placenta previa, symptoms of venous air embolism occurred some hours after air entered the circulation. This phenomenon is known as delayed air embolism.[194] The concomitant hypoxemia, ventilation/perfusion mismatch, and increased dead space ventilation will be reflected in decreased oxygen saturation by pulse oximetry and decreased end-tidal carbon dioxide as measured by capnography. These changes can be verified by blood gas analysis.

Because treatment depends on rapid diagnosis and evacuation of the air, an early sensitive method of detection is needed. A precordial ultrasonic Doppler monitor is capable of detecting as little as 0.1 mL intracardiac air.[195] It has been found that Doppler changes occur in about 50% of all patients undergoing elective cesarean delivery under regional anesthesia. Precordial Doppler monitoring is simple and noninvasive. Patients are monitored with ultrasonic Doppler in the horizontal position simultaneously with two-dimensional echocardiography. There was a 100% correlation between the simultaneous Doppler and echo-detection of emboli, which most likely meant that they saw echolucent air emboli and not echodense thromboemboli or amniotic fluid emboli. A study by Vartikar et al.[196] recommended oxygen saturation monitoring as a routine practice to detect venous air embolism in patients undergoing cesarean section. Venous air embolism was often associated with a decrease in oxygen saturation, and patients who demonstrated the greatest changes in saturation were most likely to show persistent Doppler changes and manifest clinical signs.

The role of precordial Doppler and two-dimensional echocardiography during routine cesarean section for early detection of venous air embolism is still undefined. It has been suggested that precordial Doppler monitoring should be considered for cases at risk for air embolism, such as profound hypovolemia, abruptio placentae, or placenta previa.[175]

Obstetric and Anesthetic Management

The best management of venous air embolism is prevention. Although there is no study clearly documenting a therapeutic technique for the prevention of this catastrophic event, the elimination of such etiologic factors as uterine irrigation, vaginal insufflation, knee-chest position, and Trendelenberg positions during the peripartum period has been suggested. It is further suggested that obstetricians avoid placing traction on the uterus and exteriorizing it, because exteriorization and particularly traction probably distend the venous sinuses, increasing the risk of venous air embolism.[184] Fong et al. reported that air embolism could occur at any time during a cesarean section, regardless of the anesthetic technique used: before and after uterine incision with the delivery of the infant, with the removal of the placenta, upon uterine closure, and after uterine repair. No significant difference in the formation of air emboli was found between manual extraction and passive separation of the placenta, nor was placenta previa associated with an increased risk.[181]

The foregoing findings and recommendations have since been challenged. It is claimed that modest head-up patient posture (5°–10°) did not influence the occurrence of venous air embolism, nor could the very high incidence of "definite" venous air embolism reported in the previous studies be substantiated.[197] The findings also differed regarding the distri-

bution of venous air embolism in relation to operative events: the highest incidence of venous air embolism occurred with delivery of the placenta rather than during hysterotomy or uterine closure. Perhaps these findings are to be expected, because shortly after placental separation, large uterine sinuses lie open and are vulnerable to the entry of air from a now-empty uterus.

When venous air embolism does occur, immediate treatment is needed, and the following recommendations have been made[191]:

1. Prevent further embolization by placing the patient in reverse Trendelenberg position with a 15° left-sided tilt. This position tends to prevent air from entering the right ventricle, therefore allowing easier aspiration from the superior vena cava via a central catheter. By lowering the uterus, the negative pressure gradient in the uterine venous sinuses due to gravity drainage is eliminated. The surgical field should also be flooded with normal saline to reduce and prevent further entrainment of air.
2. Discontinue nitrous oxide, and provide 100% oxygen.
3. Start immediate cardiopulmonary resuscitation should there be cardiovascular collapse.
4. Advance a catheter into the superior vena cava from a central vein or peripheral vein access, and aspirate as much air as possible.
5. If neurologic symptoms do develop, do a computed tomography scan immediately to search for possible paradoxical air embolism. If intraaxial air is present in the brain, hyperbaric oxygen therapy is necessary to reduce the bubble size. Despite the suggested findings that low-magnitude venous air embolism occurs frequently in cesarean sections, fortunately usually without major associated clinical signs and symptoms of cardiopulmonary compromise, there is little room for complacency. Although lethal venous air embolism is a rare event in obstetrics, even small air bubbles in the circulation threaten parturients with a patent foramen ovale, a surprisingly common abnormality.[187] This fact should be borne in mind during cesarean section, and the anesthetic management planned accordingly. In women with known right-to-left shunts, epidural anesthesia techniques involving the "loss of resistance with air" should be avoided.

Routine monitoring for venous air embolism using Doppler ultrasound would seem wise, especially in parturients likely to have a low CVP predisposing them to significant venous air embolism. In addition to the ultrasonic Doppler air bubble detector, the hallmark for venous air embolism detection involves end-tidal capnography as well as helpful verification by air aspiration from a previously placed central venous line. Women who are dehydrated after a prolonged labor may be especially at risk, as may parturients with compensated hemorrhagic shock. In these latter instances, the use of a multiorifice central venous catheter would seem advisable, because this device allows effective removal of air from the central circulation.[198,199] It is unclear whether venous air embolism is responsible for those electrocardiographic changes (e.g., ST-segment depression) seen in 25% to 50% of all women undergoing cesarean delivery.[200] The clinical significance of these electrocardiographic changes is also unclear.

When the venous air embolism occurs, it is most likely that the anesthetic will have already been chosen and administered. There are no studies that provide conclusive evidence that there is any particular anesthetic technique that should be either avoided or advocated. Epidural and spinal anesthesia without adequate volume preloading of the circulation could, in theory, predispose the parturient to venous air embolism by lowering CVP and increasing the right atrial to uterine "negative" venous pressure gradient. Parturients appear to be at greater risk of clinically significant venous air embolism under general anesthesia,[181] and the reduced risk with regional anesthesia could be attributed to generous volume loading before induction of epidural or spinal anesthesia. In patients under general anesthesia receiving nitrous oxide, small insignificant nondetected air emboli could expand into larger, detectable, clinically significant emboli[201] because of the solubility characteristics of N_2O. A recent report described treating a venous air embolism that had occurred during a cesarean section with hyperbaric oxygen.[202]

Further investigation is needed to determine whether nitrous oxide administration with general anesthetics increases the risk of venous air embolism during cesarean section.

Summary

The authors believe that the problem of venous air embolism during cesarean section should be taken at least as seriously as that of pulmonary acid aspiration and failed intubation. Although there is evidence that venous air embolism is a common occurrence during cesarean section, maternal morbidity and mortality are rare. Further research efforts are indicated to define more clearly those mothers at particular risk of serious venous air embolism. The contributions of different surgical techniques, intraoperative positioning, and anesthetic techniques to the incidence of venous air embolism also require elucidation.

We do not recommend the routine use of precordial Doppler monitoring during cesarean section. However, high-risk patients (those who are hypovolemic, or those with known intracardiac shunts) may benefit from the use of precordial Doppler monitoring. A high index of suspicion should accompany any complaints of chest pain or dyspnea, decreased Sao_2, hypotension, or arrhythmias. Should a parturient exhibit symptoms of venous air embolism, immediate intervention with possible central line placement and aspiration of the embolized air is required to prevent significant maternal morbidity or mortality. Early recognition of these signs and symptoms associated with venous air embolism should prompt the appropriate response.

References

1. Greer IA. Epidemiology, risk factors and prophylaxis of venous thromboembolism in obstetrics and gynaecology. Baillieres Clin Obstet Gynaecol 1997;11:403–430.
2. Confidential Enquiries into Maternal Deaths in the U.K., 1988–1990. Department of Health. London. Her Majesty's Stationery Office, 1994:28–60.
3. Rosendaal FR. Thrombosis in the young:epidemiology and risk factors. A focus on venous thrombosis. Thromb Haemostasis 1997;78:1–6.
4. Franks AL, Atrash HK, Lawson HW, et al. Obstetrical pulmonary embolism mortality: United States 1970–1985. Am J Public Health 1990; 80:720–722.
5. Gunintini C, Diricco G, Morrini C, et al. Epidemiology of deep vein thrombosis. Chest 1995;107:3–9.
6. Atrash H, Rowley D, Hogue C. Maternal and perinatal mortality. Curr Opin Obstet Gynecol 1992;4:61–71.
7. Rosendaal FR. Risk factors for thromboembolism - prevalence, risk and interaction. Semin Haematol 1997;34:171–187.
8. Sabiston DC. Pathophysiology, diagnosis and management of pulmonary embolism. Am J Surg 1979;138:384–391.
9. Laros R. Thromboembolism in pregnancy. ACOG Educ Bull 1997: 234.
10. Ng JP. Thrombosis in pregnancy. Lancet 1999;354:162–163.
11. Tan J, de Swiet M. Thromboembolism and thrombophilia in pregnancy and puerperium. In: Progress in Obstetrics and Gynaecology, vol. 13, Edinburgh: Churchill Livingstone, 1998:73–86.
12. Simpson EL, Lawrenson RA, Nightingale AL, et al. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. Br J Obstet Gynaecol 2001;108:56–60.
13. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med 2000;160:11–25; 3415–3420.
14. Sellman JS, Holman RI. Thromboembolism during pregnancy. Risks, challenges, and recommendations. Postgrad Med 2000;108:71–72.
15. Department of Health, Welsh Office, Scottish Home and Health Department, and Department of Social Services, Northern Ireland (1994): Confidential Enquiries into Maternal Deaths in the United Kingdom 1988–1989. London: HMSO, 1994.
16. Bertina RM. Introduction: hypercoagulable states. Semin Haematol 1997;34:167–170.
17. Walker ID. Thrombophilia in pregnancy. J Clin Pathol 2000;53:573–580.
18. Hiremath VS, Gaffney G. Audit of thromboprophylaxis following caeserean section. Ir Med J 2000;93:234–236.
19. Report of the RCOG Working Party on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics. London: Chamelson, 1995.
20. Ikard RW, Veland K, Folse R. Lower limb venous dynamics in pregnant women. Surg Gynecol Obstet 1979;132:483–488.
21. Sellman JS, Holman RL. Thromboembolism during pregnancy. Risks, challenges, and recommendations. Postgrad Med 2000;108:71–72, 77–78, 81–84.
22. Tanoue LT. Pulmonary problems in pregnancy. Clin Pulmon Med 1998;5:83–92.
23. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995;346:1133–1134.
24. Markisz JA. Radiologic and nuclear medicine diagnosis. In: Goldhaber SZ (ed): Pulmonary Embolism and Deep Venous Thrombosis. Philadelphia: Saunders, 1999:41.
25. Moser KM. Diagnosis and management of pulmonary embolism. Hosp Pract 1980;15:57–68.
26. Ginsberg JS, Hirsh J, Raibow AJ, et al. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. Thromb Haemostasis 1992;61:189.
27. Burns MM. Emerging concepts in the diagnosis and management of venous thromboembolism during pregnancy. J Thromb Thrombolysis 2000;10:59–68.
28. Toglia M, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996;335:108–114.
29. Kakkar V. The diagnosis of deep vein thrombosis using the ^{125}I fibrinogen test. Arch Surg 1972;104:152–159.
30. Spritzer CE, Evans AC, Kay HH. Magnetic resonance imaging of deep vein thrombosis in pregnant women with lower extremity thrombus. Obstet Gynecol 1995;85:603–607.
31. Cross JJ, Kemp PM, Flower CD. Diagnostic imaging in pulmonary embolic disease. Br J Hosp Med 1997;58:93–96.
32. Bedford R. Perioperative air embolism. Semin Anesth 1987:163–170.
33. Cranley JJ, Canos AJ, Sull WJ. The diagnosis of deep venous thrombosis: fallibility of clinical symptoms and signs. Arch Surg 1976;111: 34–43.
34. Johnston KW, Kakkar VV. Plethysmographic diagnosis of deep vein thrombosis. Surg Gynecol Obstet 1974;139:41–44.
35. Sandler DA, Martin JF, Duncan JS, et al. Diagnosis of deep venous thrombosis comparison of clinical evaluation, ultrasound plethysmography and venoscan with X-ray venogram. Lancet 1984;2:716–719.
36. Ginsberg JS, Hirsh J, Rainbow JA, et al. Risks to the foetus of radiological procedures used in the diagnosis of maternal venous thromboembolic disease. Thromb Haemostasis 1992;61:189.
37. Burns MM. Emerging concepts in the diagnosis and management of venous thromboembolism during pregnancy. J Thromb Thrombolysis 2000;10:59–68.
38. Meaney JFM, Weg JG,Chenvert Tl, et al. Diagnosis of pulmonary embolism with magnetic angiography. N Engl J Med 1997;336:1422–1427.
39. Thomson AJ, Greer IA. Non-haemorrhagic obstetric shock. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:10–41.
40. Gherman RB, Goodwin TM, Lelung B, et al. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999;94:730–734.
41. Greer IA, deSwiet M. Thrombosis prophylaxis in obstetrics and gynaecology. Br J Obstet Gynaecol 1993;100:37–40.
42. Nelson-Piercy C. Low molecular weight heparin for obstetric thromboprophylaxis. Br J Obstet Gynaecol 1994;101:6–8.
43. Sturridge F, deSwiet M, Letsky E. The use of low molecular weight heparin for thromboprophylaxis in pregnancy. Br J Obstet Gynaecol 1994;101:69–71.
44. Rey E, Rivard GE. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. Int J Gynaecol Obstet 2000; 71:19–24.
45. Salzman EW, Deykin K, Shapiro RM, et al. Management of heparin therapy—a controlled prospective trial. N Engl J Med 1975;292:1046–1050.
46. Eddleman WL, Barrett RL, Gladney JD, et al. Heparin-induced white clot syndrome. J LA State Med Soc 1989;141:20–23.
47. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 2: Oral anticoagulants. Circulation 1994;89:1469–1480.
48. Bolan JC. Thromboembolic disease in pregnancy. Am J Obstet Gynecol 1983;26:913–922.
49. LoSasso AM. Pulmonary embolism. In: Stoelting RK, Dierdorf SF (eds) Anesthesia and Co-existing Disease. New York: Churchill Livingstone, 1983:165.
50. Floyd RC, Gookin KS, Hess LW, et al. Administration of heparin by subcutaneous infusion with a programmable pump. Am J Obstet Gynecol 1991;165:93–101.
51. Ray E, Rivard GE. Prophylaxis and treatment of thromboembolic disease during pregnancy with dalteparin. Int J Gynaecol Obstet 2000; 71:19–24.
52. Lowe GD. Treatment of venous thrombo-embolism. Baillieres Clin Obstet Gynaecol 1997;11:511–521.
53. Bonnar J, Norris LA, Greene R. Low molecular weight heparin for thromboprophylaxis during caesarean section. Thromb Res 1999;96: 317–322.

54. Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. Anesthesiology 1981;55:618–620.
55. Powrie R, Star JA, Rosene-Montella K. Deep venous thrombosis and pulmonary embolism in pregnancy. Med Health R I 1998;81:141–143.
56. Phillips OC, Ebner H, Nelson AT, et al. Neurologic complications following spinal anesthesia with lidocaine. Anesthesiology 1969;30:284–288.
57. Nelson-Piercy C, Letsky EA, de Swiet M. Low molecular weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997; 176(5):1062–1068.
58. Lensing AW, Prandoni P, Prins MH, et al. Deep venous thrombosis. Lancet 1999;353:479–485.
59. Koppel C, Barkow D, Riess H. Severe white-clot syndrome after unfractionated heparin. Intensive Care Med 1991;17:185.
60. McKenzie PJ, Wishart HY, Gray I, et al. Effects of anaesthetic technique on deep vein thrombosis: a comparison of subarachnoid and general anaesthesia. Br J Anaesth 1985;57:853–857.
61. de Swiet M. Management of pulmonary embolus in pregnancy. Eur Heart J 1999;19:1378–1385.
62. Nelson-Piercy C. Obstetric thromboprophylaxis. Br J Hosp Med 1996; 55:404–408.
63. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 2: Oral anticoagulants. Circulation 1994;89:1469–1480.
64. Bick RL, Haas SK. International consensus recommendations. Summary statement and additional suggested guidelines. European Consensus Conference, November 1991. American College of Chest Physicians consensus statement of 1995. International Consensus Statement,1997. Med Clin N Am 1998;82:613–633.
65. Letsky EA. Peripartum prophylaxis of thrombo-embolism. Baillieres Clin Obstet Gynaecol 1997;11:523–543.
66. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119:176–193.
67. Kearon C. Initial treatment of venous thromboembolism. Thromb Haemostasis 1999;82:887–891.
68. Heilmann L, Schneider DM, von Tempelhoff GF. Antithrombotic therapy in high-risk pregnancy. Hematol Oncol Clin N Am 2000;145:1133–1150.
69. Ellison J. Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. Br J Obstet Gynaecol 2000;107:1116–1121.
70. Sellman JS, Holman RL. Thromboembolism during pregnancy. Risks, challenges, and recommendations. Postgrad Med 2000;108:71–72, 77–78, 81–84.
71. Shefras J, Farqharson RG. Bone density studies in pregnant women receiving heparin. Eur J Obstet Gynaecol Reprod Biol 1996;65:171–174.
72. Hass S. Low molecular weight heparins in the prevention of venous thromboembolism in nonsurgical patients. Semin Thromb Hemost 1999; 25:101–105.
73. Tan J, de Swiet M. Thromboembolism and thrombophilia in pregnancy and the puerperium. Prog Obstet Gynaecol 1998:81–82.
74. Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. Thromb Haemostasis 1993;70:238–240.
75. Bounameaux H, Vermylen J, Collen D. Thrombolytic treatment with recombinant tissue-type plasminogen activator in a patient with massive pulmonary embolism. Ann Intern Med 1985;5:103–164.
76. Baudo F, Caimi TM, Redaelli R, et al. Emergency treatment with recombinant tissue plasminogen activator of pulmonary embolism in a pregnant woman with antithrombin III deficiency. Am J Obstet Gynecol 1990;163:1274–1275.
77. Aya AG, Saissi G, Eledjam JJ. In situ pulmonary thrombolysis using recombinant tissue plasminogen activator after cesarean delivery. Anesthesiology 1999;91:578–579.
78. Fagher B, Ahlgren M, Astedt B. Acute massive pulmonary embolism treated with streptokinase during labor and the early puerperium. Acta Obstet Gynaecol Scand 1990;69:659–661.
79. Brocklehurst P. Future research needs for venous thrombo-embolic disease in obstetrics and gynaecology. Baillieres Clin Obstet Gynaecol 1997;11:601–610.
80. Barnes AB, Kanarek DJ, Greenfield AJ, et al. Vena cava filter replacement during pregnancy. Am J Obstet Gynecol 1981;140:707–708.
81. Ginsberg JS, Hirsh J, Rainbow JA, et al. Risks to the foetus of radiological procedures used in the diagnosis of maternal venous thromboembolic disease. Thromb Haemostasis 1992;61:189.
82. Wilson JT, Rogers FB, Wald SL, et al. Prophylactic vena cava filter insertion in patients with traumatic spinal cord injury: preliminary results. Neurosurgery 1994;2:234–239.
83. Narayan H, Cullimore J, Krarup K, et al. Experience with the cardial inferior vena cava filter as prophylaxis against pulmonary embolism in pregnant women with extensive deep venous thrombosis. Br J Obstet Gynaecol 1992;99:637–640.
84. Wojcik R, Cipalle MD, Fearen I, et al. Long-term follow-up of trauma patients with caval filter. J Trauma 2000;49:839–843.
85. Patton JH Jr, Fabian TC, Croce MA, et al. Prophylactic Greenfield filters: acute complications and long-term follow-up. J Trauma 1999;41: 231–236; discussion 41:236–237.
86. Miersh G, Munster W, Schopke W, et al. Gunther vena cava filter. Results of long-term follow-up. Vasa Suppl 1991;32:279–284.
87. Harries SR, Wells IP, Roobottom CA. Long-term follow-up of the antheor inferior vena cava filter. Clin Radiol 1998;53:350–352.
88. Greer IA. The challenge of thrombophilia in maternal-fetal medicine [editorial]. N Engl J Med 2000;342:424–425.
89. de Swiet M. Management of pulmonary embolus in pregnancy. Eur Heart J 1999;20:1378–1385.
90. Norris LA. Thrombosis: a threat to pregnancy. Thrombus Embolus 2000;2:5–11.
91. Alfrey DD, Benumof JL. Pulmonary diseases. In: Katz J, Beumof J, Kadis LB (eds) Anesthesia and Uncommon Diseases. Philadelphia: Saunders, 1981:227.
92. Owens EL, Kasten GW, Hessel EA. Spinal subarachnoid hematoma after lumbar puncture and heparinization: a case report, review of the literature, and discussion of anesthetic implications. Anesth Analg 1986; 65:1201–1207.
93. Odoom JA, Sih IL: Epidural analgesia and anticoagulantion therapy: experience with one thousand cases of continuous epidurals. Anaesthesia 1983;38:254–259.
94. Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. Anesthesiology 1981;55:618–620.
95. Matthews ET, Abrams LD. Intrathecal morphine in open heart surgery. Lancet 1980;2:543.
96. Phillips OC, Ebner H, Nelson AT, Black MH. Neurologic complications following spinal anesthesia with lidocaine. Anesthesiology 1969; 30:284.
97. Bromage PR. Epidural Anesthesia. Philadelphia: Saunders, 1978:229.
98. Modig J, Burg T, Karlstrom G, et al. Thromboembolism after total hip replacement: role of epidural and general anesthesia. Anesth Analg 1983;62:174–180.
99. Writer WDR. Hematologic disease. In: James FM, Wheeler AS, Dewan DM (eds) Obstetric Anesthesia: The Complicated Patient. Philadelphia: Davis, 1988:267.
100. McKenzie PJ, Wishart HY, Gray I, et al. Effects of anaesthetic technique on deep vein thrombosis: a comparison of subarachnoid and general anaesthesia. Br J Anaesth 1985;57:853–857.
101. Hendalin H, Mattila MAK, Poikolainen E. The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy. Acta Chir Scand 1981;147:425–429.
102. Mellbring G, Dahlgren S, Reiz S, et al. Thromboembolic complications after major abdominal surgery: effect of thoracic epidural analgesia. Acta Chir Scand 1983;149:263–268.

103. Janis KM. Epidural hematoma following postoperative epidural analgesia: a case report. Anesth Analg 1972;51:689–692.
104. Esposito RA, Grossi EA, Coppia G, et al. Successful treatment of postpartum shock caused by amniotic fluid embolism with cardiopulmonary bypass and pulmonary artery thromboembolectomy. Am J Obstet Gynecol 1990;163:572–574.
105. Meyer JR. Embolia pulmonary amnio-caseosa. Brazil Med 1926;2:301.
106. Warden MR. Amniotic fluid as possible factor in etiology of eclampsia. Am J Obstet Gynecol 1927;14:292.
107. Steiner PE, Lushbaugh CC. Maternal pulmonary embolism by fluid as a cause of obstetric shock and expected death in obstetrics. JAMA 1941;117:1245.
108. Schneider CC, Henry MM, Chaplick MJ. Meconium embolism in vivo. Am J Obstet Gynecol 1968;101:909–914.
109. Locksmith GJ. Amniotic fluid embolism. Obstet Gynecol Clin N Am 1999;26:435–444.
110. Bannister M. Amniotic fluid embolism. Can J Anaesth 2000;47:381.
111. Fletcher SJ, Parr MJ. Amniotic fluid embolism: a case report and review. Resuscitation 2000;43:141–146.
112. Gilbert WM, Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 1999;93:973–977.
113. Gogola J, Hankins GD. Amniotic fluid embolism in progress: a management dilemma! Am J Perinatol 1998;15:491–493.
114. Morgan M. Amniotic fluid embolism. Anaesthesia 1979;34:33–36.
115. Clark SL. New concepts of amniotic fluid embolism: a review. Obstet Gynecol Surv 1990;45:360–368.
116. Courtney LD. Amniotic fluid embolism. Obstet Gynecol Surv 1974;29: 169–177.
117. Judith A, Kuriansky J, Engelberg I, et al. Amniotic fluid embolism following blunt abdominal trauma in pregnancy. Injury 1998;29:475–477.
118. Portis R, Jacobs MA, Skerman JH, et al. HELLP syndrome: pathophysiology and anesthetic considerations. AANA J 1997;65:37–47.
119. Clark SL, Hankins GD, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995;172:1158–1167.
120. Burrows A, Khoo S. The amniotic fluid embolism syndrome: 10 years experience at a major teaching hospital. Aust N Z Obstet Gynaecol 1995;35:245–250.
121. de Swiet M. Maternal mortalilty: confidential enquiries into maternal deaths in the United Kingdom. Am J Obstet Gynecol 2000;182:760–766.
122. Benson MD. Nonfatal amniotic fluid embolism. Three possible cases and a new clinical definition. Arch Fam Med 1993;2:989–994.
123. Anderson DG. Amniotic fluid embolism: a re-evaluation. Am J Obstet Gynecol 1967;98:336.
124. Schenken JR, Slaughter GP, DeMay GH. Maternal pulmonary embolism of amniotic fluid. Am J Clin Pathol 1950;20:147.
125. Landing BJ. The pathogenesis of amniotic fluid embolism. II. Uterine factors. N Engl J Med 1950:243–590.
126. Frost AC. Death following intrauterine injection of hypertonic saline solution with hydatidiform mole. Am J Obstet Gynecol 1967;101:342.
127. Guidotti RJ, Grimes DA, Cates W. Fatal amniotic fluid embolism during legally induced abortion in the United States: 1972–1978. Am J Obstet Gynecol 1981;141:257–261.
128. Oi H, Kobayashi H, Hirashima Y, et al. Serological and immunohistochemical diagnosis of amniotic fluid embolism. Semin Thromb Hemost 1998;24:479–484.
129. Holland AJC. Amniotic fluid embolism. Anaesthesia 1968;23:273–278.
130. Noble WH, St. Amand J. Amniotic fluid embolus. Can J Anaesth 1993;40:971–980.
131. Russell W, Nicholson J. Amniotic fluid embolism: a review of the syndrome with a report of 4 cases. Obstet Gynecol 1965;26:476–485.
132. Kitzmiller JL, Lucas WE. Studies on a model of amniotic fluid embolism. Obstet Gynecol 1972;39:626.
133. Azegami M, Mori N. Amniotic fluid embolism and leukotrienes. Am J Obstet Gynecol 1986;155:1119–1124.
134. Karim SN, Devlin J. Prostaglandin content of amniotic fluid during pregnancy and labor. J Obstet Gynaecol Br Commonw 1979;74:230.
135. Dutta D, Bhargava KC, Chakravarti RN, et al. Therapeutic studies in experimental amniotic fluid embolism in rabbits. Am J Obstet Gynecol 1974;106:1201.
136. Stefanini M, Turpini RA. Fibrinogenopenic accident of pregnancy and delivery: syndrome with multiple etiological mechanism. Ann N Y Acad Sci 1959;75:601.
137. Peterson EP, Taylor HB. Amniotic fluid embolism: an analysis of 40 cases. Obstet Gynecol 1970;35:787–793.
138. Josey WE. Hypofibrinogenemia complicating uterine rupture: relationship to amniotic fluid embolism. Am J Obstet Gynecol 1966;94:29–34.
139. Malinow AM. Embolic disorders. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice. St. Louis: Mosby, 1994:722.
140. Noble WH, St-Amand J. Amniotic fluid embolus. Can J Anaesth 1993;40:971–980.
141. Dib N, Bajwa T. Amniotic fluid embolism causing severe left ventricular dysfunction and death: case report and review of the literature. Catheter Cardiovasc Diagn 1996;39:177–180.
142. Karetzky M, Ramirez M. Acute respiratory failure in pregnancy. An analysis of 19 cases. Medicine (Baltim) 1998;77:41–49.
143. Syed SA, Dearden CH. Amniotic fluid embolism: emergency management. J Accid Emerg Med 1996;13:285–288.
144. van Geijn HP, Vothknecht S. Training in the management of critical problems: a teacher's view. Eur J Obstet Gynecol Reprod Biol 1996;65: 145–148.
145. Kaptanoglu M, Dogan K, Onen A, et al. Lung mass due to amniotic fluid embolism: an intrathoracic complication of pregnancy. Scand Cardiovasc J 1990;33:117–119.
146. Sperry K. Amniotic embolism: To understand an enigma. JAMA 1986; 255:2183.
147. Schaerf RHM, DeCampo T, Avetta J. Hemodynamic alterations and rapid diagnosis in a case of amniotic fluid embolus. Anesthesiology 1977;46:155–157.
148. Lee W, Ginsburg KA, Cotton DB, et al. Squamous and trophoblastic cells in the maternal pulmonary circulation identified by hemodynamic monitoring during the peripartum period. Am J Obstet Gynecol 1986; 155:999–1001.
149. Kobayashi H, Ohi H, Terao T. A simple, noninvasive, sensitive method for diagnosis of amniotic fluid embolism by monoclonal antibody TKH-2 that recognizes NeuAc*2-6GalNAc. Am J Obstet Gynecol 1993;168: 848–853.
150. Ziadlourad F, Conklin KA. Amniotic fluid embolism. Semin Anesth 1987;6:117–122.
151. Abouleish E. Amniotic fluid embolism and disseminated intravascular coagulopathy. In: Ezzat A (ed) Pain Control in Obstetrics. Philadelphia: J. B. Lippincott 1977:160.
152. Bastien JL, Graves JR, Bailey S. Atypical presentation of amniotic fluid embolism. Anesth Analg 1998;87:124–126.
153. Sprung J, Cheng EY, Patel S, et al. Understanding and management of amniotic fluid embolism. J Clin Anesth 1992;4:504–505.
154. Benson MD, Kobayashi H, Silver RK, et al. Immunologic studies in presumed amniotic fluid embolism. Obstet Gynecol 2001;97:510–514.
155. Shechtman M, Ziser A, Markovits R, et al. Amniotic fluid embolism: early findings of transesophageal echocardiography. Anesth Analg 1999;89:1456–1458.
156. Dolyniuk M, Orfei E, Vania H, et al. Rapid diagnosis of amniotic fluid embolism. Obstet Gynecol 1983;61:28S.
157. Kanayama X, Yamazaki T, Naruse H, et al. Determining zinc coproporphyrine in maternal plasma: a new method for diagnosing amniotic fluid embolism. Clin Chem 1992;38:33–35.
158. Lunetta P, Penttila A. Immunohistochemical identification of syncytiotrophoblastic cells and megakarocytes in pulmonary vessels in a fatal case of amniotic fluid embolism. Int J Legal Med 1996;108:210–214.
159. Phillips OC, Weigel JE, McCarthy JJ. Amniotic fluid embolus. Fundamental considerations and a report of cases. Obstet Gynecol 1964;24:431.
160. Mulder JI. Amniotic fluid embolism. An overview and case report. Am J Obstet Gynecol 1985;152:430–435.

161. Alon E, Atanassoff PG. Successful cardiopulmonary resuscitation of a parturient with amniotic fluid embolism. Int J Obstet Anesth 1992;1:205.
162. Saberski LR, Kondamuri S, Osinubi OY. Identification of the epidural space: Is loss of resistance to air a safe technique? A review of the complications related to the use of air. Reg Anesth 1997;22:3–15.
163. Jaffe RA, Siegel LC, Schnittger I, et al. Epidural air injection assessed by transesophageal echocardiography. Reg Anesth 1995;20:152–155.
164. Bromage PR, Hohman WA. Uterine posture and incidence of venous air embolism (VAE) during cesarean section (CS) (abstract). Reg Anesth 1991;15:S29.
165. Lesky E. Notes on the history of air embolism. Germ Med Mon 1961; 6:159–161.
166. Magendie F. Sur l'entree accidentelle de I'air dans les veines, sur la mort subite, qui en est l'effet; sur les moyens de prevenir cet accident et d'y remedier. J Physiol Exp Pathol 1821;1:190.
167. Amussat JZ. Recherches sur l'introduction accidentale de I'air dans les veins. Germer Bailliere (Paris) 1839;255.
168. Bedford RF. Perioperative air embolism. Semin Anesth 1987:163–170.
169. Senn N. An experimental study of air-embolism. Ann Surg 1885;2:197.
170. Jensen-Bundy P. Pathophysiology and treatment of air embolism. In: Faust R (ed) Anesthesiology Review, 2nd edn. New York: Churchill Livingstone, 1994:403.
171. Matjasko J, Petrozza P, Cohen M, et al. Anesthesia and surgery in the seated position: analysis of 554 cases. Neurosurgery 1985;17:695–702.
172. Albin MS, Babinski MF, Gilbert TJ. Venous air embolism is not restricted to neurosurgery. Anesthesiology 1983;59:151.
173. Legallois E. Des maladies occasionees par la resorbtion de pus. J Heb Med 1829;3:166.
174. Merrill DG, Samuels SI, Silverberg GD. Venous air embolism of uncertain etiology. Anesth Analg 1982;61:65–66.
175. Younker D, Rodriguez V, Kavanaugh J. Massive air embolism during cesarean section. Anesthesiology 1986;65:77–79.
176. Nelson PK. Pulmonary gas embolism in pregnancy and the puerperium. Obstet Gynecol Surv 1960;15:449.
177. Barno A, Freeman DW. Amniotic fluid embolism. Am J Obstet Gynecol 1959:1199.
178. Scrimgeour JWF, Carrick JE. Fatal air-embolism associated with ruptured uterus. Lancet 1955;1:485.
179. Koonin LM, Atrash AK, Lawson HW, et al. Maternal mortality surveillance, United States 1970–1985, vol 40/SS-1. United States Public Health Service. Atlanta: Centers for Disease Control, 1991.
180. Malinow AM, Naulty JS, Hunt CO, et al. Precordial ultrasonic monitoring during cesarean delivery. Anesthesiology 1987;66:816–819.
181. Fong J, Gadalla F, Gimbel AA. Precordial Doppler diagnosis of haemodynamically comprising air embolism during cesarean section. Can J Anesth 1990;37:262–264.
182. Lew TW, Tay DH, Thomas E. Venous air embolism during cesarean section: more common than previously thought. Anesth Analg 1995; 77:448–452.
183. Hill BF, Jones JS. Venous air embolism following orogenital sex during pregnancy. Am J Emerg Med 1993;11:155–157.
184. Lowenwirt IP, Chi DS, Handwerker SM. Nonfatal venous air embolism during cesarean section: a case report and review of the literature. Obstet Gynecol Surv 1994;49:72.
185. Weissman A, Kol S, Peretz BA. Gas embolism in obstetrics and gynecology: a review. J Reprod Med 1996;41:103–111.
186. Wolffe JB, Robertson HF. Experimental air embolism. Ann Intern Med 1935;9:162.
187. Richardson HF, Coles BC, Hall GE. Experimental gas embolism: 1. Intravenous air embolism. Can Med Assoc J 1937;36:584.
188. Durant TM, Long J, Oppenheimer MJ. Pulmonary (venous) air embolism. Am Heart J 1947;33:269.
189. Boyer NH, Curry JJ. Bronchospasm associated with pulmonary embolism. Arch Intern Med 1944;73:403.
190. Wong RT. Air emboli in the retinal arteries. Arch Ophthamol 1941; 25:149.
191. Robinson DA, Albin MS. Partutition and venous air embolism. Obstet Anesth Dig 1987;7:38.
192. Black S. Venous air embolism. Probl Anesth 1997;9:113–124.
193. Roberts MW, Mathieson KA, Ho HS, et al. Cardiopulmonary responses to intravenous infusion of soluble and relatively insoluble gases. Surg Endosc 1997;11:341–346.
194. Cluroe AD. Delayed paradoxical air embolism following caesarean section for placenta previa: a case history. Pathology 1994;26:209–211.
195. Michenfelder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (doppler) for diagnosis of venous air embolism. Anesthesiology 1972;36:164–167.
196. Vartikar JV, Johnson MD, Datta S, et al. Precordial Doppler monitoring and pulse oximetry during cesarean delivery: detection of venous air embolism. Reg Anesth 1989;14:145–148.
197. Karuparthy VR, Downing JW, Husain FJ, et al. The incidence of venous air embolism (VAE) during cesarean section is unchanged by the use of 5–10° head-up tilt. Anesth Analg 1989;69:620–623.
198. Smith SL, Albin MS, Ritter RR, et al. CVP catheter placement from the antecubital veins using a J-wire catheter guide. Anesthesiology 1984; 60:238–240.
199. Artru AA, Colley PS, Bunegin-Albin. CVP catheter improves resuscitation from lethal venous air embolism in dogs. Anesth Analg 1986; 65:S7.
200. McLintic AJ, Pringle SD, Lilley S, et al. Electrocardiographic changes during cesarean section under regional anesthesia. Anesth Analg 1992; 74:51–56.
201. Munson ES, Merrick HC. Effect of nitrous oxide on venous air embolism. Anesthesiology 1966;27:783–787.
202. Davis FM, Glover PW, Maycock E. Hyperbaric oxygen for cerebral air arterial embolism occurring during cesarean section. Anaesth Intensive Care 1990;18:403–405.

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25
The Anticoagulated Patient

Shiv K. Sharma and Kenneth J. Leveno

In 1856, Virchow suggested that there were three causative factors in the development of thrombosis: stasis of blood, alteration of the vessel wall, and changes in the blood.[1] These are all physiologic and functional changes associated with normal pregnancy and implicate Virchow's causes in the predisposition of pregnant women to have thromboembolism. For these reasons, pregnant and postpartum women are five times more likely to develop a thromboembolic event compared with nonpregnant patients of the same age.[2] Deep venous thrombosis (DVT), which occurs in approximately 1 in 1000 to 1 in 2000 of all pregnancies,[3] continues to be the leading cause of pulmonary thromboembolism in the peripartum period. Septic pelvic vein thrombosis and puerperal ovarian vein thrombosis may also occur in pregnancy and result in pulmonary embolism. Thus, thromboembolism is a common cause of maternal morbidity and mortality.[4,5]

The choice of anticoagulation agents to prevent and treat thromboembolism is determined by the stage of pregnancy; unfractionated heparin or low molecular weight heparin[6] are the agents of choice before delivery because of the embryopathy attributed to warfarin. Warfarin, however, is commonly used for continuation of anticoagulation following delivery of the infant. Anticoagulation is also administered to pregnant women with a history of pregnancy loss due to the antiphospholipid antibody syndrome, as well as other diseases such as atrial fibrillation, and to those with prosthetic cardiac valves.

Anticoagulated pregnant women present a challenge to both the obstetrician and anesthesiologist. To minimize the possibility of a poor outcome, it is necessary to understand the anesthetic and obstetric implications of anticoagulation and to have an optimal plan for anesthetic and obstetric management when caring for these high-risk parturients.

Despite substantial experience, the use of anticoagulants in pregnancy and the optimum time for discontinuation of therapy remain controversial. There is difference of opinion not only about the medical and obstetric approach but also regarding anesthetic management of anticoagulated pregnant women.

The purpose of this chapter is to review the challenges and areas of controversies associated with the anesthetic and obstetric management of pregnant anticoagulated women.

Indications for Anticoagulant Therapy in Pregnancy

Anticoagulant therapy during pregnancy is indicated for the prophylaxis and therapy of several medical conditions (Box 25.1).

Venous Thromboembolic Disease

Although venous thromboembolic disease is an uncommon complication of pregnancy, it is one of the leading causes of maternal morbidity and mortality in the United States and other developed countries. Timely and appropriate treatment of DVT in pregnancy has been shown to be associated with approximately a fivefold reduction in the incidence of pulmonary thromboembolism in these women.[7,8] Available evidence suggests that the risk of venous thromboembolic disease is higher after cesarean delivery and more so after emergency cesarean compared to vaginal delivery.[9] Also, women with a history of DVT in a previous pregnancy have an increased risk (with a recurrence rate of 4%–15%) of DVT in subsequent pregnancies.[10,11] Therefore, anticoagulant prophylaxis is recommended in these women during pregnancy and in the postpartum period.[12]

More than 25% of patients who develop an acute thrombotic event may have an inherited predisposition to thrombosis.[13] Women with congenital deficiencies of antithrombin III, protein C, or protein S have approximately an eightfold increased risk of thromboembolism during pregnancy compared to normal pregnant women.[14] Resistance to activated protein C, which is frequently associated with factor V Leiden mutation, is by far the most common identified genetic predisposition to thromboembolism.[15,16] Indeed, approxi-

Box 25.1. Common indications for anticoagulant therapy in pregnancy.

Venous thromboembolic disease
Pulmonary embolism
Prosthetic heart valves
Valvular heart disease with systemic embolization
Antiphospholipid antibody syndrome
Cardiac surgery
Cerebral thrombosis
Atrial fibrillation with embolization

mately, 60% of all women who develop thromboembolism during pregnancy may have factor V Leiden.[17] Other inherited thrombophilic disorders, such as prothrombin gene mutation, hyperhomocysteinemia, and persistent antiphospholipid antibodies, may also increase the risk of thromboembolism during pregnancy. Parturients at particular risk for thromboembolic disease are summarized in Box 25.2.

Clinical signs and symptoms of DVT vary significantly and depend mostly on the site and degree of occlusion. Common clinical manifestations include pain, edema, red or pale skin discoloration, and a positive Homn's sign (calf pain on stretching of the Achilles tendon). Making the correct diagnosis is of utmost importance because the diagnosis of DVT commits the pregnant woman to a prolonged period of anticoagulation as well as treatment in future pregnancies.

Although venography or phlebography remains the standard for confirmation of DVT, noninvasive methods have largely replaced this test to make the clinical diagnosis. Venography is time consuming, expensive, cumbersome, and has serious complications. Likewise, impedance plethysmography, which was used for some time as a noninvasive screening method, is seldom used today.

Real-time ultrasonography, used along with duplex and color Doppler ultrasound, is currently the procedure of choice to detect proximal DVT.[18,19] It is important to note that a third of women with negative findings on compression sonography for DVT have an associated pulmonary embolism,[20] either because the thrombosis has already embolized, or because it arose from deep pelvic veins inaccessible to ultrasound evaluation. More specifically, the thrombosis associated with pulmonary embolism in pregnant women frequently originates in the iliac veins.

Magnetic resonance imaging is reserved for specific cases in which the ultrasound findings are equivocal or for those with negative ultrasound findings but strong clinical suspicion. This technique allows excellent delineation of anatomic detail above the inguinal ligament, and phase images can be used to diagnose the presence or absence of pelvic vein flow. An additional advantage is the ability to image in coronal and sagittal planes.[21]

Computed tomographic scanning also may be used to assess the lower extremities. It is widely available but requires contrast agents and ionizing radiation. Radiation exposure to the fetus is negligible unless the pelvic veins are imaged.

Box 25.2. Pregnant women at risk for thromboembolic events.

Thromboembolism during previous pregnancy
Prolonged bedrest
Advanced maternal age (>35 years)
Multiparity
Antithrombin III deficiency
Protein C/protein S deficiency
Activated protein C resistance (factor V Leiden mutation)
Paroxysmal nocturnal hemoglobinuria

Pulmonary Embolism

Pulmonary embolism in the pregnant woman is often a catastrophic event. Clinical symptoms of pulmonary embolism are nonspecific and range from mild to severe chest pain, shortness of breath, tachypnea, and hemoptysis to massive hypotension and sudden cardiovascular collapse. The differential diagnosis of these symptoms includes amniotic fluid embolism, air embolism, cardiac decompensation, pneumothorax, and aspiration. Blood gas analysis, electrocardiogram, and chest X-ray examination are first steps in diagnosis, but these tests are often nonspecific. Electrocardiographic changes may include ST-T wave changes, right axis deviation, P pulmonale, T-wave inversions, and dysrhythmias.[22] Echocardiography has also been used to evaluate pulmonary artery emboli.[23] Placement of a pulmonary artery catheter may reveal increased pulmonary artery pressure, increased central venous pressure, and normal pulmonary capillary wedge pressure with elevated pulmonary vascular resistance. For these reasons, pulmonary angiography remains the ultimate method for confirmation of the pulmonary embolism.

A first step in the workup of the pregnant woman for whom there is a strong clinical suspicion of pulmonary embolism usually includes perfusion lung scanning. A satisfactory scan that is read as negative strongly excludes the likelihood of pulmonary embolism. If the perfusion scan is abnormal, a ventilation scan is performed. In the presence of an abnormal ventilation scan without clinical findings of DVT, pulmonary angiography is often performed to rule out pulmonary embolism.

Atrial Fibrillation

Women with cardiac dysrhythmias are at increased risk of thromboembolic events. Because most serious dysrhythmias occur in older patients with ischemic heart conditions, there is only limited experience with this problem in pregnancy, and it is usually associated with rheumatic valvular disease. Paroxysmal atrial tachycardia and persistent atrial tachycardia may also be seen in pregnancy. Drugs of choice in treating arrhythmias in the pregnant woman include quinidine, digoxin, and beta-adrenergic blocking agents. Anticoagulation is often added to prevent arterial embolization.

Cardiac Surgery During Pregnancy

There is very little information available about the management of women undergoing cardiac surgery during pregnancy. Because of the great risk for fetal morbidity and mortality, open heart surgery is generally performed only in emergency situations. Despite the anticoagulation necessary for bypass, there have been reports of maternal and fetal survival after open heart surgery during pregnancy.[24]

Prosthetic Cardiac Valves

Hall et al.,[25] in their review of 65 women with prosthetic heart valves, reported that the 3 maternal deaths that occurred were all related to thromboembolic events. Similarly, Hirsh et al.[7] have reported that the morbidity and mortality associated with antepartum thromboembolism was 15% in untreated women. On the other hand, the risk of a thromboembolic event occurring during pregnancy was shown to be reduced from 25% to 5% if the woman with a prosthetic valve was anticoagulated.[26] Thus, the risk of withholding anticoagulation in a pregnant woman with a prosthetic heart valve may outweigh the potential risks of anticoagulation therapy. When maternal risks are carefully weighed against fetal risks, many authors agree that, for women with heart valve prostheses, anticoagulation should be used throughout pregnancy and in the postpartum period as well.[27]

Buxbaum and coworkers have found that women who stopped their anticoagulation treatment during pregnancy were at higher risk for thromboembolism than those who never received anticoagulants.[28] Chan and colleagues recently reviewed the available literature to determine fetal and maternal outcomes of pregnant women on anticoagulation therapy with prosthetic heart valves.[29] They concluded that although oral anticoagulants (warfarin) were associated with the risk of embryopathy, they were more efficacious than heparin for thromboembolic prophylaxis in pregnant women with mechanical heart valves. However, to improve outcome with heparin therapy in these women, high dose subcutaneous heparin (17,000–20,000 U every 12 h) has been suggested.[30] Some investigators have used low molecular weight heparin in pregnant women with prosthetic heart valves to reduce the risk of thrombosis.[31] Thus, when maternal risks are weighed against fetal risks, most investigators agree that anticoagulation should be used throughout pregnancy and in the postpartum period for women with prosthetic heart valves.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is an acquired hypercoagulable state that may precipitate both arterial and venous thrombosis.[32] Because this syndrome was originally described in women with lupus, and many of these women had an antiphospholipid antibody that prolongs the activated partial thromboplastin time (aPTT), it has been given the name lupus anticoagulant.[33] Although many tests can be performed to identify the woman with antiphospholipid antibody syndrome, anticardiolipin antibody is considered to be the most sensitive. Pregnant women with this syndrome, if untreated, have a high incidence of placental infarction and miscarriage[32] and may develop preeclampsia and fetal growth restriction.[34] Although there is some controversy regarding the treatment of these women, it has been suggested that fetal losses are reduced if a combination of heparin and low-dose aspirin is used.[35,36]

Anticoagulants

Anticoagulants used during pregnancy are standard unfractionated heparin and, more recently, low molecular weight heparin. Warfarin is, with rare exceptions, considered contraindicated before delivery, but it is commonly used postpartum. The major pharmacologic characteristics of these drugs are listed in Table 25.1.

Heparin

Heparin is a member of a heterogeneous group of straight chain anionic mucopolysaccharides called glycosaminoglycans that have molecular weights averaging 15,000 daltons.[37,38] Heparin is manufactured primarily by extraction from beef lung or porcine intestine. It is acidic because of its covalently linked sulfate and carboxylic acid groups and does not cross the placenta because of its large molecular weight and polarity.[39] Heparin produces its anticoagulant effect by irreversibly binding to antithrombin (previously known as antithrombin III). This cofactor is an alpha$_2$-globulin that is nor-

Table 25.1. Major pharmacologic characteristics of heparin, low molecular weight heparin, and warfarin.

	Heparin	Low molecular weight heparin	Warfarin
Molecular weight (daltons)	15,000	4,000–6,500	1,000
Route of administration	IV/SC	SC	Oral
Placental passage	No	No	Yes
Breast milk passage	No	No	Yes
Duration of action	1–3 h	10–12 h	4–5 days
Mode of action	Antithrombin III	Antithrombin III	Vitamin K-dependent factors II, VII, IX, X

Box 25.3. Side effects of anticoagulants.

General
- Hematuria
- Melena, hematemesis
- Intraperitoneal hemorrhage
- Thrombocytopenia
- Adrenal hemorrhage
- Intracranial hemorrhage
- Allergic reactions
- Anaphylactic shock
- Alopecia
- Osteoporosis (prolonged use)

Obstetric
- Hemorrhage: retroperitoneal, incisional, vaginal, cervical, perineal, episiotomy

Anesthetic
- Hematoma: epidural, spinal, subdural
- Bleeding in naso-oropharynx

mally present as a naturally circulating anticoagulant. This binding of antithrombin with heparin enhances the ability of antithrombin to inactivate thrombin and activated factors X, XII, XI, and IX. In addition to its anticoagulant effects, heparin in high doses inhibits the aggregation of platelets. Indeed, thrombocytopenia may also occur in up to 30% of heparinized patients, which is unrelated to the heparin dose.[40]

Heparin is not absorbed by the gastrointestinal tract and is usually not given intramuscularly because of the risk of hematoma formation. The anticoagulant effect of heparin is almost immediate after intravenous injection. Heparin is metabolized in the liver by heparinase, and the inactive breakdown products are excreted in the urine. Side effects may be seen even when the heparin dose is within the therapeutic range (Box 25.3).

Prophylactic Low-Dose Heparin

Low-dose heparin is given by subcutaneous injection, whereas high-dose regimens are administered by continuous or intermittent intravenous injection. Low-dose heparin is widely used in women at risk for thromboembolic disease. Subcutaneous administration of low-dose heparin also increases the activity of antithrombin III and thereby produces inhibition of activated factor X (Xa). Because factor Xa is required for thrombus formation and is included in both the intrinsic and extrinsic pathways, its inhibition produces satisfactory anticoagulation. "Minidose" regimens typically use 5,000 to 10,000 U of heparin subcutaneously every 8 to 12 h. This dose only minimally prolongs the aPTT, and theoretically there should be no increased risk of hemorrhagic complications.

Therapeutic Intravenous Heparin

The dosage schedule recommended by the American College of Obstetricians and Gynecologists[41] includes an initial intravenous bolus up to 80 U/kg (minimum, 5000 U); this is followed by a continuous infusion of heparin, 15 to 25 U/kg/h. After 4 h, the aPTT is determined and adjusted. The aPTT is measured daily once a steady state is achieved. The duration of therapeutic administration of hep-arin varies, but treatment is usually continued for at least 7 to 10 days. If intravenous heparin therapy has been initiated during pregnancy, prophylactic subcutaneous heparin is usually continued after conclusion of intravenous therapy for the remainder of pregnancy and up to 6 to 12 weeks postpartum.

Some authors, however, have reported that therapeutic levels were achieved after the administration of large doses of subcutaneous heparin.[42] Deep venous thrombosis may be treated with subcutaneous adjusted-dose heparin to maintain the aPTT at 1.5 times the control value when determined at 6 h after the last injection. The American College of Obstetricians and Gynecologists recommends therapeutic subcutaneous heparinization for 3 to 4 months, followed by prophylactic or mini-dose heparin throughout pregnancy and for 6 to 12 weeks postpartum.[41]

Risk of Heparin Use in the Pregnant Woman

Impact on the Mother

Parturients receiving heparin therapy are at increased risk of hemorrhage, with major bleeding occurring in 2% of patients.[43] During vaginal delivery, there may be prolonged bleeding from a laceration or episiotomy. Patients receiving heparin therapy who have undergone a vaginal delivery without episiotomy or laceration do not usually have increased blood loss, because hemostasis from the uterus is usually not dependent on coagulation factors. However, at the time of cesarean delivery, hemorrhage may occur at the uterine incision site as well as other incised tissues.

Impact on the Fetus

Heparin therapy is safe for the fetus.[43] It does not cross the placenta and therefore does not have the potential to cause fetal bleeding or teratogenicity. There is no firm evidence that maternal use of heparin in itself, rather than the disease process for which it is being given, leads to increased fetal loss.

Heparin Therapy for Women Approaching Labor

For some women at high risk of thromboembolism, low-dose prophylactic heparin therapy of 5000 U subcutaneously every 12 hours has been continued throughout labor. At these doses,

significant changes in the coagulation profile sufficient to cause bleeding are seldom encountered. However, the aPTT should be closely followed at least every 4 to 6 hours as well as before initiation of any regional anesthetic or invasive procedure (e.g., placement of a central venous line) during this critical period. Reversal of anticoagulation should be considered for labor and delivery in the presence of an abnormal coagulation profile (Figure 25.1). Many clinicians recommend discontinuing low-dose heparin administration about 4 to 6 h before delivery. Considering the short half-life of heparin, aPTT levels should then be normal at the time of delivery.

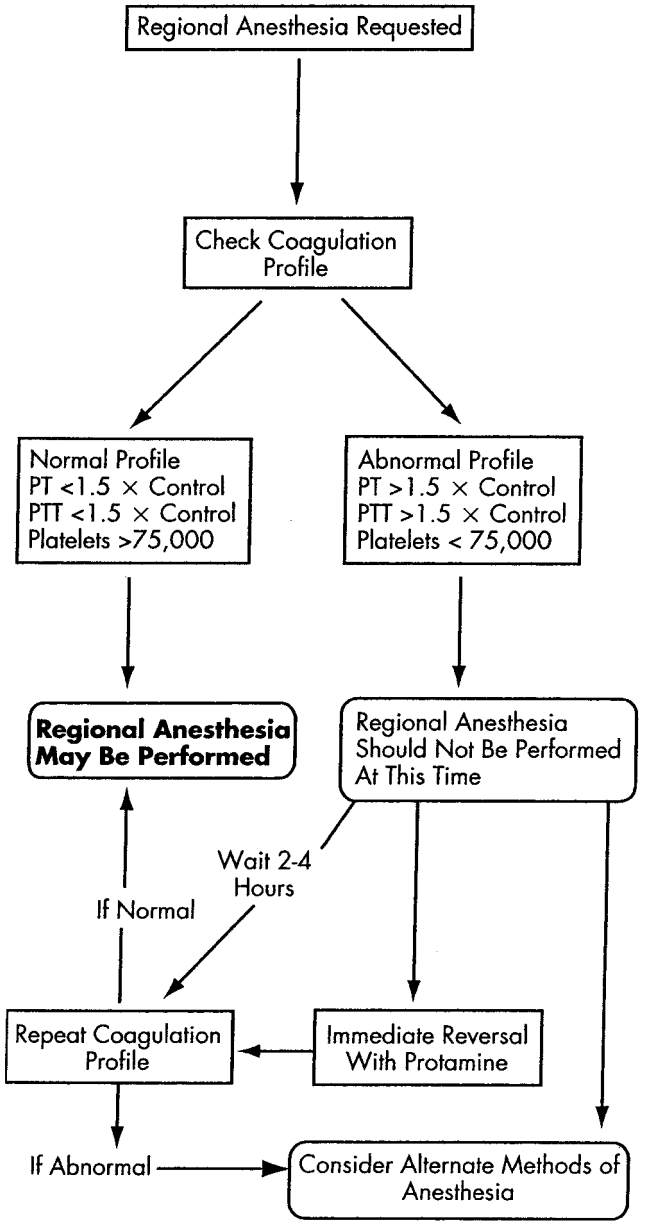

FIGURE 25.1. Regional anesthesia in the heparinized parturient.

Therapeutic Heparin Therapy in the Postpartum Woman in Different Clinical Settings

Prophylaxis for women at risk for thromboembolic disease optimally would continue throughout delivery and into the postpartum period. However, the maternal risks of therapy (i.e., hemorrhage and hematoma formation related to delivery, particularly when the woman requires cesarean delivery under regional anesthesia) usually result in discontinuation of heparinization during labor. The following are some guidelines for restarting therapeutic postpartum anticoagulation if the therapy was stopped before delivery:

1. Vaginal delivery with no lacerations or episiotomy: Anticoagulation therapy may be reinstated within a few hours after delivery.
2. Vaginal delivery with lacerations or episiotomy: Anticoagulation therapy may be restarted 1 to 2 days after delivery. Close attention should be paid to prevent hematoma formation.
3. Cesarean delivery: Anticoagulation therapy may be started 48 to 72 h postoperatively.

Heparin Antagonists (Protamine Sulfate)

If a situation arises in which the acute reversal of heparin becomes necessary, such as the occurrence of severe bleeding, protamine sulfate may be administered intravenously as a specific heparin antagonist. Protamine is a low molecular weight protein found in the sperm of salmon. When administered alone, or when given in excess of the amount needed to neutralize the heparin, protamine has an anticoagulant effect. When given to a heparinized patient, it combines ionically with heparin to form a complex that no longer has anticoagulant activity. One of several methods used to determine the dose of protamine needed for reversal of heparin is the administration of 1 to 1.3 mg protamine for every 100 U heparin remaining in the patient. Adequacy of reversal can be demonstrated by a return to normal of the activated clotting time. Protamine must be administered by slow intravenous injection at a rate of less than 20 mg/min. Adverse reactions that may occur during rapid injection include immediate or delayed anaphylactoid reactions with flushing, bradycardia, hypotension dyspnea, and pulmonary hypertension. Hypersensitivity reactions, including anaphylactic reactions, have been reported following the administration of protamine, especially in those patients with previous exposure to protamine (including protamine-containing insulins) and allergies to fish. The pulmonary hypertension that is seen is thought to be mediated by release of thromboxane.[44]

Low Molecular Weight Heparin

Low molecular weight heparin is a glycosaminoglycan that is produced by depolymerization of standard heparin. It has a

mean molecular weight of 4000 to 6500 daltons and a chain length of 13 to 22 sugars. Similar to the standard heparin, low molecular weight heparin binds to antithrombin III to inhibit procoagulant Xa and IIa. However, its anti-IIa activity is relatively less than its anti-Xa activity.[37,38,45] Low molecular weight heparin has the advantage of a longer plasma half-life and a more predictable dose response than standard heparin. Peak anti-Xa activity occurs 3 to 4 h after a subcutaneous injection, and at 12 h, anti-Xa levels are reduced to approximately 50% of peak levels. At prophylactic doses of low molecular weight heparin, anti-Xa levels, measured by clot-based assays (heptest or amidolytic assays), are a more sensitive measure of low molecular weight heparin anticoagulant activity than the aPTT level. Recent studies have shown that thromboelastography can also be utilized to assess the degree of anticoagulation produced by low molecular weight heparin.[46] In contrast to standard heparin, the anticoagulant effect of low molecular weight heparin is not fully neutralized by an equimolar dose of protamine. A dose of 1 mg protamine/100 U low molecular weight heparin reverses only 90% of anti-IIa and 60% of anti-Xa activity.[38]

Low molecular weight heparin has been used effectively in pregnant women for the prevention and treatment of DVT.[47–51] Evidence suggests that low molecular weight heparin does not cross the placenta,[52] and therefore it is safe for the fetus. Moreover, compared to standard heparin, the use of low molecular weight heparin during pregnancy has been reported to be associated with a lower risk of bleeding complications,[47–51] heparin-induced thrombocytopenia,[53] and osteoporosis.[54]

As pregnancy advances, the volume of distribution for low molecular weight heparin also changes; therefore, the dose should be adjusted according to the plasma concentration of anti-Xa. For prophylaxis of thromboembolism, common regimens include subcutaneous dalteparin 5000 U every 24 h[47] or enoxaparin 40 mg every 24 h.[50,51] The dose of low molecular weight heparin is adjusted to achieve a peak anti-Xa plasma concentration of 0.2 to 0.6 U/mL.[47,49] Optimally, low molecular weight heparin prophylaxis for women at risk for thromboembolic disease should continue throughout delivery and into the postpartum period. However, some clinicians suggest discontinuation of therapy 24 h before elective induction of labor[6] to avoid any unwanted anticoagulant effect during delivery.

Oral Anticoagulation

Warfarin sodium (Coumadin) is the most commonly used oral anticoagulant in the United States. It acts by interfering with the hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. Although hypermetabolic states usually increase the responsiveness to oral anticoagulants, it has been shown that pregnancy causes a decreased responsiveness because of the increased activity of factors VII, IX, and X.[55] Thus, there is an increased drug requirement to achieve anticoagulation in pregnancy. There are many reported drug interactions with warfarin. Aspirin, phenothiazines, and phenylbutazone increase warfarin activity, while barbiturates decrease its activity. Unlike heparin, warfarin does cross the placenta. Because the fetus lacks mature liver enzymes, it is highly susceptible to the effects of oral anticoagulants. Because of the difference between maternal and fetal pharmacodynamics, the effects of warfarin last 4 to 5 days in the mother but up to 14 days in the fetus.[56]

Warfarin compounds have significant teratogenic and fetal effects.[57] It is estimated that one in six exposed pregnancies results in an abnormal live-born infant, and that one in six results in abortion or stillbirth. When exposure occurs between the sixth and ninth week, the fetus is at risk for warfarin embryopathy, characterized by nasal hypoplasia and stippled vertebral and femoral epiphyses. During the second and third trimesters, defects associated with fetal warfarin exposure are likely the result of hemorrhage and scarring, which may lead to the central nervous system findings of agenesis of the corpus callosum, Dandy–Walker malformation, and cerebellar atrophy, microphthalmia optic atrophy, and blindness, or to developmental delay and mental retardation. For these reasons, warfarin is seldom used in the antepartum period except in unusual instances when the maternal benefits clearly outweigh the fetal risks.

When reversal of an oral anticoagulant becomes necessary, the parenteral administration of vitamin K (phytonadione) will return the prothrombin time (PT) to the normal range within 24 to 48 h. Fresh-frozen plasma is used when immediate reversal is necessary. The anticoagulant effects in the fetus may take up to 14 days to subside, but this time period may be reduced to less than 48 h by the intravenous administration of vitamin K to the fetus.[58] Maternally administered vitamin K crosses the placenta, and therefore it may also enhance the rate of formation of fetal coagulation factors. After delivery, the newborn should receive intramuscular vitamin K if the mother had warfarin reversed before delivery. If the newborn shows signs of bleeding, fresh-frozen plasma can be used.

Obstetric Management

Since the first description of a successful pregnancy in a woman with a prosthetic heart valve,[59] there have been many reports of successful outcomes in anticoagulated pregnant women.[6,60] Most authors now advocate the use of standard heparin or low molecular weight heparin in pregnancy because of the embryopathy caused by warfarin. Standard heparin has several advantages when anticoagulation is necessary in the pregnant woman. It does not cross the placenta, and if therapy is discontinued at the onset of labor or several hours before cesarean section, there should be no residual anticoagulation at the time of delivery.

Several reports have suggested that low molecular weight heparin is suitable for routine clinical use in pregnant women who require anticoagulation therapy. Parturients with venous thrombosis, pulmonary embolism, or thrombophilic disorders may be treated as effectively with such heparin as with tra-

ditional heparin[61] without much risk of hemorrhagic complications, heparin-induced thrombocytopenia, and osteoporosis. Low molecular weight heparin is also safe for the fetus because it does not cross the placenta. The ease of administration and less frequent need for laboratory monitoring provide distinct advantages for low molecular weight heparin compared with standard heparin.[61]

There appears to be no ideal anticoagulant regimen for use in pregnancy, but a compromise approach might be to use both heparin and warfarin.[62] Heparin can be used for anticoagulation during the pregnancy, and warfarin can be administered following delivery.

Anesthetic Management

Regional Anesthetic Implications of Anticoagulation

The introduction of heparin in 1937 and warfarin in 1941 in clinical practice posed new concerns regarding the regional anesthetic management of perioperative anticoagulated patients. A new challenge in the management of regional anesthesia emerged with the release of low molecular weight heparin for clinical use in the United States in 1993. If the decision has been made to anticoagulate a woman during pregnancy, the anesthetic management will be affected. The anesthesiologist, therefore, should be consulted at an early stage. Choices of anticoagulant, maternal and fetal effects of anticoagulants, the decision of when to reverse the anticoagulation as delivery approaches, and the method of this reversal must all be considered when formulating an anesthetic plan for an anticoagulated parturient.

Of all the potential complications of a spinal or epidural anesthetic, bleeding into the spinal canal is the most serious, because this bleeding is hidden from observation. Bleeding into the spinal canal most commonly occurs in the epidural space due to the prominent epidural venous plexus. Bleeding is least likely to become clinically significant in the intrathecal space because of the diluting effect of cerebral spinal fluid. Because the spinal space is nonexpandable, continued bleeding usually progresses to spinal cord compression and neurologic dysfunction.[37] Although rare, epidural hematoma is now the most common mechanism of spinal cord injury in the American Society of Anesthesiologist Closed Claims Project Database.[63] The incidence of neurologic dysfunction resulting from hemorrhagic complications is estimated to be less than 1 in 150,000 epidural and less than 1 in 200,000 spinal anesthetics.[64]

Spinal-Epidural Hematoma

Risk Factors

In 1911, Cooke first recognized that local hemorrhage could result from lumbar puncture.[65] Since then, there have been numerous reports of spinal-epidural hemorrhages following regional anesthesia in the anticoagulated patient.[37] Case reports have also described the development of hematomas when anticoagulation was initiated shortly after a lumbar puncture.[66] This understanding has important implications when considering the reinitiation of anticoagulation in the postpartum period in a patient who has had a spinal or epidural anesthetic for labor and delivery. Saka and Marx, citing a case in which extradural hematoma formation occurred when heparin therapy was started 20 min after initiation of an epidural, have suggested that heparin not be restarted until 24 h after delivery. However, there have been several reports of uneventful regional anesthetics initiated shortly before anticoagulation.[67] Rao and EI-Etr, in a study on anticoagulation following placement of epidural and subarachnoid catheters in nonpregnant patients, have reported that there was no incidence of neurologic complications arising from anticoagulant therapy after epidural or subarachnoid catheterization.[68] However, if fresh heme was aspirated any time during the procedure, the regional technique was abandoned, and the patient was rescheduled for surgery under general anesthesia for the following day.[68] Odoom and Sih have similarly reported their experience with lumbar epidural blocks in patients who received preoperative and intraoperative anticoagulation; they also reported that there were no cases of neurologic sequelae.[69]

In a review of the literature between 1906 and 1994, Vandermeulen et al.[37] reported 61 cases of spinal hematoma associated with spinal or epidural anesthesia, 5 of whom were pregnant women. In 69% (42/61) of the patients, spinal hematomas associated with central neural blockade occurred in patients with evidence of hemostatic abnormalities. Needle placement was reported as difficult in 25% of patients, and a bloody tap occurred in 25% of patients. More than one risk factor (hemostatic abnormalities, difficult needle placement, and bloody tap) was present in 33% of patients. Possible risk factors for spinal-epidural hematoma formation are included in Box 25.4.

Low-Dose Heparin Prophylaxis

The risk of spinal hematoma in patients receiving SC standard heparin is very low.[37,70] Allemann et al. studied both epidural and spinal anesthetics performed on orthopedic patients who received 5000 U heparin preoperatively and postoperatively and found no cases of neurologic dysfunction.[71] Lowson and

Box 25.4. Risk factors for development of spinal epidural hematoma.

Hemostatic abnormalities
Difficult needle placement
Spina bifida occulta
Bloody tap
Vascular abnormalities in the spinal canal
Arteriosclerotic vessels in the spinal canal
Spinal stenosis

Goodchild reported on a retrospective review of 5 years of clinical practice in patients who received spinal and epidural anesthetics associated with heparin prophylaxis. These authors used 22-gauge spinal or 16-gauge epidural needles, and if a blood vessel was punctured, the procedure was repeated at another interspace. They reported no neurologic complications.[72] In another study, which evaluated orthopedic patients who received 5000 U heparin subcutaneously, the authors found that there was a wide variation in the range of PTT values.[73]

Although such occurrences are exceedingly rare, there is a report of an epidural hematoma associated with an epidural anesthetic in a patient receiving low-dose heparin therapy. Darnat et al.[74] have reported the case of a patient who was given an epidural for chronic pain despite the administration of 5000 U heparin every 12 h. This patient developed an epidural hematoma and complete paraplegia, which did not respond to surgical intervention.[74]

Low Molecular Weight Heparin Prophylaxis

A total of 40 cases of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving low molecular weight heparin perioperatively were reported by April 1998.[75] The incidence of spinal hematomas is much higher in the United States compared to in Europe. This difference might be because the dosing of enoxaparin is 30 mg every 12 h in the United States and 40 mg once daily in Europe. The twice-daily dosage regimen may deliver a higher degree of anticoagulation and not result in the same trough of heparin activity required for the safe placement and removal of a spinal and epidural needle and catheter. The reported frequency of spinal hematoma in patients receiving low molecular weight heparin is estimated to be approximately 1 in 3,000 continuous epidural anesthetics compared to 1 in 40,000 spinal anesthetics.[76] Monitoring of the anti-Xa level is not recommended; the anti-Xa level is not predictive of the risk of bleeding and is therefore not helpful in the management of patients undergoing regional anesthesia. (In the author's institution anti-Xa level is done if indicated.)

Presentation and Management

Epidural hematomas, as previously mentioned, are exceedingly rare. Early recognition and treatment are vital if permanent neurologic disability is to be prevented. Because of the rarity of epidural hematoma, it may go unrecognized until permanent neurologic sequelae have developed. Therefore, anyone caring for patients who have received regional anesthesia should be acquainted with the signs and symptoms of a developing epidural hematoma. These signs include back pain at the spinal level involved, radiculopathy, and eventually sensory and motor deficits. Although many reports have described back or radicular pain as the first symptom of a spinal epidural hematoma, the first presentation may be muscle weakness or urinary retention. Neurologic damage is thought to be secondary to spinal cord ischemia associated with compression by the hematoma.

Once the diagnosis of epidural hematoma is entertained, radiologic examinations should be performed. Magnetic resonance imaging (MRI) is the most effective diagnostic tool to rule out the presence of an epidural hematoma, but computerized tomography or myelography must be considered if MRI is not readily available. Because rapid decompression is so vital in preventing permanent nerve damage, the neurosurgeon should be consulted at an early stage so that any necessary preparations can be made should the radiologic findings prove positive. The treatment of choice is decompressive laminectomy within 8 h of hematoma formation.

Outcome

Outcome after spinal or epidural bleeding is poor. In a series of 55 patients reviewed by Vandermeulen et al.,[37] 5 patients died, 29 had poor neurologic recovery, 11 had partial recovery, and only 10 had good recovery. The time taken to make a clinical diagnosis, perform a scan, and perform decompressive laminectomy is a key factor in recovery. A target time of less than 8 to 12 h is necessary if permanent paraplegia is to be avoided.

Guidelines for Minimizing Spinal-Epidural Hematoma

The use of spinal-epidural anesthesia is contraindicated in patients treated with full-dose heparin or warfarin. The risk of spinal hematoma versus the benefits of regional anesthesia must be weighed before deciding to perform regional anesthesia. Concomitant administration of medications affecting coagulation, such as antiplatelet drugs with heparin, represents an additional risk of spinal hematoma.

A single-dose spinal anesthetic delivered by a small-gauge spinal needle may be the safest regional technique in these patients. Needle and catheter placement during regional blockade should be as atraumatic as possible, and catheter insertion distance should be limited to 3 to 4 cm. The following guidelines, if followed, may reduce the risk of spinal hematoma after regional anesthesia in an anticoagulated patient:

1. Intravenous heparin therapy: Intravenous heparin therapy should be delayed at least 1 to 2 h after spinal or epidural needle placement. Catheter removal should be delayed for at least 4 to 6 h after heparin or until heparin activity is low (aPTT $<$ 1.5 of baseline) or completely reversed. Thrombocytopenia should be excluded.
2. Subcutaneous low-dose standard heparin prophylaxis: In patients on subcutaneous low-dose heparin prophylaxis, needle placement or catheter removal should be avoided within 4 h of administration of SC heparin, as peak plasma levels of heparin occur at 2 to 4 h in these patients.
3. Low molecular weight heparin prophylaxis: In patients on a small dose of low molecular weight heparin prophylaxis, needle placement or catheter removal should be delayed for at least 10 to 12 h after the last dose of low molecular weight

heparin. Subsequent dosing should be delayed for at least 1 to 2 hours after needle placement or catheter removal.

Short-acting local anesthetics or opioids with dilute local anesthetics should be used in patients at increased risk of spinal hematoma so that their neurologic status may be evaluated immediately postoperatively. Anticoagulated women who receive regional anesthesia should be closely monitored in the postoperative period for early signs of cord compression. Neurologic symptoms often occur after catheter withdrawal; therefore, neurologic monitoring should continue for 24 h after removal of the catheter.

Aspirin Use and the Risk of Spinal-Epidural Hematoma

It has been reported that low-dose (60–150 mg/day) aspirin administered during the second and third trimesters of pregnancy prevented preeclampsia or fetal growth restriction and was safe for the mother and fetus.[77] However, there is controversy surrounding the benefits of such low-dose aspirin. A large multicenter study examining aspirin to prevent preeclampsia found no benefits.[78]

The administration of aspirin inhibits cyclooxygenase, thereby reducing the levels of cyclic endoperoxidases synthesized from arachidonic acid; this reduces the concentration of arachidonic acid derivatives, including the potent vasoconstrictor thromboxane A2. Thromboxane A2 is also a potent stimulator of platelet aggregation and adhesion.[79] Studies in animal models indicate that the antithrombotic effects of aspirin also involve pathways other than the inhibition of cyclooxygenase and thereby inhibition of platelet aggregation. Buchanan and coworkers have reported that aspirin prolongs the bleeding time in a dose-dependent manner, and that it is not dependent on platelet aggregation, thereby showing that aspirin has an antithrombotic mechanism in addition to cyclooxygenase inhibition.[80]

The alteration of hemostatic function varies with the dose administered; low-dose aspirin prevents platelet aggregate formation at the injured vessel wall, whereas high-dose aspirin may promote platelet thrombus formation. The administration of aspirin blocks the release of platelet adenosine diphosphate (ADP), which is necessary for platelet clumping and for the growth of the platelet plug. An indicator of platelet function after aspirin administration is the bleeding time, which is increased by an average of 50% at 2 h after ingestion of an oral dose of 600 mg aspirin.[81] The duration of an abnormal bleeding time is approximately 7 days, which is roughly equal to the life span of the exposed platelet. The maximal inhibition of platelet ADP release is achieved with salicylate concentration of 0.5 mmol/L, the approximate concentration obtained by the ingestion of 640 mg aspirin.

Although aspirin is not considered an anticoagulant per se, it has significant clinical antithrombotic effects. There have been clinical reports of excessive blood loss in the perioperative period in patients who ingested aspirin preoperatively.[82] There is concern that the use of aspirin in the parturient may alter the coagulation status and increase the risk of epidural hematoma following administration of spinal and epidural anesthesia. Also, there is a report of spinal canal bleeding after regional anesthesia in patients receiving aspirin therapy.[83] However, the available evidence indicates that the risk of developing of an epidural hematoma associated with regional anesthesia in a patient receiving aspirin therapy is very low.

Benzon et al. have studied the use of regional anesthesia after aspirin ingestion and have reported uneventful epidurals and spinals in patients receiving aspirin therapy who have had bleeding times up to 10.5 min.[84] The CLASP study of 2783 pregnant women in whom epidural analgesia was uncomplicated included 1422 who were taking low-dose aspirin therapy.[85] Similarly, Sibai and colleagues did not observe any adverse effects related to epidural anesthesia in 891 women who received low-dose aspirin during pregnancy to reduce the incidence of preeclampsia.[86] Horlocker and colleagues estimated the risk for spinal hematoma at 1.1% (with 95% confidence) following regional anesthesia in patients on antiplatelet therapy.[87] In their study, in which 193 patients received aspirin before regional anesthesia, they concluded that preoperative antiplatelet therapy alone is not a significant risk factor for development of spinal hematoma in patients who undergo spinal or epidural anesthesia.[87] However, the concurrent use of other medications affecting the clotting mechanism, such as oral anticoagulant, standard heparin, and low molecular weight heparin, may increase the risk of bleeding complications in these patients.[88]

Bleeding Time

The bleeding time is no longer a popular method of assessing the risk of epidural hematoma formation in the anticoagulated patient. A meta-analysis reviewing more than 1000 publications failed to demonstrate a statistical correlation between clinical bleeding and the bleeding time.[89] An editorial in Lancet suggested that the bleeding time was of little relevance in individual patients before epidural or spinal anesthesia.[90] Furthermore, in a review of the medical literature on the use of bleeding time, authors indicate that there is no evidence that a prolonged preoperative bleeding time predicts which patients will experience excessive surgical bleeding.[91]

Thromboelastography

Thromboelastography, using a single blood sample, measures all phases of coagulation and provides information about the interaction between clotting factors and platelets, clot strength, and stability in a short time.[92] Thromboelastography may be a better representation of the in vivo coagulation sys-

tem because it provides a global assessment of hemostatic function in vitro. Although its popularity stems from increased use in liver transplantation and cardiac surgery, recent reports suggest that it may also be useful in obstetrics. Specifically, it has been used to determine the coagulation status in normal and high-risk pregnant women,[93,94] and it has been used before the administration of epidural anesthesia in pregnant women with suspected coagulopathy.[95]

There are reports suggesting that thromboelastography can be used to assess anticoagulation in women on heparin therapy. Standard heparin and low molecular weight heparin prolong the *r* value of the thromboelastograph.[96] Klein and colleagues measured anticoagulation using thromboelastography in women on low molecular weight heparin therapy and found a strong correlation between *r* time and *k* time of the thromboelastograph with the expected peak and trough levels of the anticoagulation anti-Xa levels.[46] In another study, thromboelastography allowed uneventful regional anesthesia in pregnant women on low molecular weight heparin thromboprophylaxis.[97] Orlikowski and colleagues did not find any changes in thromboelastography variables (*r*, *K*, and MA) in healthy pregnant women receiving aspirin 600 mg.[98]

Summary

Because of the fetal risks of warfarin, most obstetricians use heparin when anticoagulation is indicated during pregnancy. Recent reports indicate that the replacement of standard heparin by low molecular weight heparin may improve management of DVT in pregnancy. The use of spinal or epidural anesthesia for labor or operative delivery is relatively contraindicated in therapeutically anticoagulated parturients because of the potential for bleeding into the epidural or subarachnoid space. The risk of traumatizing a blood vessel during the administration of spinal or epidural anesthesia is real, and the anesthesiologist must ensure that the coagulation status has returned to normal before initiating regional anesthesia in a parturient who has recently been anticoagulated. However, available evidence suggests that regional anesthesia in women on low-dose aspirin therapy or low-dose standard heparin prophylaxis is associated with a very low risk of bleeding in the spinal canal. Regional anesthesia should be avoided if physical examination reveals signs of clinical bleeding such as easy bruising, petechiae, and ecchymosis.

In weighing the risks of general anesthesia against regional anesthesia, one must consider the physiologic changes of pregnancy that increase the risks associated with the induction of general anesthesia in the pregnant woman. If general anesthesia does become necessary in the anticoagulated parturient, the anesthesiologist should be experienced and should make every effort to ensure an atraumatic laryngoscopy to avoid airway trauma and bleeding. The risk of spinal hematoma versus the benefit of regional anesthesia for a specific case should be weighed in anticoagulated women. Also, parturients considered at high risk for the development of spinal hematoma should be monitored closely in the perioperative period for early signs of cord compression.

References

1. Virchow R. Phlogose and thrombose in gefass system. In Virchow R (ed) Gesamelte Abhandlungen zur wissenschaflichen medecin. Frankfurt: Von Medinger Sohn, 1856:458.
2. Laros RK, Alger LS. Thromboembolism and pregnancy. Clin Obstet Gynecol 1979;22:871–878.
3. Cunningham G, MacDonald P, Gant N, et al. Pulmonary disorders. In: Williams Obstetrics, 20th edn. Norwalk: Appleton & Lange, 1997:1112.
4. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1994–1996. London: HMSO, 1998.
5. Franks AI, Atrash HK, Lawson HW, et al. Obstetrical pulmonary embolism mortality, United States 1970–1985. Am J Public Health 1990; 80:720.
6. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 2001;119:122S–131S.
7. Hirsh J, Cade JF, Gallus AS. Anticoagulants in pregnancy: a review of indications and complications. Am Heart J 1972;83:301–305.
8. Villasanta U. Thromboembolic disease in pregnancy. Am J Obstet Gynecol 1965;93:142.
9. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999;353:1258–1265.
10. Tengborn L, Bergqvist D, Matzsch T, et al. Recurrent thromboembolism in pregnancy and puerperium. Is there a need for thromboprophylaxis? Am J Obstet Gynecol 1989;160:90–94.
11. Badaracco MA, Vessey MP. Recurrence of venous thromboembolic disease and use of oral contraceptives. Br Med J 1974;1:215–217.
12. Ginsberg JS, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 1998;114:524S–530S.
13. Bertina RM. Introduction. Hypercoagulable states. Semin Haematol 1997;34:167–169.
14. Friederich PW, Sanson BJ, Simioni P, et al. Frequency of pregnancy-related venous thrombembolism in anticoagulant factor-deficient women: implications for prophylaxis. Arch Intern Med 1996;125:955–960.
15. Zoller B, Dahlbäck B. Linkage between inherited resistance to activated protein C and factor V gene mutation in venous thrombosis. Lancet 1994;343:1536–1538.
16. Dahlbäck B. Inherited resistance to activated protein C, a major cause of venous thrombosis, is due to a mutation in the factor V gene. Haemostasis 1994;24:139–151.
17. Hallak M, Senderowicz J, Cassel A, et al. Activated protein C resistance (factor V Leiden) associated with thrombosis in pregnancy. Am J Obstet Gynecol 1997;176:889–893.
18. American College of Obstetricians and Gynecologists. Thromboembolism in pregnancy. Practice Bulletin No. 19. Washington, DC: ACOG, 2000.
19. Lensing AWA, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med 1989; 320:342.
20. Goldaber SZ. Pulmonary embolism. N Engl J Med 1998;339:93.
21. Erdman WA, Jayson HT, Redman HC, et al. Deep venous thrombosis of extremities: role of MR imaging in the diagnosis. Radiology 1990;174: 425–431.
22. Sipes SL, Weiner CP. Venous thromboembolic disease in pregnancy. Semin Perinatol 1990;14:103–118.
23. Rosenberg JM, Lefor AT, Kenien G, et al. Echocardiographic diagnosis and surgical treatment of postpartum pulmonary embolism. Ann Thorac Surg 1990;49:667–669.
24. Harthorne JW, Buckley MJ, Grover JW, et al. Valve replacement during pregnancy. Ann Intern Med 1967;67:1032.

25. Hall JG, Pauli RM, Wislon KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980;68:122–140.
26. Limet R, Crondin CM. Cardiac valve prosthesis, anticoagulation, and pregnancy. Ann Thorac Surg 1977;23:337–341.
27. Tejani N. Anticoagulant therapy with cardiac valve prosthesis during pregnancy. Obstet Gynecol 1973;42:785–793.
28. Buxbaum A, Aygen M, Shahin W, et al. Pregnancy in patients with prosthetic heart valves. Chest 1971;59:639–642.
29. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000;160:191-196.
30. Brill-Edwards P, Ginsberg JS, Johnston M, et al. Establishing a therapeutic range for heparin. Ann Intern Med 1993;119:104–109.
31. Arnaout MS, Kazma H, Khalil A, et al. Is there a safe anticoagulation protocol for pregnant women with prosthetic valves? Clin Exp Obstet Gynecol 1998;25:101–104.
32. Many A, Pauzner R, Carp M, et al. Treatment of patients with antiphospholipid antibodies during pregnancy. Am J Reprod Immunol 1992;28: 216.
33. Mannucci PM, Canciani MT, Mari D, et al. The varied sensitivity of partial thromboplastin and prothrombin time reagents in the demonstration of the lupus-like anticoagulant. Scand J Haematol 1979;22:423–432.
34. Backos M, Chilcott I, Ray R, et al. Pregnancy complications in women with recurrent miscarriage and antiphospholipid antibodies treated with aspirin and heparin. Hum Reprod 1995;12:61.
35. Reece AE, Gabrielle, Cullen MF, et al. Recurrent adverse pregnancy outcome and antiphospholipid antibodies. Am J Obstet Gynecol 1990;163: 162–169.
36. Rai R, Cohen H, Dave M. Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies for antiphospholipid antibodies. BMJ 1997;314:253–257.
37. Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg 1994;79:1165–1177.
38. Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. Anesth Analg 1997;85:874–885.
39. Flessa HC, Kapstrom AB, Glueck HI, et al. Placental transport of heparin. Am J Obstet Gynecol 1965;93:570–573.
40. Bell WR, Tomasulo PA, Alving BM, et al. Thrombocytopenia occurring during the administration of heparin. Ann Intern Med 1976;85:155–160.
41. American College of Obstetricians and Gynecologists. Thromboembolism in pregnancy. Educational Bulletin No. 234. Washington, DC: ACOG, 1997.
42. Hull R, Delmore T, Carter C, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long term treatment of venous thrombosis. N Engl J Med 1982;306:189–194.
43. Ginsberg JS, Kowalchuk G, Hirsh J, et al. Heparin therapy during pregnancy: risks to the fetus and mother. Arch Intern Med 1989;149:2233–2236.
44. Weiss ME, Nyhan D, Peng Z, et al. Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. N Engl J Med 1989;320:886–892.
45. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997;337:688–698.
46. Klein SM, Slaughter TF, Vail PT, et al. Thromboelastography as a perioperative measure of anticoagulation resulting from low-molecular-weight heparin: a comparison with anti-Xa concentrations. Anesth Analg 2000;91:1091–1095.
47. Hunt BJ, Doughty HA, Majumdar G, et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. Thromb Haemostasis 1997;77:39–43.
48. Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997;176:1062–1068.
49. Blomback M, Bremme K, Hellgren M, et al. Thromboprophylaxis with low molecular mass heparin. “Fragmin” (dalteparin), during pregnancy: a longitudinal safety study. Blood Coagul Fibrinolysis 1998;9:1–9.
50. Dulitzki M, Pauzner R, Langevitz P, et al. Low molecular weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol 1996;87:380–383.
51. Casele HL, Laifer SA, Woelkers DA, et al. Changes in the pharmacokinetics of the low molecular weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol 1999;181:1113–1117.
52. Forestier F, Daffos F, Rainaut M, et al. Low molecular weight heparin (CY 216) does not cross the placenta during the third trimester of pregnancy (abstract). Thromb Haemostasis 1987;57:234.
53. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995;332:1330–1335.
54. Monreal M, Lafoz E, Olive A, et al. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thrombembolism and contraindications to coumarin. Thromb Haemostasis 1994;71:7–11.
55. Breckenridge A, Orme M. Kinetics of warfarin absorption in man. Clin Pharmacol Ther 1973;14:955–961.
56. Pridmore BR, Murray KH, McAllen PM. The management of anticoagulant therapy during and after pregnancy. Br J Obstet Gynaecol 1975; 82:740–744.
57. Shaul WL, Hall JG. Multiple congenital anomalies associated with oral anticoagulants. Am J Obstet Gynecol 1977;127:191–198.
58. Larsen JF, Jacobsen B, Holm HH, et al. Intrauterine injection of vitamin K before delivery during anticoagulant therapy of the mother. Acta Obstet Gynecol Scand 1978;57:227–230.
59. Canfield MC, Edgar AL, Kimball AP. Successful completion of pregnancy in patient with Hufnagel valve. Calif Med 1958;88:54.
60. Dizon-Townson D, Branch D.W. Anticoagulant treatment during pregnancy: an update. Semin Thromb Hemost 1998;24:55–62.
61. American College of Obstetric and Gynecology. Anticoagulation with low-molecular-weight heparin during pregnancy. Technical Bulletin 211. Washington, DC: ACOG, 1998.
62. Lee PK, Wang RYC, Chow JSF, et al. Combined use of warfarin and adjusted subcutaneous heparin during pregnancy in patients with artificial heart valves. J Am Coll Cardiol 1986;8:221–224.
63. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia. A closed claims analysis. Anesthesiology 1999;90: 1062–1069.
64. Tryba M. Rückmarksnahe regionalanästhesie und niedermolekulare heparine. Pro Anästh Intensivmed Notfallmed Schmerzther 1993;28:179–181.
65. Cooke JV. Hemorrhage into the cauda equina following lumbar puncture. Proc Pathol Soc Phila 1911;14:104.
66. Gingrich TF. Spinal epidural hematoma following continuous epidural anesthesia. Anesthesiology 1968;29:162–163.
67. Saka DM, Marx GF. Management of a parturient with cardiac valve prosthesis. Anesth Analg 1976;55:214–216.
68. Rao TL, El-Etr A. Anticoagulation following placement of epidural and subarachnoid catheters. Anesthesiology 1981;55:618–620.
69. Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy: experience with 1,000 cases of continuous epidurals. Anaesthesia 1983;38: 254–259.
70. Liu SS, Mulroy MF. Neuraxial anesthesia and analgesia in the presence of standard heparin. Reg Anesth Pain Med 1998;23(suppl 2):157–163.
71. Allemann BH, Gerber H, Gruber UF. Peri-spinal anesthesia and subcutaneous administration of low-dose heparin-dihydergot for prevention of thromboembolism. Anaesthetist 1983;32:80–83.
72. Lowson SM, Goodchild CS. Low-dose heparin therapy and spinal anesthesia. Anesthesia 1989;44:67–68.
73. Poller L, Taberner DA, Sandilands DG, et al. An evaluation of APTT monitoring of low-dose heparin dosage in hip surgery. Thromb Haemostasis 1982;47:50–53.

74. Darnat S, Guggiari M, Grob R, et al. Lumbar epidural haematoma following the setting-up of an epidural catheter. Ann Fr Anesth Reanim 1986;5:550–552.
75. Horlocker TT, Wedel DJ. Neuraxial blockade and low molecular weight heparin: balancing perioperative analgesia and thromboprophylaxis. Reg Anesth 1998;23:164–177.
76. Schroeder DR. Statistics. Detecting a rare adverse drug reaction using spontaneous reports. Reg Anesth Pain Med 1998;23:183.
77. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for prevention of pregnancy-induced hypertensive disease. JAMA 1991;266:260–264.
78. Italian study of aspirin in pregnancy. Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. Lancet 1993;341:396.
79. Bhagwat SS, Hamann PR, Still WC, et al. Synthesis and structure of the platelet aggregation factor thromboxane A2. Nature (Lond) 1985;315: 511–513.
80. Buchanan MR, Rischke JA, Hirsh J. Aspirin inhibits platelet function independent of the acetylation of cyclooxygenase. Thromb Res 1982;25: 363–373.
81. Harker LA, Slichter SJ. The bleeding time as a screening test for evaluation of platelet function. N Engl J Med 1972;287:155–159.
82. Davies DW, Steward DJ. Unexpected excessive bleeding during operation: role of acetylsalicyclic acid. Can Anaesth Soc J 1977;24:452–458.
83. Greensite FS, Katz J. Spinal subdural hematoma associated with attempted epidural anesthesia and subsequent continuous spinal anesthesia. Anesth Analg 1980;59:72–73.
84. Benzon HT, Brunner EA, Vaisrub N. Bleeding time and nerve blocks after aspirin. Reg Anaesth 1984;9:86.
85. CLASP Collaborative Group. CLASP. A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994;343:619–629.
86. Sibai BM, Caritis SN, Thom E, et al. and the National Institute of Child Health and Human Development Maternal-Fetal Network. Low-dose aspirin in nulliparous women: safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. Am J Obstet Gynecol 1995;172:1553–1557.
87. Horlocker TT, Wedel DJ, Schroeder DR, et al. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesth Analg 1995;80:303–309.
88. Urmey WF, Rowlingson J. Do antiplatelet agents contribute to the development of perioperative spinal hematoma? Reg Anesth Pain Med 1998;23:146–151.
89. Rodgers RPC, Levin J. A critical reappraisal of the bleeding time. Semin Thromb Hemost 1990;16:1–20.
90. The bleeding time [editorial]. Lancet 1991;337:1447.
91. Lind SE. The bleeding time does not predict surgical bleeding. Blood 1991;77:2547–2552.
92. Mallett SV, Cox DJA. Thrombelastography. Br J Anaesth 1992;69:307–313.
93. Sharma SK, Philip J, Wiley J. Thromboelastographic changes in healthy parturients and postpartum women. Anesth Analg 1997;85:94–98.
94. Sharma SK, Philip J, Whitten CW, et al. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastrography. Anesthesiology 1999;90:385.
95. Gottumukkala VNR, Sharma SK, Philip J, et al. Assessment of platelet function using modified TEG in women with severe preeclampsia and thrombocytopenia. Anesthesiology (SOAP Suppl) 1999;A2.
96. Traverso CI, Caprini JA, Arcelus JI, Arcelus IM. Thromboelastographic modifications induced by intravenous and subcutaneous heparin administration. Semin Thromb Hemost 1995;21:53–58.
97. Gorton H, Lyons G. Thromboelastography (TEG) and low molecular weight heparin therapy in pregnancy. SOAP (abstract) 2001;A36.
98. Orlikowski CEP, Payne AJ, Moodley J, et al. Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects. Br J Anaesth 1991;69:159–161.

26
Infectious Disease

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Infectious diseases remain a leading cause of maternal and neonatal mortality during pregnancy, labor, and the puerperium.[1] In the United States alone, despite a fivefold reduction in the last 50 years, the pregnancy-related maternal morality rate remains at approximately 9 per 100,000 live births,[2,3] with infections still accounting for 3% to 10%.[4]

Although profound changes are observed in the immune system during pregnancy, it remains unclear whether pregnant women are more susceptible to infection. Pregnancy does, however, complicate the management of infectious diseases due to concerns regarding fetal well-being and the effect of pregnancy on antimicrobial agents. Although a detailed discussion of drug therapy in pregnancy is beyond the scope of this chapter and can be found elsewhere,[5,6] a few points should be reinforced. Pregnancy dramatically alters drug pharmacokinetics, which refers to how a drug moves through the body. Changes in drug absorption, via reductions in gastric emptying and acid secretion, increased intestinal motility, and increased pulmonary tidal volume (which may affect inhaled drugs), are observed. Furthermore, the volume of distribution for drugs is significantly enlarged during pregnancy with increases in plasma volume of 50%, total body water of 7 to 8 L, and body fat of 20% to 40%. Although these volume alterations would be expected to decrease drug levels, albumin concentrations decline, and free fatty acid and lipoprotein values rise, leading to increases in circulating free (biologically active) drug levels.[7] Metabolism and elimination of drugs are also altered in pregnancy, with hormonally mediated reductions in hepatic metabolism and increases in renal clearance. The net effect of pregnancy-induced alterations on drug pharmacokinetics and efficacy is often unpredictable.

Despite an expressed interest in conducting research in women, even during pregnancy, by governmental agencies and the pharmaceutical industry, concerns over current or future fetal well-being make drug trials difficult to conduct. Many drugs have not been validated for efficacy or safety in human pregnancy, and recommendations often rely on animal model data. Although thalidomide-associated embryopathy cast doubt on the ability of animal studies to predict human teratogenicity, every drug later found to be teratogenic in humans caused similar effects in animals (with the possible exception of misoprostol). With the exception of highly polarized large molecules such as heparin, all maternally administered drugs cross the placenta to some degree. The effect of fetal exposure depends on an interaction of gestational timing, dose, and duration of exposure, as well as poorly defined genetic and environmental factors. As a general rule, a fetus is at highest risk for injury during the period of embryogenesis (days 17–54 postconception). Certain infections, as certain drugs, have been shown to be teratogenic (Table 26.1).

The most common pregnancy and puerperium infections result from ascending contamination of the uterine cavity from the lower genital tract flora and include such conditions as intraamniotic infection (also referred to as chorioamnionitis), urinary tract infection and pyelonephritis, postpartum endometritis, and (rarely) pelvic inflammatory disease. Such infections are often polymicrobial in nature, involving both aerobic and anaerobic organisms.[5] Offending organisms may include the following:

Anaerobes: *Peptostreptococcus* spp., *Prevotella* spp., *Bacteroides fragilis* group, *Fusibacterium* spp., *Porphyromonas asacchrolyticus*, *Clostridium* spp., *Mobiluncus* spp.

Aerobes: Groups A, B, and D streptococci, enterococci, *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Staphylococcus aureus*, *Gardnerella vaginalis*

Other: Genital mycoplasmas, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*

In addition to polymicrobial infectious conditions, specific infections occur in pregnant women as they do in their nonpregnant counterparts. Due to the overwhelming diversity of these infections, a discussion of the obstetric and anesthetic implications of every infection is not possible. Thus, a series of tables summarizing the prevention (Table 26.2) and management of infections in pregnancy (Tables 26.3, 26.4) are included. Several infections have been singled out for further discussion, including a review of the causative organisms, modes of transmission, maternal and fetal effects, recommendations for counseling and management, and anesthetic implications.

TABLE 26.1. Infections with known teratogenic effects.

Infection	Effects	Comments
Cytomegalovirus	Hydrocephaly, microcephaly, chorioretinitis, microphthalmos, cerebral calcifications, intrauterine growth restriction, mental retardation, deafness.	Most common congenital infection. Congenital infection occurs in 40% of cases after primary infection during pregnancy and in 14% of cases after recurrent infection. Of infected infants, physical effects are present in 20% after primary infection and 8% after secondary infection. No effective therapy exists.
Rubella	Microcephaly, mental retardation, cataracts, deafness, congenital heart disease. All organ systems may be affected.	The rate of permanent organ damage is 50% if the infection is acquired during the first trimester; 6% if infection occurs in mid-pregnancy. Immunization of nonpregnant adults and children is necessary for prevention. Although the live attenuated virus vaccine has not been shown to cause the malformations of congenital rubella syndrome, immunization is not recommended during pregnancy.
Syphilis	Effects range from hydrops fetalis, fetal demise (if infection is severe) to detectable abnormalities of skin, teeth, and bones (if infection is mild).	Penicillin treatment is effective to prevent progression of damage. Severity of fetal damage depends on duration of fetal infection (damage is worse if infection is diagnosed at >20 weeks). Prevalence is increasing.
Toxoplasmosis	All organ systems must be affected. Most common manifestations include chorioretinitis and other central nervous system effects (microcephaly, hydrocephaly, cerebral calcifications). Severity of manifestations depends on duration of disease.	Low prevalence during pregnancy (0.1%–0.5%). Initial maternal infection must occur during pregnancy to place fetus at risk. *Toxoplasma gondii* is transmitted to humans by raw meat or exposure to infected cat feces. The incidence of fetal infection increases as gestational age increases (9%–10% in first trimester; 60% in the third trimester). However, the severity of congenital infection is greater in the first trimester than at the end of gestation.
Varicella	May affect all organ systems. Common manifestations include skin scarring, chorioretinitis, cataracts, microcephaly, hypoplasia of the hands and feet, muscle atrophy.	Overall risk of congenital varicella is low (about 2%–3%), and it occurs most commonly between 7 and 21 weeks gestation. Varicella zoster immunoglobulin should be administered to newborns exposed in utero during the last 4–7 days of gestation. No adverse effect from herpes zoster.

Source: Adapted from Teratology. ACOG Educational Bulletin No. 236, April 1997.

General Anesthetic Management

Although no clear consensus exists in the literature or from clinical practice regarding the use of regional anesthesia in parturients with suspected or documented infections, an analysis based on risk versus benefit appears to favor its use in most cases. Because most viral infections seed the central neuraxis early in their course, regional techniques offer little additional risk for viral spread. With bacterial infections, the risk of meningitis or spinal-epidural abscess formation following central neuraxial techniques appears exceedingly low. Despite the prevalence of bacteremia (up to 60% in healthy parturients with the insertion of a urinary catheter[8]) and the frequent absence of clinical signs in septic[9] or infected parturients,[10] only a few such cases of neuraxial infections have been reported following central neuraxial techniques.[11] Neuraxial techniques in high-grade infections, however, are not completely without risk. Carp et al.[12] noted that when cisternal punctures were performed in bacteremic rats, bacterial cultures could be isolated from the cerebrospinal fluid. By contrast, when the rats were pretreated with antibiotics, no bacterial cultures were obtained. Although the applicability of an animal model using cisternal punctures with bacteria of known antibiotic sensitivities has been questioned, it seems reasonable that the risk of bacterial infections can be reduced through the use of antibiotics before regional techniques in infected parturients. As such, the use of antibiotic therapies before regional anesthesia may be prudent in patients with established infections. Should a high-grade infection exist, attention to intravascular volume replacement, additional monitoring, and potentially abstaining from regional techniques, especially in parturients with overt signs of sepsis, should be considered.

Although general anesthesia is often utilized for operative deliveries in patients with suspected or documented systemic infections,[13] a 16-fold-greater incidence of mortality in all parturients has been associated with its use, primarily due to an inability to secure the airway and commence ventilation.[14] While the urgency of the situation or comorbidities may have accounted for the higher mortality observed, the use of regional techniques are often excluded without consideration of their potential benefit. However, should general anesthesia be ultimately selected, induction and maintenance agents with limited cardiovascular and hemodynamic consequences, particularly in critically ill parturients with sepsis, should be chosen with care. Ketamine and etomidate have been utilized successfully in such cases. In addition, although hyperkalemia from succinylcholine has never been reported in a patient with chorioamnionitis, should infections be severe or prolonged, the use of a rapid-acting nondepolarizing agent, such as rocuronium, should be considered.

Group B Streptococcus

Group B β-hemolytic streptococcus (GBS), or *Streptococcus agalactiae*, is the most common bacterium associated with neonatal infection and the leading cause of life-threatening

TABLE 26.2. Chemoprophylaxis in pregnancy.

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
Postpartum endometritis	Cefazolin 1 g IV × 1 dose or Ampicillin 1–2 g IV × 1 dose or Clindamycin 600–900 mg IV and gentamicin 1.5 mg/kg IV × 1 dose		Prophylaxis should be administered preoperatively to women at high risk. Once-daily dose of gentamicin has not been validated for efficacy or safety during pregnancy and in the puerperium. Other aminoglycosides may be substituted for gentamicin (Aztreonam is effective but is expensive and is therefore reserved for women with renal insufficiency).
Bacterial endocarditis (primary against enterococci)	Ampicillin 2 g IM/IV and gentamicin 1.5 mg/kg IM/IV within 30 min of delivery plus Ampicillin 1 g IM/IV or amoxicillin 1 g po × 1 dose within 6 h of delivery	Vancomycin 1 g IV over 1–2 h and gentamicin 1.5 mg/kg IM/IV within 30 min of delivery (no postdelivery dose)	The American Heart Association does not recommend antibiotic prophylaxis for cesarean delivery or normal vaginal delivery, with the possible exception of high-risk women for whom it is optional.
Pyelonephritis (mainly *Escherichia coli*)	Nitrofurantoin 50–100 mg po each night before bedtime or Sulfisoxazole 500 mg po each night before bedtime		Consider antibiotic suppression after acute pyelonephritis or recurrent urinary tract infection (UTI) in pregnancy, and in women at high risk for UTI/pyelonephritis.
Group B streptococcus (GBS)	Penicillin G 5 million units IV loading dose, followed by 2.5 million units IV q4h	Ampicillin 2 g IV loading dose, followed by 1–2 g q4–6h or Clindamycin 600 mg IV q6h or 900 mg IV q8h or Erythromycin 500 mg IV q6h	Intrapartum, but not antepartum, chemoprophylaxis against GBS has been shown to decrease early-onset neonatal GBS sepsis.
Genital herpes simples virus (usually HSV-2)	Acyclovir 200 mg po qid from 35–36 weeks gestation to delivery (not postpartum) or Acyclovir 400 mg po bid from 35–36 weeks gestation to delivery (not postpartum)	Famciclovir 250 mg po bid or Valacyclovir 250 mg po bid or Valacyclovir 500 mg po daily or Valacyclovir 1 g po daily	Suppression therapy reduces the frequency of recurrences by ~75% in patients with ≥6 recurrences/year. Goal of suppression is to decrease the incidence of HSV prodrome and/or genital lesion in labor that would necessitate cesarean delivery. Suppression may be offered to women with first-episode genital HSV infection during the index pregnancy or frequent recurrence.
Sexual assault (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*)	Ceftriaxone 125 mg IM × 1 dose PLUS Metronidazole 2 g po × 1 dose PLUS Azithromycin 1 g po × 1 dose or doxycycline 100 mg po bid × 7 days	For alternative treatments, refer to sections in this table that specifically address alternative therapeutic options for each of the potential infectious agents under consideration.	Hepatitis B vaccine should be administered with follow-up at 1–2 and 4–6 months after first dose. Testing for HIV and possible antiretroviral prophylaxis should be considered.

Source: Adapted from 1998 Recommendations by the Centers for Disease Control and Prevention. (Rayburn WF. Treatment of sexually transmitted disease. J Reprod Med 1998;43:471–476.)

perinatal infections in the United States.[15] A gram-positive encapsulated coccus that produces β-hemolysis on blood agar, GBS is responsible for an overall rate of neonatal infection of 1 to 3 per 1000 live births, 10 per 1000 deliveries in women colonized with GBS, and 40 to 50 per 1000 live births complicated by preterm delivery.[16]

Early-onset neonatal GBS infection, which accounts for 80% to 85% of all cases, is characterized by neonatal respiratory distress, apnea, pneumonia, and septic shock within 1 week of delivery. Confirmed by a positive blood culture, the infection has an overall mortality rate of 5% (but the rate may be as high as 25% among preterm infants), with surviving

TABLE 26.3. Treatment of sexually transmitted diseases in pregnancy.

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
Bacterial vaginosis (BV) (*Proteus* species, *Mobiluncus* species, *Mycoplasma hominis*, *Gardnerella vaginalis*)	Metronidazole 250 mg po tid × 7 days	Metronidazole 2 g po × 1 dose or Clindamycin 300 mg po bid × 7 days or Metronidazole gel (0.75%) one applicator full (5 g) intravaginally bid × 5 days [recommended for low-risk pregnant women only]	BV is associated with adverse perinatal outcome, including low birth weight and preterm birth. Pregnant women with symptomatic BV should be treated. It remains unclear whether screening/treatment of asymptomatic women improves perinatal outcome. Lower dose of metronidazole is recommended to reduce risk to fetus. Clindamycin vaginal gel is not recommended (may be associated with an increase in preterm delivery)
Chancroid (*Haemophilus ducreyi*)	Azithromycin 1 g po × 1 dose or Ceftriaxone 250 mg IM × 1 dose or Erythromycin base 500 mg po qid × 7 days		Exclude HSV, *T. pallidum.* Consider HIV screening (erythromycin is recommended for HIV+ women). Ciprofloxacin is an alternative treatment, but is contraindicated in pregnancy.
Chlamydial infections (*Chlamydia trachomatis*)	Erythromycin base 500 mg po qid × 7 days or Amoxicillin 500 mg po tid × 7 days	Erythromycin base 250 mg po qid × 14 days or Erythromycin ethylsuccinate 800 mg po qid × 7 days or Erythromycin ethylsuccinate 400 mg po qid × 14 days or Azithromycin 1 g po × 1 dose	Erythromycin estolate, doxycycline, and ofloxacin are contraindicated in pregnancy. There are insufficient data to recommend the routine use of azithromycin in pregnancy. Repeat cultures 3 weeks after therapy has been completed because of the high rate of noncompliance and the lower efficacy of erythromycin treatment regimens.
Gonococcal infections (*Neisseria gonorrhoeae*)	Cefixime 400 mg po × 1 dose or Ceftriaxone 125 mg IM × 1 dose plus a regimen effective against possible concomitant infection with *C. trachomatis:* Erythromycin base 500 mg po qid × 7 days or Amoxicillin 500 mg po tid × 7 days or Azithromycin 1 g po × 1 dose or Doxycycline 100 mg po × 7 days	Spectinomycin 2 g IM × 1 dose or Ceftizoxime 500 mg IM × 1 dose or Cefotaxime 500 mg IM × 1 dose or Cefotetan 1 g IM × 1 dose or Cefoxitin 2 g IM × 1 dose with probenecid 1 g po × 1 dose	Azithromycin 2 g po single dose is effective, but expensive and causes GI upset (1 g dose is ineffective). In pregnancy, quinolones (ofloxacin, ciprofloxacin, lomefloxacin, enoxacin, norfloxacin) and tetracycline are contraindicated. If cephalosporins cannot be tolerated, treat with spectinomycin 2 g IM × 1 dose. For disseminated gonococcal infection, treat in hospital setting with ceftriaxone 25–50 mg/kg/day IM/IV daily × 7 days or cefotaxime25 mg/kg IM/IV bid × 7 days (up to 10–14 days if meningitis is documented).
Genital herpes simplex virus (usually HSV-2)	First clinical episode of genital herpes: Acyclovir 400 mg po tid × 7–10 days or until clinically resolved or Acyclovir 200 mg po 5×/day × 7–10 days or until clinically resolved or Famciclovir 250 mg po tid × 7–10 days or until clinically resolved or Valacyclovir 1 g po bid × 7–10 days or until clinically resolved		Topical acyclovir is less effective than oral treatment, and is discouraged. First clinical episode during pregnancy may be treated with acyclovir. Safety of valacyclovir and famciclovir in pregnancy is not well established, but benefits may outweigh risks. Treatment must be initiated during prodrome or within 1 day of onset of lesions for patient to experience benefit from therapy.

TABLE 26.3. *Continued*.

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
	Recurrent clinical episodes of genital herpes: Acyclovir 400 mg po tid × 5 days or Acyclovir 200 mg po 5×/day × 5 days or Acyclovir 800 mg po bid × 5 days or Famciclovir 125 mg po bid × 5 days or Valacyclovir 500 mg po bid × 5 days Disseminated herpes: Acyclovir 5–10 mg/kg IV q8h × 5–7 days		
Genital warts (human papillomavirus, HPV)	Cryotherapy with cryoprobe or liquid nitrogen or Trichloroacetic acid (TCA) 80%–90%, apply only to warts. Use powder with talc or baking soda to remove unreacted acid. Repeat weekly if necessary, or Surgical removal.	Intralesional interferon or Laser surgery	Imiquimod, podofilox, and podophyllin are contraindicated in pregnancy. Thus, therapy during pregnancy is severely limited. No therapy has been shown to eradicate or affect the natural history of HPV. If lesions persist after one type of treatment, other therapies should be considered. Genital warts are not a contraindication to vaginal birth, but may bleed excessively at delivery.
Pubic lice (pediculosis pubis)	Permethrin 1% cream rinse, applied to affected areas and washed off after 10 min or Pyrethrins with piperonyl butoxide, applied to affected areas and washed off after 10 min.		Lindane 1% shampoo is not recommended for use in pregnant or lactating women. Toxicity related to prolonged lindane exposure includes seizures and aplastic anemia. Decontaminate clothing and bedding, or remove from body contact for at least 72 h. Fumigation is not necessary. Evaluate and retreat in 1 week if symptoms persist or lice observed. Treat sexual partners.
Scabies (*Sarcoptes scabiei*)	Permethrin cream (5%), applied to all areas of the body from the neck down and washed off after 8–14 h.	Sulfur (6%) precipitated in ointment, applied thinly to all areas nightly for 3 consecutive nights; wash off previous application before applying new one. Wash off thoroughly 24 h after the last application.	Lindane is not recommended in pregnant or lactating women. Decontaminate clothing and bedding. Pruritis may persist for several weeks. Consider treatment after 1 week if still symptomatic. Both sexual and close personal and household contacts within the preceding month should be examined and treated. Scabies among children is generally not sexually transmitted. Treatment of entire populations may be required to control scabies epidemics.
Trichomonas (*Trichomonas vaginalis*)	Metronidazole 2 g po × 1 dose	Metronidazole 500 mg po bid × 7 days	Metronidazole is not recommended in the first trimester. If treatment fails, consider 375–500 mg bid × 7 day regimen. If repeated failure, consider 2 daily × 3–5 days.
Syphilis[a] (*Treponema pallidum*)	Primary/secondary/early latent syphilis: Benzathine penicillin G, 2.4 million units IM × 1 dose (usually administered as 1.2 million units into each buttock). Some experts recommend a second dose of penicillin for such women 1 week after initial dose.		Routine screening for syphilis at first prenatal visit. High-risk women should be screened again at 28 weeks and at delivery. All women with syphilis should be offered HIV testing. Penicillin is effective in preventing transmission to fetuses and for treating established infection in fetuses. Women treated in the second half of pregnancy are at risk for preterm labor, possibly due to Jarisch–Herxheimer reaction.

(*Continued*)

TABLE 26.3. *Continued.*

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
	Late latent/tertiary/unknown duration: Benzathine penicillin G, 2.4 million units IM/week × 3 weeks (7.2 million units total). Neurosyphilis: Aqueous crystalline penicillin G, 12–24 million units IV daily (administered as 2–4 million units IV q4h) × 10–14 days or Aqueous procaine penicillin G, 2.4 million units IM daily plus probenecid 500 mg PO qid × 10–14 days.		If pregnant patient with syphilis is penicillin allergic, desensitize and treat with penicillin. Doxycycline and tetracycline are contraindicated in pregnancy. Erythromycin cannot be relied upon to treat the infected fetus. Insufficient data on azithromycin or ceftriaxone.

[a]Adapted from Centers for Disease Control: 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47:28–49.
Source: Adapted from 1998 Recommendations by the Centers for Disease Control and Prevention. (Rayburn WF. Treatment of sexually transmitted diseases. J Reprod Med 1998;43:471–476.)

neonates often exhibiting significant long-term neurologic sequelae. By contrast, late-onset GBS infection usually results from community- or hospital-acquired (nosocomial) infections in preterm infants and presents as meningitis or sepsis more than 1 week after birth.

Transmission of early-onset neonatal GBS infection results almost exclusively during labor and delivery in parturients from lower genital or gastrointestinal tract colonization rather than transplacental passage. Not sexually transmitted, GBS is a commensal organism that intermittently colonizes the lower genital tract of 20% (range, 15%–40%) of women at any one time.[17] An estimated 8% to 10% crossover of GBS carrier status exists during each trimester, and thus determination of GBS carrier status is not recommended at the first prenatal visit. Half of all infants born to women colonized with GBS will become colonized with GBS; however, most are asymptomatic.[15]

A number of strategies have been proposed to prevent early-onset GBS infection, including intrapartum maternal and postpartum neonatal antibiotic regimens. However, such antibiotic use has been associated with the emergence of antibiotic resistance,[18] an increased incidence of early-onset neonatal sepsis due to non-GBS organisms,[19] and maternal anaphylaxis (estimated as 1:60,000 for penicillin).[20] Because of these limitations, routine administration of GBS chemoprophylaxis is not recommended for all women in labor. Instead, two independent prophylaxis protocols have been proposed and deemed acceptable for select parturients by the American College of Obstetricians and Gynecologists (ACOG).[15,16]

A *risk factor-based protocol* involves intrapartum treatment of pregnancies with one or more risk factors, including preterm labor, preterm premature rupture of the membranes, prolonged rupture of membranes (≥18 h regardless of gestational age), a prior GBS-infected infant, maternal fever in labor (≥100.4°F), and GBS bacteriuria or urinary tract infection at any time during the index pregnancy. No attempt is made to identify women colonized with GBS. This protocol results in intrapartum treatment of 20% to 25% of pregnant women with prevention of 65% to 70% of GBS disease.[15,16]

A *culture-based protocol* involves intrapartum prophylaxis of women who are known GBS carriers or whose GBS carrier status is unknown. To predict carrier status in labor, GBS cultures should be sent as late as possible during pregnancy, but before the onset of labor (ideally, 35–37 weeks gestation), to accurately reflect GBS carrier status at delivery.[21] Because GBS colonization increases from the cervix to the introitus, the culture should be taken by generously swabbing the lower vagina, perineum, and perianal area using a single cotton swab, and the swab should be placed briefly into the anal canal. A speculum should not be used. The "perineal" (not cervical) swab should be inoculated into Todd–Hewitt broth or selective blood agar, stored at room temperature, and transported to the laboratory within 8 h of collection. Processing in the laboratory will usually take 48 h. Antimicrobial susceptibility is not routinely done, as most GBS organisms are pansensitive. Rapid screening tests for GBS carrier status in labor have been developed, but are more difficult to perform, not available in all hospitals at all times, and have poor sensitivity in identifying women with low levels of GBS colonization. The culture-based protocol results in treatment of 15% to 20% of pregnant women with prevention of 70% to 80% of GBS disease.[15,16]

Should the decision be made to proceed with intrapartum GBS chemoprophylaxis, a number of general guidelines should be followed. Intravenous penicillin G, instead of ampicillin, is the antibiotic of choice due to a narrower spectrum and reduced likelihood of leading to antibiotic resistance. A minimum of 4 h of antibiotic prophylaxis is recommended, with discontinuance at delivery.

Anesthetic Management

Although group B β-hemolytic streptococcus has been implicated as the cause of meningitis in two parturients who had

TABLE 26.4. Treatment of other infections in pregnancy.

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
Asymptomatic bacteriuria (primarily *E. coli*; also *Klebsiella/Enterobacter* sp, *Proteus* sp, Group B streptococci, enterococci)	Nitrofurantoin macrocrystals 50–100 mg po qid × 3 days or Nitrofurantoin monohydrate 100 mg po bid × 3 days or Cephalexin 250–500 mg po qid × 3 days	Ampicillin 250–50 mg po qid × 3 days or Amoxicillin 250–500 mg po tid × 3 days or Trimethaprim/sulfamethoxazole 160 mg/180 mg po bid × 3 days or Trimethoprim 200 mg po bid × 3 days or Sulfisoxazole 2 g loading dose po followed by 1 g po qid × 3 days	Complicates 2%–9% of pregnancies. Consider treatment when 25,000–100,000 colony-forming units/mL of a single pathogenic organism are found in a clean-catch midstream urine specimen. Single-dose treatment is effective but has a higher failure rate; a 3-day course is usually recommended. Obtain a follow-up culture 7–10 days after completion of treatment.
Pyelonephritis (mainly *E. coli*)	Ampicillin 1–2 g IV q6h and gentamicin 1.5 mg/kg q8h or Ceftriaxone 1–2 g IM/IV q24h	Trimethaprim/sulfamethoxazole 160 mg/800 mg IV q12h or Gentamicin 1.5 mg/kg q8h	Treat IV until asymptomatic and afebrile for 24–48 h, followed by oral antibiotics to complete 10 days of therapy. After acute treatment, obtain a follow-up culture in 7–10 days, place on prophylactic therapy, and perform periodic screening.
Intraamniotic infection (mainly Group B streptococci, *E. coli*)	Ampicillin 2 g IV q4–6h and gentamicin 1.5 mg/kg IV q8h intrapartum or Penicillin 2.5–5 million units q4–6h and gentamicin 1.5 mg/kg IV q8h intrapartum plus Clindamycin 900 IV q8h or Metronidazole 500 mg IV q8h added after delivery only if delivery is by cesarean	Ampicillin/sulbactam 3 g IV q6h or Cefotetan 2 g IV q12h or Cefoxitin 2 g IV q6h or Cefotaxime 25 mg/kg IM/IV q12h plus Clindamycin 900 IV q8h or Metronidazole 500 mg IV q8h added after delivery only if delivery is by cesarean	Intraamniotic infection remains a clinical diagnosis (fetal tachycardia, uterine tenderness and contractions, maternal tachycardia and fever). Amniotic fluid culture remains the gold standard for diagnosis; Gram stain is only 50% sensitive. Delivery should be expedited, irrespective of gestational age. Following delivery, antibiotic coverage should probably be continued. If delivery is by cesarean, antibiotic coverage should also be broadened (clindamycin is preferred over metronidazole for lactating women).
Postpartum endometritis (polymicrobial infection with both anaerobes aerobes)	Clindamycin 900 mg IV q8h and gentamicin 1.5 mg/kg IV q8h with or without Ampicillin 1–2 g IV q4–6h or penicillin 2.5–5 million units IV q4–6h	Cefotetan 2 g IV q12h or Cefoxitin 2 g IV q6h or Cefotaxime 1–2 g IM/IV q6–8h or Piperacillin 3–4 g IM/IV q4–6h or Ampicillin/sulbactam 3 g IV q6h	Treatment should be continued until the patient has been asymptomatic and afebrile for 24–48 h. Around 10% of patients will not be cured with initial therapy. Approximately 20% of treatment failures are due to resistant organisms. Women who do not respond within 48–72 h often have another source of fever (drug fever, wound infection, septic pelvic thrombophlebitis, infected hematoma, abscess, retained products of conception).
Vulvovaginal candidiasis (*Candida albicans* and other *Candida* species, *Torulopsis* species, or other yeasts)	Butoconazole 2% cream 5 g intravaginally × 3 days or Clotrimazole 1% cream 5 g intravaginally × 7–14 days or Clotrimazole 100 mg vaginal tablet × 7 days or		In pregnancy, topical azole products should be used rather than nystatin. Most effective are butoconazole, clotrimazole, and terconazole; 7-day regimens are preferred.

(*Continued*)

TABLE 26.4. *Continued.*

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
	Clotrimazole 100 mg vaginal tablet, two tablets × 3 days or Clotrimazole 500 mg vaginal tablet × 1 dose or Miconazole 2% cream 5 g intravaginally × 7 days or		Oral agents such as ketoconazole (100 mg po single dose) and fluconazole (150 mg po single dose) may be as effective as topical agents, but potential toxicity and drug interactions must be considered.
	Miconazole 200 mg vaginal suppository, 1 dose × 3 days or Miconazole 100 mg vaginal suppository, 1 dose × 7 days or Tioconazole 6.5% ointment 5 g intravaginally × 1 dose or Terconazole 0.4% cream 5 g intravaginally × 7 days or Terconazole 0.8% cream 5 g intravaginally × 3 days or Terconazole 80 mg suppository, 1 dose × 3 days		Treatment of sexual partners has not been shown to decrease frequency of recurrences.
Malaria (*Plasmodium falciparum*, *P. vivax, P. malariae, P. ovale*)	Chloroquine 1 g po × 1 dose; then 500 mg at 6, 24, 48 h; then weekly until delivery plus Proguanil 200 mg po qd	Quinine 650 mg po tid × 3–7 days plus Sulfadoxine/pyrimethamine 3 tablets × 1 dose on day 3 of treatment	Malaria is the major cause of fetal growth restriction worldwide. Primaquine should not be used in pregnancy because the drug crosses the placenta and can cause hemolytic anemia in a parturient with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Cerebral malaria should be treated with IV quinine gluconate.
Listeriosis (*Listeria monocytogenes*)	Ampicillin 1–2 g IV q6h and gentamicin 1.5 mg/kg IV q8h	Trimethaprim/sulfamethoxazole 160 mg/800 mg IV q12h or Erythromycin 500–2000 mg IV q6h	The best length of therapy is not known. Treat IV until asymptomatic and afebrile for 24–48 h. Consider prompt delivery if listeria amnionitis is confirmed.
Pelvic inflammatory disease (PID) (*N. gonorrhoeae*, *C. trachomatis*, *Gardnerella vaginalis*, etc.)	Regimen A Cefoxitin 2 g IV q6h or Cefotetan 2 g IV q12h plus Doxycycline 100 mg IV/po q12h plus Doxycycline 100 mg po bid × 14 days total Regimen B Clindamycin 900 mg IV q8h plus Gentamicin 2 mg/kg IV/IM loading dose then 1.5 mg/kg maintainence dose q8h plus Doxycycline 100 mg po bid × 14 days total or clindamycin 450 mg po qid × 14 days total	Ampicillin/sulbactam 3 g IV q6h and doxycycline 100 mg IV/po q12h or Azithromycin 500 mg IV × 2 days followed by 500 mg po × 10 days	PID in pregnancy is very rare. All pregnant women with PID should be hospitalized and treated with IV therapy. Quinolones (ciprofloxacin, ofloxacin) are contraindicated in pregnancy. Treatment may be discontinued 24 h after clinical improvement. When tubo-ovarian abscess is present, surgery may be required, and clindamycin may be preferred for continued therapy. Other 2nd- and 3rd-generation cephalosporins may be effective, but clinical data are limited.

TABLE 26.4. *Continued.*

Infection (causative organism)	Primary therapy	Alternative therapy	Comments
Tuberculosis (*Mycobacterium tuberculosis*)	Positive PPD/no active disease: Isoniazid 300 mg po daily after delivery for 6–9 months or Isoniazid 300 mg po daily after first trimester for 6–9 months (for high-risk women, including recent seroconversion, recent immigrant, known recent TB contact, immunocompromised women, skin test >15 mm and not previously treated) Active disease: Isoniazid 300 mg po daily × 9–12 months plus Rifampin 600 mg po daily × 9–12 months plus/or Ethambutol 2.5 g (15 mg/kg) po daily × 9–12 months or until sensitivity of the AFB culture returns plus Pyridoxine 50 mg po daily × 9–12 months		Isoniazid prophylaxis should be avoided in the puerperium because of the high incidence of hepatic toxicity. In pregnancy, drugs such as kanamycin, streptomycin, capreomycin (congenital deafness), ethionamide (teratogenic), and cycloserine (CNS side effects) are contraindicated Pyrazinamide may be used in place of ethambutol, but this approach is not generally recommended as there are limited data on pyrazinamide use in pregnancy.

Source: Adapted from 1998 Recommendations by the Centers for Disease Control and Prevention. (Rayburn WF. Treatment of sexually transmitted disease. J Reprod Med 1998;43:471–476.)

epidural labor analgesia,[22,23] nosocomial skin organisms are the most likely culprits for these rare cases of meningitis.[24] In addition, in three retrospective analyses of parturients with documented chorioamnionitis,[25–27] representing a total of 923 patients, no cases of epidural abscess or meningitis were noted, despite the absence of antibiotic coverage before receiving the regional techniques and the presence of fever, bacteremia, and leukocytosis in a number of parturients. Overall, these data suggest that the infectious risk following regional techniques in parturients with group B β-hemolytic streptococcus is very rare. However, as the possibility cannot be excluded, it would be prudent, as with other systemic infections, to request and initiate appropriate antibiotic therapy before the administration of regional techniques and to avoid such techniques in women with overt signs of sepsis.

Cytomegalovirus

Cytomegalovirus (CMV) is a double-stranded DNA herpesvirus transmitted by contact with infected blood, saliva, urine, breast milk, or through sexual contact. The mean incubation period is 40 days (range, 28–60 days). Although a brief, self-limited, flu-like illness with fever, chills, malaise, myalgia with leukocytosis, and elevated liver function tests may be experienced, the majority of infected adults are asymptomatic. After the initial infection, CMV, similarly to other herpesviruses, remains latent in host cells and may reactivate. In rare cases, recurrent disease may be caused by infection with a different strain of the virus.

Diagnosis requires a high index of clinical suspicion. Although the CMV virus can be detected 2 to 3 weeks following a primary infection by culture or polymerase chain reaction (PCR), the diagnosis is usually confirmed by serologic testing, either with positive seroconversion or a minimum fourfold increase in anti-CMV IgG titers over 3 to 4 weeks. The presence of anti-CMV IgM is a useful, but not completely reliable, method of establishing a primary infectious process; IgM titers may be nondetectable during an acute infection and may persist for months.[28] The reported sensitivity of CMV IgM serologic assays ranges from 50% to 90%.[28]

The prevalence of CMV infection in pregnant women varies from 0.7% to 4% for primary infections and up to 13.5% for recurrent infections.[29] Vertical transmission may occur via a transplacental route with primary or recurrent CMV infections, exposure to contaminated genital tract secretions with vaginal birth, or through breast-feeding. Occurring at any stage of pregnancy, fetal infections are most common during the third trimester; however, more serious sequelae follow first trimester transmission. The risk of vertical transmission during primary and recurrent maternal CMV infections is 30% to 40%[30] and 0.15% to 2%, respectively,[31]

with more severe fetal neurologic morbidity following primary infections.[32]

Cytomegalovirus is the most common congenital infection, occurring in 0.2% to 2.2% of all neonates,[32] and is the leading cause of congenital hearing loss. Prenatally, CMV infection can be suspected following a documented maternal primary infection or suggestive ultrasound findings; these include abdominal, liver, and lateral cerebrospinal fluid (CSF) ventricle calcifications, ventriculomegaly, hydrops fetalis, echogenic bowel, ascites, and hepatosplenomegaly.[33] Structural anomalies, especially within the central nervous system, dictate a much poorer fetal prognosis. Diagnostic confirmation can usually be made through detection of CMV in amniotic fluid by culture or PCR. Fetal blood sampling for antibody response is less sensitive due to the immaturity of the fetal immune system,[34] and alterations of platelet count and liver function tests are nonspecific. Although most infants with congenital CMV are asymptomatic at birth, evidence of the aforementioned ultrasound findings, as well as growth restriction, jaundice, petechiae, and thrombocytopenia, may be observed.[35]

No therapies are currently available for maternal or fetal CMV infection, and thus routine serologic screening for CMV during pregnancy is not recommended.[36] Although the antiretroviral therapies ganciclovir or foscarnet have been used for CMV retinitis in AIDS patients, the use of ganciclovir in combination with CMV hyperimmune gamma globulin in CMV-infected neonates has not been shown to prevent long-term neurologic sequelae.[37] A vaccine is under development but remains currently unavailable. Patient education efforts thus should focus on preventative measures, including careful handling of potentially infected articles (such as diapers) and thorough handwashing when around young children or immunocompromised individuals. In addition, avoidance of high-risk behaviors such as intravenous drug use and sharing of needles should be emphasized when appropriate. Barrier contraception should be encouraged as a method of contraception.

Anesthetic Management

To date, there are no data regarding the implications of CMV on anesthesia.

Hepatitis

One of the most serious infections that can occur during pregnancy, viral hepatitis can be caused by a diverse collection of viruses, including CMV, Epstein–Barr, varicella zoster, coxsackie B, herpes simplex, and rubella. However, a family of seven hepatitis viruses, designated by the letters A through E, G, and TT, are the predominant sources of the disease process; although the viruses are distinct, similarities in clinical manifestations, diagnosis, management, and obstetric and anesthetic implications can be observed. The following information concerns this family of hepatitis viruses.

Malaise, fatigue, anorexia, nausea, and right upper quadrant or epigastric pain are the most common symptoms of acute viral hepatitis, and these symptoms are often accompanied by signs of jaundice, upper abdominal tenderness, and hepatomegaly. Hepatitis A and E are usually self-limited, but hepatitis B, C, and D frequently progress to a chronic carrier state.[38] Hepatitis G and TT may also result in a carrier state; however, their ability to exist independent of other hepatitis forms as acute or chronic hepatitis has yet to be established.[39,40] Although the majority of chronic carriers are asymptomatic, up to one third eventually develop chronic active or persistent hepatitis. Should cirrhosis follow, the signs of end-stage liver disease, including jaundice, muscle wasting, ascites, spider angiomas, palmar erythema, and ultimately hepatic encephalopathy often ensue. Hepatitis D, the defective virus that requires hepatitis B for replication and expression, progresses to severe disease more often than any other form of viral hepatitis. Of patients with chronic hepatitis D, 70% to 80% ultimately develop cirrhosis and portal hypertension, with 15% undergoing rapid progression to death.[41] By contrast, only 15% to 30% of patients with chronic hepatitis B develop cirrhosis, and the progression is much slower.

Diagnosis of viral hepatitis usually begins with a battery of general liver tests that demonstrate a marked increase in serum concentrations of alanine aminotransferase (ALT; previously SGPT), aspartate aminotransferase (AST; previously SGOT), and bilirubin. Initial evaluation should include hepatitis A IgM (anti-HA IgM), hepatitis B surface antigen (HBsAg), and hepatitis C polymerase chain reaction (HC PCR).[42] Additional testing can include testing for hepatitis B core antibody (anti-HBc IgM), which appears between the time when surface antigen and antibodies appear, hepatitis D (HD PCR), hepatitis E (anti-HE), and hepatitis G (anti-HG). Liver biopsies are rarely required during pregnancy. With severe cases, coagulation abnormalities (especially prothrombin time) and hyperammonemia can be observed; however, neutropenia and lymphopenia are often replaced by a relative lymphocytosis.

Management of parturients infected with hepatitis should begin with avoidance of activities that can result in upper abdominal trauma, maintenance of good nutrition, and avoidance of intimate contact until the involved parties receive appropriate prophylaxis as outlined next. Should more severe signs be present, hospitalization and correction of nutritional, fluid, electrolyte, and coagulation disorders is recommended. Although not a specific therapy for the various hepatitis viruses, interferon-alpha has been demonstrated to alter the natural course of acute hepatitis B, C, and D. Multiple side effects, however, including myelosuppression, autoantibody formation, thyroid disturbances, and possible cardiotoxicity, limit its use. In addition, interferon is not recommended during pregnancy because of the possible abortifacient effect.[38]

As these treatments are not completely curative, the emphasis has been placed on the prevention of viral hepatitis through education and immunization. Passive immunization with antibody immunoglobulin (IG) preparations purified

TABLE 26.5. Incidence and transmission of hepatitis viruses.

Type	Virus	Incidence[a]	Transmission	Vertical transmission	Perinatal transmission
A	RNA	1/1000	Fecal-oral	No	No
B	DNA	Acute: 1–2/1000 Chronic: 5–15/1000	Parenteral-sexual	Yes	Yes
C	RNA	6/1000	Parenteral-sexual?	Rare	Yes
D	RNA	Unknown	Parenteral-sexual	Yes	Yes
E	RNA	Unknown	Fecal-oral	Yes	Not reported
G	RNA	Unknown	Parenteral-sexual	Yes	Not reported
TT	DNA	Unknown	Parenteral-sexual?	Yes	Not reported

[a]Incidence in the United States during pregnancy.

from the plasma of normal donors is active against hepatitis A, B, and D (through immunization against B). A specific immunoglobulin against hepatitis B (HBIG) is also available and has been demonstrated to be more efficacious than standard IG preparations. Of note, plasma-derived IG preparations are considered to be of no infectious risk because of an ethanol fractionation process that inactivates viral (including the human immunodeficiency virus, HIV) and other bloodborne infectious diseases. IG can be given during pregnancy and does not pose a risk to the woman or her fetus.[38] Two active immunizations, Recombivax HB and Engerix B, have been developed against hepatitis B and, because they are produced via yeast cultures with recombinant DNA technologies, pose no infectious risk. Should exposure to hepatitis A or B (before immunization) occur, passive immunoglobulins should be administered as soon as possible. With hepatitis B, the more specific HBIG should be given, and an immunization series of three vaccinations should be commenced. These regimens are approximately 75% effective in preventing hepatitis A and B (and thus D).[42] Currently no immunoprophylaxis is available for hepatitis C or E, and there is insufficient evidence regarding the effects of IGs on hepatitis G or TT.

The Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend hepatitis B virus screening (HbsAg) for all pregnant women.[38] Seropositive women should have serum transaminases measured and be encouraged to inform their sexual partners and children of the need for testing and vaccination. Universal active hepatitis immunization is recommended for all infants born in the United States. When the mother is seronegative, infant immunization should commence preferably before discharge and no later than 2 months of age. When the mother is seropositive (HBsAg positive) or those of unknown status, infants should receive both passive and active immunization treatments, starting within 12 h after birth (Table 26.5).

Anesthetic Management

As a principal organ responsible for glucose hemostasis, fat metabolism, drug and hormone metabolism, bilirubin formation and excretion, and protein synthesis, the liver is involved in a number of physiologic activities of great concern to anesthesiologists. Although progression to fulminant liver failure is not typical of the disease during pregnancy, rapid deterioration[43] and liver transplantation have been reported.[44] Of special relevance to the administration of regional anesthesia is the production of clotting factors; however, as only 20% to 30% of normal coagulation factors is necessary to prevent bleeding, severe liver dysfunction must be present before the onset of significant coagulopathies. Nonetheless, clotting abnormalities should be suspected and evaluated, and a low threshold for replacement of clotting factors should be considered.

In terms of general anesthesia, the accentuated effects and prolonged elimination time of drugs, due to decreased protein binding and metabolism respectively, should be considered. Infrequent reports of independent hepatic injury following administration of halothane, sevoflurane, desflurane, and even isoflurane have drawn no definitive causal relationships[45]; however, avoidance of hypoxia and reduced hepatic blood flow when using these agents, especially in patients with preexisting hepatic disease undergoing prolonged procedures with operative interventions in close proximity to the liver, has been recommended.[46]

Human Immunodeficiency Virus

An RNA virus that possesses a unique reverse transcriptase enzyme which encodes proviral DNA into the nucleus of the host cells, human immunodeficiency virus (HIV) currently affects an estimated 13.8 million women infected worldwide.[47] Delays in diagnosis and treatment of the female gender and the ease of fetal transfer[48] represent significant parturient concerns. A multisystem disease, HIV primarily attacks cells positive for the CD4 surface antigen, especially helper T lymphocytes, which play an integral role in cell-mediated immunity, B cell activation, and antibody production. Associated alterations in macrophage activation and neutrophil function lead to an overall increased vulnerability to bacterial, viral, fungal, parasitic, and mycobacterial infections, as well as certain malignancies. Although the combined effect of HIV and pregnancy on the immunologic system remains unclear,[49,50] an increase in acquired immunodeficiency syndrome (AIDS) or AIDS-related complex has been observed in the postpartum period.[51]

At any time during the course of the disease, but particularly within a month of the primary infection, patients may present with a mononucleosis-like illness with symptoms of headache, meningismus, fever, altered mental status, and isolated cranial nerve palsies. In part these alterations are the result of very early involvement of the brain and cerebral spinal fluid; before the onset of AIDS, the virus titer in the brain is higher than in any other organ.[52] With disease progression, HIV infects the microglial and monocytic cells, resulting in an often fulminate disturbance in mental function followed by motor and gait abnormalities. This process, referred to as AIDS–dementia complex (ADC), is the most frequent neurologic diagnosis in AIDS patients. Disorders of the spinal cord (vacuolar myelopathy), nerve roots (CMV polyradiculitis), and peripheral nerves [distal sensory polyneuropathy (DSP)] may also occur. A relationship between HIV and hematologic disorders including thrombocytopenia and thrombotic microangiopathies (TMA) occurs with a 5% to 15% incidence.[53] The etiology of these effects, which is independent of the clinical status of the patient,[53] has several hypothesized mechanisms, including antiplatelet antibodies, circulating immune complexes, megakaryocyte infection, and bone marrow suppression.[54]

On a population basis, pregnancy rates among women with HIV infection are comparable with uninfected women until the onset of AIDS opportunistic infections, when the rates fall considerably.[55] During pregnancy, with advanced disease (CD4 counts below 30% or progression to AIDS), an increase in adverse outcomes including miscarriage, premature rupture of membranes, preterm delivery, and low birth weight has been observed.[49,50] The transfer of HIV from mother to infant accounts for nearly all the cases of HIV infection in children and depends on a number of maternal, fetal, and viral factors. HIV transmission may occur at any time. With early gestational infection, fetal loss occurs frequently.[56] Recent randomized and observational trials in both the developing and developed nations have indicated that shorter antenatal regimens,[57] and even postpartum neonatal treatment,[58] are successful in dramatically reducing the transmission rate.

Two particular interventions deserve attention: reducing antepartum maternal plasma HIV RNA levels and limiting intra- and postpartum neonate exposure to maternal blood, genital, and breast secretions. The first intervention, using antiviral medications in therapy-naïve parturients to reduce their viral load, was validated by the AIDS Clinical Trials Group (ACTG) Protocol 076, in which zidovudine (ZDV) therapy reduced the rate of vertical transmission of HIV infection from 25.5% to 8.3%.[59] In this trial, ZDV was administered orally and intravenously to parturients before and during delivery, respectively, and orally to their infants for 6 weeks after birth. Further study is needed to identify the optimal medications, time period, and long-term impact for this and other therapies; one potential concern is the creation of multidrug-resistant strains of HIV and other comorbid infections later in the course of the parturient's disease process.

The second intervention, elective cesarean delivery before the onset of labor or membrane rupture, was evaluated by the International Perinatal HIV Group via a meta-analysis of 15 prospective cohort studies (5 European and 10 North American) conducted between 1982 and 1996.[60] The HIV transmission rate associated with elective cesarean delivery before onset of labor and membrane rupture was compared to either vaginal or cesarean delivery performed after these events. With the restriction of the primary analysis to 8533 mother–infant pairs for whom the route, circumstances of delivery, and neonatal HIV status were known, a strongly protective effect of elective cesarean delivery was discovered (odds ratio, 0.43; 95% confidence interval, 0.33–0.56). These results suggest that either labor or membrane rupture could potentially increase the risk of vertical HIV transmission. However, the indiscriminate use of cesarean delivery may not necessarily be beneficial, as an increase in maternal morbidity and mortality from an operative delivery, particularly in Third World countries, has been observed in this population.[61]

Additional fetal concerns may lead to a cesarean delivery. Because IgG antiplatelet antibodies have been detected in HIV-infected patients,[62] transplacental passage with resultant fetal thrombocytopenia and systemic or intracranial hemorrhage may occur. Thus, in addition to the inoculation risk, procedures involving the puncture of fetal skin or epithelium, including funipuncture and scalp sampling, are avoided to decrease the risk of fetal bleeding. This concern may offer another indication, in the scenario of nonreassuring external fetal monitoring with the inability to do fetal scalp pH samples or intrauterine monitoring, to perform an operative delivery.

Collectively, these concerns have shaped the components of an "optimal approach"[63] for limiting maternal fetal transmission, which includes promoting earlier HIV detection, using antiretroviral therapy during pregnancy, selecting obstetric interventions, including elective cesarean delivery, and using neonatal antiretroviral therapy.

Anesthetic Management

Patients known to be HIV positive should undergo a comprehensive evaluation, because even mild or nonspecific symptoms are compatible with advanced disease. Prior or current clinical manifestations including anemia or thrombocytopenia and other opportunistic or sexually transmitted infections, as well as current or prior use of HIV-related therapies, adverse drug events, and illicit drug use, should be documented.

When the use of a regional anesthetic is contemplated, the initial assessment should closely evaluate the status of the hematologic and neurologic systems. Although the theoretical risk of exacerbating a preexisting neurologic disorder exists, in the absence of overt disease or mass effects the limited available data confirm the safety of regional anesthesia in HIV-positive women.[64] Should a headache occur after a regional technique, a full differential diagnosis, including diseases witnessed in HIV patients, should be considered. If the

headache is deemed to result from a dural puncture, initial therapies should be conservative: bedrest, analgesics, oral hydration, and caffeinated products. Should this management fail, an epidural blood patch can be considered. Although theoretical infectious implications of a blood patch have been raised,[65,66] and alternatives such as the use of extradural saline or heterologous HIV-negative blood have been suggested,[67] it should be remembered that detection of HIV within the central nervous system occurs early within the disease course. Three reports have noted the absence of adverse events following blood patch in HIV-positive patients. Although the studies collectively represent only 13 patients,[67,68] in one study 6 patients underwent serial neuropsychologic testing for as long as 2 years,[68] and no adverse neurologic or infectious sequelae were observed.

Few data exist on the effects of general anesthesia in the HIV-infected parturient. Of concern, however, is the potential for increased sensitivity to medications and the possibility of increased morbidity. In terms of increased sensitivity, a significantly prolonged response to a single dose of vecuronium has been reported in five HIV-positive patients; although the reasons for this prolonged effect were unclear, speculation was placed on existing peripheral neuropathies due to HIV and its treatment.[69] Whether this is true for all classes and types of neuromuscular relaxant medications is not known. Also unknown are the effects of gammaaminobutyric acid (GABA) receptor drugs (i.e., barbiturates, benzodazepines, and propofol). While HIV patients are speculated to be more sensitive due to the relationship between the receptor and interleukin 1,[70] a cytokine released in response to viral and bacterial infections, the actual clinical effects have not been studied.

In terms of increased morbidity, although general anesthesia can cause a small transient depression in immune function in normal patients,[71] the effects in the parturient with HIV are unknown. Other theoretical concerns include difficulties in intubation because of the pharyngeal lymphatic hypertrophy observed in some HIV-infected patients[72] and the potential for the endotracheal tube to serve as a conduit for oral pathogens to the pulmonary tree.

Herpes Simplex Virus

A member of the DNA Herpesviridae family, herpes simplex virus (HSV) has two major types, designated HSV-1 and HSV-2, which are primarily responsible for nongenital (gingivostomatitis, keratoconjunctivitis) and genital lesions, respectively. An estimated 500,000 new cases of genital herpes, one of the most common viral pathogens, are diagnosed each year, with more than 45 million Americans infected. HSV-2 infections are more common in women, perhaps reflecting a more effective transmission rate, and approximately 30% of the female American population has antibodies to HSV-2.[73]

Three stages of HSV infection have been identified, based on clinical presentation and serology. First-episode primary genital HSV occurs when herpes antibodies are absent at the time of infection. First-episode nonprimary genital HSV occurs when the acquisition of one type of HSV occurs when antibodies to the other type exist. Recurrent infection occurs when reactivation of genital HSV occurs when antibodies of the same type are present.

Initial HSV genital infections and recurrences may be with or without symptoms. When symptomatic, primary infections appear 2 to 14 days following exposure as ruptured vesicles on the vulva, vagina, and or cervix. Lesions usually resolve within 3 weeks without treatment but may persist up to 6 weeks with secondary bacterial or mycotic infections. Commonly accompanied by localized pain, HSV infections may also present with systemic symptoms (malaise, myalgia, and fever) in up to two thirds of cases. Recurrent disease is generally accompanied with less severe symptoms. Viral shedding presents an infectious risk and may occur in the absence of symptoms (i.e., subclinical shedding). Although significant variation in the frequency, severity, and duration of shedding exists, shedding occurs less frequently with recurrent herpes. When primary genital herpes occurs during pregnancy, an increased frequency of viral shedding occurs.

Approximately 1500 to 2000 newborns contract herpes each year, mostly from contact with infected maternal secretions during the perinatal period. Although believed to be an infrequent occurrence, in utero transmission can occur, resulting in a variety of anomalies or the onset of preterm labor and delivery. Neonatal disease occurs in 30% to 60% of the cases when a neonate comes in contact with the virus and may result in localized [skin, eye, mouth, and central nervous system (CNS)] or disseminated disease. Neonatal mortality increases dramatically with the disseminated disease, that is, from 15% to 57%.[74]

Diagnosis of HSV is dependent on virus isolation; however, specimen sampling and transporting difficulties limit test sensitivity, even with overt infections, to 60% to 70%.[75] A positive test is strongly suggestive of a nonprimary first or recurrent episode. More sensitive techniques are under investigation, and serologic tests should soon be able to reliably identify and even distinguish the two HSV forms. Due to the low yield of viral cultures and the presence of asymptomatic viral shedding, virologic monitoring or screening is not recommended.

Primary HSV infection presents the highest vertical transmission risk, and antiviral therapy with acyclovir has been demonstrated to reduce viral shedding, pain, and duration. Recurrent HSV infections may benefit from acyclovir therapy as well, although smaller reductions in viral shedding are believed to occur. Acyclovir, which can cross the placenta, concentrate in the amniotic fluid and breast milk, and reach therapeutic levels in the fetus, has been safely used during pregnancy,[76] although the improved bioavailability of valacyclovir and famciclovir may provide greater benefit.[77] Be-

cause of their beneficial effects, antiviral agent prophylaxis has been recommended for those parturients closer to term (>35 weeks gestation), those experiencing first-episode primary or nonprimary genital infections, or those having frequent (>12/year) recurrences.[78] Cesarean delivery should be performed on women with first-episode or recurrent HSV who have active genital lesions or prodromal symptoms at time of delivery.

Anesthetic Management

The management of women with primary HSV remains controversial because of the viremia and CNS involvement, including headaches, meningitis, and, rarely encephalitis, that occur. Potential for inoculation of the central neuraxial tissues exists with regional anesthetic techniques, and this must be weighed against the benefit derived. By contrast, as recurrent HSV is not associated with a viremia,[79] no contradiction to regional techniques exists, provided the needle is not placed through a lesion, and no overt CNS involvement is present.

The use of central neuraxial morphine in HSV parturients also remains controversial because of the suggestion that oral HSV is reactivated by the facial itching that can follow epidural and intrathecal morphine.[80] As this facial itching has also been suggested to serve only as a marker and not a trigger of oral HSV lesions,[81] further investigation is needed to evaluate this potential association. A final concern is HSV lesions of the skin, termed herpetic whitlows, which present an occupational, infectious hazard when contact with the lesions occur. Should contact occur, handwashing and oral antiviral medications may prevent an infection from occurring.[82]

Listeria

Listeria monocytogenes is a facultative anaerobic, gram-positive rod that produces β-hemolysis on blood agar. Rarely occurring in the population at large, *L. monocytogenes* infections have been estimated to occur at a 20-fold-higher rate during pregnancy.[83] Pregnancy-related decreases in T-cell-mediated immunity, a major defense against listeriosis, have been speculated to play a role. Although the exact pathogenesis of listeriosis is poorly understood, epidemics have demonstrated an association with the ingestion of contaminated food, especially nonpasteurized dairy products.[84]

Approximately two thirds of pregnant women with listeriosis present with fever, headache, myalgias, and other nonspecific flu-like symptoms, and one third will experience gastrointestinal symptoms, particularly diarrhea. Severe complications, including meningitis, encephalitis, adult respiratory distress syndrome, and death, are usually associated with an underlying debilitating disease or immunosuppression. Maternal fever followed by preterm labor (especially in the setting of an abnormal fetal heart rate tracing and "fetal distress" in labor) or in utero fetal demise has been associated with *Listeria*. Diagnostic confirmation requires isolation of *L. monocytogenes* from maternal or neonatal blood, fetal membranes, gastric aspirates, amniotic fluid, and placental tissue. Placental histology with evidence of microabscesses and a distinct multifocal villitis can also suggest the diagnosis following delivery.[85]

Intrauterine infections during pregnancy are believed to occur through hematogenous dissemination at the time of maternal septicemia; however, ascending organisms from the lower genital tract or perirectal area may also be responsible. Adverse pregnancy outcomes from listeriosis infections may occur at any gestational age, and perinatal mortality has been estimated to range from 20% to 50%. In Europe, *Listeria* has been reported to account for 0.5% to 3% of all cases of spontaneous abortion and preterm labor.[86]

When *Listeria* infection is suspected, prompt initiation of antibiotic therapy may improve perinatal survival.[83] Although the best antibiotic regimen has not been identified by clinical trials, parenteral ampicillin with gentamicin is usually given (see Table 26.4). Trimethaprim/sulfamethoxazole and erythromycin are also effective. Neonates should treated aggressively with broad-spectrum antibiotics, although the length of therapy is unknown. Perinatal outcome is determined primarily by the gestational age at delivery and complications related to prematurity.

Anesthetic Management

To date, there are no data regarding the implications of *Listeria* on anesthesia.

Lyme Disease

A disease caused by the spirochete *Borrelia burgdorferi sensu lato*, Lyme disease is the most common vector-borne disease in the United States. Also common in Europe, the spirochete is of a different genospecies, with the two most dominant being *B. garinii* and *B. afzelii*. Transmitted by the bite of deer ticks (*Ixodes scapularis*) and western black-legged ticks (*I. pacificus*), Lyme disease in the United States has increased about 25 fold since national surveillance began in 1982, with a mean of approximately 12,500 cases annually.[87] Lyme disease is most likely transmitted to humans during the tick nymph stage, when the ticks are most likely to feed and their small size prevents them from being noticed. The transmission of the infection most likely takes place after approximately 2 or more days of feeding. Lyme disease spirochetes can spread from the site of the tick bite by cutaneous, lymphatic, and bloodborne routes and have been identified in spinal, synovial, and amniotic fluids.

The most common presentation of Lyme disease is a characteristic "bull's eye" rash called erythema migrans, accompanied by nonspecific symptoms such as fever, malaise, fatigue, headache, myalgias, and arthalgias. Most individuals present with symptoms after an incubation period of 7 to 14

days, but some infected individuals are asymptomatic or only experience nonspecific symptoms. Rarely, cardiac and neurologic manifestations may occur. During pregnancy, *B. burgdorferi* can infect both the placenta and fetus; however, the risk for and timing of infection are unknown. Although maternal infection has been associated with preterm delivery, stillbirths, fetal neurologic abnormalities, and delayed neonatal effects [respiratory distress and sudden infant death syndrome (SIDS)], the overall risk of adverse outcomes appears low. Recent prospective and case-control studies have demonstrated no association between maternal Lyme disease and fetal cardiac defects.[88,89]

Diagnosis of Lyme disease is based primarily on clinical findings, and treatment is often commenced on the basis of symptoms or known exposure. Serologic testing may provide valuable diagnostic information; however, the tests are of variable sensitivity and specificity. A number of serologic tests are available, and the CDC recommends testing initially with an enzyme-linked immunosorbent assay (ELISA) or an indirect fluorescent antibody (IFA) test, with the more specific Western immunoblot (WB) test reserved for when equivocal results are obtained.

Treatment with doxycycline or amoxicillin (cefuroxime or erythromycin in persons allergic to the first two regimens) for 3 to 4 weeks is generally effective in early disease. With more advanced disease, particularly with neurologic manifestations, administration of intravenous ceftriaxone or penicillin for at least 4 weeks, noting that treatment failures may occur and that some symptoms may persist even with successful treatment. Aggressive treatment of Lyme disease during pregnancy may be warranted with the belief that a reduction in fetal or neonatal infection may occur, although the efficacy of this therapy is unknown.[90]

Antibiotic treatment in early disease may blunt an antibody response; however, patients with disseminated or late-stage disease usually have strong serologic reactivity and demonstrate expanded WB immunoglobulin G (IgG) banding. Antibodies, which often persist for months or years even after successful treatment, do not confer immunity from reinfection. A recombinant outer-surface protein A vaccine (LYMErix) for the prevention of Lyme disease has been developed, although it is not recommended during pregnancy.[87] Unfortunately, the vaccine does not protect all recipients against infection with *B. burgdorferi* and offers no protection against other tickborne diseases.

Anesthetic Management

Although the generalized malaise, skin lesions, and arthralgias are the most prominent symptoms of Lyme disease, CNS and cardiac system involvement may occur, and these have important implications for anesthesiologists. Meningitis, encephalitis, and motor and sensory peripheral neuropathies may occur,[91] and the avoidance of central neuraxial blockade may be prudent in these patients. In terms of cardiac anomalies, conduction blockade, pericarditis, valvular disorders, and cardiomyopathy have all been noted with Lyme disease[92,93]; as a consequence, an ECG, a directed cardiac examination, and possibly other tests should be considered before anesthesia.

Parvovirus B19

Composed of a single-stranded DNA virus, parvovirus B19 is responsible for childhood exanthem erythema infectiosum (fifth disease) and transient aplastic crisis in patients with underlying hemoglobinopathy. Even in immunocompromised individuals, parvovirus B19 infections are usually mild, requiring only supportive care.[94]

The disease is transmitted most commonly through respiratory secretions and hand-to-mouth contact. Infected persons remain infectious for 5 to 10 days following exposure.[95] Household members of infected persons have an approximately 50% risk of infection.[96] With the onset of a reticular rash on the trunk or other symptoms such as peripheral arthropathy, a loss of infectious risk occurs. Maternal diagnosis can be made through ELISA or WB tests of parvovirus B19 antibodies or through direct visualization of viral particles in infected tissues. IgM and IgG antibodies are produced in response to an infection and last a few months and indefinitely, respectively. When only IgG is detected, this represents both a prior infection and immunity. Seropositivity to parvovirus B19 increases with age, and more than 60% of adolescents and adults have antibodies.

Transplacental transmission of parvovirus B19 has been reported to be as high as 33%,[97] although the risk of serious fetal morbidity, such as hydrops fetalis, and spontaneous abortion and stillbirth is low.[98] Serious sequelae occur with infections before 20 weeks gestational age; however, should the fetus survive, long-term development tends to be normal.[99] Fetal parvovirus B19 can be diagnosed through the detection of viral particles or DNA in fetal specimens, including serum, amniotic fluid, placenta, or autopsy tissues.[100] Ultrasonography to detect the presence of hydrops for up to 10 weeks following maternal infection has also been advocated.[94]

Treatment for parvovirus B19 is primarily supportive. Should hydrops fetalis occur, treatment is unfortunately limited to performing percutaneous umbilical blood sampling for transfusion preparation if anemia is present.[101]

Anesthetic Management

To date, there are no data regarding the implications of parvovirus on anesthesia.

Rubella

Rubella is caused by a single-stranded RNA virus belonging to the togavirus family for which humans are the only natural host. Extremely contagious, with an attack rate within closed popu-

lations close to 100%, rubella is infectious from 7 days before to 14 days following the associated rash. Since rubella has a peak incidence among children 5 to 9 years of age and confers immunity for life once infected, only 6% to 8% of women of reproductive age remain susceptible to infection with rubella virus.[102]

Rubella is a respiratory disease transmitted by airborne or direct contact. The incubation period varies from 14 to 21 days. Due to the usually mild presentation of the disease, clinical diagnosis may be difficult. When present, symptoms can include a maculopapular 3-day rash of the face that can spread to the trunk and extremities, postauricular or occipital adenopathy, fever, transient arthralgias, and arthritis. Pregnancy does not affect the clinical manifestations.[103] Diagnosis can occur through viral isolation from nasopharyngeal secretions; however, few laboratories provide this service, and isolation takes 4 to 6 weeks. Testing for the more sensitive rubella-specific IgM antibody, which appears rapidly and remains detectable for up to 1 month or longer, is recommended. A fourfold increase in rubella-specific IgG may also be used for diagnostic confirmation.

Although transplacental infection may occur with primary maternal rubella infection, transmission rarely occurs with reinfection. Fetal infection can be confirmed through the detection of rubella-specific IgM or viral cultures from fetal blood or by rubella DNA isolation from chorionic villi.[104] Such testing, however, is rarely utilized, as the infection severity does not correlate accurately with viral presence. Congenital rubella syndrome results in a number of manifestations, including fetal growth restriction, ophthalmologic abnormalities (cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac malformations, and neurologic manifestations (mental retardation, microcephaly, encephalitis). Sensorineural deafness is the most common consequence; however, thrombotic thrombocytopenic purpura, hepatosplenomegaly, myocarditis, pneumonitis, anemia, and jaundice may also be observed.

Although fetal infection may occur at any stage of pregnancy, the gestational age affects the manifestations,[105] with first trimester maternal infection producing a high incidence (70%–90%) of developmental malformations. By contrast, although structural defects do not occur as a consequence of infection during the third trimester of pregnancy, deafness and mental retardation may result. Moreover, the absence of clinical signs at birth does not exclude the possibility of subclinical damage or subsequent impairment; manifestations of congenital rubella infection (including endocrinopathies, hearing or visual impairment, and progressive panencephalitis) may develop up to 10 to 20 years later in 70% of individuals. Consequently, offspring of women who have sustained rubella infections during pregnancy should undergo long-term follow-up.

There is no effective treatment for rubella. Rubella vaccines produce seroconversion and long-term immunity from infection in 95% of cases. Complications of rubella vaccination include mild and self-limiting flu-like symptoms, fever, lymphadenopathy, and rash. Rubella vaccination is not recommended during pregnancy because of theoretical concerns of fetal damage. Despite this recommendation, the risk of congenital rubella syndrome from vaccination within 3 months of conception is considered negligible.[106] Clinicians should routinely offer the rubella vaccine to all potentially susceptible women lacking contraindications for vaccination.

Anesthetic Management

To date, there are no data regarding the implications of rubella on anesthesia.

Syphilis

An indolent systemic infection caused by the spirochete *Treponema pallidum*, syphilis has undergone a dramatic resurgence due to an increase in intravenous drug abuse and HIV.[107] Currently, the incidence of syphilis is 5 to 7 per 100,000 in the United States. Although men and women are currently infected in equal proportions, 80% of women with syphilis are of reproductive age, potentially risking fetal transmission.[107]

Transmitted most commonly through sexual contact, syphilis infection results in 30% to 50% of the cases where contact with a person with primary or secondary syphilis occurs.[108] This high transmission rate is due to the ability of *T. pallidum* to pass across abraded skin as well as intact mucous membranes. During pregnancy, no alterations occur in the characteristic clinical stages of the disease.

Because *T. pallidum* cannot be cultured, the diagnosis of syphilis requires either direct visualization of the organism (by dark-field microscopy or fluorescent antibody staining) or, more commonly, serologic testing. Newer diagnostic techniques (i.e., PCR) are currently being developed. Lumbar puncture is often performed, even during pregnancy, to assist in the evaluation of CNS symptoms, syphilis of unknown or advanced stages, and when concurrent immunosuppression exists. CSF abnormalities suggestive of syphilis infection include elevated counts of white cells ($\geq$5 cells/mm^3) and total proteins ($\geq$45 mg/dL), normal glucose concentrations, and a positive syphilis serologic test.

Antenatal syphilis poses a significant threat to the pregnancy and fetus and, if untreated, is associated with intrauterine growth restriction, stillbirth (30%), preterm birth, neonatal death (10%), and congenital infection (>60%).[107,109] Only 20% of children born to mothers with untreated syphilis will be normal.[110] *T. pallidum* readily crosses the placenta, and transmission can occur at any time during pregnancy and at any stage of the disease.[110] However, both the disease stage and fetal gestational age influence the rate of perinatal transmission. Vertical transmission is more common with primary (50%) and secondary syphilis (50%) as compared with early latent (40%), late latent (10%), and even tertiary syphilis (10%).[111] Universal antepartum screening and treatment with appropriate antibiotics could virtually eliminate syphilis dur-

ing pregnancy. Serologic screening should occur at the first prenatal visit and, in high-risk populations, again during the third trimester and at delivery. Mothers properly treated have a 1% to 2% risk of fetal transmission versus 70% to 100% for untreated mothers.[112]

Penicillin is the treatment of choice for syphilis in both pregnant and nonpregnant individuals due to its efficacy and the lack of resistant strains. Treatment is directed according to the stage of disease. Following treatment, treponemal antibody serologic titers should be checked at 1, 3, 6, 12, and 24 months. Titers should decrease fourfold by 6 months and become nonreactive by 12 to 24 months.[108] Titers that do not decrease appropriately suggest either treatment failure or reinfection, and treatment should be repeated. Treatment failure should be further evaluated by a lumbar puncture to evaluate CNS involvement and HIV testing.

In nonpregnant individuals with a history of penicillin allergy, recommended alternatives for the syphilis treatment include doxycycline, tetracycline, or erythromycin. In parturients, however, erythromycin fails to cross the placenta predictably, and doxycycline and tetracycline have adverse effects on developing bone and tooth enamel. As such, penicillin desensitization and treatment is the only satisfactory treatment, and treatment can be achieved either orally (which is simpler and safer) or intravenously.[113,114] Desensitization involves exposing the patient to a small amount of penicillin and gradually increasing the dose until an effective level is reached. The procedure requires approximately 4 h to accomplish and requires close patient monitoring.

Anesthetic Management

Significant concerns of late-stage syphilis include infection of the aorta and posterior neuraxial columns and roots. Aortic manifestations include regurgitation and aneurysms primarily of the ascending thoracic aorta; these entities create anesthetic implications in terms of the need for precise hemodynamic control and stability. Posterior column and root degeneration results in deterioration in sensation to position, deep pain, and temperature and disturbances in bladder control. Although little information exists on the effects of anesthesia in patients with syphilis, when significant posterior column involvement exists, consideration should be given to avoiding central neuraxial blockade, as the recovery from these forms of anesthesia may be difficult to assess.

Toxoplasmosis

Caused by the intracellular parasite *Toxoplasma gondii*, toxoplasmosis infects more than 60 million people in the United States alone.[115] Contact with infected materials such as animal feces or soil and ingestion of infected undercooked meats are common routes of infection. Rarely, infected blood transfusions or organ transplants may result in the disease.[115]

Infection usually presents as asymptomatic cervical lymphadenopathy, but after an incubation period of 5 to 18 days, nonspecific symptoms such as night sweats, fever, malaise, myalgias, and hepatosplenomegaly may occur. An intact immune system usually allows for a benign and self-limited course. By contrast, infection in immunosuppressed individuals and fetuses in utero can result in chorioretinitis, hearing loss, mental retardation, seizures, and hepatosplenomegaly. Vertical transmission risk is dependent on the timing of maternal infection, increasing from 10% to 60% from the first to third trimesters.[116] Earlier fetal transmission results in more severe disease, which is revealed in 55% to 85% of infected neonates not at birth but at later stages of life.

Although isolation of *T. gondii* from bodily fluids establishes an acute infection, serologic testing for antibodies is the primary method of diagnosis. IgM antibodies appear first, reach maximum levels in 1 month, and are followed by the immunity-conferring IgG antibodies. As high titers of both IgM and IgG may persist for years, both tests should be used for the initial evaluation. Although the Sabin–Feldman IgG test is the gold standard, it is performed in only a few laboratories; consequently, IFA, indirect hemagglutination, and ELISA testing are often used. Unfortunately, serologic assays for toxoplasmosis are not well standardized and have high false-positive rates. Therefore, serial testing 3 weeks apart, with specimen saving for repeat testing in recognized reference laboratories, has been recommended. In the United States, routine screening during pregnancy is currently not recommended, except for women with HIV or other exceptional circumstances.[117] In countries with a high prevalence of seropositivity, such as France and Austria, however, serologic screening has had a favorable impact and is routinely performed.[118]

Prior infection and treatment of toxoplasmosis before pregnancy does not confer a congenital transmission risk.[94] However, should the disease be diagnosed and treatment initiated during pregnancy, a risk of congenital infection exists.[119] Spiramycin, a drug available only through the U.S. Food and Drug Administration, may reduce fetal transmission by 60%[120] and should be started immediately. Fetal ultrasonography [for ventriculomegaly, intracranial calcifications, microcephaly, ascites, hepatosplenomegaly, and intrauterine growth restriction (IUGR)] and fetal blood sampling for IgM after 20 weeks gestation has been recommended.[94] Should fetal infection be established, pyrimethanmine, sulfonamides, and folinic acid are added to increase the efficacy against placental and fetal parasites.[121] Infants with congenital toxoplasmosis should continue treatment of pyrimethamine and sulfadiazine, alternating monthly with spiramycin, for 1 year. Treatment may diminish intracranial calcifications and improve neurologic function.[122]

Anesthetic Management

To date, there are no data regarding the implications of toxoplasmosis on anesthesia. However, as alterations in the pro-

duction or destruction of clotting proteins may occur during periods of hepatosplenomegaly, clotting parameters should be evaluated before surgical and anesthetic interventions. Should moderate or severe symptoms exist, careful evaluation for other potentially coexisting morbidities is prudent.

Tuberculosis

Tuberculosis (TB) refers to infection with *Mycobacterium tuberculosis*. After declining steadily for three decades, the number of cases of maternal and fetal TB reported annually in the United States began to rise again in the 1980s due to increases in both HIV infections and multidrug-resistant strains.[123] Although there is no apparent increase in TB progression during or immediately after pregnancy, most infected parturients are symptomatic and convert to a positive response to purified protein derivative (PPD) skin testing. Less common presentations include peritonitis, meningitis, mastitis, and paraplegia secondary to spinal osteomyelitis (Pott's disease).

Diagnosing TB can be difficult. Pregnant women considered to be at high risk for TB (including women with symptoms suggestive of TB, known recent exposure, seroconversion within the past 1 to 2 years, immunocompromised patients, and recent immigrant status) should be skin tested. Skin testing involves intradermal injection of 5 tuberculin units of PPD and measurement of the induration (not erythema) in 48 to 72 h. Interpretation of the PPD test depends on the risk status of the patient and is not affected by pregnancy. A positive reaction requires further investigation to exclude active disease, which includes a chest X-ray (usually a single anteroposterior view with abdominal shielding in pregnancy), submission of early-morning sputum specimens for smear and culture, and appropriate biopsy specimens if there is evidence of extrapulmonary disease. Although the demonstration of acid-fast bacilli (AFB) raises the possibility of TB, subsequent culture confirmation is mandatory because sputum may contain strains of nontuberculous mycobacterium.

Fetal TB transmission is believed to occur via ingestion or aspiration of infected amniotic fluid or direct seeding via the umbilical vein. During pregnancy, therapy does not differ, and a two-drug regimen, usually isoniazid (with pyridoxine) and rifampin, should be used for a minimum of 9 months. Extensive experience with isoniazid during pregnancy has noted its ability to cross the placenta with no apparent teratogenic effects.[124] Although rifampin crosses the placenta and may theoretically cause fetal injury through inhibition of DNA-dependent RNA polymerases, no such damage has been reported. Ethambutol can be added to the two-drug regimen should resistance exist, although an association with retrobulbar neuritis in adults has been noted; fetal exposure to ethambutol, however, appears safe. Streptomycin is contraindicated in pregnancy due to an association with VIIIth nerve injury and hearing impairment in up to 17% of infants. Ethionamide and cycloserine have been known to cause fetal neurologic injuries and should be avoided.

Postpartum, close physical contact with infected individuals may allow for neonatal transmission as well. Infants with congenital TB usually do not manifest signs of disease for several days to weeks after delivery, resulting in delayed treatment and a mortality rate approaching 50%.[125] In the majority of cases, nonspecific signs including respiratory distress, fever, lethargy, failure to thrive, lymphadenopathy, and hepatosplenomegaly are the only clues. With early diagnosis and treatment, however, neonatal treatment is usually successful.[126] Daily isoniazid and rifampin are the usual neonatal therapy, but a four-drug regimen (including isoniazid, rifampin, streptomycin, and pyrazinamide) is utilized for drug-resistant strains.

Mothers taking antituberculous medications can breastfeed; however, approximately 20% and 11% of the mother's isoniazid and other antituberculous drugs, respectively, appear in breast milk.[124] Thus, if an infected infant is also being independently treated, a dose reduction should be considered. With noninfected infants, although controversy surrounds leaving the child with the mother in the immediate postpartum period, in about 2 weeks on treatment, the mother should become noninfectious. Interestingly, bacille Clamette–Guérin (BCG) vaccine has limited efficacy in preventing disseminated tuberculosis in children[127] and may allow for the reactivation of an infection acquired previously. A history of BCG vaccination, which does not alter the interpretation of the PPD skin test, should not influence the subsequent management.

Anesthetic Management

Sometimes associated with severe restrictive lung disease, the pulmonary effects of TB represent the main concern for anesthesiologists. Although general anesthesia may be a consideration, should an emergent surgical delivery be necessary, the risk of massive hemoptysis with positive pressure ventilation in these patients has been described.[128] The extrapulmonary TB involvement of the CNS, pericardium, liver, and bone marrow are concerning as well. Vertebral column involvement, although usually of the thoracic spine, can affect other segments, and instability of the cervical spine has been reported.[129] This vertebral column involvement may present difficulties in placement and function of regional techniques or with induction and intubation during general anesthesia.

The treatment for TB may create important implications as well, significant toxicity of the peripheral nervous system, liver, and kidneys being reported with isoniazid. Peripheral neuropathy is preventable and reversible with pyridoxine. Should significant peripheral neuropathy and impairment of hepatic function be observed, a baseline neurologic status examination and laboratory analysis for coagulopathies, respectively, should be considered.

Varicella Zoster

Varicella zoster virus (VZV) is a DNA herpesvirus transmitted by respiratory droplets or close contact, with a very high transmission rate among susceptible contacts of 60% to 90%.[94] Known as chickenpox, the primary infection is characterized by fever, malaise, and a maculopapular, pruritic rash that is infectious 48 h before the rash until vesiculation and crusting are complete. In children, the primary infection is usually benign and self-limited. By stark contrast, in adults, severe complications such as encephalitis and pneumonitis can result; although less than 5% of varicella cases occur among individuals over 20 years of age, 55% of varicella-related deaths occur in this group.[130] Although antibodies against VZV develop within a few days of the onset of the infection and confer lifelong immunity, the virus remains latent in the sensory ganglia. With reactivation, a vesicular erythematous rash localized to one or more cutaneous dermatomes occurs, and this is known as herpes zoster.

The diagnosis of the primary infection is based on clinical findings. Although not required, tests identifying within skin lesions and vesicular fluid antigens or antibodies, by immunofluorescence or ELISA, respectively,[131] can be performed. Due to the highly contagious nature of VZV, only 5% of adults do not have protective immunity,[132] and consequently varicella infection is uncommon in pregnancy, occurring in 0.4 to 0.7 per 1000 live births.[131] Should infection occur, however, significant maternal, fetal, and neonatal effects result. Varicella pneumonitis is particularly serious in pregnancy, with a maternal mortality rate of 50%.[133] Fetal infection is difficult to diagnose. Ultrasound findings (including hydrops fetalis, echogenic foci in the liver and bowel, cardiac malformations, limb deformities, microcephaly, or IUGR) are nonspecific. Moreover, virus identification by antibodies, cultures, or DNA identification in chorionic villi, amniotic fluid, or fetal blood is difficult and does not accurately predict the severity of fetal infection.[134,135] Ultimately, fetal skin scarring, limb hypoplasia, chorioretinitis, and microcephaly may occur.[136,137] Neonatal VZV infection is associated with a high mortality rate, especially when maternal disease develops from 5 days before to 2 days after delivery. This is a result of the relative immaturity of the neonatal immune system and the lack of protective maternal antibodies.[138]

Oral acyclovir, if instituted within 24 h of the rash, has been shown to reduce the number and duration of new lesions and improve the constitutional symptoms in healthy adults.[139] Although appearing safe for use in pregnancy, oral acyclovir has not been shown to prevent or ameliorate the fetal effects of congenital varicella syndrome.[140] Maternal varicella complicated by pneumonitis should be treated with intravenous acyclovir. Varicella immunoglobulin (VZIG) should be given to infants born to women who develop varicella between 5 days before and 2 days after delivery, although this does not universally prevent neonatal varicella.[141]

Because treatment options are limited, efforts should be made to identify and vaccinate nonpregnant women of childbearing age who are nonimmune.[132] As the vaccine is a live attenuated strain, it is not approved for use during pregnancy, and conception should be delayed until 1 month after the second vaccination dose is given. Nonimmune women should also be counseled to avoid contact with individuals who have chickenpox; however, if exposure occurs, administration of VZIG should occur as soon as possible, up to 72 h afterward, to prevent or attenuate the maternal disease.[142] Unfortunately, should VZIG fail to prevent the disease, no alterations of fetal infection occur as the result of its administration.

Anesthetic Management

As mentioned, varicella pneumonia can be critical, and infected patients are often admitted to the intensive care unit, where adult respiratory distress syndrome (ARDS) therapy with intubation and ventilator support may ensue. Should anesthesia be necessary in an unintubated patient with respiratory distress, such as for cesarean delivery to improve the health of the mother as well as the fetus, the use of general anesthesia is most likely the best option. Should regional anesthesia be attempted, the degree of pulmonary compromise may become unacceptable, especially with a high anesthetic level and the patient in the supine with left uterine displacement position.

The most frequent contact anesthesiologists have with patients with VZV is when reactivation of the latent virus occurs and patients seek help for pain management. The debilitating pain is difficult to control, and a number of topical agents and invasive blockades of sympathetic, peripheral nerve, and even central neuraxial pathways have been evaluated with only limited success.[143]

Summary

A number of infections are associated with significant maternal and fetal consequences. In general, perinatal infections have more serious fetal consequences when they occur early in gestation, because they may disrupt organogenesis. By contrast, second and third trimester infections are more likely to cause neurologic impairment or growth disturbances. With few exceptions, treatment of infectious diseases is not altered substantially by pregnancy; however, as infectious diseases often dramatically affect the outcome of the pregnancy, obstetric and anesthetic management decisions should be directed with awareness of these pathogens to optimize the outcome for mother and infant.

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References

1. Liljestrand J. Reducing perinatal and maternal mortality in the world. Br J Obstet Gynaecol 1999;106:877–880.
2. NCCDPHP, CDC. State-specific maternal mortality among black and white women: United States, 1987–1996. MMWR 1999;48:492–496.
3. Sachs B, Brown D, Driscoll S, et al. Maternal mortality in Massachusetts: trends and prevention. N Engl J Med 1987;316:667–672.
4. Hogberg U, Innala E, Sabdsrom A. Maternal mortality in Sweden. Obstet Gynecol 1994;84:240–244.
5. American College of Obstetricians and Gynecologists. Antimicrobial therapy for obstetric patients. Educational Bulletin No. 245. Washington, DC: ACOG, 1998.
6. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338:1128–1137.
7. Tsen LC, Tarshis J, Denson DD, et al. Measurements of maternal protein binding of bupivacaine throughout pregnancy. Anesth Analg 1999; 89(4):965–968.
8. Sullivan NM, Sutter VL, Mims MM, et al. Clinical aspects of bacteremia after manipulation of the genitourinary tract. J Infect Dis 1973;127(1): 49–55.
9. Morgan PJ. Maternal death following epidural anaesthesia for cesarean section delivery in a patient with unsuspected sepsis. Can J Anaesth 1995;42(4):330–334.
10. Blanco JD, Gibbs RS, Castaneda YS. Bacteremia in obstetrics: clinical course. Obstet Gynecol 1981;58(5):621–625.
11. Wedel DJ, Horlocker TT. Risks of regional anesthesia—infectious, septic. Reg Anesth 1996;21(suppl 6):57–61.
12. Carp H, Bailey S. The association between meningitis and dural puncture in bacteremic rats. Anesthesiology 1992;76(5):739–742.
13. Tsen LC, Pitner R, Camann WR. General anesthesia at a tertiary care hospital 1990–1995: indications and implications. Int J Obstet Anesth 1988;7:147–152.
14. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86(2):277–284.
15. American College of Obstetrics and Gynecologists. Group B streptococcal infections in pregnancy. Technical Bulletin No. 170. Washington, DC: ACOG, 1992.
16. American College of Obstetrics and Gynecologists. Prevention of early-onset group B streptococcal disease in newborns. Committee Opinion No. 173. Washington, DC: ACOG, 1996.
17. Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidelines for prevention of group B streptococcal (GBS) infection by chemoprophylaxis. Pediatrics 1992;90:775–778.
18. Siegal JD, Cushion NB. Prevention of early-onset group B streptococcal disease: another look at single-dose penicillin at birth. Obstet Gynecol 1996;87:692–698.
19. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartum use of ampicillin. Am J Obstet Gynecol 1998; 179:879–883.
20. Dunn AB, Blomquist J, Khouzami V. Anaphylaxis in labor secondary to prophylaxis against group B streptococcus. J Reprod Med 1999;44: 381–384.
21. Yancey MK, Schuchat A, Brown LK, et al. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996;88:811–815.
22. Davis L, Hargreaves C, Robinson PN. Postpartum meningitis. Anaesthesia 1993;48(9):788–789.
23. Chopin N, Bonnet A, Gabet J. Streptococcus B meningitis after peridural obstetric anesthesia. Ann Fr Anesth Reanim 1998;17(2):195–196.
24. Kilpatrick ME, Girgis NI. Meningitis—a complication of spinal anesthesia. Anesth Analg 1983;26(5):513–515.
25. Bader AM, Gilbertson L, Kirz L, Datta S. Regional anesthesia in women with chorioamnionitis. Reg Anesth 1992;17(2):84–86.
26. Goodman EJ, DeHorta E, Taguiam JM. Safety of spinal and epidural anesthesia in parturients with chorioamnionitis. Reg Anesth 1996;21(5): 436–441.
27. Ramanathan J, Vaddadi A, Mercer BM, et al. Epidural anesthesia in women with chorioamnionitis. Anesthesiol Rev 1992;19:35–40.
28. Stagno S, Tinker MK, Elrod C, et al. Immunoglobulin M antibodies detected by enzyme-linked immunosorbant assay and radioimmunoassay in the diagnosis of cytomegalovirus infection in pregnant women and newborn infants. J Clin Microbiol 1985;21:930–935.
29. Fowler KB, Stagno P, Pass RF. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980–1990. J Infect Dis 1993;168:552–556.
30. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. JAMA 1986;256:1904–1908.
31. Fowler KB, Stagno P, Pass RF, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326:663–667.
32. Stagno S, Pass RF, Dworsky ME, Alford CA Jr. Maternal cytomegalovirus infection and perinatal transmission. Clin Obstet Gynecol 1982;25: 563–576.
33. Drose JA, Dennis MA, Thickman D. Infection in utero: ultrasound findings in 19 cases. Radiology 1991;178:369–374.
34. Stagno S. Cytomegalovirus. In: Remington JS, Klein JO (eds). Infectious Disease of the Fetus and Newborn Infant, 4th ed. Philadelphia: Saunders, 1995:312–353.
35. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus by changing behaviors: a randomized controlled trial. Pediatr Infect Dis 1996;15:240–246.
36. American College of Obstetricians and Gynecologists. Perinatal viral and parasitic infections. Practice Bulletin No. 20. Washington, DC: ACOG, 2000.
37. Attard-Montalto SP, English MC, Strimmler L, Snodgrass GJ. Cancicloviir treatment of congenital cytomegalovirus infection: a report of two cases. Scand J Infect Dis 1993;25:385–388.
38. American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. Educational Bulletin No. 248. Washington, DC: ACOG, 1998.
39. Wejstal R, Manson AS, Widell A, Norkrans G. Perinatal transmission of hepatitis G virus (GB virus type C) and hepatitis C virus infections—a comparison. Clin Infect Dis 1999;28(4):816–821.
40. Bendinelli M, Pistello M, Maggi F, et al. Molecular properties, biology, and clinical implications of TT virus, a recently identified widespread infectious agent of humans. Microbiol Rev 2001;14(1):98–113.
41. Rizzetto M. Hepatitis D: virology, clinical and epidemiological aspects. Acta Gastroenterol Belg 2000;63(2):221–224.
42. http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm
43. Sato T, Hashiguchi A, Mitsuse T. Anesthesia for cesarean delivery in a pregnant woman with acute hepatic failure. Anesth Analg 2000;91(6): 1441–1442.
44. Armenti VT, Herrine SK, Radomski JS, Moritz MJ. Pregnancy after liver transplantation. Liver Transplant 2000;6(6):671–685.
45. Eger EI. New inhaled anesthetics: Sevoflurane and Desflurane. IARS 1997 Review Course Lectures. Cleveland, OH. International Anesthesia Research Society, 1997.
46. Shingu K, Eger EI II, Johnson BH, et al. Effect of oxygen concentration, hyperthermia, and choice of vendor on anesthetic-induced hepatic injury in rats. Anesth Analg 1983;62(2):146–150.
47. Centers for Disease Control & Prevention. Basic Statistics: International Projections. Update Dec 1998. Atlanta, GA: CDC, 1998.
48. Bardequez AD. Management of HIV infection for the childbearing age woman. Clin Obstet Gynecol 1996;39:344–360.
49. Minkoff H, Henderson C, Mendez H, et al. Pregnancy outcomes among mothers infected with human immunodeficiency virus and uninfected control subjects. Am J Obstet Gynecol 1990;162;30–34.
50. Minkoff H, Henderson C, Menez R, Fikrig S. Pregnancies resulting

in infants with acquired immunodeficiency syndrome or AIDS-related complex. Obstet Gynecol 1987;69:285–291.
51. Gloeb DJ, Lai S, Efantis J, O'Sullivan MJ. Survival and disease progression in human immunodeficiency virus-infected women after an index delivery. Am J Obstet Gynecol 1992;167:152–157.
52. Denning DW, Anderson J, Rudge P, Smith H. Acute myelopathy associated with primary infection with human immunodeficiency virus. Br Med J 1987;294:143–144.
53. Kain ZN, Rimar S, Barash PG. Cocaine abuse in the parturient and effects on the fetus and neonate. Anesth Analg 1993;77:835–844.
54. Glantz JC, Roberts DJ. Pregnancy complicated by thrombocytopenia secondary to human immunodeficiency virus infection. Obstet Gynecol 1994;83:825–827.
55. Gwinn M, Wortley PM. Epidemiology of HIV infection in women and newborns. Clin Obstet Gynecol 1996;39:292–304.
56. Langston C, Lewis DE, Hammill HA, et al. Excess intrauterine fetal demise associated with maternal immunodeficiency virus infection. J Infect Dis 1995;172:1451–1460.
57. Rogers MF, Shaffer N. Reducing the risk of maternal-infant transmission of HIV by attacking the virus. N Engl J Med 1999;341:441–443.
58. Wade NA, Birkhead BS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998;339:1409–1414.
59. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173–1180.
60. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. N Engl J Med 1999;340:977–987.
61. Sempri AE, Castagna C, Ravizza M, et al. The incidence of complications after cesarean section in 156 HIV-positive women. AIDS 1995;9:913–917.
62. Glantz JC, Roberts DJ. Pregnancy complicated by thrombocytopenia secondary to human immunodeficiency virus infection. Obstet Gynecol 1994;83:825–827.
63. Riley LE, Greene MF. Elective cesarean delivery to reduce the transmission of HIV. N Engl J Med 1999;340:1032–1033.
64. Hughes SC, Dailey PA, Landers D, et al. Parturients infected with human immunodeficiency virus and regional anesthesia. Anesthesiology 1995;82:32–37.
65. Frame WA, Lichtman MW. Blood patch in the HIV-positive patient [letter]. Anesthesiology 1990;73:1297.
66. Bevacqua BK, Slucky AV. Epidural blood patch in a patient with HIV infection [letter]. Anesthesiology 1991;74:952–953.
67. Gibbons JJ. Post dural puncture headache in the HIV positive patient [letter]. Anesthesiology 1991;74:953.
68. Tom DJ, Gulevich SJ, Shapiro HM, et al. Epidural blood patch in the HIV-positive patient. Review of clinical experience. Anesthesiology 1992;76:943–947.
69. Fassoulaki A, Desmonts JM. Prolonged neuromuscular blockade after a single bolus dose of vecuronium in patients with acquired immunodeficiency syndrome. Anesthesiology 1994;80:457–459.
70. Lauretti GR. Infectious diseases. In: Gambling DR, Douglas MJ (eds). Obstetric Anesthesia and Uncommon Disorders. Philadelphia: Saunders, 1998:336.
71. Layon AJ, Peck AB. Anesthetic effects on immune function: where do we stand? In: Stoelting RK, Barash PG, Gallagher TJ (eds). Advances in Anesthesia, vol 10. St. Louis: Mosby, 1993:69–93.
72. Barzan L, Carbone A, Saracchini S, et al. Nasopharyngeal lymphatic tissue hypertrophy in HIV infected patients. Lancet 1989;1:42–43.
73. American College of Obstetricians and Gynecologists. Management of herpes in pregnancy. Practice Bulletin No. 8. Washington, DC: ACOG, 1999.
74. Jacobs RF. Neonatal herpes simplex virus infections. Semin Perinatol 1998;22(1):64–71.
75. Woods GL. Update on laboratory diagnosis of sexually transmitted diseases. Clin Lab Med 1995;15(3):665–684.
76. Frenkel LM, Brown ZA, Bryson YJ, et al. Pharmacokinetics of acyclovir in the term human pregnancy and neonate. Am J Obstet Gynecol 1991;164(2):569–576.
77. http://www.cdc.gov/nchstp/dstd/Genital Herpes facts.htm
78. Brown ZA. Genital herpes complicating pregnancy. Dermatol Clin 1998;16(4):805–810.
79. Becker TM, Blount JH, Guinan ME. Genital herpes infections in private practice in the United States, 1966 to 1981. JAMA 1985;253(11):1601–1603.
80. Crone LA, Conly JM, Clark KM, et al. Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. Anesth Analg 1988;67(4):318–323.
81. Boyle RK. A review of anatomical and immunological links between epidural morphine and herpes simplex labialis in obstetric patients. Anaesth Intensive Care 1995;23(4):425–432.
82. Manian FA. Potential role of famciclovir for prevention of herpetic whitlow in the health care setting. Clin Infect Dis 2000;31(4):E18–E19.
83. Gellin BG, Broome CV. Listeriosis. JAMA 1989;261:1313–1320.
84. Linnan MJ, Mascola L, Lou XD, et al. Epidemic listeriosis associated with Mexican-style cheese. N Engl J Med 1988;319:823–828.
85. Steele PE, Jacobs DS. *Listeria monocytogenes* macroabscesses of placenta. Obstet Gynecol 1979;53:124–127.
86. Boucher M, Yonekura ML. Perinatal listeriosis (early-onset): correlation of antenatal manifestations and neonatal outcome. Obstet Gynecol 1986;68:593–597.
87. Lyme disease—United States, 1999. MMWR (Morb Mortal Wkly Rep) 2001;50(10):181–185.
88. Strobino B, Abid S, Gewitz M. Maternal Lyme disease and congenital heart disease: a case-control study in an endemic area. Am J Obstet Gynecol 1999;180(3 Pt 1):711–716.
89. Silver HM. Lyme disease during pregnancy. Infect Dis Clin N Am 1997;11(1):93–97.
90. http://www.cdc.gov/ncidod/dvbid/lymeinfo.htm
91. Cadavid D, O'Neill T, Schaefer H, Pachner AR. Localization of *Borrelia burgdorferi* in the nervous system and other organs in a non-human primate model of Lyme disease. Lab Invest 2000;80(7):1043–1054.
92. Rosenfeld ME, Beckerman B, Ward MF, Sama A. Lyme carditis: complete AV dissociation with episodic asystole presenting as syncope in the emergency department. J Emerg Med 1999;17(4):661–664.
93. Saba S, VanderBrink BA, Perides G, et al. Cardiac conduction abnormalities in a mouse model of lyme borreliosis. J Intervent Cardiol Electrophysiol 2001;5(2):137–143.
94. American College of Obstetricians and Gynecologists. Perinatal viral and parasitic infections. Practice Bulletin. No. 20. Washington, DC: ACOG, 2000.
95. Thurn J. Human parvovirus B19: historical and clinical review. Rev Infect Dis 1988;10:1005–1011.
96. Valeur-Jensen AK, Pedersen CB, Westergaard T, et al. Risk factors for parvovirus B19 infection in pregnancy. JAMA 1999;281(12):1099–1105.
97. Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. BMJ 1990;3000(6733):1166–1170.
98. Risks associated with human parvovirus B19 infection. MMWR (Morb Mortal Wkly Rep) 1989;38:81–88.
99. Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. Br J Obstet Gynaecol 1998;105(2):174–178.
100. Dieck D, Schild RL, Hansmann M, Eis-Hubinger AM. Prenatal diagnosis of congenital parvovirus B19 infection: value of serological and PCR techniques in maternal and fetal serum. Prenat Diagn 1999;19(12):1119–1123.
101. Levy R, Weissman A, Blomberg G, Hagay ZJ. Infection by parvovirus

B 19 during pregnancy: a review. Obstet Gynecol Surv 1997;52(4):254–259.
102. Eisele CJ. Rubella susceptibility in women of childbearing age. J Obstet Gynecol Neonatal Nurs 1993;22:260–263.
103. American College of Obstetricians and Gynecologists. Rubella and pregnancy. Technical Bulletin No. 171. Washington, DC: ACOG, 1992.
104. Bosma TJ, Corbett KM, Eckstein MB, et al. Use of PCR for prenatal and postnatal diagnosis of congenital rubella. J Clin Microbiol 1995;33: 2881–2887.
105. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 1982;2:781–784.
106. Centers for Disease Control. Rubella vaccination during pregnancy—United States, 1971–1988. MMWR 1989;38:289–293.
107. Division of STD Prevention. Sexually transmitted disease surveillance, 1996. U.S. Department of Health and Human Services, Public Health Services. Atlanta, GA: Centers for Disease Control and Prevention, 1997.
108. Centers for Disease Control. 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47:28–49.
109. Hook EW, Marra CM. Acquired syphilis in adults. N Engl J Med 1992; 326:1060–1069.
110. Ray JG. Lues-Lues: maternal and fetal considerations of syphilis. Obstet Gynecol Surg 1995;50:845–849.
111. Wendel GD. Gestational and congenital syphilis. Clin Perinatol 1988; 15:287–303.
112. Hook EW, Marra CM. Acquired syphilis in adults. N Engl J Med 1992; 326:1060–1069.
113. Wendel GD Jr, Stark BJ, Jamison RB, et al. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985; 312:1229–1232.
114. Ziaya PR, Hankins GDV, Gilstrap LC, Halsey AB. Intravenous desensitization and treatment during pregnancy. JAMA 1986;256:2561.
115. http://www.cdc.gov/ncidod/dpd/parasites/toxoplasmosis/factsht toxoplasmosis.htm
116. Foulon W, Villena I, Stray-Pedersen B, et al. Treatment of toxoplasmosis during pregnancy: a multicenter study of impact on fetal transmission and children's sequelae at age 1 year. Am J Obstet Gynecol 1999;180(2 Pt 1):410–415.
117. Perinatal viral and parasitic infections. ACOG Practice Bulletin Number 20. Washington, DC: ACOG, 2001.
118. Stray-Pedersen B. Toxoplasmosis in pregnancy. Baillieres Clin Obstet Gynaecol 1993;7:107–137.
119. Daffos F, Forestier F, Capella-Pavlovsky M, et al. Prenatal management of 746 pregnancies at risk for congenital toxoplasmosis. N Engl J Med 1988;318(5):271–275.
120. Mombro M, Perathoner C, Leone A, et al. Congenital toxoplasmosis: 10-year follow-up. Eur J Pediatr 1995;154(8):635–639.
121. Stray-Pedersen B. Treatment of toxoplasmosis in the pregnant mother and newborn child. Scand J Infect Dis Suppl 1992;84:23–31.
122. Patel DV, Holfels EM, Vogel NP, et al. Resolution of intracranial calcifications in infants with treated congenital toxoplasmosis. Radiology 1996;199(2):433–440.
123. Frieden TR, Sterling T, Pabllo-Mendez A, et al. The emergence of drug-resistant tuberculosis in New York City. N Engl J Med 1993;328:521–526.
124. Robinson CA, Rose NC. Tuberculosis: current implications and management in obstetrics. Obstet Gynecol Surv 1996;51:115–124.
125. Bate TW, Sinclair RE, Robinson MJ. Neonatal tuberculosis. Arch Dis Child 1986;61:512–514.
126. Nemir RL, O'Hare D. Congenital tuberculosis. Review and diagnostic guidelines. Am J Dis Child 1985;139:284–287.
127. Kendig EL Jr. The place of BCG vaccine in the management of infants born of tuberculous mothers. N Engl J Med 1969;281:520–523.
128. Wang YL, Hong CL, Chung HS, et al. Massive hemoptysis after the initiation of positive pressure ventilation in a patient with pulmonary tuberculosis. Anesthesiology 2000;92(5):1480–1482.
129. Pollard BA, El-Beheiry H. Pott's disease with unstable cervical spine, retropharyngeal cold abscess and progressive airway obstruction. Can J Anaesth 1999;46(8):772–775.
130. Varicella-related deaths among adults—United States, 1997. MMWR (Morb Mortal Wkly Rep) 1997;46:409–412.
131. Enders G. Serodiagnosis of varicella-zoster virus infection in pregnancy and standardization of the ELISA IgG and IgM antibody tests. Dev Biol Stand 1982;52:221–236.
132. Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR (Morb Mortal Wkly Rep) 1996;45:1–36.
133. Smego RA Jr, Asperilla MO. Use of acyclovir for varicella pneumonia during pregnancy. Obstet Gynecol 1991;78:1112–1116.
134. Lecuru F, Taurelle R, Bernard JP, et al. Varicella zoster virus infection during pregnancy: the limits of prenatal diagnosis. Eur J Obstet Gynecol Reprod Biol 1994;56:67–68.
135. Isada NB, Paar DP, Johnson MP, et al. In utero diagnosis of congenital varicella zoster virus infection by chorionic villus sampling and polymerase chain reaction. Am J Obstet Gynecol 1991;165:1727–1730.
136. Enders G, Miller E, Cradock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet 1994;343:1548–1551.
137. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. N Engl J Med 1994; 330:901–905.
138. Brunell PA. Fetal and neonatal varicella-zoster infections. Semin Perinatol 1983;7:47–56.
139. Wallace MR, Bowler WA, Murray NB, et al. Treatment of adult varicella with oral acyclovir. A randomized, placebo-controlled trial. Ann Intern Med 1998;36:31–38.
140. The American Academy of Pediatrics Committee on Infectious Disease: the use of oral acyclovir in otherwise healthy children with varicella. Pediatrics 1993;91:858.
141. Miller E, Cradock-Watson JE, Ridehalgh MK. Outcome in newborn babies given antivaricella-zoster immunoglobulin after perinatal infection with varicella-zoster virus. Lancet 1989;8659:371–373.
142. Varicella-zoster immune globulin for the prevention of chickenpox. Recommendations of the Immunization Practices Advisory Committee, Centers for Disease Control. Ann Intern Med 1984;100:859–865.
143. Wu CL, Marsh A, Dworkin RH. The role of sympathetic nerve blocks in herpes zoster and postherpetic neuralgia. Pain 2000;87(2):121–129.

27
Substance Abuse

Nancy Kenepp and Ashwin Chatwani

Women of childbearing age constitute a substantial proportion of substance abusers, and an estimated 5% of births in the United States are drug exposed. In an urban emergency room, almost 50% of patients presenting in early pregnancy test positive for tobacco, marijuana, or cocaine.[1] Box 27.1 lists the substances addressed in this chapter.

Patterns of Abuse

People exhibit a continuum of patterns of drug use where movement back and forth from one phase to another is possible. On one extreme is the person who abstains totally. Most people use drugs rarely or occasionally; this is termed "social" use. Abuse occurs when use is clearly above the norm for the social group. Early addiction is present when medical and personal problems ensue and withdrawal symptoms start. Exclusive of tobacco, at any given time, about 4% of the U.S. population abuses or depends on drugs, and over the course of their lives, about 20% of the population will meet the criteria for abuse or dependence.[2]

Social Use

Several factors determine use of drugs: peer attitude toward use, parental use, socioeconomic status, education, legality, risk taking, curiosity, and individual tendency to accept social norms. Among teenagers, use correlates with symptoms of adolescent depression and dropping out of school.

Because these are legal substances, people tend to try tobacco and alcohol initially. Groups or individuals progress to illegal substances such as marijuana and cocaine; abusers often use multiple drugs.

Abuse

Causes of substance abuse are numerous. Some predictors are low self-esteem and difficulty in relating to people, in expressing feelings, in anticipating consequences, and in creating a healthy environment. As what is socially acceptable varies among groups, changing friends can be an early sign of abuse. Users often attribute medical symptoms of abuse to more socially acceptable factors, for example, childhood illnesses. Eventually addictive behavior interferes with obtaining basic human needs such as food, housing, and (prenatal) medical care.

Addiction

Addiction is using a substance for short-term pleasure at the expense of long-term adverse effects. Although addiction is obvious at this stage, users, when asked, may admit to only occasional use and repress or deny abuse.

Pharmacology

Tolerance

Addictive drugs share the capacity to produce two types of tolerance. Metabolic tolerance is increased capacity to metabolize the substance. Pharmacodynamic tolerance is decreased sensitivity of the central nervous system (CNS) to the drug effects, which is caused by autoregulating mechanisms.

Dependence

Dependence is a sign of pharmacodynamic tolerance characterized by rebound CNS hyperexcitability, or depression, as the initial drug effect wanes. Dependence causes drug-seeking behavior and is more severe with short-acting compounds. Minimal symptoms of dependence accompany drugs of longer duration of action. Substances with cross-dependence relieve the symptoms of dependence. Chronic users of a substance are less sensitive to cross-dependent drugs, but if they are acutely intoxicated, they are more sensitive.

Withdrawal

Withdrawal refers to the constellation of symptoms that develop when substance use ceases. Withdrawal symptoms are evidence that pharmacodynamic tolerance has developed.

Box 27.1. Commonly abused substances.

Alcohol
Barbiturates
Narcotics
Benzodiazepines
Marijuana
Cocaine
Amphetamines
Phencyclidine
MDMA (3,4-methylenedioxymethamphetamine)
Tobacco

Distress during pharmacologic withdrawal is modulated by environmental conditioning: the association of substance abuse with particular events. Protracted abstinence syndrome refers to the period during which subtle withdrawal symptoms interfere with the smooth progression of activities of daily living. Substances with cross-dependence suppress withdrawal symptoms but maintain dependence. Thus, cross-dependent substances can be used when the primary substance is not available, which is another reason why addicts use multiple drugs. The basis of some overdoses is inadvertent ingestion of cross-dependent substances. Cross-dependent drugs with fewer adverse health effects or withdrawal symptoms are useful for treating addiction.

Detection

Chemical Analysis

Abusive chemicals are usually assayed in urine or blood. The most common technique for initial identification of illegal substances is an enzyme-mediated immunotechnique (EMIT). Positive results should be confirmed by gas chromatography, high pressure liquid chromatography, or thin-layer chromatography. Urine screening is used for most substances, because it can be more easily obtained than blood. Handheld latex agglutination testing devices are available for screening urine when rapid results are desirable.

A major disadvantage of both urine and blood screening is the limited interval after use during which detectable levels of the substance are present. A urine test for alcohol remains positive for 8 to 16 h; that for amphetamine or cocaine, 24 to 72 h; for opiates, 2 to 4 days; and for marijuana, 7 to 30 days.[3]

Meconium Testing

Meconium collected from diapers is representative of a long period of fetal development, and meconium metabolite concentrations correlate with severity of drug exposure. Meconium analysis is capable of detecting fetal exposure that is missed with urine sampling and is well established as a method for the detection of cocaine, tobacco, and marijuana. Meconium analysis for ethyl linoleate, a metabolite of ethanol, has recently been shown to correlate with maternal reports of severity of alcohol abuse.[4]

Hair Analysis

Quantitative analysis of hair for the metabolites of nicotine and cocaine is performed by radioimmunoassay, and concentration in the hair corresponds to the amount of exposure.[5] Although hair growth is variable, the proximal 12 cm corresponds with the duration of the pregnancy. A specimen cut into three 4-cm segments, when assayed, correlates well with historical use during the trimesters of pregnancy. Cocaine and tobacco are deposited into fetal hair during the third trimester, and infant levels correlate with maternal proximal segment levels.

Self-Reporting

Reliance on self-reporting of substance abuse misses 26% to 48% of pregnancies in which it occurs.[1,6] At least 25% of parturients with positive urine screens deny use of drugs.[1] Only 3% to 6% of parturients who report never having used tobacco, marijuana, or cocaine have positive urine tests. However 23% to 25% of parturients who report using these substances in the past have positive urine tests, and 50% who deny current cocaine use have metabolites in their hair. Reporting past use of a substance is an indicator for current use. With recent publicity regarding the deleterious effects of smoking tobacco during pregnancy, denial of tobacco use is as likely as denial of other substances.[1]

Addictive Drugs in Pregnancy

Incidence

Multiple studies have attempted to assess the prevalence and types of drugs abused by pregnant women. The true incidence of perinatal substance abuse is unknown, because self-reporting is unreliable, urine screening detects only recent users, and hair and meconium analysis is too expensive for widespread use.

Reported Incidence

Although the incidence of abuse during pregnancy is probably higher than is reported in the literature (Table 27.1), screening results do delineate the magnitude of the problem. Of universally screened women on admission to the obstetric service at the University of California, Davis Medical Center, one in five were positive for an illegal substance.[7] In other

TABLE 27.1. Prevalence rates of substance abuse in pregnancy.

Substance	Percent
Tobacco	8–46
Alcohol	4–20
Marijuana	1–34
Cocaine	1–18
Amphetamine	0.3–7
All drugs	4–50

studies, positive urine tests for cocaine or marijuana have been reported to range from 8% to 32%.[6] Tobacco use, which is not included as a substance of abuse in many studies, ranges from 15% in private West Coast patients to as high as 46% in Midwest rural patients.[8,9] Tobacco use correlates with substance abuse; 78% of drug users were smokers in one study,[7] and 15% of drug users smoke compared to 5% of nonusers.[9,10]

Geographic Differences

In rural areas and the Southeast, tobacco, alcohol, and marijuana are commonly abused substances. In urban East and West Coast areas, cocaine use is more prevalent. Amphetamine use is not as prevalent as cocaine except in selected urban areas on the West Coast.

Demographic Characteristics

Various demographic characteristics correlate with drug use. Most studies describe drug users as older,[7] single,[8] from a lower socioeconomic class,[7] clinic patients,[8] less educated,[8] depressed,[11] and without prenatal care.[11,12] Many are victims of abuse, childhood rape, and sexual molestation, and the progeny of substance-abusing parents.[11,13] African-Americans seem more likely to use cocaine, whereas Asians and Hispanics are unlikely to use illicit drugs.[7,8] Private parturients are less likely to use cocaine.[8]

Caveats Regarding Interpreting Studies

When interpreting results, it is important to consider the study protocol, especially regarding the effects of drug exposure on the fetus. Separating the effects of a particular drug from the detrimental effects of concomitantly used drugs or socioeconomic circumstances is difficult. Problems attributed to drug abuse may actually be related to heavier tobacco use by addicts.

Separating users from nonusers, for study purposes, is difficult. In one study, 25% of parturients with negative urine screens gave a history of drug use;[7] in another report only half of parturients reporting drug use had positive drug screens.[14] Screening infant urine misses 50% of exposed fetuses.

Urine screen timing alters user population estimates: analysis early in gestation includes those who abstain after the first trimester; analysis late in gestation or at delivery may classify first and second trimester users as abstainers. Because there is a continuum of severity of drug abuse, reporting exposure as positive or negative lumps together rare users and addicts. Once made aware of possible detrimental effects, a high percentage of women reduce or abstain from tobacco and alcohol use soon after discovering their pregnancy.[15] One study shows that 57% of parturients at a teaching hospital and 61% at a private hospital had alcohol before or during pregnancy, whereas only 12% and 7%, respectively, "binged" before pregnancy, and 6% and 1%, respectively, binged during the pregnancy.[8] "Lumped data" are especially misleading when entered into multivariate regression analysis.

Consequences of Self-Reporting

Persons admitting drug use are sometimes reported to child protection services, causing loss of custody, or, as in Wisconsin, court jurisdiction over the unborn child. Women in Charleston, South Carolina, who had positive urine screens for cocaine were arrested for delivering drugs to a minor. Mandatory reporting is not always enforced uniformly,[11] as in Pinellas County, Florida, where black women with positive urine screens were reported at 10 times the rate of Caucasian women.[16] Fearing nonmedical consequences, pregnant women are reluctant to report illicit drug use. Of parturients with positive urine, 82% deny marijuana use, and 44% deny cocaine use.[17] Comparison of anonymous responses with meconium results shows that even anonymous forms are not reliable in assessing the incidence of illicit drug use.[18]

Identifying Parturients

Demographic results of prevalence studies can be applied to identify substance abusers. The medical, social, or obstetric history may reveal problems associated with substance abuse.[19] Universal urine screening is not cost-effective unless a majority of parturients are abusing drugs.

Effects of Pregnancy on Substance Abuse

Pharmacologic

Physiologic changes in body water and plasma volume during pregnancy alter the peak concentration, half-life, and volume of distribution of drugs.[20] Sensitivity to and metabolism of drugs change during pregnancy. Pregnancy increases sensitivity to cocaine, whereas methadone requirements increase due to increased volume of distribution. Pregnancy lowers cytochrome P_{450} enzymes, glucuronyl transferase, and microsomal monooxygenase[21]; progesterone increases N-demethylation.[22] These changes alter metabolism of cocaine, heroin, alcohol, barbiturates, and marijuana. Metabolism of alcohol via aldehyde dehydrogenase and of cocaine via N-demethylation may cause liver cellular damage.[23]

Placental Effects

Placental transport is established by the fifth week of life, and placental drug metabolism is determined by the quality and quantity of enzymes present, which are in turn determined by maternal environment. Placental microsomes are capable of metabolizing cocaine.[24] The placenta metabolizes alcohol in a manner similar to the liver.[25]

Maternal Effects of Substance Abuse

Effects of Parenteral Abuse

Administering drugs by injection subjects users to complications associated with use of nonsterile equipment and impure

Box 27.2. Implications of parenteral drug abuse.

Hepatitis
HIV infection
Sexually transmitted disease
Cellulitis
Superficial or deep abscess
Tetanus
Septic phlebitis
Foreign body emboli
Lymphedema
Tricuspid insuffiency
Bacterial endocarditis
Septic pulmonary infarct
Cerebral abscess
Vertebral osteomyelitis
Pulmonary hypertension
Pulmonary edema
Pulmonary bullae
Pulmonary abscess
Tuberculosis
Pneumonia

Source: Modified from N. Kenepp. Substance abuse. In: James FM, Wheeler AS, Dewan DM (eds) Obstetric Anesthesia: The Complicated Patient, 2nd edn. Philadelphia: Davis, 1987: 507. Used by permission.

drugs. These complications (Box 27.2) include hepatitis, human immunodeficiency virus (HIV), endocarditis, and pulmonary hypertension.

With the use of newer preparations of cocaine and amphetamine by inhalation rather than injection and the decreased popularity of black tar heroin, one would expect HIV among drug users to decline. The high incidence of HIV among cocaine users is attributed to drug-related sexual activity.[26] In Atlanta, 0.6% of pregnant women were HIV positive, and half of those who admitted risk factors were cocaine users. The probability of acquiring HIV infection with a history of intravenous drug administration was 5 in 19 and with cocaine use, 3 in 5.[26]

Maternal Detrimental Effects of Substance Abuse

Because of pregnancy associated increased cardiac output, minute ventilation, and oxygen consumption, respiratory or cardiac failure occurs with lower serum levels of barbiturates, opiates, or alcohol than in the nonpregnant state. Nutritional needs are increased in pregnancy, but drug abuse is associated with poor dietary habits. Parturients with marijuana, phencylidine (PCP), or cocaine in their urine had lower serum folate and ferritin levels.[27] Urinary tract infections, pneumonia,[28] and higher blood leukocyte counts are associated with antepartum drug use.[27] Elevated maternal carboxyhemoglobin levels and airway hyperreactivity will be present when drugs are smoked. Physical signs associated with drug use include abnormal pupil size, cough, rhonchi or wheezing, staining of fingers and teeth, palmar erythema, liver flap, skin ulcers or needle tracks, emaciation, poor hygiene, inattentiveness, and narcolepsy.

Psychosocial Effects

Pregnant women delay obtaining medical care (Table 27.2). Drug users are more likely to be physically abused.[29] African-American women and non-Hispanic Caucasians who use drugs are 3.7 and 2.1 times, respectively, more likely to be battered than nonusers. Abusers and addicts use their energy obtaining drugs, not on assuring personal needs, so their lifestyle is chaotic. They resort to prostitution for drug money or trade sex for drugs. Money for food may be spent on drugs. Homelessness or housing without heat, running water, or telephone are not infrequent. Compounding the problem, treatment facilities for drug users are not adequate in either scope or number.[10]

Uteroplacental Effects of Substance Abuse

Membrane characteristics, pH, lipid solubility, protein binding, and molecular weight determine the placental transfer of nutrients and drugs. Placental metabolism, uteroplacental blood flow, and placental transfer of oxygen and nutrients are all affected by substance abuse.

Placental Transfer

Nutrient transfer is affected by cocaine,[22] alcohol,[30] and tobacco.[31] Impaired placental nutrient transfer associated with substance abuse may result from changes in placental membranes.

Placental Blood Flow

Uteroplacental blood flow is determined by maternal and fetal cardiac output, uterine tone, and vascular resistance. Depressant drugs, such as barbiturates, may decrease cardiac output and thus impair delivery of nutrients and oxygen. Increased sympathetic activity, produced by cocaine, amphetamine, tobacco, narcotic, or alcohol withdrawal, and hypercarbia and hypoxia from narcotics may impair nutrient delivery by causing vasoconstriction of placental and uterine blood vessels.[32] Vasoconstriction can increase the incidence of abruptio placentae, as seen with nicotine,[33] heroin,[34] amphetamine,[35] and cocaine.[36] Table 27.3 shows the incidence of placental abruption with drug abuse compared to control populations.

TABLE 27.2. Prenatal care in substance abusers.

Prenatal care	Controls (%)	Cocaine (%)	Amphetamine (%)	Multidrug (%)	Opiate (%)
First trimester	13	6	6	11	21
Second trimester	35	25	18	26	47
Third trimester	30	21	27	20	21
None	11	40*	40*	40*	11

*$p < 0.01$, comparison with controls.

Source: Modified from Gillogley KM, Evans AT, Hansen RL, et al. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. Am J Obstet Gynecol 1990;163:1535. Used with permission.

TABLE 27.3. Placental abruption and substance abuse.

Drug or condition	Control rate of abruption (%)	Drug or condition rate of abruption (%)
Amphetamine	0.7	0.9
Methadone	0	0.7
Tobacco	—	1.6–2.8
Heroin	0	3.2
No prenatal care	0	4.0
Multidrug abuse	0.7	5.7
Cocaine	0.3–0.8	0.7–15

TABLE 27.4. Birthweight deficits.

Substance abused	Birth weight deficit (g)	Head circumference deficit (cm)
Cocaine	125*	0.41*
Cocaine + multidrugs	195**	1.09**
Cocaine + marijuana	170*	0.41**
Cocaine + opiates	237**	0.95**
"Crack"	200**	0.84**

*$p < 0.05$; **$p < 0.01$.

Source: Modified from Bateman DA, Ng SK, Hansen CA, et al. The effects of intrauterine cocaine exposure in newborns. Am J Public Health 1993;83(2):190. Used by permission.

Fetal Effects of Substance Abuse

Birth Defects

Birth defects in substance abusers can result from malnutrition, direct effects of drugs or their metabolites, infarction from vasoconstriction, and alteration in neurotransmitters.[37] Malnutrition, specifically defiency of folic acid in substance abusers, can cause neural tube defects.[38] Vasoconstriction and resultant free radicals may cause limb reduction defects,[39] skull defects,[40,41] genitourinary tract anomalies,[42] and ileal atresia.[43]

Fetal Alcohol Syndrome (FAS)

Acetaldehyde is thought to be involved in the development of fetal alcohol syndrome (FAS).[44,45] Although there is no clear-cut evidence of barbiturate-induced fetal damage in humans, barbiturates are behavioral teratogens in animals, and early gestational exposure produces neuromorphic changes similar to FAS.[46] FAS-like anomalies have been reported with exposure to marijuana, but alcohol and malnutrition may have also been factors.[47]

Intrauterine Growth Restriction (IUGR)

Tobacco,[48] alcohol,[49] heroin,[50] marijuana,[6] amphetamine,[51] and cocaine[52,53] use are all associated with intrauterine growth restriction (IUGR). Table 27.4 shows the effect of some of these drugs on birth weight. IUGR is most severe in polydrug users and bingers.[28,54] Multiple reasons are proposed for growth retardation, such as drug-induced decreased delivery of oxygen and nutrients via the placenta,[55] fetal hypoxia or ischemia, and accumulation of carbon monoxide.

Spontaneous Abortion

Multiple reports link drug abuse with an increased incidence of spontaneous abortion. This is most likely linked to tobacco use.[56]

Preterm Labor

The incidence of preterm labor is higher with use of cocaine,[57] marijuana,[58] heroin,[59] and tobacco.[60] Parturients abusing multiple drugs or binge cocaine users are more likely to have preterm delivery.[17,61]

Fetal Distress

Fetal distress, associated with abruptio placentae and placental insuffiency, increases in drug abusers. Opiate use causes loss of fetal heart rate variability. Cocaine, PCP, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and alcohol all cause fetal tachycardia.

Neonatal Effect of Substance Abuse

Neonates continue to be affected by maternal drug use via vertical transmission of HIV, hepatitis, and sexually transmitted diseases (STDs), delayed metabolism and excretion of drugs with the absence of placental transfer back to the mother, and necessary treatment of withdrawal symptoms. The cost of neonatal care is increased for drug-exposed neonates.[62]

Neonatal development is influenced by environmental factors related to maternal lifestyle. Breast-feeding[63] and postpartum maternal smoking, which lead to positive infant urine screens for cocaine and tobacco, prolong drug exposure.[64] Sudden infant death syndrome (SIDS) incidence increases with tobacco, opiates, and cocaine abuse.[65,66]

Neonatal Abstinence Syndrome

Adverse neurologic findings include neonatal depression from intoxication and withdrawal symptoms. Withdrawal symptoms are observed with opiates and, to a lesser extent, with alcohol, cocaine, benzodiazepines, and barbiturates. Opiate withdrawal symptoms are shown in Box 27.3. Neonates with withdrawal symptoms have excessive weight loss.[34] Perinatal mortality is increased 25% to 35% in infants exposed to tobacco.[67]

Neurologic Outcome

Intellectual and behavioral problems, which may be socioeconomic rather than directly drug derived, have been documented in children of drug abusers. Determination of the effect of drug exposure on infant development is hampered by the presence of many confounding variables and a lack of appropriate outcome measures. A growing number of reports in-

Box 27.3. Neonatal withdrawal symptoms.

Tremor
Irritability
Jittery behavior
Excessive crying
Hyperactive reflexes
Yawning
Sneezing
Sweating
Increased respirations
Seizures
Alkalosis
Hypocapnia
Fever
Increased stools
Vomiting
Dehydration
Uncoordinated sucking
Increased flexor tone
Disorganized responses

dicate an association of motor tone abnormalities, behavioral problems, auditory and visual processing deficits, and attentional deficits in children of drug-abusing mothers.[68]

Obstetric Care for Substance Abusers

All pregnant women need substance avoidance education. Care of substance abusers starts with getting the mother to the health care system. Because of prior negative experiences with health care and child protective services, mothers may present an uncaring and indifferent facade and be difficult to manage. They cannot be forced to cease taking drugs and instead should be helped to seek appropriate assistance[69] with referral to substance abuse professionals. For addicts, intervention requires programs designed to handle all the woman's needs, rather than only maternal and fetal care. The environment should be supportive, nonjudgmental, and nonpunitive. Parturients need access to food, housing, child care, and drug and nutrition counseling to be able to take advantage of health care opportunities. Workers should actively recruit parturients and bring them to clinics if appointments are missed. Clinics focusing on family and drug abuse care retain parturients and succeed in improving obstetric outcome.[70,71]

Prenatal Care

General prenatal care for drug abusing mothers is outlined in Box 27.4. At the initial visit, the presence of associated historical and physical findings helps in assessing degree of abuse. The duration of the pregnancy at the initial visit often reflects the degree of drug dependence. Admission to a detoxification unit may be necessary. Parturient education should include information regarding fetal growth restriction, premature labor, abruptio placentae, and general medical hazards of drug abuse.

Education, however, may lead to complications of its own. Adolescent girls may increase smoking to limit the size of the baby and the amount of pain in giving birth.[72] Parturients may use cocaine as an abortifacient or to induce labor. Narcotic addicts may try to substitute benzodiazepines for methadone, thereby exacerbating neonatal withdrawal.[73]

Box 27.4. Obstetric management of drug-dependent parturients.

First prenatal visit
1. History
    - Drug use
    - Obstetric history
        - Preterm birth
    - Medical history
        - STDs
        - Endocarditis
2. Laboratory tests
    - Syphilis test
    - Hepatitis test
    - HIV test
    - Tuberculosis test
    - CBC
    - Hepatic function
    - GC and *Chlamydia*
3. Ultrasound
    - Gestational age
    - For anomalies
4. Drug abuse treatment
    - Detoxification
    - Substitution therapy

Subsequent prenatal visits
1. Education
    - HIV infection
    - Fetal drug effects
2. Nutrition
3. Psychosocial services
4. Third trimester fetal testing
    - Ultrasound for growth
    - Biophysical score

Intrapartum care
1. Maternal monitoring
    - Oxygenation
    - Hyperpyrexia
    - Abruption
2. Fetal monitoring
3. Patients with CNS depression
    - Reduce acidity
4. Support of addiction
5. Cesarean section for fetal indication

Ultrasound assessment is an important tool for care of substance abusers. An initial assessment for dates is important for addicts: even if the parturient presents in the first trimester, the date of the last menstrual period may not be reliable. Early confirmation of dates also aids evaluation of growth restriction and diagnosis of fetal anomalies. Later in gestation, ultrasound is useful for assessing fetal growth.

Laboratory studies include serum hepatitis, HIV, alpha-fetoprotein titers and liver enzymes, and possibly folate levels, as well as routine prenatal testing. Parturients have an increased incidence of STDs. Tuberculin testing is indicated; an EKG or echocardiogram may also be indicated. Interval urine toxicologic screening is useful for assessing parturient

compliance. Nonstress tests or biophysical profiles are indicated after 32 weeks.[13] Expected maternal and infant needs after delivery should be assessed before parturition to avoid delayed discharge from the hospital.

HIV and Consultation

Pregnant women who are HIV positive require consultation with an infectious disease specialist. Pregnancy does not appear to affect progression of the disease, the major risk being that of transmission to the fetus.[74] Maternal antepartum zidovudine therapy lowers the rate of vertical transmission from 25% to 8%.[75] Laboratory studies in these parturients include CD4 counts and viral load. Pregnant women also may need consultations for cardiopulmonary or hepatic problems or for referral to a tertiary care facility.

Intrapartum Care

The presence of associated maternal disease causes an increase in induction of labor in drug abusers. Parturients in labor require careful monitoring for signs of placental insuffiency and fetal hypoxemia. Mothers frequently self-medicate before arrival in the delivery room. Central vein catheterization sometimes is required for IV access. Pregnant women who are HIV positive are treated with zidovudine (AZT) during the intrapartum period. Cesarean section for failed induction or fetal distress is more common in substance abusers. Short umbilical cords and resulting complications may be associated with abuse of depressant drugs.[76]

Intoxicated parturients are stabilized. Oxygenation needs to be supported. Depending upon the agent of abuse, the cardiovascular system may be stimulated or depressed. CNS-depressed parturients, at risk for aspiration, need medication to reduce gastric acidity and volume. Metaclopromide is indicated with alcohol, narcotic, and barbiturate intoxication. Acute cocaine or amphetamine toxicity may present as apparent preeclampsia.[77] Marijuana, PCP, MDMA, amphetamine, and cocaine intoxication are associated with hyperpyrexia, which increases oxygen consumption in both mother and fetus. Hyperpyrexia may be treated with acetaminophen. Detoxification is contraindicated during labor, because the stress of withdrawal reduces uterine blood flow and thereby increases fetal risk. Obstetric management is expectant, unless the maternal or fetal condition deteriorates, in which case delivery by cesarean section is indicated.

Anesthetic Implications in Drug Addiction

Drug Interactions

Multiple interactions of illicit drugs and anesthetic agents occur. Abusive substances alter metabolism of anesthetics. Conversely, spinal anesthesia and halothane induce increased hepatic metabolism of the abused agent.[78] Drug interactions may adversely affect cardiovascular, respiratory, uteroplacental, and fetal functions, limiting anesthetic choices. Barbiturates, PCP, and alcohol increase sensitivity to narcotics, whereas opiate abuse increases the need for narcotics. Careful titration evades morbidity.

Medical Complications

Medical complications associated with parenteral drug abuse (Box 27.2) are treated as in nonabusing parturients and may further limit anesthetic options. Table 27.5 outlines the anesthetic management of potential problems that may occur before or after administration of an anesthetic. Parturients with significant myocardial valvular disease or pulmonary hypertension require careful titration of anesthetic agents to avoid hypotension. Document myelopathy and neuropathy present before conduction anesthesia and vaginal delivery. Myopathy may increase the incidence of postdelivery backache.

HIV seropositive parturients may have regional anesthetics safely.[79] The risk of spreading HIV infection to the CNS is not clinically relevant, because CNS involvement occurs early in the course of the disease.[80] Minimize duration of epidural catheters and invasive monitoring, because impaired immunity increases infections resulting from attraction of bloodborne pathogens to the catheter.[81]

Anesthetic Management for Labor

Laboring parturients may need pulse oximeters in addition to routine monitoring. Because drug tolerance depresses the response to endogenous opiates, addicts frequently react poorly to stress and require more pain medication. Pregnant women receiving epidural analgesia deliver infants with better Apgar scores, so conduction anesthesia is desirable.[82] Excess sympathetic activity associated with withdrawal may decrease placental blood flow; thus, epidural analgesia is efficacious when withdrawal symptoms are present. Intravenous narcotics or mild tranquilizers help irritable parturients, who are in pain,

TABLE 27.5. Anesthesic management in drug abuse.

Coma	Intubate, administer antagonist
Respiratory depression	Administer antagonist, intubate, ventilate
Hypotension	Fluid, inotropes, invasive monitoring
Bradycardia	Atropine, isoproterenol, pacemaker
Vasodilation	Hydration, vasoconstrictors
Myocardial depression	Inotropes, delivery of fetus, mechanical support devices
Myocardial ischemia	Invasive monitoring, afterload reduction, nitroglycerine, inotropes
Hypertension	Vasodilators, No beta-selective blockers alone, or ACE inhibitors
Hypovolemia	Crystalloid, colloid, blood
Seizures	Ventilate, intubate, pentathol or benzodiazepine
Combative	Ventilation and circulation adequate? if yes: analgesic, sedation
Fetal distress	Ventilation and circulation adequate? if yes: oxygen, uterine relaxation, delivery

to cooperate for spinal or epidural procedures. Cocaine abusers have a higher visual analogue pain score before epidural analgesia, but when a block is established, their pain scores are similar to controls.[83]

Avoiding Complications

Drug abuse may cause coagulopathy; appropriate coagulation studies should be available before administering the block, unless the clinical situation dictates proceeding immediately. Although hypotension is primarily treated with ephedrine, small doses of phenylephrine may be necessary in some situations. Ephedrine administration is less reliable with marijuana, because both cause tachycardia; with PCP, because PCP increases ephedrine sensitivity; and with cocaine, because there may be no response due to inadequate norepinephrine stores. Intrathecal or epidural agonist-antagonist administration may precipitate withdrawal symptoms.[84] After intrathecal or epidural narcotics are administered, intensive monitoring of ventilation is important, because parturients may have self-administered narcotics.

Anesthesia for Cesarean Section

Choice of anesthetic technique for cesarean section depends upon maternal and fetal circumstances, as with normal parturients. General anesthesia is usually necessary for emergency cesarean section precipitated by severe fetal distress. Intoxicated parturients are not good candidates for regional anesthetic techniques because of anxiety, stress intolerance, and lack of cooperation. Neither are they good candidates for general anesthesia, because cross-tolerance with general anesthetics hampers determining an induction dose that will ensure unconsciousness yet avoid hypotension and neonatal depression. Patients with advanced acquired immunodeficiency syndrome-(AIDS)related pulmonary disease, or sepsis, may need general anesthesia for ventilatory control.

Regional Analgesia

Epidural and spinal anesthesia avoid airway and aspiration risks and depress the neonate least; they are the methods of choice. If necessary, minimal sedation with benzodiazepines prevents anxiety-induced decrease in placental blood flow during block administration. Careful titration of epidural anesthetics minimizes the incidence of hypotension. Severe valvular disease or pulmonary hypertension might be an indication for general anesthesia, but such parturients have been treated successfully with epidural anesthesia and intrathecal narcotics.[85] Postoperative pain relief with intrathecal or epidural narcotics is recommended in this group of pregnant women.

General Anesthesia

Thiopental is the induction drug of choice, with appropriate dosage reductions for the presence of CNS or myocardial depression. Succinylcholine is the muscle relaxant of choice. Although pseudocholinesterase may be inhibited by PCP, depleted by cocaine metabolism, or decreased by alcohol, the intubating dose is not decreased, as succinylcholine is suffiently short-acting. Intoxication delays extubation and prolongs recovery. Patient-controlled analgesia (PCA) may increase these patients' satisfaction by enhancing their perception of control over medication.

Ethanol

Pharmacology

Ethanol is a CNS depressant and a central sympathetic stimulant. Although pharmacologic tolerance develops, it does not elevate the lethal blood level. Ethanol is cross-tolerant with most CNS depressants, including general anesthetics.

Metabolism

Alcohol is metabolized to acetaldehyde. Conversion of alcohol to acetaldehyde by alcohol dehydrogenase occurs only if aldehyde dehydrogenase removes acetaldehyde. Five genes determine multiple isoenzymes of alcohol dehydrogenase.[86] Racial variations in aldehyde dehydrogenase activity are responsible for flushing reactions. Drugs inhibiting acetaldehyde metabolism increase flushing and ethanol-induced CNS depression.

Pathophysiology

Excessive acetaldehyde oxidation in liver or muscle results in peroxidation of lipid by oxygen radicals, producing hepatitis, myopathy, cardiomyopathy, and damage to other tissues and membranes. Acute alcohol intoxication inhibits cytochrome P_{450}-dependent drug oxidation; this increases levels of drugs predominantly eliminated by hepatic metabolism (e.g., propranalol, lidocaine). Chronic abuse stimulates hepatic oxidation and decreases bioavailability of drugs metabolized by the liver.

Prostaglandin Depletion

Alcohol depletes prostaglandin E_1 (PGE_1); it enhances conversion of dihomogamma-linolenic acid (DGLA) to PGE_1 and acutely increases PGE_1, but it blocks delta-8-6-desaturase, which replenishes DGLA. The absence of PGE_1 causes fibrosis, cardiomyopathy, reproductive failure, gastritis, and pancreatitis; this may be a factor in the development of FAS (fetal alcohol syndrome) because lithium, diphenylhydantoin, and zinc defiency (which also decrease PGE_1) all produce conditions similar to FAS.[87]

Withdrawal

Symptoms of withdrawal appear within 6 to 24 h. Withdrawal seizures are common in binge drinkers. Delirium tremens,

typically occurring 48 to 72 h after ceasing to drink, is life threatening and requires treatment with benzodiazepines, phenobarbital, or clonidine.

Pregnancy and Ethanol Abuse

Incidence

Alcohol abuse is reported in 5% to 46% of clinic populations; 3% of mothers drink enough for FAS to occur.[17] Alcohol is seldom the sole agent of maternal abuse; it is associated with marijuana (75%), cocaine (73%), and methadone abuse.[17] Women who drink heavily are usually young, Caucasian, educated, single, and have high incomes; but those drinking in the third trimester are older, black, less educated, lower in social status, and abusing other drugs.[88] Adolescent alcohol use decreases from 82% before pregnancy to 19% and 15% in the second and third trimesters, respectively. Binge drinking decreases during pregnancy, and with the exception of tobacco, other substance abuse also decreases.[89] MAST (Michigan Alcohol Screening Test) and "Ten Questions Drinking History" are two established interview techniques for identifying abusers.[90]

Maternal Effects

Table 27.6 outlines the extensive pathophysiology of alcohol abuse. Alcohol abuse causes hyperglycemia, congestive cardiomyopathy, arrhythmias, gastritis, elevated hepatic enzymes, pancreatitis, polyneuropathy, and seizures. Ethanol acutely alters both cardiac mechanical function and electrophysiologic properties. Alcohol also antagonizes folic acid. By altering the endocrine response to stress, alcohol increases cortisol, aldosterone, prolactin, epinephrine, and norepinephrine secretion and decreases growth hormone.[91] Ethanol exacerbates hypoglycemia of fasting by glycogen depletion from malnourishment, alcohol-induced glycogenolysis, and alcohol-impaired gluconeogenesis. Alcohol depresses the immunologic system and increases vulnerability to bacterial and viral infections, tuberculosis, and cancer.[92] The HIV-positive mother who uses ethanol is especially vulnerable to these infections. Muscle cell membrane damage and intracellular phosphate defiency produce acute myopathy and myoglobinuria, with selective atrophy of type II muscle fibers.[93] Myelopathy is characterized by spastic paraparesis and signs of both lateral and dorsal column involvement.[94] Advanced alcoholic liver disease results in coagulation factor defiency and thrombocytopenia. Qualitative platelet abnormalities include decreased cyclic adenosine monophosphate, monoamine oxidase, and nucleotide storage pool, and decreased release and aggregation.

Fetal Effects

Alcohol impairs the placental transfer of nutrients[95] but has no direct effect on placental blood flow as measured by umbilical artery impedance.[96] Alcohol appears to interfere with the development of cells that are exiting mitosis at the time of exposure, which may account for some of the variability in structural and behavioral anomalies in infants.[95] Heavy alcohol consumption causes developmental defects in a dose-dependent fashion in the first trimester.[44] Maternal consumption of more than 90 mL/day absolute alcohol produces IUGR in the third trimester.[45] Ethanol ingestion in the third trimester delays expected rises in amniotic levels of phosphatidylglycerol and the lecithin/sphingomyelin (L/S) ratio.[97]

TABLE 27.6. Pathophysiology of alcohol abuse.

Site	Pathophysiology
CNS	Acute: depression, "partially anesthetized"
	Chronic: myelopathy, polyneuropathy, Wernicke–Korsakoff syndrome, cerebellar degeneration, cortical damage, withdrawal seizures, hepatic encephalopathy
Lungs	Acute: respiratory failure, pulmonary shunting, surfactant and macrophage inhibition, aspiration pneumonia
	Chronic: ventilation/perfusion mismatch, intrapulmonary shunting, chronic infection
Cardiovascular	Acute: myocardial depression, abnormal electrophysiology, arrhythmia, cellular damage
	Chronic: alcoholic and nutritional cardiomyopathy, increased catecholamines, hypertension
Hepatic	Acute: cellular damage, hypoglycemia from inhibition of gluconeogenesis, decreased drug metabolism
	Chronic: fatty infiltration, hepatitis, enzyme induction, cirrhosis, portal hypertension, decreased hepatic flow, decreased drug metabolism, decreased protein and coagulation factor synthesis
Gastrointestinal	Peptic ulcer disease, gastritis, esophagitis, pancreatitis, malabsorption, bleeding esophageal varices, gallstones
Nutritional	Dietary deficiencies, vitamin deficiencies, malabsorption
Hematologic	Coagulopathy (multifactorial); platelet, leukocyte, and erythrocyte dysfunction
Renal	Acute: diuresis with sodium and potassium loss
	Chronic: antidiuresis with sodium retention, hypokalemia, hypomagnesemia, intracellular calcium derangement, renal failure
Muscular	Myopathy
Endocrine	Alterations of insulin, cortisone, aldosterone, catecholamines, growth hormone, prolactin, luteinizing hormone
Ophthalmic	Abnormal zinc and vitamin A reduce dark adaptation
Immunologic	Suppression; vulnerable to bacterial, viral infections, cancer

Source: From Kenepp N. Substance abuse. In: James FM, Wheeler AS, Dewan DM (eds) Obstetric Anesthesia: The Complicated Patient, 2nd edn. Philadelphia: Davis, 1987: 510. Used by permission.

Neonatal Effects

Acute ethanol intoxication depresses the newborn; chronic intrauterine exposure causes neonatal abstinence symptoms. There is a dose-related decrement in fetal size associated with maternal alcohol consumption.[98] Premature infants whose mothers are heavy alcohol users are more likely to have brain injuries on ultrasound examinations.[99] Neonates exposed to alcohol during the first and second trimester exhibit on EEGs decreased quiet and active sleep and frequent arousals still present at age one; findings are postulated to be related to serotonin effects.[100] Infants exposed to first trimester alcohol binges have decreased Bayley scores at 8 months, poor attention and fine motor skills at 4 years, and minimal brain damage (memory, attention, and processing deficits) at 7 years.[101] Children exposed to cocaine and alcohol have proportionately decreased gross motor functioning scores on the Peabody Developmental Motor Scales as alcohol exposure increases.[102]

Fetal Alcohol Syndrome

Neonates exposed to alcohol prenatally exhibit variable symptoms ranging from no apparent effect to fetal alcohol syndrome (FAS). FAS consists of growth retardation and CNS and craniofacial abnormalities and may present with other major and minor anomalies, neuropsychologic impairment, and mental retardation.[45] Variability of occurrence represents an important aspect, with full expression in 1 per 1000 live births and partial involvement in 1 child per 600 to 700 children.[103] Partial involvement is termed fetal alcohol effect.

A similar syndrome is seen with fetal exposure to solvents such as toluene.[104] The prominent facial abnormalities are a drawn appearance, midface hypoplasia, diminished philtrum, and small mandible. Ocular manifestations include Peters anomaly, lens opacification, and external eye lesions. Linear growth and weight gain are decreased despite normal nutrient absorption and growth hormone levels, resulting in decreased weight, length, head circumference, and skinfold thickness at age ten.[105] The CNS is very sensitive to alcohol, and children may have neurobehavioral abnormalities such as attention deficit disorder, learning disabilities, memory problems, and impulsivity without demonstrating the characteristic facial dysmorphism.

Obstetric and Anesthetic Considerations

Prenatal Care

Alcoholics require special surveillance for defiency anemias, glucose intolerance, and coagulopathy. Education includes warning that binge drinking and fluctuating ethanol levels are detrimental to the fetus. If alcohol abuse is suspected, serum levels of alpha-fetoprotein and pregnancy-specific beta-1-glycoprotein have predictive value for development of FAS.[106] Maternal serum gamma-glutamyl transpeptidase[107] and red cell Hb-Ach[44] also correlate with degree of ethanol consumption. Physical abuse may be a sign of alcohol dependence; Caucasians and African-Americans who drink are three and six times more likely to be battered, respectively, than abstainers.[29]

Detoxification

Addicts are ideally withdrawn from alcohol in a detoxification facility before pregnancy or as soon as pregnancy is diagnosed. Parturients may require detoxification during pregnancy to decrease the risk of FAS. Acamprosate and naltrexone are the drugs being used for relapse prevention.[108] If the parturient does not abuse multiple drugs, prescribing an occasional anxiolytic might prevent further alcohol abuse. Detoxification late in the pregnancy reduces placental blood flow from sympathetic stimulation.

Obstetric Management

Intrapartum care is as for other substance-abusing parturients. Preterm labor is not associated with ethanol abuse. Alcohol abusers need coagulation parameters, serum electrolytes, and serum ethanol levels on admission. Glucose and electrolyte derangements require slow correction as rapid correction of hyponatremia may induce central pontine myelinolysis.[109] Alcohol inhibits uterine contraction; thus, labor does not progress in acutely intoxicated parturients. Pregnant women with coagulopathy or myocardiopathy should receive appropriate medical treatment.

Anesthetic Management for Labor

Narcotic metabolism is prolonged in alcoholics, and administration exacerbates hypoxia induced from pulmonary shunting. Naloxone partially reverses ethanol intoxication and sobers uncooperative parturients.[10] Epidural or spinal analgesia provides superior pain relief, avoids cross-tolerance with narcotics, and is preferred. Impaired local anesthetic metabolism is not clinically significant in laboring women. Parturients may have decreased cutaneous sensation from neuropathy.

Cesarean Section

Because regional anesthesia produces better initial neonatal neurobehavioral scores, and alcoholic pathology alters so many facets of general anesthesia, regional anesthesia is preferred in chronic alcoholics without coagulapathy. General anesthesia is indicated for depressed airway reflexes in intoxicated parturients. Neonatal depression from alcohol and general anesthesia is likely.

The pathophysiologic changes of chronic alcohol abuse affect responses to general anesthesia. Hypovolemia and depressed myocardial contractility are present even with ethanol levels less than 100 mg/dL. Pulmonary shunting increases the risk of hypoxia during induction. Although the requirement for thiopental is not changed, the induction dose may need to

be reduced.[111] Minimum alveolar concentration for inhalational anesthetics is increased, but uterine relaxant effects are unchanged. Ethanol increases enflurane defluorination.[112] Of the halogenated agents, isoflurane interferes least with alcohol metabolism. Decreased cholinesterase prolongs the effect of some muscle relaxants.

Barbiturates

Incidence

Barbiturate addiction among women of reproductive age is uncommon.

Pharmacology

Barbiturates block arousal from brainstem stimulation by stimulating gammaaminobutyric acid (GABA) receptors. Parturients usually take barbiturates to enhance the effect of other drugs or relieve withdrawal symptoms. Intoxication resembles alcohol intoxication, and as with ethanol, tolerance does not alter the lethal dose. Barbiturates can be detected in the urine for as long as 2 to 3 weeks after last use. Withdrawal is treated with oral phenobarbitol.[113]

Pregnancy

Maternal Effects

Barbiturates depress respiratory and cardiovascular function. Chronic intoxication impairs nutrient intake.

Uteroplacental, Fetal, and Neonatal Effects

No clear-cut evidence of barbiturate-induced fetal damage in humans exists. Barbiturates are behavioral teratogens in animals, and early gestational exposure produces neuromorphologic changes similar to FAS.[46] Phenobarbital induces fetal hepatic enzymes capable of decreasing neonatal bilirubin levels. Infants of epileptic mothers on phenobarbital are passively addicted.

Obstetric and Anesthetic Management

Prenatal needs include detoxification in a appropriate setting, proper nutrition, and correction of anemia. Pregnant women on phenobarbital for seizure disorders have no increased maternal risk. During the intrapartum period, small incremental doses of antihistamines or phenothiazines control combative behavior in mildly intoxicated parturients. Sensitivity to narcotics is increased, and tolerance to the cardiac depressant effects of the barbiturates does not occur. The depressant effects of inhalation agents are potentiated. Hypertension and pulmonary edema were associated with ketamine administration in a parturientt whose infant tested positive for barbiturate.[114]

Narcotics

Pharmacology

Mechanism of Action

Narcotic agonists bind to opioid receptors located in the brain and spinal cord. The rewarding effects of opiates are primarily mediated through actions at the mu receptors. Extended use leads to physical dependence and withdrawal. More tolerance develops with less-potent drugs, which require binding to many receptors to produce an effect.[115] Heroin is the commonly abused opiate; recently, abuse of oxycodone controlled-release tablets, which can be crushed and snorted or smoked, has emerged.

Treatment of Intoxication

Opiate antagonists reverse the effects of narcotic overdose. Naloxone, a pure antagonist, must be given as a continuous intravenous infusion because of its short half-life. Nalmefene, also administered intravenously, is equipotent with naloxone and lasts for 4 h.

Treatment of Withdrawal

Symptoms of narcotic withdrawal include anxiety, tremor, rhinorrhea, yawning, sweating, vomiting, tachycardia, and hypotension or hypertension. Common withdrawal treatments are detoxification with tapering doses of methadone (5–20 mg orally initially, 5–10 mg for recurrent symptoms), symptomatic treatment with oral clonidine and benzodiazepines, or a combination of naltrexone and clonidine.[82] Recently, rapid detoxification under anesthesia using nalmefene, clonidine, and octreotide has been reported.[116] Chronic abstinence symptoms occur after detoxification, are of long duration, and are probably related to gradual restoration of normal receptor function. During this time, parturients are overconcerned about discomfort, tolerate stress poorly, and are likely to relapse.

Relapse Prevention

A majority of patients relapse after detoxification alone, so maintenance therapy is commonly prescribed. The usual replacement drug is methadone or LAAM (L-alpha-acetylmethadol), which is longer acting. Alternative drugs are buprenorphine, which is considerably less successful, and naltrexone.[117]

Pregnancy

Maternal Effects

Narcotics decrease hypothalamic secretion of luteinizing hormone-releasing hormone (LHRH) and decrease plasma levels of luteinizing hormone (LH), adrenocorticotropic hormone

(ACTH), and testosterone. More severe effects of maternal narcotic abuse (see Box 27.2) are those associated with drug-seeking behavior and intravenous drug abuse. Infectious diseases such as tuberculosis, hepatitis, bacterial pneumonia, HIV, and STDs are increased. Syphilis is reported in 20% of pregnant narcotic addicts, and hepatitis in 5%.[118]

Uteroplacental Effects

Withdrawal from opioids is associated with elevated catecholamines, which increase uterine vascular resistance and decrease placental blood flow. Insufficient drug access and repeated episodes of withdrawal compromise placental function.

Fetal Effects

Accelerated differentiation of alveolar epithelium, induced by elevated levels of prolactin in fetal cord serum of addicted mothers, decreases the incidence of respiratory distress syndrome (RDS).[119] Intrauterine fetal demise is more common with heroin use but not with methadone maintainence.[13] Decreased gestation and neonatal size have been reported, but when adjustments are made for confounding factors such as prenatal care, maternal weight gain, and smoking, there is no difference in neonatal size related to drug use.[120]

Animal Studies

The results of animal studies of opioid administration vary. Controlled-release implants of sufentanil, alfentanil, and fentanyl, which mimic methadone maintainence, produce no deleterious effects in rats.[121] Repeated morphine and L-alpha-acetylmethadol (LAAM) administration, which mimics erratic levels associated with heroin use, decreases maternal weight gain, increases fetal mortality, matures female fetuses early, and interferes with postnatal physical growth and neurobehavioral development.[122,123] Intrauterine withdrawal from narcotics produced more detrimental effects in rats than continued exposure.[124]

Neonatal Abstinence

Neonatal abstinence is a hallmark of opiate addiction.[125] After birth, a dramatic increase in plasma beta-endorphin, beta-lipoprotein, and metenkephalin concentrations coincides with the onset of withdrawal symptoms,[126] which occur in 80% of methadone- or heroin-exposed infants. Methadone treatment is associated with less severe but longer-lasting symptoms, and withdrawal severity correlates with maternal dose.[127] Maternal self-administration of diazepam to enhance an inadequate methadone dose is associated with severe late withdrawal symptoms in neonates.[73] Neonatal abstinence decreases ventilatory response to carbon dioxide, causes tolerance to endogenous opiates, and increases the frequency of SIDS.[65] Symptoms and need for treatment are rated using the Brazelton Neonatal Behavioral Assessment Scale or withdrawal-specific scales such as the Finnegan scale.

Neonatal Outcome

Preschool children of mothers who are able to stay in methadone treatment programs are more likely to remain in their mother's custody.[118] Although reports of neurologic function in preschool children are not consistent and may be due to environmental factors, some reported deleterious effects of methadone include attention deficit[120] and poor fine and gross motor control.[120] Long-term impaired behavioral, organizational, and perceptual abilities are also described.[128]

Obstetric Management

Prenatal Care

The number of pregnant women who abuse opiates has decreased in the last decade to 0% to 2%.[9,10] Of these, 20% to 50% also abuse cocaine. Because many administer drugs via parenteral routes, narcotic abusers have more medical problems and are more likely to be HIV positive. Treatment by methadone maintenance and detoxification both have drawbacks.

Detoxification

Detoxification decreases fetal exposure and avoids neonatal withdrawal; however, almost all parturients undergoing detoxification return to drugs.[108,117] Additionally, detoxification during the first trimester risks inducing abortion.[13] If detoxification is performed, it is carried out by physicians experienced in perinatal addiction with fetal monitoring. A recent report of midtrimester detoxification using clonidine indicates 60% were successful.[129] Rapid detoxification is not recommended.[116]

Low-Dose Methadone Maintenance

Instead of detoxification, prescribing low doses of methadone and tapering the dose of methadone at the end of pregnancy (to reduce neonatal withdrawal) has been recommended. This plan is suboptimal because parturients on low-dose methadone supplement it with additional psychoactive drugs at least 80% to 93% of the time.[129] Furthermore, because of changes in the volume of distribution, serum methadone levels decrease at the end of pregnancy. Reducing methadone doses at the end of pregnancy further increases maternal need for supplemental drugs.[13]

Methadone Maintenance

Methadone maintenance, in combination with a comprehensive prenatal care program, reduces maternal and infant morbidity and mortality.[13] It prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal while allowing the mother to return to a more normal lifestyle. Parturients should be maintained on the lowest effective dose of methadone and may require dose increases in the third trimester.[13] Certain drugs, such as rifampin and phenytoin,

increase methadone metabolism, and their administration can precipitate withdrawal,[117] as can administration of opioid agonist/antagonists.[84] To avoid withdrawal symptoms, it is important to maintain methadone levels above 150 mg/mL.[118]

The long half-life of methadone presumably permits stable maternal plasma levels and avoids repeated withdrawal and drug-seeking behavior. Parturients on methadone are more likely than heroin users to seek prenatal care.[13] Liberal dosing is associated with improved maternal weight gain and fetal growth and less prematurity.[34] However, in a recent study, neonatal outcome in parturients treated with methadone was no better than that with cocaine abuse.[130]

Buprenorphine Maintenance

Buprenorphine, although associated with reduced compliance, produces fewer neonatal abstinence symptoms. More motivated parturients are considered candidates for buprenorphine maintenance.[131]

Human Immunodeficiency Virus

In New York City, 40% of pregnant women enrolled in a methadone clinic were HIV positive.[132] Antepartum retroviral therapy is aimed at preventing vertical transmission and at optimizing maternal treatment. The standard is zidovudine monotreatment, regardless of CD4 cell count, to prevent vertical transmission.[133] Parturients with low CD4 counts or high viral loads should receive combination therapy. A combination of zidovudine, lamivudine, and retinovir has been recommended.[133] Methadone can increase blood levels of zidovudine.[117]

Other Prenatal Care

Cardiopulmonary reserve may be decreased by valvular vegetations or pulmonary hypertension from filtering talc. Medical complications are managed as they would be in nonabusing parturients. Methadone increases the frequency of nonreactive nonstress tests, so doses and timing of testing may need to be correlated.[134]

Intrapartum Management

Pregnant women may confuse signs of early labor with withdrawal, self-medicate, and arrive in labor with high narcotic levels. In one study, 40% of parturients had taken heroin for labor pain before entering the hospital.[76] The usual dosage of methadone is administered. If a woman appears to be withdrawing, an additional dose may be given.[13]

As with the general drug-abusing population, the overall rate of medical and obstetric complications is higher (Table 27.7).[82] Parturients who are HIV positive need intrapartum AZT prophylaxis.[133] It is not necessary to deliver HIV-positive parturients by cesarean section to prevent vertical transmission.[135] Low Apgar scores are more prevalent in addicts who receive no analgesia during labor. Emergency cesarean section, prompted by fetal distress, is five times more frequent than in a control group.[118]

Anesthetic Management

Labor

Epidural analgesia avoids further respiratory compromise and fetal depression in intoxicated mothers and is the anesthetic of choice for parturients who abuse opiates. Mixed opioid agonists such as butorphenol given intrathecally or epidurally can cause withdrawal.[84]

Narcotic requirements are increased, and narcotics for analgesia, such as meperidine or alfentanil, may be given in addition to methadone. Protease inhibitors affect the cytochrome P_{450} system in the liver, and narcotics and benzodiazepines should be used with caution in their presence.[136] Benzodiazepines are not recommended with nelfinavir; meperidine is not recommended with ritonavir. Agonist-antagonist agents are avoided to prevent undetected intrapartum fetal withdrawal. Parturients abusing agonist-antagonist agents are tolerant to similar compounds.

Cesarean Section

Epidural or spinal anesthesia will affect the neonate less than general anesthesia and is the method of choice. Potent short-

TABLE 27.7. Medical and obstetric complications among narcotic abusers.

	Narcotic abusers (%) (n = 112)	Controls (%) (n = 224)	p
Premature delivery (gestation <37 weeks)	27.7	13.8	<0.005
Abruptio placentae	8.0	3.1	<0.02
Hypertensive disorders	16.1	7.1	<0.02
Preeclampsia	8.0	4.9	NS
Chronic hypertension	8.0	2.2	<0.02
Thrombophlebitis/cellulitis/abscess	14.3	0.5	<0.001
History of hepatitis	10.7	0.9	<0.001
One or more medical complications	42.0	27.7	<0.01
One or more obstetric complications	56.3	40.6	<0.01

NS, not significant.

Source: Modified from Silver H, Wapner R, Loriz-Vega M, et al. Addiction in pregnancy: high risk intrapartum management and outcome. J Perinatol 1987;7:178–181. Used by permission.

acting narcotics such as fentanyl can be used to supplement analgesia. Long-acting intrathecal or epidural narcotics increase the danger of apnea with unsupervised heroin administration, but PCA narcotics have the same risk. If general anesthesia is necessary, narcotized women require less barbiturate. Unexplained hypertension during general anesthesia can sometimes be relieved by narcotic administration, as this is a sign of withdrawal.

Benzodiazepines

Pharmacology

Substance abusers use benzodiazepines to enhance the effect of narcotics, relieve ethanol or narcotic withdrawal symptoms, or, unknowingly, as a "date rape" drug. Pharmacodynamic tolerance develops within 24 h, but hepatic enzyme induction (metabolic tolerance) is negligible. Naloxone partially reverses benzodiazepines.[110]

Maternal Effects

Benzodiazepines depress nocturnal gastric acid excretion. Withdrawal symptoms and seizures rarely occur because of the drug's long duration of action.

Neonatal Effects

Benzodiazepines cause neonatal hypotonia and depress thermoregulation. The half-life of the drug in infants is prolonged, so neonatal withdrawal occurs at 7 to 14 days of age, and subacute effects can last 3 to 4 months.[73] Transient neurobehavioral changes occur in human neonates exposed to benzodiazepines.

Marijuana

Pharmacology

Delta-9-tetrahydrocannabinol, the active marijuana ingredient, alters GABA functions affecting acetylcholine turnover in the CNS, producing sleepiness, ataxia, and decreased motor and cognitive ability. It may act indirectly to block dopamine reuptake in the reward or pleasure areas of the brain, such as the nucleus accumbens.[137] Marijuana use improves self-esteem and produces euphoria, relaxation, and temporal disintegration. Higher doses trigger paranoid feelings, delusions, and hallucinations. Hypothalamic-pituitary axis effects include interference with secretion of LH, follicle-stimulating hormone (FSH), and prolactin, as well as oligospermia.[138]

The serum half-life of marijuana is 7 days, and a single dose may take as long as a month to be excreted. It can be detected in the urine for 3 to 5 days in light users and for as long as a month in heavy users.[3] Tolerance develops to some behavioral effects, and the lethal dose increases with abuse. Cross-tolerance develops to ethanol, but not other hallucinogens. No recognized withdrawal syndrome occurs, but irritability, insomnia, restlessness, and nervousness can accompany discontinuation.

Pregnancy

Maternal Effects

Elevated carbon monoxide levels from smoking marijuana impair fetal oxygenation. Beta-adrenergic effects may decrease placental blood flow by causing postural hypotension. African-American mothers using marijuana are five times more likely to be physically abused.[29]

Fetal Effects

In rats, marijuana reduces maternal weight gain and decreases birth weight and neonatal weight gain.[139] In humans, where concomitant tobacco use may influence results, marijuana decreases gestational length.[140] Two prospective studies demonstrated decreased maternal weight gain and decreased birth weight.[6,140] Other studies have failed to confirm these findings when confounding factors were controlled.[141,142]

Neonatal Effects

In one report, prenatal exposure to marijuana was associated with increased circulating norepinephrine in newborns.[137] Maternal marijuana use is associated with neonatal tremors, startles, poor visual habituation, and retarded maturation of the visual components of the human nervous system.[143] The latency of the visual provoked response is prolonged in infants exposed to marijuana and nicotine.[144] Other studies, particularly one of "ganja" use in Jamaica, where other drug use was absent, have failed to confirm these observations.[141] At age ten, marijuana-exposed children demonstrated increased hyperactivity, impulsivity, and inattention symptoms[145] and lower scores on tests requiring impulse control and visual analysis or hypothesis testing.[146,147]

Obstetric and Anesthetic Management

Antenatal

The incidence of marijuana use among pregnant women is as high as 25% to 30%, and it may be, aside from tobacco, the most frequently abused drug among parturients.[88] In one study, 87% of the urine screens positive for illicit drugs contained marijuana.[90] Marijuana abusers are likely to also abuse tobacco (80%) and alcohol (76%).[6] Commonly users are young, Caucasian, and single, but those who continue its use during pregnancy tend to be older, African-American, less educated, and of lower socioeconomic class.[88] Prenatal care is as for other substance-abusing parturients.

Intrapartum Obstetric and Anesthetic Management

Because of the long serum half-life of marijuana, parturients in labor frequently have residual drug levels. Tachycardia up to 140 beats/min is not uncommon and can be treated with propranolol. If pregnant women require sedation, phenothiazines, which potentiate postural hypotension, and barbiturates, which increase hallucinations, should be avoided. With general anesthesia, the problems are bronchial irritability from smoking and reduced minimal alveolar concentration (MAC) for anesthetic agents.

Cocaine

Pharmacology

Mechanism of Action

Cocaine, or benzoylmethylecgonine, blocks the presynaptic uptake of norepinephrine, thereby activating adrenergic nerve synapses, causing severe hypertension, tachycardia, and vasoconstriction.[148] It blocks presynaptic dopamine reuptake, thereby activating pathways in the mesolimbus or mesocortex responsible for its euphoric and reinforcing qualities. Chronic use leads to depletion of presynaptic norepinephrine and dopamine stores and reduced neurotransmitter release in the CNS. Dopamine depletion is thought to be responsible for tolerance to rewarding effects and the dysphoria associated with its withdrawal.[53]

Cocaine also blocks the uptake of tryptophan and serotonin. Derangements in serotonin may enhance the effects of dopamine or account for the changes in sleep–wake cycles seen in cocaine abusers.[53] In high concentrations, cocaine blocks the sodium channel, preventing the conduction of action potentials and producing negative inotropic and chronotropic effects on the heart muscle and local anesthetic effects.[149] Repeated cocaine administration causes adaptive, tolerance-producing changes such as alpha$_2$-adrenergic and presynaptic cholinergic-mediated, decreased norepinephrine release at the motor endplate.[150] Cocaine lowers the seizure threshold and produces "kindling" (enhancement of seizures).[148]

Preparations

When dissolved in hydrochloric acid, cocaine yields the hydrochloride, a white powder, which can be inhaled or dissolved in water and injected. When the powder is "snorted," vasoconstriction of the mucous membranes limits its absorption rate, and the peak concentration is only 20% to 40% of that achieved with injection. Ether extraction separates cocaine from adulterants and yields "freebase." When the hydrochloride is dissolved in water and baking soda and heated, cocaine precipitates into a lump, which hardens; it makes a popping noise when heated and is known as "crack." Both freebase and crack volatilize without degradation and can be smoked in a pipe or mixed with tobacco or marijuana and smoked in a cigarette.[148] Freebase and crack are highly lipid soluble and contain methylecognine, a pyrolysis product, which is also active.[151] Smoking yields serum cocaine concentrations only 60% of those achieved with intravenous injection, but the brain concentration is higher because absorption across the pulmonary membranes delivers undiluted cocaine directly to the brain.

Metabolism

Cocaine is metabolized primarily by plasma cholinesterase and liver cholinesterase and by nonenzymatic hydrolysis, mainly to benzoylecgonine, an active metabolite, and ecgonine methyl ester, which is inactive. In addition, 20% of cocaine is metabolized in the liver by N-demethylation to norcocaine, which is more active than cocaine in inhibiting norepinephrine uptake.[20] Norcocaine may be responsible for prolonged cardiovascular effects in humans.[152] Concomitant use of cocaine and alcohol can lead, in rats, to the ethyl transesterification of cocaine to cocaethylene, which, like norcocaine, is more potent than cocaine.[153] Cocaine's half-life in the blood depends upon total dose and method of administration and is variously reported to be from 12 to 90 min.[154]

Bingeing

Because of its rapid metabolism, the effects of crack last only a few minutes. To sustain the "high," users engage in a practice known as bingeing. Repetitive doses are administered, usually along with shared tobacco, marijuana, and alcohol. The bingeing stops when neurotransmitters become depleted and additional drug ceases to be rewarding. During a binge, mood is intensely elevated, appetite is decreased, energy and alertness are increased, sexual feelings are accentuated, and social inhibitions are decreased. Bingeing results in exclusion of all thoughts unrelated to the next dose.[28]

Withdrawal

Withdrawal is not seen in casual users, and a dangerous physiologic withdrawal syndrome does not occur. In habitual users, however, autonomic depression and craving occur.[148] No effective substitution treatment has been found. Dopamine agonists such as bromcoriptine, amantadine, mazindol, and methylphenidate have not been consistently better than placebo.[117]

Based on blocking reuptake of norepinephrine and serotonin, antidepressants such as desipramine, imipramine, bupropion, and fluoxetine have been studied but are only of use in treating patients with concomitant depression.[117] Carbamazepine, given on the basis that it might prevent craving if caused by kindling, is not effective.[108] Buprenorphine has not been more efficacious than methadone in decreasing cocaine use among patients abusing both opioids and cocaine.[108]

Box 27.5. Complications of cocaine use.

Cardiac
- Chest pain
- Myocardial infarction
- Arrhythmias
- Cardiomyopathy
- Myocarditis

Pulmonary
- Pneumothorax
- Pneumomediastinum
- Pneumopericardium
- Pulmonary edema
- Exacerbation of asthma
- Pulmonary hemorrhage
- Bronchiolitis obliterans
- "Crack lung"

Psychiatric
- Anxiety
- Depression
- Paranoia
- Psychosis
- Delirium
- Suicide

Gastrointestinal
- Intestinal ischemia
- Gastroduodenal perforations
- Colitis

Renal
- Rhabdomyolysis

Head and neck
- Erosion of dental enamel
- Gingival ulceration
- Keratitis
- Corneal epithelial deficits
- Chronic rhinitis
- Perforated nasal septum
- Aspiration of nasal septum
- Midline granuloma
- Altered olfaction
- Optic neuropathy
- Osteolitic sinusitis

Neurologic
- Headaches
- Seizures
- Cerebral hemorrhage
- Cerebral infarctions
- Cerebral atrophy
- Cerebral vasculitis

Endocrine
- Hyperprolactinemia

Other
- Sudden death
- Sexual dysfunction
- Hyperpyrexia
- Thrombocytopenia

Source: Modified from Warner EA. Cocaine abuse. Ann Intern Med 1993;226:235. Used by permission from the American College of Physicians.

Pathophysiology

Complications associated with cocaine use are listed in Box 27.5. Their spectrum and frequency has shifted in the past decade because the predominant preparation has changed from the hydrochloride to crack.[148] Nasal administration causes septal necrosis and perforation. Transmission of blood-borne pathogens is associated with intravenous injection.

Smoking Effects

Smoking involves prolonged inspiration with Valsalva's maneuver and mouth-to-mouth positive pressure administration of smoke to augment the intensity of cocaine's effects.[148] Smoking can cause thermal injury, cough with carbonaceous sputum, chest pain, hemoptysis, pulmonary edema, pneumothorax, pneumomediastinum, and pneumopericardium. Smoking results in bronchospasm, with wheezing and dyspnea in 50% of users.[155] Pulmonary artery medial hypertrophy, bronchiolitis obliterans, organizing pneumonia,[155] and a constellation of symptoms known as "crack lung" (that consists of chest pain, fever, hemoptysis, eosinophilia, and diffuses alveolar infiltrates) are associated with crack inhalation.[156]

Sympathomimetic Effects

Blood pressure, heart rate, peripheral vascular resistance, and myocardial oxygen consumption increase, sometimes causing myocardial infarction even with normal coronary arteries. Coronary artery spasm causes focal endothelial injury and platelet aggregation, resulting in acute vascular platelet thrombosis and chronic intimal proliferation, thus accelerated atherosclerosis. Cocaine causes myocarditis, pulmonary edema, or arrhythmias in some individuals and, like pheochromocytoma, has been associated with contraction band necrosis. Other vasoconstrictive sequelae include cerebral hemorrhage and infarction, aortic rupture, bowel infarction, and pseudomembranous colitis.[148]

Other Medical Effects

Neurologic complications include seizures and vascular headaches, which occur in two-thirds of cocaine hotline callers.[148] Cocaine may also cause hemolytic uremic syndrome,[157] hyperpyrexia, platelet aggregation,[158] and thrombocytopenia.[159]

Pregnancy

Incidence

In certain high-risk populations, such as Northeast inner-city hospitals, cocaine use during pregnancy may approach 50%. Parturients using cocaine are older,[88] less educated,[8] single,[88] African-American,[8] and urban poor.[90] They also smoke,[61] use other drugs,[90] and fail to obtain prenatal care[12] (Table 27.8). In one study, 83% used tobacco, 43% used alcohol, and 31% used marijuana.[61] Parturients abusing cocaine usually do not stop as the pregnancy progresses.[90] A history of no prenatal care and drug and tobacco use predicts a positive urine screen

TABLE 27.8. Effects of cocaine bingeing on pregnancy.

Binge pattern	Erratic use	Daily use	Every 3 to more than 7 days
Maternal weight less than 100 lb (%)	10	33	15
No prenatal care (%)	68	63	43
Positive urine at delivery (%)	45	50	20
Vaginal bleeding (%)	22	9	5
Placental abruption (%)	14	3	1.2
Stillbirth (%)	20	16	5
Small for gestational age (SGA) (%)	13	33	17
Birth weight (g)	2295	2579	3129
Gestational age (weeks)	32.4	34.5	37.2

Source: Modified from Burkett G, Yasin SY, Palow D, et al. Patterns of cocaine bingeing: effect on pregnancy. Obstet Gynecol 1994;171:372. Used with permission from the American College of Obstetricians and Gynecologists.

for cocaine 70% of the time, and the absence of these factors predicts no cocaine use 70% of the time.

Maternal Effects

The problems associated with cocaine use during pregnancy cannot be attributed to cocaine alone, because multiple drugs are being abused, tobacco use is increased, and maternal lifestyle changes. Cocaine users may have serious medical complications during pregnancy. Myocardial infarction,[160] arrhythmias,[161] pneumothorax,[162] renal failure from rhabdomyolysis,[163] hepatic rupture,[23] sudden death, and cerebrovascular accidents are reported.[164] Anorexia from bingeing decreases maternal weight gain and sometimes causes malnutrition (see Table 27.8). Postpartum cardiomyopathy,[165] ruptured uterus,[166] and ruptured ectopic pregnancy are associated with cocaine use.[167]

Thrombocytopenia

Maternal thrombocytopenia with a platelet count as low as 34,000 has been reported.[168] Thrombocytopenia is thought to result from platelet aggregation caused by increased platelet factor 4 and (beta)-thromboglobulin.[158]

HIV Infection

Sexual practices associated with cocaine abuse increase exposure to HIV. Neopterin, a marker of cell-mediated immunity that is associated with higher transmission rates of HIV, is elevated in cocaine users.[169] Cocaine-induced susceptibility to viral infection may account for increased HIV infection observed in sexually active cocaine abusers.

Animal Studies

In pregnant sheep, cocaine increases heart rate, systemic vascular resistance, and myocardial oxygen consumption while decreasing cardiac output and stroke volume and causes an increase in blood pressure twice that observed in nonpregnant ewes.[170] In ewes, platelets can decrease to 30,000 with a cocaine infusion.[171] One of the causes of increased sensitivity during pregnancy may be increased N-demethylation to norcocaine, a more active substance.[22] Another cause is thought to be secondary to progesterone-induced changes other than altered alpha-adrenergic receptor sensitivity.[151]

Uteroplacental Effects

Cocaine has two effects on the uterus: increased uterine contractility and vasoconstriction.[172,173] These effects, along with decreased placental human chorionic gonadotrophin production, probably cause the observed increase in spontaneous abortion.[151,174] Cocaine abuse reduces gestational age.[175] In 25% of cocaine users with preterm labor, umbilical artery Doppler velocimetry measured systolic–diastolic ratios are abnormally high, indicating the presence of vasoconstriction.[176]

Cocaine-induced vasoconstriction may cause abruptio placentae.[36,174] Table 27.8 shows the risk for abruption in cocaine abusers. Cocaine increases uterine contractility[172,173] and may lead to preterm premature rupture of membranes[174,177] with parturients presenting with more cervical dilation on admission[177,178] and a shorter latency period to delivery.[177,179]

Animal Studies

Cocaine administration to pregnant rats decreases blood flow to the placenta by increasing uterine vascular resistance.[152] Cocaine also reduces uterine blood flow in pregnant sheep.[170,180] Cocaine-induced vasoconstriction of the uterine blood vessels in sheep is not prevented by prior infusion of phentolamine, indicating a direct or dopamine-mediated effect by cocaine.[180] Uterine contractility is not always increased by cocaine in sheep[181] but is increased in rats[152] and rabbits.[182]

Placental transfer of cocaine has been extensively studied in sheep and rats. The species differ importantly: in sheep the major metabolite is ecgonine methyl ester; in rats, as in humans, it is benzoylecgonine.[152] Cocaine crosses the placenta by simple diffusion, and fetal organs have up to one third of maternal brain concentrations. The placenta metabolizes cocaine to norcocaine.[183] Placental microsomes also have the capacity to bind and hydrolyze cocaine.[22] The transfer of cocaethylene is inhibited by placental uptake on both the maternal and fetal sides and by uptake by the amnion, which acts as a reservoir for both cocaethylene and benzoylecogonine.[153] Placental and amniotic reservoirs prolong the duration of fetal exposure.[153] Higher fetal concentrations of benzoylecogonine indicate that fetal metabolism occurs.[22]

Fetal Effects

If cocaine impairs placental blood flow for a significant period, decreased transfer of oxygen and nutrients may harm the fetus. Fetal hypoxia has been demonstrated in ewes.[170,180] Human case reports describe fetal death[184] and necrotizing enterocolitis in utero.[185] Among bingers with a very chaotic lifestyle, stillbirth occurred in 20% of parturients[28] (see Table 27.8). In bingers with a more stable environment, one third of the infants were small for gestational age.[28] Some studies, such as those cited in Table 27.9, demonstrate decreased infant size with more moderate cocaine use.[52]

Birth weight, length, and head circumference are inversely related to meconium benzoylecgonine concentration.[186] In a controlled study of low and high cocaine exposure, as determined by maternal hair assay, increasing exposure to cocaine was associated with growth retardation with a disproportionate reduction in head circumference.[187] Adequacy of prenatal care does not affect the reduction of growth in offspring exposed to cocaine.[175]

Congenital Anomalies

Cocaine has the potential to produce fetal anomalies through infarction, malnutrition, and changes in neurotransmitters. Because it lacks a skin barrier, the midterm fetus has prolonged periods of direct contact with high concentrations of cocaine in the amniotic fluid.[188] In animals, cocaine disturbs neuronal differentiation in the cerebral, diencephalic, and brainstem structures, with subsequent defects in memory and learning.[53] A derangement of neurotransmitters, specifically monoamines,[189] in the fetus exposed to cocaine may impair the development of normal neuronal pathways in the angular cingulate cortex, which is involved in attention.[151]

Destructive ischemic abnormalities of the fetal brain may occur later in gestation, after blood vessels develop the capacity to contract on exposure to cocaine and reperfusion releases free radicals.[39] Although genitourinary tract anomalies,[42] cranial anomalies,[190] ileal atresia,[43] microcephaly,[6,35] cardiac abnormalities,[40] limb reduction abnormalities,[41] and neural tube malformations[40] are reported in offspring of mothers abusing cocaine, controlled studies fail to demonstrate an increase in congenital anomalies, perhaps with the exception of genitourinary anomalies.[191]

Neonatal Effects

Classification of neonates as exposed or nonexposed is difficult. Of neonates exposed by maternal report, 38% have positive urine screen, 52% have positive meconium screen, and 78% have positive hair analysis (hair analysis misses recent exposure).[5]

Nursery Problems

Neonates have withdrawal symptoms, but these are less severe than opiate withdrawal symptoms. Transient neonatal ventricular tachycardia[192] and transient ST-segment elevation are reported in infants exposed to cocaine.[193] Plasma norepinephrine levels are elevated between 24 and 72 h postpartum,[137] and cardiac output is decreased.[194] Increased norepinephrine may be caused by depleted dopamine, resulting in down regulation of descending inhibitory pathways regulating sympathetic outflow. Although fetal stress from cocaine-related changes in placental perfusion induces respiratory maturity,[195] periodic breathing and apnea of infancy, are reported in cocaine-exposed infants.[196] SIDS is two to three times more likely in cocaine-exposed infants.[53] The cost of neonatal care for predominantly cocaine-exposed infants is higher, partly because discharge is delayed while social issues are resolved.[62]

Neurologic Function

Anterior and middle cerebral artery Doppler interrogation at birth demonstrates changes in flow velocity consistent with the vasoconstrictive effects of cocaine.[197] Infants with infarction of the middle cerebral artery at birth, presumably from cocaine-induced vasospasm, are reported.[198] Early reports conflict regarding neurosonographic abnormalities associated with cocaine use,[198,199] but matched control studies report a dose-related increase in subependymal hemorrhage in the caudothalamic groove.[200]

Neonatal Hypertonia

The odds ratio for the presence of global hypertonia, coarse tremor, and extensor leg posturing in newborns increases with increasing cocaine exposure, as determined by hair analysis.[201] When tobacco exposure is measured with urine coti-

TABLE 27.9. Perinatal outcome of fetal cocaine exposure.

	Cases (n = 55)	Controls (n = 55)	p
Gestational age (weeks)	37.36 ± 3.0	37.18 ± 1.9	<0.02[a]
Birth weight (g)	2528 ± 619	3506 ± 500	<0.05[b]
Birth weight (mean percentile for gestational age)	31.9 ± 21.4	48.2 ± 22.8	<0.05[a]
Head circumference (cm)	31.8 ± 2.6	33.7 ± 1.7	0.09[b]
Head circumference (percentile for gestational age)	33.6 ± 27.0	51.7 ± 23.5	<0.05[a]

Study infants were identified at birth and matched with controls. Values shown are mean ± SD.

[a]After adjustment for sex of child, length of gestation, and maternal smoking.

[b]After adjustment for sex of child and maternal smoking.

Source: Modified from Cherukuri R, Minkoff H, Feldman J, et al. Obstet Gynecol 1988;72:147–151. Reprinted with permission from the American College of Obstetricians and Gynecologists.

nine levels rather than maternal reporting, and cocaine exposure is measured by meconium levels, cocaine is not a significant predictor of hypertonia.[202]

Neurobehavioral Testing

Bayley cognitive and psychomotor scores[203] and a recent meta-analysis[204] fail to demonstrate consistent developmental defects associated with cocaine that are different in scope from that of other abused substances. However, cocaine exposure appears to have a lasting neurobehavioral effect on arousal and attention regulation.[189] Impaired processing of auditory information is observed in newborns exposed to cocaine.[205] At 43 weeks postconception, heavily cocaine-exposed infants have more jitteriness, correlating with meta-hydroxybenzolyecgonine levels, and attentional problems, correlating with cocaethylene levels.[206] At age 2 years, cocaine use independently predicts poorer hand use and eye–hand coordination with the Peabody Developmental Motor Scales.[102] By 6 years of age, significant teacher-identified behavior problems are present.[207]

Obstetric Management

The effects of cocaine on pregnancy are summarized in Box 27.6. Cocaine abusers may have no prenatal care: in Brooklyn, 43% of unregistered patients tested positive for cocaine. Parturients need to be identified in the community and encouraged to attend a clinic. Maternal health education should stress nutrition, STDs, urinary tract infections, hemorrhage, and premature labor. Parturients experiencing chest pain need cardiology consultation. Cocaine use may elevate blood sugar and interfere with glucose tolerance testing. Urine screening for abusive substances is useful. Patients abusing both cocaine and heroin sometimes receive buprenorphine.[117] With the PACE program in New York City, long-term treatment at "one-stop shopping" clinics resulted in less fetal exposure to cocaine, with less fetal growth retardation and low birth weight.[208] By age 18 months, one third of infants exposed to cocaine are placed outside the home; prearranging postnatal care results in a better infant outcome.[209]

Intrapartum Management

Cocaine abuse should be suspected whenever a pregnant woman presents without prenatal care.[12] Parturients often arrive with emergency situations, such as preterm labor, intrauterine fetal demise, severe pregnancy-induced hypertension, precipitate labor, uterine rupture, placental abruption, or perhaps placenta previa. A handheld rapid latex agglutination urine assay facilitates determining cocaine use in the last 72 h.[210] Cocaine abusers can present with signs of preeclampsia such as hypertension, blurred vision, headache, abdominal pain, or seizures. The symptoms resolve within 45 to 90 min.[77] Parturients are treated with magnesium sulfate until the diagnosis is clear.

Hemodynamic changes induced by pregnancy, preeclampsia, and recent cocaine use may cause myocardial infarction, which is difficult to diagnose during pregnancy because of EKG and creatinine kinase-7 (CK-MB) changes induced by both pregnancy and cocaine.[211] Increased troponin I has a high specificity for myocardial infarct (MI) even in the presence of recent cocaine use and is not increased in peripartum women. In a parturient experiencing chest pain, the combination of troponin I level and echocardiography are the best predictors of adverse cardiac events.[211]

Cocaine Intoxication

Signs and symptoms of cocaine toxicity are listed in Table 27.10. Psychosis responds to benzodiazepines, neuroleptics, or lithium. Severe intoxication is associated with end-organ ischemia, which may decrease pH and require treatment with sodium bicarbonate. Drug treatment of choice for hypertension and tachycardia is controversial. Hydralazine treatment exacerbates tachycardia.[212] Labetalol, instead of pure beta-adrenergic antagonists, is usually recommended, because unopposed alpha-adrenergic activity increases blood pressure and exacerbates decreased myocardial and uterine blood flow.[213] However, labetalol use is criticized because its beta antagonism is more potent than its alpha antagonism.[214] Calcium channel blockers are associated with paradoxical responses,[215] and although they are cardioprotective in rats,[216] the use of nifedipine to treat both preeclampsia and cocaine toxicity was associated with a perioperative MI.[211] Nitroglycerine is indicated when chest pain is present. Although

Box 27.6. Cocaine effects on pregnancy.

Spontaneous abortion
Intrauterine growth retardation
Placental abruption
Premature rupture of membranes
Preterm delivery
Low birth weight
Transient neurobehavioral abnormalities
Congenital anomalies (still theoretical)
Impaired neuronal differentiation (still theoretical)

TABLE 27.10. Signs of cocaine toxicity.

Central nervous system	Psychologic	Cardiovascular	Miscellaneous
Delirium	Irritability	Arrhythmia	Fever
Convulsions	Restlessness	Pallor	Diaphoresis
Hyperreflexia	Tenseness	Tachycardia	Dry mouth
Tremor	Anxiety	Hypertension	Dilated pupils
Dizziness	Garrulousness	Angina	
Hallucinations	Euphoria	Headache	
Coma	Insomnia	Flushing	
Cerebral hemorrhage	Panic	Circulatory collapse	
	Suicidal		
	Homicidal		

Source: Modified from Kenepp N. Substance abuse. In: James FM, Wheeler AS, Dewan DM (eds) Obstetric Anesthesia: The Complicated Patient, 2nd edn. Philadelphia: Davis, 1987: 523. Used by permission.

lidocaine might be cumulatively toxic with cocaine, it is used successfully to treat myocardial arrhythmias.[217]

Placental Abruption

Pregnant women can present with abruptio placentae, tetanic contraction, and fetal bradycardia.[176] In the absence of abruption, esmolol, nitroglycerine, and tocolysis can resolve tetanic contraction and fetal bradycardia. With abruption, tocolysis with magnesium sulfate may sustain the fetus until delivery by cesarean section can be accomplished. Cocaine increases the likelihood of tachyarrhythmias with ritodrine and terbutaline.

Animal Studies

Pretreatment of ewes with 5 mg/kg magnesium attenuates seizures and corrects maternal and fetal heart rate changes.[171] Magnesium may prevent thrombocytopenia associated with cocaine administration.

Anesthetic Management

Labor Analgesia

Epidural or spinal analgesia is indicated if platelets are adequate.[149] Ephedrine, theoretically less effective when norepinephrine stores are depleted, is safer than risking an exaggerated response with a direct-acting agent.[218] Occasionally, however, phenylephrine may be needed instead of ephedrine. Cocaine users are more sensitive to pain but have normal epidural anesthetic requirements.[219]

Anesthesia for Cesarean Section

Regional techniques are preferred. Hypotension resulting from epidural or spinal analgesia can be life threatening but was not increased with spinal anesthesia in one study[220]; it can usually be treated with ephedrine or phenylephrine. Although cocaine metabolism is rapid, residual cocaine may decrease the amount of free plasma cholinesterase, affecting metabolism of 2-chloroprocaine. As local anesthetics and cocaine are epileptogenic, total local anesthetic dose should be conservative.

General Anesthesia

Cesarean section in cocaine-abusing parturients is often performed for fetal distress or placental abruption under emergency conditions. In one study, two thirds of pregnant women received general anesthesia.[220]

Induction Agents

Severe hypertension and arrhythmias are more common under general anesthesia, especially during induction; hypertension should be controlled before induction.[221] Cocaine causes bronchospasm and increases general anesthetic requirements.[222] Thiopental is commonly used for induction. Extreme caution is advised with ketamine, which is associated with excessive catecholamines and may cause MI or pulmonary edema.[130,210,218] Etomidate does not prevent a hypertensive response to intubation. Alfentanil is recommended to blunt the hypertensive response to intubation.[157]

Muscle Relaxants

Decreased serum and cholinesterase may prolong the duration of succinylcholine, mivacurium, all metabolized by cholinesterase. Succinylcholine is nevertheless recommended because of its short duration. In vitro hydrolysis of cocaine is prolonged in parturients who have pseudocholinesterase deficiency, and lower plasma cholinesterase levels are associated with more severe toxicity to cocaine (Figure 27.1).[223] Lower cholinesterase levels may be the primary cause of the observed sensitivity to cocaine or the result of cholinesterase depletion by previously administered cocaine.

Maintenance

Agents such as halothane that sensitize the myocardium to epinephrine are avoided. Isoflurane has been used successfully,[157] but it also may induce arrhythmias and has been reported to increase systemic vascular resistance in swine.[221] Chronic neurotransmitter depletion from cocaine is postulated to decrease anesthetic requirements, but MAC for isoflurane is increased significantly in sheep exposed to a cocaine infusion for 2 weeks.[222] Hyperpyrexia and sympathomimetic activity can mimic malignant hyperthermia.[224] Atropine blocks presynaptic cholinergic regulation of norepinephrine release, thereby increasing hypertension, and increases the risk of central cholinergic syndrome.[150]

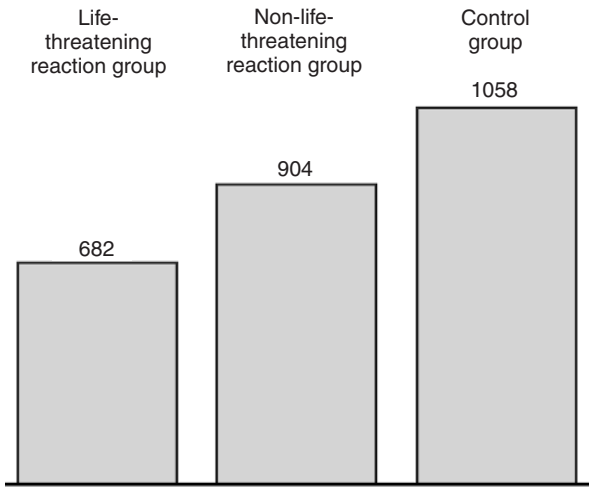

FIGURE 27.1. Plasma cholinesterase activity in Michel units/L in three groups of patients: those with life-threatening reactions to self-administered cocaine, those with minor problems following cocaine, and controls. $p = 0.05$. (Adapted from Hoffman RS, Henry GC, Howland MA, et al. Association between life-threatening cocaine toxicity and plasma cholinesterase activity. Ann Emerg Med 1992;21:247, with permission.)

Amphetamines

Pharmacology

Amphetamine causes release of norepinephrine and serotonin from presynaptic terminals, decreases neurotransmitter reuptake, and increases norepinephrine, serotonin, and perhaps dopamine availability in the brain. Although their specific actions are different, methamphetamine is generally indistinguishable from cocaine in both its pharmacologic and addictive characteristics.[225] Amphetamine is metabolized in the liver, but at least 50% of a dose is excreted unchanged in the urine. Ammonium chloride acidification hastens its excretion.[226] The plasma half-life of amphetamine is 12 h, 10 times longer than cocaine.[225] Because of its longer duration of action, psychotic symptoms develop more slowly than with cocaine. A smoked form, "ice," which produces an instant high of long duration, is more prevalent in Hawaii and California.[226]

Pregnancy

Amphetamine use is most common on the West Coast.[7] The maternal and fetal problems associated with cocaine abuse, are also reported with amphetamines.[35]

Animal Studies

In pregnant sheep, amphetamine increases maternal heart rate, blood pressure, and uterine vascular resistance and decreases uterine and umbilical blood flow. After an initial decrease, fetal heart rate and umbilical blood flow increase to levels above baseline for 2 to 3 h. The fetal pH and Po_2 decrease gradually.[227] Amphetamine decreases uterine blood flow and umbilical blood flow in pregnant sheep.[228]

Maternal and Fetal Effects

Acute intoxication can be mistaken for eclampsia or preeclampsia.[229] There are no large studies of amphetamine use alone, but it is associated with placental abruption, intrauterine growth retardation, decreased gestational length, and increased perinatal mortality.[230] Infants of mothers who use amphetamine are small for gestational age and premature, with a high neonatal mortality rate.[231] Cleft lip and cardiac defects are associated with amphetamine use.[225] In a study of 13 cocaine and 28 methamphetamine abusers, no differences in pregnancy and neonatal outcome were noted.[35] At 8 and 14 years of age, amphetamine-exposed children lagged in mathematics, language, and physical training.[232]

Obstetric and Anesthetic Management

Obstetric and anesthetic care is as for cocaine abusers. Methamphetamine abusers respond poorly to indirect-acting sympathomimetic agents. Absorption of oral amphetamine continues during labor, and with its longer duration, fetal distress is less likely to improve than with cocaine abusers. Inhalational anesthetic requirements are increased,[233] and in a case report of methamphetamine abuse, fentanyl and nitrous oxide requirements were increased.[234] Cardiac arrest under general anesthesia for cesarean section has been reported.[235]

Phencyclidine

Pharmacology

Phencyclidine (PCP), an arylcyclohexylamine, is a potent psychomimetic agent capable of producing a state indistinguishable from schizophrenia. Its sympathomimetic pharmacologic effects are similar to those of cocaine.[154] Its mechanism of action may involve binding to a low-affinity sigma-opiate receptor site, blockade of *N*-methyl-D-aspartate (NMDA) and glutamate channels, inhibition of dopamine and norepinephrine uptake, and interference with 5-hydroxyindole metabolism. Users usually smoke it with tobacco or marijuana. Low doses produce agitation, depersonalization, altered sensory perception, sweating, tachycardia, and hypertension.[154] Intoxication produces slurred speech, anesthesia, hypersalivation, catatonia, fever, ataxia, clonus, tremors, rhabdomyolysis, and seizures. PCP induces acute reversible pathomorphic changes in rat brain neuron[236] and is associated with perfusion defects on brain scans in humans.[237]

Pregnancy

Phencyclidine use is less common, occurring in 1% of positive urine screens[7] or 0.3% of the pregnant population.[14] The placenta has the ability to metabolize PCP by monohydroxylation.[154]

Fetal serum levels may exceed maternal levels by as much as 10 fold.[154] PCP is detectable in breast milk, amniotic fluid, and neonatal urine in the first few days of life. One study reported a 32% incidence of growth retardation and a 43% incidence of precipitous labor, figures higher than those for cocaine abusers.[238] Another study found that PCP is not associated with decreased birth weight but is possibly associated with a reduction in gestational age.[239] Neonatal symptoms include jitteriness, hypotonicity, vomiting, and diarrhea, which are unrelieved by phenobarbital. In a clinical report, microcephaly occurred in one of two exposed infants.[55]

Obstetric and Anesthetic Management

Intrapartum Management

Parturients are managed as other drug abusers. PCP potentiates narcotics and intoxication may be treated with chlorpromazine or haloperidol. Because fever increases fetal and maternal oxygen consumption, it is recommended to control hyperthermia with acetaminophen. It is probably prudent to avoid pure beta-blocking agents when treating hypertension and tachycardia. Dantrolene has been recommended for treatment of rhabdomyolysis, along with urine alkalinization and mannitol.[154]

Anesthetic Management

Acute intoxication with PCP potentiates sympathomimetics, and dosage of sympathomimetic drugs such as ephedrine should be accordingly reduced. Because of its hyperthermic effect, patients may require a cooling blanket during general anesthesia. Ketamine, because of its similarity to PCP, is probably contraindicated. Because PCP inhibits cholinesterase, neuromuscular blocking agents metabolized by cholinesterase should be used with caution.

Methylenedioxymethamphetamine

Pharmacology

Methylenedioxymethamphetamine (MDMA) (ecstasy) is an easily synthesized designer amphetamine used at raves and on college campuses. Supplied in pill form, it is frequently cut with ephedrine, amphetamine, lysergic acid diethylamide (LSD), or ketamine. Onset of action begins in 30 min; peak effects at 90 min and last up to 8 h.[240] It is metabolized by N-demethylation to methylenediozyamphetamine, which is active and is another drug of abuse. Approximately 65% of MDMA is excreted in the urine.[241]

MDMA releases serotonin, dopamine, and norepinephrine from presynaptic neurons and inhibits their reuptake. It also inhibits monoamine oxidase and can increase dopamine synthesis. It increases extracellular dopamine in the nucleus accumbens. MDMA possesses some properties of amphetamines as a central stimulant, as well as psychedelic properties likely mediated by dopamine and serotonin.[241] The desired effects of MDMA are enhanced empathy and a feeling of togetherness, mood alteration with sensual and emotional overtones, euphoria, increased energy and self-esteem, and altered visual perceptions.

Adverse Effects

Adverse effects include those seen with psychedelics, sympathomimetics, and monoamine oxidase (MAO) inhibitors. Mild intoxication causes hyperthermia, diaphoresis, locomotor hyperactivity, dysphoria, and confusion. Long-term damage to both dopamine and serotonin neurons in the brain has been demonstrated in animals. Positron emission tomography in humans shows reduction in the number of serotonin transporters.[242] The reduction in transporters correlates with impairment of visual and verbal memory.

Intoxication

Patients requiring treatment present with hyperthermia, dehydration, elevated creatine phosphokinase (CPK), hypertension, and tachycardia. Rhabdomyolysis, or a picture similar to serotonin syndrome, or neuroleptic malignant syndrome may be present. Serious cardiovascular complications such as arrhythmia, atrioventricular (AV) block, cardiogenic shock, cardiac arrest, and pulmonary edema can occur. CNS complications include hyperreflexia, ataxia, dizziness, and seizure; intracranial hemorrhage, cerebral infarction, coma, and status epilepticus may also occur. Adverse psychologic effects range from paranoia, obsessive behavior, depression, and panic attack to frank psychosis.

Treatment of Intoxication

Treatment is directed toward restoring airway, breathing, and circulation, then correcting hyperthermia, hypertension, dehydration, and electrolyte abnormalities and preventing renal damage from rhabdomyolysis. Often tachycardia and hypertension abate with benzodiazepine sedation. As with cocaine, pure beta-adrenergic blocking agents should not be used to control blood pressure. Rapid cooling and paralysis to control shivering are indicated.[241]

Pregnancy

Maternal Effects

Mothers who use ecstasy frequently use other substances potentially harmful to the pregnancy and child. As with cocaine, because of changes in sensitivity to adrenergic agents and increased N-demethylation to MDA, the effects of MDMA are likely to be increased during pregnancy.

Fetal Effects

Because hyperthermia is a prominent effect of MDMA, fetal hypoxia may occur, both from impairmant of placental perfusion and from increased oxygen consumption induced by hyperthermia. As with other drugs of abuse, changes in fetal brain monoamine concentration may alter neurologic development and result in behavioral abnormalities. The serotonin-releasing effect of MDMA is of concern because serotonin is a potent teratogen and is embryotoxic.[225] A study of 43 pregnancies of parturients who used ecstasy did not find an increase in spontaneous abortions or congenital anomalies.[243]

Tobacco

Pharmacology

Nicotine, the active agent in tobacco, stimulates the CNS and autonomic ganglia, triggering release of epinephrine from the adrenal medulla. In large doses, it produces ganglionic blockade. Tolerance develops to some of its effects. Withdrawal symptoms, including irritability, aggressiveness, hostility, depression, and concentration difficulties, result from both environmental conditioning and pharmacologic dependence. Nicotine is metabolized to cotinine, and levels in the urine quantitatively reflect tobacco exposure.[244]

Pregnancy

Maternal Effects

From 17% to 30% of mothers smoke during pregnancy.[9,14] Women who start smoking before age 15 tend to be heavy smokers prepregnancy and at the first prenatal visit.[89]

Smokers are usually younger, Caucasian, single, and less educated.[8] Smoking alters the hypothalamic pituitary axis, inhibiting release of LH and prolactin, and decreasing fertility and gestational length. Spontaneous abortion[56,245] and preterm labor increase.[179] Placental abruption results from decidual necrosis at the placental margin.[33] Abruption and placenta previa account for one-half to one-third of the increased perinatal mortality in smokers.[67,246] Although smoking reduces the risk of developing preeclampsia,[247] it increases its morbidity by increasing abruption, IUGR, and mortality.[248]

Uteroplacental Effects

Nicotine and cotinine cross the placenta, and significant levels have been detected in amniotic fluid, fetal serum, and placental tissues throughout the pregnancy. Fetal nicotine levels exceed maternal,[249] but fetal cotinine levels are lower than maternal levels.[249,250]

Placental impairment is thought to be caused by nicotine-induced vasoconstriction.[251] Placentas of heavy smokers exhibit atrophic hypovascular villi, causing reduced estradiol conversion and uptake of alphaaminobutyric acid.[30] Components of cigarette smoke depress cellular uptake of amino acids, reducing placental transfer of amino acids and lowering amino acids levels in the umbilical vein.[31] Cyanide from tobacco smoke crosses the placenta and depletes fetal vitamin B_{12}.[252]

Fetal Effects

In rats, nicotine retards embryo cell cleavage, reducing cell number and provoking developmental abnormalities. In humans, fetal heart rate and umbilical and fetal aortic blood flow,[253] erythropoietin, hemoglobin concentration, and carboxyhemoglobin concentrations are increased, suggesting chronic fetal hypoxia.[32] Smoking is associated with second trimester abortion, as is maternal exposure to passive smoke.[254] Although nicotine increases maternal thromboxane A_2, it has been noted to inhibit fetal thromboxane A_2.[250] Fetal respiratory movements in utero are depressed by tobacco smoking.[255]

Fetal Growth

Tobacco causes fetal growth restriction.[246] Decrements in birth weight and birth length correlate with maternal serum cotinine concentration[256]; the average weight reduction equates to 1 week of fetal growth in late pregnancy.[48] Fifteen percent of cases of low birth weight could be attributed to tobacco in one study. Smoking especially decreases infant size with concomitant alcohol consumption.[49] Passive smoking decreases birth weight.[257] In infants, especially those who are preterm, prolactin, growth hormone, and insulin-like growth factor I are increased by tobacco exposure.[258]

Neonatal Effects

Infants of smokers have lower forced expiratory flow (FEF) rates shortly after birth, indicating tobacco-impaired in utero lung development or altered lung elastic properties.[259] These effects persist in childhood.[260] Infants exposed to tobacco have an increased incidence of asthma.[261] Infants exposed to passive smoke have cotinine levels in meconium similar to those of neonates whose mothers are light smokers.[244]

Sudden Infant Death Syndrome

Neonatal mortality increases with maternal smoking.[48] Infants are at greater risk of sudden infant death syndrome (SIDS), especially if the mother or father continues to smoke.[262] If women refrained from smoking during pregnancy, up to 30% of SIDS might be prevented.[263]

Neurologic Function

In a controlled study, increasing maternal urine cotinine levels increased the odds ratio of neonatal hypertonia.[202] At age two, the amount of tobacco exposure varied inversely with gross motor balance and fine motor eye–hand coordination as assessed by the Peabody Developmental Motor Scales.[102]

The evidence for specific cognitive deficits is inconsistent; however, children show a pattern of decreased cognitive development, behavioral difficulties, social maladjustment, and hyperactivity.[264] Altered auditory function is manifested in lower language and reading scores, and verbal WISC scores.[146]

Obstetric Management

The effects of tobacco on pregnancy are summarized in Box 27.7. Patients should stop smoking, but this is more difficult than stopping other drugs.[265] Nicotine replacement therapy has been recommended, but nicotine is the primary cause of decreased placental perfusion, so this may be of limited benefit.[266] Stopping smoking is beneficial even in late gestation, because nicotine and carbon monoxide are eliminated within 12 to 24 h.[267] Patients need instructions regarding preterm labor and surveillance for growth retardation. At term, smoking causes fetal tachycardia and decreases beat-to-beat vari-

Box 27.7. Tobacco effects on pregnancy.

Spontaneous abortion
Preterm delivery
Low birth weight
Sudden infant death syndrome
Decreased small airway diameter
Attention and behavioral problems

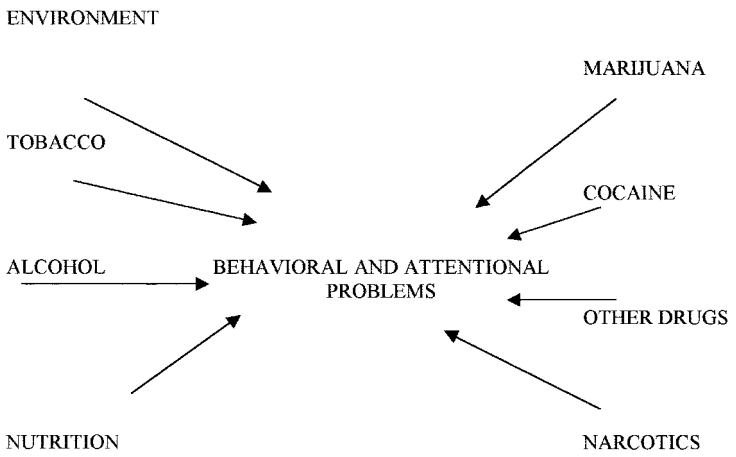

FIGURE 27.2. Factors contributing to neonatal outcome with drug abuse.

ability.[268] When preterm premature rupture of membranes (PROM) occurs, tobacco use decreases the time interval between rupture and delivery, when obstetric management is "expectant."[177]

Anesthetic Management

Smoking is an established cause of increased anesthetic risk. Stopping for 48 h produces an 8% increase in available oxygen in pregnant women.[269] Smoking on the day of surgery increases gastric volume and risk for aspiration.[270] Bronchitis and increased levels of carbon monoxide increase the risk of bronchospasm and hypoxia after intubation. Smoking alters anesthetic drug metabolism via hepatic enzyme induction.[267] Regional anesthesia avoids these risks and is preferred.

Summary

Maternal use of substances that are potentially harmful to the fetus and neonate immediately before and during pregnancy is widespread. Few substance abusers use a single agent, and the effects of a particular drug are difficult to establish. Neonatal outcome (Figure 27.2) depends upon maternal lifestyle as well as the degree of substance abuse. Drug abuse is sustained by behavioral reinforcement and dependence.

Maternal health, fertility, prenatal care, placental function, fetal development, neonatal morbidity, parenting, and child development and behavior all undergo adverse effects as a result of substance abuse. The combination of tobacco, alcohol, marijuana, and heroin or cocaine abuse results in drug-seeking behavior, which increases the likelihood of maternal malnutrition and HIV infection. Alcohol addiction causes severe permanent morphologic and neurologic damage to the fetus. Cocaine, tobacco, and multiple substance abuse are associated with significant behavioral and attentional problems for the child.

Prenatal care must be nonpunitive and directed toward early intervention and obtaining the patient's participation in altering her lifestyle and reducing substance abuse. Altered maternal physiology and metabolic and pharmacologic drug interactions affect obstetric and anesthetic care in the delivery room. Abortion, preterm labor, premature rupture of membranes, placental abruption, intrauterine fetal growth retardation, and preterm delivery occur more frequently in parturients who are substance abusers. Epidural or intrathecal narcotic analgesia decreases maternal and fetal stress during labor. Administration of anesthesia for cesarean section must be altered to accommodate the interactions of abused substances with anesthetics. The proportion of parturients for whom general anesthesia for cesarean section is necessary increases with substance abuse.

References

1. Markovic N, Ness RB, Cefilli D, et al. Substance use measures among women in early pregnancy. Am J Obstet Gynecol 2000;183:627–632.
2. Doweiko HF. Concepts of Chemical Dependency. Pacific Grove: Brooks/Cole, 1993:1–14, 69–78, 141–152.
3. Hawks RL, Chiang CN, eds. Urine testing for drugs of abuse. NIDA Research Monograph. 1986;73.
4. Bearer CF, Lee S, Salvator AE, et al. Ethyl linoleate in meconium: a biomarker for prenatal ethanol esposure. Alcohol Clin Exp Res 1999;23: 487–493.
5. Kline J, Ng SK, Schittini M, et al. Cocaine use during pregnancy: sensitive detection by hair assay. Am J Public Health 1997;87:352–358.
6. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320:762–768.
7. Gillogley KM, Evans AT, Hansen RL, et al. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. Am J Obstet Gynecol 1990;163:1535–1542.
8. Streissguth AP, Grant TM, Barr HM, et al. Cocaine and the use of alcohol and other drugs during pregnancy. Am J Obstet Gynecol 1991; 164:1239–1243.
9. Sloan LB, Gay JW, Snyder SW, et al. Substance abuse during pregnancy in a rural population. Obstet Gynecol 1992;79:245–248.
10. Slutsker L, Smith R, Higginson G. Recognizing illicit drug use by pregnant women: reports from Oregon birth attendants. Am J Public Health 1993;83:61–64.
11. Hans SL. Demographic and psychosocial characteristics of substance-abusing pregnant women. Clin Perinatol 1999;26:55–74.

12. Spence MR, Williams R, DiGregorio GJ, et al. The relationship between recent cocaine use and pregnancy outcome. Obstet Gynecol 1991;78: 326–329.
13. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence in pregnancy: effects and management. Obstet Gynecol Clin 1998;25:139–151.
14. Christmas JT, Knisely JS, Dawson KS. Comparison of questionnaire screening and urine toxicology for detection of pregnancy complicated by substance abuse. Obstet Gynecol 1992;80:750–754.
15. Kruse J, Lefevre M, Zweig S. Changes in smoking and alcohol consumption during pregnancy. A population based study in a rural area. Obstet Gynecol 1986;67:627–632.
16. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. N Engl J Med 1990;322:1202–1206.
17. Vaughn AJ, Carzoli RP, Sanchez-Ramos L, et al. Community-wide estimation of illicit drug use in delivering women: prevalence, demographics, and associated risk factors. Obstet Gynecol 1993;82:92–96.
18. Schultzman DL, Frankenfield-Chernicoff M, Clatterbaugh HE, et al. Incidence of intrauterine cocaine exposure in a suburban setting. Pediatrics 1991;88:825–827.
19. Klein RF, Friedman-Campbell M, Tocco RV. History taking and substance abuse counseling with the pregnant patient. Clin Obstet Gynecol 1993;36:338–346.
20. Mucklow JC. The fate of drugs in pregnancy. Clin Obstet Gynecol 1986; 13:161–175.
21. Woods JR Jr, Plessinger MA. Pregnancy increases cardiovascular toxicity to cocaine. AM J Obstet Gynecol 1990;162:529–533.
22. Plessinger MA, Woods JR Jr. Maternal placental, and fetal pathophysiology of cocaine exposure during pregnancy. Clin Obstet Gynecol 1993;36:267–278.
23. Moen MD, Caliendo MJ, Marshall W, et al. Hepatic rupture in pregnancy associated with cocaine use. Obstet Gynecol 1993;82:687–689.
24. Roe DA, Little BB, Bawdon RE, et al. Metabolism of cocaine by human placentas: implications for fetal exposure. Am J Obstet Gynecol 1990;163:715–718.
25. Rice PA, Nesbitt RE, Cuenca VG, et al. The effect of ethanol on the production of lactate, triglycerides, phospholipids and free fatty acids in the perfused human placenta. Am J Obstet Gynecol 1986;155:207–211.
26. Lindsay MK, Peterson HB, Boring J, et al. Crack cocaine: a risk factor for human immunodefiency virus infection type 1 among inner city parturients. Obstet Gynecol 1992;80:981–984.
27. Knight EM, James H, Edwards CH, et al. Relationships of serum illicit drug concentrations during pregnancy to maternal nutritional status. J Nutr 1994;124:973S–980S.
28. Burkett G, Yasin SY, Palow D, et al. Patterns of cocaine bingeing: effect on pregnancy. Am J Obstet Gynecol 1994;171:372–378.
29. Berenson AB, Stiglich NJ, Wilkinson GS, et al. Drug abuse and other risk factors for physical abuse in pregnancy among White non-Hispanic, Black and Hispanic women. Am J Obstet Gynecol 1991;164:1491–1496.
30. Fisher SE, Atkinson M, Van Thiel DH. Selective fetal malnutrition: the effect of nicotine, ethanol and acetaldehyde upon in vivo uptake of alpha-amino butyric acid by human term placental villous slices. Dev Pharmacol Ther 1984;7:229–238.
31. Sastry BVR, Mouton S, Janson VE. Tobacco smoking by pregnant women: disturbances in metabolism of branched chain amino acids and fetal growth. Ann N Y Acad Sci 1989;678:361.
32. Varvarigou A, Beratis NG, Makri M, et al. Increased levels and positive correlation between erythropoietin and hemoglobin concentrations in newborn children of mothers who are smokers. J Pediatr 1994;124: 480–482.
33. Naeye RL, Harkness WL, Utts J. Abruptio placentae and perinatal death: a prospective study. Am J Obstet Gynecol 1977;128:740–746.
34. Finnegan LP. Effects of maternal opiate abuse on the newborn. Fed Proc 1985;44:2314–2317.
35. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. J Pediatr 1987;111:571–578.
36. Acker D, Sachs BP, Tracey KJ, et al. Abruptio placentae associated with cocaine use. Am J Obstet Gynecol 1983;146:220–221.
37. Martin JC. Irreversible changes in mature and aging animals following intrauterine drug exposure. Neurobehav Toxicol Teratol 1986;8:335–343.
38. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA 1989;262:2847–2852.
39. Woods JR Jr, Plessinger MA, Fantel A. An introduction to reactive oxygen species and their possible roles in substance abuse. Obstet Gynecol Clin 1998;25:219–236.
40. Bingol N, Fuchs M, Diaz V, et al. Teratogenicity of cocaine in humans. J Pediatr 1987;110:93–96.
41. Hoyme HE, Jones KL, Dixon SD, et al. Prenatal cocaine exposure and fetal vascular disruption. Pediatrics 1990;85:743–747.
42. Chasnoff IJ, Chisum GM, Kaplan WE. Maternal cocaine use and genitourinary tract malformations. Teratology 1988;37:201–204.
43. Chasnoff IJ, Griffith DR, MacGregor S, et al. Temporal patterns of cocaine use in pregnancy. JAMA 1989;261:1741–1744.
44. Niemela O, Halmesmaki E, Ylikorkla O. Hemoglobin-acetaldehyde adducts are elevated in women carrying alcohol damaged fetuses. Alcohol Clin Exp Res 1991;15:1007–1010.
45. Ernhart CB, Sokol RJ, Ager JW, et al. Alcohol-related birth defects: assessing the risks. Ann N Y Acad Sci 1989;678:159–172.
46. Fishman RH, Yanai J. Long-lasting effects of early barbiturates on central nervous system and behavior. Neurosci Biobehav Rev 1983;7:19–28.
47. Hingson R, Alpert N, Day E, et al. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics 1982;70:539–546.
48. Bardy AH, Seppala T, Lillsunde P, et al. Objectively measured tobacco exposure during pregnancy: neonatal effects and relationship to maternal smoking. Br J Obstet Gynecol 1993;100:721–726.
49. Olsen J, Pereira A da C, Olsen SF. Does maternal tobacco smoking modify the effect of alcohol on fetal growth. Am J Public Health 1991; 81:69–73.
50. Ryan L, Erlich S, Finnegan L. Cocaine abuse in pregnancy: effects on the fetus and newborn. Neurotoxicol Teratol 1987;9:295–299.
51. Little BB, Snell LM, Gilstrap LD III, et al. Patterns of multiple substance abuse during pregnancy: implications for mother and fetus. South Med J 1990;83:507–509, 518.
52. Bateman DA, Stephen KC, Hansen CA, et al. The effects of intrauterine cocaine exposure in newborns. Am J Public Health 1993;83:190–193.
53. Volpe J. Review article: Mechanisms of disease: effect of cocaine use on the fetus. N Engl J Med 1992;327:399–407.
54. Chasnoff IJ, Griffith DR, Freier C, et al. Cocaine polydrug use in pregnancy. Two-year followup. Pediatrics 1992;89:284–289.
55. Strauss AA, Mondaniou HD, Bosu SK. Neonatal manifestations of maternal phencyclidine (PCP) use. Pediatrics 1981;68:550–552.
56. US Department of Health, Education, and Welfare. Health consequences of smoking for women. A report of the Surgeon General. DHEW Publication No. (NIH) 0-326-003. Washington, DC: USDHEW, 1980.
57. Chouteau M, Namerow PB, Leppert P. The effect of cocaine abuse on birth weight and gestational age. Obstet Gynecol 1988;72:351–354.
58. Fried PA, Watkinson B, Willan A. Marijuana use during pregnancy and decreased length of gestation. Am J Obstet Gynecol 1984;150:23–27.
59. Pelosi MA, Frattarola M, Apuzzio J, et al. Pregnancy complicated by heroin addiction. Obstet Gynecol 1975;45:512–515.
60. Russell CS, Taylor R, Maddison RN. Some effects of smoking in pregnancy. J Obstet Gynecol Br Commonw 1966;73:742–746.
61. MacGregor SN, Keith LG, Chasnoff IJ, et al. Cocaine use during pregnancy: adverse perinatal outcome. Am J Obstet Gynecol 1987;157:686–690.
62. Phibbs CS, Bateman DA, Schwartz RM. The neonatal cost of maternal cocaine use. JAMA 1991;266:1521–1526.
63. Chasnoff IJ, Lewis DE, Squires L. Cocaine intoxication in a breast fed infant. Pediatrics 1987;80:836–838.
64. Lustbader AS, Mayes LC, McGee BA, et al. Incidence of passive exposure to crack/cocaine and clinical findings in infants seen in an outpatient service. Pediatrics 1998;102:e5.

65. Kandall SR, Gaines J, Habel L, et al. Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring. J Pediatr 1993;123:120–126.
66. Durand DJ, Espinoza AM, Nickerson BG. Association between perinatal cocaine exposure and sudden infant death syndrome. J Pediatr 1990;117:909–911.
67. Meyer MB, Tonascia JA. Maternal smoking, pregnancy complications, and perinatal mortality. Am J Obstet Gynecol 1977;128:494–502.
68. Leech SL, Richardson GA, Goldschmidt L, et al. Prenatal substance exposure: effects on attention and impulsivity in 6-year-olds. Neurotoxicol Teratol 1999;21:109–118.
69. Fost N. Maternal-fetal conflict. Ethical and legal considerations. Ann N Y Acad Sci 1989;678:248–254.
70. Howell EM, Chasnoff IJ. Perinatal substance abuse treatment. Findings from focus groups with clients and providers. J Subst Abuse Treat 1999; 17:139–148.
71. MacGregor SN, Keith LG, Bochicha JA, et al. Cocaine abuse during pregnancy: correlation between prenatal care and perinatal outcome. Obstet Gynecol 1989;74:882–885.
72. Lawson EJ. The role of smoking in the lives of low income pregnant adolescents: a field study. Adolescence 1994;29:61–79.
73. Sutton LR, Hinderliter SA. Diazepam abuse in pregnant women on methadone maintenance: implications for the neonate. Clin Pediatr 1990;29:108–111.
74. Alger LS, Farley JJ, Robinson BA, et al. Interactions of human immunodeficiency virus infection and pregnancy. Obstet Gynecol 1993;82:787–796.
75. Conner ED, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type I with zidovudine treatment. N Engl J Med 1994;331:1173–1180.
76. Blinick G, Wallach RC, Jerez E, et al. Drug addiction in pregnancy and the neonate. Am J Obstet Gynecol 1976;125:135–142.
77. Towers CV, Pircon RA, Nagoette MP, et al. Cocaine intoxication presenting as preeclampsia and eclampsia. Obstet Gynecol 1993;81:545–547.
78. Loft S. Increased hepatic microsomal enzyme activity after surgery under halothane or spinal anesthesia. Anesthesiology 1985;62:11–16.
79. Hollander H, Levy JA. Neurologic abnormalities and recovery of human immunodeficiency virus from cerebrospinal fluid. Am J Intern Med 1987;106:692–695.
80. Du Pen SL, Peterson DG, Williams A, et al. Infection during chronic epidural catheterization: diagnosis and treatment. Anesthesiology 1990; 73:905–909.
81. Hughes SC, Dailey PA, Landers D, et al. Parturients infected with human immunodeficiency virus and regional anesthesia. Anesthesiology 1995;82:32–37.
82. Silver H, Wapner R, Loriz-Vega M, et al. Addiction in pregnancy: high risk intrapartum management and outcome. J Perinatol 1987;3:178–184.
83. Ross VH, Moore CH, O'Rourke PJ, et al. Cocaine abusing parturients do not require more epidural pain medication for labor and delivery. Anesthesiology 1994;81:A1184.
84. Weintraub SJ, Naulty JS. Acute abstinence syndrome after epidural injection of butorphanol. Anesth Analg 1985;64:452–453.
85. Kafle SK. Intrathecal meperidine for elective cesarean section: a comparison with lidocaine. Can J Anesth 1993;40:718–721.
86. Li TK, Bosron WF. Genetic variability of enzymes of alcohol metabolism in human beings. Ann Emerg Med 1986;21:997–1046.
87. Horrobin DF. A biochemical basis for alcoholism and alcohol-induced damage including the fetal alcohol syndrome and cirrhosis. Med Hypotheses 1980;6:929–942.
88. Day NL, Cottreau CM, Richardson GA. The epidemiology of alcohol, cocaine, and marijuana use among women of childbearing age and pregnant women. Clin Obstet Gynecol 1993;36:232–245.
89. Cornelius MD, Day NL, Cornelius JR, et al. Drinking patterns and correlates of drinking among pregnant teenagers. Alcoholism 1993;17:290–294.
90. George SK, Price J, Hauth JC, et al. Drug abuse screening of childbearing-age women in Alabama Public Health Clinics. Am J Obstet Gynecol 1991;165:924–927.
91. Ylikahri RH, Huttunen MO, Hardoven M. Hormonal changes during alcohol intoxication and withdrawal. Pharmacol Biochem Behav 1980; 13(suppl 1):131–137.
92. MacGregor RR. Alcohol and immune defense. JAMA 1986;256:1474–1479.
93. Martin F, Peters TJ. Alcoholic muscle disease. Alcohol Alcohol 1985; 20:125–136.
94. Sage JI, Van Uitert RL, Lepore FE. Alcoholic myelopathy without substantial liver disease: a syndrome of progressive dorsal and lateral column dysfunction. Arch Neurol 1984;41:999–1001.
95. Wagner CL, Katikaneni LD, Cox TH, et al. Substance abuse in pregnancy. Obstet Gynecol Clin 1998;25:169–194.
96. Erskine RL, Ritchie JW. The effect of maternal consumption of alcohol on human umbilical artery blood flow. Am J Obstet Gynecol 1986; 154:318–321.
97. Halvorsen PR, Gross TL, Sokol RJ. The effect of heavy maternal alcohol intake on amniotic fluid phospholipids in late pregnancy. Am J Perinatol 1985;2:173–177.
98. Day NL, Jasperse D, Richardson G, et al. Prenatal exposure to alcohol: effect on infant growth and morphologic characteristics. Pediatrics 1989:84:536–541.
99. Holzman C, Paneth N, Little R, et al. Perinatal brain injury in premature infants born to mothers using alcohol in pregnancy. Pediatrics 1995;95:66–73.
100. Scher MS, Richardson GA, Day NL. Effects of prenatal cocaine/crack and other drug exposure on electroencephalographic sleep studies at birth and one year. Pediatrics 2000;105:39–48.
101. Streissguth AP, Sampson PD, Barr HM. Neurobehavioral dose–response effects of prenatal alcohol exposure in humans from infancy to adulthood. Ann N Y Acad Sci 1989;678:145–158.
102. Arendt R, Angelopoulos J, Salvatore A, et al. Motor development of cocaine-exposed children at age two years. Pediatrics 1999;103:86–92.
103. Coles CD. Impact of prenatal alcohol exposure on the newborn and the child. Clin Obstet Gynecol 1993;36:255–266.
104. Jones HE, Balster RL. Inhalant abuse in pregnancy. Obstet Gynecol Clin 1998;25:153–167.
105. Day NL, Zuo Y, Richardson GA, et al. Prenatal alcohol use and offspring size at 10 years of age. Alcohol Clin Exp Res 1999;23:863–869.
106. Halmesmaki E, Autti I, Granstrom ML, et al. Alpha-fetoprotein, human placental lactogen, and pregnancy-specific beta-1-glycoprotein in pregnant women who drink: relation to fetal alcohol syndrome. Am J Obstet Gynecol 1986;155:598–602.
107. Reyes E. The role of gamma-glutamyl transpeptidase in alcoholism. Neurobehav Toxicol Teratol 1985;7:171–175.
108. Kranzler HR, Amin H, Modesto-Lowe V, et al. Pharmacologic treatments for drug and alcohol dependence. Psychiatr Clin N Am 1999; 22:401–423.
109. Nakada T, Knight RT. Alcohol and the central nervous system. Med Clin N Am 1984;68:121–131.
110. Lorens SA, Sainati SM. Naloxone blocks the excitatory effect of ethanol and chlordiazepoxide on lateral hypothalamic self-stimulation behavior. Life Sci 1988;23:1359.
111. Swerdlow BN, Holley FO, Maitre PI, et al. Chronic alcohol intake does not change thiopental anesthetic requirement, pharmacokinetics, or pharmacodynamics. Anesthesiology 1990;72:455–461.
112. Pantuck EJ, Pantuck CB, Ryan DE, et al. Inhibition and stimulation of enflurane metabolism in the rat following a single dose or chronic administration of ethanol. Anesthesiology 1985;62:255.
113. Janacek E, Kapur BM, Devenyi P. Oral phenobarbitol loading: a safe method of barbiturate and non-barbiturate hypnosedative withdrawal. Can Med Assoc J 1987;137:410–412.
114. Murphy JL. Hypertension and pulmonary oedema associated with ketamine administration in a patient with a history of substance abuse. Can J Anaesth 1993;40:160–169.
115. Christie MJ, Williams JT, North RA. Cellular mechanisms of opiate tolerance: studies in single brain neurons. Mol Pharmacol 1987;32:633–638.
116. Gold CG, Cullen DJ, Gonzales S, et al. Rapid opioid detoxification dur-

ing general anesthesia: a review of 20 patients. Anesthesiology 1999; 91:1639–1647.
117. Warner EA, Kosten TR, O'Connor PG. Pharmacotherapy for opioid and cocaine abuse. Med Clin N Am 1997;81:909–925.
118. Connaughton JF, Resser D, Schut J, et al. Perinatal addiction: outcome and management. Am J Obstet Gynecol 1977;129:679–686.
119. Parekh A, Mukherjee TH, Jhaveri R, et al. Intrauterine exposure to narcotics and cord blood prolactin concentrations. Obstet Gynecol 1981; 57:477–479.
120. Wilson GS. Clinical studies of infants and children exposed prenatally to heroin. Ann N Y Acad Sci 1989;562:183–194.
121. Fujinaga M, Mazzi RI, Jackson EC, et al. Reproductive and teratogenic effects of sufentanil and alfantanil in Sprague-Dawley rats. Anesth Analg 1988;67:166–169.
122. Lapointe G, Nosal G. Morphine treatment during rat pregnancy. Biol Neonate 1982;42:22–30.
123. Mercurio SD, Lichtblau L, Sparber SB. Separation of *n*-hepatic-demethylase-inducing and opiate dependence producing doses of levo-alpha-acetylmethadol in the pregnant rat. Life Sci 1984;33:1127–1134.
124. Lichtblau L, Sparber SB. Opiate withdrawal in utero increases neonatal morbidity in the rat. Science 1981;212:943–945.
125. Little BB, Snell LM, Klein VR, et al. Maternal and fetal effects of heroin addiction during pregnancy J Reprod Med 1990;35:159–165.
126. Panerai AE, Martini A, Di Giulio AM, et al. Plasma beta-endorphin, beta-lipotropin and metenkephalin concentrations during pregnancy in normal and drug-addicted women and their newborn. J Clin Endocrinol Metab 1983;57:537–543.
127. Doberczak TM, Kandall SR, Freidman P. Relationship between maternal methadone dosage, maternal-neonatal methadone levels, and neonatal withdrawal. Obstet Gynecol 1993;81:936–940.
128. Wilson GS, Mc Creary R, Kean J, et al. The development of preschool children of heroin addicted mothers: a controlled study. Pediatrics 1979; 63:135–141.
129. Dashe JS, Jackson GL, Olscher DA, et al. Opioid detoxification in pregnancy. Obstet Gynecol 1998;95:854–858.
130. Murphy JL. Hypertension and pulmonary oedema associated with ketamine administration in a patient with a history of substance abuse. Can J Anaesth 1993;40:160–169.
131. Fisher G, Johnson RE, Edger H, et al. Treatment of opioid-dependent pregnant women with buprenorphine. Addiction 2000;95:239–244.
132. Selwyn PA, Schoenbaum EE, Davenny K, et al. Prospective study of human immunodeficiency virus infection and pregnancy outcome in intravenous drug users. JAMA 1989;261:1289–1294.
133. Minkoff H, Augenbraun M. Antiretroviral therapy for pregnant women. Am J Obstet Gynecol 1997;176:478–489.
134. Anyaegbunam A, Tran T, Randolph G, et al. Assessment of fetal well-being in methadone-maintained pregnancies: abnormal nonstress tests. Gynecol Obstet Invest 1997;43:25–28.
135. Clarke EM, Muleahy F, Healy CM, et al. The efficacy and tolerability of combination antiretroviral therapy in pregnancy: infant and maternal outcome. Int J STD AIDS 2000;11:220–223.
136. Hughes SC. Human immunodeficiency virus and obstetric anesthesia. Anesth Clin N Am 1998;16:397–418.
137. Mirochnick M, Meyer J, Frank DA, et al. Elevated plasma norepinephrine after in utero exposure to cocaine and marijuana. Pediatrics 1997;99:555–559.
138. Mendelson JH, Mello NK. Effects of marijuana on neuroendocrine hormones in human males and females. NIDA Res Monogr 1984;44:97–114.
139. Abel EL, Tan SE. Effects of delta-9-tetrahydrocannabinol, chlordiazepoxide (Librium), and their combination on pregnancy and offspring in mice. Reprod Toxicol 1987;1:37–40.
140. Sherwood RA, Keating J, Kavvadia V, et al. Substance misuse in early pregnancy and relationship to fetal outcome. Eur J Pediatr 1999;158: 488–492.
141. Dreher MC, Nugent K, Hudgins R. Perinatal marijuana exposure and neonatal outcome in Jamaica: an ethnographic study. Pediatrics 1994; 93:254–260.
142. Shiono PH, Klebanoff MA, Nugent RP, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. Am J Obstet Gynecol 1995;172:19–27.
143. Fried PA. Postnatal consequences of maternal marijuana use during pregnancy: consequences for the offspring. Semin Perinatol 1991;15: 280.
144. Tanley BW, Fried PA, Mount HTJ. Visual processing in children prenatally exposed to marijuana and nicotine: a preliminary report. Can J Public Health 1986;77:72.
145. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22:325–326.
146. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1997;19:171–183.
147. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. Neurotox Teratol 1998;20:293–306.
148. Warner EA. Cocaine abuse. Ann Intern Med 1993;119:226–235.
149. Kain ZN, Rimar S, Barash PG. Cocaine abuse in the parturient and effects on the fetus and neonate. Anesth Analg 1993;77:835–845.
150. Wilkerson RD. Cardiovascular effects of cocaine: enhancement by yohimbine and atropine. J Pharmacol Exp Ther 1989;248:57–61.
151. Plessinger MA, Woods JR Jr. Cocaine in pregnancy. Recent data on maternal and fetal risks. Obstet Gynecol Clin 1998;25:99–118.
152. Nakahara K, Iso A, Chao CR, et al. Pregnancy enhances cocaine-induced stimulation of uterine contractions in the chronically instrumented rat. Am J Obstet Gynecol 1996;175:188–193.
153. Morishima HO, Whittington RA, Zhang Y, et al. The disposition of cocaethylene in rat maternal, placental, and fetal compartments. Am J Obstet Gynecol 1999;180:1289–1296.
154. Glantz JC, Woods JR. Cocaine, heroin, and phencyclidine: obstetric perspectives. Clin Obstet Gynecol 1993;36:279–301.
155. Haim DY, Lippman ML, Goldberg SK, et al. The pulmonary complications of crack cocaine: a comprehensive review. Chest 1995;107:233–240.
156. Forrester JM, Steele AW, Waldron JA, et al. Crack lung: an acute pulmonary syndrome with a spectrum of clinical and histopathologic findings. Am Rev Respir Dis 1990;142:462–467.
157. Campbell D, Parr MJ, Shutt LE. Unrecognized "crack" cocaine abuse in pregnancy. Br J Anaesth 1996;77:553–555.
158. Heesch CM, Wilhelm CR, Ristich J, et al. Cocaine activates platelets and increases the formation of circulating platelet containing microaggregates in humans. Heart 2000;83:688–695.
159. Orser B. Thrombocytopenia and cocaine abuse. Anesthesiology 1991; 74:195–196.
160. Liu SS, Forrester RM, Murphy GS, et al. Anaesthetic management of a parturient with myocardial infarction related to cocaine use. Can J Anaesth 1992;39:858–861.
161. Chao CR. Cardiavascular effects of cocaine during pregnancy. Semin Perinatol 1996;20:107–114.
162. Bernasko JW, Brown G, Mitchell JL, et al. Spontaneous pneumothorax following cocaine use in pregnancy. Am J Emerg Med 1997;15:107.
163. Lampley EC, Williams S, Myers SA. Cocaine-associated rhabdomyolysis causing renal failure in pregnancy. Obstet Gynecol 1996;87: 804–806.
164. Mercado A, Johnson G Jr, Calver D, et al. Cocaine, pregnancy, and postpartum intercerebral hemorrhage. Obstet Gynecol 1989;73:467–468.
165. Mendelson MA, Chandler J. Postpartum cardiomyopathy associated with maternal cocaine abuse. Am J Cardiol 1992;70:1092–1094.
166. Mishra A, Landzberg BR, Parente JT. Uterine rupture in association with alkaloidal cocaine use. Am J Obstet Gynecol 1995;173:243–244.
167. Thatcher SS, Cortman R, Grossman J, et al. Cocaine use and acute rupture of ectopic pregnancies. Obstet Gynecol 1989;74:478–479.
168. Abramowicz JS, Sherer DM, Woods JR Jr. Acute transient thrombocytopenia associated with cocaine abuse in pregnancy. Obstet Gynecol 1991;78:499–501.

169. Weiss SH. Links between cocaine and retroviral infection. JAMA 1989;261:607–609.
170. Woods FR Jr, Plessinger MA, Clark KE. Effect of cocaine on uterine blood flow and fetal oxygenation. JAMA 1987;257:957–961.
171. Weaver K, Merrell CL, Griffin G. Effect of magnesium on cocaine-induced catecholamine-mediated platelet and vascular response in term pregnant ewes. Am J Obstet Gynecol 1989;161:1331–1337.
172. Monga M, Weisbrodt NW, Andres RL, et al. The acute effect of cocaine exposure on pregnant human myometrial contractile activity. Am J Obstet Gynecol 1993;169:782–785.
173. Hurd WW, Guavin JM, Dombrowski MP, et al. Cocaine selectively inhibits beta-adrenergic receptor binding in pregnant human myometrium. Am J Obstet Gynecol 1993;169:644–649.
174. Slutsker L. Risks associated with cocaine use during pregnancy. Obstet Gynecol 1992;79:778–789.
175. Richardson GA, Hamel SC, Goldschmidt L, et al. Growth of infants prenatally exposed to cocaine/crack: comparison of a prenatal care and a no prenatal care sample. Pediatrics 1999;104:e18.
176. Hoskins IA, Friedman DM, Frieden FJ, et al. Relationship between antepartum cocaine abuse, abnormal umbilical artery Doppler velocimetry and placental abruption. Obstet Gynecol 1991;78:279–282.
177. Dinsmoor MJ, Irons SJ, Christmas JT. Preterm rupture of the membranes associated with cocaine use. Am J Obstet Gynecol 1994;171:305–308.
178. Delaney DB, Larrabee KD, Monga M. Preterm premature rupture of the membranes associated with recent cocaine use. Am J Perinatol 1997;14: 285–288.
179. Myles TD. Effects of smoking, alcohol, and drugs of abuse on the outcome of "expectantly" managed cases of preterm premature rupture of membranes. J Matern Fetal Med 1998;7:157–161.
180. Moore TR, Sorg J, Miller L, et al. Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. Am J Obstet Gynecol 1986; 155:883–888.
181. Owiny JR, Myers T, Massman GA, et al. Lack of effect of maternal cocaine administration on myometrial electromyogram and maternal plasma oxytocin concentrations in pregnant sheep at 124–126 days gestational age. Obstet Gynecol 1992;79:81–84.
182. Hurd WW, Robertson PA, Riemer RK, et al. Cocaine directly augments the alpha-adrenergic contractile response of the pregnant rabbit uterus. Am J Obstet Gynecol 1991;164:182–187.
183. Little BB, Roe DA, Stettler RW, et al. A new placental enzyme in the metabolism of cocaine: an in vitro animal model. Am J Obstet Gynecol 1995;172:1441–1445.
184. Critchley HO, Woods SM, Barson AJ, et al. Fetal death in utero and cocaine abuse. Case report. Br J Obstet Gynecol 1988;95:195–196.
185. Telsey AM, Merrit TA, Dixon SD. Cocaine exposure in a term neonate: necrotizing enterocolitis as a complication. Clin Pediatr 1988;27:547–550.
186. Mirochnick M, Frank DA, Cabral H, et al. Relation between meconium concentration of the cocaine metabolite benzoylecgonine and fetal growth. J Pediatr 1995;126:636–638.
187. Bateman DA, Chiriboga CA. Dose-response effect of cocaine on newborn head circumference. Pediatrics 2000;106:e33.
188. Woods JR Jr. Maternal and transplacental effects of cocaine. Ann N Y Acad Sci 1998;846:1–11.
189. Mayes LC. Developing brain and in utero cocaine exposure: effects on neural ontogeny. Dev Psychopathol 1999;11:685–714.
190. Dominguez R, Vila-Coro AA, Slopis JM, et al. Brain and ocular abnormalities in infants with in utero exposure to cocaine and other street drugs. Am J Dis Child 1991;145:688–695.
191. Eyler FD, Behnke M, Conlon M, et al. Birth outcome from a prospective matched study of prenatal crack/cocaine use: 1. Interactive and dose effects on health and growth. Pediatrics 1998;101:229–237.
192. Geggel RL, McInery J, Estes NAM III. Transient neonatal ventricular tachycardia associated with maternal cocaine use. Am J Cardiol 1989;63:383–384.
193. Mehta SK, Finkelhor RS, Anderson RL, et al. Transient myocardia ischemia in infants prenatally exposed to cocaine. J Pediatr 1993;122: 945–949.
194. van de Bor M, Walther FJ, Ebrahimi M. Decreased cardiac output in infants of mothers who abused cocaine. Pediatrics 1990;85:30–32.
195. Hanlon-Lundberg KM, Williams M, Rhim T, et al. Accelerated fetal lung maturity profiles and maternal cocaine exposure. Obstet Gynecol 1996;87:128–132.
196. Chasnoff IJ, Hunt CE, Kletter R, et al. Perinatal cocaine exposure is associated with respiratory pattern abnormalities. Am J Dis Child 1989;143:583–587.
197. King TA, Perlman JM, Laptook AR, et al. Neurologic manifestations of in utero cocaine esposure in near-term infants. Pediatrics 1995; 96:259–264.
198. Singer LT, Yamashita YS, Hawkins S. Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. J Pediatr 1994;124:765–771.
199. Dixon SD, Bejar R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: incidence and clinical correlates. J Pediatr 1989;115:770–778.
200. Frank D, McCarten KM, Robson CD, et al. Level of in utero cocaine exposure and neonatal ultrasound findings. Pediatrics 1999;104:1101–1105.
201. Chiraboga CA, Brust JC, Bateman D, et al. Dose-response effect of fatal cocaine exposure on newborn neurologic function. Pediatrics 1999; 103:79–85.
202. Dempsey DA, Hajnal BL, Partridge JC, et al. Tone abnormalities are associated with maternal cigarette smoking during pregnancy in in utero cocaine-exposed infants. Pediatrics 2000;106:79–85.
203. Hurt H, Brodsky NL, Betancourt L, et al. Cocaine exposed children: follow-up through 30 months. J Dev Behav Pediatr 1995;16:29–35.
204. Frank DA, Augustyn M, Knight WG, et al. Growth, development, and behavior in early childhood following prenatal cocaine exposure. JAMA 2001;285:1613–1625.
205. Potter SM, Zelazo PR, Stack DM, et al. Adverse effects of fetal cocaine exposure on neonatal auditory information processing. Pediatrics 2000;105:E40.
206. Singer LT, Arendt R, Minnes S, et al. Neurobehavioral outcomes of cocaine exposed infants. Neurotoxicol Teratol 2000;22:653–656.
207. Delaney-Black V, Covington C, Templin T, et al. Prenatal cocaine exposure and child behavior. Pediatrics 1998;102:945–950.
208. McMurtrie C. A unique drug treatment program for pregnant and postpartum substance-using women in New York City: results of a pilot project, 1990–1995. Am J Drug Alcohol Abuse 1999;25:701–713.
209. Singer LT, Garber R, Kleigman R. Neurobehavioral sequelae of fetal cocaine exposure. J Pediatr 1991;119:667–672.
210. Birnbach DJ, Stein DJ, Grunebaum A, et al. Cocaine screening of parturients without prenatal care: an evaluation of a rapid screening assay. Anesth Analg 1997;84:76–79.
211. Livingston JC, Mabie BC, Ramanathan J. Crack cocaine, myocardial infarction, and troponin I levels at the time of cesarean delivery. Anesth Analg 2000;91:913–915.
212. Vertommen JD, Hughes SC, Rosen MA, et al. Hydralazine does not restore uterine blood flow during cocaine-induced hypertension in the pregnant ewe. Anesthesiology 1992;76:580–587.
213. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Intern Med 1990;112:897–903.
214. Hollander JE. The management of cocaine-associated myocardial ischemia. N Engl J Med 1995;333:1267–1271.
215. Derlet RW, Albertson TE. Potentiation of cocaine toxicity with calcium channel blockers. Am J Emerg Med 1989;7:464–468.
216. Trouve R, Nahas G. Nitrendipine: an antidote to cardiac and lethal toxicity of cocaine. Proc Soc Exp Biol Med 1986;183:392–397.
217. Shih RD, Hollander JE, Burstein JL, et al. Clinical safety of lidocaine in patients with cocaine-associated myocardial infarction. Ann Emerg Med 1995;26:702–706.
218. Singh PP Dimich I, Shamsi A. Interoperative pulmonary edema in a young cocaine smoker. Can J Aneasth 1994;41:961–964.

219. Ross VH, Moore CH, O'Rourke PJ, et al. Cocaine abusing parturients do not require more epidural pain medication for labor and delivery. Anesthesiology 1994;81:A1184.
220. Kain ZN, Mayes LC, Ferris CA, et al. Cocaine-abusing parturients undergoing cesarean section: a cohort study. Anesthesiology 1996;85: 1028–1035.
221. Birnbach DJ. Anesthesia and the drug abusing parturient. Anesth Clin N Am 1998;16:385.
222. Bernards CM, Cullen BF, Powers K. Chronic cocaine increases isoflurane MAC in sheep. Anesth Analg 1995;80:S42.
223. Hoffman RS, Glendon CH, Howland MA, et al. Association between life-threatening cocaine toxicity and plasma cholinesterase activity. Ann Emerg Med 1992;21:247–253.
224. Cheng D. Perioperative care of the cocaine abusing patient. Can J Anaesth 1994;41:883–887.
225. Plessinger MA. Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy. Obstet Gynecol Clin 1998;25:119–138.
226. Cho AK. Ice: a new dosage form of an old drug. Science 1990;249:631.
227. Burchfield DJ, Lucas VW, Abrams RM, et al. Disposition and pharmacodynamics of methamphetamine in pregnant sheep. JAMA 1991; 265:1968–1973.
228. Stek AM, Fisher BK, Baker RS, et al. Maternal and fetal cardiovascular responses to methamphetamine in pregnant sheep. Am J Obstet Gynecol 1993;169:888–897.
229. Elliot RH, Rees GB. Amphetamine ingestion presenting as eclampsia. Can J Anaesth 1990;37:130–133.
230. Little BB, Snell LM, Gilstrap LC. Methamphetamine abuse during pregnancy: outcome and fetal effects. Obstet Gynecol 1988;72:541–544.
231. Erikson M, Larsson G, Zetterstrom R. Amphetamine addiction and pregnancy. II. Pregnancy, delivery and the neonatal period: socio-medical aspects. Acta Obstet Gynecol Scand 1981;60:253–259.
232. Cernerud RH, Eriksson M, Jonsson B, et al. Amphetamine addiction during pregnancy: 14 year follow-up of growth and school performance. Acta Paediatr 1996;85:204–208.
233. Johnstone RR, Way WL, Miller RD. Alteration of anesthetic requirement by amphetamine. Anesthesiology 1972;36:357–363.
234. Michel R, Adams AP. Acute amphetamine abuse: problems during general anesthesia for neurosurgery. Anaesthesia 1979;34:1016–1019.
235. Smith DS, Gutsche BB. Amphetamine abuse and obstetrical anesthesia. Anesth Analg 1980;59:710–711.
236. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 1989; 244:1360–1362.
237. Hertzman M, Reba RC, Kotylarov EV. Single photon emission computed tomography in phencyclidine and related drug abuse. Am J Psychiatry 1990;147:255.
238. Tabor BL, Smith-Wallace T, Yonekura ML. Perinatal outcome associated with PCP versus cocaine use. Am J Drug Alcohol Abuse 1990; 16:337–348.
239. Mvula MM, Miller JM, Ragan FA. Relationship of phencyclidine and pregnancy outcome. J Reprod Med 1999;44:1021–1024.
240. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. Pediatrics 1997;100:705–708.
241. Graeme KA. New drugs of abuse. Emerg Med Clin N Am 2000;18.
242. McCann UD, Szabo Z, Scheffel U, et al. Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. Lancet 1998;352:1433–1437.
243. van Tonnigen-van Driel MM, Garbis-Berkvens JM, Reuvers-Lodewijks WE. Pregnancy outcome after ecstasy use: 43 cases followed by the Teratology Information Service of the National Institute for Public Health and Environment (RIVM). Ned Tijdschr Geneeskd 1999;143: 27–31.
244. Ostrea EM, Knapp DK, Romero AI, et al. Meconium analysis to assess fetal exposure to nicotine by active and passive maternal smoking. J Pediatr 1994;124:471–476.
245. Kline J, Levin B, Kinney A, et al. Cigarette smoking and spontaneous abortion of known karotype: precise data but uncertain inferences. Am J Epidemiol 1995;141:417–427.
246. Andres RL. The association of cigarette smoking with placenta previa and abruptio placentae. Semin Perinatol 1996;20:154–159.
247. Lain KY, Powers RW, Krohn MA, et al. Urinary cotinine concentration confirms the reduced risk of preeclampsia with tobacco exposure. Am J Obstet Gynecol 1999;181:1192–1196.
248. Cnattingius S, Mils JL, Yuen J, et al. The paradoxical effect of smoking in preeclamptic pregnancies: smoking reduces the incidence but increases the rate of perinatal mortality, abruptio placentae and intrauterine growth restriction. Am J Obstet Gynecol 1997;177:156–161.
249. Luck W, Nau H, Hansen R, et al. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. Dev Pharmacol Ther 1985;8:384–395.
250. Donnenfeld AE, Pulkkinen A, Palomakig, et al. Simultaneous fetal and maternal cotinine levels in pregnant women smokers. Am J Obstet Gynecol 1993;168:781–782.
251. Walsh RA. Effects of maternal smoking on adverse pregnancy outcomes: examination of the criteria of causation. Hum Biol 1994;66: 1059–1092.
252. McGarry JM, Andrews J. Smoking in pregnancy and vitamin B_{12} metabolism. Br Med J 1972;2:74–77.
253. Sindberg EP, Marsal K. Acute effects of maternal smoking on fetal blood flow. Acta Obstet Gynecol Scand 1984;63:391–397.
254. Windham GC, Swan SH, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. Am J Epidemiol 1992;135:1394–1403.
255. Manning FA, Feyerabend C. Cigarette smoking and fetal breathing movements. Br J Obstet Gynecol 1976;83:262–270.
256. Haddow JE, Knight GJ, Polomaki GE, et al. Cigarette consumption and serum cotinine in relation to birth-weight. Br J Obstet Gynecol 1987; 94:678–681.
257. Fortier I, Marcoux S, Brisson J. Passive smoking during pregnancy and the risk of delivering a small-for-gestational-age infant. Am J Epidemiol 1994;139:294–301.
258. Beratis NG, Varvarigou A, Makri M, et al. Prolactin, growth hormone, and insulin-like growth factor-I in newborn children of smoking mothers. Clin Endocrinol 1994;40:179–185.
259. Hanrahan JP, Tager IB, Segal MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992;145:1129–1135.
260. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. J Epidemiol 1994; 139:1139.
261. Stick SM, Burton PR, Gurrin L, et al. Effects of maternal smoking during pregnancy and a family history of asthma on respiration function in newborn infants. Lancet 1996;348:1060–1064.
262. Mitchell EA, Ford RPK, Stewart AW, et al. Smoking and the sudden infant death syndrome. Pediatrics 1993;91:893–896.
263. Taylor JA, Sanderson M. A reexamination of the risk factors for the sudden infant death syndrome. J Pediatr 1995;126:887–891.
264. Rush D, Callahan KR. Exposure to passive cigarette smoking and child development: a critical review. Ann NY Acad Sci 1989;678:74–100.
265. Kozlowski LT, Wilkinson DA, Skinner W, et al. Comparing tobacco cigarette dependence with other drug dependencies. JAMA 1989;261:898–901.
266. Benowitz NL. Nicotine replacement therapy during pregnancy. JAMA 1991;266:3174–3177.
267. Pearce AC, Jones RM. Smoking and anesthesia: preoperative abstinence and perioperative morbidity. Anesthesiology 1984;61:576–584.
268. Sindberg EP, Gennser G, Lindvall R, et al. Acute effects of maternal smoking on fetal heart beat intervals. Acta Obstet Gynecol Scand 1984;63:385–390.
269. Davies JM, Latto IP, Jones JG, et al. Effects of stopping smoking for 48 hours on oxygen availability from the blood. A study on pregnant women. Br Med J 1979;2:355–356.
270. Wright DJ, Pandya A. Smoking and gastric juice volume in outpatients. Can Anaesth Soc J 1979;26:328–330.

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The Febrile Parturient

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Fever is a common occurrence in labor and delivery suites. It poses not only a diagnostic challenge but also a therapeutic dilemma. The pregnant state with its associated immunosuppression predisposes the gravida to infectious processes and increases the severity of their manifestations. Conversely, the consequences of the inflammatory cascade can be deleterious to the woman or the fetus. Recognition of infection may actually be hampered by the difficulty of routine history and physical assessment in the late gestational period and particularly during labor.

When approaching the febrile patient, three questions must be addressed. First, how does pregnancy alter the normal human anatomic and physiologic state, and how will these alterations change the ability to assess and treat the patient? Second, will the process adversely affect the pregnant woman or her fetus? Third, is the etiology of the fever unique to pregnancy (i.e., chorioamnionitis)?

Temperature Regulation and Pathogenesis of Fever

The core body temperature is regulated by the central nervous system. Heat is generated by the basal metabolic activity of the organism and is lost to the environment. The resultant temperature is set by the hypothalamic thermostat and influenced by feedback mechanisms. Receptors sense the central temperature. Mechanisms including the vasomotor, sudomotor, and metabolic effectors influence the regulation of heat production and elimination. Integrative structures determine whether the core temperature is too low or high and activate the appropriate response. There is a diurnal variation in temperature with the nadir in the early morning.[1]

Various processes are associated with fever. Obviously, infection is the most common pathology in pregnancy. However, immunomediated conditions such as connective tissue disorders, vascular thrombosis, granulomatous disease, inflammatory bowel disease, neoplasms, and metabolic disorders such as Addison's and thyroid crises may be the source of fever. Cerebral tumors, hemorrhage, or thrombosis, if affecting the central thermoregulatory center, are rare in childbirth but can also cause fever.

Pyrogens can either be exogenous, such as bacteria and their toxins and viruses, or endogenous, including cytokines. Cells interacting with exogenous pyrogens produce these substances. The endogenous pyrogens act centrally on the thermosensitive neurons in the hypothalamus to initiate increases in heat production and decreases in heat loss. This cycle continues until a new setpoint is met in the hypothalamus. The endogenous pyrogens, which include the interleukins, cachectin, and tumor necrosis factor, are released by stimulated monocytes, macrophages, and macrophage-derived cells but are also found in endothelium, astrocytes, and keritanocytes. Therefore, in infection-related fever, an interaction by the exogenous insult and the organism immune system mediate the temperature response. Although the benefits of fever are uncertain, there are suggestions that the increased temperature aids in the activation of the host immune response with augmentation of chemotactic, phagocytotic, and bactericidal properties of polymorphonuclear leukocytes. The negative aspects include muscle wasting, fat loss, increased basal metabolic rate, and cardiac demand. Insensible water and salt loss is increased, and metabolic and central nervous system changes can occur.[2] The fetus also responds with increases in cardiac output to radiate heat out through the placenta, giving rise to the tachycardia noted in febrile gravidas.

Obstetric Management

Workup and therapy of the febrile pregnant women should generally not be altered from that of any adult. However, specific anatomic and physiologic changes in pregnancy lead to difficulties in diagnosis and therapy. Laboratory alterations may be misleading, and radiographic studies cannot be utilized as freely because of the potential risks of fetal exposure.

Medications used must be evaluated for safety and must pose little or no risk to the fetus. Understanding the changes in serum proteins and renal clearance will modify drug dosage and timing.

The anatomic changes associated with pregnancy predispose women to certain infections; infection of the urinary tract is the classic example. The renal collecting system tends to dilate secondary to compression by the gravid uterus, aggravated by increased smooth muscle relaxation and subsequent decreased ureteral motility caused by progesterone. Therefore, urinary tract infection is common, and the incidence of pyelonephritis is approximately 1%. Cholecystitis appears to increase because of sluggish motility and increases in gallstone production. The pregnant uterus may impair the clinician's ability to diagnose abdominal processes. The classic example is appendicitis, for which failure to diagnose may be as high as 30% in the third trimester, in part because of the different anatomy and displacement of the appendix superiorly and also the interference of the uterus with the classic peritoneal response.

Classic laboratory values use, to aid in the diagnosis of infection are not as helpful in pregnancy. White blood cell counts, which are routinely elevated in pregnancy, may be 15,000 or more. Erythrocyte sedimentation rates and C-reactive proteins are useless in pregnancy, as they normally increase. Complement levels also increase during gestation; therefore, unless there are baseline values for comparison, they may not be easy to interpret.

The concern over fetal effects of radiation exposure, including poor neurologic development and childhood leukemia, limit the practitioner's arsenal of ancillary studies. Ultrasound and magnetic resonance imaging appear to be safe, but X-rays and computed tomographic (CT) scanning pose some degree of fetal risk and therefore should be utilized only if the benefit clearly exceeds the risk. However, the clinician must be aware of the limitations of various imaging modalities, particularly with respect to the interference of the pregnant uterus, and utilize the safest, yet best, available test to avoid an untimely delay in the workup and management of an infectious process.

In most cases, management of a serious infectious process should not be altered greatly by the pregnant condition. Deviations from routine treatment rarely benefit the fetus and may be more deleterious to the pregnant woman. The classic example of this is appendicitis, where there is a known delay of recognition in the latter part of gestation and consequently an increase in both maternal and perinatal mortality. Prompt surgical treatment is curative, usually without any subsequent effect on the fetus. However, there is the continued reticence of practitioners to perform needed surgical procedures because of the concern over subsequent pregnancy loss or preterm labor, when, in actuality, the converse is more likely.

Medications must be chosen to avoid potential fetal harm. Tetracyclines, quinolones, and chloramphenicol are contraindicated in pregnancy. Aminoglycosides carry the potential of ototoxicity in the fetus but are used commonly in the treatment of pyelonephritis and chorioamnionitis. Sulfonamides may be used in the second and early third trimester but are best avoided during the period of neural tube development in the period when the neural tube is forming and in the late third trimester where there is potential of bilirubin displacement during the neonatal period. With few exceptions, corticosteroids do not cross the placental barrier but may increase the risk of premature rupture of membranes. The clinician must be aware of the teratogenic potential of medications and select the most appropriate agent with respect to the parturient's clinical condition, weighing the risks and benefits.

Medication dosages may need to be altered due to the physiologic changes of pregnancy. Glomerular filtration rate increases by 50%, which increases clearance of renally excreted drugs. Plasma proteins that bind many agents and therefore diminish the amount of free drug are decreased during gestation. Alterations in the normal physiologic state by pathologic processes associated with pregnancy, such as preeclampsia and upper urinary tract obstruction, influence drug clearance. If unrecognized, these pathologic alterations can lead to potentially grave medication errors.

The physician must determine whether a febrile process may affect the uteroplacental unit. In most cases, significant illness leads to some degree of uterine contractions but less often to true labor and delivery. The recognized initiators of labor are usually chorioamnionitis and urinary tract infections. Overt sepsis is often associated with labor and delivery. Conditions that initiate the inflammatory cascade promote release of arachadonic acid and subsequent formation of prostaglandins, leading to increased uterine activity. Maternal dehydration may result in oligohydramnios, usually responsive to reestablishment of a normal circulation volume.

Another concern is the development of direct fetal harm caused by a maternal infection. Most bacterial infections, with the exceptions of syphilis, *Listeria*, and Group B β-hemolytic streptococci, do not commonly cross the placenta in an immunocompetent individual. The bulk of intraamniotic infections are the result of ascending infection from the lower genital tract and are usually associated with either premature membrane rupture or labor. Viral infections commonly can and do cross the placenta. Cytomegalovirus, adenovirus, parvovirus, rubella, and coxsackie are known to access the fetal environment. Fortunately, most such occurrences do not cause harm to the fetus, but on occasion, they will.

Anesthetic Management

Regional Anesthesia

The physiologic changes of pregnancy, the effects of regional anesthesia on uteroplacental perfusion, and the etiology of fever all need to be taken under consideration before neuraxial blocks can be safely induced in febrile parturients. The lack of autoregulation of uterine perfusion, combined with peripheral vasodilation secondary to sympathectomy induced by

regional anesthesia, may at least theoretically compromise the fetal oxygen supply. Supplemental oxygen should be administered with all regional anesthetics provided to this group of parturients. Pregnancy is associated with decreased function of the immune system, and some febrile diseases may take a more severe course in pregnancy leading to transplacental transmission and fetal jeopardy. The source of fever should be identified, and possible fetal implications clearly considered. Upper respiratory or urinary tract infections, for example, are less likely to pose a significant danger to the fetus as compared to human immunodeficiency virus (HIV) infection or chorioamnionitis. The possibility of peripartum transmission affects both the obstetric and anesthetic management of these parturients.

The overall incidence of maternal infection in labor has been estimated as 3.1%.[3] The presence of bacteria in blood samples obtained from parturients seems quite common, and even routine procedures in labor such as insertion of a urinary catheter may result in transient bacteremia. However, the clinical significance of these findings and the anesthetic implications remain unclear. Animal studies have found evidence to suggest that bacteremia may increase the risk of meningitis after subarachnoid block.[4] The extrapolation of this data to humans is questionable, and the importance in clinical practice uncertain.

The complications of epidural, spinal, or combined spinal-epidural anesthesia can result in permanent disability. Kindler et al. reported two cases of an epidural abscess in a series of 4,162 pregnant parturients who received labor epidural analgesia.[5] Hlavin et al. reported an incidence of 0.2 to 1.2 per 10,000 of spontaneous epidural abscess in the general hospital population of patients.[6] Mamourian et al. reported three magnetic resonance imaging(MRI)-confirmed cases of spinal-epidural abscess following spinal epidural injections.[7] Epidural abscess formation was reported in a parturient who received epidural anesthesia for cesarean section.[8] Streptoccocus-induced bacteremia and meningitis after spinal anesthesia have been reported.[9] Three cases of meningitis following increasingly popular spinal-epidural anesthesia have recently been described.[10,11] Review of older literature also documents the association of epidural-spinal abscess formation and neuraxial analgesia-anesthesia.[12] In an editorial article, Chestnut recommended that antibiotic therapy should be initiated before induction of regional anesthesia in febrile parturients in the presence of systemic signs of infection.[13] The majority of epidural-spinal infections appear to be related to surgical procedures or hematogenous spread rather than to regional anesthetic techniques.

In conclusion, the decision to administer regional anesthesia in a febrile parturient should be based on an individual risk-to-benefit ratio, and the anesthetic plan should be tailored on a case-by-case basis. Consideration of available alternatives, such as parenteral analgesia for labor or general anesthesia for operative delivery, is necessary. However, if general anesthesia is selected for a parturient with fever, significant risk factors such as aspiration of gastric contents, neonatal depression, and the potential for a difficult airway do exist.[14] There are no well-established guidelines to aid an anesthesiologist in the use of regional anesthesia for febrile parturients. The history and physical examination aided by the laboratory investigations usually identify the etiology, and careful assessment of intravascular volume status and hemodynamic stability will serve as a guide to appropriate anesthetic selection. Spinal, combined spinal-epidural, or epidural anesthesia may be selected depending upon parturient assessment and the purpose of the regional anesthetic, such as labor analgesia or operative delivery.

Spinal anesthesia can be safely administered for abdominal delivery in the presence of maternal fever. Administration of empirical antibiotic therapy is recommended by most authorities and should be initiated before induction of anesthesia.[13] Interestingly, combined spinal-epidural analgesia has been associated with more rapid cervical dilation compared to conventional labor epidural analgesia.[15] Because prolonged labor is a significant risk factor for maternal fever, combined spinal-epidural analgesia may be associated with less fever compared to conventional epidural labor analgesia. Both conventional lumbar epidural and combined spinal-epidural anesthesia may be safely conducted in febrile parturients for either labor analgesia or cesarean delivery.

Regional Anesthesia and Maternal Temperature Regulation

It has been well established that induction of surgical epidural anesthesia, including that performed in pregnant women undergoing abdominal delivery, causes sympathectomy associated with vasodilation and increased heat loss leading to hypothermia. Hypothermia occurs secondary to redistribution of body heat from the core to the periphery, where it is lost to the environment.[16] However, laboring parturients who receive epidural labor analgesia may in fact experience an increase in body temperature following the induction of epidural block.

In 1989, Fusi et al. compared parturients receiving epidural bupivacaine labor analgesia with those receiving intravenous meperidine.[17] Increased maternal temperature, averaging 0.14°C/h, was reported after induction of epidural analgesia. No increase in maternal temperature was noted following intravenous meperidine administration. Camann et al. studied changes in maternal temperature regulation in 53 laboring women who received either parenteral opioids or epidural analgesia.[18] Oral and tympanic temperature were monitored in each study group. Administration of epidural analgesia did not affect maternal temperature for the first 4 h following induction of the block. However, increasing maternal temperature in the epidural group was noted beginning approximately 5 h after initiation of epidural analgesia. No temperature changes were reported in parturients receiving parenteral opi-

oids for pain in labor. No difference in temperature measurements were reported between parturients receiving epidural local anesthetics only and epidural local anesthetics with opioids. Both Fusi et al. and Camann et al. used higher bupivacaine concentrations than those used currently in obstetric anesthesia practice.[17,18] Similar findings have been reported by other investigators.[19,20] The observed temperature increase in laboring parturients averaged 0.1°C/h of epidural analgesia, usually following a lag of 4 to 5 h. Herbst et al. concluded that, despite other risk factors such as prolonged labor and preterm rupture of membranes, there was an independent association between epidural analgesia and maternal temperature regulation.[21] The mechanism of maternal hyperthermia following induction of epidural analgesia remains unclear. Possible explanations include the cessation of hyperventilation that follows pain relief, increased incidence of shivering, and decreased sweating.[16–18,21]

Glosten et al. evaluated the effect of epidural analgesia on sweating in nonpregnant volunteers.[22] Higher core temperatures were needed to induce sweating in patients who received epidural analgesia. Additionally, decreased sweating was reported below the level of sensory block, probably secondary to blockade of sympathetic nerve fibers. Panzer et al. showed that many parturients do not sweat, even in the presence of fever.[23] Shivering was frequently not related to hypothermia, and sweating was often not triggered by hyperthermia in the studied subjects. Simultaneous sweating and shivering were reported. Kim et al. reported that shivering associated with epidural analgesia was primarily caused by normal physiologic thermoregulatory mechanisms.[24] In contrast, other investigators concluded that shivering was primarily caused by a nonthermogenic mechanism.[25,26]

Possible detrimental effects of maternal fever on the fetus have been a subject of significant controversy. Macaulay et al. recorded intrauterine and fetal scalp temperature in a group of 57 parturients.[27] Increase in the intrauterine temperature was noted in those parturients who received labor epidural analgesia, and 3 of 57 fetuses had scalp temperature exceeding 39°C. Camann et al. concluded that epidural analgesia is unlikely to increase maternal temperature sufficiently to have an adverse effect on the fetus.[18]

Lieberman et al. reported an association between epidural analgesia, maternal fever, and neonatal sepsis evaluation.[19] The study, originally intended to evaluate active management of labor, reported the incidence of fever ranging from 7% to 36% of the parturients receiving epidural analgesia. Fever in a parturient was defined as an increase in body temperature greater than 38°C. Fever was reported in 7% of parturients receiving epidural analgesia with labor duration less than 6 h and increased to 36% of parturients who were in labor longer than 18 h. The incidence of fever in parturients who did not receive epidural analgesia remained approximately 1%, regardless of the duration of labor. The neonatal sepsis evaluation was performed in 34% of neonates born to mothers with increased temperature in the epidural group compared with 9.8% in the nonepidural group. Interestingly, confirmed neonatal sepsis was not different between the two study groups; it occurred in less than 1% of neonates. Unfortunately, the study was not randomized, and the two groups of parturients differed significantly. Additionally, specific criteria for neonatal sepsis evaluations were not precisely established, and more than 63% of the neonatal sepsis evaluations included were performed for reasons other than maternal fever. Nevertheless, logistic regression analysis confirmed the association between epidural analgesia and fever, even after consideration of other variables.

Philip et al. prospectively randomized 613 laboring women to either an epidural or intravenous meperidine analgesia study group.[28] Epidural labor analgesia was independently associated with maternal temperature elevation when compared with intravenous patient-controlled meperidine administration. Neonatal sepsis evaluations were strongly associated with maternal fever.

In summary, although there seems to be enough evidence to support the association between epidural analgesia in labor and maternal temperature elevation, especially after 4 h or more of epidural analgesia,[17–19,21,27,28] most of the studies have not been randomized, suggesting parturient selection bias. There is no evidence that frequency of neonatal sepsis is increased secondary to epidural labor analgesia. In contrast, the association between labor epidural analgesia and neonatal sepsis evaluation is less clear. Many factors other than maternal fever are involved in the decision to initiate such an evaluation. Finally, most randomized studies compared temperature changes in parturients who received epidural analgesia with controlled groups receiving parenteral meperidine.[28] Meperidine selectively decreases the shivering threshold and is widely used as a postoperative treatment to reduce shivering. Therefore, its selection as the control group analgesia remains questionable, and further investigations are needed.

General Anesthesia

Although regional anesthesia is the generally preferred and potentially safer method for cesarean delivery in a febrile parturient, general anesthesia may be necessary for selected parturients. Uncertainty of fetal well-being in the presence of infection and fever, the possible legal implications of delayed delivery, and concerns of appropriate labor analgesia technique may create some urgency and lead to abdominal delivery. It is believed that laboring parturients with fever seem more likely than nonfebrile parturients to receive general anesthesia.

When time is of essence, general anesthesia offers speed of induction, reliability, and avoidance of sympathectomy-induced hypotension. Late septic shock, for instance, is usually associated with low cardiac output, significant fluid losses, and hypotension, a combination that precludes the administration of regional anesthesia. If general anesthesia is se-

lected for a febrile parturient, significant risk factors such as aspiration of gastric contents, neonatal depression, and potential for a difficult airway should also be taken under consideration. Maternal mortality rate remains 16 times higher in parturients who undergo abdominal delivery under general anesthesia as compared to those who receive regional anesthesia. Despite technical advances in airway equipment and fiberoptic bronchoscopy, complications of airway management still remain a primary cause of anesthesia-related morbidity and mortality.[14]

Careful preanesthetic evaluation should include the cause and duration of fever as well as obstetric indications, urgency, and planned mode of delivery. Upper respiratory tract infections may increase airway irritability and result in increased bronchial and oropharyngeal secretions. Fever increases maternal oxygen consumption and may compromise transplacental oxygen delivery to the fetus. Therefore, adequate preoxygenation with 100% O_2 before induction of general anesthesia is very important to optimize maternal and fetal oxygen saturation.[29] Aspiration prophylaxis and correction of other physiologic abnormalities are necessary. The need to proceed with emergency delivery should be weighed against the need for insertion of appropriate monitoring devices and resuscitation efforts aimed at the optimal maternal condition for delivery.

Maternal hemodynamic stability and maintenance of uteroplacental blood flow should determine the choice of anesthetic agents for induction and maintenance of general anesthesia in febrile parturients. Prolonged anesthetic induction should be avoided to prevent neonatal depression at delivery.[30] Although rapid sequence induction with cricoid pressure and intravenous administration of sodium thiopental or propofol and succinylcholine is the standard technique, induction agents that tend to support the cardiovascular system, such as etomidate or ketamine, should be considered. Sodium pentothal and propofol may depress myocardial contractility in critically ill parturients; thus, some advocate use of etomidate in these parturients. Use of ketamine has been recommended, although its hemodynamic response may be unpredictable in critically ill patients with depleted catecholamine stores.[31]

Hyperkalemia following the use of succinylcholine may be a problem in febrile patients, especially those with prolonged sepsis.[32] Therefore, it appears important to correct fluid and electrolyte abnormalities before anesthesia is induced and to avoid succinylcholine in parturients with hyperkalemia. Rocuronium offers fast onset and intermediate duration and is often used for induction of general anesthesia in pregnancy. Drug interactions that occur between muscle relaxants and antibiotics should be anticipated, and appropriate dose adjustment undertaken to prevent prolonged muscle paralysis. Monitoring of the neuromuscular junction is mandatory.

Although regional anesthesia is the preferred method for cesarean delivery, general anesthesia remains an option for selected parturients with infection and fever. It offers rapid onset of induction, reliability, and predictability necessary in emergency situations. However, despite technical advances in airway management, the consequences of failed intubation or aspiration of gastric contents may be catastrophic.[14]

Infections Specific to Pregnancy

Chorioamnionitis

Intraamniotic infection is the most common antepartum and intrapartum infection seen in labor and delivery suites, occurring in up to 10% of pregnancies.[33] It is usually caused by an ascending infection from the lower genital tract; however, certain agents may seed the uterus by the hematogenous route. Symptoms and signs include fever, uterine tenderness, and fetal tachycardia. The fetal heart rate elevation invariably exceeds what one would expect from fever alone. Other findings may include a malodorous amniotic fluid and elevated white cell count. Invasive testing via amniocentesis may aid in diagnosis when the clinical situation is confusing. The gold standard antenatal test is the amniotic fluid culture, but gram stain, white cell count, and glucose concentrations produce more immediate results, albeit with less sensitivity. Placental pathology imparts a definitive diagnosis. Unfortunately, there are limitations to making a diagnosis antenatally, as well as discrepancies between the intrapartum assessment and the final placental pathology.

The infection is usually polymicrobial in origin. Samples of amniotic fluid may contain isolates of *Bacteroides* species and gram-negative enteric Group B and other streptococci. These organisms ascend from the colonized vagina, usually when the membranes are ruptured. However, chorioamnionitis occurs in the absence of amniorrhexis. In these cases, bacteria such as Group B streptococci and gram-positive anaerobes migrate across the amniochorionic membrane, likely because of the production of extracellular products such as lipases and collagenases. Direct hematogenous infection with *Listeria monocytogenes* and *Treponema pallidum* occur, albeit rarely.

Two clinical scenarios are commonly associated with chorioamnionitis. Although their presentation differs in some respects, the diagnosis and management are similar. The first situation is premature rupture of membranes (PROM). Membranes rupture when the parturient is in labor; however, approximately 8% of parturients at term and about 4% preterm parturients have PROM. Of parturients with term PROM, 95% will be delivered by 28 h.[34] If membranes rupture before term, the concern is the development of chorioamnionitis, not only because of the prolonged latency period associated with preterm PROM but also because approximately 26% of parturients with PROM have amniotic fluid colonization on admission to the hospital.[35]

The management of term PROM is fairly straightforward, with some minor differences depending on the institution. Usually the parturient is allowed to labor spontaneously

within some arbitrary time frame. If labor has not ensued, induction will be initiated to reduce the potential of chorioamnionitis. Preterm PROM is more conservatively managed. The risks of prematurity are weighed against the risks of conservative management (chorioamnionitis, abruptio placentae, umbilical cord prolapse). Administration of steroids to enhance pulmonary maturity and antibiotics to prolong the latency period is routine. Delivery occurs when the parturient goes into spontaneous labor, develops signs of fetal compromise, or develops chorioamnionitis. The latter may be difficult to detect in that the early clues are subtle and difficult to rely on, particularly in the extremely premature gestation. Therefore, amniocentesis may be used to assess the amniotic fluid. If chorioamnionitis is diagnosed, the parturient usually is in labor. However, if she is not, induction is necessary to protect the mother from overwhelming infection, as well as to minimize the risks of fetal infection. Although there is no absolute time frame in which delivery must occur, clinical judgment is important in the parturient extremely remote from delivery. In those cases, cesarean section may be necessary. Antibiotics are initiated upon diagnosis and should not be withheld for any reason.

The second scenario, more commonly noted in labor and delivery, is the presentation of chorioamnionitis in the course of term labor. The clinical diagnosis requires either a fever (>38°C) or rupture of membranes plus two of the following: white blood cell count (WBC) greater than 15,000, fetal tachycardia, maternal tachycardia, uterine tenderness, or a malodorous amniotic fluid. Risks for this situation include prolonged labor, preexisting lower genital tract pathogens, multiple vaginal examinations, or intrauterine manipulations. Management includes the use of broad-spectrum antibiotics covering the common gram-negative enteric bacteria and streptococci. There is no reason to delay initiating antibiotics, because the risks of neonatal sepsis are higher in the untreated mother.[36,37]

Anesthetic Management

There is no evidence that neuraxial blocks are contraindicated in a febrile parturient with intraamniotic infection. Because most obstetricians administer parenteral antibiotics once the diagnosis of chorioamnionitis is established, it is justified to delay labor analgesia until after the parturient has received antibiotics.[38] However, administration of regional anesthesia before antibiotic therapy in parturients with clinical symptoms of chorioamnionitis and proven bacteremia has not been shown to be deleterious.[39,40]

Herpes Simplex Virus

Management of pregnancies complicated by maternal herpes simplex virus (HSV) remains a frustrating dilemma for the obstetrician. Although the rate of vertical transmission remains low, the sequelae of neonatal infection may be devastating. There are two main types of HSV: HSV-1 is mainly associated with nongenital lesions and is usually acquired in childhood, whereas HSV-2 is associated with the classic genital lesions and is usually acquired in the late teens and early twenties. Both types can infect the neonate. Approximately 5% of women of childbearing age have a history of genital herpes, and approximately 30% have antibodies to HSV-2.[41] The clinical designation of HSV infection includes primary, antibodies are absent at the time the parturient acquires genital HSV, and recurrent, in which the parturient is antibody positive from prior genital outbreaks.[42] In nonprimary first-episode HSV, antibodies are present at the time the parturient acquires genital HSV, and thought to be associated with cross-reactivity of the anti-HSV-1 and anti-HSV-2 antibodies, thus conferring some degree of partial protection. The importance of this differentiation is due to the degree of risk of neonatal transmission, which approaches 50% in primary HSV compared to 0.3% in recurrent HSV. Approximately 2000 newborns contract herpes each year, most of whom are born to women who are asymptomatic and without visible lesions.[43] Infected neonates may be asymptomatic, have localized involvement (central nervous system, eyes, skin, or mucosa), or be systemically affected. Transmission is usually through shedding of the virus from the cervix and lower genital tract and occurs during labor or prolonged rupture of membranes. The virus rarely crosses the placenta or intact membranes. The major risk is delivery during a primary episode of HSV, likely because of the lack of protective antibodies in the maternal serum and therefore passive immunity in the neonate. The risk is less with a recurrent infection, but rarely, infection does occur with asymptomatic shedding.[44]

Management of the parturient with a history of HSV requires the understanding of the limitations of the health care provider to accurately predict which individual may be asymptomatically shedding. Conversely, the overall incidence of neonatal infection is low. Current recommendations include the performance of cesarean section if the parturient has an active lesion at the time of labor. Even though silent shedding may cause infection, there is no role for outright cesarean section in all pregnant women known to have HSV.[42] Controversy exists in the case of a parturient with preterm PROM in whom there is a dilemma of ascending infection in an otherwise early fetus with potential consequences of morbidity and mortality if the fetus is delivered. The use of antiviral agents to reduce the recurrences of lesions, while effective in the nonpregnant woman, is somewhat controversial during gestation.

Anesthetic Management

Several issues need to be considered before regional anesthesia can be safely conducted in these parturients. Differentiation between the primary and secondary infection is of clinical significance and may influence the decision regarding

obstetric management and anesthetic practice. However, clinical differentiation often proves very difficult.[46] The issue of concern to an obstetric anesthesiologist is possible introduction of the virus into the central nervous system and the possibility of a disseminated disease. Although highly theoretical, such concerns seem more likely in primary infections with transient viral presence in the systemic circulation.

In primary infection, there is a transient viremia followed by permanent antibody production 4 to 6 weeks later. Clinical symptoms such as fever, myalgia, and headache might be present, although 30% of these parturients are asymptomatic, which further clouds the decision-making process.[47] The coexistence of typical genital lesions with systemic symptoms usually suggests a primary infection. When a primary infection is acquired in the peripartum period, the risk of neonatal transmission is very high.[48] The safety of neuraxial blocks in primary HSV has not been established. Therefore, the potential adverse effects of general anesthesia should be carefully weighed against the risk of introducing virus to the central nervous system during regional anesthesia.

Anesthetic management of parturients with recurrent HSV type 2 infection seems well established. Viremia is rarely present in these parturients, and several investigators have documented the safety of regional anesthesia.[49–51] The presence of an active lesion at the site of needle insertion would preclude regional anesthesia. Otherwise, spinal, combined spinal-epidural, and epidural blocks may be selected depending on an individual parturients needs and the anesthesiologist's preference.

Epidural anesthesia utilizing opioids, particularly morphine, has been suspected of reactivating the HSV-1 lesions in thoracic and perioral locations.[52,53] Similar findings have been reported with intrathecal opioids.[54] The pathophysiology of this reactivation remains obscure, although pruritis and scratching as well as the activation of the fifth cranial nerve nucleus by opiate binding have all been postulated.[55,56] These findings, however, remain controversial, and not all investigators have documented such an association.[57] It is interesting to note that no association has been reported between neuraxial administration of opioids and increased recurrence of HSV-2 infections.

Infections Not Specific to Pregnancy

Bacterial Infections

The most common bacterial infections in pregnancy include urinary tract infections, chorioamnionitis, respiratory tract infections, and postpartum endometritis. Systemic bacterial illness, irrespective of its origin, may lead to serious consequences for the mother and her developing fetus. The incidence of maternal bacterial infection during labor in obstetric anesthetic practice is 3.1%.[3] Septicemia is reported in 0.07% of pregnancies. The most common etiology is due to gram-negative organisms (95%); the remaining are caused by gram-positive and other bacteria.[58]

Urinary Tract Infection

Asymptomatic bactinuria is commonplace in pregnancy, occurring in approximately 10% of women. Urinary tract infections are an important cause of preterm uterine contractions. All parturients should be screened for bactinuria at their first prenatal visit as well as on any presentation for suspected preterm labor. Asymptomatic parturients with more than 100,000 colonies/mL have a risk of acute infection of about 25%. The potential of covert infection may be significant; there is an association with low birth weight and prematurity.[59] Pyelonephritis is likely the most common nonobstetric bacterial infection in pregnancy, with an incidence of 1% to 2% of gestations. The monetary cost is significant, because the majority of such parturients are admitted to the hospital. In contrast to a nonpregnant patient, the sequelae of pyelonephritis are potentially morbid to the mother and her fetus. Bacteremia and sepsis are more common, as is urosepsis, with adult respiratory distress syndrome occurring in 1% to 2% of parturients with pyelonephritis. The predisposing risk factors are the increased rate of asymptomatic bactinuria and the increased stasis of the upper urinary tract due to mild obstruction by the uterus and decreased ureteral motility.

Symptoms include fever, chills, and back or flank pain. Anorexia, nausea, and vomiting may complicate the clinical picture and lead to confusion over the possibility of a viral illness or appendicitis. A spiking fever is common, consistent with a deep soft tissue infection. The physical examination reveals tenderness in the costovertebral area, right usually more so than left, because of the dextrorotation of the uterus. The chest examination may reveal some adventitial sounds in those with pulmonary edema. The WBC may not reflect the degree of illness. The urine usually contains bacteria, white cells, and leukocyte esterase. Culture of the urine, in most parturients, will exhibit gram-negative coliforms, streptococci, or enterococci. Parturients with complicated urinary tract infections, such as those with coexistent urinary calculi, may have atypical bacteria. Blood cultures should be performed in the case of high fevers. A mild degree of renal dysfunction may be noted on serum chemistries. Uterine tocodynamometry will reveal irritability or uterine contractions. The fetal heart rate is elevated in response to the maternal fever and returns to a normal baseline when the fever abates.

Treatment includes hydration, as these parturients are usually hemoconcentrated. Antibiotics are selected to treat gram-negative bacteria empirically. Usually an aminoglycoside is chosen, and its dosage must be adjusted carefully to avoid renal toxicity and ototoxicity. Once the culture and sensitivity results are available, a 7-day course of antibiotics, with a proven safety record in pregnancy should be used. Urologic consultation may be necessary if the infection is complicated

by a stone or by an obstruction, and imaging with an ultrasound or intravenous pyelogram may be required.

Anesthetic Management

Hemodynamic alterations may be present in a parturient with acute pyelonephritis even in the absence of overt sepsis. Ultrasonographic studies have documented decreased mean arterial pressure and systemic vascular resistance associated with increased heart rate and cardiac output in infected febrile parturients.[60] Most parturients with pyelonephritis are dehydrated secondary to fever, vomiting, and anorexia.[61] These changes as well as possible electrolyte imbalances should be considered and corrected before the administration of anesthesia. Aspiration prophylaxis is of utmost significance and antibiotic therapy is indicated before a regional block. There is no evidence that regional anesthesia is detrimental in parturients with a urinary tract infection and spinal and combined spinal and epidural anesthesia may be safely performed.

Pneumonia

Community-acquired pneumonia is still a potentially serious illness; it is the sixth leading cause of death in the general population and the number one cause of death from infectious diseases.[62] Approximately 66% of cases of pneumonia in pregnancy are bacterial in origin, the same as for nonpregnant patients. Mortality may be as high as 25% if hospitalization is required. Fortunately, these figures do not take into consideration the fact that most pregnant women are otherwise healthy, but maternal deaths do occur. The etiologies in pregnancy are no different than the nonpregnant state. *Streptococcus pneumoniae* is the most common bacterial pathogen isolated, but species of *Mycoplasma* and *Haemophilus* have also been implicated. Viral agents such as influenza and varicella can cause pneumonia. Typical symptoms include productive cough, fever, chest pain, and dyspnea. Chest X-ray is mandatory to aid in the diagnosis and should not be deferred because of potential fetal concerns. Treatment should not be altered. Consequences of intubation (25%), empyema, pneumothorax, pericardial tamponade (~30%), and even death (~6%) do occur.[63,64] Treatment is supportive, with oxygen and antibiotics. Ongoing assessment of therapy is important, as the pregnant woman will appear better than she actually is, and chest X-rays may not reflect the severity as the findings tend to lag behind the clinical course. Fetal concerns of hypoxia are in most cases not an issue, as the fetal venous Po_2 is reflective of the maternal venous Po_2. Key points of prevention include pneumococcal vaccination for at risk women and influenza vaccination for all pregnant women in the second and third trimester.

Anesthetic Management

The physiologic changes of pregnancy, such as decreased functional residual capacity, increased oxygen consumption, capillary engorgement, hypersecretion of respiratory tract mucosa, and decreased cellular immunity, can predispose to the development of pneumonia. A chest radiograph should confirm the diagnosis. The parturient with pneumonia is susceptible to the development of pulmonary edema.[65] Appropriate oxygen administration should maintain Sao_2 above 95% and Pao_2 above 70 to 80 mm Hg. Administration of epidural anesthesia may attenuate the increased oxygen consumption during labor in these parturients.[66] Ideally, intravenous antibiotics should be administered before induction of regional anesthesia. When general anesthesia is selected for obstetric emergencies, increased airway reactivity, increased mucociliary secretions, and other physiologic changes of pregnancy should be taken under consideration in the preanesthetic evaluation of these parturients.

Septic Shock

Although rare, septic shock can be a complication in most infectious diseases in pregnancy. It has been reported with chorioamnionitis, endometritis, and pyelonephritis most commonly but also has been reported with pneumonia, appendicitis, toxic shock syndrome, septic pelvic thrombophlebitis, septic abortion, and endocarditis.[67] Mortality in pregnancy is lower (~3%) than in the nonpregnant state (40%–90%), again reflecting the underlying healthy state of the gravida and the absence of complicating processes associated with aging.[68,69]

The pathogenesis includes the release of endotoxin, a lipopolysaccharide that is released when the cell wall of gram-negative bacteria is disrupted. Exotoxins that are produced by gram-positive bacteria such as *Staphylococcus* will also mediate hemodynamic alterations. The signs of septic shock include alterations of temperature including both hypothermia and hyperthermia. In early shock, otherwise known as the warm phase, temperature is elevated, usually with shaking chills. Tachycardia with a normal to low blood pressure is usually seen. Systemic perfusion appears normal because of the warm extremities, but centrally there is hypoperfusion. Behavioral changes may be manifested because of a reduction in cerebral blood flow. The parturient may have nausea, vomiting, and tachypnea. Shortness of breath is thought to be caused by the direct effect of endotoxin on the central nervous respiratory center or, later, through direct pulmonary injury preceding the development of adult respiratory distress syndrome. Laboratory findings are variable. The WBC may initially be depressed, followed by leukocytosis. Serum glucose is usually elevated in the early phase but falls if there is hepatic dysfunction. Disseminated intravascular coagulation, as evidenced by decreases in platelet count and fibrinogen with elevations in partial thrombroplastin time (PTT), prothrombin time (PT), and fibrin split products, is common.

In the cold phase of shock, there is marked hypotension and hypoperfusion. The parturient has systemic vasoconstriction and clinically cold extremities, oliguria, metabolic acidosis, and electrolyte disturbances. Disseminated intravascular coagulation is profound. Finally, end-organ failure and subsequent cardiovascular collapse are the preterminal events.

Management should have the following aims:

1. Reestablishing a normal circulating vascular volume
2. Determining the site of the septic focus
3. Initiating broad-spectrum antibiotics to eradicate the most likely pathogens
4. Protecting against end-organ damage

The mainstay of initial management is volume expansion to maintain adequate tissue perfusion and oxygen delivery. The problem, however, is one of increased capillary permeability and extravasation of fluid into the extravascular space. Therefore, if fluid balance is in question, a Swan–Ganz catheter may be necessary. If fluid resuscitation is not corrective, inotropic support is indicated. Unfortunately, most agents may actually decrease uterine blood flow, and fetal compromise may occur. Fetal monitoring is needed to ensure appropriate uteroplacental perfusion.

Determining the source of infection is usually straightforward, as most cases are associated with uterine infection or pyelonephritis. In the absence of either cause the workup is more difficult. Cultures of blood, urine, sputum, and amniotic fluid should be obtained quickly, and broad-spectrum antibiotics initiated. Assessment of end-organ disease includes a chest X-ray, serum chemistries including electrolytes, blood urea nitrogen (BUN) and creatinine, liver function tests, and coagulation studies. A Foley catheter should be placed to ensure adequate urine output. Ancillary studies to further evaluate the infectious source may be necessary, including a CT scan of the abdomen, an echocardiogram, and a lumbar puncture. Eradication of the source of infection may occur with antibiotics alone. However, delivery is indicated for chorioamnionitis. If a deep-seeded infection of the uterus occurs that is unresponsive to antibiotics, hysterectomy should be considered.

Anesthetic Management

Invasive monitoring modalities such as arterial line, central venous line, or pulmonary artery catheter are indicated to guide volume expansion, inotropic support, and choice of vasopressors. The need for emergency delivery must be weighed against the need for insertion of appropriate monitoring devices and for resuscitation efforts to provide the optimal maternal condition for delivery. Because hypovolemia is common, regional anesthesia for cesarean section may be contraindicated and general anesthesia selected. If coagulopathy is absent, appropriate antibiotic therapy administered, and volume replacement deemed adequate, a slowly titrated epidural anesthetic may be considered for a very few select parturients.

Viral Infections

Viruses most commonly encountered in parturients include HIV, hepatitis viruses, HSV, influenza virus, cytomegalovirus, and papillomavirus. Febrile diseases caused by measles, rubella, and chickenpox viruses may also appear during pregnancy.

Human Immunodeficiency Virus

The incidence of acquired immunodeficiency syndrome (AIDS) has grown from negligible numbers in 1980 to a cumulative total of 8.4 million cases reported by the World Health Organization as of 1997.[70] In the United States, women have been identified as the fastest growing group of new AIDS patients.[71] Pregnant women are not excluded from contracting this disease; women of childbearing age constitute a large percentage of the new cases.[72] Identification of the pregnant woman with HIV infection is of significant importance to all involved in her care. Unfortunately, few physicians inquire about the possibility of HIV infection when interviewing their patients.[73]

Can neuraxial anesthesia be safely performed in the parturient who is HIV positive? This question has become a controversial issue in obstetric anesthesia.[74] The issue involving the safety of neuraxial blocks in HIV-infected parturients began when it was suggested that the introduction of a spinal needle into the subarachnoid space would spread the disease into the central nervous system.[75] It is now well established that HIV infection does not contraindicate the administration of regional anesthesia.[74,76] HIV is a neurotropic virus, and central nervous system infection takes place early in the course of the disease process.[74,76,77] Neurotropic predisposition of an HIV virus is responsible for symptoms of neurologic dysfunction manifested clinically at the time of initial AIDS diagnosis in up to 40% of infected patients.[77] Regional anesthetic techniques will not accelerate HIV progression to the central nervous system.[74,76]

The HIV-positive parturient, irrespective of her clinical condition, meets the criteria for AIDS by definition when her CD4+ T-cell count drops below 200 cells/μL.[78] A high maternal viral load increases the likelihood of perinatal transmission of HIV.[79,80] Clinical evidence suggests that most perinatal HIV transmissions occur during labor and delivery.[81,82] Kind et al. studied the effect of elective cesarean section and zidovudine prophylaxis on vertical HIV transmission and concluded that elective cesarean section and zidovudine prophylaxis appear to have an additive effect in the prevention of vertical HIV transmission.[83] Because of these recent findings, many HIV-positive women are being advised to undergo elective cesarean section.

Anesthetic Management

HIV is a neurotropic virus with low infectivity. Central nervous system invasion occurs in early stages of the primary infection. Therefore, neuraxial anesthetic techniques may be safely used in many HIV-infected parturients for labor analgesia and cesarean section. Anesthetic management of abdominal delivery must be tailored for individual obstetric indications, the urgency of the delivery, and the presence of

coexisting disease. HIV seropositivity alone, however, should not determine the preferred method of anesthesia. A significant number of HIV-infected women have a past medical/social history that has in some way contributed to infection with HIV. Substance abuse (intravenous drug abuse in particular) remains a significant risk factor and may have anesthetic implications. The coexistence of other sexually transmitted and needle-transmitted diseases such as hepatitis B and syphilis should also be taken into consideration when developing an anesthetic plan. Careful physical examination and documentation of neurologic deficits should therefore be undertaken before induction of regional anesthesia.

Involvement of the respiratory system with oropharyngeal and esophageal pathology may make these parturients more prone to regurgitation, difficult intubation, and aspiration. Opportunistic pulmonary infections may necessitate prolonged mechanical ventilation in the postoperative period. Examination of the cardiovascular system (subclinical cardiomyopathy), renal system (nephropathy), and hematologic studies (neutropenia, thrombocytopenia) are indicated as part of the preanesthetic assessment in patients with advanced disease. Patients with AIDS may exhibit electrolyte disturbances such as hyponatremia that may be caused by adrenal infection with cytomegalovirus or mycobacteria. If severe, these should be corrected before anesthesia is induced. Although thrombocytopenia may occur in the HIV-positive patient, it is rare for the platelet count to be low enough to affect the anesthetic choice. If, however, the platelet count falls below 50,000, the risk of bleeding and epidural hematoma increase. Alternative choices of anesthetic technique, such as spinal or general anesthesia, should be considered on an individual basis.

Treatment of complications of neuraxial anesthesia, including management of postdural puncture headache, should not differ from the management used in HIV-negative parturients. Specifically, should postdural puncture headache occur, an epidural blood patch with autologous blood is safe and effective in HIV-seropositive patients.[84]

If general anesthesia is selected, dose adjustments may be necessary for parturients with a history of drug abuse, compromised hepatic and renal function, or generalized muscle wasting. Additionally, HIV-related pulmonary pathology may necessitate a higher fraction of inspired oxygen concentration intraoperatively. Increased sensitivity to opioids and benzodiazepines may occur, particularly in patients with HIV-associated mental changes. Concerns have also been raised that potent volatile agents may significantly depress the immune system in HIV-infected patients.[85]

The risk of occupational exposure to infected blood and body fluids should be considered by all involved in the parturient's care. Necessary safety measures (universal/standard precautions) must be employed when handling blood, blood products, body fluids, and tissue of all parturients, not just those known to be HIV positive. There is a "window period" between the primary HIV infection and seroconversion during which the diagnosis can be delayed; however, viral transmission can occur. The use of gloves prevents 98% of an anesthesiologist's contact with the parturient's blood and body fluids.[86,87] The risk of HIV transmission from a needle-stick injury with HIV-infected blood is approximately 0.32%.[88] In summary, there seems to be enough evidence to support the statement that most febrile parturients with HIV infection and AIDS can safely receive regional anesthesia.[74]

Hepatitis

Viral hepatitis results from infection by a spectrum of viruses that may vary in the mode of transmission and clinical expression. Hepatitis viruses A, B, C, D, and E have been identified. Additionally, viruses such as Epstein–Barr virus and cytomegalovirus may affect the hepatic system. The onset of the disease may be gradual or fulminant. The incubation period and seroconversion may vary from 2 to 24 weeks. Clinical symptomatology may include fever, anorexia, fatigue, nausea, vomiting, and abdominal discomfort and jaundice. Not surprisingly, some of these symptoms might receive insufficient attention because their occurrence in normal pregnancy is quite common.[90]

Anesthetic Management

Although mild hepatitis does not significantly alter anesthetic management or pregnancy outcome, careful preanesthetic evaluation should determine the degree of hepatic impairment. Laboratory evaluation should include serum electrolytes, creatinine, BUN, bilirubin, transaminases, alkaline phosphatase, albumin, and PT. Whenever possible, maternal serum should be checked for hepatitis B surface antigen (HBsAg). If a pregnant woman with acute viral hepatitis must undergo an emergency delivery, prompt correction of electrolyte abnormalities and dehydration is recommended. Fresh-frozen plasma may be necessary to correct a coagulopathy.

If general anesthesia is selected, anesthetic agents with known extrahepatic metabolism are recommended. Standard (for normal pregnancy) doses of intravenous induction agents are generally used, because their action is terminated by redistribution rather than metabolism or excretion. Isoflurane remains the volatile agent of choice because it has the least effect on hepatic blood flow. Factors such as hypotension, excessive sympathetic stimulation, and high airway pressure should be avoided, as they are well-known causes of reduced hepatic blood flow. Regional anesthesia may be safely employed in febrile parturients with viral hepatitis provided platelet abnormalities are absent, coagulation studies remain normal, and hypotension is avoided.

The risk of vertical transmission of hepatitis C is significantly increased during the peripartum period.[91] Therefore, universal safety precautions are recommended when handling blood and body fluids from these patients at delivery. As a history of intravenous drug abuse and coexisting HIV infection are common, combative behavior, abnormalities in endorphin

levels, and altered pain perception may be encountered when regional anesthesia is selected for these parturients.[92]

Malignant Hyperthermia

Malignant hyperthermia (MH) rarely presents during pregnancy.[93,94] It occurs in 1/15,000 to 1/100,000 anesthetics depending upon age, gender, and the regional population gene pool. MH is a genetic disorder that results in a massive increase in skeletal muscle metabolism after exposure to certain triggering agents such as succinylcholine or inhaled agents. The inherited defect is in the regulation of intramuscular calcium. The clinical picture includes rapid increase in temperature, tachycardia, hypercarbia, hyperkalemia, myoglobinuria, metabolic acidosis, renal failure, cardiac arrhythmias, and death. In addition to cooling measures and symptomatic treatment, dantrolene is the primary treatment for an MH crisis. Its early use during MH crisis has reduced the mortality from nearly 80% to approximately 4%.[95] The diagnosis is suspected when the clinical constellation occurs in the presence of a markedly elevated creatine phosphokinase level and is confirmed by muscle biopsy. Anesthesia for the known MH-susceptible patients requires avoidance of triggering agents, use of an anesthesia machine free of volatile agents, and advance preparation for treatment should a crisis occur.

Anesthetic Management

The presence of fever associated with general anesthesia during pregnancy does not always indicate an infectious process. MH is a rare but possible cause of hyperpyrexia, tachycardia, and other symptoms that might suggest infection in the parturient after induction of general anesthesia. The differential diagnosis should include sepsis, pheochromocytoma, and thyroid storm. Muscle rigidity associated with succinylcholine administration is suggestive of uncontrolled skeletal muscle metabolism and may lead to the diagnosis, as this occurs in greater than 50% of the cases. All reported cases of MH during pregnancy occurred during administration of general anesthesia.[96] Administration of regional anesthesia appears safe for the MH-susceptible parturient. Local anesthetics, opioids, epinephrine, and vasopressors such as ephedrine and phenylephrine may be safely administered.[97] The volatile inhalation agents and succinylcholine are proven trigger agents and must be avoided. Oxytocin is considered safe in MH patients. Routine prophylactic administration of dantrolene is not recommended.[94]

Summary

The febrile parturient poses a challenge for the obstetrician and anesthesiologist. The source and treatment, if neccessary, of the fever and the timing and permissibility of regional anesthetic techniques are important considerations discussed in this chapter. The association of epidural analgesia during labor and increased maternal temperature is also discussed here.

References

1. Petersdorf RG. Hypothermia and hyperthermia. In: Wilson JD, Braunwald E, Isselbacher KJ, et al (eds) Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991:2184–2200.
2. Root RK, Petersdorf RG. Chills and fever. In: Wilson JD, Braunwald E, Isselbacher KJ, et al (eds) Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991:125–133.
3. Ducloy AS, Buy E, Ducloy JC, et al. Prediction of maternal infection before performing epidural analgesia in labor. Anesthesiology 1993;100: A192.
4. Carp H, Bailey S. The association between meningitis and dural puncture in bacteremic rats. Anesthesiology 1992;76:739–742.
5. Kindler C, Seeberger M, Siegemund M, et al. Extradural abscess complicating lumbar extradural anaesthesia and analgesia in an obstetric population. Acta Anaesthesiol Scand 1996;64:537–541.
6. Hlavin ML, Kaminski HJ, Ross JS, et al. Spinal epidural abscess: a ten-year perspective. Neurosurgery (Baltim) 1990;27:177–184.
7. Mamourian AC, Dickman CA, Drayer BP, et al. Spinal epidural abscess: three cases following spinal epidural injection demonstrated with magnetic resonance imaging. Anesthesiology 1993;78:204–207.
8. Ngan Kee WD, Jones MR, Thomas P, et al. Extradural abscess complicating extradural anaesthesia for cesarean section. Br J Anaesth 1992; 69:647–652.
9. Blackmore TK, Morely HR, Gordon DL. *Streptococcus mitis*-induced bacteremia and meningitis after spinal anesthesia. Anesthesiology 1993; 78:592–594.
10. Cascio M, Heath G. Meningitis following a combined spinal-epidural technique in a labouring term parturient. Can J Anaesth 1996;43:399–402.
11. Harding SA, Collins RE, Morgan BM. Meningitis after combined spinal-extradural anaesthesia in obstetrics. Br J Anaesth 1994;73:545–547.
12. Baker AS, Olejmann RG, Swartz MN, et al. Spinal-epidural abscess. N Engl J Med 1975;293:463–468.
13. Chestnut DH. Spinal anesthesia in a febrile patient [editorial]. Anesthesiology 1992;76:667–669.
14. Hawkins JL, Koonin LM, Palmer SK, et al. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
15. Tsen L, Thue B, Datta S, et al. Is combined spinal-epidural analgesia associated with more rapid cervical dilation in nulliparous patients as compared with conventional epidural analgesia? Anesthesiology 1999;91:920–925.
16. Hynson JM, Sessler DI, Glosten B, et al. Thermal balance and tremor patterns during epidural anesthesia. Anesthesiology 1991;74:680–690.
17. Fusi L, Maresh MJA, Steer PJ, et al. Maternal pyrexia associated with the use of epidural analgesia in labor. Lancet 1989;3:1250–1252.
18. Camann WR, Hortvet LA, Hughes N, et al. Maternal temperature regulation during extradural analgesia for labour. Br J Anaesth 1991;67: 565–568.
19. Lieberman E, Lang JM, Frigoletto F, et al. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. Pediatrics 1997;99:415–419.
20. Mayer DC, Cherscheir NC, Spielman FJ. Increased intrapartum antibiotic administration associated with epidural analgesia in labor. Am J Perinatol 1997;14:83–86.
21. Herbst A, Wolner-Hanssen P, Ingaemarsson I. Maternal fever in term labour in relation to fetal tachycardia, cord artery acidaemia and neonatal infection. Br J Obstet Gynaecol 1997;104:363–366.
22. Glosten B, Savage M, Rooke G, et al. Epidural anesthesia and the thermoregulatory responses to hyperthermia: preliminary observations in volunteer subjects. Acta Anaesthesiol Scand 1998;42:442–446.

23. Panzer O, Ghazanfari N, Sessler D, et al. Shivering and shivering-like tremor during labor with and without epidural analgesia. Anesthesiology 1999;90:1609–1616.
24. Kim J, Ikeda T, Sessler D. Epidural anesthesia reduces the gain and maximum intensity of shivering. Anesthesiology 1998;88:851–857.
25. Buggy D, Gardiner J. The space blanket and shivering during extradural analgesia in labor. Acta Anaesthesiol Scand 1995;39:551–553.
26. Ponte J, Collette B, Walmsley A. Anesthetic temperature and shivering in epidural anesthesia. Act Anesthesiol Scand 1986;30:574–577.
27. Macaulay J, Bond K, Steer P. Epidural analgesia in labor and fetal hyperthermia. Obstet Gynecol 1992;80:665–669.
28. Philip J, Alexander J, Sharma S, et al. Epidural analgesia during labor and maternal fever. Anesthesiology 1999;90:1271–1275.
29. Byrne F, Oduro-Dominah A, Kipling R. The effect of pregnancy on pulmonary nitrogen wash-out: a short study of pre-oxygenation. Anaesthesia 1987;42:148–150.
30. Datta S, Ostheimer GW, Weiss JB, et al. Neonatal effect of prolonged anesthetic induction for cesarean section. Obstet Gynecol 1981;58:331–335.
31. Kohlschutter B, Baur H, Roth F. Suxamethonium-induced hyperkalemia in patients with severe intra-abdominal infections. Br J Anaesth 1976;48:557–562.
32. Way WL, Trevor AJ: Ketamine. In: Miller RD (ed) Anesthesia, 2nd edn. New York: Churchill Livingstone, 1986:813.
33. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intra-amniotic infection. Am J Obstet Gynecol 1991;164:1317–1326.
34. Hannah ME, Ohlsson A, Farine D, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. N Engl J Med 1996;331:1005–1010.
35. Romero R, Quintero R, Oyarzun E, et al. Intra-amniotic infection and the onset of labor in preterm rupture of the membranes. Am J Obstet Gynecol 1988;159:661–666.
36. Sperling RS, Ramamurthy RS, Gibbs RS. A comparison of intrapartum versus immediate postpartum treatment of intra-amniotic infection. Obstet Gynecol 1987;70:861–865.
37. Gilstrap LC, Leveno KJ, Cox SM, et al. Intrapartum treatment of acute chorioamnionitis: impact on neonatal sepsis. Am J Obstet Gynecol 1988; 159:579–583.
38. Beilin Y, Bodian CA, Haddad EM, et al. Practice patterns of anesthesiologists regarding situations in obstetric anesthesia where clinical management is controversial. Anesth Analg 1995;83:735–741.
39. Goodman EJ, DeHorta E, Taguiam JM. Safety of spinal and epidural anesthesia in parturients with chorioamnionitis. Reg Anesth 1996;21: 436–441.
40. Bader AM, Gilbertson L, Kirz L, Datta S. Regional anesthesia in women with choriamnionitis. Reg Anesth 1992;17:84–86.
41. Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med 1997;337:1105–1111.
42. Riley LE. Herpes simplex virus. Semin Perinatol 1998;2:284–292.
43. Baker DA. Management of herpes in pregnancy. ACOG Practice Bulletin. Washington, DC: ACOG, 1999:8.
44. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med 1991;324:1247–1252.
45. Roberts SW, Cox SM, Dax J, et al. Genital herpes during pregnancy: no lesions, no cesarean. Obstet Gynecol 1995;85:261–264.
46. Hensleigh PA, Andrews WW, Brown Z, et al. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol 1997;337:509–515.
47. Scott LL, Hollier LM, Dias K. Perinatal herpes virus infections. Infect. Dis Clin N Am 1997;11:27–53.
48. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987;317: 1246–1251.
49. Bader AM, Camann WR, Datta S. Anesthesia for cesarean delivery in patients with herpes simplex virus type-2 infections. Reg Anesth 1990;15: 261–263.
50. Ramanathan S, Sheth R, Turndorf H. Anesthesia for cesarean section in patients with genital herpes infections. A retrospective study. Anesthesiology 1986;64:807–809.
51. Crosby ET, Halpern SH, Rolbin SH. Epidural anesthesia for cesarean section in patients with active genital herpes simplex infections. A retrospective review. Can J Anaesth 1989;36:791–794.
52. Valley MA, Bourke DL, McKenzie AM. Recurrence of thoracic and labial herpes simplex virus infection in a parturient receiving epidural fentanyl. Anesthesiology 1992;76:1056–1057.
53. James CF. Recurrence of herpes simplex virus blepharitis after cesarean section and epidural morphine. Anesth Analg 1996;82:1094–1096.
54. Cascio MG, Mandell GL, Ramanathan S. Reactivation of herpes simplex labialis with intrathecal morphine in cesarean section patients. Anesthesiology 1997;87:A868.
55. Boyle RK. A review of anatomical and immunological links between epidural morphine and herpes simplex labialis in obstetric patients. Anaesth Intensive Care 1995;33:425–432.
56. Boyle RK. Herpes simplex labialis after epidural or parenteral morphine. A randomized prospective trial in an Australian obstetric population. Anaesth Intensive Care 1995;33:433–437.
57. Norris MC, Weiss J, Leighton BL. The incidence of herpes simplex virus labialis after cesarean delivery. Int J Obstet Anesth 1994;3:127–131.
58. Lee W, Clark SL, Cotton DB, et al. Septic shock during pregnancy. Am J Obstet Gynecol 1988;159:410–416.
59. Romero R, Oyarzun E, Mazor M, et al. Meta-anaylsis of the relationship between aymptomatic bacteriuria and pretterm delivery/low birth weight. Obstet Gynecol 1989;73:576.
60. Twickler DM, Lucas MJ, Rowe L, et al. Ultrasonographic evaluation of central and end-organ hemodynamics in antepartum pyelonephritis. Am J Obstet Gynecol 1994;170:814–818.
61. Lucas MJ, Cunningham FG. Urinary infection in pregnancy. Clin Obstet Gynecol 1993;36:855–868.
62. American Thoracic Society: Medical Section of the American Lung Association. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993;142:1418.
63. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161:657.
64. Richey SD, Roberts SW, Ramin KD, et al. Pneumonia complicating pregnancy. Obstet Gynecol 1994;84:525.
65. Goodrum LA, Pneumonia in pregnancy. Semin Perinatol 1997;21:276–283.
66. Ackerman WE III, Molnar JM, Juneja MM. Beneficial effect of epidural anesthesia on oxygen consumption in a parturient with respiratory distress syndrome. South Med J 1993;86:361–364.
67. Mabie WC, Baron JR, Sibai BM. Septic shock in pregnancy. Obstet Gynecol 1997;90:553–561.
68. Ledger WJ, Norman M, Gee C, Lewis W. Bacteremia on an obstetric gynecologic service. Am J Obstet Gynecol 1975:121:205–212.
69. Parker MM, Parillo JE. Septic shock: hemodynamics and pathogenesis. JAMA 1983:250:3324.
70. WHO. Weekly Epidemiological Record, vol 27. Geneva: WHO, 1997: 197–200.
71. Newman MD, Wofsy CB. Gender-specific issues in HIV disease. In: Sande MA, Volberding PA (eds) The Medical Management of AIDS, 5th edn. Philadelphia: Saunders, 1997:475–490.
72. Hughes SC. Editorial AIDS: the focus turns to women. Int J Obstet Anesth 1993:2:1–2.
73. Ogilvie G, Adsett S, MacDonald G. Do physicians discuss HIV testing during prenatal care? Can Fam Physician 1997;43:1376–1381.
74. Kuczkowski KM, Birnbach DJ. The HIV-infected parturient: is neuroaxial anesthesia contraindicated? Curr Anesthesiol Rep 2000;2:118–121.

75. Greene ER Jr. Spinal and epidural anesthesia in patients with the acquired immunodeficiency syndrome. Anest Analg 1986:65(10):1090–1091.
76. Hughes SC, Dailey PA, Landers D, et al. Parturients infected with human immunodeficiency virus and regional anesthesia: clinical and immunologic response. Anesthesiology 1995;82:32–36.
77. Kanzer MD. Neuropathology of AIDS. Crit Rev Neurobiology 1990; 5(4):313–362.
78. Fauci AS, Lane HC. Human immunodeficiency virus (HIV) disease: AIDS and related disorders. In: Isselbachen KJ, Kasper DL, Hauser SL, et al. (eds) Harrison's Principles of Internal Medicine, 14th edn. New York: McGraw-Hill, 1994. pp. 1852–1913
79. Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. AIDS 1997;11(4):437–444.
80. Stratton P, Tuomala RE, Abboud R, et al. Obstetric and newborn outcomes in a cohort of HIV infected pregnant women: a report of the women and infants transmission study. J AIDS 1999;20:179–186.
81. Mock PA, Shaffer N, Bhadrakom C, et al. Maternal viral load and timing of mother-to-child HIV transmission, Bangkok, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. AIDS 1999; 13(3):407–414.
82. St. Louis ME, Kamenga M, Brown C, et al. Risk of perinatal HIV-1 transmission according to maternal immunologic, virologic and placental factors. JAMA 1993;269:2853–2859.
83. Kind C, Rudin C, Siegrist CA, et al. Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group. AIDS 1998; 12(2):205–210.
84. Tom DJ, Gulevich SJ, Shapiro HM, et al. Epidural blood patch in the HIV-positive patient: review of clinical experience. Anesthesiology 1992; 76:943–947.
85. Markovic SN, Knight PR, Marusko DM. Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. Anesthesiology 1993;78:700.
86. American Society of Anesthesiologists, Subcommittee on Infection Control Policy. Recommendations for Infection Control for the Practice of Anesthesiology. Park Ridge, IL: ASA, 1994.
87. Kristensen MS, Sloth E, Jensen TK. Relationship between anesthetic procedure and contact of anesthesia personnel with patient body fluids. Anesthesiology 1990;73:619–624.
88. Gerberding JL. HIV transmission to providers and their patients. In: Sande MA, Volberding PA (eds) The Medical Management of AIDS, 5th edn. Philadelphia: Saunders, 1997:54–64.
89. Zambon MC, Lokwood MJD. Hepatitis C seroconversion in pregnancy. Br J Obstet Gynaecol 1994;101:722.
90. Kelen GD, Green GB, Purcell RH, et al. Hepatitis B and hepatitis C in pregnancy in emergency department patients. N Engl J Med 1992;326: 1399.
91. Wejstal R, Widell A, Persson HJ, et al. Mother-to-infant transmission of hepatitis C. Ann Intern Med 1992;117:887.
92. Kuczkowski KM, Birnbach DJ, van Zundert A., Drug abuse in the parturient. Semin Anesth Perioper Med Pain 2000;19:216–224.
93. Johnson C. Pregnancy and malignant hyperthermia. J Clin Anesth 1992; 4:173.
94. Lucy SJ. Anaesthesia for caesarean delivery of a malignant hyperthermia-susceptible parturient. Can J Anaesth 1994;41:1220–1226.
95. Allen GC. Malignant hyperthermia susceptibility. Anesth Clin N Am 1994;12:513–535.
96. Halpern S. Anaesthesia for cesarean delivery of a malignant hyperthermia-susceptible parturient [commentary]. Can J Anaesth 1994;41:1223–1224.
97. Rosenberg H. Malignant hyperthermia. In: 1999 Annual Refresher Course Lecture, No 511. Dallas, TX. American Society of Anesthesiologists, 1999.

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Psychiatric Disease

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Mental illness is a topic that is seldom discussed in association with pregnancy. The literature, however, indicates that mental illness during pregnancy is probably more common than preeclampsia, diabetes, abruptio placentae, and premature delivery. Despite this high prevalence, mental illness in pregnancy is frequently underdiagnosed and undertreated.[1,2] Persistent, untreated, mental illness can have important adverse effects on the pregnancy, labor and delivery, and the postpartum period. It can also complicate the administration of anesthesia and the response to anesthetic modalities. This chapter discusses the eight most common types of mental illness and the prevalence, risk factors, and management techniques for each. The grief response to intrauterine fetal demise, pseudocyesis, and adolescent pregnancy is also discussed.

Mood Disorders

Depression affects a higher frequency of women than men during their lifetime (20% versus 10%). Eight to 10% of all reproductive-age women are depressed, and 50% of all depressed women are between 20 and 50 years old.[3] Therefore, a significant number of women who are in their childbearing years are at a high risk for a mood disorder.[4] There are two types of mood disorders: unipolar (depression) and bipolar (manic/depression). Depression may be further subdivided into major depressive disorders and dysthymic (low grade, more persistently depressed). There is controversy about the frequency and the severity of mood disorders in pregnancy, resulting from a variety of factors, such as the type of assessment or questionnaire used, the sample of women being assessed (variables include age, marital status, socioeconomic status, and parity), and time during pregnancy when assessments are performed.[5] In general, prevalence estimates have been placed between 10% and 20%.[6] During the past 15 years, database studies have consistently validated that, following childbirth, there is a markedly higher rate of psychiatric hospital admissions in women for the first 3 months and a somewhat higher rate up to 2 years postpartum.[7] Medical complications such as obstetric hemorrhage, severe pregnancy-induced hypertension, and even unplanned cesarean section have been reported to double the risk of postpartum depression.[8,9] A recent large cohort study found that depression during pregnancy is actually more common than postpartum depression. The most common timing of depression was between 18 and 32 weeks.[10]

Major Depression

A thorough psychiatric history should be taken during the first prenatal visit. Major risk factors that should be documented during the history-taking examination include the following:

1. A personal or family history of depression
2. Stressful life events
3. Lack of social support
4. Current substance abuse
5. Prior suicide attempts
6. Current or previous psychiatric drugs[11]

Not surprisingly, tobacco and drug abuse during pregnancy were associated with depressive symptoms.[12] If a parturient reports a prior history of depression, she has a 50% rate of recurrence. With two prior episodes of depression, the recurrence rate increased to 70%. With three or more prior episodes of depression, the recurrence rate is as high as 90%. A family history of depression carries a 12% risk of attack. The depression may occur antepartum, postpartum, or both.[11] Companionship during labor has been reported to modify the factors that contribute to depression.[13]

There are nine diagnostic criteria for a major depressive episode. Five or more of the following symptoms must be present daily for at least a 2-week period and must represent a change from previous functioning. One of the symptoms must be either a depressed mood or loss of interest.

Clinical Features

1. Depressed mood most of the day as indicated by either subjective account or observation by others

2. Significantly diminished interest or pleasure in all, or almost all, activities most of the day
3. Significant weight loss or weight gain when not dieting (more than 5% of body weight in a month) or a decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate
9. Recurrent thoughts of death[14]

When depression occurs, a search for possible medications that may induce depression should be performed. Aldomet, the traditional drug of choice for hypertension, has been associated with depression. The stressor responsible for a posttraumatic stress disorder from a previous pregnancy has also precipitated depression. The most common findings are flashbacks and hypervigilance.

Postpartum blues and postpartum depression have been linked with important hormonal changes in the puerperium.[15] The postpartum "blues" are estimated to affect 40% to 85% of women who give birth.[16] The symptoms include sadness, crying spells, irritability, anxiety, mood lability, confusion, and sleep and appetite disturbances.[17] Typically, these symptoms begin during the first postpartum week and then quickly decline.[18] The primary factors that differentiate this from a major depressive disorder are that the blues are short lived and there is no loss of self-esteem.[19] Although pregnancy is a time of happiness, it is also a time of fear and change. The first trimester can be marked with anxiety regarding the threat of miscarriage, the perceived diminished standard of living that will occur, or simply the change in status and life patterns.[20] The last 3 months are a time of fatigue. The pregnant woman feels bulky and clumsy. Her sleep patterns are disturbed. Life becomes unpredictable, and she begins to need to rely on others. There is a fear of the actual delivery and of hospitalization.[8]

Postpartum, there are physical consequences that include the following:

1. Painful episiotomy
2. Incontinence
3. Hemorrhoids
4. Breast engorgement
5. Cracked nipples
6. Backache
7. Fatigue[21]

When depression is diagnosed early in pregnancy, visual and verbal feedback with ultrasound evaluation of the fetus has been shown to improve the abnormal mood state.[22] Fear that the baby is not normal can create significant anxiety and depression. One study reported that parturients undergoing a chorionic villus sampling were noted to have a reduction in anxiety up to 10 weeks earlier than women undergoing an amniocentesis.[23]

Treatment

There are five interventions for depression:

1. Psychotherapy
2. Pharmacotherapy
3. A combination of psychotherapy and pharmacotherapy
4. Electroconvulsive therapy
5. Phototherapy

Most patients with a major depressive disorder respond partially to medication within 2 to 3 weeks and achieve full remission within 6 to 8 weeks. Likewise, patients receiving psychotherapy also respond partially to psychotherapy within 5 to 6 weeks and fully by 10 to 12 weeks.[11]

A complete review of the obstetric history should be performed before assuming care of a parturient in labor. When greeting the parturient, it is important to make her feel comfortable and to prepare her for the procedures to be performed. Some obstetric programs offer pregnant women the opportunity to attend an anesthesia class or review a video prepared by the anesthesia department. This presentation provides an introduction to the procedures that are available during labor and delivery. It also allows parturients who are particularly anxious or who have had previous undesirable anesthesia experiences to speak with an anesthesiologist. These parturients then have ample time to prepare for the anesthetic experience. Most parturients respond to reassurance, careful listening of their fears and physical discomforts, and a validation that it is "okay to feel this way." Complications during labor and delivery, such as preeclampsia, eclampsia, fetal distress, cesarean section, fetal anomalies, or fetal injuries, may place women at an increased risk for postpartum depression.[8,9] Anesthetic problems such as "hot spots" or "high blocks" may also contribute. Postpartum complaints of a headache or backache may be the first symptoms to appear in a depressive episode.

Bipolar (Manic Depressive) Disorder

Incidence

Bipolar disease affects the sexes equally, with a lifetime prevalence between 0.8% and 1.2%.[11] The mean age of onset of bipolar disease is in the twenties. Morbidity and mortality can be high, because as many as 10% to 15% of untreated patients commit suicide (this is 15 to 20 times higher than the suicide rate in the general population). Bipolar disorders classically feature episodes of major depression interspersed with episodes of mania or hypomania. The DSM III-R criteria for a manic episode include the following clinical features.

Clinical Features

1. A discrete period of abnormal persistently elevated, expansive, or irritable mood
2. At least three of the following in the same period:

   a. Inflated self-esteem/grandiosity
   b. Significant decrease in need for sleep
   c. Much more talkative (pressured speech) than usual
   d. Flight of ideas
   e. Pronounced distractibility
   f. Increased goal-directed activity/psychomotor agitation
   g. Excessive involvement in pleasurable activities without regard for negative consequences (e.g., unrestrained buying sprees, sexual indiscretions, foolish business ventures)
3. Symptoms severe enough to significantly impair function or require hospitalization to prevent harm to self or others
4. The condition is not caused by schizophrenia, schizoeffective disorders, or substance abuse.[14] The rapid cyclings involve four or more mood episodes per year. Bipolar disease usually responds well to lithium. The effects of lithium in pregnancy and the anesthetic management of a parturient on lithium are discussed elsewhere in this chapter.
5. Manic episodes may be precipitated by the parturient's discontinuation of medication because of fear of causing fetal problems. Sometimes the use of burst-dose steroids to treat pruritic urticarial papules of pregnancy can trigger a manic episode.

Non-Mood Disorders

Obstetricians and obstetrical anesthesiologists also encounter non-mood disorders in pregnancy. There are six main non-mood disorders:

1. Eating disorders. The eating disorders include anorexia nervosa and bulimia, which occur in up to 1% of the general population and are very difficult to manage during pregnancy. They are associated with increased perinatal morbidity and mortality and have been linked with a high rate of postpartum depression. An eating disorder should be suspected if poor weight gain is observed. Hyperemesis that does not respond to conventional management may suggest an eating disorder. These parturients should be questioned about a prior history of eating disorders. There is considerable new information about eating disorders and their detection. A recent article by Franko reviews the use of an eating disorder examination.[24] The disorder may present as hyperemesis that does not respond to conventional management; these should be managed in conjunction with a psychiatrist.
2. Obsessive/compulsive disorders. An obsessive/compulsive disorder is a condition that is characterized by the presence of obsessions and/or compulsions. Obsessions are recurrent, intrusive thoughts—usually irrational worries—that often necessitate behaviors to prevent untoward consequences (e.g., fears of contamination from dirt, requiring the individual to wear gloves at all times). Compulsions are recurrent behaviors beyond the normal range that the individual feels compelled to undertake, usually to preserve personal safety, to avoid embarrassment, or to perform adequately (e.g., checking multiple times to see if the gas is turned off before leaving home). This disorder affects 1% to 2% of the population and has a high frequency of concurring with depression. A recent report revealed that 39% of these parturients develop their obsessive/compulsive disorder during pregnancy.[25] Another study demonstrated that pregnant women were twice as likely to exhibit obsessive/compulsive behavior when compared with nonpregnant women in the community.[26]
3. Personality disorders. This is the chronic expression of a learned behavior that deviates markedly from the expectations of the individual's culture. Personality disorders are estimated to occur in at least 10% of the population.[27] The DSM-III-R personality disorders are grouped into three clusters:
   Cluster A: paranoid, schizoid
   Cluster B: antisocial, histrionic, and narcissistic
   Cluster C: avoidant, dependent, passive/aggressive
4. Generalized anxiety disorders. This is the most common disease affecting mental health. The prevalence in females (9.7%) is higher than in males (4.7%). More important is the fact that only 23% have received treatment.[28]
5. Panic disorders. A panic disorder is an anxiety disorder characterized by discrete, intense periods of fear and associated symptoms. A panic disorder may be accompanied by agoraphobia. Panic disorders affect about 5% of the general population and seem to occur twice as frequently in women. They are not infrequently encountered in the operating room when a parturient is being prepared for a cesarean section. The epidural has been placed, and the parturient's arms are secured in an outstretched manner. This feeling of claustrophobia induces a panic attack. Previous studies have indicated that panic disorder can be induced by the infusion of sodium lactate.[29] A recent report by Tsen and Datta found no relationship between panic disorder and lactated Ringer's solution.[30] Estrogen has been suggested to be a panicogenic hormone, and the marked rise in pregnancy has been proposed to make pregnancy a panic-prone state.[31] Progesterone may be a natural anxiolytic, which may actually reduce panic and related symptoms.[32]

Postpartum Psychosis

Postpartum psychosis refers to the presence of hallucinations or delusions. Numerous studies confirm that the incidence in the pregnant population is constant at 2 to 4 per 1000.[33] Risk factors for postpartum psychosis are the following:

1. A previous psychiatric history (present in 98% of cases)
2. A complication during the first 3 months or last 3 months of pregnancy
3. A high proportion of unpleasant or abnormal experiences during labor

4. Conflicts related to family or marriage
5. Physical puerperal illness, trauma, infection, and anemia

Although postpartum psychoses are rare, Kendell et al. reported a 20-fold increase in admissions for psychosis within 30 days of childbirth when compared with the normal rate in the general population.[34] Postpartum psychosis requires psychiatric hospitalization. Generally, the prognosis is good. Physical complaints associated with psychotic behavior should be thoroughly evaluated. There have been unusual reports of a chronic subdural hematoma presenting as puerperal psychosis.[35]

Maternal Response to Perinatal Death

Perinatal death can occur as a spontaneous abortion, an induced abortion for the prenatal diagnosis of a fetal anomaly, a stillbirth, or an unexpected neonatal death. These events are commonplace in the practice of any obstetrician and anesthesiologist. Accompanying these events are uncertainties about what one should do with a grieving parturient who has experienced a perinatal death. Should the doctor discuss the event with the parturient after delivery? Does the couple want to view the baby? These and other questions concerning perinatal death are discussed here.

Grieving is a normal healthy process after the loss of a life. It is not unexpected that women who experience a perinatal death grieve. Zeahan et al.[36] compared the grief responses of women who had their pregnancy terminated after prenatal diagnosis of fetal anomaly with women who experienced a spontaneous perinatal loss. Women in the prenatal diagnosis group were different than the spontaneous group because they had to make the difficult decision to terminate the pregnancy. Once the decision to terminate the pregnancy was done, they next had to choose between a dilatation and evacuation (D&E) or a prostaglandin (PGE_2) induction of labor. Younger women and women who had experienced other stressful life events in the past year had a more intense grieving process and a higher level of depression. Interestingly, there was not a significant difference between women who elected a D&E versus a PGE_2 induction. However, women who underwent a D&E regretted not being able to see their babies. All the women who underwent a PGE_2 induction saw and held their babies without regret. This study illustrated that women who terminate their pregnancies because of diagnosed fetal anomalies and women with spontaneous perinatal loss undergo similar patterns of grieving and depression but generally have a good outcome.[36] These findings should prompt clinicians to offer anticipatory grief counseling to these women and support the decision they have made.

The psychologic adjustment to perinatal death occurs differently among women. The following parturient characteristics studied by Graham et al.[37] were found to influence the degree of depression associated with a fetal death. Women who are married and those women who have demonstrated the ability to deliver a healthy baby are significantly less depressed than single primiparous women who undergo a fetal death. Women who blame themselves for the loss, as opposed to attributing the death to God, can be expected to be more depressed. Interestingly, pictures of the deceased infant helped to significantly reduce the amount of depression measured. Women in this investigation consistently benefited from outward shows of sympathy from the medical staff and being kept informed of any problems that developed during their pregnancy.[37] Women who were told "everything is all right" with their pregnancy and then experienced a fetal death resented the false reassurance they had been given. This investigation supports the intuitive thoughts of many clinicians and offers help in identifying parturients who may experience significantly greater depression.

When a couple experiences a perinatal death, the benefits of proactive, rather than reactive, psychologic parturient management are appreciated and will aid parturients. Delivery of a stillborn fetus after 24 weeks usually requires induction of labor if spontaneous labor does not occur. Pain management during this time of intense psychoemotional stress can be complex. Some parturients will request the physician to "knock me out," while other want to be alert and coherent during the process. The labor and delivery process should be thoroughly discussed before beginning the induction: this includes the options of analgesia, epidural anesthesia, or a combination of both. Patient-controlled analgesia (PCA) is sometimes the ideal method of pain control. Some parturients may begin the healing process if they are lucid at delivery and able to see and hold their baby.

Kellner et al.[38] reported the results from treating 165 families with a Perinatal Mortality Counseling Program that consisted of an obstetrician, pathologist, social worker, and psychologist. Kellner wanted to let parents make their own choice on how to handle their baby's death. He measured specific parturient requests concerning seeing the baby, holding the baby, having an autopsy, disposing of the remains, returning to postpartum, and accepting follow-up counseling. Ninety percent of parents chose to see their baby regardless of its appearance. Half the parents held their baby. The babies were wrapped in an infant blanket and presented to the families, taking care to point out the normal features and simply explaining any maceration or abnormalities. Families tend to remember the normal aspects of the dead baby. Eighty-five percent of women who had other children at home and 70% of women without other children named the deceased baby. Women with other children at home named their baby so that their other children would know they had a brother or sister who died. A funeral or memorial service was chosen more by women who had a longer gestation and who had asked to see and hold their baby. Interestingly, none of the parents who elected not to see their baby chose a funeral or memorial service. If an autopsy was done, the majority of families selected cremation rather than a funeral service.[38] Allowing families

to make choices in a professional atmosphere targeted at dealing with their perinatal death helped them adjust to the death of their baby. Families should be given the choice to see, hold, and name the baby. In addition, assistance should be offered with the decisions concerning cremation, funeral, and a memorial service. Parents resented being left alone to handle the death of their baby and attempts to discharge them early. The choices made by parents should help us anticipate the needs of families that experience a perinatal death.

Within the family unit, mothers tended to show depression early, within the first 6 weeks after delivery, whereas symptoms were delayed in fathers.[39] Paternal depression was delayed until a mean of 25 months following the loss. Speculation about the delay in paternal depression centers around the belief that fathers may feel so compelled to support their wives during the initial grieving process that not until later does their need for social support become apparent. Married couples tend to support each other through the grieving process, and although there is obvious stress with a perinatal death, this life event typically strengthens a couple's relationship. Recognition by a family that during the first 6 weeks after a fetal death the wife is usually more depressed, and that the social needs for coping become more evident later for the father, will help in counseling families after a prenatal death.

When a couple has experienced a perinatal loss with a previous pregnancy, stress and anxiety about the current pregnancy is common. Women feel this anxiety to a greater degree than the fathers. In fact, pregnant women who have experienced a previous perinatal loss differ significantly from pregnant women who have not in measurements of anxiety.[40] Fathers in both groups do not differ when anxiety levels are measured. Fathers who have experienced a previous perinatal loss see this new pregnancy as unencumbered by the previous loss. Clinically, women who experienced a previous perinatal loss will benefit from reinforcement, when appropriate, that they are expected to carry the current pregnancy to term and that any problems which arise will be discussed.

The story of a young Hispanic couple that delivered a stillbirth was published on the front page of The Wall Street Journal. This couple experienced a perinatal loss at 8 months gestation. After a PGE_2 induction, a 4-pound 2-ounce stillborn girl was delivered. The couple was given an opportunity to hold the baby, received a photograph of the baby, named the baby (Frances Elaine), and consented to an autopsy. The problem arose when, after the autopsy, the couple was not given the opportunity to have a funeral mass for their daughter because the hospital had lost the baby. In addition, the autopsy report was not delivered to the couple until more than 4 years had elapsed after the stillbirth. The couple filed a negligence suit against the hospital 10 months after delivery. At issue are not the rights of a stillborn baby, but the rights of the couple, as survivors, to complete the grieving process with a funeral mass.[41]

In summary, families that experience a perinatal loss need to be managed in a direct compassionate fashion. They have specific needs that should be met to help them with the grieving process both intrapartum and postpartum.

Adolescent Pregnancy

The U.S. teen birth rate began to decrease in the early 1990s and reached a new record low in 2000. The Surgeon General participated in a national campaign to prevent teen pregnancy. The American College of Obstetricians and Gynecologists formed a committee on adolescent health care, and many other organizations joined forces to effect this decline. Despite this decline, however, almost 4 of 10 teenagers become pregnant, leading to almost 1 million teen pregnancies each year. The U.S. teen birth rate remains the highest among developed countries. Only half of all teenage mothers will graduate from high school. Teenage mothers are almost twice as likely to conceive again within 1 year of delivery of their first child. The U.S. government spent over $21 billion in 1989 for services to families of teenage mothers.[42] A recent study has reported that early-onset psychiatric disorders are associated with subsequent teenage parenthood.[43] Some teenagers become pregnant as a way of protecting against depression.[44] Teenagers who are emotionally deprived have described a sense of well-being during pregnancy. In July 2001, Health and Human Services Secretary Tommy G. Thompson announced more than $17.1 million in new grants to help communities develop programs to continue the downward trend in the teen birth rate. Physicians need to be aware that teenagers with depression or other emotional disorders are more prone to pregnancy.

Posttraumatic Stress Disorder After Childbirth

The diagnosis of posttraumatic stress disorder (PTSD) involves exposure to a traumatic stressor that gives rise to a persistent reexperiencing of the event, avoidance of reminders, numbing of responsiveness, and increased arousal.[45] Childbirth can be a very painful experience and is described as a cause of PTSD. PTSD was first described among U.S. men who served in the Vietnam War. In the 1980s, in the U.S. population, the prevalence of PTSD was 5 per 1000 men and 13 per 1000 women. Physical attack (rape), threats, and childbirth are common causes among women. The estimated rate for childbirth as a cause of PTSD is 0.2%.[46]

Women affected by PTSD generally have several common features: (1) a sense of being out of control, (2) extreme, traumatizing pain, (3) lack of consent for interventions, (4) inadequate information, and (5) hostility on the part of the clinical staff.[46,47] Childbirth that is long, difficult, and painful characterizes the stressor that can give rise to PTSD. A study of 500 women found that 1 in 5 reported having found an ob-

stetric or gynecologic procedure very distressing or terrifying.[47] After a traumatic painful childbirth, women may avoid sex, future pregnancies, or subsequent attempts at vaginal delivery. A case report describes a woman who had a long painful labor without epidural anesthesia who subsequently suffered from PTSD. She abstained from sex for the first year after childbirth. Then, she insisted that her husband use a condom in addition to her use of oral contraceptive therapy. She suffered from severe headaches during sex because she was worried about conceiving. Eventually she had herself sterilized to avoid any chance of a future pregnancy.[45] Women suffering from PTSD have aborted a pregnancy to avoid the potential trauma of childbirth. A planned cesarean section is a common method used to avoid trauma during labor and delivery.[46]

Women who have experienced a sexual assault as a cause of PTSD require special care during labor and delivery. Pain, loss of control, and exposure can be common to both events. Intravenous lines and monitoring cables can make a woman feel tied down. Attendants should be sensitive to any commands used with a parturient. For example, the phrase "open your legs" may have been used during a sexual assault.

A Practical Approach to Women at Risk for Traumatic Childbirth

During pregnancy:
- Take a careful history

During delivery:
- Ensure good, appropriate communication
- Ensure excellent pain control

After delivery:
- Encourage discussion of the birth experience
- Rule out postpartum depression

During a subsequent pregnancy:
- Take a careful history
- Consider an elective cesarean section[46]

After delivery, both postpartum depression and PTSD, although very different, can occur. One should rule out postpartum depression first. The treatment for PTSD can be difficult, and drug therapy may only be partially helpful. Behavioral techniques can be beneficial with symptoms of flashbacks.[46]

Pseudocyesis

Pseudocyesis is derived from the Greek words *pseudes* (false) and *keysis* (pregnancy). It is a condition in which a patient has physical signs and symptoms of pregnancy and firmly believes them even when they are not pregnant.[48] Pseudocyesis has been described in both men and women.[49] Pseudocyesis was first described by Hippocrates in 300 B.C. Since then, several hundred cases have been reported. The rate of pseudocyesis ranges from 1 in 200 maternity clinic admissions to 1 in 4000 births.[50] The majority of women are married, with symptoms lasting 9 months in almost half of them, but symptoms have been documented to last several years.

Pseudocyesis can present as a simulated pregnancy, pregnant changes resulting from a hormone-producing tumor, and pelvic masses mimicking pregnancy. Pseudopsyesis in a psychotic patient can manifest as a delusional pregnancy in which a patient has a persistent false belief with severely impaired thinking, emotions, and behavior. Pseudocyesis vera (true false pregnancy) will occur in nonpsychotic women. It can mimic pregnancy to the extent that a professional can be fooled without the help of a pregnancy test or abdominal ultrasound.[48]

Clinical Features and Diagnosis

The symptomatology, in order of decreasing frequency, occurs as follows:

1. Abdominal enlargement, usually resulting from exaggerated lordosis and retention of waste products
2. Abnormal menses, most frequently seen as amenorrhea
3. Patient perception of fetal movements
4. Gastrointestinal symptoms, manifested as nausea and vomiting and increased appetite
5. Breast swelling, breast tenderness, and areolar pigmentation, as well as labor pains and uterine enlargement[49,50]

The diagnosis of pseudocyesis is easily made by a pregnancy test as well as abdominal or vaginal ultrasound. A physical diagnosis sign thought to be pathognomic for pseudocyesis is an inverted umbilicus.[51] Other disorders mistaken for pseudocyesis include ectopic pregnancy, a corpus luteum cyst, gestational trophoblastic disease, morbid obesity, ascites, central nervous system tumors, pelvic tumors, and drug side effects.[50,51] Interestingly, pseudocyesis associated with a false-positive pregnancy test is reported to have occurred in a patient with bronchogenic carcinoma.[52] The false-positive pregnancy test was due to ectopic gonadotropin production by the bronchogenic carcinoma. The author warns, "Don't ignore a positive pregnancy test."

The basis of pseudocyesis is psychologic, but a single psychologic process does not exist for these patients. In fact, most of these patients do not appear psychotic. Pseudocyesis can be viewed as a conversion syndrome motivated by narcissism, dependency, body image, power, and guilt. A conversion syndrome is a condition in which a functional aberration occurs that is not explained by normal physiologic arguments. Narcissistic motivation can derive from the personal and social (marriage) gratification of pregnancy. Pregnancy can also provide a woman with the power to dominate a relationship or motivate a couple to marry. In some cases the hope of pregnancy can help women cope with guilt from some other source.[50,51] Pseudocyesis is also described to occur as a manifestation of postpartum psychosis.[53] Psychotherapy is useful as the ultimate treatment for these patients.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) was introduced in 1934 when the Hungarian psychiatrist Ladislus Meduna recognized that naturally occurring convulsions produced mental relief in some patients. ECT is designed to induce a grand mal seizure by means of an electric current applied across scalp electrodes. The convulsion, not the electrical current, is therapeutic through an unknown mechanism. Induction of seizure activity with an electrical stimulus produces a more reliable brief ictal response with fewer side effects than oil of camphor, insulin coma, or metrazol. In addition, the incidence of fetal morbidity was found to be 35% in pregnant women treated for depression by insulin coma.[54] Improvements in ECT include placement of a unilateral electrode on the nondominant hemisphere instead of bilateral placement and use of pulsatile waveforms, which induce seizure activity with half the electrical energy of a sine-wave stimulus. Most therapies consist of 8 to 12 separate ECT sessions over several weeks.[55,56]

ECT is used primarily in patients suffering from depression and less frequently in schizophrenia, mania, and catatonic stupor.[57] ECT is most effective in severe major depressive episodes when rapid therapy is needed or pharmacologic therapy has failed.[58] ECT is not indicated for treatment of anorexia nervosa, obsessional illnesses, psychogenic pain, or confusional states unless the patient is concomitantly depressed. ECT should never be used to control aggressive or violent behavior. ECT is a safe and effective therapy in pregnancy. Although there is no controlled study of ECT in pregnancy, multiple case reports exist supporting its safety in the mother and fetus.[54,55,59–63]

Contraindications to ECT are based on patient tolerance of the physiologic changes that occur during treatment. The electrical stimulus used to produce a grand mal seizure produces an increase in cerebral blood flow, cerebral oxygen consumption, and cerebrospinal fluid pressure. The grand mal seizure consists of a 10-s tonic phase and a 30- to 50-s clonic phase. Activation of the autonomic nervous system begins during the tonic phase with a central vagal discharge characterized by bradycardia and a decrease in blood pressure. The sympathetic outflow characterized during the clonic phase is accompanied by a rise in circulating catecholamines,[61] hypertension, tachycardia, and rarely, premature ventricular contractions and ventricular tachycardia. Asystole has been described to occur during subconvulsive ECT, presumably because the tonic (parasympathetic) phase occurs without opposition from the clonic (sympathetic) phase.[64] Oxytocin increases during ECT are small and transient and typically do not result in uterine contractions.[61] The only absolute contraindication to ECT is increased intracranial pressure. Of the deaths occurring during ECT, 85% result from cardiovascular or pulmonary factors. It follows that relative contraindications to ECT include recent myocardial infarction, coronary artery disease, congestive heart failure, bronchopulmonary disease, carotid stenosis, hypertension, and venous thrombosis. The potential of increased uterine activity points to placenta previa, incompetent cervix, history of premature labor, multiple gestation, and hydramnios as relative contraindications to ECT. The sympathetic discharge that occurs during the clonic phase may result in a pronounced hypertensive response in the preeclamptic parturient or fetal morbidity in a mother with impaired uteroplacental perfusion. The presence of a cardiac pacemaker should not be considered a contraindication to ECT. These relative contraindications must be weighed against the benefits of ECT.[55] ECT is a relatively safe procedure with a mortality rate of 4.5 per 100,000 treatments.[65]

ECT during pregnancy has been shown to be safe and effective for both the mother and fetus in many case reports.[54,55,59–63] Because of the lack of a controlled study, obstetric and anesthetic management must be derived from the existing case reports and common sense. A review of 300 case reports of ECT during pregnancy concluded that it is a relatively safe treatment if steps are taken to decrease potential risks. Reported complications consisted of transient benign fetal arrhythmias, vaginal bleeding, abdominal pain, and uterine contractions.[66] ECT is indicated in the severely depressed parturient, especially when rapid conversion is required, pharmacologic therapy has failed, and there is hesitancy to use psychotropic drugs during fetal organogenesis. The following guidelines address the special consideration a parturient requires during ECT.

1. A psychiatrist, obstetrician, and anesthesiologist should all be members of the treatment team. ECT should be performed in a facility where all members of the treatment team can be assembled, and a labor and delivery unit is in close proximity.
2. The obstetrician should begin with a complete obstetric history and physical examination of the patient. A maternal history of placenta previa, incompetent cervix, history of premature labor, multiple gestation, hydramnios, uteroplacental insufficiency, and preeclampsia are relative contraindications to ECT. ECT has been used successfully in a twin gestation complicated with severe depression and psychotic behavior.[67] Increased blood oxytocin levels[61] and uterine activity[63] described during ECT may adversely affect pregnancy outcome in parturients with placenta previa, incompetent cervix, history of premature labor, multiple gestation, or hydramnios. ECT-induced premature labor was described in a pregnant woman with chronic paranoid schizophrenia. Treatment with ritodrine and indomethacin arrested the uterine contractions. For subsequent ECT during the pregnancy, the parturient was pretreated with terbutaline and indomethacin.[68] A uterine tocolytic (terbutaline 0.25 mg intravenous) should eliminate the small risk of increased uterine activity in high-risk parturients and provide prophylaxis for the increased vagal tone during the tonic phase of ECT.

Increased blood catecholamine levels during ECT[61] in the parturient may cause fetal compromise if uteroplacen-

tal insufficiency is present. A rise in maternal catecholamine levels may result in an amount of uterine artery vasoconstriction not tolerated by the fetus. Uterine and umbilical artery Doppler measurements in a 32-week-gestation pregnancy showed a slightly increased systolic/diastolic ratio and resistance index immediately after ECT.[61] Ultrasonography conducted during and immediately after ECT on a second trimester parturient showed no significant change in fetal movement or other activity. The same parturient demonstrated a stable fetal heart rate during ECT.[59] Case reports indicate that ECT is safe for the fetus in parturients without uteroplacental insufficiency. In parturients for whom ECT therapy is strongly indicated and uteroplacental insufficiency is suspected, measures to optimize fetal blood flow should be taken; these include preoperative intravenous hydration, left uterine displacement, continuous fetal and uterine monitoring, inhibition of the vagal tone during the tonic phase of ECT (atropine 0.4 mg intravenous), and use of a tocolytic if increased uterine activity is measured. Increased catecholamines may result in an exaggerated hypertensive response in the preeclamptic parturient during the sympathetic discharge associated with the clonic phase of ECT; this can be treated with intravenous labetalol or trimethaphan.

3. Anesthetic management of ECT during pregnancy begins with a thorough anesthetic-focused history and physical examination. Drug interactions with current psychotropic medications should be understood before ECT begins (see section on psychotropic drugs). The airway examination is important because a rapid sequence induction is required for ECT in the parturient. The anesthetic goals for ECT in the parturient are to (1) provide oxygenation with a protected airway; (2) prevent recall; (3) prevent long bone fractures during tonic-clonic contractures; (4) moderate hemodynamic responses; (5) optimize uteroplacental circulation; and (6) allow a rapid emergence. Standard intraoperative monitoring, a uterine tocodynamometer, and continuous external fetal monitoring should be used during ECT for the parturient. Continuous fetal monitoring may be replaced with Doppler measurement of fetal heart sounds before and after the procedure in the previable fetus. Consultation with the obstetrician before ECT will help in the selection of appropriate fetal surveillance.

   Preoperative hydration (0.5–1 L isotonic crystalloid solution) and left uterine displacement will help prevent hypotension during the procedure.[59] Preoxygenation, a rapid sequence and induction intubation are necessitated because of concerns about maternal aspiration and oxygenation. Methohexital (0.5–1.0 mg/kg) or thiopental (2–3 mg/kg) and succinylcholine (1.0–1.5 mg/kg) are acceptable induction agents. The primary function of succinylcholine is to provide optimal intubating conditions, and its secondary function is to blunt the muscular response of the seizure. Inflation of a blood pressure cuff placed on the bicep or calf at twice the systolic pressure will allow for identification of seizure activity in the isolated extremity, attenuation of the muscular response in the important long bones, and use of a full intubation dose on induction. Ventilation should be controlled[68] with the same fractional inspiratory oxygen (FiO_2) (>50%) for all sessions. The use of 100% oxygen has been demonstrated to increase the duration of seizure activity but only by a mean value of 18 s.[69] Consistent use of the same FiO_2 during all sessions of ECT with a parturient is more important than the actual percentage of oxygen (maintained at >50%) delivered.[70] Pretreatment with atropine or a tocolytic should be given immediately before ECT begins. After a seizure activity has been documented, the parturient should be awake before extubation. Fetal monitoring should be continued for 1 to 2 h after ECT because little is known about uterine physiology associated with ECT. The obstetrician should make the decision for further fetal monitoring in high-risk obstetric patients.

Psychotropic Drugs

Obstetric and Anesthetic Implications

The use of psychotropic drugs during pregnancy presents a dilemma to the clinician. How do you treat a pregnant woman suffering with psychopathology and at the same time protect the fetus from teratogenicity? How does one counsel a woman who has conceived and undergone significant first trimester exposure to psychotropic drugs? What do you tell the parturient who wants to breast-feed her infant? This section addresses the teratogenic risk, maternal and neonatal side effects, drug interactions, and breast-feeding recommendations (Table 29.1).

Selective serotonin reuptake inhibitors (SSRIs) are indicated for depression, obsessive-complusive disorder, and panic disorder. The mechanism of action of SSRIs is linked to their inhibition of central nervous system (CNS) neuronal uptake of serotonin. SSRIs are widely described and well studied. Chambers et al.[65] concluded from a prospective cohort study of 228 women taking fluoxetine (Prozac) that infants of women exposed in the first trimester are at increased risk for minor anomalies. Third trimester exposure was associated with an increased risk for premature delivery, poor neonatal adaptation, cyanosis on feeding, and jitteriness. These finding generated interesting controversy. Cohen and Rosenbaum[72] criticized Chambers' control group, noting that "higher rates of complications, including lower birth weight, neonatal distress, and prematurity" already exist in infants of women with mood and anxiety disorders who do not take psychotropic drugs. In addition, other cohort studies[73–77] did not show an increased risk of birth defects, poor perinatal condition, or neurodevelopmental delay.[78] In summary, it appears that fluoxetine is not embryotoxic, nor does it cause major fetal anomalies.[79] Kulin et al.[80] investigated 267 pregnant women exposed to SSRIs during embryogensis in a prospective multicenter study. Exposure to an SSRI was not associated with either increased

risk for major malformations or higher rates of miscarriage, stillbirth, or prematurity. Kulin concluded that fulvoxamine, paroxetine, and sertraline do not appear to increase teratogenic risk when used in recommended doses. Clinical judgment based on the risk of complications should be used to guide therapy of SSRIs in pregnancy. Unnecessary exposure to drugs must be balanced against the risk of relapse of major depression after discontinuation of therapy.

Common maternal side effects of fluoxetine include headache, nausea, anxiety, tremor, and increased appetite. Significant cardiovascular or pulmonary adverse effects are rare with fluoxetine use. Blockade of serotonin uptake into platelets by fluoxetine may be the mechanism for the rare occurrence of an increased bleeding time. Neonatal jitteriness, hypertonia, and bruising have been described. Significant anesthetic drug interactions with fluoxetine have not been reported. Described SSRIs are present in breast milk in extremely low levels with no adverse effects noted.[81]

Tricyclic antidepressant drugs are widely prescribed and studied psychotropic medications used during pregnancy. A meta-analysis of 414 cases of first trimester exposure to tricyclic antidepressants found no significant association between exposure to tricyclic antidepressants and congenital malformations.[82] There is no evidence that tricyclic anti-depressants cause major birth defects in either humans or animals.[83]

Teratogenic effects of first trimester exposure to tricyclic antidepressants observed in a small prospective study (19 women taking imipramine and 28 women using amitriptyline) and in a larger investigation of 15,000 births showed no evidence of gross congenital abnormalities.[84,85] The study by Pastuszak et al. of first-trimester exposure to fluoxetine documented an increase in the rate of miscarriage in women in the fluoxetine and tricyclic antidepressant group.[74] Fetal tricyclic antidepressant exposure and associated diaphragmatic hernia, hypospadias, limb and craniofacial deformities, meningocele, hydrocephalus, and cardiac anomalies have been reported in older case reports.[86–88] In summary, tricyclic antidepressants have maintained widespread use during pregnancy without evidence of major teratogenic effects. The teratogenic risk of tricyclic antidepressants should be considered to be small to nonexistent.

Neonatal effects of maternal tricyclic therapy may be apparent in the immediate postpartum period. Neonatal signs of fetal exposure to desipramine, imipramine, and nortriptyline include periodic apnea, cyanosis, tachypnea, irritability, seizures, feeding difficulties, heart failure, tachycardia, myoclonus, respiratory distress, and urinary retention.[89] Clinical judgment suggests that neonatal toxicity and withdrawal symptoms can be minimized if tricyclic medications are tapered and discontinued 1 to 2 weeks before delivery. In utero exposure to tricyclic antidepressants or fluoxetine does not affect major malformations, global IQ, verbal comprehension, or language or behavioral development in preschool children aged 16 to 86 months.[90]

Maternal side effects of tricyclic antidepressants manifest as anticholinergic or sedative effects. Constipation, sedation, weight gain, orthostatic hypotension, and blurred vision are all side effects of tricyclic antidepressants. Nortriptyline and desipramine are generally preferred during pregnancy because they cause milder tricyclic side effects. These side effects can be additive to normal symptoms seen in pregnancy. Amitriptyline, nortriptyline, desipramine, and clomipramine were not found in quantifiable amounts in breast-fed infants, and no adverse effects have been reported. However, breast-fed infants less than 10 weeks old of mothers who were taking doxepin experienced sedation. The sedation was probably a result of the desmethl metabolites of doxepin found in the infants.[81] Women on tricyclics should be allowed to breast-feed their infants.

The interactions of tricyclic antidepressants with anesthetic drugs are important. Tricyclic agents inhibit the uptake of norepinephrine into the postganglionic sympathetic nerve ending. The use of an indirect sympathomimetic such as ephedrine will result in an exaggerated increase in maternal blood pressure. Phenylephrine used in 40-μg boluses to correct maternal hypotension would produce an appropriate rise in blood pressure. The combination of imipraimine, pancuronium, and halothane caused increased incidence of tachyarrhythmias in anesthetized dogs.[91] In addition, the dose of epinephrine required to produce ventricular dysrhythmias is reduced during anesthesia with volatile anesthetic agents.[92] The anticholinergic effect of tricyclic antidepressants (especially amitriptyline) may be additive with centrally active anticholinergic drugs (scopolamine and atropine). Central anticholinergic syndrome manifests as delirium or prolonged somnolence following anesthesia. Tricyclic antidepressants may augment the analgesic and ventilatory depressant effects of opioids and the sedative effect of barbiturates.

Monoamine oxidase inhibitors (MAOI) increase intraneuronal levels of neurotransmitters (serotonin, norepinephrine, epinephrine, dopamine, and octopamine) by irreversibly binding to the enzyme MAO. These drugs are indicated for the treatment of depression and obsessive-compulsive, panic, and appetite disorders. MAOIs are known teratogens in animals; in a small prospective study, tranylcypromine was associated with human malformations.[93] A small group of women treated with tranylcypromine and phenelzine had a higher rate of congenital malformations in their offspring.[94] MAOIs should probably be avoided in pregnancy given the sparse reports available. Other treatment options, including ECT, should be considered in the severely depressed parturient.[82,95]

MAOIs have significant side effects and interactions with other drugs. They can exacerbate hypertension, and their drug and food interaction profile is extensive, complicating treatment.[89] Hypotension in the parturient is typically treated with ephedrine causing an exaggerated release of vasoactive intraneuronal neurotransmitters that results in an unpredictable increase in blood pressure. An exaggerated increase in maternal blood pressure may compromise uteroplacental

TABLE 29.1. Psychotropic medications.

Drug	Indication	Anesthetic interactions	Toxicity	Teratogenicity	Breast-feeding effects
Selective serotonin reuptake inhibitors (SSRIs) Fluoxetine (Prozac) Fluvoxamine (Luvox) Paroxetine (Paxil) Sertraline (Zoloft) Venlafaxine (Effexor)	Depression, obsessive-compulsive disorder, (fluoxetine) prevention of panic disorder	Rare occurrence of an increased bleeding time	Maternal: headache, nausea, anxiety, tremor, increased appetite Neonatal: jitteriness, hypertonia, bruising	No increased risk of spontaneous pregnancy loss or major fetal malformations, controversy concerning minor fetal anomalies	Sertraline is present in breast milk, infant levels are extremely low with no adverse effects reported, accumulation reported with fluoxetine
Tricyclic antidepressants Amitriptyline (Elavil) Amoxapine (Asendin) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Sinequan) Imipramine (Tofranil) Maprotiline (Ludiomil) Nortriptyline (Pamelor) Protriptyline (Vivactil) Trimipramine (Surmontil)	Depression (Imipramine), prevention of panic disorder	Indirect vasopressors, halothane and pancuronium, scopolamine, opioids, barbiturates, monoamine oxidase inhibitors (MAOIs)	Maternal: sedation, constipation, orthostatic hypotension, dry mouth Neonatal: neonatal withdrawal syndrome (transient seizures and jerky movements), direct anticholinergic effects, cardiac rhythm	No known teratogenic effect in humans	Infants older than 10 weeks are at low risk for adverse effects of tricyclics with no evidence of accumulation; sedation reported with Doxepin metabolites
Monoamine oxidase inhibitors Isocarboxizid (Marplan) Phenelzine (Nardil) Tranylcypromine (Parnate)	Depression, obsessive-compulsive, panic and appetite disorders, hypertension	Excitatory response with meperidine, tyramine-induced hypertension, exaggerated response to ephedrine	Maternal: exacerbate hypertension, sedation, blurred vision, dry mouth Neonatal: none reported	Found to be teratogenic experimentally; fetal malformations reported	Minimal transfer reported in breast milk
Antipsychotic drugs Risperidone (Risperdal) Olanzapine (Zyprexa) Haloperidol (Haldol) Thiothixene (Navane) Clozapine (Clozaril)	Schizophrenia	Potentiates respiratory depressant, sedative, and analgesic actions of opioids	Maternal: hypotension, increased Q-T, extrapyramidal, tardive dyskinesia Neonatal: tachycardia, GI dysfunction, sedation, hypotension	Agranulocytosis reported with clozapine; no other current teratogenicity reported	Haloperidol is significantly excreted in breast milk with no adverse effects; clozapine; is concentrated in breast milk with adverse infant effects
Phenothiazines Chlorpromazine (Thorazine) Thioridazine (Mellaril) Fluphenazine (Permatitil) Perphenazine (Trilafon) Trifluoperazine (Stealzine) Methotrimeprazine Oxomemazine	Schizophrenia, hyperemesis gravidarum	Potentiates respiratory depressant, sedative, and analgesic actions of opioids	Maternal: neuroleptic malignant syndrome (NMS), extrapyramidal, jaundice, isolated idiosyncratic fall in blood pressure, sedation Neonatal: extrapyramidal, jaundice, respiratory depression, cyanosis	Previous isolated reports concerning chlorpromazine not supported by recent studies; small increase in congenital anomalies	Phenothizines are excreted in breast milk; no adverse effects reported with chlorpromazine

Benzodiazepines Alprazolam (Xanax) Clonazepam (Klonopin) Diazepam (Valium) Lorazepam (Ativan)	Panic disorder	Respiratory depression	Maternal: respiratory depression, sedation Neonatal: floppy infant syndrome, withdrawal	Low risk of cleft lip with diazepam; major defects reported with clonazepam; none with lorazepam or alprazolam	Benzodiazepines are excreted in breast milk in low levels; apnea, cyanosis hypotonia reported
Lithium carbonate (Lithane)	Bipolar disease	Potentiates the action of muscle relaxants and barbiturates; ST depression during anesthesia	Maternal: diabetes insipidus, hypothyroidism Neonatal: diabetes insipidus, cyanosis, hypotonia, seizures, cardiac arrhythmias, hypothyroidism	Rare occurrence of congenial cardiac (Ebstein's anomaly) malformations	Excreted in breast milk and detected in infant serum with reported adverse effects; contraindicated
Carbamazepine (Tegretol)	Epilepsy, trigeminal neuralgia, bipolar disease, psychosis, alcohol withdrawal	None	Maternal: aplastic anemia, agranulocytosis Neonatal: deficiency of vitamin K, fetal hydantoin syndrome	Spina bifida, cranio-facial defects, developmental delay	Excreted in breast milk at low levels with reported cases of transient hepatic toxicity and seizure-like activity; considered safe
Valproic acid (Depakote)	Epilepsy, bipolar disease	None	Maternal: nausea and vomiting, impaired platelet aggregation, hepatotoxicity Neonatal: deficiency of vitamin K clotting factors, hypoglycemia, fetal hydantoin syndrome	Causes major and minor congenital anomalies, intrauterine growth restriction (IUGR), spina bifida	Excreted in breast milk at low levels; thrombocytopenia and hepatotoxicity reported; considered safe

blood flow. Phenylephrine, a direct-acting sympathomimetic agent, administered in boluses of 40 μg would be an good choice for treating hypotension in a parturient receiving MAOIs.[96] A recent case report concerning anesthetic management of the labor and delivery of a parturient taking long-term MAOI recommended an epinephrine or norepinephrine infusion for the treatment of maternal hypotension.[97] Meperidine, a commonly administered intrapartum analgesic, impairs the neuronal uptake of serotonin. If cerebral serotonin levels are increased to a critical level, a potentially fatal excitatory response will occur. This excitatory response is characterized by hyperthermia, hypertension, hypotension, depressed ventilation, skeletal muscle rigidity, seizures, coma, and, potentially, death. This response occurs in approximately 20% of patients receiving MAOIs who are given meperidine.[98]

Morphine and fentanyl appear to be safe alternative analgesic agents in patients chronically treated (longer than 3 weeks) with MAOIs.[99] Tricyclic antidepressants and serotonin uptake inhibitors block neuronal uptake of neurotransmitters. MAOIs produce an accumulation of these neurotransmitters. The release of increased amine neurotransmitters combined with impaired neuronal uptake presents the potential for a fatal drug interaction between MAOIs, tricyclic antidepressants, and serotonin uptake inhibitors. Tyramine, normally metabolized by MAO in the gastrointestinal tract and liver, produces a release of endogenous catecholamines. Normal metabolism of tyramine (contained in cheese, chicken liver, chocolate, beer, and wine) is impaired in parturients treated with MAOIs. The increased release of endogenous amine neurotransmitters by tyramine-containing foods in parturients treated with MAOIs can result in a life-threatening hypertension response that would put both mother and fetus at risk. MAOI inhibition of hepatic enzymes is the proposed mechanism of the exaggerated depressant effect produced by opioids and barbiturates.[98] Transfer of MAOI into breast milk is reported to be minimal, so that breast-feeding neonates are exposed to only very small amounts of drug.[100] The numerous potentially fatal drug interactions and the risk of teratogenicity make MAOIs a poor choice in the parturient.

Antipsychotic drugs are indicated for the treatment of schizophrenia. These drugs freely cross the placenta. Most antipsychotic agents are not known to cause structural birth defects.[89] Haloperidol is the most thoroughly studied antipsychotic drug. An early case report noted fetal limb reduction defects associated with haloperidol.[101] Other large prospective studies were not able to demonstrate an increased teratogenic risk of haloperidol.[102,103] Currently pregnant and breast-feeding women can be treated with haloperidol if the benefit exceeds the small risk of treatment. Olanzapine was found to be of no significant teratogenic risk in a report of 23 prospectively and 9 retrospectively studied pregnancies.[104] The use of olanzapine in breast-feeding women is not well studied. Clozapine can cause agranulocytosis in the first 6 months of treatment. One third of parturients who had agranulocytosis from clozapine died.[102] Infants of mothers who received clozapine during pregnancy or while nursing should be tested for white blood cell counts, because there is not a good understanding of the risk of clozapine-induced agranulocytosis.[105] Encouragingly, reports of clozapine use before and during gestation have found no adverse fetal effect.[106,107] Risperidone and thiothixene are sparsely studied in humans,[96] and it is not possible to assess their teratogenic or breast-feeding implications.

Antipsychotics can cause maternal hypotension, an increased Q-T interval, extrapyramidal effects, and tardive dyskinesia. Extrapyramidal effects in the neonate are typically self-limited. Hyperactivitiy, hyperactive deep tendon reflexes, motor restlessness, tremors, and abnormal movements characterize extrapyramidal effects; these signs may persist for several months. Antipsychotic drugs can potentiate the respiratory depressant, sedative and analgesic effects of opioids.

Phenothiazine medications are used to treat schizophrenia and hyperemesis gravidarum in lower doses. They produce their clinical effect by dopaminergic blockade. Phenothiazines are known to freely cross the placenta.[102] A meta-analysis of first trimester exposure to phenothiazines, including 74,337 births, reported a statistically significant, but small, increase in the risk of congenital anomalies.[82] This additional risk was assessed to be 4 in 1,000. No increase in organ malformation was identified. The relative risk of the psychotic illness itself confers a greater risk than low-potency phenothiazines. An earlier report of pheonothiazines containing a 3-carbon aliphatic side chain (chlorpromazine, methotrimeprazine, timeprazine tartrate, oxomemazine) found an increase in congenital anomalies.[108] More recent studies do not support this finding for chlorpromazine, prochlorperazine, triflupromazine, or thioridazine.[89]

Neonatal side effects of phenothiazine agents include jaundice, respiratory depression, intestinal hypomotility, and extrapyramidal syndrome. Extrapyramidal syndrome is manifested by tremors, flapping of the hands, hypertonia, arching of the back, and a persistent shrill cry. These symptoms typically begin during the first days of life and may persist for up to 6 months. This reaction displays a familial tendency.[93]

Maternal side effects such as sedation, decreased gastric motility, and orthostatic hypotension compound these symptoms routinely seen during pregnancy. Extrapyramidal effects are characterized by facial grimacing, torticollis, and tardive dyskinesia. Treatment of extrapyramidal side effects during pregnancy can be hazardous to the fetus. Diphenhydramine and anticholinergic agents have been associated with morphologic teratogenicity.[93] Maternal diphenhydramine administration can result in neonatal withdrawal, which is characterized by tremulousness and diarrhea. Routine prophylaxis of extrapyramidal side effects is not recommended during pregnancy. Other measures to improve maternal symptoms include calcium supplementation with prenatal vitamins, lowering the dose, or switching to another less potent antipsychotic medication. If extrapyramidal symptoms do require

treatment, an attempt should be made to discontinue the anticholinergic medication or the diphenhydramine 2 weeks before delivery. Other maternal side effects of phenothiazine antidepressants include increased prolactin secretion, jaundice, anticholinergic effects, hypothermia, decreased seizure threshold, urticaria, skeletal muscle relaxation, and neuroleptic malignant syndrome. Neuroleptic malignant syndrome can appear more severe during pregnancy. Drug interactions with anesthetic medications can produce a potentiation of ventilatory depression as well as miotic, sedative, and analgesic actions of opioids. All phenothiazines are excreted into breast milk. Chlorpromazine can be safely used by nursing women.[102] Other phenothiazines have not been well studied in nursing infants.

Benzodiazepines are used for the treatment and prevention of panic disorders during pregnancy. Alprazolam or lorazepam are the preferred benzodiazepines for treatment during pregnancy. No birth defects have been linked to alprazolam or lorazepam. At best, the risk of oral cleft formation resulting from first trimester exposure to alprazolam is small. Lorazepam is preferred over alprazolam because it has a longer duration of action, it lacks active metabolites, and it is not associated with an immediate and as severe a withdrawal syndrome in the neonate as alprazolam.[89] Oral cleft malformation resulting from first trimester exposure to benzodiazepines is controversial. A conservative assessment of the 14 studies in the literature assessing first trimester exposure and congenital anomalies finds significantly increased odds of clefts regarding diazepam.[82] Major birth defects have been associated with clonazepam exposure. Therefore, a maternal ultrasound exam of the fetus exposed to clonazepam should target ureteropelvic junction obstruction, inguinal hernias, an undescended testicle, and ventricular septal defect.[102]

Neonatal side effects of benzodiazepines include sedation and withdrawal. Neonatal withdrawal is characterized by hypertonia, hyperreflexia, restlessness, irritability, seizures, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, chewing movements, and abdominal distension. These symptoms can occur at birth or up to 3 weeks later and last up to several months. "Floppy infant syndrome" is characterized by muscular hypotonia, low Apgar scores, hypothermia, impaired response to cold, and neurologic depression.[89] Benzodiazepines are excreted in breast milk in low concentrations. Apnea, cyanosis, hypotonia, and periodic breathing were reported in an infant breast-fed by a mother taking clonazepam.[102]

Lithium carbonate is an alkali metal used for the treatment of manic-depressive illness. The dose of lithium is usually increased in pregnancy to compensate for increased renal clearance. Lithium freely crosses the human placenta resulting in equal maternal, umbilical, and neonatal levels.[109,110]

In the 1970s it was assumed that a strong association existed between maternal lithium treatment during pregnancy and Ebstein's anomaly based on biased retrospective reports. Recent reports from cohort and case-control studies concluded that Ebstein's anomaly is rare, and that lithium treatment in bipolar parturients should not be discontinued.[111,112] The baseline risk of Ebstein's anomaly is 1 in 20,000. The current risk for this anomaly after first trimester exposure to lithium is 1 in 1,000, 10 to 20 times the rate of the general population. Women treated with lithium during pregnancy should be offered a level II ultrasound and fetal echocardiography. Jacobson et al. also found that babies exposed to lithium were heavier than controls despite a higher proportion of cigarette smokers in the group of women taking lithium.[111] Women with bipolar disease who are pregnant or desire pregnancy can be reassured that lithium has been used safely during pregnancy by many parturients.[102]

Lithium is excreted almost exclusively through the kidneys. The dose of lithium in the pregnant patient should be increased to accommodate the increase in glomerular filtration rate seen in pregnancy, and then should be decreased after delivery to the prepregnant dose. Making these changes in lithium dosing will avoid an underdosage in the parturient and an overdosage accompanied by signs of intoxication immediately after delivery.[95,102] Lithium can impair the synthesis and release of thyroid hormones, resulting in a rise in the pituitary secretion of thyroid-stimulating hormone. Nontoxic goiters have been reported both in mothers treated with lithium and in their infants. A fetal goiter may necessitate a cesarean section for delivery.[102]

Maternal overdose of lithium has caused fetal and neonatal cyanosis, hypotonia, bradycardia, atrial flutter, hepatomegaly, T-wave inversion, cardiomegaly, gastrointestinal bleeding, diabetes insipidus, seizures, and shock.[89] Most of these adverse reactions are self-limited, resolving within 1 to 2 weeks after delivery. A 5-year follow-up study of children exposed to lithium in the second and third trimesters found no significant differences in developmental anomalies when compared to siblings not exposed to lithium.[82] Lithium drug levels found in breast milk are typically 50% of those in the mother's serum. Lithium toxicity, as described here, has been reported in breast-feeding infants. The toxicity is thought to arise from poor neonatal elimination of the lithium because of immature renal function.[103] Nursing mothers should either be partially or totally discontinued from lithium therapy.

Anesthetic implications with the use of lithium begin with parturient evaluation for diabetes insipidus and hypothyroidism.[113] Chronic therapy with lithium can produce benign reversible depression of T waves and make parturients susceptible to ST depression during anesthesia.[114] Lithium may also prolong the actions of both depolarizing and nondepolarizing muscle relaxants and potentiate barbiturates. Lithium therapy should not be discontinued before anesthesia, but the dose should be reduced to the lowest therapeutic level.

Carbamazepine is indicated in the treatment of epilepsy, trigeminal neuralgia, epilepsy, bipolar depression, psychosis, and alcohol withdrawal. Placental transfer of carbamazepine occurs freely, resulting in nearly equal maternal and umbilical blood levels.[115] Holmes et al. recently assessed the risk

of teratogenicity of anticonvulsant drugs.[116] They found a distinctive pattern of physical abnormalities in infants of mother taking anticonvulsant drugs. Epilepsy alone was not a risk factor for an increased rate of abnormalities. The frequency of embryopathy was higher in women taking one or more than one anticonvulsant when compared to controls. Carbamazepine was associated with tetralogy of Fallot, ventricular septal defects, esophageal atresia, vertebral anomalies, and multiple terminal transverse limb defects. The authors did not find an increased rate of hypoplasia of the face and fingers previously described in infants exposed to carbamazepine during pregnancy. Fetal carbamazepine exposure has also been associated with an increased incidence of spina bifida.[102] Carbamazepine should be viewed as a human teratogen. Monotherapy is less teratogenic than combination therapy.

Carbamazepine can cause vitamin K deficiency during the last half of pregnancy. Abnormal coagulation can result with uncontrolled bleeding in the central nervous system and permanent neurologic damage.[102] A transient vitamin K deficiency can also occur in the neonate may lead to intracerebral hemorrhage.[89] Vitamin K supplementation is required during pregnancy to reduce the risk of maternal and neonatal vitamin K-related coagulopathy. Carbamazepine levels in the infant's serum are typically low during breast-feeding.[102,103] Breast-feeding while taking carbamazepine is considered safe.

Valproic acid is indicated for the treatment of epilepsy and bipolar disease. Valproic acid readily crosses the placenta.[102] Holmes' assessment of the teratogenicity of anticonvulsant drugs included valproic acid.[116] Combination therapy with carbamazepine and phenytoin or phenobarbital and carbamazepine was associated with spina bifida and aortic valve stenosis. Prenatal exposure to valproic acid is typically associated with an increased risk of spina bifida.[82] A 10- to 20-fold increase in spina bifida is described with an incidence of 1% to 2% after first trimester exposure.[102] Deficiencies of vitamin K-dependent clotting factor occur as with carbamazepine. In addition, thrombocytopenia, reduced platelet aggregation, and low fibrinogen have been reported in pregnant women taking valproic acid.[102] Vitamin K supplementation is suggested to protect the mother and infant from valproate-induced coagulopathy. Valproic acid should be considered a human teratogen that can result in both major and minor congenital anomalies.

Valproic acid has been associated with intrauterine growth retardation, hyperbilirubinemia, hepatotoxicity, skeletal dysplasia, spina bifida, and fetal or newborn distress.[89] Valproic acid is excreted in breast milk in low concentrations, approximately 1% to 10% the concentration of maternal serum.[103] Fetal thrombocytopenia and hepatotoxicity have been reported, but the bulk of evidence indicates that breast-feeding is safe.

St. John's Wort is a nonprescription herbal treatment for depression. Grush[117] warned in a letter to the editor that St. John's wort has caused increased uterine tonicity in animals and perhaps should be avoided during pregnancy. Parturients assume that a nonprescription medication is "safe." Grush described two parturients who suffered from depression and took St. John's wort without telling their physician. One parturient actually discontinued her regular antidepressant and replaced it with St. John's wort. Both women delivered healthy infants.

Summary

Psychiatric disease is common during pregnancy, as a significant number of childbearing women are at a high risk for a mood disorder. This chapter summarizes the common psychiatric disorders and conditions unique to pregnancy, such as maternal response to perinatal death and adolescent pregnancy. Finally, the obstetric and anesthetic implications of electroconvulsive therapy and psychotropic drugs are thoroughly discussed here.

References

1. Saks BR, Frank JB, Lowe TL. Depressed mood during pregnancy and the puerperium: clinical recognition and implications for clinical practice. Am J Psychiatry 1985;142:728–731.
2. Schaper AM, Rooney BL, Kay NR, et al. Use of the Edinburgh postnatal depression scale to identify postpartum depression in a clinical setting. J Reprod Med 1994;39(8):620–624.
3. ACOG Technical Bulletin No. 182. ACOG, 1993.
4. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. Int J Psychiatry Med 1991;21(2):157–171.
5. Tunis SL, Golbus MS. Assessing mood states in pregnancy: survey of the literature. Obstet Gynecol Surv 1991;46(6):340–346.
6. Ballard CG, Davis R, Cullen PC, et al. Prevalence of postnatal psychiatric morbidity in mothers and fathers. Br J Psychiatry 1994;164: 782–788.
7. Gitlin MJ, Pasnau RO. Psychiatric syndromes linked to reproductive function in women: a review of current knowledge. Am J Psychiatry 1989;146:1413–1422.
8. Tylden E. Psychiatric disorders including drug therapy and addiction. Clin Obstet Gynecol 1977;4(2):435–439.
9. Burger JA, Horwitz SM, Forsyth WC, et al. Psychological sequelae of medical complications during pregnancy. Obstet Gynecol Surv 1993; 48(10):649.
10. Evans J, Heron J, Francombe H, et al. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001;323:257.
11. Depression in Primary Care, Vol 1. Detection and Diagnosis. AHCPR Publication No. 93-0550. Washington, DC: U.S. Department of Health and Human Services. 1993.
12. Zuckerman B, Amaro H, Bauchner H III, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989;160:1107–1111.
13. Wolman WL, Chalmers B, Hofmeyr GJ, et al. Postpartum depression and companionship in the clinical birth environment: a randomized, controlled study. Am J Obstet Gynecol 1993;168:1388–1393.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 3rd edn. Washington, DC: American Psychiatric Press, 1987.
15. Harris B, Lovett L, Newcombe RG. Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. BMJ 1994;308:949–953.

16. Quadagno DM, Dixon LA, Denney NW, et al. Postpartum moods in men and women. Am J Obstet Gynecol 1986;154:1018–1023.
17. Coyne JC, Schwenk TL. Depression in the female patient. Female Patient 1994;19:59.
18. O'Hara MW, Engeldinger J. Postpartum mood disorders—detection and prevention. Female Patient 1989;14:19.
19. O'Hara MW. Social support, life events, and depression during pregnancy and the puerperium. Arch Gen Psychiatry 1986;43:569–573.
20. Standley K, Soule B, Copans S. Dimensions of prenatal anxiety and their influence on pregnancy outcome. Am J Obstet Gynecol 1979;135: 22–26.
21. Romito P. Unhappiness after childbirth. In: Effective Care in Pregnancy and Childbirth. New York: Oxford University Press, 1991.
22. Michelacci L, Fava GA, Grandi S, et al. Psychological reactions to ultrasound. Psychother Psychosom 1988;50:1–4.
23. Spencer JW, Cox DN. Emotional responses of pregnant women to chorionic villi sampling or amniocentesis. Am J Obstet Gynecol 1987;157: 1155–1160.
24. Franko DL, Spurrell EB. Detection and management of eating disorders during pregnancy. Obstet Gynecol 2000;95:942–946.
25. Neziroglu F, Anemone R, Yaryura-Tobias JA. Onset of obsessive-compulsive disorder in pregnancy. Am J Psychiatry 1992;149:947–950.
26. Otchet F, Carey MS, Adams L. General health and psychological symptoms status in pregnancy and the puerperium. What is normal? Obstet Gynecol 1999;94:935–941.
27. Oldham JM. Personality disorders: current perspectives. JAMA 1994; 272:1770–1776.
28. Leaman TL. Anxiety disorders: reaching the untreated. Female Patient 1983;18:78.
29. McArthur P, Kellner CH, Pritchett JT. Panic induced by lactate infusion during electroconvulsive therapy. J Nerv Ment Dis 1994;182(1): 55–56.
30. Tsen LC, Datta S. Panic attacks and lactated Ringers solution: is there a relationship? Anesth Analg 1999;88:795–796.
31. Ware MR, DeVane CL. Imipramine treatment of panic disorder during pregnancy. J Clin Psychiatry 1990;51:482–484.
32. Villeponteaux VA, Lydiard RB, Laraia MT. The effects of pregnancy on pre-existing panic disorder. J Clin Psychiatry 1992;53:201–203.
33. Gottlieb SE, Barrett DE. Effects of unanticipated cesarean section on mothers, infants, and their interaction in the first month of life. J Dev Behav Pediatr 1986;7(3):180–185.
34. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychosis. Br J Psychiatry 1987;150:662–673.
35. Campbell DA. Chronic subdural hematoma following epidural anaesthesia presenting as puerperal psychosis. Br J Obstet Gynecol 1993; 100:782–784.
36. Zeanah CH, Dailey JV, Rosenblatt M, et al. Do women grieve after terminating pregnancies because of fetal anomalies? Obstet Gynecol 1993;82:270–275.
37. Graham MA, Thompson SC, Estrada M, et al. Factors affecting psychological adjustment to a fetal death. Am J Obstet Gynecol 1987; 157:254–257.
38. Kellner KR, Donnelly WH, Gould SD. Parental behavior after perinatal death: lack of predictive demographic and obstetric variables. Obstet Gynecol 1984;63:809–814.
39. Wilson AL, Witzke D, Fenton LJ, et al. Parental response to perinatal death. AJDC (Am J Dis Child) 1985;139:1235–1238.
40. Theur SK, Pedersen FA, Zaslow MJ, et al. Pregnancy subsequent to a perinatal loss: parental anxiety and depression. J Am Acad Child Adolesc Psychiatry 1988;27(3):289.
41. Lambert W. The loss of a baby is doubly crushing to a young couple. Wall Street J 1995:A11.
42. Harlap S, Kost K, Forrest JD. Preventing Pregnancy, Protecting Health: A New Look at Birth Control Choices in the U.S. New York: The Alan Guttmacher Institute, 1991.
43. Kessler RC, Berglund PA, Foster CL, et al. Social consequence of psychiatric disorders. II. Teenage parenthood. Am J Psychiatry 1997;154: 1405–1411.
44. Wagner KD, Berenson A, Harding O, et al. Attributional style and depression in pregnant teenagers. Am J Psychiatry 1998;155:1229–1233.
45. Fones C. Posttraumatic stress disorder occurring after painful childbirth. J Nerv Ment Dis 1996;184(3):195–196.
46. Reynolds LJ. Post-traumatic stress disorder after childbirth: the phenomenon of traumatic birth. Can Med Assoc J 1997;156(6):831.
47. Goldbeck-Wood S. Post-traumatic stress disorder may follow childbirth. BMJ 1996;313:774.
48. Grossi NA. A little pregnant, or not at all? Pharos 1999;16.
49. Silva AJ, Leog GB, Weinstock R. Misidentification syndrome and male pseudocyesis. Psychosomatics 1991;32(2):228–230.
50. Small GW. Pseudocyesis: an overview. Can J Psychiatry 1986;31:452.
51. O'Grady JP, Rosenthal M. Pseudocyesis: a modern perspective on an old disorder. Obstet Gynecol Surv 1989;44(7):500–511.
52. Snyder RW. Brochogenic carcinoma presenting as a pseudopregnancy. Chest 1995;108(3):885.
53. Fennig S, Chelban J, Naisberg-Fennig S, Neumann M. Pseudopregnancy, prenatal, and postpartum psychosis: a case study. J Nerv Ment Dis 1995;183(2):114–115.
54. Sobel DE. Fetal damage due to ECT, insulin coma, chlorpromazine or resperpine. Arch Gen Psychiatry 1960;2:606.
55. Crowe RR. Electroconvulsive therapy—a current perspective. N Engl J Med 1984;311(3):163–167.
56. Katz G. Electroconvulsive therapy from a social work perspective. Soc Work Health Care 1992;16(4):55–68.
57. Kendell RE. The present status of electroconvulsive therapy. Br J Psychiatry 1981;139:265–283.
58. Weiner RD. Convulsive therapy: 50 years later. Am J Psychiatry 1984; 141(9):1078–1079.
59. Repke JT, Berger NG. Electroconvulsive therapy in pregnancy. Obstet Gynecol 1984;63:39S–41S.
60. Yellowlees PM, Terissa P. Safe use of electroconvulsive therapy in pregnancy. Med J Aust 1990;153:679–680.
61. Griffiths EJ, Lorenz RP, Baxter S, et al. Acute neurohumoral response to electroconvulsive therapy during pregnancy. J Reprod Med 1989; 34(11):907–911.
62. Sherer DM, D'Amico ML, Warshal DP, et al. Recurrent mild abruptio placentae occurring immediately after repeated electroconvulsive therapy in pregnancy. Am J Obstet Gynecol 1991;165:652–653.
63. Boyd DA, Brown DW. Electric convulsive therapy in mental disorders associated with childbearing. J Mo Med Assoc 1948;45(8):573.
64. Wells DG, Zelcer J, Treadrae C. ECT-induced asystole from a subconvulsive shock. Anaesth Intensive Care 1988;16(3):368–371.
65. Heshe J, Roeder E. Electroconvulsive therapy in Denmark. Br J Psychiatry 1976;128:241–245.
66. Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry 1994;45(5):444–450.
67. Livingston JC, Johnstone WM, Hadi HA. Am J Perinatol 1994;11(2): 116.
68. Polster DS, Wisner KL. ECT-Induced premature labor: a case report. J Clin Psychiatry 1999;60(1):53–54.
69. Lew JK, Eastley RJ, Hanning CD. Oxygenation during electroconvulsive therapy. Anaesthesia 1986;41:1092–1097.
70. Räsänen J, Martin JB, Hodges MR. Oxygen supplementation during electroconvulsive therapy. Br J Anaesth 1988;61:593–597.
71. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–1015.
72. Cohen LS, Rosenbaum JF. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1997;336:872.
73. Nulman I, Rovert J, Stewart D, et al. Neurodevelopment of children exposed to antidepressant drugs. N Engl J Med 1997;336:258–262.
74. Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993; 269(17):2246–2248.

75. Goldstein DJ. Effect of third trimester fluoxetine exposure on the newborn. J Clin Psychopharmacol 1995;15:417–420.
76. McElhatton PR, Garbis HM, Elefant E, et al. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 1996;10:285–294.
77. Goldstein DJ, Corbin LA, Sundell KL. Effects of first-trimester fluoxetine exposure on the newborn. Obstet Gynecol 1997;89:713–718.
78. Robert E. Treating depression in pregnancy. N Engl J Med 1996; 335:1056.
79. Nerhood RC. Fluoxetine and pregnancy a safe mix? Postgrad Med 1998;104(5):37–38.
80. Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors. JAMA 1998;279:609–610.
81. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. Am J Psychiatry 1996;153(9):1132–1137.
82. Altshuler L, Choen L, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606.
83. Wisner KL, Gelenberg AJ, Leonard H, et al. Pharmacologic treatment of depression during pregnancy. JAMA 1990;282:1264–1269.
84. Miller LJ. Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatr Med 1991;9(2):276–298.
85. Guze BH, Guze BA. Psychotropic medication use during pregnancy. West J Med 1989;151:296–298.
86. Kuenssberg EV, Knox JDE. Impraminie in pregnancy. Br Med J 1972; 2:292.
87. Rachelfsky GS, Flynt JW, Ebbin AJ, et al. Possible teratogenicity of tricyclic antidepressants. Lancet 1972;1:838.
88. Idanpaan-Heikkila J. Possible teratogenicity of Imipramine/chloropyramine. Lancet 1972;2:282–284.
89. American Academy of Pediatrics, Committee on Drugs. Use of psychoactive medication during pregnancy and possible effects of the fetus and newborn. Pediatrics 2000;105(4):880.
90. Nulman I, Rovet J, Stewart DE, et al, for the Motherisk Program, Hospital for Sick Children and University of Toronto. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258–262.
91. Edwards RP, Miller RD, Roizen RF, et al. Cardiac responses to imipramine and pancuronium during anesthesia with halothane or enflurane. Anesthesiology 1979;50:421–425.
92. Wong KC, Puerto AX, Puerto BA, et al. Influence of imipramine and pargyline on the arrhythmogenicity of epinephrine during halotane, enflurane, or methoxyflurane anesthesia in dogs. Life Sci 1980;27:2675–2678.
93. Miller LJ. Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatr Med 1991;9(2):276–298.
94. Poulson E, Robson J. Effect of phenelzine and some related compounds on pregnancy. J Endocrinol 1964;30:205.
95. Schou M. Treating recurrent affective disorders during and after pregnancy. Drug Saf 1988;18(2):143–152.
96. Moran DH, Perillo M, LaPorta RF, et al. Phenylephrine in the prevention of hypotension following spinal anesthesia for ceasarean delivery. J Clin Anesth 1991;3:301–305.
97. Pavy TJ, Kliffer PA, Douglass JM. Anaesthetic management of labour and delivery in a woman taking long-term MAOI. Can J Anesth 1995; 42(7):618–620.
98. Stack CG, Rogers P, Linter SPK. Monoamine oxidase inhibitors and anaesthesia. Br J Anaesth 1988;60:222–227.
99. El-Ganzouri AR, Ivankovick AD, Braverman B. Monoamine oxidase inhibitors: should they be discontinued preoperatively? Anesth Analg 1985;64:592–596.
100. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamine oxidase-A inhibitor moclobemide. Clin Pharmacokinet 1995; 29(5):292–332.
101. Kopelman AE, McCullar FW, Heggeness L. Limb malformations following maternal use of haloperidol. JAMA 1975;231:62.
102. Iqbal MM, Gundlapalli SP, Ryan WG, et al. Effects of mood-stabilizing drugs on fetuses, neonates, and nursing infants. South Med J 2001; 94(3):304–322.
103. Kuller JA, Katz VL, McMahon MJ, et al. Pharmacologic treatment of psychiatric disease in pregnancy and lactation: fetal and neonatal effects. Obstet Gynecol 1996;87:789–794.
104. Goldstein DJ, Corbin LA, Fung MC. Olanzapine exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000;20:399–403.
105. Pinkofsky HB, Fita-Gerald MJ, Reeves RR. Psychotropic treatment during pregnancy. Am J Psychiatry 1997;154(5):718–719.
106. Waldman MD, Saffeman AZ. Pregnancy and clozapine. Am J Psychiatry 1993;150:168–169.
107. Lieberman J, Safferman AZ. Clinical profile of clozapine: adverse reactions and agranulocytosis. Am J Psychiatry 1993;150:168.
108. Rumeau-Roquette C, Goujard J, Huel G. Possible teratogenic effects of phenothiazines in human beings. Teratology 1977;15:57.
109. Linden S, Rich CL. The use of lithium during pregnancy and lactation. J Clin Psychiatry 1983;44:358–361.
110. Mackay AV, Loose R, Glenn AI. Labor on lithium. Br Med J 1976; 1:878.
111. Jacobson SJ, Jones K, Johnson K. et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992;339:530–533.
112. Cohen LS, Friedman MD, Jefferson JW, et al. A reevaluation of risk in in utero exposure to lithium. JAMA 1994;271:146–150.
113. Havdala HS, Borison RL, Diamond BI. Potential hazards and applications of lithium in anesthesiology. Anesthesiology 1979;50:534–537.
114. Pratila MG, Pratilas V. ST depression under anesthesia in a patient on lithium carbonate. Mt Sinai J Med 1979;46(6):549–551.
115. Niebyt JR, Blake DA, Freeman JM, et al. Carbamazepine levels in pregnancy and lactation. Obstet Gynecol 1979;53:139–140.
116. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344:1132–1138.
117. Grush LR. St. John's wort during pregnancy. JAMA 1998;28(18):1566.

30
Hepatic Disease

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There are many associations between liver dysfunction and pregnancy, but isolated liver disease rarely occurs during pregnancy. Some normal pregnancy-induced changes occur in the physiology, chemistry, and anatomy of the liver, but such changes, if taken to the extreme, can cause perturbations in maternal and fetal outcome. There are a few, fortunately very rare, disorders such as acute fatty liver of pregnancy (AFLP) and hepatic rupture that carry a high mortality rate for both the mother and baby.[1,2] In addition, maternal hepatic disease may pose an infectious risk to the fetus, such as some forms of hepatitis or cytomegalovirus virus infection (CMV), which may pose serious consequences for the neonate.[3,4]

It is relatively common to have a benign hyperbilirubinemia with associated pruritis and mild jaundice in pregnancy. However, if this situation is progressive, it can present as a severe condition such as intrahepatic cholestasis of pregnancy or symptomatic cholecystitis.[5,6] Most of the life-threatening disorders affecting the liver during pregnancy are variants of the late gestational hypertension-related syndromes such as the syndrome of hemolysis, elevated liver function tests, and low platelets (HELLP syndrome), AFLP, or acute hepatic rupture.[7] Pregnancy-related liver dysfunction, regardless of its morbidity potential, often poses a diagnostic dilemma because the presenting symptoms tend to be very nonspecific. These symptoms may be difficult to differentiate from normal symptoms related to pregnancy, such as nausea, lethargy, abdominal bloating, and pain. In other cases, coexisting maternal hepatic disease may affect the management and outcome of the pregnancy, as in the case of a woman with a prior liver transplant or a woman with alcoholic liver dysfunction.

In this chapter, we address the common and uncommon hepatic disorders occurring during pregnancy and the clinical management of altered hepatic function. Disorders that define a pregnancy as high risk are specifically addressed. The obstetric and anesthetic management of these women is discussed.

Normal Physiologic and Laboratory Alterations of Pregnancy

In uncomplicated pregnancies, physiologic changes and laboratory test abnormalities occur that may mimic liver disease.[8] Skin changes such as palmar erythema and telangiectasia occur in more than half of pregnant women. The liver is not usually enlarged or painful during pregnancy, but abdominal distension and stretching caused by the gravid uterus may confuse the physical examination. In addition the liver is forced superiorly and posteriorly as the pregnancy progresses, with a palpable liver in the third trimester indicating hepatic disease. Liver size normally stays the same, as does liver blood flow during pregnancy. However, the fraction of the cardiac output devoted to the liver is reduced approximately 35% in pregnancy, preferentially perfusing the uterus instead. Engorged hepatic veins are visible in more than one-half of pregnancies on endoscopy or laparotomy.

Usually, no changes in laboratory values occur for most liver enzymes during pregnancy. However, up to a fourfold increase in alkaline phosphatase in the third trimester may occur due to placental enzyme production. Late pregnancy decreases in serum albumin (but not of α-globulins and β-globulins) are normal. Triglyceride and cholesterol levels often rise during pregnancy. Bile formation and its transport are inhibited normally during pregnancy.[9] Therefore, at term, bilirubin may be at the upper limits of normal or slightly higher without liver disease. A leukocytosis (to 18,000–20,000/mm^3) and a dilutional anemia are normal during pregnancy. Normally, there is a tendency to become hypercoagulable during pregnancy with increases in many clotting factors and normal platelet counts, except in some hypertension-related syndromes.[10]

Cytochrome P_{450} activity is decreased during pregnancy, whereas hepatic mixed function oxidase activity is induced. Decreased levels of plasma esterases responsible for degrading succinylcholine and ester local anesthetics normally occur during pregnancy. The effects of these changes on anesthetic drug metabolism are unpredictable.

TABLE 30.1. Liver function tests in normal pregnancy and disease states compared to normal nonpregnant females.

Diagnosis	Normal pregnancy	ICP	Cirrhosis	Acute hepatitis	Preeclampsia	HE LLP	AFLP
Onset		Third trimester	Precedes pregnancy	Any time	After 20 weeks	After 20 weeks	After 20 weeks
Albumin	−10%–60%	0	− to −−				—
Total protein	−15%	0	−		—		—
Total bilirubin	Normal range	+		0 to +++		0 to ++	+ to ++
Bilirubin direct	Normal range	+		+ marked			
Bilirubin indirect	Normal range	+					
AST/SGOT	0	0 or mild +	0 to ++	0 to ++++	0 to ++	+ to ++	++ to +++
ALT/SGPT	0	0 or mild +	0 to ++	0 to ++++	0 to ++		+ to ++
Lactate dehydrogenase	0	+					>500
5′-nucleotidase							
γ-GGT	0, possible increase in third trimester					0 to ++	+ to ++
Total alkaline phosphatase	+ 200 to 400%	0 or slight +	++				0 or ++
α- and β-globulins	Variable		—				
Cholesterol	+ 200%	0	?				
Glucose	0	0	− to −−	0 or −		0	—
Ammonia	0	0	+ with porto-systemic shunting	0 or rarely +	—	0	+
Platelets	0 or slight −	0	− with 2° hypersplenism	0	—	− to −−	− to −−
Fibrinogen	+ 50%	0	−	+/−			
Prothrombin time	Normal	0 if + then R_x with vitamin K	0 to ++	0 to ++	0 to ++	0 to ++	++

LFT, liver function test; ICP, intrahepatic cholestasis of pregnancy; HELLP, hemolysis/elevated liver enzymes/low platelets syndrome; AFLP, acute fatty liver of pregnancy; AST/SGOT, aspartate aminotransferase; ALT/SGPT, alanine aminotransferase; γ-GGT, gamma-glutamyl transpeptidase.

The physiologic and laboratory abnormalities that occur in the normal pregnant state and also in pregnancies complicated by different liver diseases are shown in Table 30.1.[11]

Hepatic Dysfunction During Pregnancy

Symptoms of hepatic dysfunction during pregnancy are notoriously insidious and the diagnosis elusive. When serious and unmistakable liver disease does occur, the differentiation between diagnosis is subtle initially and may be impossible except in retrospect.[9] The decrease in the proportion of cardiac output devoted to the liver in the latter half of pregnancy diminishes hepatic reserve if a decrease in perfusion pressure or blood volume occurs. Some women with liver disease may ignore their symptoms, because of normal pregnancy-related discomfort, until late-stage disease when intraperitoneal hemorrhage, variceal bleeding, or encephalopathy occur. Certainly if a physician should discover signs of jaundice, hepatomegaly, ascites, or right upper quadrant pain in the mother, these symptoms should prompt intensive investigation (see Table 30.1).[11]

Implications of Altered Hepatic Function for the Parturient and Fetus

Mild alterations in hepatic function are usually well tolerated by mother and fetus. With concurrent asymptomatic liver disease, however, the rate of maternal inability to conceive is greater. Infertility may be multifactorial, and menstrual irregularities may be the only symptom of liver disease.[12] Disturbances of the hypothalamic–pituitary axis may exist, as well as increased production of prolactin and disturbances of peripheral estrogen conversion to androgenic compounds, when liver dysfunction is severe enough to produce portal sytemic shunting.[13]

If the mother does conceive, the whole maternofetal unit may be affected if liver disease is severe enough to be symptomatic or require medical treatment. At times the coagulation system is altered, maternal acid–base status is affected, or uterine irritability occurs related to hepatic dysfunction. Hepatic dysfunction then can have profound implications on the outcome of the pregnancy as well as the anesthetic choices feasible for the anesthesiologist.

Pathophysiology

The liver performs a variety of important physiologic and metabolic functions (Table 30.2). The liver is responsible in part for glycogenesis, glycogenolysis, and gluconeogenesis. There is no evidence that the hepatic contribution to these processes is altered in normal pregnancy, but parturients with liver disease may require close monitoring for hypoglycemia. In addition, severe forms of liver disease may affect both lactate production and elimination. Fat metabolism may be af-

TABLE 30.2. Physiologic and metabolic functions of the liver.

Carbohydrate metabolism	Glycogenesis, glycogenolysis, gluconeogenesis
Protein synthesis	Coagulation factors, esterases, plasma proteins
Fat metabolism	
Hormone synthesis	
Bilirubin formation and excretion	
Toxin degradation	Exogenous and endogenous toxins (ammonia to urea)
Bacterial phagocytic activity`	

fected in a variety of ways. In the event of cholestasis, fat absorption (including the fat-soluble vitamins A, D, E, and K) may be impaired. Derangement of hepatic synthetic activity may also decrease cholesterol available for bile acid and sex hormone production.

Alpha- and beta-globulins, ceruloplasmin, transferrin, coagulation factors, and several hormone-binding globulins are synthesized at a higher rate during pregnancy, although total body albumin levels are decreased. Gravidity, already a state of low oncotic pressure, when combined with liver disease can lead to ascites, pleural and pericardial effusions, and substantial soft tissue edema. Decreased protein binding of some drugs affects their metabolism and requires dosage adjustments, especially in the case of some nondepolarizing muscle relaxants, amide local anesthetics, diazepam, meperidine, morphine, and some others (Table 30.3).

In addition to altered metabolism of exogenous substances, endogenous ammonia metabolism may be affected. The presence of hyperammonemia is usually indicative of severe hepatic dysfunction and is seen commonly in patients with portal hypotension with portosystemic shunting and in AFLP.

The discussion of all the implications associated with liver function tests is beyond the scope of this chapter, but in general, several key points must be kept in mind.

Intrinsic Hepatocellular Dysfunction

When abnormal transaminase levels are seen, it should be remembered that alanine aminotransferase (ALT) is found primarily in the liver, whereas aspartate aminotransferase (AST) is found also in the heart, muscle, kidney, and brain. Elevations of one or the other of these hepatic markers may roughly indicate the severity of hepatic involvement, but serial assays are recommended because correlation is poor. Most commonly, the ratio of AST/ALT is approximately 1:1. Exceptions include alcoholic hepatitis with an AST/ALT ratio greater than 2 (due to the vitamin B deficiency-induced reduction of hepatic ALT); in AFLP the AST/ALT also may be greater than 1. Alkaline phosphatase elevations may be useful to indicate hepatocellular dysfunction versus cholestatic hepatic disease.

Sulfobromophthalein (BSP) and indocyanine green (ICG) aminopyrine breath test and antipyrine clearance, galactose elimination capacity (GAL), and monoethylglycinexlidid formation (MEGX-F) are tests that utilize dyes or drugs injected intravenously followed by periodic blood concentration sampling to determine hepatic metabolic function. Interpretation of these tests is difficult, and clinical use is limited, but the later two have been used to predict the safe limits for hepatectomy.[14,15]

Cholestatic Dysfunction

Cholestasis indicates that there is a reduction in the hepatic excretion of bile. Bilirubin can be toxic to several enzyme systems involved in oxidative phosphorylation, glycolysis, protein biosynthesis, and metabolism. Membrane function may be adversely effected by high concentrations of bilirubin. Direct bilirubin is not neurotoxic, whereas elevated indirect bilirubin levels are neurotoxic. A combined elevation of both direct and indirect bilirubin levels implies impaired secretion into the bile, whereas an isolated increased indirect bilirubin implies impaired conjugation. This latter problem occurs with hemolytic anemias, Gilbert's syndrome, and Crigler–Najjar syndrome. Cholemia may impair myocardial function and blunt the response to endogenous vasopressors, augmenting the myocardial dysfunction that is more importantly associated with the physiologic changes associated with cirrhosis. In addition, elevated levels of bile affect vitamin K absorption and augment coagulopathy. Vitamin K is often supplemented in patients with hyperbilirubinemia, and a failure to respond to supplementation may indicate parenchymal hepatic dysfunction.

Coagulation Cascade Dysfunction

Most of the coagulation factors are synthesized in the liver, so abnormalities of these herald severe hepatic dysfunction. Decreases in platelet counts, that is HELLP syndrome, and some cases of severe preeclampsia primarily diagnose specific hepatic diseases.

Metabolic Problems

In very severe liver disease, renal failure with subsequent acidosis may develop, which will be indicated by elevations in blood urea nitrogen (BUN) and rising creatinine. The hepatorenal syndrome carries a very high mortality rate. Although not a true liver function test, a low BUN in hepatic disease may indicate severe deterioration in the hepatic synthesis of urea.

It has been suggested that when liver disease is suspected that laboratory examination should include AST, ALT, alkaline phosphatase, total bilirubin and bilirubin fractionation, LDH (lactate dehydrogenase), albumin, a complete blood count including platelet count, and prothrombin time.[11] Viral and infectious markers are required if hepatitis is suspected. Measurements of the coagulation parameters, especially the protime (PT), and albumin levels are the most common clinical tests utilized to classify hepatic synthetic dysfunction and to provide prognosis for hepatic disease; this is commonly referred as the Child–Turcotte classification with Pugh modification (Table 30.4).[16] Ultimately, liver biopsy is needed to diagnose many types of disease, but in acute hepatic failure the

TABLE 30.3. Anesthetic agents used in pregnant patients with liver disease.

Type of drug	Drug name	Pharmacokinetic alterations in cirrhotics	Notes
Intravenous induction agents	Thiopental	Unaltered metabolism due to redistribution as termination effect	Smaller induction doses recommended in severe disease
	Propofol	Unaltered	Duration is prolonged
	Etomidate	Metabolic half-life prolonged twofold	Hemodynamics stable in hypovolemia
	Ketamine	Insufficient data	Side effects profile; arrhythmia inducing
Narcotic agents	Morphine	Conflicting reports	Reports of prolonged effects; potentiates encephalopathy
	Meperidine	Metabolic half-life prolonged	Prolonged effects; Spincter of Oddi spasm may occur
	Fentanyl	At normal clinical doses (<15 μg/kg) unaltered; large V_D, fat and muscle	Probable narcotic of choice; avoid large doses; sphincter of Oddi spasm possible
	Sufentanil	Same as fentanyl	Same as fentanyl
	Alfentanil	Protein bound (small V_D); accumulation occurs	Poor choice in cirrhosis
	Remifentanil	Unaltered?	No postoperative pain relief
Antianxiety/amnestic agents	Valium	Metabolic half-life prolonged	Active metabolites, thrombophebitis
	Midazolam	Metabolic half-life slightly prolonged	Potentiates hepatic encephalopathy
	Ativan		Prolonged effects
Muscle relaxants	Succinylcholine	Decreased plasma cholinesterase levels	Possible prolonged effects, especially with redosing
	Rapacuronium	Insufficient data	Bronchoconstriction reported
	Atracurium	No hepatic degradation; Hoffman elimination	Histamine release; laudanosine production
	Cisatracurium	Similar to atracurium	Minimal histamine release
	Vecuronium	Dose-dependant clearance	Prolonged effects at higher doses (>0.1 mg/kg)
	Mivacurium	Insufficient data; decreased plasma esterases	Greater histamine release than atracurium
	Rocuronium	Normal metabolism; increased Vdl; prolonged recovery at higher doses	Careful dosing at larger doses
	Pancuronium	Normal metabolism; increased Vdl; prolonged recovery	Careful dosing; full reversal; tachycardia and proarrhythmia effects
	Pipecuronium	Insufficient data	Probably similar to pancuronium without heart rate effects
	D-Tubocurare	?Unaltered	Histamine release; prolonged action in large doses
Muscle relaxant reversal agents	Neostigmine	Unaltered metabolism	
	Edrophonium	Unaltered	Recurarization possible with longer-acting muscle relaxants
	Robinol		
	Atropine	Prolonged effects	Undesired tachycardia
Inhalation agents	Halothane	Rare idiosyncratic hepatitis	Avoid in hepatic disease
	Sevoflurane	Insufficient data	
	Isoflurane	Dose-dependent reduction of liver blood flow	Good experience with this agent
	Enflurane	Lowers hepatic blood flow	Renal toxicity
	Desflurane	Insufficient data	Similar to isoflurane
	Nitrous oxide	Unchanged, insoluble gaseous agent	Probably safe; increased pulmonary arterial pressures
Local anesthetics (epidural)	Lidocaine	Amide local anesthetic; prolonged metabolism and active metabolite (MEGX)	Use minimum dose
	Bupivacaine	Amide, no active metabolite	Probably similar dosing to lidocaine; cardiotoxic effects reported in pregnancy
	Chirocaine	Amide local anesthetic; insufficient data	Less cardiotoxicity than bupivicaine
	Ropivacaine	Amide local anesthetic; insufficient data	Less cardiotoxicity than bupivacaine; less motor blockade
	2-Chloroprocaine	Ester local anesthetic; rapid degradation by cholinesterases	May be best choice; toxicity reported in cases of abnormal cholinesterases
Miscellaneous	Metaclopramide		Dysphoric effects
	Droperidol	Prolonged effect in severe liver failure	Dysphoric effects; enhanced opiate effects
	Odansetron	Unchanged	Fewer CNS side effects

mother may require stabilization and correction of coagulation defects before obtaining the biopsy. Liver biopsy is required to diagnose definitively diseases such as alcoholic cirrhosis, AFLP, some types of hepatitis, and Wilson's disease.[17]

Fetal Considerations

Hepatic dysfunction in the parturient may cause placental insufficiency or maternal hyperbilirubinemia. The rate of vertical transmission of maternal infection varies with the type of infectious agent. Many of the hypertensive-related diseases of pregnancy have associated placental insufficiency on the basis of placental infarction and abnormal cellular development. This dysfunction will result in a failure of normal neonatal weight gain and growth and activity and in some cases serves as an obstetric indication to deliver the baby. With chronic liver disease, concomitant maternal malnutrition also will accentuate the poor placental supply of nutri-

Table 30.4. Child-Turcotte classification with Pugh modification.

Condition	Mild liver disease	Moderate liver disease	Severe liver disease
Albumin (g/dL)	>3.5	3.0–3.5	<3.0
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Ascites	None	Controlled	Uncontrolled
Encephalopathy	None	Minimal	Coma
Nutrition[a]	Excellent	Good	Wasted
Prothrombin time (PT) prolongation(s)[a]	<4.0	4.0–6.0	>6.0
Operative mortality	0%–10%	4%–31%	19%–76%

[a]The Pugh modification replaces nutrition with PT prolongation.
Source: Pugh R, Murray-Lyon I, Dawson J, et al. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973;60:646–649. Used with permission.

ents. Maternal hyperbilirubinemia: has been associated with increased irritability and tonus in the uterus and a propensity to develop preterm labor.[5]

The ability for infection to be transmitted from the mother to the baby varies with different types of hepatitis and other infections [cytomegalovirus (CMV), human immunodeficiency virus (HIV), etc.], the timing and chronicity of maternal infection, and the type of infectious vector.

Obstetric and Anesthetic Management

Once it is known that a parturient has hepatic disease, the next logical step in her management is an assessment of the severity of liver dysfunction. The etiology of the disease should be determined also, so as to specifically detail treatment. The majority of early chronic or benign hepatic disorders do not change the normal management of the pregnancy, other than close monitoring to ensure that preexisting liver function is maintained. The following general recommendations apply to general liver dysfunction management; diagnosis-specific management is discussed in the following individual sections.

Obstetric Management

High surgical morbidity is associated with most severe hepatic diseases; therefore, these women are generally advised to deliver vaginally if that is a feasible option.[18] Operative delivery is reserved for those cases where maternal health is rapidly declining or the fetus is in imminent danger. The care of these parturients and their offspring can be very expensive in terms of level of care, time, and resources. A decision must be made early in the management whether the institution is capable of the care required for these women. In some cases, the best decision may be to triage these women early in the pregnancy to an appropriate care facility with an intensive care nursery capable of taking care of very premature and sick neonates. In some cases of established or impending maternal fulminant liver failure, triage to a facility with liver transplantation services is the best choice.

In other cases in which maternal health is jeopardized by the pregnancy, preconception counseling will allow the woman to make the best decisions. A pregnant woman may choose early termination of the pregnancy. If the mother elects to carry her pregnancy to delivery, then plans for the timing and mode of delivery should be made and coordinated with the other specialties involved in her care, such as medicine and pediatric services as well as the obstetrician and anesthesia team.

Anesthetic Management

When approaching the parturient with hepatic disease, it must be determined if cirrhosis or hepatocellular destruction exists. If there is no hepatic damage, then for the most part, these women can be treated no differently than other parturients. The differentiation between chronic stable disease and acute disease must be determined. Any woman with cirrhosis has an increased anesthetic risk, but those women with more advanced disease present special problems with minimal room for error or inattention. A careful preoperative search for the sequelae of cirrhosis is mandatory. A common approach to classification of the severity of the liver disease has been that based on that the Child–Turcotte description system[16,19] (see Table 30.4). A multidisciplinary approach is optimal for management of these parturients.

A search for the systems affected by the liver disease that will affect anesthetic management must be made, including the coagulation system, cardiac and pulmonary systems, vascular system, and the presence or absence of esophageal varices.[20] Predelivery interventions should be directed at normalizing coagulation, nutritional, and cardiovascular parameters. A hematology consult may be required if early attempts to correct coagulation defects are not successful. Vitamin K supplementation and other dietary management with attention to protein intake should be instituted early. Immediately before anticipated delivery, careful optimization of volume status must be achieved, which may involve guidance by monitors of central venous, peripheral arterial, and pulmonary artery pressures. Frequent laboratory studies often accompany the perioperative period and are facilitated by large-bore vascular catheters. Appropriate blood bank arrangements are mandatory because parturients with liver disease require albumin infusion frequently, and the potential for hemorrhage

exists. In the delivery room, it may prove useful to have immediate access to blood products, because hypotension and intravascular depletion are poorly tolerated by the parturient's compromised liver.

Women with ascites, encephalopathy, and pregnancy are at higher risk for aspiration. Gastroentestinal prophylactic measures against aspiration are prudent in these cases, but drugs with sole hepatic metabolism, such as cimetidine, are better avoided. Hypoxemia in the perioperative period can be a source of ischemic hepatitis, and adequate oxygenation is especially important in the parturient with preexisting hepatic compromise. Supplemental oxygen is often required by these women.

Choice of Anesthetic and Agents

Choices depend on the timing and urgency of delivery, mode of delivery chosen by the obstetrician, and the condition of the mother or fetus at that time. The scenario can be extremely dynamic, and therefore anesthetic plans must be made for a variety of possible situations: vaginal delivery (spontaneous, assisted, or instrumental), planned cesarean section, emergency cesarean section (with concomitant maternal or fetal deterioration), and emergency laparotomy for hemorrhage.

When the delivery situation is not urgent, and maternal coagulation status allows consideration of central neuraxial regional techniques, a scrupulously titrated epidural anesthetic is the preferred technique in the woman with severe hepatic dysfunction. This technique allows the flexibility to adjust local anesthetic solutions so as to utilize dilute concentrations of the agents for labor analgesic techniques, but higher concentrations should then be employed for surgical procedures such as operative instrumental vaginal delivery or cesarean section. Studies have documented well that epidural anesthetic techniques can decrease systemic perfusion to the liver in hepatic disease, and a variety of solutions have been proposed for correction.[21,22] However, epidural anesthetic techniques may preserve hepatic blood flow better than the alternative general anesthesia or spinal anesthesia techniques. Epidural anesthesia has additional benefits for the parturient by avoiding intubation, decreasing systemic drug administration, and maintaining maternal awareness.[23] The decrease in hepatic blood flow observed with epidural anesthesia is more gradual than that seen with spinal anesthesia, and once the sympathetic blockade is established, then intensifying the concentration of the local anesthetic has less dramatic hemodynamic effects. When the maternal coagulation status is borderline and stable, correction of minor defects is advocated with vitamin K and possibly transfusion. However, if the mother has a rapidly progressive coagulopathy, or if ongoing bleeding is occurring, then a regional technique is unwise.

A more difficult clinical situation exists in the case of the urgent or emergent need to deliver the baby, often presenting as the "stat" cesarean section. In this situation, poor communication between the obstetrician and anesthesiologist can have very dire consequences for the mother and child. It is important to not easily succumb to the temptation to induce a hurried general or regional anesthetic induction in this situation, especially if maternal health will be compromised and fetal outcome potentially unchanged. If an epidural catheter is present and functioning well when this situation occurs, the block can often be intensified and brought to a level satisfactory for an operation relatively rapidly with a concentrate local anesthetic. Many prefer 2-choroprocaine in a 3% solution for this purpose, because it is not an amide local anesthetic that requires hepatic metabolism. It will, however, decrease the efficacy of later administration of epidural morphine for postoperative pain relief, leading to the potential administration of parenteral narcotics that may be poorly metabolized by the compromised liver.[24]

General anesthesia may be the only option for emergency operation if the maternal coagulopathy is severe or maternal hemodynamic instability or neurologic deterioration is severe. In that case, it should be remembered that parturients with severe liver dysfunction poorly tolerate hypotension and hypoxia from any cause. The effects of the most common anesthetic induction agents and supplemental agents are reviewed in Table 30.3. In general, it is advisable to avoid large doses of fixed intravenous agents in the setting of severe hepatic disease. Even the induction agents touted for their lack of hypotensive hemodynamic effects, such as etomidate, ketamine, and midazolam, may be associated with a reduction in hepatic blood flow and reduced clearance.[25,26] Halothane, enflurane, isoflurane, and sevoflurane have all been associated with case reports of toxic hepatitis.[27,28] In swine, desflurane does not appear to cause hepatocellular injury even after prolonged exposure, but a case of hepatitis has been reported in a human after a desflurane anesthetic.[29] With the possible exception of halothane, there is no convincing evidence that administration of these drugs is more likely to result in a postoperative hepatitis rate higher than the background rate for the population.

It has previously been noted that supplemental parenteral narcotics such as morphine and demerol may act as long-lasting agents in this population. Fentanyl and sufentanyl have a favorable pharmacologic profile in these cases, whereas alfentanyl suprisingly has a prolonged metabolism and remifentanyl provides no postoperative pain relief.[30,31] Odansetron may be a good choice for antiemetic therapy, because it has fewer sensorial side effects than many of the other choices, and it has the additional benefits of reducing pruritis and reducing fatigue in chronic liver disease.[32–34]

Many of the muscle relaxants used clinically, including rocuronium and vecuronium, have prolonged pharmacokinetic metabolic profiles in the setting of severe liver disease.[35–38] A good choice may be atracurium because it undergoes spontaneous degradation by plasma esterase and Hoffman elimination and is not associated as frequently with the histamine side reaction seen with mivacurium and rapacuronium.[39–42] A normal one-time intubating dose of succinylcholine is usually well tolerated for a cesarean section,

and no further supplemental muscle relaxant administration may be required. Prolonged neuromuscular block has been reported with succinylcholine administration in parturients with ACLP or with the concomitant adminstration of magnesium because of decreased plasma esterases or increased receptor sensitivity, respectively.[43]

Some types of liver disease, such as acute viral hepatitis, acute fatty liver, and alcoholic hepatitis, affect the pericentral hepatic lobules more than others, which results in a marked decrease in oxidative metabolism of drugs. Other liver diseases (primary biliary cirrhosis and chronic active hepatitis) affect the periportal regions of the liver more, with little effect on drug metabolism.[30] The important point is that drug metabolism in severe liver disease may be unpredictable, and prolonged effects may occur; thus, minimal doses of short-acting agents may be preferable in this situation.

If regional techniques are employed, much effort must be made to attenuate the results of the subsequent sympathectomy on the adequacy of liver perfusion.[22] This effort may be facilitated by the use of adequate preload techniques and with the aid of central hemodynamic monitors. Rapid correction of hypotension, should it occur, with the administration of appropriate vasopressor agents is paramount. In addition it must be remembered that most of the amide local anesthetics, even the newer ones such as ropivacaine and levobupivacaine, have a prolonged metabolism in severe liver disease that may make them prone to accumulation with sustained epidural administration.[44–46] Subsequently, the chance of a toxic reaction to accumulated local anesthetic is greater in these patients. Local anesthetics with a shorter duration of action and with less motor muscle blockade may have an advantage when the maternal coagulation status is borderline, and monitoring for a neuraxial bleed should be meticulous.[10]

Another concern in the use of regional techniques is the possible transmission of infection to the central nervous system in these often infected or infection-prone women. In most cases, this is not a clinical concern, because hepatitis viruses are not usually associated with encephalitis, meningitis, cerebritis, or neuritis.[47,48] However, herpesviruses, CMV, and HIV can be associated with these neurologic disasters.[49–51] A careful, well-documented baseline neurologic exam and search to preclude acute systemic viremia is advisable in these already immunocompromised women.

Perioperative monitoring of these cases should often be facilitated in an intensive care setting. Induction of anesthesia reduces hepatic blood flow by 30% to 50% regardless of mode of induction. Persistent low perfusion states, hypoxemia, or prior hepatic disease predispose the liver to injury during anesthesia. In addition, the stress response to surgery also causes sympathetic-mediated reduction in splanchnic blood flow.[26] An arterial catheter greatly facilitates the fine adjustments required with any anesthetic administration in women with severe hepatic dysfunction; it also allows for drawing the serial blood samples that are needed in the course of the mother's care. The need for central venous pressure monitoring must be individualized, keeping in mind the deleterious consequences of a peritracheal hematoma and that most of these patients have a hyperdynamic circulation based on functional cardiovascular shunts. Urine output should be routinely monitored as an indicator of the adequacy of intravascular hydration. Indications for pulmonary artery catheter placement and monitoring include the presence of suspected pulmonary hypertension, pulmonary edema, persistent oliguria despite hydration, or the need for aggressive vasoactive agent administration (especially vasodilators.) If adequate peripheral venous access can not be assured in these women with a propensity for hemorrhage, then central venous access should be obtained for this purpose and may be optimized in many cases by the placement of a sheath introducer or other single-lumen wide-bore access catheter. Pulse oximetry is invaluable as a constant indication of the adequacy of oxygenation in these women.

Specific Diseases Occuring in Pregnancy with Hepatic Disease

In this section, we describe the clinical and diagnostic features of pregnancy-associated hepatic disorders. Much is unknown about the etiology or management of liver disease intrinsic to pregnancy, and there is no widely accepted obstetric management plan. Very little has been written to describe the anesthetic management of patients with these disorders. An attempt is made to outline credible obstetric and anesthetic goals. It is difficult, if not impossible, to make blanket treatment recommendations, and we believe that for most patients with significant hepatic disease, therapy must be individualized.

Acute Hepatic Failure in Pregnancy

Obstetric Management

Acute hepatic failure can develop remarkably rapidly in some pregnancies from multiple etiologies. Symptoms of acute hepatic failure may be insidious, and the diagnosis may be delayed until encephalopathy and hyperventilation has developed, primarily due to hyperammonemia.[52,53]

Progress of acute liver failure may soon lead to increased intracranial pressure and cerebral edema, which are ultimately the most likely causes of demise. The hyperammonemia is in part caused by failure of hepatic conversion of ammonia to urea but is also caused by portal–systemic shunting phenomena. The hypoglycemia that accompanies failure results from decreased hepatic degradation of insulin as well as impaired glucose production mechanisms, because normally two thirds of insulin is removed from the portal systemic blood. Lactic acidosis develops in this scenario readily, causing an acidotic state that further impairs multisystemic bodily functions.

The elevated cardiac output that occurs with chronic liver impairment due to arteriovenous shunting and decreased sys-

temic vascular resistance may overwhelm the cardiac reserve. The development of arrhythmias, pulmonary edema, and possibly cardiac arrest may follow. Low cardiac output states, with or without intravascular depletion, make renal failure and the resultant electrolyte abnormalities common. The hepatorenal syndrome carries a dismal prognosis for survival once it develops. These patients are also at increased susceptiblility to infection because of impaired white blood cell activity of many types. Sepsis may be the final blow in the case of chronic liver dysfunction, as well as the possible immunocompromised state of pregnancy. Treatment options are outlined in Box 30.1.

Bleeding diathesis may also present with minor insults caused by failure of clotting factor synthesis, increased fibrin split products due to decreased hepatic clearance, and contributory thrombocytopenia partially secondary to hypersplenism. If liver dysfunction has been chronic, an anemia may preexist acute failure because of poor nutritional states or bleeding from esophageal varices or gastric sites. Disseminated intravascular coagulopathy may occur easily in these circumstances and may be disastrous when the woman delivers vaginally or in the setting of any operative procedure. Correction of coagulation disorders should be done as indicated, and surgery avoided if possible.

Prevention of acute hepatic failure is paramount, and in the setting of chronic liver failure, surgical portal–systemic shunting procedures have been employed.[12,54–56] However, the onset of liver failure may be precipitous, and surgical approaches may not be an option. In anticipation of hyperammonemia, the parturient with severe hepatic failure should be considered for an altered low-protein diet. Ammonia-producing intestinal flora can be suppressed with the administration of oral neomycin (which is, however, controversial in pregnancy). Ammonia fixation plus removal may be facilitated with the administration of oral lactulose. Blood glucose levels must be closely monitored, and the risk for fetal hypoglycemia minimized. Electrolytes, urine output, and renal function tests should also be closely monitored and corrected if necessary. With the onset of renal dysfunction, arrangements for hemodialysis may need to be made rapidly. Deterioration of cardiopulmonary status may necessitate symptomatic and supportive treatment, including oxygen supplementation and ultimately mechanical ventilatory support.

If the etiology of the acute liver failure is unknown, liver biopsy may be the best diagnostic methodology, but the woman may not be hemodynamically or hematologically stable enough for this. In early pregnancy, if tissue diagnosis will alter the patient's decision to continue the pregnancy, liver biopsy should be offered. In later pregnancy, the benefits of tissue diagnosis must be weighed against the technical difficulty and risks of obtaining the specimen. Even in AFLP, biopsy may only be warranted in clinically atypical cases.[17]

Unfortunately, for most cases of acute hepatic failure, liver transplant may be the only viable solution.

Box 30.1. Treatment options for acute liver failure.

- Correct underlying cause if possible
- Transjugular intrahepatic portosystemic shunt (TIPSS) early in the course; prophylactic variceal sclerotherapy if indicated
- Altered low-protein diet with enriched branched-chain amino acids
- Neomycin if necessary (controversial)
- Vitamin B_6, folate, and thiamin supplementation
- Close monitoring of blood glucose levels for hypoglycemia, correction if indicated
- Ascites present: low-salt diet, fluid restriction, and spironolactone
- Volume expansion with salt-poor albumin carefully; risk of variceal bleed with aggressive rehydration
- Variceal bleeding present; emergent sclerotherapy
- Transfusion of blood products as indicated by clinical situation: packed red blood cells, platelets, and clotting factors (fresh-frozen plasma)
- Isolated coagulopathy existent; treatment based on laboratory values and the anticipated intervention; consider vitamin K supplementation
- Consideration of liver biopsy if etiology unclear

Anesthetic Management

When it is necessary to provide anesthesia during an episode of acute hepatic failure during pregnancy, a coagulopathic state often precludes the use of regional anesthesia. However, if the alterations in the coagulation status are not great, or if the alterations can be corrected in isolated cases, regional techniques are preferable because of the usual concerns of anesthesia administration during pregnancy. There have been several case reports and reviews of anesthesia administered under these conditions.[6,55,57]

All drugs with an hepatic mode of metabolism administered to these women should be considered as fixed agents. Many opiates and sedatives should be avoided (see Table 30.3).

Hypertensive Disorders of Pregnancy

Pregnancy-related hypertension is an umbrella term that describes a group of pregnancy-associated disorders. The classification includes chronic hypertension, preeclampsia, eclampsia, preeclampsia superimposed upon chronic hypertension, and transient hypertension. The toxemias of pregnancy classification is no longer used. Classically, preeclampsia and eclampsia did not include the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). The syndrome is probably a variant of severe preeclampsia. The two disorders certainly share many features and coexist with a frequency that precludes random chance. Approximately one half of the women who are later diagnosed with AFLP also have evidence of preeclampsia or eclampsia as well as laboratory findings that are characteristic of the HELLP syndrome.[1] There are a great many theories attempting to explain

Box 30.2. Etiologic or associated factors of preeclampsia.

Early injury to the placental development
Decreased levels of endothelium-derived nitric oxide (EDRF)
Inherited factors
Autoimmune disorder
Thromboxane: prostacyclin imbalance
Inadequate maternal response to placentation
Abnormal hemostasis
Endothelial cell damage
Increased sensitivity to catecholamines
Retained sensitivity to angiotensin II
Microvesicular fat disease of the liver

the etiology of these disorders, some of the most recent involving hereditary factors, early endothelial cell dysfunction, or placental damage[58–60] (Box 30.2). There are an equal number of treatment modalities (Box 30.3). No theory or treatment comprehensively addresses all facets of these disorders.[61]

Even more puzzling is that for one of these "hypertensive disorders," the HELLP syndrome, hypertension is not always present. Perhaps pregnancy-induced microvascular endothelial damage would be a better term to describe these disorders. If one looks broadly at this disease entity, it may be that hemolytic uremic syndrome (HUS) of pregnancy, AFLP, and some forms of pregnancy-associated renal failure are all interrelated disease states. In addition, many surgical and medical diagnoses may be commonly confused with that of preeclampsia (Box 30.4).

Preeclampsia/Eclampsia with Hepatic Involvement

Preeclampsia and eclampsia are accompanied by hepatic manifestations in only a minority of cases, but this minority contributes greatly to the small percentage of maternal mortality in women with this disorder.[7] More than 80% of maternal deaths from these two disorders are caused by central nervous system complications, but hepatic complications account for the majority of the rest of maternal deaths in this population. Although liver function tests can be elevated in preeclampsia, these elevations are typically much less than those seen with HELLP or in AFLP (see Box 30.2).[7] The obstetric and anesthetic management of preeclampsia and eclampsia is covered extensively elsewhere in this volume; however, some recent trends in management are briefly discussed here.

Box 30.3. Treatment options for preeclampsia.

Postpartum corticosteroids (HELLP)
Antepartum corticosteroids (HELLP)
Early plasmapheresis (HELLP)
Observation (HELLP with subcapsular hematoma)
Vaginal delivery
Immediate cesarean section
Volume expansion and hemodynamic monitoring
Conservative versus early intervention

Box 30.4. Pregnancy-associated microvascular endothelial damage disorders and related disorders.

Probably related disorders:
Preeclampsia (with hepatic involvement)
HELLP
Acute fatty liver of pregnancy (AFLP)
Hemolytic uremic syndrome (HUS)
Immune thrombocytopenic purpura (ITP)
Thrombotic thrombocytopenic purpura (TTP)
Possibly related disorders:
"Gestational" thrombocytopenia
Disseminated intravascular coagulopathy (DIC)
Acute renal failure in pregnancy
Common misdiagnoses:
Cholecystitis
Appendicitis
Hepatitis
Gastroenteritis

Obstetric Management

In the past few years there has been an obstetric trend toward the expectant management of extremely preterm severe preeclampsia so as to improve fetal outcomes by maturation in utero. This approach has been advocated for fetuses with gestational ages from 24 to 32 to 34 weeks in a tertiary care setting, where daily antenatal testing and rapid intervention can occur. The HELLP syndrome, thrombocytopenia, and cerebral manifestations of preeclampsia remain endpoints for delivery, however.[62,63] Also, several investigational pharmacotherapies of severe preeclampsia have been introduced. Variable results have been seen with the use of antepartum or postpartum plasmapheresis in the setting of severe preeclampsia or HELLP syndrome, and most favorable results have been seen in postpartum plasmapheresis in HELLP where severe thrombocytopenia has been alleviated.[64] The use of corticosteroids in severe preeclampsia and HELLP has gained increased popularity, both for inducing fetal lung maturation and for reducing refractory hematologic and hepatic sequelae.[65,66] Other investigative therapies are the clinical use of epostenol (prostacyclin) and the research use of nitric oxide.[63]

Obstetric and anesthetic management of the various syndromes related to the hypertensive disorders of pregnancy is discussed in the following sections. These women are routinely placed on antihypertensive therapy if elevated blood pressures are part of their symptomatology, as well as seizure prophylactic therapy (most commonly magnesium). Each institution's protocol varies, but the side effects and interactions of these therapies must be considered with the administration of any other pharmacologic medications or other medical or surgical interventions.

Fetal Considerations

The management goals for these babies are always based on optimizing the maternal situation while weighing the risks of

a hostile intrauterine environment and premature delivery. Fetal evaluation should be performed early and serially to monitor for placental insufficiency that mandates delivery. If appropriate, the woman and baby should be transported early to an appropriate tertiary care facility for previously stated reasons. In pregnancies that are premature (gestational age less than 34 weeks) with undocumented fetal lung maturity, a 48-h course of glucocorticoids is administered to the mother to promote lung maturity of the fetus. This course must depend on maternal hemodynamic and other medical stability and may be foreshortened if maternal deterioration occurs.[2,7]

Hepatic Hematoma and Hepatic Infarction

The most important hepatic complication of preeclampsia or eclampsia is subcapsular hematoma, with or without subsequent rupture, which may present clinically as a biphasic pattern of right upper quadrant pain, nausea, and vomiting that may be followed by cardiovascular collapse, typically in the third trimester. In one recent meta-analysis of preeclampsia-associated hepatic hemorrhage and rupture, the three most common presenting findings were epigastric pain, hypertension, and shock. The diagnosis of hepatic bleeding in this series proved to be elusive in many cases, made most frequently at laparotomy.[67] The formation of the hematoma probably occurs because of vasospasm-induced hepatic infarction. Rupture of the hematoma is accompanied by sudden hypotension and has an associated mortality of up to 75% maternal and 60% fetal[68]; 80% of spontaneous hepatic ruptures occur in women with preeclampsia or eclampsia.[69,70]

Obstetric Management

When suspected in the antepartum period, the presence of a subcapsular hepatic hematoma usually is an indication for prompt delivery, often by cesarean section to avoid trauma of the collection by pushing efforts and to confirm diagnosis.[2]

Ultrasonography may be diagnostic if hematoma or rupture is suspected, but a negative ultrasound does not rule out the diagnosis. Computerized tomography (CT) may also be diagnostic if clinical circumstances allow its use. Frequently, diagnosis is made retrospectively at the time of laparotomy in the presence of maternal cardiovascular collapse.

Management choices at laparotomy include surgical packing, use of topical hemostatic agents, vascular ligation, hepatic artery embolization, and hepatic lobectomy.[71,72] In several series, conservative management and use of hepatic artery embolization have resulted in improved maternal outcomes; however, this may be merely selection bias of less clinically severe cases.[73] Perioperative management is often complicated in these cases by disseminated intravascular coagulation (in addition to preexisting platelet and coagulation factor disorders), acute renal failure, fluid overload and pulmonary edema, and postoperative sepsis.

A closely related phenomenon is hepatic infarction associated with preeclampsia. This rare disorder presents in the third trimester with fever, abdominal pain, extremely high transaminases, and other laboratory values consistent with severe hepatic dysfunction. As with hepatic hematoma, diagnosis is assisted by CT but in the case of suspected infarction is confirmed by biopsy.[17]

Anesthetic Management

Anesthetic management of preeclampsia-associated hepatic hematoma is controversial. If the surgical plan includes hepatic repair, general anesthesia will provide more hemodynamic stability and acceptable intraoperative comfort. For ruptured hematoma, the management is very clear; emergency laparotomy under general anesthesia is the only recourse. Delivery and anesthetic management of hepatic infarction depend on individual case characteristics; there are insufficient published experiences to make specific recommendations.

The use of regional anesthesia is, as always, dictated by the coagulation status of the mother, with a risk–benefit analysis applied to the entire maternofetal unit. If the mother is so thrombocytopenic or coagulopathic on the basis of her preeclampsia and concomitant hepatic dysfunction, alternatives other than epidural or other regional techniques may be advisable. These techniques are certainly not feasible in the case of probable hepatic rupture.

Because there is the possibility for enormous fluid and blood losses and replacement with this disorder, plus the possibility that rupture may occur on the slightest provocation, invasive monitoring is often indicated. Arterial catheterization and central venous access should be placed proactively, rather than in haste after losses have occurred.

The Syndrome of Hemolysis, Elevated Liver Enzymes, and Low Platelets

The hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs in 1 to 6 pregnancies per 1000 (or approximately 10% of preeclamptic pregnancies), with current maternal and fetal mortality rates less than 20%.[64] Platelet counts tend to be severely depressed in this disorder (no greater than 100,000/mm^3), primarily on the basis of platelet destruction. The nadir of the platelet count is often reached several days postpartum.[66] The thrombocytopenia as well as a hemolytic anemia (microangiopathic with microscopic schistocytes and burr cells), elevated LDH levels, and elevated liver function tests (bilirubin and transaminases) are the hallmarks of the disease. This syndrome must be differentiated from thrombocytopenia purpura, HUS, systemic lupus erythematosus, idiopathic thrombocytopenia purpura, and AFLP for appropriate management purposes.[62] Unlike classic preeclampsia, hypertension and proteinuria may be mild in the disease, and liver involvement much more profound (Table 30.5). Although HELLP syndrome is a disease of the third trimester, it may occur much more remote from term than the syndrome of acute fatty liver of pregnancy

TABLE 30.5. Acute liver failure in pregnancy.

Sign	AFLP	HELLP syndrome	Acute hepatitis
Abdominal pain	One half of women	Almost 100%	More than one half
Jaundice	All women	Less than one half	All women
Serum transaminases (elevation)	Less than 10-fold elevation	Greater than 10-fold elevation	Greater than 10-fold elevation
Scans	Diffuse changes	Focal abnormalities	Diffuse changes
Coexisting preeclampsia	One half of women	100% of women	Less than one quarter
Liver biopsy	Microvesicular fat	Sinusoidal fibrin	Acute hepatocyte inflation
Liver failure	Present	Usually absent	Variable

AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelets.

(AFLP). Generally, the profound decrease in platelet count differentiates HELLP from other pregnancy-induced hepatic diseases or other surgical or medical diseases. Although transaminases are elevated in the HELLP syndrome, they are not so severely elevated as in hepatitis (see Table 30.1).

Obstetric Management

Upon diagnosis, the mother is stabilized, and a delivery plan is made to include the location and mode of delivery. This plan may include cervical ripening and induction of labor with normal vaginal delivery or cesarean delivery.

Anesthetic Management

The anesthetic management of the HELLP syndrome is dictated by the usual concerns that must be addressed when taking care of a woman with severe preeclampsia along with the additional concerns of impending liver dysfunction and thrombocytopenia. Hypertension may not be an overwhelming concern in patients with the HELLP syndrome, but a thorough evaluation of the woman's cardiovascular status must be performed. In preeclampsia there is a tendency to develop intravascular volume depletion but also an increased risk to develop pulmonary edema with the fluid shifts that accompany labor and delivery. The pulmonary edema is especially likely to develop in the postpartum period. The use of invasive monitors must be individualized for each patient's condition. In general, arterial catheterization or central venous/pulmonary artery catheterization are indicated in severe preeclampsia complicated by refractory oliguria, refractory hypoxemia or pulmonary edema, and hypertensive crisis.[65] The practitioner must keep in mind the potential complications of arterial puncture and airway compromise in a parturient who is thrombocytopenic and is subjected to internal jugular vein or subclavian vein access attempts.

Regional anesthesia, although the preferred technique in preeclampsia, may not be feasible in the patient with HELLP syndrome. Certainly if the platelet count is less than 50,000 cells/mm^3, the possibility of providing a regional anesthetic for labor and delivery is not advisable because of concerns about bleeding around the spinal structures.[10,74] It also must be acknowledged by the practitioner that, even if the platelet count and coagulation parameters are adequate for epidural placement at one time, there may be a rapid decline in platelets and other factors within several hours.[75] The nadir of the platelet count and maximum liver dysfunction in HELLP often occurs 1 to 2 days after delivery. Therefore, care must be taken to serially monitor coagulation parameters before removal of epidural catheters as well as to monitor the neurologic status of the patient should she become coagulopathic or thrombocytopenic during the period when an epidural catheter is in place. Prophylactic platelet or fresh-frozen plasma transfusions before epidural placement or operation are not generally recommended, because the transfused products tend to be rapidly consumed and eliminated before delivery of the placenta.[76] Hence, proper timing is important.

General anesthesia administration in these women carries the concern about airway issues, especially bleeding and friability, and potential hypertensive responses during the induction and emergence periods. As in all pregnant individuals, the risk of aspiration is increased and must be actively avoided with the use of cricoid pressure and rapid sequence intubation techniques. Administration of narcotics for labor analgesia in a woman in whom regional analgesic techniques are not advisable may only heighten the chance of vomiting. Concomitant administration of antiseizure and antihypertensive medications must be taken into consideration when devising an anesthetic plan. Parturients receiving magnesium infusions require less (after the administration of the normal intubation dose) of both the depolarizing and nondepolarizing muscle relaxants for subsequent doses. Close monitoring of the intensity of neuromuscular blockade in these cases is imperative, with the full return of consciousness and airway protective reflexes being a prudent practice.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is an obstetric emergency and is thought by many to represent a variant of severe preeclampsia.[63,77] Severe liver failure is the usual scenario in AFLP, unlike the usual case of severe preeclampsia, developing over the course of 1 to 2 weeks after the onset of vague abdominal symptoms such as nausea, vomiting, and abdominal pain. Initially, AFLP may be confused with hepatitis, but the liver edge is usually not palpable in AFLP, and the progression to profound liver failure is more rapid. Disseminated intravascular coagulopathy develops in more than one half of women with AFLP but is not so common with hepatitis. Jaun-

dice uniformly develops, followed by the development of hyperammonemia, hyperaminoacidemia, mental confusion, hypoglycemia, coagulopathy, and ascites in cases of AFLP. Renal failure may develop, and in severe cases, liver transplantation may be the only hope for survival for the mother.

Histologically, AFLP may be distinguished from preeclampsia because in AFLP there is a microvesicular fatty infiltration of swollen hepatocytes, whereas sinusoidal fibrin is found in preeclamptic hepatocytes. Definitive diagnosis requires liver biopsy with special stains for fat but may not always be clinically feasible because of coagulopathy. Laboratory findings help differentiate the disorder, with transaminase elevations being less severe than in preeclampsia or hepatitis and hypoglycemia pronounced (see Tables 30.1, Table 30.5). The role of CT or magnetic resonance imaging (MRI) lacks well-substantiated data.

It is thought that AFLP may belong to a group of microvesicular fat diseases such as Reyes syndrome and congenital urea cycle defects.[78] However, the hepatic steatosis is seen also after other toxic and infectious liver diseases, and thus the etiology remains unclear. There does appear to be, in some cases of AFLP, a genetic deficiency of fatty acid beta-oxidation.[79] The offspring of this group of women are often male, and it is recommended that infants of these affected mothers be tested for this metabolic defect.[80]

Obstetric Management

Cesarean delivery may improve both maternal and fetal outcomes but may be associated with profound bleeding problems. Perinatal morbidity is high, with hepatic encephalopathy in 60% of cases, severe coagulopathy in 55%, and renal failure in 60%.[81–83] Maternal mortality in original studies approached 100% but, with advances in critical care medicine, is now closer to 25%.

Anesthetic Management

The management of anesthesia depends on the type of delivery planned in the particular case and the urgency of the delivery. Ideally, anesthesia involvement in patient management is included early in the hospital admission to optimize maternal condition and avoid haphazardous anesthetic management later in a "stat" cesarean delivery. Although the diagnosis of AFLP is often unclear at first, the management of these cases clinically does not differ greatly from the other syndromes that present in late pregnancy with hepatic involvement (severe preeclampsia, HELLP, and hepatitis.)[6] These women are optimally managed in the tertiary care facility ICU setting employing continuous fetal heart rate monitoring, with delivery facilitated as soon as possible after diagnosis. Vaginal delivery is optimal but may be precluded by worsening maternal status or fetal indications. Cesarean delivery is often the mode of delivery. Although transfusion of blood products is indicated in some cases, the temptation to do so prophylactically should be avoided. Administration of these products should be based on laboratory evaluation of coagulation deficiencies. Blood product transfusions constitute a large protein and volume load for these women as hepatic and renal function deteriorates. This load may worsen encephalopathy and cardiopulmonary function even though many of these cases may already be mechanically ventilated.

Invasive monitoring is ideal for case management but, as in the HELLP syndrome, may be confounded by the presence of coagulopathy. Along the same line, regional anesthesia is the preferred choice for delivery by any method, but may be precluded by maternal coagulation problems. If regional anesthesia is to be provided, it is imperative to correct coagulation deficits and volume deficits before administration or removal of any indwelling catheters. There are reports of successful administration of epidural anesthesia in these cases, and it may be the optimal anesthetic choice to preserve hepatic blood flow in parturients with AFLP, so long as hypotension is avoided.[84]

The woman's condition will remain critical long into the postoperative course and, in many cases, will require prolonged ventilatory support.

Neonatal Considerations

These infants, although less likely to be premature than in other cases of pregnancy-related hypertensive disorders, are delivered from a hostile intrauterine environment. Fetal mortality is as high as 14% to 60%, depending on the series.[1,83] Appropriate tertiary care neonatal ICU settings must be available for their care before delivery if at all possible. The possibility of a genetic metabolic deficiency of fatty acid oxidation should be remembered, and appropriate testing performed, along with future surveillance.[79,80]

Intrinsic Hepatic Dysfunction

Hepatitis

Hepatitis in pregnancy is the most common cause of jaundice in pregnancy, and viral etiologies are the most common of these.[3] Many cases of viral infection and other forms of hepatitis are clinically silent; therefore, the true incidence of hepatitis is unknown. Usually the clinical course of chronic hepatitis is unaffected by the pregnancy, but there are exceptions.[9,85] A serious infectious risk exists for the neonate for vertical transmission of disease, which is variable depending on the type of hepatitis. The most common viral types are hepatitis A through E, although CMV, Epstein–Barr virus (EBV), and most significantly herpes simplex virus (HSV) also are causal agents. HSV hepatitis requires tissue diagnosis if suspected and rapid treatment of the mother and newborn with acyclovir. In many cases, it also necessitates a cesarean section.[7]

Numerous drugs have been implicated as being hepatotoxic and resulting in hepatitis, cholestasis, or even cirrhosis.[86] Types of drug agents that have been repeatedly implicated have been antihypertensive agents (including alpha methyl-

dopa and labetolol), anticonvulsant agents, antibiotics (erythromycin), chemotherapeutic agents, antiinflammatory agents (methotrexate), acetaminophen overdose, anesthetic agents, and of course chronic alcohol abuse.[87–89] Direct hepatoxins are defined as those drugs that produce a dose-related, reproducible liver injury in all exposed individuals. Such toxins include amanita phalloides mushrooms, chloroform, carbon tetrachloride, and several chemotherapeutic agents. At high doses, some drugs can overwhelm the liver's metabolic activity. Acetaminophen, furosemide, and salicylates are examples of this kind of hepatotoxin. Certain anabolic steroids and estrogens at high doses can cause cholestasis, which is centrilobular and associated with little or no hepatocellular necrosis. Several coexisting disease states may result in hepatitis such as hyperparathyroidism,[90] autoimmune diseases, and pancreatitis.[91]

Most drug reactions occur with a very low frequency and are idiosyncratic. Also, most drug-induced hepatitis represents immunologic or metabolic reaction to a specific drug. As such, any drug is potentially hepatotoxic, but some drugs are more frequently associated with hypersensitivity reactions than others. Interestingly, there have been several reports of acute hepatitis associated with tocolytic use (antiinflammatory agents, terbutaline, and ritodrine) in the recent past.[92,93]

Hepatitis can either be a chronic disease that predates pregnancy or can be contracted during pregnancy. If it worsens or is developed during pregnancy, the clinical presentation is not unlike early signs of other liver diseases in pregnancy; that is, nonspecific flu-like symptoms, fatigue, anorexia, and diarrhea. Later, there may be signs of cholestasis including jaundice, pruritis, pale stools, and dark urine. The severity of disease may vary from subclinical self-limited disease to fulminant hepatic failure (often confused with the diagnosis of HELLP syndrome or AFLP). Laboratory analysis will first reveal liver parenchymal damage in the form of significantly elevated transaminases. Specific viral markers should be obtained if causal (see Table 30.1).

Viral Hepatitis

Hepatitis A

Pathophysiology

The incidence of hepatitis A virus (HAV) in pregnancy is less than or equal to 1 in 1000, whereas hepatitis B (HBV) viral infection in pregnancy is estimated to occur in 1 to 2 in 1000 pregnancies in the United States.[3] In both diseases, the infections may be of greater incidence due to unrecognized subclinical disease states.

In the case of HAV, infection involves fecal oral contamination and is facilitated by intimate contact with infected individuals, poor hygiene, and poor sanitary conditions. Epidemics of HAV disease usually occur as a result of ingestion of contaminated food or water. The incubation period of the disease is short (15–50 days) with a similar duration of viremia. Fecal excretion of virus is the cause of contamination in most cases and occurs primarily during the asymptomatic, prodromal phase of the disease. The infection and illness are generally self-limited and last approximately 6 weeks. Fulminant hepatic failure is rare, and there is not a carrier state of the disease. In many developing nations, the disease is endemic, and parturients who have recently been in these nations are at increased risk of HAV disease.[94]

Diagnosis of HAV disease is made by positive antibody titers of IgM to HAV which rise acutely and persist for 6 months. IgG antibodies also elevate early, persist for life, and infer immunity to subsequent HAV disease. Vertical transmission of HAV disease has not been reported at the time of delivery.[86] The effects of HAV on pregnancy do not appear to be deleterious in well-nourished parturients.[95] The reports of increased severity of maternal disease and fetal morbidity in developing nations are probably related to nutritional deficiencies and epidemiologic factors.[96,97]

Hepatitis B

Pathophysiology

In the United States, the predominant mode of transmission is direct person-to-person spread. High-risk individuals include health care workers, hemodialysis patients, hemophiliacs, illicit drug users, sexually promiscuous persons, and persons with long-term exposure to infected individuals. Infection is also more prevalent in people of Asian extraction, where the primary mode of transmission is perinatal.[98]

The likelihood of vertical transmission depends on several factors. The trimester in which maternal infection occurs is of foremost importance. Parturients who are hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) seropositive at time of delivery have a 90% rate of vertical transmission to the neonate because of very high viral inoculums. Seropositivity to HbsAg only at term carries a 10% to 20% risk of neonatal transmission without administration of immunoprophylaxis. Acute maternal infection that occurs in the first trimester without advancement to a chronic disease state is associated with a 10% vertical transmission rate, but transmission is 80% to 90% if it occurrs in the third trimester.[99] Presence of antihepatitis B e antigen antibody (anti-HBe) reduces the likelihood of vertical transmission to 12% to 25%.[3]

In the United States, mandated immunization helps prevent neonatal transmission of disease. It is advocated that pregnant women in high-risk groups should receive passive and active immunization against hepatitis B should they have no prior immunity to the infection. Individuals who have been exposed to the hepatitis B virus before they are vaccinated should receive passive immunization with hepatitis B immunoglobulin (HBIg) and then the usual immunization series. Regimens vary according to the type of exposure (percutaneous versus transmucosal).[85,99]

Parturients with hepatitis B present a special problem for those involved in their care. After identification of the

HBsAg-positive individual, initial efforts should be to stage the disease (active or chronic) and identify sequelae of hepatitis B infection. Unfortunately, even a careful history and physical examination may be misleading in the pregnant woman with hepatitis due to nonspecific findings such as spider angiomata, palmar erythema, and edema, as well as other symptomatology which are indistinguishable from nonspecific complaints of normal pregnancy. If the woman has a palpable liver edge or elevated serum transaminases, additional serology would include IgM anti-HBc, HBeAg, and possibly HBV DNA. HBsAg positivity in the absence of IgM anti-HBc is indicative of a chronic infection. Consultation by a gastroenterologist or infectious disease specialist is appropriate at this point, as these cases will need long-term follow-up care aside from current obstetric needs.[97] One half of asymptomatic carriers have chronic active hepatitis.[85] Liver needle biopsy is not diagnostic, but it is the only means of assessing the severity of hepatocellular damage. Recommendation of liver biopsy and its timing should be individualized based on maternal and fetal triage issues.

The course of hepatitis B, whether acute or chronic, is unaffected by pregnancy. There is some disagreement over the effect of hepatitis B on pregnancy. Some authors believe that there is an increased risk of premature delivery in parturients infected during the third trimester, although, as in hepatitis A, this may reflect maternal nutritional status and access to health care.[96]

Interferon therapy has shown promising results for the treatment of well-compensated chronic hepatitis B, C, and D infections but has not been studied in parturients except in isolated case reports.[100–102] Although no real problems have been found in the pregnancies that have gone to term in women taking interferon, it is contraindicated for use in pregnancy because of multiple side effects such as myelosuppression, autoantibody formation, thyroid disturbances, and possible cardiotoxicity.[103] In addition, its use has been associated with possible abortifacient effects.[104] As stated, the potential for postpartum use warrants a thorough evaluation and plan by a gastroenterologist.

Hospitalization is unnecessary unless clinically indicated, and care is supportive. Acute fulminant hepatic failure is rare with hepatitis, and there is no treatment other than liver transplantation. Mortality from acute hepatitis B is less than 1%.[98] Isolation of the woman and blood and body fluid precautions should be instituted to protect health care personnel and close contacts.

Delivery by cesarean section does not alter the risk of vertical transmission; the mode of delivery should be based on obstetric criteria.[99,105]

Hepatitis C

Pathophysiology

With the advent of specific serologic markers, we now know that hepatitis C virus (HCV) is responsible for more than 90% of non-A non-B hepatitis (NANB). Before screening of the blood supply, 95% of transfusion-related hepatitis was due to HCV. Currently, most HCV is contracted by intravenous drug abusers, followed by sexually promiscuous heterosexuals; a small number of cases are transfusion related, and a high percentage of patients have no identifiable risk factors.[106] Vertical transmission of HCV is less extensively studied than HBV, but it appears that this form of transmission is uncommon and occurs in 7% to 8% of cases; it can occur with breast-feeding.[99]

The clinical course of acute HCV is usually very mild. Less than 30% of infected individuals exhibit jaundice, and thus most cases of acute infection go undiagnosed. Important, however, is the fact that up to half of HCV infections subsequently develop chronic liver disease. Chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) are all well-documented potential sequelae of HCV infection. Progression from acute infection to chronic disease is very slow, and many individuals, even those with cirrhosis, are asymptomatic. Maternal disease may be helped by receiving interferon, but this therapy is not routinely advised during pregnancy. There are no specific recommendations against pregnancy in HCV-seropositive women. Pregnancy in women with chronic active hepatitis and cirrhosis is rare in the active forms of disease because of a greater incidence of concurrent infertility in these women. Becoming more common with the advent of liver transplantation is the posttransplantation woman who becomes pregnant with previous hepatitis infection.

No neonatal effects have been reported other than an increase in prematurity in children born to mothers infected in the third trimester.[47] There are no formal neonatal prophylactic recommendations, although some authors recommend administering immunoglobulin (IgM) to neonates born to mothers with acute HCV in the third trimester.[107] Concurrent HIV infection increases transmission rates.

Hepatitis D

Pathophysiology

Delta hepatitis is caused by a defective RNA virus that requires HBV for replication. Hepatitis D virus (HDV) can only infect patients with HBV, either as coinfection at the time HBV is acquired or as superinfection at a time subsequent to HBV infection. Disease course is similar to hepatitis B in the case of coinfection, but in the case of superinfection, 70% to 80% of patients will progress to cirrhosis and portal hypertension. Mortality due to hepatic failure is 25%, and disease progression is frequently rapid. Because of the typically severe course of chronic active delta hepatitis, the incidence in parturients is undoubtedly very low. Vertical transmission has been reported. Immunization efforts directed at avoiding HBV infection would be equally effective against HDV.[108]

Hepatitis E

Pathophysiology

Until the recent development of serologic tests for hepatitis E (anti-HEV), the diagnosis was made in the event of clinical hepatitis with negative serology for A, B, and C and recent travel to a developing nation. HEV is not endemic to the

United States. Transmission is by the fecal–oral route, with contaminated water being most frequently implicated. There is a potential for vertical transmission. Most investigators believe that there is no chronic HEV infectious state, although this has been questioned.[99] In the nonpregnant individual, HEV is similar to HAV in most respects. Hepatitis E is the exception in terms of the effects of pregnancy on disease course; for reasons that are unclear, maternal mortality is 15% to 20%. Standard immunoglobulin prophylaxis measures are unlikely to be protective against HEV.

Hepatitis G

Pathophysiology

This hepatitis is more likely in people already infected with hepatitis B, C, or HIV, or with a history of intravenous drug use. Vertical transmission can occur, actually to a greater extent than with HBC, but there is probably not a chronic active state; nor does it lead to cirrhosis.[99]

Anesthetic Management

The woman with hepatitis receives an anesthetic based on the severity of her liver disease. Chronic disease may lead to problems with coagulation, which may preclude regional anesthetic techniques. If a general anesthetic must be administered, it is important to provide hemodynamic stability to support remaining hepatic function. Induction of anesthesia reduces hepatic blood flow by 30% to 50%, regardless of mode of induction. In addition, the stress response to surgery also causes sympathetic nervous system-mediated reductions in splanchnic blood flow.[26,109] Persistent low perfusion states, hypoxemia, or prior hepatic disease predispose the liver to additional injury during anesthesia.

Choice of muscle relaxants and other anesthetic agents should include those drugs that do not rely solely on hepatic metabolism (see Table 30.3). Choice of anesthetic agents in the patient with prior hepatic disease is difficult because of the unpredictable nature of pharmacokinetics in these cases.

It is paramount to remember how infectious viral hepatitis can be to the caregiver, although most anesthesiology personnel now receive routine hepatitis B immunization. Because most obstetric anesthesia involves regional techniques, it is paramount to observe universal and needle-stick precautions when caring for these women.

If the patient is on interferon therapy, it must be kept in mind that this drug has been associated with decreases in the platelet count as well as reductions in granulocyte counts that might pose an increased infection risk. Many neurologic side effects have been attributed to the administration of this drug. Persistent paresthesia might provide a confusing scenario if a neurologic deficit should occur after a regional anesthetic administration. Facial swelling and cardiovascular problems have also been attributed to this drug.[110]

Fetal and Neonatal Risk

The American College of Obstetrics and Gynecologists (ACOG), American Academy of Pediatrics (AAP), and Advisory Committee on Immunization Practices (ACIP) have recommended routine screening of all parturients in early pregnancy in an effort to identify newborns who will require immunoprophylaxis against hepatitis B.[99,107,108] In states where adherence to these recommendations is required by law, identification and immunoprophylaxis of neonates at risk approaches 100%. Universal active immunization for hepatitis B is now recommended for all infants born in the United States. Combined passive and active immunization of neonates is 85% to 95% effective in preventing perinatal transmission of maternal hepatitis B virus[99,111] (Table 30.6).

Research is ongoing regarding breast-feeding recommendations for mothers with hepatitis C infection.

Cirrhotic Liver Disease and Portal Hypertension

Cirrhosis

Pathophysiology

Hepatic cirrhosis is an irreversible chronic injury to the liver parenchyma resulting in histologic changes of extensive fi-

TABLE 30.6. Summary of recommendations for passive and active hepatitis B immunoprophylaxis for neonates.

Maternal HBsAg status	Vaccine dose	Age of infant
HBsAg (+)	HBV 1	At birth (within 12 h)
	HBI	At birth (within 12 h)
	HBV 2	1 month
	HBV 3	6 months
Unknown (draw and send maternal blood for HBsAg at earliest opportunity)	HBV 1	At birth (within 12 h)
	HBIg	Give immediately (within first week of life) if maternal status found to be (+)
	HBV 2	1–2 months
	HBV 3	6 months
HBsAg (−)	HBV 1	At birth (before discharge)
	HBV 2	1–2 months
	HBV 3	6–18 months

HBsAg, hepatitis B surface antigen; HBV, hepatitis B antigen.

Box 30.5. Clinical signs and symptoms of portal hypertension.

Can be clinically silent
Anorexia
Weakness
Spider angiomata
Palmar erythema
Kaput medusa
Icterus
Ascites
Varices/upper gastrointestinal bleed
Lower gastrointestinal bleed
Tachypnea
RUQ pain

Box 30.6. Potential causes of portal hypertension.

Cirrhosis
Chronic hepatitis/postviral cirrhosis
Alcoholic (Laennec's) cirrhosis
Primary (autoimmune) biliary cirrhosis
Secondary biliary cirrhosis (postobstructive)
Cardiac cirrhosis
Advanced alpha$_1$-antitrypsin deficiency
Advanced Wilson's disease
Advanced hemochromatosis
Cryptogenic cirrhosis
Hereditary hemorhagic telectangia syndrome
Mass lesions
Cysts
Abscess
Hemangioma
Carcinoma
Budd–Chiari syndrome (hepatic vein thrombosis)
Extrahepatic portal vein obstruction (EHPVO)

brosis and regenerative nodules. Alcohol abuse is the most common cause of cirrhosis in the general population, but postnecrotic cirrhosis as a result of chronic viral hepatitis is the most common etiology in young women. There does seem to be an increasing use of alcohol in some young female populations, which, along with increasing maternal age, may lead to an increase in this disease in the future. A separate section on alcohol-related liver disease is presented later in this chapter.

The signs, symptoms, and causes of cirrhosis are summarized in Boxes 30.5 and 30.6, respectively. The diagnosis of cirrhosis per se is not as important to pregnancy outcome as is the recognition of significant sequelae. The sequelae most important to the obstetrician and anesthesiologist are portal hypertension, coagulopathy, pulmonary hypertension, and fulminant hepatic failure with its associated encephalopathy. The most common cause of death in cirrhotics is massive gastrointestinal bleeding. In advanced cirrhosis, liver transplantation may offer the only prolonged chance of survival.[112]

Portal Hypertension in Pregnancy

Pathophysiology

The incidence of pregnancy in women with advanced portal hypertension is generally low because its existence often hallmarks severe liver impairment with subsequent infertility. Causes of portal hypertension include cirrhosis, noncirrhotic portal fibrosis, and portal venous obstruction, with a protean list of potential etiologies (see Box 30.6). The obstetric and anesthetic management of these parturients is dependent on understanding and avoiding variceal hemorrhage, encephalopathy, and renal failure. Maternal prognosis depends much on the degree of hepatic impairment during pregnancy, which can be expected to decline in about one third of the cases.[20]

Cases of portal hypertension are unlikely to occur in women of childbearing years, but a few deserve special mention here. There are case reports of penicillamine with and without zinc salts being administered during pregnancy in Wilson's disease to reduce maternal copper accumulation with good pregnancy outcomes despite previous concerns over teratogenicity from these agents.[113] Pregnant patients with Wilson's disease should continue to take the chelating agent, but the clinician must be aware of the possibility of penicillamine-induced maternal thrombocytopenia that might affect anesthetic choices and lead to a need for transfusion. Focal nodular hyperplasia (FNH) and liver cell adenoma (LCA) are histologically benign mass lesions associated with pregnancy and oral contraceptive use. LCA, although not highly vascular, has been associated with high maternal and fetal mortality when intraperitoneal rupture occurs.[79] Budd–Chiari syndrome is highly associated with a variety of hypercoagulable states, including pregnancy and oral contraceptive use.[114] When acute hepatic vein thrombosis occurs in pregnancy, it is almost always in the early postpartum period[115] and has been reported to lead to a need for liver transplantation.[116,117] Similarly, portal hypertension has been reported in women with hereditary hemorrhagic telangeictasia.[118]

The reported experience of pregnancy in women with portal hypertension is small. Obstetric management studies are inconsistent, unstandardized, and frequently contradictory. Anesthetic management is rarely reported. Although it is not realistic to advocate a certain treatment plan for all patients, there are basic management goals for parturients with this ailment. In general, women with advanced portal hypertension or cirrhosis tolerate laparotomy poorly, so it is optimal if these women deliver vaginally rather than by cesarean section. This general operative risk has been described for the nonpregnant population by the Childs–Pugh classification that is described in Table 30.4.[16] Forceps use or vacuum extraction is often advocated, because it is considered prudent to foreshorten the second stage of labor as portal pressures can be increased by prolonged straining.[119]

Any patient with cirrhosis has an increased anesthetic risk, but those patients with more advanced disease present special problems and leave no room for error or inattention. A treatment approach is advocated here for those pregnant women with more advanced disease.[20] A careful preoperative search for the sequelae of cirrhosis is mandatory and should

begin at the first case contact. A multidisciplinary approach is optimal, and if adequate obstetric, anesthesiology hepatology, and neonatology services are not available, transfer to an appropriate institution should be considered.

Esophageal Varices

Pathophysiology

In the second trimester of pregnancy, there is a progressive increase in maternal circulating blood volume, a normal elevation of portal pressure, and an increase in compression by the enlarging uterus on the inferior vena cava; this results in more and more of the venous return being routed through the azygous system. Therefore, it has been reported that at least one half of healthy pregnant women have transient esophageal varices in the latter part of pregnancy.[8] However, large esophageal varices in the parturient are the most ominous predicating factor in the setting of portal hypertension. In nonpregnant females with cirrhosis, mortality is 38% when varices bleed, and cumulative mortality is 65% in the year following a variceal bleed.[120]

One large retrospective review of parturients with esophageal varices found the perinatal mortality in this population to be 18%.[119] This lower mortality was most likely a result of demographic factors, including a relatively "healthy" subgroup compared to all patients with esophageal varices. However other studies have reported a 67% to 78% chance of bleeding in parturients with known cirrhosis if varices are demonstrable to preexist pregnancy.[20] Several authors have concluded that pregnancy has no effect on the underlying disease or on the overall frequency of hemorrhage,[120,121] but this does not explain the predisposition to hemorrhage in the second trimester as reported by these same authors. It is probable that the expansion in blood volume, especially rapid during the second trimester, places parturients at increased risk for variceal bleeding during the latter half of pregnancy.

Predicting which women will bleed from their varices does seem impossible, and bleeding does not correlate with any known variceal property or maternal factor. For this reason prophylactic sclerotherapy of esophageal varices early in pregnancy is the preferred management for these patients, especially because the outcome after emergency sclerosing procedures is much less optimal.[122] In the small number of women reported to have been treated in this manner, maternal and fetal mortality has been close to zero. Other therapies that have been reported are portosystemic shunting procedures, esophageal transection, and medical therapy with beta-blocking agents and vasodilators.[20,123] Although the use of surgical portosystemic shunting in severe cirrhotics has not improved survival, in one large study of cirrhosis in pregnancy severe hemorrhage was seven times more frequent in the nonshunted group.[54] Fetal wastage and perinatal loss primarily due to prematurity have been reported in nonshunted parturients with cirrhosis.

Transjugular intrahepatic portal–systemic shunts (TIPSS) have been proposed as a means of reducing esophageal venous pressures.[56] TIPSS is a radiologic procedure performed under intravenous sedation in the fluoroscopy suite and has a low-risk profile compared to surgical shunting.[124] Via an internal jugular introducer sheath, a stent is radiographically guided and placed as a fistula between the portal and hepatic venous systems. Many believe that TIPSS is indicated early in pregnancy before the increased blood volume seen late in the second trimester. Serial endoscopy and hepatic ultrasound with Duplex should indicate the need for shunt revision.

Encephalopathy

Pathophysiology

Encephalopathy in hepatic disease is seen whenever the liver is no longer able to metabolize a variety of gut-derived compounds including ammonia, endogenous GABAergic substances, and other neuroactive peptides. The two common situations in which this occurs are with fulminant hepatic failure or as a secondary effect of any portosystemic shunting procedure. If left untreated, encephalopathy can progress to cerebral edema and result in coma and death. Some reports exist of attempts to treat acute hepatic coma with cross-circulation or exchange transfusion in the past with variable success.[125]

Treatment of hepatic encephalopathy is largely supportive and includes efforts to control precipitating events such as gastrointestinal bleeding, infection, excess dietary protein intake, and overzealous use of sedatives or potassium-wasting diuretics in chronic liver failure. A low-protein diet enriched with branched-chain amino acids should be started at the first sign of encephalopathy, and neomycin may be used if necessary. Correcting underlying causes of encephalopathy before delivery is necessary, whenever feasible. For operative or vaginal delivery, regional anesthesia is not contraindicated but will depend on the patient's ability to cooperate and maintain her airway. Adherence to minimal dosing recommendations for both local anesthetic and opioids is advisable, for these will not be well metabolized in women with encephalopathy and will produce prolonged effects.

Renal Failure

Pathophysiology

A variety of mechanisms have been proposed to explain the renal failure and electrolyte disturbances that comprise hepatorenal syndrome. The most salient points are twofold, as follows. First, there is renal tubular sodium avidity due to increased aldosterone, and this is combined with reduced "effective" plasma volume. Also, there is decreased oncotic pressure, and there are increased hydrostatic pressure states in these cases. All these factors lead to redistribution of fluids from intravascular to interstitial spaces, with the ultimate formation of ascites, pulmonary effusions or edema, and cerebral edema. Second, the decrease in intravascular volume leads to increases in renin and angiotensin production, which then alter intrarenal blood flow redistribution, with the final resultant oliguria.

Pulmonary Hypertension

Pathophysiology

Pulmonary hypertension is an uncommon complication of portal hypertension, occurring in only 0.25% to 2%. Mortality is reported to be increased in these patients.[18] Pathophysiology is not entirely understood, but there are two likely theories: (1) repeated embolization of pulmonary arteries by microthrombi arising from the hepatic vascular bed and (2) alteration of pulmonary vascular tone by as yet unidentified substances originating in the gut and escaping liver inactivation. Pulmonary hypertension accompanying portal hypertension has been reported with or without portocaval shunting and in pregnancy.[20] Liver transplantation does not reverse the pulmonary hypertension.[126]

Presenting signs are likely to be nonspecific, but any patient with hepatic disease presenting with dyspnea, syncope, hemoptysis, or chest pain deserves a workup to exclude pulmonary hypertension. Chest X-ray, arterial blood gas determination, and electrocardiogram may be helpful, but definitive diagnosis will probably require transthoracic echocardiography or pulmonary artery catheterization. The accurate determination of pulmonary artery pressures by echocardiography is technique dependent and may be difficult in the presence of a gravid uterus. In patients with hepatic disease and concomitant pulmonary hypertension, assisted vaginal delivery is the preferred mode of delivery, and operative delivery is indicated only by deteriorating maternal or fetal status. If a cesarean section must be performed, there are anecdotal reports of delivery by cesarean section using a slowly titrated epidural induction and maintenance. Pulmonary artery catheter placement may be valuable for monitoring trends in central pressures, but it must be kept in mind that pulmonary artery ruptures have been reported if overzealous balloon inflation is utilized.

Coagulopathy

Pathophysiology

The liver is responsible for synthesizing protein clotting factors, and the majority of patients with cirrhosis have some quantitative diminution of factor activity. Fortunately, clinically normal clotting is possible with even 10% to 30% of most normal factor levels. A rise in prothrombin time (PT) or the international normalized ratio (INR) in the absence of disseminated intravascular coagulopathy (DIC) indicates severe hepatic dysfunction and is an indicator of poor prognosis (see Table 30.4). Unlike cholestasis, where there is malabsorption of vitamin K, hepatocyte function in cirrhosis is insufficient to meet synthetic demands, and vitamin K may be ineffective in reversing coagulopathy.

Splenomegaly and bone marrow suppression frequently accompany cirrhosis and account for the thrombocytopenia often seen in these cases. Replacement of clotting factors is achieved by administering fresh-frozen plasma (FFP) 10 to 15 mL/kg of body weight. Postpartum bleeding due to thrombocytopenia in this population is unlikely with platelet count above 40,000 to 50,000 platelets/mm^3, and platelets should be transfused only for clinical bleeding supported, when possible, by laboratory confirmation.[74] The use of desmopressin (DDAVP) to improve the qualitative function of platelets may have a role, but this has not been substanciated in pregnancy. In the absence of clinical bleeding, prophylactic platelet and FFP transfusion before regional anesthesia or surgery is controversial, poorly supported by the literature, and probably unnecessary for stable platelet counts above 50,000 and PT or INR less than 1.5.

Fulminant Hepatic Failure

Pathophysiology

Fulminant liver failure may be triggered in these women by minor infections, dehydration, hypotension from any cause, and medication alterations or misadministration. Acute hepatic failure, regardless of the etiology, is characterized by initial tachypnea and progressive encephalopathy frequently accompanied by some combination of hypoglycemia, lactic acidosis, hypoxemia, hyperdynamic heart, renal failure, and increasing coagulation abnormalities. Liver "function" tests, with the possible exceptions of PT and albumin levels, are not reliable indicators of the severity of disease. Stabilization of the mother and a search for the etiology are necessary steps before the initiation of delivery. The prognosis for patients with acute hepatic failure is poor, as discussed more extensively in other parts of this chapter.

Anesthetic Management

In the cirrhotic parturient with stable hepatic function and no evidence of any coagulopathy, the anesthetic management of the peripartum period does not differ from that of any other parturient. If abnormalities in the coagulation system do exist, they preclude safe administration of regional anesthetic techniques unless corrected. Elective administration of blood products solely to correct such coagulopathies for peripartum analgesia administration is extremely controversial and is usually reserved for the case of operative delivery. Tests that should be performed in parturients with cirrhosis or portal hypertension upon the arrival in the delivery suite include a complete blood count with differential and platelet count, PT, PTT, and INR, followed by peripartum liver function tests and renal function tests. Blood products should be available if coagulopathy exists, and in this patient population, there is a high suspicion for postpartum hemorrhage.

It may often be the obstetric plan to foreshorten the second stage of labor and to use forceps so as to avoid maternal straining efforts. Regional anesthesia, if feasible, is best provided with a labor epidural and has potentially less precipitous hemodynamic effects than spinal anesthesia. In this particular scenario, it may be neccessary to provide denser sensory blockade of the perineum than with the usual labor epidural,

which can be facilitated at delivery by administration of 3% 2-chloroprocaine and meticulous blood pressure control.[127]

The usual precaution to avoid hypotension or any degree of oxygen deprivation in the administration of anesthesia is especially important in these mothers, as it will potentially exacerbate permanent maternal disease. If coagulation abnormalities exist, extreme care must be maintained in the management of the airway, because all membranes may be especially friable, and any bleeding elicited may persist. Patients with Wilson's disease may have difficulty in speaking, and baseline neurologic status is always important to document before any anesthetic.[128] Encephalopathic patients may require airway control if mental deterioration continues.

Fetal Considerations

Perinatal mortality is increased in the babies born to these women, primarily as a result of prematurity.[119] In late pregnancy, there may be a need to prematurely terminate pregnancy due to maternal condition deterioration (jaundice, hepatic decompensation, bleeding from varices, etc.) Also, in mothers in poor medical condition, the stillborn rate is increased.[20] If prophylactic procedures such as TIPPS, esophageal variceal injection, or portal–systemic shunting have been done before pregnancy or in early pregnancy, the fetal prognosis improves.[20,122] Surviving babies from these pregnancies usually do well if they do not have fetal alcohol syndrome or have not contracted hepatitis, and they generally do not show sequelae of maternal hepatic dysfunction.[129]

Alcoholic Liver Disease

Pathophysiology

Recent reports have indicated that there are increased rates of alcohol use among pregnant women,[130] which is probably correlated with an increased rate of alcohol-related liver disease in this population. There is evidence that gender differences in alcohol metabolism exist between women and men. Females have higher blood alcohol levels than males for the same amount of ingestion and therefore show a greater tendency to develop the adverse acute and chronic problems associated with drinking alcohol.[131] Women who drink alcohol are more likely to develop alcoholic liver disease, including cirrhosis, than men drinking comparable amounts of alcohol.[132] Infertility and increased rates of spontaneous abortion are common among women with very heavy alcohol ingestion histories (more than two drinks per day). However, many such women still achieve pregnancy, and their alcohol ingestion may complicate the obstetric and anesthetic management of the pregnancy and delivery as well as affecting their fetus. The paturient is encouraged to participate in an alcohol treatment program and seek regular prenatal care. Perioperative alcohol use has been correlated with adverse postoperative outcomes in several studies.[133,134] Therefore, morbidity after cesarean delivery may be greater for these women. Liver transplantation is performed for some cases of severe cirrhosis secondary to alcohol abuse but is controversial.[112]

Anesthetic Management

The anesthetic implications of alcoholic use may be categorized by the effects of acute alcohol ingestion by the parturient versus the effects of chronic alcoholism on her perioperative course. Acute ingestion of alcohol will decrease the parturient's requirement for injected or inhaled anesthetic agents and leave the woman with an altered sensorium as well as an increased propensity to vomit and aspirate.[135] Chronic use of alcohol causes deterioration in hepatic function, which may alter the metabolism of hepatic drugs as well as result in a state of persistent chemical hepatitis. Also, chronic alcohol use is associated with multisystem effects with adverse impact on perioperative outcome.[136,137] Immunoincompetence, alcoholic cardiomyopathy, hemostatic imbalance (decreased platelet number and function, as well as alteration in clotting factors) which may increase bleeding problems, and decreased wound healing have been found to exist in women who abuse alcohol.

If the labor is prolonged and the woman has a substantial alcohol dependence, it is possible that alcohol withdrawal syndrome may develop during hospitalization. In that case, it may be necessary to administer vitamins and seizure prophylaxis to these women to maintain hemodynamic stability and avoid further deterioration during labor.[137,138]

Fetal Considerations

Acute alcohol ingestion has been correlated with increased rates of fetal acidosis and depression of fetal cardiac performance in some studies.[139] In the past, ethanol infusions were used as tocolytic agents for preterm labor clinically, but these have now been replaced by other agents.

Chronic alcohol use has been associated with the fetal alcohol syndrome (FAS), which is associated with heavy alcohol consumption throughout the pregnancy.[129] Hallmarks of FAS include abnormal facies (including short palpebral fissures, micrognathia, and thin upper lips), severe developmental delays, cardiac septal defects, hypotonicity, and tremulousness. Even in infants who do not meet the criteria for FAS, alcohol ingestion during pregnancy has been associated with decreased fetal growth, developmental delay, an array of subtle physical findings, and adverse psychosocial and behavioral characteristics that carry on into adulthood in these infants.[140]

Cholestatic Liver Disease in Pregnancy

Etiology and Pathophysiology

Pruritis, jaundice, or both are the hallmark features of the presentation of this disorder that primarily occurs in late pregnancy. Intrahepatic cholestasis of pregnancy (ICP), primary biliary cirrhosis, hepatotoxic drug reactions, and rarely exac-

erbations of the Dubin–Johnson syndrome are included in this category. Most diseases in this group do not present with abdominal pain. However, biliary tract disease accompanied by cholestasis is usually caused by gallstones, may occur at any time during pregnancy, and is often associated with right upper quadrant pain and fever. The etiology of these diseases is different depending on the disorder and includes an inherited defect of hepatic excretion of organic anions in the case of Dubin–Johnson syndrome, obstructive pathology in the case of gallstone disease, and a possible estrogen-induced disturbance of enterohepatic circulation in the case of ICP.[5] The incidence of biliary tract disease and drug-induced cholestatic hepatitis is unknown during pregnancy, but it has been said that the incidence of ICP is 0.1% to 0.2%. Hyperemesis gravidarum is more frequent, with an incidence in pregnancy of 0.3% to 1.0%, and is the only disorder in this category that occurs early in pregnancy.[12]

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy has been associated with increased perinatal mortality, preterm labor and prematurity, meconium-stained amniotic fluids, and a high incidence of abnormal intrapartum fetal heart rate tracings.[141] The effect of this disorder for the mother is usually benign, but not so for the developing fetus. Maternal puritis usually develops in late pregnancy, followed by jaundice in 2 to 4 weeks with an obstructive symptomatology such as pale stools (steatosis) and dark urine. The pathogenesis of the disease is not fully understood, and the optimal treatment is controversial.[8] There seems to be a genetic predisposition for this disorder among some Scandinavian (Swedish), Hispanic (Chilean), and American populations.[47] This disorder may involve a deficiency of the enzyme sulfotransferase or a hypersensitivity to estrogens at the gene level in the liver in these women.[9]

Obstetric Management

Increased fetal surveillance is utilized in many protocols along with early induction of labor at term. Medical therapy has included antipruritic medications such as antihistamines and minor tranquilizers. Cholestyramine has been used widely for treatment of pruritis, acting as an anion-exchange resin to bind bile acids in the intestinal lumen. It may worsen coagulopathy, however, by further interference with vitamin K absorption, which is already impaired in these mothers. Other medications that have been utilized are *S*-adenyl-methionine (SAMe) and ursodeoxycholic acid (UDCA). SAMe reverses the negative effects of estrogen on bile flow, whereas UDCA acts to modify the bile acid pool to one that is less cytotoxic to liver cell membranes.

Anesthetic Management

The anesthetic concerns in these women focus on impaired drug metabolism via the hepatic route, but more important is a heightened concern for vitamin K deficiency and subsequent coagulopathy. Anesthetic agents that are primarily metabolized via the hepatic route, such as some of the muscle relaxants and sedatives, may have prolonged duration of effects (see Table 30.3). It may be necessary to administer exogenous vitamin K to these parturients, and to reverse the coagulopathy with FFP, etc., before operative intervention.[5] Regional anesthesia is not well advised if the coagulopathy persists.

Neonatal Considerations

Prematurity of these infants is common, so close scruitiny for preterm labor and delivery in a capable facility is advisable.[7]

Hyperemesis Gravidarum

Pathophysiology

Hyperemesis gravidarum is relatively frequent, occurring most often by the end of the first trimester of pregnancy. Risk factors include obesity, primiparity, nonsmoker status, and multiple gestation. It is an unwelcome diagnosis and may lead to dehydration requiring intravenous hydration and nutrition; however, in one prospective study it has been associated with decreased fetal wastage and improved pregnancy outcome.[142] Other studies have shown that the mean birth weight of babies born to women with severe hyperemesis gravidarum (those who have lost more than 5% of their body weight) were significantly lower that than those women who had only mild hyperemesis gravidarum.[12] Although the etiology is unknown and probably multifactorial, liver function tests are abnormal in at least 50% of patients with hyperemesis gravidarum.[143] The mechanism of the hyperbilirubinemia is also unclear but may be related to the malnutrition and subsequent impaired excretion of bilirubin.

Obstetric Management

In most cases, this is a self-limited disease that responds to conservative measures such as parenteral hydration and nutrition, psychologic counseling, vitamins, and antiemetic therapy. There has been use of various sedative regimens (including valium therapy) for these women with variable success.[144] Odansetron has been used during pregnancy for antiemesis, and there is some evidence that it may be associated with an increased sense of well-being as well as a decrease in pruritis.[33,34]

Anesthetic Management

Hyperemesis gravidarum is a disease of early pregnancy and fortunately should not present frequently to the anesthesiologist. Other than the logistical concerns one has with any case afflicted by intractable vomiting and hydration and electrolyte disturbances, there are no other particular concerns regarding the anesthetic management of these women. There is no published experience of anesthetic administration in this population.

Neonatal Concerns

Inconclusive concerns exist for the ultimate development and birth weight of the infant. Also, mention has been made anecdotally of problems with maternofetal bonding.

Gallstone-Related Disease and Cholecystitis Disease During Pregnancy

Pathophysiology

Cholecystectomy is the second most common abdominal operation required by pregnant women for nonobstetric surgery, with appendectomy being the most common.[23] Both female hormones that are increased in pregnancy contribute to symptomatic gallstone disease. Progesterone inhibits cholecystokinin and is a general smooth muscle relaxant helping to create a stagnant, sluggish gallbladder. Estrogen increases the chance of gallstone formation due to cholesterol hypersaturation. Historically, symptomatic gallstone-related disease during pregnancy carried a high morbidity for both the pregnant mother and her unborn child in terms of preterm labor and delivery and fetal loss. However, in the past decade there has been an improvement in these statistics.[145] Recent estimates of the incidence of symptomatic gallstone-related disease during pregnancy place it at slightly over 0.15%.[146]

In most series, conservative therapy (hydration, starvation, bowel rest, and antibiotics) are the mainstay for these women until after delivery, with surgery required by less than one half of the women. In some cases, endoscopic techniques have been employed sucessfully to manage biliary tract disease during pregnancy.[147] Laparoscopic approaches to cholecystectomy and biliary tract operations are increasingly prevalent with women who do require surgery. Generally the operation is delayed until the second trimester, if feasible, to minimize possible fetal teratogenicity more likely in the first trimester and to minimize technical surgical difficulties and the risk of preterm labor if performed in the third trimester.[146] Symptomatic disease if left untreated will tend to reoccur and eventually may present as obstructive jaundice and pancreatitis and sepsis, all which carry a high risk of perinatal morbidity.

Obstetric Management

It is controversial whether to operate on a semiurgent basis on the pregnant woman with symptomatic gallbladder disease.[148,149] If operation is required, it can be done with the traditional open surgical approach that requires a larger incision (increased subsequent incidence of incisional hernias), more postoperative analgesic requirement by the mother, increased maternal immobility (and subsequent risk of thromboembolic phenomenon), and a longer hospital stay. The recent use of laparoscopic surgical approaches has shown reasonable success rates with low maternofetal morbidity, but concern still exists over possible uterine trocar-related trauma and deleterious effects of the pneumoperitoneum on the fetal environment.[150–152] Disturbing reports of fetal acidosis and tachycardia associated with laparoscopy employed during the latter half of pregnancy exist.[153] Noninsufflation techniques are considered by some for laparoscopy during pregnancy. One group has made recommendations regarding the performance of laparoscopic cholecystectomy during pregnancy that include informed consent about potential risks, the use of prophylactic tocolytics and pneumatic compression devices, fetal monitoring perioperatively, trocar placement, and limitations on pneumoperitoneum inflation pressures.[145]

Anesthetic Management

The main concerns that the anesthesiologist has to address when providing anesthesia for the pregnant woman with gallstone-related disease include the changes in maternal physiology related to pregnancy, the pregnant airway, and the challenge of the pnuemoperitoneum if laparoscopy is the surgical approach.[23,154,155] Also, adequate fetal monitoring and surveillance must be provided as appropriate for gestational age. Precautions should be taken for both the unlikely possibility of anesthetic drug teratogenicity and the more frequent occurrence of preterm labor in the postoperative period. In most cases, general anesthesia is chosen for the procedure, with a rapid sequence induction and intubation sequence. Regional anesthetic techniques are difficult to use successfully due to the subcostal position of the operative site and retractor use and also diaphragmatic irritation by the pneumoperitoneum. The administration of nitrous oxide is controversial in pregnancy, but high doses of volatile inhalation agents only accentuate the hypotensive effects of anesthesia. Extubation should be performed after the woman has gained full airway reflexes, for there is a predilection for silent regurgitation in pregnancy due to the gastrointestinal changes related to pregnancy.

After a gestational age of 16 weeks, a wedge should be placed under the right hip to prevent aortacaval compression by the gravid uterus and decreased venous return. In nonpregnant individuals, hemodynamic changes that occur with laparoscopic cholecystectomy have been a decreased venous preload and subsequent decrease in cardiac index due to the head-up position and pneumoperitoneum.[156] It would appear that pregnancy only accentuates these changes, translating into deleterious effects on uterine blood flow, which is dependent on the mother's cardiac output for perfusion. The gas now most commonly used to insufflate the abdomen during laparoscopy is carbon dioxide, which is readily absorbed into the circulation. Thus, it is paramount that adequate controlled ventilation be provided for the mother while she is receiving general anesthesia, or maternal respiratory acidosis will develop with subsequent fetal acidosis.[155] Even though there does seem to be the potential for fetal compromise if laparoscopy is performed during pregnancy, several groups have performed this procedure successfully with low maternal or fetal morbidity.[146,151]

Neonatal Considerations

Several groups have attempted, with variable success, to continuously monitor the fetus intraoperatively because of attenuation of the fetal heart rate signal during laparoscopy by the insufflated gas, interference with the surgical trocars (Figure 30.1), and fetal movements.[145,150] Intraoperative fetal continuous monitoring may not always be feasible, but it is important to monitor the baby closely preoperatively and postoperatively. There is an increased risk of preterm labor after surgery performed during pregnancy, especially if this occurs during the third trimester.[157] Some centers routinely administer prophylactic tocolytics to these women.

Liver Transplantation and Pregnancy

Pathophysiology

Liver transplantation is rarely performed during the peripartum period, but when necessary, it is precipitated by acute hepatic failure and performed as a last resort to save the mother.[116] The incidence is so rare that there are fewer than 30 reported cases. Reports exist for need for liver transplantation on an acute basis secondary to hepatic rupture, AFLP, fulminant hepatitis, Budd-Chiari syndrome, and other reasons.[29,114,115,158,159] In these scenarios, maternal survival has been much better than fetal, and there are some reports of urgent fetal delivery immediately before the transplantation procedure.[117,160,161] Intrauterine demise may occur as a result of the extreme metabolic derangement or significant hyotension/hypoxemia episode. However, there are a few cases in which normal infants have been delivered to women who had undergone liver transplantation earlier in the pregnancy.[162,163] Gestational age and maternal condition largely guide the sequence of delivery and transplantation.

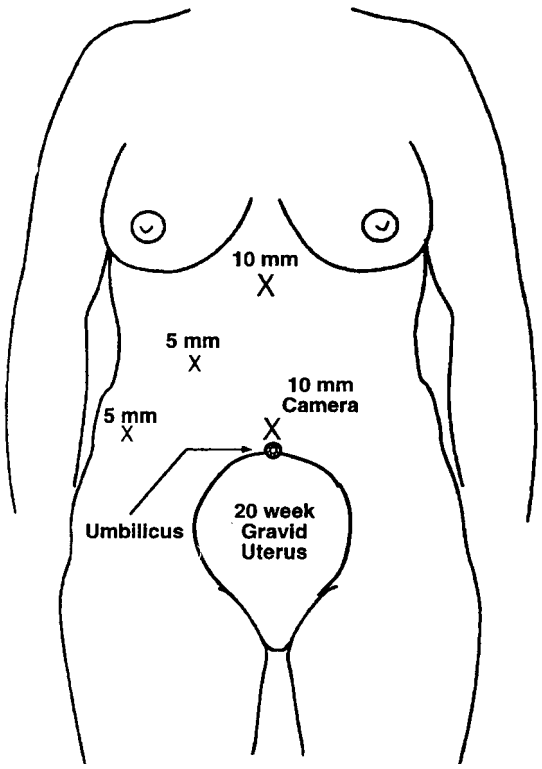

FIGURE 30.1. Placement of trocars for second trimester laparoscopic cholecystectomy. (From Glascow RE, Visser BC, Mulvihill SJ, et al. Changing management of gallstone disease during pregnancy. Surg Endosc 1998;12:244, with permission.)

Obstetric Management

Increasingly, there is the more common management problem encountered in high-risk obstetric practice of the pregnant mother who has had a liver transplant before the current pregnancy. Six months after liver transplantation, if no graft rejection is apparent, pregnancy is not contraindicated in these women. Fertility is the rule rather than the exception in these women.[164,165] In this situation there are the considerations of maternal immunosuppression medications and residual maternal end-organ disease.[166] Maternal hypertension, preeclampsia, anemia, renal insufficiency, and preterm delivery are reported in these pregnancies, but hepatic graft survival does not appear to be affected.[167] There is a reported increased incidence of fetal and neonatal problems in these pregnancies due to an increased incidence of spontaneous abortion, prematurity, low birth weight (intrauterine growth restriction), and neonatal immunosuppression and infection.[165,168] The majority of newborn outcomes have been favorable. No specific syndrome attributable to liver transplantation has been identified. Long-term follow-up is ongoing to best determine the later life effects on immune function and fertility in the children born to liver recipients. Chronic exposure to pharmacotherapies including cyclosporine A, tacrolimus, and steroids require such a long-term look. Beginning in 1991, the National Transplantation Pregnancy Registry (NTPR) has evaluated the pregnancy outcomes in solid organ transplant patients. Biopsy-proven acute rejection in the liver transplant parturient appears to pose a greater risk to the newborn and the mother. A significant number of these mothers may have recurrent rejection.

Preconception counseling, early consultation, and intensive, coordinated follow-up are necessary to optimize the pregnancy outcome. Genetic couseling related to the original etiology of the hepatic failure and medication exposure is indicated.The risk of CMV disease in the recipient and the potential for CMV disease in the fetus may require exposure to medications such as ganciclovir. The most commonly reported maternal complications include anemia and pregnancy-related hypertension, followed by preterm premature rupture of the membranes and preterm delivery. The largest series have been reported by the University of Pittsburgh in the United States and another group in France.[165,168,169]

The discussion of fetal liver transplantation is beyond the scope of this chapter.

Management of Immunosuppressant Medications

It is necessary to continue immunosuppressive medications if the woman has been taking these medications for liver transplantation during the pregnancy. In general, the risk of these medications to the fetus is outweighed by the disastrous consequences of allograft rejection if the mother stops the medications.[162,170] Many different drugs may be in this regimen including steroids, azothiaprine, cyclosporine, tracolimus (FK5096), rapamycin, OKT3, and antilymphocyte globulin.[171,172] Table 30.7 shows the different considerations of the various agents in pregnant transplant recipients. The regimens differ among the different transplantation centers and with patient tolerance. These agents may make the mother and her fetus more susceptible to infection or adrenal suppression, and close observation for these conditions must be maintained.

Anesthetic Management

In the majority of cases in which transplantation has been performed during the pregnancy or the peripartum period, the maternal state has been one of rapid hepatic decompensation with the concomitant encephalopathy, coagulopathy, and near anhepatic state. These conditions preclude regional anesthesia and necessitate the use of general anesthesia after stabilization of the mother has been attempted by replacement of coagulation factors and, in some cases, by portocaval shunt procedures.[112,113]

General anesthesia is administered in many cases after administration of bicitra and a modified rapid-sequence induction with cricoid pressure to guard against maternal aspiration. Fetal intraoperative heart rate monitoring is advocated but may not be technically feasible. Induction regimens have employed moderate to high doses of narcotics, etomidate, and a nondepolarizing muscle relaxant to maintain maternal hemodynamic stability. After 16 to 20 weeks, a wedge to tilt the right hip to 30° is advocated to reduce maternal aortocaval compression and improve uterine perfusion.[23] Many times, the maternal condition requires preoperative ventilatory support and vasopressors as well as bicarbonate and electrolyte administration to maintain acid–base balance and seizure prophylaxis. In all cases, invasive monitoring is required, usually in the form of arterial catheterization and pulmonary artery catheters, although in some cases large-bore central venous catheters bilaterally (two 8.5F percutaneous sheaths) have been used.[173] Also, there is the requirement for large-bore venous access to replace potentially massive blood loss during the transplantation procedure and postoperatively. Many institutions routinely employ rapid infusion systems to facilitate replacement of blood loss intraoperatively with the administration of massive quantities of packed red blood cells, FFP, cryoprecipitate, and platelets. At the University of Pittsburgh, thromboelastography (TEG) is used to assess the clinical clotting profile perioperatively.[174,175] Venovenous bypass has been employed in many cases to provide maternal and fetal hemodynamic support, to decompress the inferior vena cava and preexisting varices, and to provide metabolic support in the anhepatic phase.[173]

The major surgical stages of liver transplantation are trifold. The first stage is the dissection, which may be prolonged and associated with much bleeding due to coagulopathies or scarring secondary to previous surgeries. The second stage is the anhepatic stage in which the portal vein, hepatic artery, and inferior vena cava are clamped below and above the diaphragm. Obviously this stage is associated with the potential for cardiovascular decompensation. Venovenous bypass during this time via femoral or portal vein catheters will decompress the venous system and augment preload by returning blood to the right atrium via axillary or jugular approaches. The last stage, the neohepatic stage, may have transient but profound hemodynamic instability in the form of hypotension, high ventricular filling pressures, and bradycardia, with significant decreases in systemic vascular resistance. In this stage, the new liver graft is perfused, and adequate function of the graft is indicated by correction of the PT to less than 16 s or, in some centers, by TEG values.[173,175] During any of these stages, electrolyte imbalances, hemorhage, and hemodynamic instability may persist, and vasopressor support (usually in the form of dopamine infusions) may be necessary. Rapid access to arterial blood gas analysis and electrolyte determination are necessary intraoperatively due to a tendency to develop hypocalcemia and potassium abnormalities.[162]

Intensive care postoperatively is universal in these cases until they have stabilized. There is a risk of right heart fail-

TABLE 30.7. Implications of immunosuppressive medications for pregnant transplant recipients.

Immunosuppressive medications	Maternal concerns	Fetal concerns
Steroids	Hypertension, Cushing's syndrome, wound problems, hyperglycemia	Premature rupture of membranes, fetal lung immaturity
Azothiaprine	Pancytopenia, decreased muscle relaxant requirement	Intrauterine growth retardation, chromosomal aberrations
Cyclosporine	Nephrotoxicity, hypertension, insulin sensitivity, neurologic deficits	Intrauterine growth retardation, no evidence of teratogenesis
Tracolimus (FK-506)	Nephrotoxicity, blocks intraleukin (IL) production and T-cell proliferation	
Rapamycin	Same as FK-506	
OKT3	Serum sickness syndrome, vunerable to cytomegalovirus infection	CMV infection from maternal transmission
Antilymphocyte globulin	Leukopenia, thrombocytopenia, serum sickness syndrome	

ure after liver transplantation on the basis of preexisting arteriovenous malformations as well as the massive fluid and blood transfusion requirements, and the persistence of a hyperdynamic syndrome of hemodynamic parameters has been described in some patients.[176] Postoperatively, liver recipients are at great risk for sepsis, graft rejection, bleeding, and anemia. Significant postoperative pain is associated with this surgery, which is usually managed with parenteral narcotics; patient-controlled analgesic pumps may be utilized once the transplant recipient is awake enough to comprehend how to use the pump. Many liver recipients require ventilatory support and anticoagulation (with heparin in the case of pregnancy) for a time period to improve graft survival. Postoperatively, there may be a need for tocolytic regimens and fetal monitoring, seizure prophylaxis with magnesium if preeclampsia coexists, and oxytocin administration if a surgical delivery was performed.

The anesthesia considerations are different if the woman has undergone a prior liver transplantation, is without evidence of graft rejection, on a stable regimen of antirejection medications, and otherwise healthy with a viable pregnancy. In this case a close inspection should be made for evidence of coexisting preeclampsia, which has an apparent increased incidence in women who have undergone transplantation procedures.[116] Whether preeclampsia is a primary event or secondary to side effects of immunosuppression agents (especially cyclosporine, FK, and steroids) is controversial.[177] If there is any question of superimposed preeclampsia, laboratory studies should include a blood count, differential, platelets, coagulation studies (PT, PTT, INR, TEG), and liver and renal function studies. In any case there should be an attempt to obtain recent maintainance laboratory studies in these cases, who are often followed closely by a transplant sevice. There is some evidence that renal insufficiency is increased in the women who receive cyclosporine to prevent hepatic rejection during their pregnancy.[171,178] The airway in these women should be assessed carefully and handled with care, because cushionoid changes can superimpose difficulty with intubation and also increase mucous membrane friability. In most cases the choice of anesthetic is based on obstetric indications, and there is no reason not to provide a labor epidural or other regional anesthetic technique if maternal coagulation profile permits. Regional anesthesia is in fact preferable in these individuals, because mother and baby receive less systemic medication. If general anesthesia is employed for an urgent cesarean section, there is some evidence that the combination of cyclosporine and muscle relaxants, especially with the coadministration of magnesium, can prolong neuromuscular blockade.[171]

When considering regional techniques in these women, one should be aware that both the S− and R+ enatiomers have been found to have a prolonged elimination phase in patients after liver transplants.[179] However, neither enantiomer elimination phase was preferentially prolonged. Epidural or intrathecal narcotics are the preferred forms of postoperative pain relief (if the patient is not coagulopathic) because of a decreased requirement for systemic medications.[180] Ketorolac is contraindicated in these patients because of a propensity for gastrointestinal bleeding disorders.

Summary

The liver is one of the most important organs of the body which undergoes a significant change during pregnancy. Various enzymes as well as clotting factors are formed in the liver; it is also responsible for metabolism of different chemicals in the body. Liver disease is associated with clotting abnormalities as well as metabolism of drugs given for medical reasons. These obviously will affect the anesthetic of choice and technique.

References

1. Bacq Y. Acute fatty liver of pregnancy. Semin Perinatol 1998;22: 134–140.
2. Rinehart BK, Terrone DA, Magann EF, et al. Preeclampsia-associated hepatic hemorrhage and rupture: mode of management related to maternal and perinatal outcome. Obstet Gynecol Surv 1999;54:196–202.
3. Magriples U. Hepatitis in pregnancy. Semin Perinatol 1998;22:112–117.
4. Laifer SA, Ehrlich GD, Scantlebury VP. Congenital cytomegalovirus infection in offspring of liver transplant recipients. Clin Infect Dis 1995;20:52–55.
5. Davidson KM. Intrahepatic cholestasis of pregnancy. Semin Perinatol 1998;22:104–111.
6. Corke PJ. Anaesthesia for caesarean section in a patient with acute fatty liver of pregnancy. Anaesth Intensive Care 1995;23:215–218.
7. Pereira SP, O'Donohue J, Wendon J, Williams R. Maternal and perinatal outcome in severe pregnancy-related liver disease. Hepatology 1997;26:1258–1262.
8. Hunt CM, Sharara AI. Liver disease in pregnancy. Am Fam Physician 1999;59:829–836.
9. Knox TA, Olans LB. Liver disease in pregnancy. N Engl J Med 1996;335:569–576.
10. Schindler M, Gatt S, Morgans D, Cheung A. Thrombocytopemia and platelet functional defects in pre-eclampsia: implications for regional anaesthesia. Anaesth Intensive Care 1990;18:169–174.
11. Knox TA. Evaluation of abnormal liver function in pregnancy. Semin Perinatol 1998;22:98–103.
12. Samuels P, Cohen AW. Pregnancies complicated by liver disease and liver dysfunction. Obstet Gynecol Clin N Am 1992;19:745–763.
13. Becker U. The influence of ethanol and liver disease on sex hormones and hepatic oestrogen receptors in women. Dan Med Bull 1993;40:447459.
14. Ercolani G, Grazi GL, Mazziotti A. The Lidocain (MEGX) test as an index of hepatic function: its clinical usefulness in liver surgery. Surgery (St. Louis) 2000;127:464–471.
15. Zoeder T, Ebener C, Becker H, Roeher HD. Evaluation of liver function tests to predict operative risk in liver surgery. HPB Surg 1995; 9:13–18.
16. Pugh R, Murry-Lyon I, Dawson J. Transection of the esophagous for bleeding esophageal varices. Br J Surg 1973;60:646–649.
17. Bravo AA, Sheth SG, Chopra S. Liver biopsy: current concepts. N Engl J Med 2001;344:495–500.
18. Ziser A, Plevak D, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology 1999;90:42–53.
19. Child C, Turcotte J. Surgery and portal hypertension. In: Child C (ed) The Liver and Portal Hypertension. Philadelphia: Saunders, 1964:1–85.

20. Cerqui AJ, Haran M, Brodribb R. Implications of liver cirrhosis in pregnancy. Aust N Z J Obstet Gynaecol 1998;38:93–95.
21. Kennnedy WF, Everett GB, Allen GD. Simultaneous systemic and hepatic hemodynamic measurements during high peridural anesthesia in normal presence of blood flow and decreased blood flow. Anesth Analg 1971;50:1069–1078.
22. Nobuhiko T, Nagata N, Mayumi T. The effect of dopamine on hepatic blood flow in patients undergoing epidural anesthesia. Anesth Analg 1997;85:286–290.
23. Rosen MA. Management of anesthesia for the pregnant surgical patient. Anesthesiology 1999;91:1159–1163.
24. Hasselstrom J, Eriksson S, Sawe J. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br J Clin Pharmacol 1990;29:289–297.
25. Sear JW. Toxicity of Intravenous anesthetics. Br J Anaesth 1987;59: 24–28.
26. Gelman S. Anesthesia and the liver. In: Barash PG, Cullen BF, Stoelting RK (eds) Clinical Anesthesia. Philadelphia: Lippincott, 1992:1185–1214.
27. Friak EJ, Morgan SE, Cortezce A. The effects of sevoflurane, halothane, enflurane and isoflurane on hepatic blood flow and oxygenation in chronically instrumented dogs. Anesthesiology 1992;76:85–90.
28. Eger E II, Johnson BH, Strum DP. Studies of the toxicity of I-653, halothane, and isoflurane in enzyme induced, hypoxic rats. Anesth Analg 1987;66:1227–1230.
29. Hunter SK, Martin M, Zlatnik FJ. Liver translant after massive spontaneous hepatic rupture in pregnancy complicated by preeclampsia. Obstet Gynecol 1995;85:819–822.
30. Bower S, Sear JW, Roy RC, Carter RF. Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. Br J Anaesth 1992;68:462–465.
31. Glass PS, Camu F, Roscow CE. The clinical pharmacology of remifentanyl. Anesth Analg 1999;89(4S):S1–S49.
32. Yeh HM, Chen LK, Tsai SK. Prophylactic intravenous ondansetron reduces the incidence of intrathecal morphine-induced pruritis in patients undergoing cesarean delivery. Anesth Analg 2000;91:172–175.
33. Muller C, Pongazt S, Ferenci P. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 agonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. Eur J Gastroenterol Hepatol 1998;10:865–870.
34. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondasetron therapy. Lancet 1999;354:397.
35. Magorian T, Wood P, Miller R. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg 2000;80:754–759.
36. Duvaldestin P, Slavov V, Revufat Y. Pharmacokinetics and pharmacodynamics of rapacuronium in patients with cirrhosis. Anesthesiology 1999;91:1305–1310.
37. Magorian T, Wood P, Miller R. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg 1995;80:754–759.
38. Khalil M, D'Honneur G, Gomeni R. Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. Anesthesia 1994;80: 1241–1247.
39. Bevan DR, Donatti F, Brandom BW, et al. Rapacuronium. Anesth Analg 2000;90(5S):S1–S28.
40. Levy JH, Pitts M, Kim J. The effects of rapacuronium on histamine release and hemodynamics in adult patients undergoing general anesthesia. Anesth Analg 1999;89:290–295.
41. Cook DR, Brandom BW, Slater J. Pharmacokinetics of atracurium in normal and liver failure patients. Anesthesia 1984;61:A433.
42. Bevan DR. Prolonged mivacurium-induced neuromuscular block [editorial]. Anesth Analg 1993;77:4–6.
43. Thomas SD, Boyd AH. Prolonged neuromuscular block associated with acute fatty liver of pregnancy and reduced plasma cholinesterase. Eur J Anaesthesiol 1994;11:245–249.
44. Foster RH, Markam A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 2000;59:551–579.
45. Polley LS, Columb MO, Naughton NN. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indixes. Anesthesiology 1999;90:944–950.
46. Yun EM, Meadows W, Santos AC. New local amides for obstetric use. Bailliere's Clin Obstet Gynaecol 1998;12:461–471.
47. Floreani A, Paternoster DM, Chiaramonte M. Hepatitis C virus infection in pregnancy. Br J Obstet Gynaecol 1996;103:325–329.
48. Davies JM, Thistlewood JM, Rolbin SH, Douglas JM. Infections and the parturient: anaesthetic considerations. Can J Anaesth 1988;35:270–277.
49. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1742–1750.
50. Hughes SC, Dailey PA, Landers D, et al. Parturients infected with human immunodeficiency virus and regional anesthesia. Clinical and immunologic response. Anesthesiology 1995;82:32–37.
51. Birnbach DJ, Bourlier RA, Choi R, Thys DM. Anaesthetic management of caesarean section in a patient with active recurrent genital herpes and AIDS-related dementia. Br J Anaesth 1995;75:639–641.
52. Pang WW, Lei CH, Chang DP, et al. Acute jaundice in pregnancy: acute fatty liver or acute viral hepatitis? Acta Anaesthesiol Sin 1999;37: 167–170.
53. Brown MS, Reddy KR, Hensley GT, et al. The initial presentation of fatty liver of pregnancy mimicking acute viral hepatitis. Am J Gastroenterol 1987;82:554–557.
54. Duke J. Pregnancy and cirrhosis: management of hematemesis by Warren shunt during third trimester gestation. Int J Obstet Anesth 1994;3:97–102.
55. Sladen RN. Perioperative care for the patient with renal or hepatic disease. IARS Rev Course Lect 2001;5:99–103.
56. Conn HO. Transjugular intrahepatic portal-systemic shunts: the state of the art. Hepatology 1993;17:148–158.
57. Chan WH, Lee TS, Lin CS, et al. Anesthetic management for cesarean section in a pregnant woman with impending acute liver failure—a case report. Acta Anaesthesiol Sin 1999;37:141–146.
58. Chambers JC, Fusi L, Kooner PW. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001;285:1607–1612.
59. Esplin MS, Faucett MB, Varner MW. Paternal and maternal components of the predisposition to preeclampsia. N Engl J Med 2001;344: 867–872.
60. Pipkin FB. Risk factors for preeclampsia. N Engl J Med 2001;344: 900–901.
61. Schuiling GA, Faas MM. Etiology and pathogenesis of preeclampsia: current concepts [letter; comment]. Am J Obstet Gynecol 1999;181: 1036–1037.
62. Barton JR, Sibai BM. Care of the pregnancy complicated by HELLP syndrome. Gastroenterol Clin N Am 1992;21:937–950.
63. Van Hook JW. Management of complicated preeclampsia. Semin Perinatol 1999;23:79–90.
64. Saphier CJ, Repke JT. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a review of diagnosis and management. Semin Perinatol 1998;22:118–133.
65. Lewis R, Sibai B. Recent advances in the management of preeclampsia. J Matern Fetal Med 1997;6:6–15.
66. Magann EF, Perry KG, Martin JM. Postpartum corticosteroids: accelerated recovery from the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol 1994;171: 1154–1158.
67. Wijesinghe PS, Gunasekera PC, Sirisena J. Spontaneous hepatic rupture in pregnancy. Ceylon Med J 1998;43:109–111.
68. Luna R, Bolsan HE, Skerly J, et al. Hepatic rupture in pregnancy: report of a case and review of the literature. Acta Gastroenterol Latinoam 2000;30(2):121–126.
69. Yagmurdur MC, Agalar F, Daphan CE. Spontaneous hepatic rupture in pregnancy. Eur J Emerg Med 2000;7:75–76.
70. Karadia S, Walford C, McSwiney M, Nielsen MS. Hepatic rupture complicating eclampsia in pregnancy. Br J Anaesth 1996;77:792–794.

71. Matsuda Y, Maeda T, Hatae M. Spontaneous rupture of the liver in an uncomplicated pregnancy. J Obstet Gynaecol Res 1997;23:449–452.
72. Sheikh RA, Yasmeen S, Pauly MP, Riegler JL. Spontaneous intrahepatic hemorrhage and hepatic rupture in the HELLP syndrome: four cases and a review. J Clin Gastroenterol 1999;28:323–328.
73. Terasaki KK, Quinn MF, Pentecost MJ. Spontaneous hepatic hemorrhage in preeclampsia: treatment with hepatic arterial embolization. Radiology 1990;174:1039–1041.
74. Roberts WE, Perry KG, Martin JN. The intrapartum platelet count in patients with HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome: is it predictive of later hemorhagic complications? Am J Obstet Gynecol 1994;171:799–804.
75. Ramanathan J, Sibai BM, Vu T, Chauhan D. Correlation between bleeding times and platelet counts in women with preeclampsia undergoing cesarean section. Anesthesiology 1989;71:188–191.
76. Wulf H. Anesthesia and intensive therapy of pregnant women with the HELLP syndrome. Anaesthesist 1990;39:117–121.
77. Jwayyed SM, Blanda M, Kubina M. Acute fatty liver of pregnancy. J Emerg Med 1999;17:673–677.
78. Glasgow JF, Moore R. Current concepts in Reye's syndrome. Br J Hosp Med 1993;50:599–604.
79. Strauss AW, Benett MJ, Sims HE. Inherited long chain 3-hydroxyl acylco A dehydrogenase deficiency and a fetal-maternal interaction causing maternal liver diseas and other pregnancy complications. Semin Perinatol 1999;2:100–112.
80. Ibdah JA, Bennett MJ, Strauss AW. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. N Engl J Med 1999;340:1723–1730.
81. Korducki SA. Acute fatty liver of pregnancy [see comments]. Wis Med J 1996;95:163–164.
82. Visconti M, Manes G, Giannattasio F, Uomo G. Recurrence of acute fatty liver of pregnancy. J Clin Gastroenterol 1995;21:243–245.
83. Watson WJ, Seeds JW. Acute fatty liver of pregnancy. Obstet Gynecol Surv 1990;45:585–591.
84. Antognini JF, Andrews S. Anaesthesia for caesarean section in a patient with acute fatty liver of pregnancy. Can J Anaesth 1991;38:904–907.
85. Baldo V, Floreani A, Trivello R. Hepatitis C virus, hepatitis B virus and human immunodeficiency virus infection in pregnant women in North-East Italy: a seroepidemiological study. Eur J Epidemiol 2000;16:87–89.
86. Syndham D. Hepatitis in pregnancy. N Engl J Med 1985;313:1398–1400.
87. Chon EM, Middleton RK. Labetolol hepatotoxicity. Ann Pharmacother 1992;26:344–345.
88. Danan G, Benichou C. Causality assessment of adverse reactions to drugs. I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323–1330.
89. Zachariae H. Methotrexate side-effects [see comments]. Br J Dermatol 1990;122(suppl 36):127–133.
90. Kort KC, Schiller HJ, Numann PJ. Hyperparathyroidism and pregnancy. Am J Surg 1999;177:66–68.
91. Swisher SG, Schmit PJ, Hunt KK, et al. Biliary disease during pregnancy. Am J Surg 1994;168:576–579; discussion 580–581.
92. Quinn PG, Sherman BW, Tavill AS, Gibas AL. Terbutaline hepatitis in pregnancy: report of two cases and literature review. Am J Gastroenterol 1994;89:781–784.
93. Castro Fernandez M, Romero Gomez M, Grande Santamaria L, Caballero Manzano M. Acute hepatitis due to ritodrine [letter]. Med Clin (Barc) 1999;113:239.
94. Van Dyke R. The Liver in pregnancy. In: Zakim D, Boyer T (eds) A Textbook of Liver Disease. Philadelphia: Saunders, 1990:200–230.
95. Tong M, Thursky M, Rakela J. Studies on maternal infant transmission of the viruses which cause acute hepatitis. Gastroenterology 1981;80:999–1003.
96. Mishra L, Seeff L. Reilly C, Abell T (eds). Gastrointestinal and Liver Problems in Pregnancy: Viral Hepatitis A thru E, Complicating Pregnancy. 1992;21, 873.
97. Berry M, Herrera J. Diagnosis and treatment of chronic viral hepatitis. Compr Ther 1994;20:16.
98. Koff RS. Viral hepatitis. In: Schiff L, Schiff ER (eds) Diseases of the Liver, 7th edn. Philadelphia: Lippincott, 1993:492–577.
99. Anonymous. Viral Hepatitis in Pregnancy. ACOG Educational Bulletin No. 248. Chicago: ACOG, 1998:248.
100. Vento S, Cainelli F, Concia E, Ferraro T. Steroid and interferon therapy in liver/kidney microsomal antibody-positive patients with chronic hepatitis C [letter]. J Hepatol 1997;26:955–956.
101. Keefe EB, Hollinger FB. Therapy of hepatitis C: consensus interferon trials. Hepatology 1997;26:101S–107S.
102. Ruggeriero G, Andreana A, Zampino R. Normal pregnancy under inadvertent alpha-interferon therapy for chronic hepatitis C. J Hepatol 1996;286:646.
103. Heathcote EJ, Shiffman ML, DePamphilis J. Peginterferon alpha-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;243:1673–1680.
104. Zeuzem S, Feinman SV, Brunda MJ. Peginterferon alpha-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666–1672.
105. Lin H, Kao J, Chen D. Least microtransfusion from mother to fetus in elective cesarean delivery. Obstet Gynecol 1996;87:244–246.
106. Latt NC, Spencer JD, Cossart YE. Hepatitis C in injecting drug-using women during and after pregnancy. J Gastroenterol Hepatol 2000;15:175–181.
107. Anonymous. Protection Against Viral Hepatitis: Recommendations of the Immunization Practices Advisory Committee (ACIP). Atlanta, GA. U.S. Dept of Health and Human Services, CDC, 1990.
108. Anonymous. Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP). Atlanta, GA: U.S. Dept of Health and Human Services, CDC, 1991.
109. Levy DM. General anaesthesia for caesarean section—noradrenaline response [letter; comment]. Anaesthesia 1993;48:640–641.
110. Coleman M, Traynor C. Anaesthesia for a patient on interferon therapy [letter]. Acta Anaesthesiol Scand 1999;43:115–116.
111. Anonymous. Hepatitis in Pregnancy. ACOG Technical Bulletin No. 174. Chicago: ACOG, 1992:174.
112. Romano DR, Jimenez C, Rodriguez F, et al. Orthotopic liver transplantation in alcoholic liver cirrhosis. Transplant Proc 1999;31:2491–2493.
113. Hartard C, Kunze K. Pregnancy in a patient with Wilson's disease treated with D-penicillamine and zinc sulfate. Eur Neurol 1994;34:337–340.
114. Ramsey PS, Hay JE, Ramin KD. Successful pregnancy following orthotopic liver transplantation for idiopathic Budd–Chiari syndrome. J Matern Fetal Med 1998;7:235–237.
115. Salha O, Campbell DJ, Pollard S. Budd–Chiari syndrome in pregnancy treated by caesarean section and liver transplant. Br J Obstet Gynaecol 1996;103:1254–1256.
116. Laifer SA, Abu-Khalaf M, Fung JJ. Hepatic transplantation during pregnancy and the puerperium. J Matern Fetal Med 1997;6:40–44.
117. Valentine JM, Parkin G, Pollard SG, Bellamy MC. Combined orthotopic liver transplantation and caesarean section for the Budd–Chiari syndrome. Br J Anaesth 1995;75:105–108.
118. Garcia-Tsao G, Korzenik JR, White RI. Liver disease in patients with hereditary hemorragic telangiectasia. N Engl J Med 2000;343:931–937.
119. Teisala K, Tuimala R. Pregnancy and esophageal varices. Ann Chir Gynaecol Suppl 1985;197:65–66.
120. Smith J, Grahm D. Variceal hemmorhage: a critical evaluation of survival analysis. Gastroenterology 1982;82:968–975.
121. Hamberg R, Buyer I, Lurie B. Bleeding esophageal varices in pregnancy: a report of 2 cases. J Reprod Med 1988;33:784
122. Iwase H, Morise K, Kawase T, Horiuchi Y. Endoscopic injection scle-

rotherapy for esophageal varices during pregnancy. J Clin Gastroenterol 1994;18:80–83.
123. Wellborn WR Jr, Greiss FC Jr, Johnston FR. Pregnancy following esophagectomy for bleeding varices in a patient with extrahepatic portal hypertension. Am J Obstet Gynecol 1973;117:181–183.
124. Conn HO. Transjugular intrahepatic portal-systemic shunts: the state of the art. Hepatology 1998;17:148–158.
125. Burnell JM, Dawborn JK, Epstein RB, et al. Acute hepatic coma treated by cross-circulation or exchange transfusion. N Engl J Med 1967;276: 935–943.
126. Douds A, Neuberger J. Liver transplantation for alcoholic cirrhosis: current situation [editorial] [see comments]. Hosp Med 1998;59:604–605.
127. Heriot JA, Steven CM, Sattin RS. Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices. Br J Anaesth 1996;76:325–327.
128. el Dawlatly AA, Bakhamees H, Seraj MA. Anesthetic management for cesarean section in a patient with Wilson's disease. Middle East J Anesthesiol 1992;11:391–397.
129. Conrad C. Physician awareness and screening for fetal alcohol syndrome. J Health Hum Serv Adm 2000;22(3):257–276.
130. Diekman ST, Floyd RL, Decoufle P, et al. A survey of obstetrician-gynecologists on their patients' alcohol use during pregnancy. Obstet Gynecol 2000;95(5):756–763.
131. Chang G, Wilkins-Haug L, Berman S, Goetz MA. Brief intervention for alcohol use in pregnancy: a randomized trial. Addiction 1999;94: 1499–1508.
132. Bradley KA, Badrinath S, Bush K, et al. Medical risks for women who drink alcohol [see comments]. J Gen Intern Med 1998;13:627–639.
133. Tonnesen H, Peterson KR, Kehlet H. Postoperative morbidity among alcohol abusers. Ugeskr Laeger 1994;156:287–290.
134. Felding C, Jensen LM, Tonnesen H. Postoperative morbidity after hysterectomy is related to alcohol consumption. Ugeskr Laeger 1994;156: 292–294.
135. Tonnesen H, Kehlet H. Preoperative alcoholism and postoperative morbidity. Br J Surg 1999;86:869–874.
136. Tonnesen H. The alcohol patient and surgery. Alcohol Alcohol 1999; 34:148–152.
137. Chiang PP. Perioperative management of the alcohol-dependent patient. Am Fam Physician 1995;52:2267–2273.
138. Lohr RH. Treatment of alcohol withdrawal in hospitalized patients [see comments]. Mayo Clin Proc 1995;70:777–782.
139. Goldaber KG, Gilstrap LC III. Correlations between obstetric clinical events and umbilical cord blood acid-base and blood gas values. Clin Obstet Gynecol 1993;36:47–59.
140. Alpert JJ, Zuckerman B. Alcohol use during pregnancy: what is the risk? Pediatr Rev 1991;12:375–379;discussion 380–381.
141. Rioseco AJ, Ivankovic MB, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994;170:890–895.
142. Weigel R, Weigel M. Nausea and vomiting of early pregnancy and pregnancy outcome: a meta-analytical review. Br J Obstet Gynaecol 1989; 96:1312.
143. Abell T, Reilly C. Hyperemesis gravidarum. Gastrointest Clin N Am 1992;21:835.
144. Ditto A, Morgante G, La Marca A, DeLeo V. Evaluation of treatment of hyperemesis gravidarum using parenteral fluid with or without diazepam. Gynecol Obstet Invest 1999;48(4):232–236.
145. Glascow RE, Visser BC, Mulvihill SJ. Changing management of gallstone disease during pregnancy. Surg Endosc 1998;12:241–246.
146. Davis A, Katz VL, Cox R. Gallbladder disease in pregnancy. J Reprod Med 1995;40:759–762.
147. Nesbitt TH, Kay HH, McCoy MC, Herbert WN. Endoscopic management of biliary disease during pregnancy. Obstet Gynecol 1996;87: 806–809.
148. Daradkeh S, Sumrein I, Daoud F, et al. Management of gallbladder stones during pregnancy: conservative treatment or laparoscopic cholecystectomy? Hepatogastroenterology 1999;46:3074–3076.
149. Block P, Kelly TR. Management of gallstone pancreatitis during pregnancy and the postpartum period. Surg Gynecol Obstet 1989;168:426–428.
150. Gouldman JW, Sticca RP, Rippon MB, McAlhany JC Jr. Laparoscopic cholecystectomy in pregnancy. Am Surg 1998;64:93–97; discussion 97–98.
151. Curet MJ, Allen D, Josloff RK, et al. Laparoscopy during pregnancy. Arch Surg 1996;131:546–550; discussion 550–551.
152. Martin IG, Dexter SP, McMahon MJ. Laparoscopic cholecystectomy in pregnancy. A safe option during the second trimester? Surg Endosc 1996;10:508–510.
153. Wishner JD, Zolfaghari D, Wohlgemuth SD, et al. Laparoscopic cholecystectomy in pregnancy. A report of 6 cases and review of the literature. Surg Endosc 1996;10:314–318.
154. Nelles J. Identifying anaesthetic risks in pregnant surgical patients. Can Oper Room Nurs J 1989;7:15–19.
155. Barnard JM, Chatin D, Phernetton T. Fetal response to carbon dioxide pneumoperitoneum in the pregnant ewe. Obstet Gynecol 1995;85:669–674.
156. Joris JL, Nairot DP, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 1993;76:1067–1071.
157. Duncan PG, Pope WD, Cohen MM. Fetal risk of anesthesia and surgery during pregnancy. Anesthesiology 1986;64:790.
158. Zaballos J, Perez-Cerda F, Riano D, et al. Anesthetic management of liver transplantation in a pregnant patient with fulminant hepatitis. Transplant Proc 1991;23:1994–1995.
159. Perez J, Talavera A, Castro F, Torres EA. Budd–Chiari syndrome in early pregnancy. P R Health Sci J 1998;17:285–287.
160. Merritt WT, Dickstein R, Beattie C, et al. Liver transplantation during pregnancy: anesthesia for two procedures in the same patient with successful outcome of pregnancy. Transplant Proc 1991;23:1996–1997.
161. Fair J, Klein AS, Feng T, et al. Intrapartum orthotopic liver transplantation with successful outcome of pregnancy. Transplantation 1990;50: 534–535.
162. Hamilton MI, Alcock R, Magos L, et al. Liver transplantation during pregnancy. Transplant Proc 1993;25:2967–2968.
163. Ville Y, Fernandez H, Frydman R. Pregnancy in liver transplant recipients: course and outcome in 19 cases. Am J Obstet Gynecol 1993; 896–902.
164. Jorgensen FS, Bock JE, Hansen BA, Kirkegaard P. Successful pregnancy after liver transplantation. Acta Obstet Gynecol Scand 1996;75: 678–680.
165. Laifer SA, Guido RS. Reproductive function and outcome of pregnancy after liver transplantation in women. Mayo Clin Proc 1995;70:388–394.
166. Riley T. Obstetric management of patients with transplants. Int Anesthesiol Clin 1995;33:125–140.
167. Pruvot FR, Declerck N, Valat-Rigot AS, et al. Pregnancy after liver transplantation: focusing on risks to the mother. Transplant Proc 1997; 29:2470–2471.
168. Radomski JS, Ahlswede BE, Armenti VT. Outcomes of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc 1995;27:1089–1090.
169. Laifer SA, Darby MJ, Scantlebury VP, et al. Pregnancy and liver transplantation. Obstet Gynecol 1990;76:1083–1088.
170. Casele HL, Laifer SA. Association of pregnancy complications and choice of immunosuppressant in liver transplant patients. Transplantation (Baltim) 1998;65:581–583.
171. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimize fetal risks in organ transplant patients. Ann Pharmacother 1994;28:1355–1356.
172. Bourget P, Fernandez H, Quinquis V, Delouis C. Pharmacokinetics of cyclosporin A during pregnancy; monitoring of treatment and specific assays of cyclosporin, based on five liver transplant patients. J Pharm Biomed Anal 1993;11:43–48.

173. Carton EG, Plevak DJ, Kranner PW. Perioperative care of the liver transplant patient. Anesth Analg 1994;78:120–123.
174. Whitten CW, Greilich PE. Thromboelastography: past, present, and future [editorial; comment]. Anesthesiology 2000;92(5):1223–1225.
175. Samama CM. Thromboelatography: the next step. Anesth Analg 2001; 92:563–564.
176. Gadano A, Hadenque A, Lebrec D. Hemodynamics after orthotopic liver transplantation: study of associated factors and long-term effects. Hepatology 1995;22:458–465.
177. Paternoster DM, Floreani A, Burra P. Liver transplantation and pregnancy [letter]. Int J Gynaecol Obstet 1995;50:199–200.
178. Avraamides EJ, Craen RA, Gelb AW. Anaesthetic management of a pregnant, post liver transplant patient for dental surgery. Anaesth Intensive Care 1997;25:68–70.
179. Mather LE, McCall PF, McNichol PL. Bupivacaine enantiomer pharmacokinetics after intercostal neural blockade in liver transplantation patients. Anesth Analg 1995;80:328–335.
180. Koch M, Banys P. Liver transplantation and opioid dependence. JAMA 2001;285:1056–1058.

31
Fetal Distress

Andrew P. Harris and Frank R. Witter

To optimize neonatal outcome, obstetricians strive to identify those in utero conditions that cause a clinical fetal state which, if ignored, would result in fetal compromise. This clinical state is frequently referred to as fetal distress. This term, although widely used to describe various antepartum and intrapartum in utero conditions, is rarely well defined. Any discussion of the pathophysiology, diagnosis, or management of this condition necessarily centers on the exact definition used. Although some authors use terms solely related to fetal heart rate tracing interpretation in their definition of fetal distress,[1,2] others relate the term to depressed Apgar scores or fetal acidosis[3] or even to a requirement that positive pressure ventilation is necessary in the newborn.[4]

Definition of Fetal Distress

In a recent review, Parer and Livingston[5] concluded that fetal distress is best defined through its relationship to asphyxia; that is, fetal distress is the end result of physiologic and pathophysiologic responses to an asphyxiated state in utero. They suggest this definition of fetal distress: "progressive fetal asphyxia that, if not corrected or circumvented, will result in decompensation of the physiologic responses (primarily redistribution of blood flow to preserve oxygenation of vital organs) and cause permanent central nervous system damage and other organs damage or death." An alternate definition proposed by Harris[6] is "a pathophysiologic condition in which oxidative metabolic substrate (in acute circumstances, oxygen) becomes available to the fetus in quantities insufficient to sustain in utero life for a prolonged period of time." These definitions, which encompass the physiologic basis for the clinical patterns readily identified with both fetal distress and suboptimal outcome, appear to be among the best available.

Incidence

To understand the scope and potential importance of the diagnosis of fetal distress, estimates of the incidence must be made. Such estimates can be derived from qualitative and quantitative data regarding the in utero fetus as well as outcome measures. For instance, it has been variously estimated that approximately 4% to 7% of all infants born in developed countries can be classified as "growth retarded."[7] Of these, one third exhibit congenital anomalies. In those without congenital anomalies, the impairment of normal in utero growth patterns can easily be understood to be the result of some extent of fetal compromise (i.e., fetal distress) occurring in utero or at some point during gestation. The potential extent of fetal compromise can be surmised from the incidence of one endpoint, fetal death in utero, in fetuses demonstrating growth retardation. Clearly, some of these growth-retarded infants were exposed to life-threatening conditions in utero, because there is an eightfold increase in stillbirth rate in those fetuses 25% or more underweight (below the 2.5th percentile).[8] In a study of 2 million births in California, rising fetal mortality occurred with advancing gestational age in fetuses demonstrating intrauterine growth restriction (IUGR).[9] In another study of cause of death of 765 stillbirths, hypoxia was identified as the major cause of death in 43%.[10] Interestingly, approximately 80% of in utero deaths of IUGR fetuses occur at or beyond the 35th week of gestation.[11,12] Data such as these indicate that there are indeed a significant number of infants who exhibit signs of chronic fetal distress in utero as defined here.

An estimate of the incidence of intrapartum fetal distress can be made from data regarding the management of labor when fetal distress is deemed present. Numerous studies report the rate of operative delivery for the diagnosis of fetal distress. For example, in the Dublin randomized trial of intrapartum fetal heart rate monitoring, in those infants randomized to electronic fetal heart rate monitoring, the incidence of fetal distress (defined by fetal heart rate monitoring and scalp pH criteria) requiring operative delivery was 3.3%.[13] In this trial, 16% of all cesarean sections were performed for the indication of fetal distress. In the United States, 10% to 15% of all cesarean sections are performed for the diagnosis of fetal distress.[14]

Given these data regarding the antepartum and intrapartum incidence of fetal distress, the importance of accurately diagnosing fetal distress is clear: if delivery of an asphyxiated fetus is achieved before fetal compensatory mechanisms fail, one would predict that the rate of intact survival (including a good neurologic outcome) can be improved by avoidance of severe asphyxia. In the Dublin trial, the diagnosis of fetal distress by continuous electronic fetal heart monitoring was associated with a lower incidence of at least one indicator of poor outcome (i.e., neonatal seizures) secondary to fetal distress, compared with a group with less stringent intermittent auscultation.[13] In addition to the obvious individual and societal benefit of diagnosing and treating fetal distress before permanent organ damage occurs, increasingly scarce health care resources could be reallocated from chronic care of the neurologically impaired infant to other health care needs.

The goal of the accurate diagnosis and management of fetal distress should be to reduce the risk of both fetal and neonatal death as well as a lifelong organ system impairment, especially neurologic impairment. Long-term adverse neurologic outcome can include behavioral difficulties, cerebral palsy, and mental retardation.[14] Although fetal distress can obviously occur throughout gestation as well as intrapartum, it is estimated that only a small minority of children with cerebral palsy or severe retardation had evidence of fetal distress during the intrapartum period.[15–18]

In utero asphyxia almost always precedes and is associated with fetal distress. Asphyxia is best defined as a pathophysiologic condition in which there is insufficient exchange of respiratory gases including both carbon dioxide and oxygen. In the fetus, an isolated decrease in Pa_{O_2} separate from an elevation in Pa_{CO_2} usually is not seen (the postnatal analogy being that hypoventilation is associated with both increased P_{CO_2} and decreased P_{O_2}). Oxygen and carbon dioxide changes occur in tandem. Therefore, fetal asphyxia is associated with hypoxemia, hypercarbia, and a resulting acidosis. This acidosis may be respiratory acidosis secondary to hypercarbia alone (early) or combined with metabolic acidosis secondary to accumulation of lactic acid by-products of anaerobic metabolism occurring pursuant to a hypoxemic condition (late). Because all fetuses have arterial oxygen tensions lower and arterial carbon dioxide tensions higher than normally seen postnatally, the term asphyxia, as the terms hypoxemic and hypercarbic, must only be used to describe fetal conditions relative to normal in utero fetal physiology. Any discussion of diagnosis and management of fetal distress (and therefore asphyxia) must be preceded by discussion of the relevant in utero fetal physiology.

Normal Fetal Physiology

Normal patterns of fetal physiology differ from postnatal physiology in many ways. These differences must be understood to recognize deviations that occur as a result of asphyxia in utero.

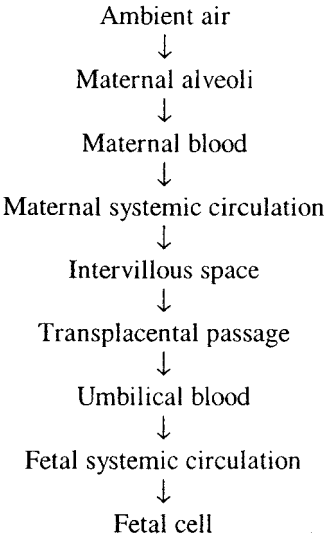

FIGURE 31.1. Pathway of oxygen to the fetal cell.

Fetal metabolism is primarily oxidative, as is seen in postnatal animals. However, the fetus has a much smaller oxygen reserve within its body and therefore depends on ongoing transport of oxygen from the mother through the placenta. A study of the pathway of oxygen from the ambient environment to the fetal cell will identify the points along that pathway at which impairment can occur and cause a hypoxic state in the fetus (Figure 31.1). The most common areas for interference with oxygen transport include decreases in uterine blood flow, alterations in placental function, and compression of umbilical arteries. The P_{O_2} in each step of this process cascades in such a way that umbilical venous P_{O_2} (which approximates the P_{O_2} of preductal blood perfusing the brain and myocardium) is approximately 28 torr.[19] Under chronic basal conditions, the fetus is thus exposed to relatively low oxygen levels.

Despite this chronic exposure to relatively low in utero P_{O_2}, there is good evidence that the fetus is not normally hypoxic. That hypoxia is not present at this normal P_{O_2} is evidenced by these mechanisms: (1) there is net lactate uptake by the fetus; (2) only small amounts of hydrogen ion are transferred from fetus to mother; (3) oxygen consumption does not increase when additional oxygen is made available to the fetus; and (4) the healthy fetus has a normal basal pH.[20]

Fetal Response to Asphyxia

The fetus, although chronically exposed to relatively low P_{O_2}, nonetheless responds with dramatic circulatory changes to further decreases in oxygenation that threaten survival. The physiologic responses to isolated hypoxemia have been widely studied in fetal sheep. The responses to decreased oxygenation include redistribution of blood flow away from the kidneys, spleen, carcass, and skin and toward the heart, brain,

placenta, and adrenal glands.[21] In the heart and brain, the resulting increase in myocardial and cerebral blood flow can completely compensate for the decreased oxygen content of the blood, maintaining myocardial and cerebral oxygen delivery even through episodes of relatively severe hypoxemia (i.e., decreases in arterial oxygen content of 80%).[22] At modest levels of hypoxemia, combined ventricular output is not decreased, and blood pressure and heart rate are unchanged.[23] However, at extreme levels of hypoxemia, cardiac output is decreased secondary to the bradycardic response of chemoreceptor stimulation.[23] This decrease in cardiac output may be exacerbated by the presence of acidemia.[24] In such extreme hypoxemic states, when oxygen content is reduced by 80%, combined blood flow to the heart and brain, which normally accounts for only 7% to 8% of cardiac output, increases to approximately 25% of cardiac output.[22]

During severe fetal hypoxemia, fetal oxygen consumption may be depressed by as much as 40% in fetal lambs.[25] This decrease is associated with decreased metabolism in the fetal liver, intestines, and kidney, while cerebral and myocardial oxygen uptake are unchanged.[25–27] Fetal skeletal muscle activity (including fetal breathing movements) decreases. Glycogenolysis occurs, resulting in increased substrate availability for the brain and heart. If bradycardia occurs in conjunction with severe fetal hypoxemia, myocardial oxygen consumption decreases.[23] This level of decreased oxygen consumption can be maintained up to 45 min and appears to be completely reversible with cessation of hypoxemia.[5]

Other fetal sheep experimental models have studied hypoxemia combined with hypercarbia (i.e., asphyxia), the more clinically relevant scenario. In one study in which fetal asphyxia was induced by decreasing uterine blood flow in pregnant sheep,[24] a 50% decrease in uterine blood flow was associated with neither a decrease in pH nor a decrease in myocardial or cerebral blood flow. At extremes of asphyxia, however, these compensatory mechanisms fail. When uterine blood flow was further decreased to 25% of normal, myocardial blood flow and cerebral blood flow decreased from the levels seen with only a 50% decrease in uterine blood flow to a level below baseline flow. Given the simultaneous fall in Po_2, oxygen delivery to the brain and myocardium decreased to levels at which life was threatened.

At this extreme level of asphyxia, in contrast to what is observed at lesser levels of asphyxia, vasoconstriction appeared to occur in all organs (including the heart and brain) except the adrenal glands. At that extreme level of asphyxia, fetal pH decreased significantly, and base excess increased, suggesting that normal compensatory mechanisms that had successfully compensated for lesser levels of asphyxia were beginning to fail. Parer and Livingston[5] thought that this stage of failing compensatory mechanisms most likely results in bradycardia, hypotension, and death unless corrected within a relatively short time. They postulate that it is also during this phase that irreversible hypoxic organ damage may occur. Therefore, recognition of less-severe in utero asphyxia before this stage might allow treating fetal distress more promptly and effectively.

Conditions Predisposing to Fetal Distress

Various conditions at the maternal, fetal, and placental level are associated with an increased risk of fetal distress developing during pregnancy and labor (Box 31.1). When these conditions are suspected, antepartum testing is frequently used to determine in utero fetal well-being and to plan appropriate treatment strategies for infants suffering chronic fetal distress in utero. For many of these conditions, even if chronic fetal distress is not seen during pregnancy, the fetus may be at greatly increased risk of developing fetal distress during the physiologic stress of labor.

Diagnosis

Clinically, the means of diagnosis of fetal distress are nonspecific and imprecise with low positive predictive values even in high-risk populations.[28] The methods available for intrapartum fetal observation, although very rarely incorrect in identifying the fetus without clinically significant intrapartum fetal distress, are frequently incorrect when a possibly compromised fetus is identified. Intervention is undertaken more often than absolutely necessary, given that a nonreassuring fetal observation does not reliably predict perinatal asphyxia.

Asphyxia associated with fetal distress can occur either chronically antepartum or acutely intrapartum. The diagnosis

Box 31.1. Risk factors for fetal distress.

Maternal
- Cardiopulmonary disease
- Renal failure
- Extremes of childbearing age
- Low socioeconomic class
- Small size/stature
- Tobacco use
- Alcohol use
- Drug use (i.e., heroin, cocaine)
- Hypertensive and vascular disease
- Malnutrition
- History of small-for-gestational-age (SGA) infant

Placental
- Retroplacental bleeding (abruption)
- Circumvallate placenta
- Placental infarct
- Chorioangioma

Fetal
- Infection
- Multiple gestation
- Karyotypic anomaly
- Long umbilical cord
- Fetal anomaly

of chronic fetal distress is best made through antepartum fetal assessment; these techniques may include evaluation of fetal growth, biophysical profile scoring, cordocentesis, and Doppler ultrasound velocimetry.

Evaluation of fetal growth is undertaken to detect those infants demonstrating IUGR. Identification of fetuses whose growth does not proceed at a normal rate may indicate chronic in utero asphyxia. In cases in which asymmetric IUGR is identified, ongoing in utero placental insufficiency should be considered a cause of relatively normal head growth with lagging body growth. When such uteroplacental insufficiency is chronically present, the fetus is much more likely to experience intrapartum decompensation of physiologic compensatory mechanisms when asphyxia occurs during labor and results in fetal distress.[29]

The biophysical profile score and its components may also be useful in detecting chronic in utero asphyxial conditions.[30] The biophysical profile consists of evaluation of fetal breathing, gross body movements, fetal tone, quantitative amniotic fluid volume, and reactivity of the fetal heart rate (nonstress test). The contraction stress test (also called the oxytocin challenge test) might aid in determining a chronic fetal state that would lead to acute decompensation during continued gestation or labor.[31]

Umbilical venous blood can be sampled directly (via cordocentesis) to assess in utero fetal oxygenation and acid–base status in settings of severe IUGR or when fetal compromise is suspected. Umbilical blood gas measurements can provide direct evidence of the presence or absence of in utero chronic asphyxia; this provides useful guidance regarding further management.

Doppler ultrasound velocimetry can be used to measure systolic–diastolic (SD) ratios in the umbilical artery. An increased SD ratio signifies decreased diastolic umbilical arterial flow, which suggests increased placental vascular resistance. This increase in resistance indirectly implies a severe hypoxemic state because umbilical vasoconstriction occurs as a relatively late response to asphyxial challenges.[24] This decreased diastolic flow is found most often in pregnancies complicated by maternal hypertension or IUGR.[32,33] Completely absent diastolic flow suggests either a fetal anomaly or severe fetal growth restriction and indicates the need for immediate evaluation of in utero fetal distress.[34]

Intrapartum diagnosis of fetal distress can be attempted by examination of the fetal heart rate trace, fetal blood sampling, in utero pulse oximetry, and fetal EEG and ECG monitoring. The first two techniques are widely used; pulse oximetry is licensed in Europe, and the latter two are still being studied experimentally. It should be noted that only scalp sampling or in utero pulse oximetry gives direct evidence of fetal hypoxemia or asphyxia. The remaining techniques are all indirect methods that rely on our ability to detect the physiologic result of decreased oxygenation in the fetus.

Intrapartum electronic fetal heart rate monitoring can demonstrate patterns that have been associated with an increased incidence of fetal compromise:

1. Severe bradycardia (fetal heart rate less than 80 beats/min persisting for 3 min or more)
2. Repetitive late decelerations (a symmetric fall in the fetal heart rate that begins at or after the peak of the uterine contraction and returns to baseline after the contraction ends
3. Undulating baseline (a pattern of rapid change between tachycardia and bradycardia)
4. Any nonreassuring pattern associated with unexplained poor or absent baseline variability

The interested reader can find further details of the definitions of fetal heart rate patterns in the American College of Obstetricians and Gynecologists Technical Bulletin on Intrapartum Fetal Heart Rate Monitoring.[35] Recently, the results of computerized power spectral analysis of fetal heart rate variability have been shown to be a good predictor of fetal distress.[36]

When intrapartum electronic fetal heart rate monitoring is nonreassuring, the condition of the fetus should be confirmed by further testing, because 40% of fetuses with recurrent late decelerations, for example, have normal cord pH values at birth.[37] Intrapartum assessment of fetal acid–base status can confirm potential fetal compromise, and, if reassuring, it can reduce the number of unnecessary cesarean sections for suspected fetal distress.[38]

Indirect assessment of fetal acid–base status through the noninvasive techniques of vibroacoustic stimulation[39] or scalp stimulation[40] should be the initial approach to further testing when a nonreassuring fetal heart trace is present. An acceleration in fetal heart rate in response to these maneuvers indicates that fetal acidosis is not present. Unfortunately, half of fetuses stimulated do not respond, and direct measurement of fetal acid–base status via scalp blood sampling may be necessary.

The gold standard for intrapartum assessment of fetal acid–base remains direct fetal scalp blood sampling, which requires ruptured membranes and a cervix that is at least 2.5 cm dilated. The fetal vertex must be firmly applied to the cervix, and the scalp cleansed of possible contaminants. The scalp is then incised at a point away from the fontanelles with a long-handled, 2-mm blade. A capillary tube is used to collect fetal blood from the small wound for analysis. Because scalp blood flow is preductal, and scalp oxygen consumption is very low, a sample thus obtained is considered arterialized. A normal scalp pH is above 7.25; values between 7.20 and 7.25 should cause suspicion and should be interpreted in light of the fetal heart rate pattern and progress in labor. In general, fetal scalp blood sampling should be repeated in 15 to 30 min to determine if there is a downward trend in the pH. A scalp pH less than 7.20 is abnormal and requires medical or surgical intervention for expeditious delivery.

Intrauterine fetal pulse oximetry has been shown to correlate with fetal scalp pH. Utilizing fetal pulse oximetry, an arterial oxygen saturation less than 30% for at least 10 min correlates with a fetal scalp pH less than 7.20.[41] When fetal pulse oximetry is added to standard electronic fetal monitoring, the diagno-

sis of fetal distress is more than halved, from 10.2% to 4.5%.[42] This improvement in specificity is similar to the use of fetal scalp blood sampling. To utilize fetal pulse oximetry, however, the cervix must be at least 2 cm dilated, and the fetal presenting part at −2 station or lower with ruptured membranes.

The postpartum diagnosis of fetal distress can be attempted by evaluation of the Apgar score at birth, the umbilical cord blood gas values at birth, birth weight of the infant, and neonatal neurologic testing. The Apgar score was not designed as a predictor of neurologic outcome. In term infants with a 5-min Apgar score of 0 to 3 and a 10-min Apgar score of 4 or greater, 99% do not subsequently develop cerebral palsy. In fact, 73% of infants who went on to develop cerebral palsy had a 5-min Apgar score of at least 7.[43] These data demonstrate that the Apgar score is useful to detect only a small percent of infants with significant intrapartum fetal distress.

Although it would seem that umbilical cord blood gas values would be quite useful in predicting those infants with clinically significant asphyxia, they are much more useful only as a means of ruling out the presence of intrapartum fetal distress in infants with low Apgar scores at birth. In fact, low pH, like a low Apgar score, is only rarely associated with poor outcome. In a recent study of 1601 women undergoing elective cesarean section, 9 infants had an umbilical artery blood pH of less than 7, yet none of these infants demonstrated any neonatal morbidity.[44] Umbilical blood gas values, through analysis of base deficit, may yield information regarding the acuity of fetal acidemia. Such information may be important because partial asphyxia can be tolerated for some period of time before compensatory mechanisms begin to fail. Unfortunately, however, the level of base deficit associated with evidence of failure of compensatory mechanisms is unknown.

For the same reasons that in utero growth and size may be a marker of chronic fetal distress, decreased size for gestational age at birth (small for gestational age, SGA) is somewhat correlated with outcome. However, Allen[45] reviewed developmental outcome in SGA infants and found that, although SGA infants have a small increased risk for cerebral palsy, most have normal intelligence and no major neurologic deficits.

Finally, although careful neonatal neurologic testing may be able to detect those infants who have suffered in utero fetal distress with resulting impaired neurologic outcome, it cannot differentiate antepartum from intrapartum asphyxia. As with the other postpartum indicators of in utero fetal distress, the post hoc diagnosis may be of limited usefulness. For this reason, the major monitoring efforts are turned toward antepartum and intrapartum, not postpartum, detection of fetal distress.

Obstetric Management

Once the tentative antepartum or intrapartum diagnosis of fetal distress has been made, treatment modalities include improvement of in utero conditions to restore normal respiratory gas exchange or delivery of the infant from in utero conditions (Box 31.2). Improvement of in utero conditions in a chronic situation might include bedrest with left uterine displacement. In an acute situation, treatment of hypotension, assurance of optimal maternal oxygenation and ventilation, proper maternal positioning, tocolysis, and amnioinfusion are used. Expedited delivery of the infant is the only option if in utero improvement cannot be achieved or is deemed futile. Time is of the essence in such cases, because irreversible damage to the fetus has been shown to occur with as little as 10 min of oxygen deprivation in a primate experimental model.[46]

Box 31.2. Management of suspected fetal distress.

- Confirm diagnosis of fetal distress
  - Examine fetal heart rate trace
  - Consider scalp pH or fetal pulse oximetry
  - Provide vibroacoustic or tactile stimulation
- Conduct pelvic examination to exclude cord prolapse and vaginal bleeding
- Treat relative or absolute maternal hypovolemia
  - Avoid venocaval compression
  - Restore intravascular volume if necessary
  - Treat maternal hypotension if present
  - Use β-adrenergic agonist, such as ephedrine
- Administer supplemental oxygen
- Decrease uterine tone
  - Discontinue oxytocin
  - Use a tocolytic agent
- Use amnioinfusion if indicated
- If none of these measures succeed, plan expeditious medical or surgical delivery

Treatment of Maternal Hypotension

Adequate uterine blood flow depends to a large extent on the maintenance of uterine arterial perfusion pressure. Because uterine blood flow is not autoregulated[47] (i.e., will not increase in response to decreased perfusion pressure), it is essential that maternal arterial blood pressure not be allowed to fall to extreme levels of hypotension. If maternal blood pressure is low and judged to be contributing to ongoing fetal distress, various methods can be used to raise maternal blood pressure. Assuming that left uterine displacement is already being used, maternal interavascular volume can be restored toward normal by the rapid intravenous infusion of crystalloid solutions. In one study in pregnant sheep,[48] intervillous blood flow increased dramatically following rapid crystalloid infusion in sheep with signs of intravascular volume depletion. If hemorrhage is a cause of the hypotension, attention obviously should be paid to intravascular volume repletion as well as restoration of oxygen-carrying capacity of the blood through appropriate transfusion. If vasopressors must be used to restore maternal blood pressure toward normal, the general consensus is to use a predominantly beta-adrenergic agonist such as ephedrine in preference to a predominantly alpha-adrenergic agonist such as phenylephrine.[49] Although two recent studies[50,51] suggest that using the alpha-adrenergic agonist phenylephrine

to restore maternal blood pressure to normal following regional anesthesia for elective cesarean section may not cause worse fetal acid–base status relative to the use of ephedrine, these results may be partially explained by the relatively large fetal reserve present in a healthy fetus before elective cesarean section. Thus, such results should not be extrapolated without caution to situations in which fetal distress is known or suspected.

Ensuring Optimal Maternal Oxygenation and Ventilation

Decreased maternal Pa_{O_2} is rarely the primary cause for fetal distress. Nonetheless, increasing maternal Pa_{O_2} above normal values by the administration of supplemental oxygen may improve fetal condition. Supplemental maternal oxygen administration will increase maternal Pa_{O_2} and concurrently increase umbilical venous Pa_{O_2} in patients undergoing elective cesarean section.[52,53] Similar results are found in rhesus monkey studies.[54] This increase in fetal Pa_{O_2} appears likely to occur in conditions associated with fetal distress. Morishima et al.[55] administered supplemental oxygen to laboring primates whose fetuses were relatively acidotic and hypoxemic and exhibited late decelerations on their fetal heart rate tracings. Following oxygen supplementation, fetal Pa_{O_2} increased, and late decelerations were abolished. Edelstone et al.[56] studied the effect in sheep of increasing maternal oxygenation on fetal P_{O_2} while occluding the umbilical vessels to various degrees. Over a wide range of umbilical blood flows, increased supplemental maternal oxygen administration improved fetal P_{O_2}. The best explanation for these uniform results are that even small changes in fetal Pa_{O_2} may be significant, because they are occurring on a relatively steep portion of the oxygen dissociation curve of fetal hemoglobin.

The administration of supplemental maternal oxygen in the second stage in the absence of signs of fetal distress has recently come under question. In one study, infants born to mothers receiving supplemental oxygen versus those born to mothers receiving no supplemental oxygen during the second stage had a significantly lower umbilical blood pH at birth.[57] The cause and significance of this finding are unclear at this time and should not be extrapolated to situations where fetal distress is suspected.

Proper Maternal Positioning

Improper maternal positioning can exacerbate fetal distress secondary to a partial occlusion of either the inferior vena cava or the distal aorta.[58–60] Occlusion of the aorta, which may occur in the supine position, results in decreased perfusion pressure in the uterine arteries with a resulting decrease in uterine blood flow. Partial occlusion of the vena cava almost uniformly occurs in the supine position in the latter half of gestation, and it causes decreased venous return to the heart, transient hypotension, and increased downstream pressure to the uterus (thus decreasing uterine perfusion pressure). The subsequent baroreceptor response, by eliciting catecholamines, will adversely affect placental perfusion despite return of blood pressure to normal. Therefore, whenever fetal distress is present, left uterine displacement or left lateral positioning should be used.

Tocolysis

Acute fetal distress has been treated successfully in utero with tocolytic agents. If excessive uterine activity has compromised uteroplacental perfusion, prompt uterine relaxation may reverse the condition. The first step, however, should be discontinuation of oxytocin if it is being administered.

The use of tocolytics to decrease uterine activity has been referred to as in utero resuscitation. The goal of this approach is to improve uterine blood flow and allow improved fetal oxygenation, thereby reversing fetal compromise. Even when fetal distress is not due to excessive uterine activity but is occurring during active labor, uterine relaxation might transiently help to improve uterine blood flow, thereby improving fetal status before cesarean delivery.

The β_2-sympathomimetic tocolytics ritodrine (as an IV bolus of 6 mg administered over 3 min) and terbutaline (250-μg IV bolus or subcutaneously) have both been shown to improve fetal acidosis in fetuses showing nonreassuring fetal heart rate findings confirmed by abnormal fetal pH values.[61,62] However, enthusiasm for this approach must be tempered by the known ability of β_2-sympathomimetic infusion to decrease uterine blood flow in animal studies.[63]

There are anesthetic considerations for patients receiving β_2-sympathomimetics for acute tocolysis in the setting of fetal distress. The cardiovascular system is affected in several ways. Neither terbutaline nor ritodrine is entirely β_2 selective; thus, some β_1 activity will also occur. Maternal tachycardia is extremely common.[64] Increased automaticity of the sinoartrial node and other intrinsic pacing cells, as well as increased stimulation through the atrioventricular node, may lead to dangerous supraventricular and ventricular arrhythmias. Patients with preexcitation syndrome (Wolff–Parkinson–White and Lown–Ganong–Levine) may be especially at risk for supraventricular tachyarrhythmias caused by increasing conduction velocity through accessory pathways.[65]

There are numerous reports of parturients undergoing β_2-sympathomimetic therapy, usually for preterm labor, who demonstrated ST-T wave depression and/or T-wave flattening; this often presents within the first 2 h of therapy. Similar changes have been noted to occur in both asymptomatic women and in others with symptoms of chest discomfort. Some have attributed these changes to tachycardia and acute hypokalemia, while others have suspected subendocardial ischemia in symptomatic cases.[65] β_2-Sympathomimetic therapy has also been associated with pulmonary edema. In most of these cases, the etiology appeared to be noncardiogenic. The exact mechanisms have not been convincingly elucidated.

Ravindran et al.[66] reported the development of pulmonary edema in a patient who received a single IV dose of 250 μg terbutaline; fortunately, this resolved within 2 h of the conclusion of surgery.

Maternal blood pressure is also affected by β_2-sympathomimetic agents. Increased inotropy, chronotropy, and peripheral vasodilation result in variable effects on maternal blood pressure. Increases in systolic blood pressure, decreases in diastolic blood pressure, and no significant changes in blood pressure have all been reported.[61,62,64–67] The peripheral vasodilation associated with β_2-sympathomimetic therapy may be especially dangerous in the hypovolemic woman, in such cases involving suspected abruption.

Intravenous or sublingual nitroglycerin can also be used for acute tocolysis. Nitroglycerin 60 to 90 μg IV has been found effective in relieving intrapartum fetal distress from uterine hyperactivity.[68]

Amnioinfusion

When fetal heart rate testing is nonreassuring with deep variable decelerations or in the presence of thick meconium, amnioinfusion can improve perinatal outcome.[69,70] Variable decelerations, most likely caused by cord compression, can be relieved, and cesarean section rates due to fetal intolerance of labor can be decreased by amnioinfusion.[69–71] In cases of thick meconium, it can also decrease the incidence of meconium below the vocal cords and meconium aspiration.[72,73]

Intrapartum amnioinfusion is performed using a transcervical intrauterine pressure catheter. Normal saline or Ringer's lactate is infused at 600 mL for the first hour, followed by 180 mL/h until delivery. The choice of fluid has no clinically significant effect on neonatal electrolytes.[74] Intrapartum amnioinfusion has been associated with increased risk for chorioamnionitis and postpartum endometritis.[75] Two cases of fatal amniotic fluid embolism have been reported, complicating intrapartum amnioinfusion.[76] However, despite these risks, amnioinfusion is a worthwhile technique to treat certain cases of fetal distress.

Anesthetic Management

Antepartum Fetal Distress

The anesthetic management for vaginal delivery or cesarean section when fetal distress is diagnosed depends on the condition of the fetus and thus the urgency of the situation. When presumed antepartum fetal distress is present, such as a term fetus with IUGR and uteroplacental insufficiency, anesthesia should be planned to minimize any further decrement in oxygen delivery to the fetus during labor.

The methods potentially useful for providing analgesia for anticipated vaginal delivery in women with chronic fetal distress include psychoprophylaxis, systemic agents, regional anesthetics, and major conduction analgesia. Psychoprophylaxis, especially education techniques, can be quite instrumental in reducing parturient fear and resulting stress of labor. It is now appreciated, from animal experiments,[77,78] that maternal stress adversely affects placental perfusion and fetal oxygenation. Such changes that may be clinically insignificant in healthy fetuses may prove detrimental in fetuses with chronic distress. Systemic medication such as narcotics or sedatives can likewise prove useful in these situations if they can ameliorate the stress and pain of labor. Unfortunately, they have been proved to provide inferior levels of analgesia when compared with lumbar epidural analgesia or spinal anesthesia. When lumbar epidural analgesia is provided using local anesthesia or a local anesthetic/narcotic mixture, hypotension should be avoided or treated. Even with the use of pure narcotic spinal analgesia for labor, the question has been raised regarding the occurrence of hypotension following dosing.

In situations requiring cesarean delivery for chronic fetal stress, the anesthetic technique of choice is regional anesthesia, either spinal or epidural anesthesia. The relative slow onset of epidural anesthesia relative to spinal anesthesia allows anticipation and treatment of the hypotension that may occur with sympathetic blockade. The epidural catheter provides the ability to titrate the sensory level and extend the duration of the blockade as dictated by surgical circumstances. That being said, carefully conducted spinal anesthesia is appropriate as well.

When maternal blood pressure is maintained with routine hydration and ephedrine when necessary, epidural anesthesia to a T4 sensory level does not appear to significantly alter intervillous blood flow.[79,80] Brizgys et al.[81] published data on the incidence of maternal hypotension and neonatal effects of lumbar epidural anesthesia for cesarean delivery. In this study, prophylactic intramuscular (IM) ephedrine was not significantly effective in reducing the incidence of maternal hypotension with lumbar epidural anesthesia. Hypotension occurred in 41% of nonlaboring parturients and in 27% of those in labor. These authors found no difference between the two groups of neonates with respect to acid–base status or time to spontaneous respiration, which was attributed to aggressive prompt treatment of hypotension. This study also examined the impact of superimposed maternal hypotension on infants who were already considered to be in moderate distress by fetal heart rate (FHR) parameters. When maternal hypotension was aggressively treated, it did not result in a further deterioration of the previously stressed infants.

Anesthesia with Intrapartum Fetal Distress

In the case of acute fetal distress during labor, delivery by emergency cesarean section is often deemed necessary. In such cases, anesthesia should be planned to provide the most rapid, safe anesthetic for both the mother and fetus. In an emergency cesarean section, the paramount anesthetic decision is the type of anesthesia. It should be remembered that

emergency cesarean sections account for the majority of maternal mortality secondary to anesthesia.[82] For this reason, decision-making algorithms regarding the type of anesthesia to be selected should be developed beforehand to avoid confusion during the actual emergency.

A categorization of emergency cesarean section and the types of anesthetic choices available for each has been suggested by Harris[82] (Table 31.1). Cesarean section for acute fetal distress in labor invariably falls into the second or third category, that of urgent or immediate cesarean section. The determination of which category is correct for a given clinical situation depends on the instability of the underlying physiology (i.e., degree of asphyxia present) and whether it is immediately life threatening. When fetal distress is present but not thought to be immediately life threatening, more anesthetic options are available, with the caveat that fetal monitoring must be continued during a somewhat longer induction of epidural anesthesia or spinal anesthesia in comparison with general anesthesia. Above all, once the decision has been made to perform a cesarean section for the diagnosis of fetal distress, the anesthetic plan should be implementated as quickly as possible regardless of the technique chosen. In an attempt to correlate decision-to-delivery interval with neonatal admission rate to the neonatal intensive care unit, Dunphy et al. found that the rate doubled with extension of the interval from 10 to 35 min.[83] There is evidence that time-consuming anesthesia preparatory steps, such as crystalloid infusion before major regional anesthesia, may be curtailed to some extent in an emergency without demonstrably increasing fetal risk or worsening outcome.[84]

In cases of severe persistent fetal distress requiring "stat" cesarean section (persistent fetal bradycardia or severe fetal scalp acidosis), the most widely employed anesthetic technique is general anesthesia. It has become the technique of choice in these clinical situations because of its speed of onset and reliability. Alternatives to general anesthesia for emergent delivery include spinal anesthesia, extension of a labor epidural that has already been established at least to a T10 level, or local infiltration and field block. In 1984, Marx et al.[85] compared anesthetic technique for emergent cesarean delivery in 126 cases. The anesthetic technique was selected by the anesthesiologist and the parturient undergoing the cesarean delivery; 71 women received general anesthesia, 55 received spinal block, and the previously placed lumbar epidurals of 33 were redosed for the cesarean section. Of note, none of the spinal or epidural anesthesia patients experienced hypotension or required vasopressor therapy. This study found similar umbilical arterial acid–base values between the general and regional anesthesia groups. The 1-min Apgar scores were better in the regional group, but there was no difference in the 5-min scores. The conclusion in this study was that spinal anesthesia is a safe approach to emergent cesarean delivery for fetal distress when a functioning epidural catheter is not present.

In another study of regional versus general anesthesia for emergency cesarean section, Ramanathan et al.[86] found that extension of epidural anesthesia with 2-chloroprocaine for emergent cesarean delivery for fetal distress did not adversely affect fetal acid–base status when compared with general anesthesia. However, both these studies were retrospective and cannot be used as sole evidence to support a delay to establish spinal anesthesia (as opposed to general anesthesia) for an immediate cesarean section without further justification. This caveat is especially true in light of a study by Roberts et al. on the effect of anesthetic techniques on umbilical artery blood pH in 1601 patients. They found that spinal anesthesia was associated with occasionally severe fetal acidemia when compared with epidural anesthesia and general anesthesia.[44]

For stat cesarean delivery, if a continuous labor epidural has already been placed and is functioning (with a preexisting T10 or greater sensory level), it can be rapidly extended with 2-chloroprocaine or lidocaine. Simultaneous fluid loading with a nondextrose-containing solution should be administered to offset the hypotension that may occur with the ensuing higher sensory block. If inadequate anesthesia has developed by the time the obstetricians are ready to begin surgery, intravenous supplementation with ketamine in 10- to 20-mg increments can be used until delivery of the infant, when intravenous narcotics (such as fentanyl) can be added.

TABLE 31.1. Categories of emergency cesarean section.

Category	Examples	Preferred anesthetic
Stable	Chronic uteroplacental sufficiency Malpresentation with ruptured membranes (not in labor) Previous lower-segment cesarean section, even in labor	Epidural, spinal
Urgent	Failure to progress Active herpes with rupture of membranes Nonbleeding placenta previa in labor	Spinal, epidural (extended from labor)
Stat	Agonal fetal distress Cord prolapse with fetal distress Massive hemorrhage Ruptured uterus	General, local, epidural (if T10 or higher level is present)

Source: Adapted from Harris AP. Emergency cesarean section. In: Rogers MC (ed) Current Practice in Anesthesiology. St. Louis: Mosby, 1990:361.

If the maternal airway is suspected to be challenging, and an epidural is not already in place, spinal anesthesia may be considered. Although some anesthesiologists maintain that a difficult airway may be a relative contraindication to spinal anesthesia, the need to deliver the asphyxiated fetus quickly may justify its use. Alternatives include an awake intubation (which can be technically challenging and time consuming) and local anesthesia infiltration/field block. A local field block of the abdominal wall for cesarean section was described in one series of 218 patients using approximately 60 mL 1% procaine with excellent success.[87] Despite such reports, many obstetricians are unfamiliar with this technique, thus rendering it impractical.

General Anesthesia with Intrapartum Fetal Distress

Before proceeding with the induction of general anesthesia, the urgency of the delivery must be weighed against the potential risk of general anesthesia. This consideration requires close communication between the obstetric and anesthesia teams.

Inability to secure the maternal airway continues to be a major cause of maternal and fetal morbidity and mortality.[88] The incidence of failed intubation during induction of general anesthesia for cesarean section is approximately 1 in 249.[89] Preoperative assessment of the airway should include visual inspection of the face, neck, and oropharynx for soft tissue swelling. Head and neck flexion and extension, ability to open the jaw, and temporomandibular joint function as evidenced by the ability to move the lower incisors anterior to the upper incisors should be assessed. Inadequate hyoidmental distance may indicate an anterior larynx and a subsequent difficult intubation.[90] A Mallampati classification as modified by Samsoon should be determined, as it predicts difficult intubation in pregnant women.[90] The Mallampati score increases toward term gestation[91] and has been observed to acutely increase during cesarean hysterectomy.[92]

If the ability to rapidly secure the airway following a rapid sequence induction is in serious question, alternative approaches must be considered; that is, the parturient's airway should be secured while the woman is awake. Techniques in the awake obstetric case include oral fiberoptic intubation and direct awake laryngoscopy following application of a topical anesthetic to the airway. The risk of epistaxis from a nasotracheal intubation is significantly higher in the obstetric case secondary to hyperemic, engorged mucous membranes.

If preoperative assessment of the airway suggests that intubation should not be difficult, a rapid sequence induction is planned. The clinician should consider the alternative options in the event of a failed intubation. Emergency airway equipment must be immediately available. Figure 31.2 outlines a suggested protocol for failed intubation. Such an algorithm should be reviewed and be available before its use in an emergency setting.

Maternal aspiration is an important concern in obstetric anesthesia. The complications of maternal aspiration can be minimized by the use of oral nonparticular antacids within 1 h of induction.[93] A rapid sequence induction and intubtion with cricoid pressure is normally employed to decrease the risk of regurgitation and aspiration. The importance of proper instruction to the person applying cricoid pressure cannot be overemphasized, because misapplied cricoid pressure can displace the larynx and complicate endotracheal intubation. The

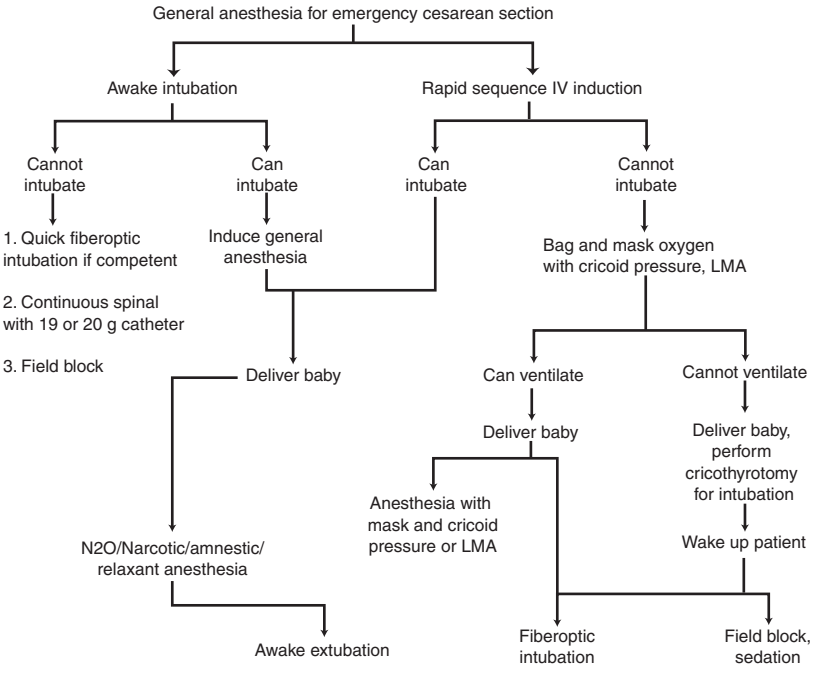

FIGURE 31.2. Example of a difficult airway algorithm for immediate emergency cesarean section.

efficacy of metoclopramide to stimulate gastric emptying and increase lower esophageal sphincter tone is not guaranteed. However, Murphy et al.[94] demonstrated a significant increase in gastric emptying in all patients within 1 h of receiving 10 mg intravenous metoclopramide before elective cesarean section. Histamine type 2 (H_2) blocking agents have also been shown to be effective in increasing gastric fluid pH and decreasing gastric volume.[95,96] However, there is almost certainly inadequate time for these latter two pharmacologic methods before a stat cesarean section.

Following antacid prophylaxis in the operating room, left uterine displacement, continued FHR monitoring, and maternal preoxygenation should be ensured. The widespread practice of 3 to 5 min of 100% oxygenation before induction may be replaced by four tidal volume breaths of 100% oxygen over 30 s when time is extremely critical. Norris and Dewan compared these two techniques in parturients undergoing elective cesarean delivery and demonstrated no difference in maternal blood gas values or umbilical arterial and venous blood gas values at birth.[97]

Rapid sequence induction and endotracheal intubation are facilitated by rapid-onset muscle relaxation, which is best achieved by succinylcholine, which also confers the advantage of rapid recovery. Although plasma cholinesterase activity is 20% to 30% lower in pregnant women, recovery of twitch is not delayed.[98,99] Rapid recovery from succinylcholine neuromuscular blockade may not occur in preeclamptic patients, however, if magnesium sulfate is being administered. A defasiculating dose of a nondepolarizing muscle relaxant is generally not suggested, because it necessitates a higher dose of succinylcholine and results in a more prolonged neuromuscular blockade. Rocuronium may be used as an alternative to a depolarizing agent for rapid sequence induction, but a longer neuromuscular block than necessary for cesarean section may result from that dose, and the time to adequate intubating conditions is longer than with succinylcholine. All nondepolarizing agents produce small amounts of placental transfer but insignificant effects on the newborn.[100–102]

Choice of Induction Agents in Fetal Distress

An ideal induction agent for general anesthesia for cesarean delivery should provide rapid onset, brief duration (to allow spontaneous recovery of respirations if intubation proved difficult), minimal maternal hemodynamic effects, and minimal fetal effects. Maternal and fetal effects of anesthetic agents are most critical in the setting of fetal physiologic distress in which much of the fetal reserve has already been depleted. Several induction agents have been used to induce general anesthesia for cesarean delivery. The most commonly used induction agents in obstetric anesthesia are thiopental and ketamine. Etomidate, propofol, midazolam, and narcotic agents have also been used.

Thiopental is highly lipid soluble and therefore rapidly crosses the placenta; peak umbilical venous levels are reached in less than 1 min. The commonly recommended dose of thiopental, 4 mg/kg, has its origin in a study that compared dosages from 4 to 8 mg/kg. In this study, Kosaka et al. described better Apgar scores in the neonates who received 4 mg/kg.[103]

Ketamine is a potent amnestic and analgesic drug with rapid onset and short duration. In pregnant ewes, Levinson et al. demonstrated that anesthetic doses of ketamine increased maternal blood pressure but did not affect fetal acid–base status.[104] In addition, the use of ketamine was associated with increased uterine blood flow. Ketamine increases the intensity and frequency of uterine contractions but does not alter the resting intrauterine pressure. The recommended dose of ketamine for induction of general anesthesia is 1 mg/kg. In acidotic lamb models, ketamine is associated with a decrease in fetal lamb mean arterial pressure (MAP), but the preservation of fetal cerebral and myocardial blood flow is maintained.[105] Fetal acid–base status was unchanged by this dose of ketamine. The conclusion in this study was that ketamine was a safe drug for the induction of general anesthesia in cases with fetal distress. A dose of 1 mg IV diazepam after induction with ketamine has been reported to significantly reduce the incidence of unpleasant postoperative dreams.[106]

Thiopental 4 mg/kg has been compared with ketamine 1 mg/kg for induction in 62 normotensive patients undergoing elective cesarean delivery. MAP increased 20% to 30% with laryngoscopy with both these induction agents. In acidotic fetal sheep, 2 mg/kg ketamine better preserved fetal blood pressure and cerebral blood flow than did 6 mg/kg thiopental for induction in the presence of fetal asphyxia.[107] Thus, both sodium thiopental (4 mg/kg) and ketamine (1 mg/kg) appear to be acceptable choices for rapid sequence induction in normotensive patients in the presence of fetal asphyxia.

A few alternative agents have been studied for obstetric applications. In 1979, Downing et al. compared etomidate 0.3 mg/kg with a historical control group of 3.5 mg/kg thiopental and found a reduced base deficit in the cord gases in the etomidate group.[108] Midazolam has been studied in patients undergoing elective cesarean delivery. Bland et al. found that a significantly higher number of newborns required resuscitation following induction with midazolam as compared with induction with thiopental. This study concluded that midazolam was inferior to thiopental induction for cesarean deliveries.[109] This result was confirmed by Ravlo et al., who reported that infants in the midazolam group scored less well with respect to temperature control, general body tone, and arm recoil.[110]

An initial study comparing propofol (2.5 mg/kg) with thiopental revealed no differences in umbilical blood gases or neurobehavioral scores.[111] Propofol readily crosses the placenta, with a fetal/maternal ratio of approximately 0.25 at time of delivery following induction with 2 mg/kg.[112] Although propofol has a relaxant effect on smooth muscle, it has a relaxant effect on uterine smooth muscle only at concentrations greater then those observed following an induction dose.[113]

Thus, although newer induction agents are being studied, there are inadequate data to support the routine use of agents other than thiopental and ketamine in the setting of fetal asphyxia.

Anesthetic Maintenance

A high inspired oxygen concentration improves fetal oxygen stores. Before delivery, the addition of a halogenated volatile anesthetic as a replacement for nitrous oxide in the traditional nitrous oxide/oxygen obstetric anesthetic allows the use of higher inspired oxygen concentration. Animal and human experimental data indicate that halothane and isoflurane can both be used for limited times in the setting of fetal distress without evidence of a significant worsening of fetal condition.[114–119]

Numerous reports associating prolonged induction of general anesthesia to delivery (I-D interval) with newborn depression were published in the 1960s and 1970s. In 1976, Crawford et al.[120] first reported on the relationship between a prolonged uterine incision to delivery interval (UI-D interval) and fetal acidosis. They noted an even greater correlation between fetal acid–base status and UI-D interval than between fetal acid—base status and I-D interval. Following this report, Datta et al. studied I-D interval and UI-D interval in 105 patients undergoing repeat elective cesarean delivery under either general or spinal anesthesia. With general anesthesia, either an I-D interval greater than 8 min or an UI-D interval greater than 3 min was correlated with worsening Apgar scores and umbilical acid–base status.[121] In the absence of hypotension, a prolonged I-D time did not affect either Apgar scores or acid–base values with spinal anesthesia. However, an UI-D interval greater than 3 min was associated with higher incidences of neonatial acidosis. Datta et al. have also observed a correlation between UI-D interval and fetal norepinephrine levels.[122] Hence, a shorter UI-D interval may be beneficial during both general and regional anesthesia, especially in the presence of fetal distress.

Following induction of general anesthesia, maintenance of eucapnia appears to be an important consideration. In a comparison of patients undergoing cesarean delivery under general anesthesia, parturients were hyperventilated to a $Paco_2$ of 23 mm Hg or kept eucapnic at a $Paco_2$ of 39 mm Hg. Significantly better values for umbilical vein Po_2, fetal acid–base status, and 1-min Apgar scores were observed in the eucapnic group.[123] In all cases, the parturient should not be extubated until the return of spontaneous ventilation and adequate protective airway reflexes.

A team trained in neonatal resuscitation should always be present to resuscitate the newborn who is born depressed.

Summary

Non-reassuring fetal status confirmed by fetal heart and/or fetal scalp pH sampling is a dire emergency. It is always beneficial to know about the high risk parturients in the obstetric floor and think about the game plan after consulting with the obstetricians.

References

1. Haverkamp AD, Orleans M, Langendoerfer S, et al. A controlled trial of the differential effects of intrapartum fetal monitoring. Am J Obstet Gynecol 1979;134:399–412.
2. Haesslein HC, Niswander KR. Fetal distress in term pregnancies. Am J Obstet Gynecol 1980;137:245–253.
3. Sykes GS, Johnson P, Ashworth F, et al. Do Apgar scores indicate asphyxia? Lancet 1982;1:494–496.
4. MacDonald H, Mulligan J, Allen A, et al. Neonatal asphyxia. I. Relationship of obstetric and neonatal complications to neonatal mortality in 38,405 consecutive deliveries. J Pediatr 1980;96:898–902.
5. Parer JT, Livingston EG. What is fetal distress? Am J Obstet Gynecol 1990;162:1421–1425.
6. Harris AP. Sudden fetal distress. In: Datta S (ed) Common Problems in Obstetric Anesthesia. St. Louis: Mosby, 1995:263.
7. Creasy RK, Resnik R. Intrauterine growth retardation. In: Creasy RK, Resnick R (eds) Maternal-Fetal Medicine: Principles and Practice. Philadelphia: Saunders, 1989:547–564.
8. Scott KE, Usher R. Fetal malnutrition: its incidence, causes and effects. Am J Obstet Gynecol 1966;94:951–963.
9. Williams RL, Creasy RK, Cunningham GC, et al. Fetal growth and perinatal viability in California. Obstet Gynecol 1982;159:624–632.
10. Morrison I, Olsen J. Weight specific stillbirths and associated causes of death: an analysis of 765 stillbirths. Am J Obstet Gynecol 1985;152: 975–980.
11. Usher RH. Clinical and therapeutic aspects of fetal maturation. Pediatr Clin N Am 1970;17:169–183.
12. Tejani N, Mann LI, Weiss RR. Antenatal diagnosis and management of the small for gestational age fetus. Obstet Gynecol 1976;47:31.
13. MacDonald D, Grant A, Sheridan-Pereira M, et al. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. Am J Obstet Gynecol 1985;152:524–539.
14. Rosen MG (chairman). Consensus Task Force on Cesarean Childbirth. Publication No. 82–2067. Bethesda: NIH, 1981.
15. Smeriglio VL. Developmental sequelae following intrauterine growth retardation. In: Gross TL, Sokol RJ (eds) Intrauterine Growth Retardation. Chicago: Year Book Medical, 1989:34–53.
16. Niswander K, Elboure D, Redman C, et al. Adverse outcome of pregnancy and the quality of obstetric care. Lancet 1984;1:827–831.
17. Pareth N, Start R. Cerebral palsy and mental retardation in relation to indicators of perinatal asphyxia. Am J Obstet Gynecol 1983;147:960–966.
18. Nelson K. Ellenberg J. Obstetric complications as risk factors for cerebral palsy or seizure disorders. JAMA 1984;251:1843–1848.
19. Ramanthan S. Obstetric Anesthesia. Philadelphia: Lea & Febiger, 1988:27.
20. Philipps AF. Carbohydrate metabolism of the fetus. In: Polin RA, Fox WW (eds) Fetal and Neonatal Physiology, vol 1. Philadelphia: Saunders, 1992:373–384.
21. Cohn HE, Sacks EJ, Heymann MA, et al. Cardiovascular responses to hypoxemia and academia in fetal lambs. Am J Obstet Gynecol 1979;120: 817–824.
22. Sheldon RE, Peeters LLH, Jones MD Jr, et al. Redistribution of cardiac output and oxygen delivery in the hypoxemic fetal lamb. Am J Obstet Gynecol 1979;135:1071–1078.
23. Harris AP. Fetal physiology. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice. St. Louis: Mosby, 1994:76–88.
24. Yaffe H, Parer JT, Block BS, et al. Cardiorespiratory responses to graded

reductions in uterine blood flow in the sheep fetus. J Dev Physiol 1987; 9:325–336.
25. Edelstone DI. Fetal compensator responses to reduced oxygen delivery. Semin Perinatol 1984;8:184–191.
26. Bristow J, Rudolph AM, Itskovitz J. A preparation for studying liver blood flow, oxygen consumption, and metabolism in the fetal lamb in utero. J Dev Physiol 1981;3:255–260.
27. Peeters LL, Sheldon RE, Jones MD Jr, et al. Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 1979;135: 637–646.
28. ACOG Committee on Obstetrical Practice. Fetal distress and birth asphyxia. Committee opinion no. 137. Washington, DC: ACOG, 1994.
29. Butler NR, Alberman EF. In: Butler NR (ed) Perinatal Problems: The Second Report of the British Perinatal Mortality Survey. Edinburgh: Churchill Livingstone, 1969.
30. Vintzileos AM, Campbell WAS, Ingardia CJ, et al. The fetal biophysical profile and its predictive value. Obstet Gynecol 1983;62:271–278.
31. Murata Y, Martin CB, Ikenoue T, et al. Fetal heart rate accelerations and late decelerations during the course of intrauterine death in chronically catheterized rhesus monkeys. Am J Obstet Gynecol 1982;144: 218–223.
32. Rochelson B, Schulman H, Fleischer A, et al. The clinical significance of Doppler umbilical artery velocimetry in the small for gestational age fetus. Am J Obstet Gynecol 1987;156:1223–1226.
33. Ducey J, Schulman H, Farmalcaides G, et al. A classification of hypertension I pregnancy based on Doppler velocimetry. Am J Obstet Gynecol 1987;157:680–685.
34. Wenstrom KD, Weiner CP, Williamson RA. Diverse maternal and fetal pathology associated with absent diastolic flow in the umbilical artery of high risk fetuses. Obstet Gynecol 1991;77:374–378.
35. American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring. Technical Bulletin No. 132: Washington, DC: ACOG, 1989.
36. Chung DY, Sim YB, Park KT, et al. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73(2):109–116.
37. Cohen W, Schifri B. Diagnosis and management of fetal distress during labor. Semin Perinatol 1978;2:155–167.
38. American College of Obstetricians and Gynecologists. Assessment of fetal and newborn acid-base status. Technical Bulletin No. 132: Washington, DC: ACOG, 1989.
39. Smith CV, Nguyen HN, Phelan JP, et al. Intrapartum assessment of fetal well-being: a comparison of fetal acoustic stimulation with acid-base determinations. Am J Obstet Gynecol 1986;155:726–728.
40. Clark SL, Timovsay ML, Miller FC. The scalp stimulation test: a clinical alternative to fetal scalp blood sampling. Am J Obstet Gynecol 1984;148:274–277.
41. Kuhnert M, Seelbach-Goebel B, Butterwegge M. Predictive agreement between the fetal arterial oxygen sturation and fetal scalp pH: results of the German multi-center study. Am J Obstet Gynecol 1998;178:330–335.
42. Garite T, Dildy G, McNamara H, et al. A multi-center controlled trial of fetal pulse oximetry in the intrapartum management of non-reassuring fetal heart rate patterns. Am J Obstet Gynecol 2000;183:1049–1058.
43. Nelson K, Ellenberg J. Apgar scores as predictors of chronic neurologic disability. Pediatrics 1981;68:36–44.
44. Roberts SW, Leveno KJ, Sidawi E. Fetal acidemia associated with regional anesthesia for elective cesarean delivery. Obstet Gynecol 1995;85:79.
45. Allen M. Developmental outcome and follow-up of the small for gestational age infant. Semin Perinatol 1984;8:123–156.
46. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. Am J Obstet Gynecol 1972;112:246–276.
47. Greiss FC Jr, Anderson SG, Still JG. Uterine pressure-flow relationships during early gestation. Am J Obstet Gynecol 1976;126:799–808.
48. Crino JP, Harris AP, Parisi VM. Effect of rapid intravenous crystalloid infusion on uteroplacental blood flow and placental implantation-site oxygen delivery in the pregnant ewe. Am J Obstet Gynecol 1993;168: 1603–1609.
49. Ralston D, Shnider S, Delorimer A. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40:3541–3570.
50. Ramanathan S, Grant G. Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 1988; 32:559–565.
51. Moran D, Perillo M, LaPorta RF, et al. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. J Clin Anesth 1991;3:301–305.
52. Marx GF, Mateo C. Effects of different oxygen concentrations during general anesthesia for elective cesarean section. Can Anesth Soc J 1971; 18:587–593.
53. Ramanathan S, Gandhi S, Arismendy J, et al. Oxygen transfer from mother to fetus during Cesarean section under epidural anesthesia. Anesth Analg 1982;31:576–581.
54. Myers RE, Stange L, Joelssen I, et al. Effects upon the fetus of oxygen administration to the mother: a study in monkeys. Acta Obstet Gynecol Scand 1977;56:195–203.
55. Morishima H, Daniel S, Richards R, et al. The effect of increased maternal PaO_2 upon the fetus during labor. Am J Obstet Gynecol 1975;123: 257–264.
56. Edelstone D, Peticca B, Goldblum L. Effects of maternal oxygen administration on fetal oxygenation during reductions in umbilical blood flow in fetal lambs. Am J Obstet Gynecol 1985;152:351–358.
57. Thorp JA, Trobough T, Evans R, et al. The effect of maternal oxygen administration during the second stage labor on umbilical cord blood gas values: a randomized controlled prospective trial. Am J Obstet Gynecol 1995;172:465–474.
58. Bieniarz J, Crottoginin JJ, Curuchet E, et al. Aorto-caval compression by the uterus in late human pregnancy. II. An arteriograpic study. Am J Obstet Gynecol 1968;100:203–217.
59. Lees MM, Scott DB, Kerr MG, et al. The circulatory effects of recumbent postural change in late pregnancy. Clin Sci 1967;332:453–463.
60. Eckstein KL, Marx GF. Aortocaval compression and uterine displacement. Anesthesiology 1974;40:92–96.
61. Mendez-Bauer C, Shekarloo A, Cook V, et al. Treatment of acute intrapartum fetal distress by β_2-sympathomimetics. Am J Obstet Gynecol 1987;156:638–642.
62. Patriarco M, Viechnicki B, Hutchinson T, et al. A study on intrauterine fetal resuscitation with terbutaline. Am J Obstet Gynecol 1987;157: 384–387.
63. Ehrenkranz R, Walker A, Oakes G, et al. Effect of ritodrine infusion on uterine and umbilical blood flow in pregnant sheep. Am J Obstet Gynecol 1976;126:343–349.
64. Ingemarson I, Arulkumaran S, Ratnam S. Single injection of terbutaline in term labor. II: Effect on uterine activity. Am J Obstet Gynecol 1985;153:865–869.
65. Beneditti T. Life-threatening complications of betamimetic therapy for preterm labor inhibition. Clin Perinatol 1986;13:843–852.
66. Ravindran R, Vilgus O, Padilla L, et al. Anesthetic considerations in pregnant patients receiving terbutaline therapy. Anesth Analg 1980;59: 391–392.
67. Fishburne J, Dormer K, Payne G, et al. Effects of amrinone and dopamine on uterine blood flow and vascular responses in the gravid baboon Am J Obstet Gynecol 1988;158:829–837.
68. Mercier FJ, Dounas M, Bouaziz H, et al. Intravenous nitroglycerin to relive intrapartum fetal distress related to uterine hyperactivity: a prospective observational study. Anesth Analg 1997;84(5):1117–1120.
69. Paszkowski T. Amnioinfusion: a review. J Reprod Med 1994:39:588–594.
70. Cialone PR, Sherer DM, Ryan RM, et al. Amnioinfusion during labor complicated by particulate meconium-stained amniotic fluid decreases neonatal morbidity. Am J Obstet Gynecol 1994;170:842–849.
71. Miyazaki FS, Nevarez F. Saline amnioinfusion for relief of repetitive variable decelerations: a prospective randomized study. Am J Obstet Gynecol 1985;153:301–306.
72. Eriksen NL, Hostetter M, Parisi VM. Prophylactic amnioinfusion in

pregnancies complicated by thick meconium. Am J Obstet Gynecol 1994;171:1026–1030.
73. Dye T, Aubry R, Gross S, et al. Amnioinfusion and the intrauterine prevention of meconium aspiration. Am J Obstet Gynecol 1994;171:1601.
74. Puder KS, Sorokin Y, Bottoms SF, et al. Amnioinfusion: does the choice of solution adversely affect neonatal electrolyte balance? Obstet Gynecol 1994;84:956–959.
75. Spong CY, Ogundipe OA, Ross MG. Prophylactic amnioinfusion for meconium-stained amniotic fluid. Am J Obstet Gynecol 1994;171:9311–9315.
76. Maher JE, Wenstom KD, Hauth JC, et al. Amniotic fluid embolism after saline amnioinfusion: two cases and review of the literature. Obstet Gynecol 1994;83:851–854.
77. Shnider SM, Wright RG, Levinson G, et al. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology 1979;50:524–527.
78. Myers RE. Maternal psychological stress and fetal asphyxia: a study in the monkey. Am I Obstet Gynecol 1975;122:47–59.
79. Jouppila R, Jouppila P, Kuikka J, et al. Placental blood flow during caesarean section under lumbar extradural analgesia. Br J Anaesth 1978;50: 275–279.
80. Houvinen K, Lehtovirta P, Forss M, et al. Changes in placental intervillous blood flow measured by the ^{133}Xenon method during lumbar epidural block for elective caesarean section. Acta Anaesth Scand 1979; 23:529–533.
81. Brizgys R, Dailey P, Shnider S, et al. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987;67:782–786.
82. Harris AP. Emergency cesarean section. In: Rogers MC (ed) Current Practice in Anesthesiology. St. Louis: Mosby, 1990:361.
83. Dunphy BC, Robinson JN, Sheil OM, et al. Caesarean section for fetal distress, the interval from decision to delivery, and the relative risk of poor neonatal condition. J Obstet Gynecol 1991;11:241–244.
84. Rout CC, Rocke DA, Levin J, et al. A reevaluation of role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology 1993;79:262–269.
85. Marx GF, Luykx W, Cohen S. Fetal-neonatal status following caesarean section for fetal distress. Br J Anaesth 1984;56:1009–1013.
86. Ramanathan J, Ricca D, Sibai B, et al. Epidural versus general anesthesia in fetal distress with various abnormal fetal heart rate patterns (abstract). Anesth Analg 1988;67:S180.
87. Ranney B, Stanage W. Advantages of local anesthesia for cesarean section. Obstet Gynecol 1975;45:163–167.
88. Moir D. Maternal mortality and anaesthesia. Br J Anaesth 1980;51:1.
89. Barnado PD, Jenkins JG. Failed tracheal intubation in obstetrics: a 6-year review in a UK region. Anaesthesia 2000;55(7): 690–694.
90. Wong SH, Hung CT. Prevalence and prediction of difficult intubation in Chinese women. Anaesth Intensive Care 1999;27(1):49–52.
91. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth 1995;74(6):638–642.
92. Bhavani-Shankar K, Lynch EP, Satta S. Airway changes during Cesarean hysterectomy. Can J Anaesth 2000;47(4):338–341.
93. Dewan D, Floyd H, Thistlewood J, et al. Sodium citrate pretreatment in elective cesarean section patients. Anesth Analg 1985;64:34–37.
94. Murphy D, Nally B, Gardiner J, et al. Effect of metoclopramide on gastric emptying before elective and emergency caesarean section. Br J Anaesth 1984;56:1113–1116.
95. Solanki D, Suresh M, Ethridge C. The effects of intravenous cimetidine and metolopramide on gastric volume and pH. Anesth Analg 1984;63: 599–602.
96. Morrison D, Dunn G, Fargus-Babjak A, et al. A double blinded comparison of cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome. Anesth Analg 1982;61:988–992.
97. Norris M, Dewan D. Preoxygenation for cesarean section: a comparison of two techniques. Anesthesiology 1985;62:827–829.
98. Blitt C, Petty W, Alberternst E, et al. Correlation of plasma cholinesterase activity and duration of action of succinylcholine during pregnancy. Anesth Analg 1977;56:78–83.
99. Dowling B, Cheek T, Gross J, et al. Succinylcholine pharmacodynamics in peripartum patients (abstract). Anesthesiology 1987;63:A431.
100. Tessen J, Johnson T, Skjonsby B, et al. Evaluation of vecuronium for rapid sequence induction in patients undergoing cesarean section (abstract). Anesthesiology 1987;67:A452.
101. Dailey P, Fisher D, Shnider S, et al. Pharmacokinetics, placental transfer, and neonatal effects of vecuronium and pancuronium administered during cesarean section. Anesthesiology 1984;60:569–574.
102. Flynn P, Frank M, Hughes R. Use of atracurium in caesarean section. Br J Anaesth 1984;56:599–605.
103. Kosaka Y, Takahashi T, Mark L. Intravenous thiobartiturate anesthesia for cesarean section. Anesthesiology 1969;31:489–506.
104. Levinson G, Shnider S, Gilden J, et al. Maternal and fetal cardiovascular and acid-base changes during ketamine anaesthesia in pregnant ewes. Br J Anaesth 1973;45:1111–1115.
105. Swartz J, Cumming M, Biehl D. The effect of ketamine anaesthesia on the acidotic fetal lamb. Can J Anaesth 1987;34:233–237.
106. Dich-Nielsen J, Holasek J. Ketamine as induction agent for caesarean section. Acta Anaesth Scand 1982;26:139–142.
107. Pickering B, Palahnuik R, Cote J, et al. Cerebral vascular responses to ketamine and thiopentone during foetal acidosis. Can Anaesth Soc J 1982;29:463–467.
108. Downing J, Buley R, Brock-Utne J, et al. Etomidate for induction of anaesthesia at caesarean section: comparison with thiopentone. Br J Anaesth 1979;51:135–140.
109. Bland B, Lawes E, Duncan P, et al. Comparison of midazolam and thiopental for rapid sequence induction for elective cesarean section. Anesth Analg 1987;66:1165–1168.
110. Ravlo O, Carl P, Crawford M, et al. A randomized comparison between midazolam and thiopental for elective cesarean section: II. Neonates. Anesth Analg 1989;68:234–237.
111. Dailland P, Cockshott ID, Lirzin JD, et al. Placental transfer and neonatal effects of propofol administered during cesarean section (abstract). Anesthesiology 1987;67:A454.
112. Sanchez-Alcaraz A, Quintana MB, Laguarda M. Placental transfer and neonatal effects of propofol in caesarean section. J Clin Pharm Ther 1998;23(1):19–23.
113. Shin YK, Kim YD, Collea J. The effect of propofol on isolated human pregnant uterine muscle. Anesthesiology 1998;89(1):105–109.
114. Palahniuk RJ, Doig GA, Johnson GN, et al. Maternal halothane anesthesia reduces cerebral blood flow in the acidotic sheep fetus. Anesth Analg 1980;59:35–39.
115. Yarnell R, Biehl DR, Tweed WA, et al. The effect of halothane anaesthesia on the asphyxiated foetal lamb in utero. Can Anaesth Soc J 1983; 30:474–479.
116. Swartz J, Cummings M, Pucci W, et al. The effects of general anaesthesia on the asphyxiated foetal lamb in utero. Can Anaesth Soc J 1985; 32:577–582.
117. Cheek DBC, Hughes SC, Dailey PA, et al. Effect of halothane on regional cerebral blood flow and cerebral metabolic oxygen consumption in the fetal lamb in utero. Anesthesiology 1987;67:461–466.
118. Baker BW, Hughes SC, Shnider SM, et al. Maternal anesthesia and the stressed fetus: effects of isoflurane on the asphyxiated fetal lamb. Anesthesiology 1990;72:65–70.
119. Mokriski BK, Malinow AM. Neonatal acid-base status following general anesthesia for emergency abdominal delivery with halothane or isoflurane. J Clin Anesth 1992;4:97–100.
120. Crawford J, James F, Davids P, et al. A further study of general anaesthesia for caesarean section. Br J Anaesth 1976;48:661–667.
121. Datta S, Ostheimer G, Weiss J, et al. Neonatal effect of prolonged anesthetic induction for cesarean delivery. Obstet Gynecol 1981;58:331–335.
122. Bader AM, Datta S, Arthur GR, et al. Maternal and fetal catecholamines and uterine incision-to-delivery interval during elective cesarean section. Obstet Gynecol 1990;75:600–603.
123. Peng A, Blancato L, Motoyama E. Effect of maternal hypocapnia versus eucapnia on the foetus during cesarean section. Br J Anaesth 1972; 44:1173–1178.

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Critical Care Anesthesia for High-Risk Parturients

Sumedha Panchal and Geeta Sharma

Morbidity and mortality continue to occur in obstetric cases.[1–8] The critically ill pregnant woman poses unique challenges because of the physiologic changes of pregnancy and the needs of the fetus. Early involvement of all physicians (obstetrician, anesthesiologist, and critical care specialist) utilizing a team approach to optimize care may alleviate progression of organ dysfunction and improve care.[9] Most obstetric cases admitted to the intensive care unit (ICU) have complications related to pregnancy, but some may have an underlying medical condition worsened by the pregnancy, and others may have a nonobstetric etiology (i.e., trauma) necessitating ICU admission.[10] During childbirth, the maternal need for ICU services is not well defined.[1] Panchal et al. found that ICU utilization during hospital admission for delivery was low (0.12%).[1] Also, the criteria for admission to the ICU may vary. These factors emphasize the need for adequate coordination of many physicians for optimizing maternal and fetal outcome. This chapter briefly reviews the physiologic changes of pregnancy and the general principles of diagnosis and management of critical illnesses in the expectant mother.

Physiologic Changes of Pregnancy

Hemodynamic

Numerous cardiovascular changes occur during pregnancy. Maternal blood volume increases progressively, reaching a peak level of 40% above baseline by the third trimester.[11,12] Plasma volume increases more than red blood cell mass, giving rise to the physiologic anemia of pregnancy.[11] The cardiac output increases 30% to 50% above baseline by 32 weeks of gestation; this increase in cardiac output is due to an increase in both stroke volume and heart rate combined with a decrease in afterload.[13,14] Cardiac output increases to 50% above prepregnancy levels in labor and increases to 75% above prepregnancy levels after delivery of the placenta as a result of autotransfusion.[15] This autotransfusion may lead to pulmonary edema in those cases with valvular cardiac disease because of the abrupt increase in preload secondary to autotransfusion. The cardiac output returns to prepregnancy levels by 2 weeks postpartum.[16–18]

Systemic blood pressure decreases during pregnancy due to peripheral vasodilation mediated by increased synthesis of prostacyclin and progesterone.[19] Blood pressure slowly increases throughout the third trimester but remains below prepregnancy levels. Blood pressure returns to prepregnancy levels shortly after delivery. Systemic and pulmonary vascular resistances are decreased 20% to 30%.[19]

Uterine blood flow is approximately 500 to 700 mL/min at term.[20] The enlarged uterus may compress surrounding vascular structures, resulting in aortocaval compression. Aortocaval compression, in turn, may compromise uteroplacental blood flow and decrease venous return with a resultant drop in stroke volume and cardiac output.

Respiratory

There is evidence of airway mucosal changes during pregnancy characterized by mucosal capillary engorgement of the nasopharynx and mucosal edema. These changes deserve attention when attempting to secure the airway. Thus, smaller endotracheal tubes (6.0–7.0 mm) and oral tracheal intubation are recommended based on the airway changes occurring during pregnancy.[21,22]

Oxygen consumption is increased as much as 20% over nonpregnant values near the end of pregnancy owing to the increased metabolic demands of the placenta and fetus. Increased oxygen consumption is associated with increased carbon dioxide production, requiring greater alveolar ventilation. The augmented alveolar ventilation is attributed to increased circulating progesterone.[23]

Minute ventilation increases by as much as 50%, primarily through an increase in tidal volume with little change in respiratory rate. Arterial blood gases reveal a compensated respiratory alkalosis with a normal or slightly elevated partial pressure of oxygen and a decrease in the partial pressure of

carbon dioxide to approximately 30 to 32 mm Hg. The pH remains normal owing to increased excretion of bicarbonate by the kidneys. Decreases in the expiratory reserve volume and residual volume from elevation of the maternal diaphragm by the enlarging uterus produce a 20% reduction in functional residual capacity.[24,25]

These changes place the pregnant patient at risk for oxygen desaturation and hypoxemia during periods of apnea such as endotracheal intubation. Thus, adequate preoxygenation and denitrogenation before endotracheal intubation are important.

Renal

Renal blood flow increases throughout the first and second trimesters to a level 60% to 80% above baseline.[19,26–28] Glomerular filtration rate increases early in the first trimester, reaching a value 50% above prepregnancy levels at 16 weeks gestation, and remains elevated throughout pregnancy.[19,28–29] As a result, the normal serum creatinine level is about 0.5 mg/dL.[19,26,29] Creatinine levels considered normal in nonpregnant patients may actually indicate renal compromise during pregnancy.

Coagulation

There is an increased risk of thromboembolism in pregnancy because of the hypercoagulable state and predisposition to venous stasis in the lower extremities. Heparin is considered the anticoagulant of choice in pregnancy, as it does not cross the placenta.[30] Low molecular weight heparin (LMWH) is another anticoagulant used for thromboprophylaxis during pregnancy.[30]

Fetal Oxygenation

Fetal oxygen delivery is dependent upon several factors including maternal cardiac output, uterine blood flow, maternal partial pressure of oxygen (Po_2), maternal hemoglobin concentration and saturation, and maternal oxygen content. Uterine artery venoconstriction secondary to maternal alkalosis will decrease fetal oxygen delivery. Sympathetic stimulation and maternal hypotension are factors associated with uterine artery vasoconstriction and, therefore, a decrease in fetal oxygen delivery.[23]

The uterine vasculature is normally maximally dilated and is not autoregulated. Rather, uterine blood flow, and thus fetal oxygen delivery, is dependent on maternal cardiac output. Thus, maternal hypotension must be aggressively treated so as not to compromise fetal well-being. The fetus is protected from hypoxic insult by the affinity of fetal hemoglobin for oxygen (leftward shift of the oxyhemoglobin dissociation curve) and the tolerance of fetal tissues to a low Po_2 ($\sim$30 mm Hg in the fetal umbilical vein).[23]

Critical Care Management in Pregnancy

Hemodynamic Monitoring

Hemodynamic monitoring can be very helpful in the management of the critically ill obstetric cases. Pulmonary artery catheter placement must be individualized and may aid in the management of the women with severe preeclampsia, septic shock, or adult respiratory distress syndrome (ARDS). It is important to note that the hemodynamic findings in pregnancy vary compared to the nonpregnant patient. Cardiac output in pregnancy is increased by 30% to 50%, and systemic and pulmonary vascular resistances are decreased by 20% to 30%.[19,31]

Federal Drug Admininstration Drug Classification

It is useful to be aware of the U.S. Federal Drug Administration (FDA) pregnancy category classifications, because critically ill pregnant cases may require multiple pharmacologic interventions. Category A drugs are those that have undergone adequate controlled studies in pregnant women and failed to demonstrate risk to the fetus. Category B drugs are those with no evidence of fetal risk in human beings (animal studies demonstrate risk but human studies do not; or animal studies findings are negative and human studies are inadequate). Category C drugs are those in which risk cannot be ruled out (human studies are lacking, and animal studies are either positive for fetal risk or lacking; however, potential benefits may outweigh risk). Category D refers to agents with positive evidence of fetal risk by virtue of investigational human data (but in critical illness, potential benefits may outweigh risks). Category X includes those drugs that are contraindicated in pregnancy.[23]

Scoring Systems

Potential differences exist among physicians in the criteria for ICU admissions. Different predictive scoring systems have been developed to forecast patient outcome in an attempt to assist physicians in clinical decision making.[32–35] The application of these scoring systems to the obstetric population has been controversial, as these scoring systems have not been validated for these patients. Accurate assessment of the severity of disease in critically ill obstetric cases would not only contribute to the quality of parturient care but would also enhance risk stratification of pregnant women in the evaluation of new therapies.[32]

Radiology Exposure

Irradiation during pregnancy is undesirable because it increases the risk of fetal anomalies. This risk is increased by

1% to 3% when a woman receives more than 5 rad to the pelvis during the first trimester. A chest roentgenogram exposes the fetus to 36 mrad; this is further decreased by abdominal shielding with a lead apron.[36] Techniques such as shielding the abdomen with a lead apron and using a well-collinated X-ray beam can effectively reduce exposure.[19,37] Plain chest films necessary for diagnosis and safe management of the pregnant patient should not be withheld on the basis of undue concern over fetal exposure.[10,38]

Critical Illness in Pregnancy

The pregnant patient may have underlying comorbidities that become exacerbated by the physiologic changes of pregnancy resulting in critical illness requiring ICU admission. In addition, the pregnant woman may present with a critical condition (i.e., trauma) unrelated to the pregnancy and requiring an ICU admission.

Respiratory

Airway Management

Difficulties in airway management should be anticipated in the pregnant patient. The incidence of failed or difficult intubation is 8 to 10 times greater in the obstetric population compared to the general surgical population, with an estimated occurrence of 1 in 280.[39] The presence of nasopharyngeal and laryngeal edema, as well as mucosal capillary engorgement of the upper airway, require the use of smaller endotracheal tubes (6.0–7.0 mm). In addition, an increased risk of aspiration may exist because of delayed gastric emptying, increased intraabdominal pressure, and diminished competence of the gastroesophageal sphincter.[19,40–47] The diminished functional residual capacity and increased oxygen consumption in pregnancy lower the oxygen reserve, and significant arterial desaturation may occur following a relatively short period of apnea during intubation.[19,48,49] The airway should be secured early in a controlled setting so that maternal and fetal well-being are not compromised.

Asthma

Asthma is identified by the presence of three characteristic findings: (1) reversible airway obstruction, (2) airway inflammation, and (3) airway hyperresponsiveness.[50,51] The overall course of asthma has been reported to improve, worsen, or stay the same during pregnancy.[52–54] Acute exacerbations of asthma should be aggressively treated to preserve maternal and fetal oxygenation and well-being.[55] Pharmacologic therapy of asthma during pregnancy is directed toward avoiding acute exacerbations and episodes of status asthmaticus.[51] Bronchodilators (beta-adrenergic agonists, methylxanthines, and anticholinergic agents) and antiinflammatory agents (corticosteroids and cromolyn sodium) are considered safe during pregnancy. In severe asthma, consideration may be given to magnesium sulfate, which has been shown to enhance bronchodilation and to improve weaning in asthmatic patients.[10,56] Chest radiographic examination helps diagnose precipitating or complicating conditions such as pneumonia. During acute exacerbations, arterial blood gas analyses often reveal hypoxemia and respiratory alkalosis. After a prolonged severe episode, arterial carbon dioxide tension rises as a result of fatigue. The most convenient indirect measurement for assessing airway obstruction during pregnancy is the peak expiratory flow rate, which can be measured at the bedside.[51,57]

Ventilatory Failure, Respiratory Failure, and Acute Respiratory Distress Syndrome

Many conditions may lead to ventilatory failure, respiratory failure, and acute respiratory distress syndrome (ARDS). These conditions may include pulmonary edema due to preeclampsia or the use of tocolytics, amniotic fluid embolism, infection, pulmonary thromboembolism, hemorrhage, and aspiration of gastric contents. ARDS is an acute lung injury that results in diffuse bilateral radiographic infiltrates, marked intrapulmonary shunting, and decreased lung compliance. The clinical course is variable, ranging from rapid reversal in a few days to delayed reversal requiring prolonged mechanical ventilation. Overall mortality is 50% to 70%.[58–60]

Mechanical ventilation should aim at achieving an arterial partial pressure of carbon dioxide (P_{CO_2}) of 28 to 32 mm Hg. Hyperventilation and respiratory alkalosis should be avoided to prevent potential decreases in uterine blood flow and to prevent barotraumas (pneumothorax or pneumomediastinum.[58] It is important to maintain these patients with left uterine displacement to minimize decreases in venous return. Maintenance of oxygen delivery to the fetus is also very important. Progression to ventilatory failure will compromise maternal and fetal oxygenation and well-being; thus, early institution of mechanical ventilation is recommended.

Respiratory Infection

Consideration of potential fetal toxicity is important in determining appropriate antimicrobial therapy for respiratory infection during pregnancy.[61] Favorable results have been obtained using acyclovir to treat pregnant women with varicella pneumonia.[23]

Hemodynamic

Cardiopulmonary Arrest and Arrhythmias

Because of the many anatomic and physiologic changes of pregnancy, cardiopulmonary resuscitation (CPR) merits special consideration in the pregnant patient.[25] The gravid uterus produces significant mechanical obstruction to venous return. Thus, left manual displacement of the uterus should be attempted. The saphenous and femoral routes for the adminis-

tration of medications should be avoided, as partial occlusion of the vena cava by the gravid uterus makes these routes less efficient for delivery of crucial drugs than venous access above the level of the diaphragm.[25] Perimortem cesarean delivery may be indicated when initial attempts at resuscitation have failed in a woman with a viable fetus.[19,62] The duration from the onset of cardiac arrest to the delivery of the infant is the single most important prognostic factor.[62] Data suggest that infant survival without neurologic sequelae is greatest if the perimortem cesarean delivery is initiated within 4 min of the cardiac arrest, and the fetus is delivered within 5 min of maternal cardiac arrest.[19,62–65]

Digoxin and quinidine have been used extensively in pregnancy without adverse effects in the fetus. Adenosine is effective in treating arrhythmias involving the atrioventricular node and has been successfully used in pregnancy to treat supraventricular tachycardia and Wolff–Parkinson–White syndrome. There is limited use during pregnancy of disopyridamide, lidocaine, and flecainide. Long-term use of beta-adrenergic blocking agents is not advisable in cases of known intrauterine growth restriction. Amiodarone causes the risk of neonatal hypothyroidism.[10]

Obstetric Hemorrhage

Obstetric hemorrhage is a leading cause of maternal and fetal morbidity and mortality.[1–7,66] Blood flow to the uterus at term is approximately 500 to 700 mL/min.[20] Etiologies of antepartum hemorrhage include placenta previa, placental abruption, uterine rupture, and vasa previa. Etiologies of postpartum hemorrhage include uterine atony, genital trauma (cervical or vaginal lacerations), retained products of conception (including retained placenta, placenta accreta, placenta increta, and placenta percreta), and uterine inversion. Placenta accreta is defined as a placenta abnormally adherent to the myometrium without uterine muscle invasion. Placenta increta is defined as an abnormally adherent placenta with invasion into the myometrium. Placenta percreta is defined as an abnormally adherent placenta with invasion into the uterine serosa or other pelvic structures.[67,68] In a prospective study, Chattopadhyay et al.[67,68] noted a 5% incidence of placenta accreta when placenta previa occurred in patients with an unscarred uterus. In women with one previous cesarean section, the incidence of placenta accreta was 10%, but the incidence increased to 59% in women with a history of two or more cesarean sections. Two thirds of the cases with placenta previa, placenta accreta, and a preexisting uterine scar required cesarean hysterectomy.[67,68] If a placenta percreta is suspected, confirmation with a magnetic resonance imaging (MRI) study is recommended to further delineate pelvic structure involvement and guide appropriate surgical therapy at the time of cesarean delivery.

Patients at increased risk of hemorrrhage should, if possible, be identified early for establishment of appropriate intravenous access and blood products. The initial management of hemorrhage involves establishment of adequate intravenous access and fluid resuscitation with crystalloid or colloid until blood products become available. Dilutional coagulopathy in massive hemorrhage should be anticipated. Treatment of massive hemorrhage includes supportive measures with fluid resuscitation, pharmacologic interventions, and sometimes surgical interventions. The airway should be secured for airway protection and to provide adequate oxygenation and ventilation.

In the presence of uterine atony, pharmacologic intervention includes the use of oxytocin, ergot derivatives (contraindicated in women with hypertension), and 15-$F_{2\alpha}$ methyl prostaglandin (contraindicated in cases with reactive airway disease). If pharmacologic interventions fail, surgical intervention is required. The mode of surgical intervention (uterine artery embolization, hypogastric artery ligation, or hysterectomy) requires a team approach discussion between the obstetrician and anesthesiologist.

Septic Shock

Infection is an important cause of maternal morbidity and mortality.[2,6,8,69] Most obstetric sepsis occurs in the postpartum period.[19,70] Urinary and genital tract infections from the uterus, vagina, and episiotomy site are the most common sources.[23,71] Septic shock commonly occurs in the postpartum period, associated with premature rupture of membranes and the development of chorioamnionitis and postpartum endometritis or as a result of septic abortion.[70]

Hemodynamic resuscitation with volume expansion and possibly inotropic therapy is indicated for the management of septic shock. Initial broad-spectrum antibiotic therapy is essential until culture results become available. Consideration should be given to the potential for a localized abscess, a resistant organism, or septic pelvic thrombophlebitis in the management of septic shock in those patients refractory to appropriate antibiotic therapy. Women with septic pelvic thrombophlebitis usually present in the early postpartum period, with an incidence of approximately 0.1%.[72] Computerized tomography of the pelvis is commonly used to diagnose septic pelvic thrombophlebitis.[73]

Preeclampsia/Eclampsia

Preeclampsia is a disorder of pregnancy characterized by the onset of hypertension with proteinuria after the 20th week of gestation. The incidence of preeclampsia is approximately 5% of all pregnancies.[74] Risk factors for the development of preeclampsia include nulliparity at the extremes of reproductive age, chronic hypertension, multiple gestation, diabetes mellitus, antiphospholipid syndrome, gestational trophoblastic disease, and family or previous history of preeclampsia.[75] Preeclampsia is unpredictable and can progress rapidly to produce life-threatening complications.[19] Preeclampsia is a significant cause of maternal morbidity and mortality and

is one of the most common diagnoses associated with ICU admission.[1,2]

Three categories define hypertensive disorders of pregnancy. First, pregnancy-induced hypertension refers to sustained blood pressure values greater than or equal to 140/90 not associated with edema, proteinuria, or abnormal end-organ symptoms. Second, preeclampsia and its variant forms include the classic triad of hypertension, proteinuria, and edema. Hypertension is defined as sustained measurements of blood pressure greater than or equal to 140/90. Preeclampsia can be further classified as mild, severe, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Third, eclampsia refers to the occurrence of convulsions or coma associated in association with signs and symptoms of preeclampsia.[75,76]

The etiology of preeclampsia is unclear. The vascular pathology of preeclampsia ensues from the initial insult of abnormal placentation. It is believed that the remodeling of the spiral arterioles during the second wave of trophoblastic invasion is mediated by multifactorial sources.[76,77] Genetic, immune, and vasoactive-mediated features play a role in the dynamic process of normal and abnormal placentation.[78] Preeclampsia may be a manifestation of the progression of genetic susceptibility to inadequate trophoblastic invasion resulting in placental ischemia, endothelial damage, and vasoconstriction with evidence of platelet and leukocyte activation and, ultimately, the clinical syndrome of preeclampsia.[79]

Hematologic Changes

The physiologic anemia of pregnancy may not be apparent in preeclampsia due to hypovolemia. Hemoconcentration results from an increase in red blood cell mass without a concomitant increase in plasma volume. Altered perfusion and the stimulation of cytokines and vasoactive substances create a cycle of platelet and neutrophil activation and continued cytokine release. Endothelial cell injury is a hallmark of preeclampsia. Platelet activation leads to endothelial cell hyperplasia and microthrombi in the placental bed and end organs. Rapid platelet turnover can result in thrombocytopenia. Disseminated intravascular coagulation and multiorgan failure can result in severe cases.[80–83]

Hemodynamic Changes

The suboptimal dilation of the spiral arterioles creates placental hypoperfusion. Vasoconstriction and an imbalance between prostacyclin and thromboxane A2 develops.[84] Colloid oncotic pressure is decreased in pregnancy and is further decreased in preeclampsia[84]; this may further exacerbate the hypovolemic state of preeclamptic women. The low colloid oncotic pressure increases the risk of pulmonary edema in these cases. Preeclamptic women display a decreased stimulation of the renin-angiotensin-aldosterone system and an associated increase in vascular sensitivity to angiotensin II and norepinephrine.[85]

The hemodynamic findings of preeclampsia represent a clinical spectrum of the severity of the disease. These findings can range from a hyperdynamic state of high cardiac output to a state characterized by a markedly elevated systemic vascular resistance and severe left ventricular dysfunction.[86] There is a very poor correlation between central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) in these cases.[87] A recent review of published studies does not support the use of pulmonary artery catheters in women with uncomplicated preeclampsia.[88,89] Invasive hemodynamic monitoring in women with preeclampsia must be individualized. Consideration for invasive monitoring may be needed in those cases with refractory oliguria, refractory hypertension, pulmonary edema, or cardiovascular decompensation.[90]

Renal Changes

Renal plasma flow and glomerular filtration increase in normal pregnancy due to expanded plasma volume. In preeclampsia, however, the glomerular filtration rate and renal perfusion are decreased secondary to hypovolemia. Elevations in serum creatinine and uric acid may occur. Oliguria and acute renal failure may occur in severe cases. Vasospasm, fibrin deposition, and glomerular injury lead to proteinuria.[91]

Respiratory Changes

Pulmonary edema is a complication of preeclampsia. The pathogenesis of pulmonary edema may involve decreased oncotic pressure with resultant leaky capillaries, myocardial dysfunction, and rapid plasma volume expansion. A small subset of preeclamptic women may present with severe left ventricular dysfunction and resultant pulmonary edema. Invasive monitoring may be indicated in these cases if inotropic or vasodialator therapy is instituted.[77,92] Upper airway edema commonly develops in preeclampsia, an important consideration in this population when control of the airway is necessary. Aspiration pneumonia secondary to eclampsia may occur. In addition, ARDS secondary to prolonged ventilation may develop in preeclampsia.[58]

HELLP syndrome is a unique variant of preclampsia characterized by hemolysis, elevated liver enzymes, and low platelets. Hepatic hypoperfusion results in periportal and focal parenchymal necrosis and elevated liver enzymes.[92] The incidence of HELLP syndrome in preeclampsia ranges from 2% to 12%.[92] Parturients may present with epigastric or right upper quadrant pain, nausea and vomiting, or nonspecific viral syndrome-like symptoms.[75] Subcapsular liver hematoma and rupture of the subcapsular liver hematoma are rare complications of HELLP syndrome associated with a high incidence of maternal morbidity and mortality. The presence of a ruptured subcapsular liver hematoma is a surgical emergency requiring a multidisciplinary approach for intraoperative and postoperative care.[75]

The management of preclampsia involves stabilization of the mother and delivery of the fetus. Optimizing end-organ perfusion with plasma volume expansion is essential to pre-

vent maternal end-organ damage and to maintain fetal well-being. Early consideration of invasive monitoring is warranted in those cases with severe preclampsia who do not respond to fluid therapy and show evidence of pulmonary edema. Evidence of maternal or fetal decompensation mandates immediate delivery of the fetus. Early communication and discussion between the obstetrician and anesthesiologist is important to formulate an effective management plan for delivery and postpartum care.

Antihypertensive therapy is used in conjunction with plasma volume expansion to increase end-organ perfusion and prevent maternal hypertensive vascular damage. Hydralazine is a vasodialator commonly used for antihypertensive therapy. Side effects include reflex tachycardia and headache. Hydralazine can be administered as an initial intravenous dose of 5 mg followed by a second dose of 5 to 10 mg. Labetolol is a combined alpha- and beta-blocker that can be utilized as antihypertensive therapy in those women who have a hyperdynamic myocardium. Initial intravenous boluses of 5 to 10 mg may be given. Calcium channel blockers are another class of antihypertensives that may be utilized in preeclampsia. These agents can be given sublingually, orally, or intravenously; they are not recommended in those cases with left ventricular dysfunction. Concomitant administration of magnesium sulfate may potentiate the hypotensive effects of calcium channel blockers. Nitroglycerin and sodium nitroprusside may be used in those cases refractory to the foregoing antihypertensives. Invasive monitoring is recommended when nitroglycerin or sodium nitroprusside is administered for careful, continuous blood pressure monitoring to gauge pharmacologic therapy. It is important to note that those women receiving concomitant administration of magnesium sulfate, labetolol, and calcium channel blockers are at high risk for the development of pulmonary edema secondary to myocardial depression.[75]

Seizure prophylaxis with magnesium sulfate is one of the mainstays of therapy for preeclampsia. The Eclampsia Trial Collaborative Group showed a significant decrease in risk of recurrent seizures in eclamptic women who were given intravenous magnesium sulfate compared to those women given phenytoin or diazepam.[93] Magnesium sulfate is administered as an initial intravenous bolus of 4 to 6 g over 20 min followed by an infusion of 1 to 3 g/h. Patellar reflexes, respiratory status, serum magnesium levels, and urine output must be monitored during magnesium sulfate therapy. Magnesium sulfate is continued for 12 to 24 h postpartum until there is evidence of diuresis and stable maternal hemodynamics.[75]

Eclampsia

Eclampsia, defined as the occurrence of convulsions or coma unrelated to other cerebral conditions with signs and symptoms of preclampsia, is associated with a very high incidence of maternal and fetal morbidity and mortality.[1,2,75] The etiology of eclamptic seizure is unknown but may be related to cerebral vasospasm, ischemia, hypertensive encephalopathy, or cerebral edema.[19,94] Management of eclampsia involves rapid termination of the seizure, airway control, and maintenance of oxygenation and ventilation. Aspiration may occur during an eclamptic seizure with the potential for pneumonia, prolonged controlled ventilation, and possibly ARDS. Direct laryngoscopy and intubation of a preeclamptic should proceed with caution, as the sympathetic release associated with direct laryngoscopy and intubation in these cases may precipitate a hypertensive crisis, resulting in a cerebrovascular accident. Pretreatment with antihypertensives may be necessary to blunt the sympathetic response before direct laryngoscopy and intubation. In addition, laryngeal edema may be encountered in the preeclamptic women necessitating the use of smaller endotracheal tubes.

Trauma and Burns

Trauma occurs in 5% to 10% of all pregnancies and ranks first among nonobstetric causes of maternal mortality[95,96] Injuries and hemorrhagic shock account for most maternal deaths secondary to trauma.[95] Maternal death and placental abruption are the most frequent causes of fetal death secondary to trauma.[95,97,98] More than half the cases of blunt trauma in pregnancy are related to vehicular accidents, with the remaining cases divided approximately equally between falls and assaults.[25,98] Head injury is a leading cause of maternal death after trauma.[99]

Trauma to the gravid uterus threatens both the fetus and the mother. Maternal resuscitation is the most effective method of assuring fetal circulation. Fetomaternal hemorrhage may occur after trauma during pregnancy, especially when injury to the uteroplacental circulation permits fetal red blood cells to enter the maternal circulation.[95,100,101] Fetomaternal hemorrhage may cause Rh isosensitization in the Rh-negative mother. The initial management of the pregnant trauma patient includes airway assessment and management, oxygenation and ventilation, and circulatory support with volume replacement. Early consultation with the obstetrician is recommended for evaluation and monitoring of the fetus. The principles of management of the pregnant trauma patient are shown in Box 32.1.[95]

Approximately 7% of women of reproductive age who are seen for treatment of burn injuries are pregnant.[102–105] Ma-

Box 32.1. Management of the pregnant trauma patient.

Optimize gas exchange
Restore blood volume and tissue perfusion
Protect the brain and spinal cord
Maintain uteroplacental circulation and fetal oxygenation
Prevent maternal awareness
Detect unrecognized injuries
Correct coagulopathy
Maintain normovolemia
Prevent preterm labor

ternal and perinatal morbidity and mortality increase as total body surface area burned increases, with the greatest risk occurring with a total body surface area burn greater than 60%.[102]

Burns are classified as follows: minor burns involve less than 10% of total body surface area burned, and major burns involve greater than 10% of total body surface area burned. Major burns can be further classified as follows: moderate, 10% to 19% total body surface area burned; severe, 20% to 39% total body surface area burned; and critical, more than 40% total body surface area burned. Five factors must be considered for burn classification: size of burn, depth of burn, part of body burned, concurrent injuries, and past medical history.[102,106]

Burn injuries during pregnancy can lead to preterm labor and intrauterine fetal death. The risk of preterm labor increases with increasing total body surface area burned. Treatment of hypovolemia, sepsis, hypoxia, and electrolyte imbalance is essential to decrease the potential for fetal demise.[102]

Inhalation injuries can occur in burn patients. Carbon monoxide is frequently inhaled in a closed fire and freely crosses the placenta.[102] Fetal hemoglobin has a higher affinity for binding carbon monoxide. Exposure to carbon monoxide in utero may affect cardiac development and may produce fetal cardiac edema.[102,107] Oxygenation and ventilation with 100% oxygen is the treatment of choice.

In cases in which the fetus is viable in a pregnant burn patient, early delivery is advocated and has been associated with excellent maternal and fetal survival.[107,108] In the absence of maternal sepsis or abruption, and with evidence of a reassuring fetal heart rate, tocolysis may be considered for preterm labor.

It is important to consider the avoidance of certain therapies in the pregnant woman with burns that may be harmful to the fetus. Topical povidine-iodine solution for wound cleaning should be avoided because of adverse effects in the fetal thyroid gland.[102,109] Silver sulfadiazine has been used as a topical antibiotic.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare but lethal complication of pregnancy that occurs in 1 in 8000 to 1 in 30,000 pregnancies.[110] Maternal and fetal mortality rates are both approximately 60%.[110] The inciting event is fetal squamous cells in the maternal vasculature. Amniotic fluid embolism most often presents during labor but can occur during cesarean delivery or even the postpartum period. The clinical picture includes acute respiratory compromise, hypotension, seizure activity, coagulopathy, and cardiopulmonary arrest. Cases progress rapidly from dyspnea and hypotension to disseminated intravascular coagulopathy, ARDS, and possibly death from exsanguination and multiple organ failure.[111] The precipitous decompensation characteristic is likely caused by a convergence of anaphylactic shock and septic shocklike states.[112] The etiology and pathophysiology remain unclear. Clark et al. have proposed an anaphylactoid reaction to fetal elements in the maternal circulation, leading to a release of a cascade of endogenous mediators.[113] Hemodynamic features suggest pulmonary hypertension and ventricular dysfunction. Early institution of inotropic support guided by a pulmonary artery catheter is crucial. Transfusion of blood products is required to control bleeding from coagulopathy. The airway should be secured and ventilation controlled to ensure adequate oxygenation.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) occurs in the third trimester in approximately 1 in 11,000 pregnancies, with maternal mortality ranging from 0% to 18% and fetal mortality approaching 47%.[19,114] Women can present with right upper quadrant pain, nausea, vomiting, proteinuria, edema, mild hypertension, jaundice, coagulapathy, encephalopathy, hypoglycemia, and elevated serum ammonia levels.[114] The clinical distinction between preeclampsia, HELLP syndrome, and AFLP is confounded by their similar clinical symptoms and abnormal laboratory values. The distinction between HELLP and AFLP is made on histopathology, with evidence of microvesicular fatty infiltration in women with AFLP. The liver dysfunction in AFLP can rapidly progress to fulminant liver failure. Maternal stabilization and prompt delivery of the fetus are mainstays of therapy. Supportive therapy includes administration of lactulose, vitamin K, and glucose, correction of coagulopathy, and airway protection in those cases who become comatose.

Valvular Cardiac Disease and Peripartum Cardiomyopathy

A multidisciplinary team approach for parturients with cardiac disease is essential for maternal and fetal well-being. The New York Heart Association[115] functional classification defines four patient groups to delineate severity of heart disease based on functional classification. Class I is defined as no limitation of physical activity; class II is defined as symptoms with ordinary physical activity; class III is defined as symptoms with less than ordinary physical activities; and class IV is defined as symptoms at rest. Those women in class I or II have a maternal mortality rate less than 1%, whereas women in class III or IV have a maternal mortality rate between 5% and 15%.[116,117]

The acquired cardiac lesions that present the most concern in pregnancy are stenotic lesions, because volume fluctuations and the increase in cardiac output requirement that accompany pregnancy may not be tolerated.[19,118] The pregnant cardiac patient is at most risk for cardiac deterioration during the following time periods: the second trimester, when the phys-

Box 32.2. Anesthetic management of parturients with mitral stenosis.

Avoid tachycardia Maintain sinus rhythm and contractility Avoid increases in preload Maintain systemic vascular resistance (SVR) for end-organ perfusion

iologic changes of pregnancy result in increased blood volume; in labor and delivery, where an increase in cardiac output occurs secondary to sympathetic stimulation from pain and anxiety; and immediately postpartum, as a result of the large increase in venous return after delivery of the placenta.

Mitral stenosis is the most common rheumatic valvular lesion encountered in pregnancy.[19] Approximately 90% of pregnant women with rheumatic heart disease have mitral stenosis.[119,120] The normal mitral valve area is 4 to 6 cm^2; reduction to 1 cm^2 or less is considered severe. Prevention of emptying of the left atrium due to the stenotic valve results in pulmonary hypertension and subsequent compensatory right ventricular hypertrophy. Mitral stenosis is associated with significant maternal morbidity and mortality. Parturients with symptomatic mitral stenosis require invasive hemodynamic monitoring during labor and delivery. Parturients with mitral stenosis should not push during the second stage, as the Valsalva maneuver may result in sudden increased venous return and subsequent maternal decompensation.[119] The principles of anesthetic management of paturients with mitral stenosis (Box 32.2) are (i) avoid tachycardia, (ii) maintain sinus rhythm and contractility, (iii) avoid increases in preload, and (iv) maintain systemic vascular resistance (SVR) for end-organ perfusion.

Aortic insufficiency is a more common lesion than aortic stenosis in women of childbearing age.[119,120] Rheumatic heart disease is the etiology for approximately 75% of affected cases.[119] For the anesthetic management of women with regurgitant valvular lesions: (i) avoid bradycardia, (ii) maintain sinus rhythm and contractility, (iii) avoid increases in SVR, and (iv) avoid decreases in preload to maintain cardiac output for end-organ perfusion (Box 32.3).

Peripartum cardiomyopathy is a rare disorder occurring in 1 in 10,000 deliveries[119,121,122] that presents in the third trimester of pregnancy or in the early postpartum period. The etiology is unknown, and the disorder is a diagnosis of exclusion. Maternal mortality has been reported to be as high as 60%.[119]

Box 32.3. Anesthetic management of parturients with regurgitant valvular lesions.

Avoid bradycardia Maintain sinus rhythm and contractility Avoid increases in SVR Avoid decreases in preload to maintain output for end-organ perfusion

Peripartum cardiomyopathy is more common in women with multiple gestation, preeclampsia, obesity, and advanced maternal age.[119] Treatment is supportive. Women who survive peripartum cardiomyopathy do not regain their baseline cardiac function.[119,123,124] If supportive measures fail, cardiac transplantation is recommended.[119,125]

Summary

The critically ill pregnant patient poses unique challenges to the health care provider. A multidisciplinary approach is essential for formulating a clear management plan. This approach requires good communication and collaboration between the obstetrician and anesthesiologist to ensure stable maternal and fetal outcomes.

References

1. Panchal S, Arria AM, Harris AP. Intensive care utilization during hospital admission for delivery: prevalence, risk factors, and outcomes in a statewide population. Anesthesiology 2000;92:1537–1544.
2. Panchal S, Arria AM, Labhsetwar SA. Maternal mortality during hospital admission for delivery: a retrospective analysis using a state-maintained database. Anesth Analg 2001;93:134–141.
3. Jacob S, Bloebaum L, Shah G, et al. Maternal mortality in Utah. Obstet Gynecol 1998;91:187–191.
4. Hawkins JL, Koonin LM, Palmer SK, et al. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
5. Berg CJ, Atrash HK, Koonin LM, et al. Pregnancy-related mortality in the United States, 1987–1990. Obstet Gynecol 1996;88:161–167.
6. Atrash HK, Alexander S, Berg CJ. Maternal mortality in developed countries: not just a concern of the past. Obstet Gynecol 1995;86: 700–705.
7. Sachs BP, Oriol NE, Ostheimer GW, et al. Anethetic-related mortality, 1954–1985. J Clin Anesth 1989;1:333–338.
8. Rochat RW, Koonin LM, Atrash HK, et al. The Maternal Mortality Collaborative. Maternal mortality in the United States: report from the Maternal Mortality Collaborative. Obstet Gynecol 1988;72:91.
9. Umo-Etuk J, Lumley J, Holdcroft A. Critically ill parturient women and admission to intensive care: a 5-year review. Int J Obstet Anesth 1996; 5:79–88.
10. James MF, Anthony J. Critical care management of the pregnant patient. In: Birnbach DJ, Gatt SJ, Datta S (eds). Textbook of Obstetric Anesthesia, 1st edn. New York: Churchill Livingstone, 2000:716–717.
11. Sullivan JM, Ramanathan KB. Management of medical problems in pregnancy: severe cardiac disease. N Engl J Med 1985;313:304.
12. Ueland K. Maternal cardiovascular dynamics. VII: Intrapartum blood volume changes. Am J Obstet Gynecol 1976;126:671–677.
13. Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. Am J Obstet Gynecol 1989;161:1449.
14. Mabie WC, DiSessa TG, Crocker LG, et al. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol 1994; 170:849–856.
15. Robson SC, Dunlop W, Boys RJ. Cardiac output during labour. BMJ 1994;295:1169–1172.
16. Robson SC, Dunlop W, Hunter S. Haemodynamic changes during the early puerperium. Br Med J 1987;294:1065.
17. Hunter S, Robson SC. Adaption of the maternal heart in pregnancy. Br Heart J 1992;68:540–543.

18. Robson SC, Boys RJ, Hunter S, et al. Maternal hemodynamics after normal delivery and delivery complicated by postpartum hemorrhage. Obstet Gynecol 1989;74:234–239.
19. Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med 1995;152:427–455.
20. Metcalfe J, Romney LH, Ramsey D, et al. Estimation of uterine blood flow in normal human pregnancy at term. J Clin Invest 1955;34:1632–1638.
21. Jouppila R, Jouppila P, Hollman A. Laryngeal oedema as an obstetric anaesthesia complication. Acta Anaesth Scand 1980;24:97.
22. Boliston TA. Difficult tracheal intubation in obstetrics. Anaesthesia 1985;40:389.
23. Hall JB, Schmidt GA, Wood LD. Principles of Critical Care, 1st edn. New York: McGraw Hill, 1992:1030–1046.
24. Weinberger SE, Weiss ST, Cohen WR, et al. State of the art: pregnancy and the lung. Am Rev Respir Dis 1980;121:559.
25. Moise KJ, Belfort MA. Damage control for the obstetric patient. Surg Clin N Am 1997;77(4):835–851.
26. Davison M. Overview: kidney function in pregnant women. Am J Kidney Dis 1987;9:248–252.
27. Dafnis E, Sabatini S. The effect of pregnancy on renal function: physiology and pathophysiology. Am J Med Sci 1992;303:184–205.
28. Davison JM, Dunlop W. Renal hemodynamics and tubular function in normal human pregnancy. Kidney Int 1980;18:152–161.
29. Duvekot JJ, Cheriex EC, Pieters FA, et al. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol 1993;169:1382–1392.
30. American College of Obtetricians and Gynecologists Committee on Education. Thromboembolism in Pregnancy. ACOG Educational Bulletin No. 234. Washington, DC: ACOG, 1997.
31. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439–1442.
32. El-Solh AA, Grant BJ. A comparison of severity of illness scoring systems for critically ill obstetric patients. Chest 1996;110:1299–1304.
33. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–829.
34. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiologic score (SAPSII) based on a European/North American multicenter study. JAMA 1993;270:2957–2963.
35. Lemeshow S, Teres D, Klar J, et al. Mortality probability models (MPMII) based on an international cohort of intensive care unit patients. JAMA 1993;270:2478–2486.
36. Hoyt JW, Tonnesen AS, Allen SJ. Critical Care Medicine, 1st edn. Philadelphia: Saunders, 1991:454–465.
37. Houston CS. Diagnostic irradiation of women during the reproductive age. Can Med Assoc J 1977;117:648–651.
38. Critchow JF. Obstetric problems in the intensive care unit. In: Rippe JM, Irwin RS, Fink MP, Cerra FP (eds) Intensive Care Medicine, 3rd edn. Boston: Little, Brown, 1996:1846–1853.
39. Lyons G. Failed intubation: six years' experience in a teaching maternity unit. Anaesthesia 1985;40:759–762.
40. Marrero JM, Goggin PM, de Caestecker KS, et al. Determinants of pregnancy heartburn. Br J Obstet Gynaecol 1992;99:731–734.
41. Macfie AG, Magides AD, Richmond MN, et al. Gastric emptying in pregnancy. Br J Anaesth 1991;67:54–57.
42. Whitehead EM, Smith M, Dean Y, et al. An evaluation of gastric emptying times in pregnancy and the puerperium. Anaesthesia 1993;48:53–57.
43. La Salvia LA, Steffen EA. Delayed gastric emptying time in labor. Am J Obstet Gynecol 1950;59:1075–1081.
44. Davison JS, Davison MC, Hay DM. Gastric emptying time in late pregnancy and labour. J Obstet Gynaecol Br Commonw 1970;77:37–41.
45. Hunt JN, Murray FA. Gastric function in pregnancy. J Obstet Gynaecol Br Emp 1958;65:78–83.
46. O'Sullivan GM, Sutton AJ, Thompson SA, et al. Noninvasive measurement of gastric emptying in obstetric patients. Anesth Analg 1987;66:505–511.
47. Sandhar BK, Elliott RH, Windram I, et al. Peripartum changes in gastric emptying in obstetric patients. Anaesthesia 1992;47:196–198.
48. Elkas R, Popovich J. Respiratory physiology in pregnancy. Clin Chest Med 1992;13:555–565.
49. Archer GW, Marx GF. Arterial oxygenation during apnea in parturient women. Br J Anaesth 1974;46:358–360.
50. Expert Panel Report. Definition and diagnosis. Executive Summary: Guidelines for the Diagnosis and Management of Asthma. DHHS Publication No. 91-3042A. Bethesda, MD: Public Health Service, National Institutes of Health, 1991.
51. Lindeman KS. In: Chestnut DH (ed). Obstetric Anesthesia: Principles and Practice, 2nd edn. St. Louis: Mosby, 1999:1011–1023.
52. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43:12–18.
53. Schatz M, Harden K, Forsythe A, et al. The course of asthma during pregnancy, postpartum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81:509–516.
54. White RJ, Coutts II, Gibbs CJ, et al. A prospective study of asthma during pregnancy and the puerperium. Respir Med 1989;83:103–106.
55. Hollingsworth HM, Pratter MR, Irwin RS. Acute respiratory failure in pregnancy. J Intensive Care Med 1989;4(1):11.
56. Frakes MA, Richardson LE. Magnesium sulfate therapy in certain emergency conditions [review]. Am J Emerg Med 1997;15:182–187.
57. Wright BM, McKerrow CB. Maximum forced expiratory flow rate as a measure of ventilatory capacity. Br Med J 1959;2:1041–1051.
58. Mabie WC, Barton JR, Sibai BM. Adult respiratory distress syndrome in pregnancy. Am J Obstet Gynecol 1992;167:950–957.
59. Fowler AA, Hamman RF, Zerbe GO, et al. Adult respiratory distress syndrome: prognosis after onset. Am Rev Respir Dis 1985;132:472–478.
60. Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985;132:485–489.
61. Noble PW, Lavee AL, Jacobs MM. Respiratory diseases in pregnancy. Obstet Gynecol Clin N Am 1988;15:391.
62. Strong TH, Lowe RA. Perimortem cesarean section. Am J Emerg Med 1989;7:489–494.
63. Katz VL, Dotters DJ, Droegemueller W. Perimortem cesarean delivery. Obstet Gynecol 1986;68:571–576.
64. Lopez-Zeno JA, Carlo WA, O'Grady JP, et al. Infant survival following postmortem cesarean delivery. Obstet Gynecol 1990;7:991–992.
65. Lanoix R, Akkapeddi V, Goldfeder B. Perimortem cesarean section: case reports and recommendations. Acad Emerg Med 195;2:1063–1067.
66. Koonin LM, Atrash HK, Lawson HW, et al. Maternal mortality surveillance: United States, 1979–1986, vol 40/SS-1. Atlanta, GA: U.S. Public Health Service, Centers for Disease Control and Prevention, 1991.
67. Mayer DC, Spielman FJ. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice, 2nd edn. St. Louis: Mosby, 1999:725–748.
68. Chattopadhyay SK, Kharif H, Sherbeeni MM. Placenta praevia and accreta after previous caesarean section. Eur J Obstet Gynecol Reprod Biol 1993;52:151–156.
69. The Centers for Disease Control and Prevention. Maternal Mortality: United States, 1982–1996. MMWR (Morbid Mort Wkly Rep) 1998;47:705–707.
70. Lee W, Clark SL, Cotton DB, et al. Septic shock during pregnancy. Am J Obstet Gynecol 1988;159:410–416.
71. Gibbs RS. Severe infections in pregnancy. Med Clin N Am 1989;73:713.
72. Brown CEL, Lowe TW, Cunningham FG, et al. Puerperal pelvic thrombophlebitis: impact in diagnosis and treatment using X-ray computerized tomography and magnetic resonance imaging. Obstet Gynecol 1986;68:789–794.
73. Brown CEL, Dunn DH, Harrell R, et al. Computerized tomography for evaluation of puerperal infections. Surg Gynecol Obstet 1991;172:285–289.

74. American College of Obstetricians and Gynecologists. Hypertension in Pregnancy. Technical Bulletin No. 219. Washington, DC: ACOG, 1996.
75. Sibai BM. In: Gabbe SG, Niebyl JR, Simpson JL (eds) Obstetrics: Normal and Problem Pregnancies, 3rd edn. New York: Churchill Livingstone, 1996:935–996.
76. Sibai BM. Hypertension in pregnancy. Obstet Gynecol Clin N Am 1992; 19:615.
77. Mroz LA. Hypertensive disorders of pregnancy. Anesth Clin N Am 1999;17:679–691.
78. Dilly OC, Robson A, Robson SC. Management of preeclampsia and haemolysis, elevated liver enzymes, and low platelets syndrome. Curr Opin Obstet Gynecol 1999;11:149–156.
79. Higgins JR, Brennecke SP. Preeclampsia—still a disease of theories? Curr Opin Obstet Gynecol 1998;10:129–133.
80. Pijnenborg R, Anthony R, Davev DA, et al. Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol 1991;98:648–655.
81. Pijnenborg R. The placental bed. Hypertens Pregnancy 1996;15:7–23.
82. Roberts JM, Taylor RN, Musci TJ, et al. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200–1204.
83. McCarthy AL, Woolfson RG, Raju SK, et al. Abnormal endothelial cell function of resistance arteries from women with preeclampsia. Am J Obstet Gynecol 1993;168:1323–1330.
84. Perloff D. Hypertension and pregnancy-related hypertension. Cardiol Clin 1998;16:79–101.
85. Weiner C, Liu KZ, Thompson L, et al. Effect of pregnancy on endothelium and smooth muscle: their role in reduced adrenergic sensitivity. Am J Physiol 1991;261:1275–1283.
86. Cotton DB, Lee W, Huhta JC, et al. Hemodynamic profile of severe pregnancy-induced hypertension. Am J Obstet Gynecol 1988;158:523–529.
87. Newsome LR, Bramwell, Curling PE. Severe preeclampsia: hemodynamic effects of lumbar epidural anesthesia. Anesth Analg 1986;65:31–36.
88. Leibowitz AB, Beilin Y. Pulmonary artery catheters and outcome in the perioperative period. New Horiz 1997;5:214–221.
89. Gambling DR, Writer D. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice, 2nd edn. Mosby: St. Louis, 1999:875–920.
90. American College of Obstetricians and Gynecologists. Invasive hemodynamic monitoring in obstetrics and gynecology. ACOG Technical Bulletin No. 175. Washington, DC: ACOG, 1992.
91. Krane NK. Acute renal failure in pregnancy. Arch Intern Med 1988; 148:2347–2357.
92. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol 1990;162:311.
93. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995;345:1455–1463.
94. Dildy GA, Cotton DB. Management of severe preeclampsia and eclampsia. Crit Care Clin 1991;7:829–864.
95. Baker BW. Trauma. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice, 2nd edn. Mosby: St. Louis, 1999:1041–1050.
96. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support Student Manual. Chicago: American College of Surgeons, 1989.
97. Perlman MA, Tintnalli JE, Lorenz RP. A prospective controlled study of outcome after trauma during pregnancy. Am J Obstet Gynecol 1990; 162:1502–1510.
98. Rothenberger D, Quattlebaum FW, Perry JF, et al. Blunt maternal trauma: a review of 103 cases. J Trauma 1978;18:173–179.
99. Luce JM. Medical management of head injury (a review). Chest 1986;89:864–872.
100. Pak LL, Reece EA, Chan L. Is adverse pregnancy outcome predictable after blunt abdominal trauma? Am J Obstet Gynecol 198;179:1140–1144.
101. Rose PG, Strohm PL, Zuspan FP. Fetomaternal hemorrhage following trauma. Am J Obstet Gynecol 1985;153:844–847.
102. Polko LE, McMahon MJ. Burns in pregnancy. Obstet Gynecol Surv 1997;53(1):50–56.
103. Akhtar MA, Mulawkar PM, Kulkarni HR. Burns in pregnancy: effect in maternal and fetal outcomes. Burns 194;20:351–355.
104. Amy BW, McManus WF, Goodwin CW. Thermal injury in the pregnant patient. Surg Gynecol Obstet 1985;161:209–212.
105. Gang RK, Bajec J, Tahboub M. Management of thermal injury in pregnancy: an analysis of 16 patients. Burns 1992;18:317–320.
106. Reiss G. Thermal injuries. In: Lopez-Viego MA (ed) The Parkland Trauma Handbook. St. Louis: Mosby, 1994:389–412.
107. Fechter LD, Thakur M, Miller B. Effects of prenatal carbon monoxide exposure in cardiac development. Toxicol Appl Pharmacol 1980;56: 370–375.
108. Ullmann Y, Blumenfeld Z, Hakim M. Urgent delivery, the treatment of choice in term pregnant women with extended burn injury. Burns 1997;23:157–159.
109. Pietsch J, Meaklins JL. Complications of povidine-iodine absorption in topically treated burn patients. Lancet 1976;1:280–282.
110. Clark SL. New concepts of amniotic fluid embolism: a review. Obstet Gynecol Surv 1990;45:360–368.
111. Locksmith GJ. Amniotic fluid embolism. Obstet Gynecol Clin 1999;26: 435–444.
112. Clark SL, Hankins GDV, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995;172:1158–1169.
113. Clark SL. Anaphylactoid syndrome of pregnancy. Reply. Am J Obstet Gynecol 1996;175:750.
114. Reyes H. Acute fatty liver of pregnancy: a cryptic disease threatening mother and child. Clinics Liver Dis 1999;3:69–81.
115. Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. New York: New York Heart Association, 1979.
116. Hess DB, Hess WL. Cardiovascular disease and pregnancy. Obstet Gynecol Clin N Am 1992;19:679–692.
117. American College of Obstetrics and Gynecology. Cardiac Disease in Pregnancy. ACOG Technical Bulletin No. 168. Washington, DC: ACOG, 1992.
118. Clark SL. Cardiac disease in pregnancy. Crit Care Clin 1991;7:777–797.
119. Camann WR, Thornhill ML. In: Chestnut DH (ed) Obstetric Anesthesia: Principles and Practice, 2nd edn. St. Louis: Mosby, 1999:776–808.
120. Paulus DA, Layon AJ, Mayfield WR. Intrauterine pregnancy and aortic valve replacement. J Clin Anesth 1995;7:338–346.
121. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. Am J Obstet Gynecol 1997;176:182–188.
122. Brown CS, Bertolet BD. Peripartum cardiomyopathy: a comprehensive review. Am J Obstet Gynecol 1998;178:409–414.
123. Lampert MB, Weinert L, Hibbard J. Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. Am J Obstet Gynecol 1997;176:189–195.
124. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: a longitudinal echocardiographic study. Am J Obstet Gynecol 1997;177: 1129–1132.
125. Aravot DJ, Banner NR, Ohalia N. Heart transplantation for peripartum cardiomyopathy. Lancet 1987;2:1024.

33
Intrauterine Fetal Death

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Although many of the risks of pregnancy and childbirth have been alleviated or minimized during the past century, intrauterine fetal demise (IUFD) remains a significant obstetric problem. IUFD can occur without warning during an uncomplicated pregnancy, or it may be associated with specific medical conditions and social behaviors. This chapter discusses the definition, epidemiology, etiology, prevention, and management of IUFD, with special emphasis on anesthetic management.

Definition

The study of IUFD has been hampered by two factors: a lack of consensus with respect to the definition of this event and the fact that there is no organized mechanism for its reporting. In the early 1950s, the World Health Organization (WHO) defined fetal death as "death occurring prior to the complete expulsion or extraction from the mother of a product of conception, irrespective of duration of pregnancy; the death is indicated by the fact that after such separation, the fetus does not breathe or show any evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definitive movement of voluntary muscles."[1]

This definition was adopted to show a distinction between spontaneous abortion and stillbirth and to allow collection of statistics based on a consistent standard. However, many issues worldwide continue to preclude our ability to reach consensus on definition. For example, in the United States, the National Center for Health Statistics has adopted the WHO definition. In most other nations, registration of a fetal death is required only if it occurs after the 20th week of gestation.[2]

Another factor affecting the definition of IUFD has been the advancement of neonatal medicine and obstetric care, which continually affects the minimal gestational age at which fetal viability can occur. For many years, viability was considered to be possible only with birth after 28 weeks gestation. It is now possible, in some circumstances, for infants weighing as low as 500 g, coinciding with 24 weeks gestation, to survive with a reasonable prognosis and quality of life.

Overall, the incidence of IUFD in the United States is 6 to 7 per 1000 births; however, inconsistencies in both the definition of fetal death and in its reporting make it difficult to accurately estimate the true incidence of this condition. Poor documentation of IUFD also affects statistics regarding the causal factors.[3] Indeed, as recently as June 2000, WHO demonstrated that up to 27% of stillbirths are reported without an attributable cause.[4]

Epidemiology

During the period between 1981 and 1991, there were a total of 62 million pregnancies in the United States; of these, 62.5% resulted in live births, 21.9% in legal abortions, 13.8% in spontaneous abortions, 1.3% in ectopic pregnancies, and 0.5% in fetal deaths.[5] Since 1950, there has been a progressive decline in the crude fetal death rate in the United States, from 18.4 to 6.8 per 1000 total births in 1997.[2] Race can be an important factor in the incidence of fetal death. For instance, fetal death rate is lower for whites (Caucasian patients) as compared to all other racial groups, perhaps due to differences in gestational weight distribution. Other factors that have been linked to unexplained fetal death include older maternal age, low socioeconomic status, poor prenatal care (fewer than four antenatal visits), prepregnancy weight greater than 68 kg, primiparity and multiparity (>3), and large-for-gestational-age fetus.[6]

A woman's social behavior and habits can also affect pregnancy outcome and affect the incidence of IUFD. For instance, smoking is associated with a higher incidence of fetal death, and the effects of smoking are more pronounced during pregnancy of older compared to younger women. The risk of fetal mortality is 77% greater when alcohol is consumed during pregnancy than when no alcohol is consumed.[2] Illicit drug abuse, particularly of crack/cocaine, can have many negative effects on a pregnancy and can also result in IUFD.[7]

Diagnosis

As stated, IUFD is diagnosed when a fetus has no cardiac activity, umbilical cord pulsation, or definitive movement of voluntary muscles.[1] Suspicion of fetal death is confirmed by either radiographic or biochemical tests that identify degenerative changes in the fetus resulting from intrauterine death.

A common symptom associated with IUFD is a report that the mother no longer "feels pregnant." Fetal movements may be absent or decreased, and there may be a loss of breast discomfort and nausea. Clinical signs indicative of IUFD may be a lack of interval examination fundal height growth, inability to auscultate fetal heart tones, maternal weight loss, or vaginal bleeding. The presence of any of these signs indicates the need for further evaluation of the fetus by ultrasound to identify the presence or absence of fetal heart activity.

If fetal heart tones cannot be auscultated, cardiac movement, as determined by real-time ultrasonography, is the clearest, most direct sign of fetal life. If sonography indicates that an IUFD has occurred, the cause of death may be subsequently identified by pathologic examination of the fetus and placenta.

Other sonographic signs associated with IUFD are dependent on the gestational age and the time interval since the fetal death. In addition to the absence of cardiac motion, other key diagnostic signs suggestive of fetal death are the absence of fetal limb or trunk movements and the absence of umbilical cord pulsations. In modern practice, fetal movement, particularly cardiac activity, can be visualized from as early as 8 weeks gestation by transabdominal sonography, but the resolution may be affected by maternal body habitus. In contrast, transvaginal ultrasound has become the preferred modality for confirming fetal cardiac activity for two reasons. First, the resolution is not dependent on body habitus, because the examination is performed with an endovaginal probe; second, this technique allows for the use a higher-frequency transducer (6.5 MHz) capable of determining fetal cardiac activity by the sixth week of gestation. The presence of an intrauterine gestational sac with a fetal pole and the absence of cardiac activity by ultrasound indicate fetal nonviability. In very early pregnancy, an empty gestational sac without a fetal pole may represent an error in dating the pregnancy rather than indicating an embryonic demise or blighted ovum. In such a case, the patient is usually rescanned in 7 to 14 days, at which time the presence of a normal pregnancy can be distinguished from a blighted ovum or embryonic demise. Fetal movements are a less reliable sign of fetal life, as they may be passive, caused by maternal movement, great vessel pulsations, or uterine positioning, or active, originating from the fetus itself.

After the death of a fetus, secondary signs related to degenerative changes may be observed by ultrasound. Twelve hours after IUFD, the intracranial anatomy becomes obscure due to degeneration of neural tissue. Within 72 hours, the calvaria collapses, and the cranial bones overlap. The fetal outline is also said to become "fluffy" due to the absorption of amniotic fluid by the skin, resulting in edema.[8]

After fetal death, amniotic fluid volume decreases because of both a lack of production by the fetus and absorption of the remaining fluid by the mother. As a result, severe oligohydramnios is an associated finding in many cases of IUFD. However, skeletal deformities, skin edema, and severe oligohydramnios may be also observed in a living fetus with specific congenital abnormalities. For this reason alone, it must be emphasized that the only definitive sign of fetal death is the absence of cardiac motion.

Etiology

Chromosomal Causes

Chromosomal abnormalities are the single most common cause of pregnancy loss. Up to 50% of first trimester losses and 5% to 10% of midpregnancy stillbirths are related to chromosomal abnormalities.[9] Chromosomal abnormalities vary with both maternal and gestational age. For instance, the most common abnormality associated with first trimester pregnancy loss is Turner's syndrome (45X), which is usually linked to young maternal age. Trisomy is the most frequent chromosomal abnormality found in fetal deaths at a more advanced gestational age. For the most part, fetuses with autosomal trisomies rarely survive until term; however, trisomies 13, 18, and 21 may be compatible with life. A genetic analysis of fetal tissue is essential because diagnosis of a chromosomal abnormality may have major implications in counseling the family for future pregnancies.

Fetal Malformations

Approximately one in four stillborn infants has a congenital malformation, and half of these are related to a genetic problem.[10] Many of the malformations associated with stillbirth are also commonly seen in spontaneously aborted fetuses. It is often difficult to determine the exact frequency of a specific malformation. For instance, some malformations may be underreported because degenerative changes in the dead fetus preclude accurate identification. Alternatively, rates of some malformations have been reported to be higher in stillborn fetuses because the condition is generally more severe and easier to identify.

In order of decreasing frequency, the most common chromosomal common malformations associated with stillbirth are cardiac defects, urogenital anomalies, polydactyly/syndactyly/oligodactyly, omphalocele/gastroschisis, hydrocephalus, cleft lip/palate, microphopthalmia/anopthalmia, intestinal atresia, and midline brain defects. Nonchromosomal congenital defects linked with stillbirth include neural tube defects, anomalies in infants born to diabetic mothers, amniotic band syndrome, Potter's syndrome, gastrointestinal conditions including gastroschisis, omphalocele, and dwarfism.[11]

Multiple Pregnancies

Recent advances in assisted reproduction have increased the incidence of multiple-gestation pregnancy, which is associated with higher maternal and fetal morbidity and mortality due to intrauterine growth restriction, twin-to-twin transfusion, preeclampsia, preterm delivery, and IUFD. It has become apparent that the true incidence of twin conceptions is greater than the incidence of living twin births. For instance, multiple studies using serial ultrasound examinations beginning in the early stages of pregnancy have noted the presence of twin pregnancy that either reduces to a singleton pregnancy or aborts completely.[12,13]

An IUFD of one twin in the second or third trimester occurs in 2.6% to 6.8% of twin pregnancies[14–16] and more often in monochorionic than in dichorionic twins.[17] The etiology may be umbilical cord insertion abnormalities, such as a velamentous or a marginal origin of the cord from the placenta. Twin-to-twin transfusion syndrome due to arteriovenous anastomosis between the two fetuses may result in fetal growth restriction of one twin and polycythemia and hydrops of the other.[18] If death of one twin occurs, the surviving fetus may be at increased risk for cerebral necrotic lesions, and the mother at risk for developing coagulopathy. Uteroplacental insufficiency, which in itself can result in fetal growth retardation and death, is a potential complication of multiple gestations.

There are no set recommendations for management of a multiple pregnancy complicated by fetal death when one or more fetuses survive. The risk of premature delivery of the surviving fetus must be balanced against the risk of prolonging the pregnancy versus maternal coagulopathy and fetal cerebral necrotic syndrome. Numerous retrospective studies have reported favorable outcomes by allowing the pregnancy to continue. The incidence of maternal clotting abnormalities in these studies ranged from 0% to 25%, depending on the duration of pregnancy following the IUFD.[19–21]

Maternal Infection

Maternal infection has been a well-recognized cause of fetal morbidity and mortality. Most infectious pathogens in the mother can cross the placenta and cause a fetal infection, potentially leading to IUFD. Because infections such as toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus are known to be a major cause of fetal death, in the past, IgM and IgG titers were routinely ordered following a diagnosis of IUFD. Today, however, this practice has been abandoned, because it is now recognized that the number of pregnant women exposed to these pathogens before pregnancy is increasing. Thus, in the absence of baseline titers, a single elevated titer cannot confirm the etiology of an IUFD as related to fetal infection. Indeed, a recent study found no correlation between elevated IgM antibody titers and placental or autopsy findings consistent with infection.[22]

Bacterial infection of the amniotic cavity is also an important cause of perinatal mortality and maternal morbidity. Clinical evidence of amnionitis occurs in 0.5% to 10% of pregnancies.[23] Most cases are related to vaginal pathogens such as Group B *Streptococcus*, *Escherichia coli*, and enterococci following rupture of membranes. However, transplacental and hematogenous spread of infection may occur, and unlike vaginal pathogens, these do not require rupture of the membranes. Amnionitis may also be iatrogenic following cervical cerclage, amniocentesis, or intrauterine transfusion.

Listeriosis (*Listeria monocytogenes*) may be asymptomatic or result in a flu-like illness in the mother but can prove fatal to the fetus. It is also one of the causes of chorioamnionitis that can occur even if the amniotic membranes are intact. It is thought that the immunologic alterations of pregnancy may make pregnant women more susceptible to this pathogen and the fetus more prone to infection.[24]

More recently, other pathogens have been linked with IUFD. Parvovirus B19 is a common viral infection that has been increasingly associated with adverse pregnancy outcome in infected women. It may be asymptomatic or manifest with fetal anemia, hydrops fetalis, spontaneous abortion, and even IUFD. Previously, it was thought that parvovirus B19 infection was mostly linked to second trimester fetal losses. However, a recent study of IUFDs over a 6-year period suggests that up to 7.5% of third trimester IUFDs may be the result of parvovirus B19 infection.[25] It is now recommended that parvovirus B19 polymerase chain reaction (PCR) testing be included in the routine evaluation of an IUFD.

Lyme disease (*Borrelia burgdorferi*) has also been suggested as a possible cause of IUFD.[26,27] Group B Coxsackie virus infection can also be transmitted across the placenta, but the magnitude of the risk to the fetus has not been quantified. For the most part, Coxsackie virus infection has no demonstrable adverse fetal effects; however, the virus has been isolated from stillborn infants.

Placental Pathology

Placental Abruption

Placental abruption, a partial or complete separation of the placenta before delivery of the fetus, is estimated to occur in 1.3% to 1.6% of pregnancies and is estimated to be associated with 5% to 15% of all IUFDs.[28–31] Preexisting conditions such as chronic hypertension, pregnancy-induced hypertension, preeclampsia, maternal cocaine use, excessive alcohol intake, smoking, and a previous history of abruption are all risk factors associated with placental abruption.

Placental abruption may manifest with vaginal bleeding and uterine tenderness. However, blood loss can often be underestimated due to the potential for substantial hemorrhage that is concealed behind the placenta. Abruption may be mild, moderate, or severe depending on the degree of placental sep-

aration. Separation of the placenta greater than 50% has been associated with an increased risk of stillbirth.[30] Disseminated intravascular coagulation (DIC) may occur with abruptio placentae. The incidence of DIC may be as great as 30% with an abruption large enough to result in fetal death.[32,33]

Obstetric management depends on the severity of bleeding and fetal status. Large-bore intravenous access should be established on admission, and blood samples drawn for baseline hematocrit, coagulation studies, fibrinogen degradation products, and blood type and crossmatch. If fetal death has already occurred, vaginal delivery is preferred to hysterotomy unless there is severe ongoing hemorrhage. Treatment of associated DIC involves delivery of the fetus and placenta, restoration of maternal blood volume, and correction of coagulation status with the use of blood components. If an operative procedure is considered necessary, general endotracheal anesthesia is preferable to regional anesthesia in those women with hemodynamic instability or coagulopathy.

Placenta Previa

Placenta previa occurs when implantation of the placenta is low in the uterus, either overlying or encroaching on the cervical os. Placenta previa is present in approximately 0.6% of all pregnancies and is associated with an increased risk of fetal death.[34] Placenta previa may be categorized as "total" if the placenta completely covers the os; "partial" if there is some encroachment on the os by the placenta; and "marginal" if the placenta is not covering but is close to the internal os. The condition is more common in multiparous women, especially those with a previous cesarean section. Typically, in contrast to placental abruption, placenta previa presents with painless vaginal bleeding in the third trimester. Bleeding may stop spontaneously, in which case conservative management is recommended. However, if bleeding persists, stabilization of the mother and delivery of the fetus may be required.

Vasa Previa

Vasa previa is an uncommon placental condition that carries with it a high fetal mortality.[35] It occurs when there is a velamentous insertion of the umbilical vessels so that they run through amniotic membranes traversing between the fetal presenting part and the cervical os. These vessels have little support and are very susceptible to trauma during labor. A diagnosis of vasa previa is suspected when vaginal bleeding occurs immediately on rupturing the amniotic membranes and is accompanied by fetal heart rate abnormalities. Because bleeding with vasa previa is fetal rather than maternal in origin, only a small amount of blood loss may result in fetal demise unless the problem is recognized quickly and an emergency cesarean section can be performed immediately.[36]

Umbilical Cord Accidents

Stillbirth resulting from cord accidents or umbilical cord compression has typically been a diagnosis made in hindsight and on the basis of exclusion. Conditions that can predispose to cord accident include polyhydramnios, amniotic bands, monoamniotic twins, and an unstable fetal lie, all of which may be identified antenatally by ultrasound.

Uteroplacental Insufficiency

Uteroplacental insufficiency is an important cause of IUFD in a small, yet significant, number of pregnant women. Reduced uteroplacental blood flow may result in decreased oxygenation to the fetus, which in turn can result in chronic fetal hypoxia and subsequent intrauterine growth retardation (IUGR). In general, fetuses manifesting IUGR have a perinatal mortality rate approximately 5 to 30 times greater than infants whose birth weight is appropriate for gestational age.[37] IUGR is present if weight is estimated to be less than the 10th percentile for that gestational age. There is an inverse relationship between fetal weight percentile and the incidence of perinatal mortality; perinatal mortality increases exponentially in infants weighing less than the 6th percentile weight for their gestational age.[37] A variety of maternal conditions can be associated with uteroplacental insufficiency. Identification of at-risk women and intensive surveillance and monitoring for suspected IUGR are crucial in decreasing the risk of IUFD.

There is a twofold to threefold increase in the incidence of IUGR in pregnant women with chronic hypertension as compared with normotensive pregnant women.[38] It has been suggested that IUGR in these women may be the result of vasospasm causing a reduction in uterine blood flow or related to an observed increase in the incidence of preeclampsia.[39]

With maternal diabetes, the risk of IUGR increases with the duration and severity of the disease. Damage to the maternal microcirculation due to diabetes results in uteroplacental insufficiency and IUGR. IUGR may also be associated with an increased frequency of preeclampsia as noted in diabetic women during pregnancy. Although the reason is unclear, systemic lupus erythematosus (SLE) is associated with a decrease in uteroplacental perfusion, and IUGR may occur in up to 23% of pregnancies complicated by SLE.[40]

Abnormalities of the placenta, such as placenta previa or abruption, can cause an increased incidence of IUGR due to an abnormal maternal–placental transfer interface. Conditions such as multiple gestation, grand multiparity, and structural uterine abnormalities can also result in placental insufficiency, IUGR, and IUFD due to limited uterine surface.

Conditions that may impair maternal oxygen delivery, such as severe sickle cell anemia and cyanotic heart disease, are also associated with IUGR and IUFD, because a decrease in uteroplacental perfusion may occur as a result of a chronic maternal hypoxic state. Behavioral habits such as smoking and drug abuse decrease placental perfusion related to an increase in the release of maternal catecholamines. With cigarette smoking, fetal oxygenation may be further compromised by carbon monoxide, which decreases the oxygen-carrying capacity of fetal hemoglobin. In women who already have un-

derlying uteroplacental insufficiency, smoking and drug abuse can worsen the fetal prognosis even further.

Intensive surveillance of the fetus with suspected IUGR is believed to decrease the risk of subsequent IUFD when the fetus is in jeopardy by allowing for an earlier delivery. It is important to identify patients at risk for IUGR before pregnancy so that gestational age can be accurately determined by ultrasound evaluation. Thereafter, serial ultrasound examinations of the fetus will be more reliable to ensure adequate growth of the fetus and should be useful in identifying a lag in fetal growth late in pregnancy.

Normal umbilical artery flow indices are indicative of fetal well-being, whereas increased resistance to blood flow is associated with IUGR. A meta-analysis by Nielson et al. demonstrated that the use of umbilical artery flow velocity studies identifies those IUGR fetuses at risk and reduces the risk of perinatal death.[41] Determination of the fetal biophysical profile (BPP) is also recommended as a means of monitoring fetal well-being in a suspected IUGR fetus. Vintzileos et al. demonstrated that the specific components of the BPP become abnormal at different levels of fetal hypoxemia.[42] For example, an early indication of IUGR on the BPP is a loss of nonstress test reactivity and the absence of fetal breathing.

Oligohydramnios is often associated with severe fetal growth restriction. With chronic fetal hypoxemia, there is a compensatory diversion of fetal blood flow in the hypoxic fetus from the kidneys to more vital organs. As a result, fetal urine output and amniotic fluid volumes are decreased. Accordingly, oligohydramnios in the presence of IUGR may be suggestive of fetal compromise and therefore may indicate that immediate delivery of the fetus is necessary.

Although the data are inconclusive, maternal bedrest and oxygen therapy may improve umbilical Pao_2 in the hypoxic growth-retarded fetus and thus may improve the perinatal outcome.[43] Maternal low-dose aspirin administration has not been proven to be effective in reducing the incidence of IUGR in at-risk pregnancies. Cessation of smoking, alcohol use, and illicit drug use are particularly required in at-risk women, because these are clearly preventable causes of IUGR and IUFD.

Postdates Gestation

Postmature pregnancy (greater than 42 weeks) is associated with an increased risk of perinatal morbidity and mortality because fetal demands exceed the ability of the placenta to provide adequate nutrient supply and gas exchange.[44] Postdates pregnancy is also associated with a higher incidence of placental infarcts and areas of calcification, intervillous thrombus formation, arterial thrombosis, and endarteritis.[45]

The incidence of fetal death in all postdates pregnancy is estimated to be 0.1%. However, after 41 weeks gestation, there is a significant increase in odds ratio (OR) for fetal death occurring, particularly if IUGR is present.[46]

The management of a postdates pregnancy remains controversial. A recent study comparing active versus expectant management of postterm pregnancy demonstrated no discernible improvement in fetal outcome with elective induction of labor at 41 weeks gestation as compared to serial fetal monitoring of the fetus to identify those who require urgent delivery.[47] To reduce the incidence of fetal death, close monitoring of the postdates pregnancy is advised. Fetal nonstress test and amniotic fluid index measurements should be performed twice weekly. Some practitioners also recommend monitoring of fetal growth over a 10- to 14-day interval to screen for the occurrence of IUGR, which may complicate postdates pregnancy.

Immunologic and Rheumatologic Diseases

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease commonly associated with a poor pregnancy outcome. It is a multisystem inflammatory disease characterized by antibody and complement-fixing immune complex deposition within body tissues. This condition has a prevalence of 1 in 700 in women 15 to 65 years old and is predominantly seen in young females.[48] Immunosuppression with steriods is the preferred treatment and may be used to control exacerbations of SLE flare-ups during pregnancy.

Women with SLE often have poor obstetric outcome and higher incidences of spontaneous abortion, preterm labor, preeclampsia, IUGR, and stillbirth. The risk of IUFD is eight times greater in women with SLE as compared to normal women.[39] The presence of active disease or a recent flare-up has been associated with poor perinatal outcome, specifically an increased risk of stillbirth. However, in a recent large prospective study comparing pregnant women with active versus inactive SLE, there was no statistically significant difference in the rate of stillbirth between the two groups, 6.0% and 3.9%, respectively.[49,50]

When SLE is complicated by renal involvement or hypertension, a higher risk of stillbirth may be present. Gimovsky et al. reported that 12.5% of women with lupus nephritis had an IUFD as compared with 2.5% in women having SLE without nephritis.[51] In addition, these women are also predisposed to develop gestational hypertension or preeclampsia, which in itself can also increased the risk of fetal morbidity and mortality.[52] Women who have SLE should be counseled not to become pregnant unless there is optimal control of their disease for at least 6 months before conception and renal function is near normal (indicated by serum creatinine of 1.5 mg or less, creatinine clearance of 60 mL/mm or more, or proteinuria of less than 3 g/day).[53]

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS), or Hughes syndrome, is a condition in which circulating antibodies (lupus anticoagulant or anticardiolipin) react with negatively charged phos-

pholipids. It can occur as an isolated entity or in conjunction with SLE and other autoimmune diseases. Pregnancy outcome is generally worse in patients having APS in conjunction with another autoimmune disease.[54] The syndrome is usually asymptomatic in women of reproductive age. However, it is suspected and usually diagnosed in those women with thrombotic phenomena or poor obstetric history. The concurrence of thrombocytopenia and severe preeclampsia in women with APS heralds poor maternal and fetal prognosis.

The reason for fetal demise with APS remains unclear, but it is thought to result from thrombosis of the placental vessels causing areas of infarction and fetal hypoxia. The treatment of choice is anticoagulation with heparin and aspirin. Both low molecular weight and unfractionated heparin may be used for antithrombotic prophylaxis, usually in combination with low-dose aspirin; this regimen has been shown to result in more favorable obstetric outcome than treatment with aspirin alone.[55] Activated partial thromboplastin time (aPPT) may be used to assess heparin activity but may be impossible to interpret in the presence of circulating lupus anticoagulant.[56] For that reason, the thrombin time may be preferred to the aPPT. Measurement of whole blood heparin may be useful in managing such women during the peripartum period. Therapy with anticoagulants may be a contraindication to the use of regional anesthesia.

Patients on low molecular weight heparin (LMWH) prophylaxis therapy can be assumed to have altered coagulation. A single-dose spinal anesthetic may be the safest neuraxial technique in such patients, but epidural techniques may also be used. The timing of regional anesthesia is controversial. There should be a time interval of at least 10 to 12 h between the last dose of LMWH and needle placement. For continuous epidural techniques, the concentration of local anesthetic in the anesthetic solution used for analgesia should be minimized, because higher concentrations may interfere with neurologic assessment by causing numbness and weakness.[57]

Rheumatologic conditions, which are fortunately rare in pregnant women, include scleroderma, progressive systemic sclerosis, rheumatoid arthritis, mixed connective tissue diseases, polymyositis, dermatomyositis, Sjogrën's syndrome, and polyarteritis nodosa. These diseases, which are also autoimmune in nature, may be associated with a potentially increased rate of IUFD.[58]

Endocrine Disorders

Diabetes Mellitus

Type 1 diabetes mellitus (DM) occurs in less than 0.5% of all pregnancies. Before the introduction of insulin, high maternal and neonatal morbidity was associated with DM. In the past, sudden unexplained fetal death was reported to occur in 10% to 30% of all pregnancies complicated by type 1 diabetes.[59] However, in current practice, insulin therapy, improved maternal glycemic control, and intensive fetal monitoring have decreased the incidence of IUFD to 2% to 4%.[60,61] Nevertheless, unexplained stillbirths and congenital abnormalities still occur in pregnancies complicated by DM. In fact, one study has suggested that the rate of IUFD was nine times higher in mothers having DM during pregnancy as compared to a control group of nondiabetic mothers.[62] The greatest risk to the fetus of IUFD occurred after 36 weeks gestation, especially in mothers with inadequate glycemic control.

Type 1 diabetes often manifests with generalized vasculopathy, which can interfere with uteroplacental perfusion and have an adverse effect on fetal nutrient and oxygen supply. Chronic fetal hypoxia is thought to cause IUFD because evidence of extramedullary hematopoiesis is often noted on autopsy.[63] With diabetic ketoacidosis, fetal loss is reported to be as high as 50% if it is not treated promptly.[64] IUFD may also be related to a reduction in uterine and placental blood flow due to maternal hypovolemia.

Congenital anomalies occur more frequently in pregnancies of mothers complicated by pregestational diabetes and are thought to be related to poor preconception glycemic control.[65] A percentage of these anomalies may result in stillbirth. Fetal hypertrophic cardiomyopathy is a potential cause of sudden IUFD in poorly controlled diabetic pregnancies. Fetuses of diabetic mothers, especially those with gestational diabetes, are at risk for developing macrosomia, a condition of organomegaly. Macrosomia is associated with increased risk of birth trauma and neonatal metabolic disturbances. On the other hand, there is also a risk of IUGR occurring in pregnancies complicated by DM as a result of vasculopathy and placental insufficiency.[66] Diabetic mothers also have an increased rate of coexistent conditions such as hypertension, preeclampsia, and infections, all of which may also increase the risk of IUFD.

The key to managing pregnancy of the diabetic woman is to achieve optimal glycemic control during pregnancy. Intensive fetal surveillance during the third trimester is essential in reducing the incidence of IUFD and other related obstetric complications of diabetic women.[67]

Thyroid Diseases

Thyroid disease is a relatively common disorder during pregnancy. Thyroid disorders are considered to be autoimmune diseases and, in the past, have been associated with an increased incidence of stillbirth if left untreated. Hypothyroidism occurs in approximately 0.2% of all pregnancies.[68] It is most often caused by Graves' disease, which is an autoimmune illness associated with increased thyroid-stimulating antibody (TSAb) activity. Before the introduction of antithyroid therapy, a high incidence of IUFD was reported to occur with Graves' disease.[69] However, with early diagnosis and treatment, fetal outcome is now excellent. Medications used to treat Graves' disease are not associated with an increased risk of congenital defects and are well tolerated by the expectant mother.[70,71]

Rarely, transplacental passage of TSAbs may cause fetal hyperthyroidism and result in tachycardia in the fetus, which may be fatal if severe and left untreated.[72]

Thyrotoxicosis, and in particular thyroid storm, occurs in up to 2% of all thyrotoxic patients. The potential for maternal hypertension and hyperthermia with thyrotoxicosis increases the risk of IUFD.[68] Thyroid storm may be triggered by preeclampsia, hemorrhage, infection, and induction of labor. Under these conditions, admission of the mother to an intensive care unit is advisable. Treatment should be directed at inhibiting thyroid hormone production (i.e., thiourea compounds) and controlling clinical manifestations such as tachycardia and hypertension with beta-adrenergic blockers. Continuous fetal heart rate monitoring should be performed until thyroid storm abates.

The most common cause of hypothyroidism in pregnant women is autoimmune thyroiditis. Hypothyroidism carries a twofold-increased risk of miscarriage, congenital and developmental abnormalities, and stillbirth.[73] The exact cause for the increased risk of miscarriage is not fully understood but may be related to direct toxic effects of antithyroid antibodies on the fetus.[74] A prospective study of 68 pregnant women demonstrated that there was a significant increase in the incidence of gestational hypertension in women with hypothyroidism as compared to the general population. Pregnancy outcome is generally good and comparable to the general population in women with hypothyroidism who are maintained in an euthyroid state.[75]

Hematologic Disorders

Hematologic disorders, such as hemoglobinopathies (sickle cell, thallasemia), thrombocytopenia, polycythemia rubra vera, and thrombocytopenic purpura may occur during pregnancy and increase the risk of fetal growth retardation related to uteroplacental insufficiency. Appropriate therapy specific to each condition in conjunction with close clinical monitoring is required to improve maternal and fetal outcome.[76]

Hemolytic Disease

Rhesus (Rh) isoimmunization may occur if an Rh-negative woman receives an Rh-positive transfusion or if she is exposed to Rh-positive fetal red cells. The latter may occur during pregnancy or after spontaneous or induced abortion. When Rh sensitization occurs during pregnancy, Rh-positive red blood cells are destroyed by maternal Rh-IgG antibodies, resulting in fetal anemia and a greater production of fetal erythropoietin. In turn, extramedullary hematopoiesis occurs to compensate for maternal antibody-induced fetal red blood cell destruction. If severe and untreated, hydrops fetalis occurs with high-output cardiac failure and ascites, generalized edema, and pleural and pericardial effusions.

A rhesus-negative woman who is sensitized has a greater than 40% chance of having a stillbirth with a subsequent rhesus-positive pregnancy unless there is obstetric intervention. In Rh-sensitized pregnancy, 21% of stillbirths occurred between 33 and 35 weeks gestation, 15% between 26 and 37 weeks, and 45% at 37 weeks gestation.[77] Fortunately, Rh-isoimmunization is no longer considered to be a major cause of perinatal morbidity and mortality since the introduction of screening for and appropriate therapy of rhesus incompatibility. However, to be successful, therapy must occur well before there is a maternal immune response to fetal Rh-positive cells.

ABO incompatibility is the most common cause of hemolytic disease in newborns. Approximately 20% of all infants have an ABO maternal blood group incompatibility, but only 5% will show overt signs of hemolytic disease.[78] Most cases are subclinical and generally require no treatment. In some affected pregnancies, mild hyperbilirubinemia may occur in the neonate. Hydrops and mortality are extremely rare consequences of ABO incompatibility.

Inherited Coagulopathies

The inherited coagulopathies are autosomal dominant conditions that are major causes of thromboembolic disease in predisposed women. The most common conditions are deficiencies of antithrombin III (At III), protein C, protein S, and factor V Leiden mutation that cause resistance to protein C. Women with these genetic thrombophilias have an increased incidence of serious obstetric complications.[79] The hypercoagulable state that naturally occurs during pregnancy may exacerbate the pathologic effects of these diseases and result in an increased risk of maternal thromboembolism, IUGR, severe preeclampsia, and fetal loss. Women with inherited coagulopathies have a threefold increase in the rate of spontaneous abortion.[80]

Factor V Leiden mutation is the most common inherited coagulopathy. This single-point mutation confers resistance to normal inactivation of factor V by protein C or protein S. The risk of thromboembolism during an affected patient's lifetime is 30%. Pregnancy normally reduces protein S levels, thus potentially worsening the thrombotic effects of factor V Leiden mutation. Patients who are heterozygous for the mutation have a 5- to 10-fold-increased risk of having a thromboembolic event during their lifetime; however, during pregnancy, the risk increases to 50 fold higher than for those without the factor V Leiden mutation. The risk of thromboembolism is even higher in the patient who is homozygous, but fortunately this condition is rare.[81]

One study reported an eightfold increase in recurrent spontaneous abortions and IUFDs in women with factor V Leiden mutation as compared to women without the mutation.[82] However, another study found no significant difference in the rate of miscarriage and stillbirth in women with factor V Leidin disease compared with a control group. There also appears to be a high incidence of miscarriage and placental infarcts[80] when the fetus itself carries the mutation.

Antithrombin III deficiency is associated with the greatest risk of thrombotic disease of the inheritable thrombophilias, with a greater than 70% risk of a thrombotic event during the lifetime of the patient. Fortunately, this disease is rare, representing only about 1% of patients with thromboembolism.[79] Women with antithrombin III deficiency have almost a twofold higher rate of miscarriage and a fivefold higher rate of stillbirth than those without inherited coagulopathies.[80]

Deficiency of protein C or protein S is also associated with thromboembolic events during pregnancy and a threefold increase in the rate of stillbirth compared to the general population.[80] Other rare, inherited coagulopathies, such as a mutation of the prothrombin gene, appear to be associated with an increased risk of stillbirth, IUGR, and thromboembolic events.

In general, women with inherited coagulopathies and a poor obstetric history should receive prophylactic heparin during gestation, particularly those cases with AT III deficiency. Prophylactic heparin therapy should be strongly considered in women with factor V Leiden, protein S, and protein C deficiencies and other inheritable coagulation disorders, even though they are asymptomatic (Table 33.1).

Hypertension

Hypertensive diseases during pregnancy may have adverse effects on maternal and fetal well-being. A retrospective study found that women with chronic hypertension had the highest risk of fetal loss after 28 weeks gestation as compared to women with eclampsia or pregnancy-induced hypertension.[83] Shah and Reed have suggested that the severity and duration of hypertension correlates with the incidence of adverse perinatal outcomes.[84] Other studies, however, have suggested that women with mild to moderate chronic hypertension have perinatal outcomes similar to those of normotensive women.[85,86]

Placental abruption, or fetal asphyxia due to chronic placental insufficiency, are the most frequent causes of IUFD in pregnant women with chronic hypertension. Early diagnosis of hypertension and adequate medical therapy may help reduce the risk of stillbirth.

Drug Abuse, Alcohol, and Smoking

Drug Abuse

Illicit drug use among women of reproductive age has increased during the past decade. In 1994, the National Institute on Drug Abuse (NIDA) estimated that an alarming 5% of American women used illicit drugs during pregnancy.[87,88] In fact, women who abuse drugs often receive little or no antenatal care, which further increases the risk of maternal and fetal morbidity and mortality, as does the drug use itself. The prevalence of antepartum cocaine use was reported to be as high as 68% among unregistered women as compared to the registered population of women seeking routine antenatal care at an urban hospital. Polysubstance abuse is also common among unregistered women.[89]

Cocaine use during pregnancy is associated with an increased risk of early spontaneous abortion, preterm labor, placental abruption, uterine rupture, and IUFD.[90] Cocaine, because of its sympathomimetic effects, reduces uteroplacental blood flow, results in IUGR, and may even cause fetal death. Thrombocytopenia related to cocaine use may also place women at an increased risk for epidural or spinal hematoma following placement of regional anesthesia.[91] There may also be an enhanced response to succinylcholine and ephedrine resistance in cocaine-abusing parturients.[92,93] In women with polysubstance abuse, extreme care should be exercised if using opioid antagonists such as naloxone, because maternal drug withdrawal, fetal distress, or even fetal death may ensue.[7] Beta blockade can precipitate unopposed alpha stimulation, which may precipitate a hypertensive crisis and have an impact on the fetus.[94]

Alcohol and Smoking

Chronic alcohol consumption during pregnancy has been associated with harmful effects on the fetus, including an increased risk of spontaneous abortion, IUGR, and fetal death.[95] Fetal alcohol syndrome may also occur with alcohol use during pregnancy.

Smoking during pregnancy has been associated with spontaneous abortion, growth restriction, premature rupture of membranes, placenta previa, placental abruption, and sudden infant death syndrome.[96,97] Placental blood flow may be decreased by the vasoconstrictor effects of nicotine. Placental abruption and placenta previa also occur with greater frequency in smokers.[98]

Environmental and Occupational Exposures

Women exposed to high doses of radiation may be at increased risk for spontaneous abortion and fetal malformations.

TABLE 33.1. Prevalence of adverse pregnancy outcome associated with inherited coagulopathies.

Coagulopathy	Prevalence of SAB (%)	Risk of SAB (*X*)	Prevalence of IUFD (%)	Risk of IUFD (*X*)
Factor V Leiden	10	0.9	1.2	2.0
AT III	17	1.7	2.3	5.0
Protein C	16	1.4	1.2	2.0
Protein S	15	1.2	1.9	3.0

SAB, spontaneous abortion, IUFD, intrauterine fetal death; AT III, antithrombin III.

However, there is no apparent association between adverse obstetric outcome and the diagnostic use of X-ray.[99]

An increased risk of spontaneous abortions during the first trimester has been reported in medical personnel and is possibly related to occupational exposure to anesthetic agents, such as nitrous oxide (N_2O), and antineoplastic drugs.[100] However, other studies have failed to demonstrate such a relationship.[101,102] Today, most operating rooms have scavenging systems, thus decreasing the risk. Women working in the metal, electrical, and chemical industries as well as those women exposed to low-level pesticides in the workplace have an increased risk of stillbirth.[103]

Prescription Medications

Many prescription medications have been associated with congenital malformations if taken during the first trimester. Warfarin, aminopterin, and methotrexate (folic acid antagonists) and other chemotherapeutic agents have been linked to fetal loss if used during pregnancy.[104,105]

Trauma

Injury related to trauma occurs in up to 6% to 7% of all pregnancies and is perhaps the most common cause of nonobstetric maternal mortality.[106–108] Motor vehicle accidents are responsible for the majority of injuries, followed by domestic abuse and, to a lesser extent, falls.[109,110] The fetal death rate after maternal injury ranges from 4% to as high as 61%, depending on the severity and magnitude of the injury.[111] In contrast to nonpregnant women, abdominal injuries are more likely than head injury in pregnant women.[110]

The direct causes of fetal death with trauma are maternal death, placental abruption, or direct fetal injury. Placental abruption is reported to occur in 1.6% to 4.4% of trauma cases and is associated with a fetal mortality greater than 50%.[109,112–114]

Rapid assessment, hemodynamic stabilization, and treatment of maternal injuries are essential for fetal survival. It is important to remember that the anatomic and physiologic changes associated with pregnancy may cause the clinician to underestimate the true extent of hypovolemia. For instance, shock in a pregnant woman may not be clinically evident until 25% to 30% of the maternal blood volume is lost, at which point the fetus may already be in jeopardy. In hemorrhagic shock, maternal blood is shunted away from the uterus to preserve perfusion to vital maternal organs at the expense of the fetus, thus causing fetal hypoxemia and even death.[115]

Fetal heart rate should be determined as early as possible during initial maternal assessment; fetal bradycardia or tachycardia are possible indicators of fetal jeopardy. Ultrasonography may help to confirm placental abruption; however, it is not sufficiently sensitive to exclude that diagnosis.[116] Continuous fetal cardiotocography is considered to be a more sensitive indicator of impending fetal compromise and should be used routinely in the continuous assessment of the fetus in pregnant patients following trauma injury.[117]

Obstetric and Anesthetic Management of Intrauterine Fetal Demise

When spontaneous abortion occurs in the first trimester, dilatation and sharp or suction curettage is usually performed. The anesthetic options include local (paracervical block), regional, or general anesthesia. The optimal anesthetic technique chosen may depend on individual maternal preferences and on physical as well as psychologic condition. The gestational age at which endotracheal intubation becomes necessary is a controversial subject. Often it is difficult to predict true gestational age with certainty at the time of the procedure; therefore, precautions should be taken to prevent gastric acid aspiration. Volatile anesthetic agents may cause uterine relaxation in a dose-related manner and increase the potential for blood loss.[118] Indeed, greater blood loss has been shown to occur with the use of volatile agents for suction termination of pregnancy as compared to propofol alone.[119–121]

For second trimester fetal demise, dilatation and evacuation (D&E) may be required. This technique involves the use of specialized instruments due to the larger fetal size and increased tissue mass. Gastric acid aspiration prophylaxis including rapid-sequence induction of general endotracheal anesthesia is necessary after the first trimester.

Induction of labor may be an alternative option to D&E in a woman with a second trimester fetal demise. A variety of prostaglandin derivatives, such as $PGE_{2\alpha}$, may be used for cervical ripening and for the initiation of labor. Higher doses of $PGE_{2\alpha}$ and intravenous oxytocin solutions may be required at early stages of gestations. Hygroscopic or osmotic cervical dilators (laminaria japonicum) may also be used.[122] Anesthesiologists should be aware of the potential side effects of prostaglandins, such as nausea, vomiting, diarrhea, and hypotension. With the use of PGE_2, there have also been isolated reports of hypertension and arterial vasospasm,[123] possibly related to the central effects of prostaglandins.

In cases of IUFD that are closer to term, intravenous oxytocin is often used for both induction and augmentation of labor. The uterine response to oxytocin depends on gestational age. A gradual increase in responsiveness occurs between 20 and 30 weeks of gestation and once again from 34 weeks onward until term of pregnancy.[124]

Special consideration is required in the management of a multiple pregnancy where one or more fetuses have died and at least one survives. As discussed earlier, this is a complicated issue for which no clear guidelines have been established. Zorlu et al. suggested taking an expectant approach unless risks develop to the mother or the surviving fetus.[125] The risk of complications for the surviving fetus is high, varying from 0% to 46%.[126] The incidence of maternal clotting

abnormalities may be as high as 25% depending on the interval after IUFD.[20,127,128]

Complications related to premature delivery of the surviving fetus must be balanced against both the hazards of leaving the surviving twin in utero and the risks of maternal complications such as coagulopathy and sepsis. Recent studies are inconclusive regarding the incidence of the woman developing a coagulopathy when the dead fetus remains in utero for a prolonged period.[20,129,130] It has been proposed that the surviving twin and the placenta act as a filter for thromboplastin, preventing its entry into the maternal circulation and thus reducing the likelihood of DIC[131] (see coagulopathies).

Analgesia

Effective analgesia and rapid progression of labor are desirable for mothers with an IUFD to lessen the woman's psychologic anguish. In the absence of coagulopathy or other contraindications to regional anesthesia, planned epidural catheter placement before induction of labor provides safe and effective analgesia without interfering with the labor process.[132] In fact, the first stage of labor has been shown to be shortened in women with a fetal demise who had epidural analgesia for their labor as compared to a similar group of women given meperidine and promethazine.[133]

In addition, the epidural is available for use should a postpartum operative intervention be required (i.e., for retained placenta), thus potentially avoiding the risks of general anesthesia.[134] Alternatives to regional anesthesia may include parenteral opioids administered as needed or with the use of an intravenous patient-controlled analgesia device. Nausea, itching, and maternal somnolence may occur, especially when opioids are combined with phenothiazines. Somnolence may be regarded as a benefit by some women, whereas other mothers want to be as awake as possible to begin the grieving process immediately.

Coagulopathy

Coagulopathy may occur in up to 13% of women with an IUFD. In 1950, Weiner et al. first used the term dead fetus syndrome to refer to the association of DIC with IUFD.[135] It is now known that DIC can occur independently of the etiology of fetal demise. The incidence of DIC may be higher when coexistent conditions such as placental abruption or uterine perforation are present.[20,136–138]

Mechanism

The proposed mechanism for coagulopathy associated with IUFD involves the release of phospholipids from the retained dead fetus that act as thromboplastins once in the maternal circulation, activating the maternal coagulation cascade and causing intravascular consumption of platelets and clotting factors. Microvascular thrombosis may result in tissue ischemia and subsequent organ damage. As a result, excess amounts of plasmin are produced, causing systemic and local firbinolysis in an attempt to maintain vascular patency. There may also be associated hypofibrinogenemia, thrombocytopenia, and primary or secondary fibrinolysis.[139,140]

Current Statistics

Since the 1950s, there has been a progressive reduction in the incidence of DIC associated with fetal demise,[141] which is a result of both earlier diagnosis of IUFD and changes in obstetric management. For instance, mothers who have experienced an IUFD are no longer managed expectantly. Current obstetric practice is to induce labor once the diagnosis of IUFD is made to reduce the risk of maternal complications such as coagulopathy and infection and also to lessen the emotional trauma for the mother.[136,137]

Diagnosis and Treatment

The recurrence of DIC with fetal demise still remains a serious challenge with major anesthetic and obstetric implications. The main goal of treatment is removal of the dead fetus and replenishment of depleted blood components. The diagnosis of DIC is made on clinical grounds. However, several laboratory tests are available to confirm the diagnosis of DIC. Coagulation status of patients with IUFD should be determined on admission to provide a baseline before obstetric or anesthetic interventions. Routine coagulation studies should include a prothrombin time (PT), activated partial thromboplastin time (aPPT), fibrinogen, platelet count, fibrin degradation products, and AT III activity. PT and PPT may remain within normal limits in pregnant women with DIC.[142] However, as the factors required for clot formation are eventually consumed, these values will become abnormal. In cases where fetal death is caused by placental abruption or uterine rupture, there is an even greater risk of coagulopathy, which should be considered in developing an obstetric and anesthetic management plan.

In emergency situations, if laboratory test results are still pending, the clot observation test is a useful bedside test of general coagulation status. Approximately 5 mL blood is drawn from the woman and placed in a dry 10-mL round-bottom glass tube. If the blood clots within 5 to 6 min and remains so for 30 min, coagulopathy is unlikely. If the blood fails to form a clot, the presence of a coagulation defect can be assumed.

The main goal of treatment of DIC is removal or correction of the underlying cause with restoration of circulating blood volume and replacement of blood components and clotting factors as indicated. The American Society of Anesthesiologists (ASA) has developed guidelines regarding blood component therapy.[143] Their recommendations for red blood cell (RBC) transfusion include transfusion of RBC when hemoglobin falls below 6 g/dL, especially when blood loss is

acute. Transfusion of RBC for hemoglobin (Hb) levels between 6 and 10 mg/dL should be based on the woman's risk for complications because of reduced oxygenation. Transfusion of one unit of packed red cells generally increases Hb by 1 g/dL or the hematocrit by 3%. Platelet transfusion is recommended in surgical and obstetric cases with a platelet count less than 50,000/μl if microvascular bleeding is present. With abnormal coagulation and low levels of fibrinogen, replacement of coagulation factors is necessary. Fresh-frozen plasma (FFP), 15 mL/kg, contains all the necessary clotting factors. If FFP transfusion cannot maintain fibrinogen levels above 0.5 g/L, cryoprecipitate, which contains a greater portion of fibrinogen than FFP, should also be given. The administration of cryoprecipitate for treatment of DIC associated with placental abruption has been shown to increase plasma fibrinogen levels.[143] Heparin therapy is rarely, if ever, used nowadays in the management of DIC.

Psychologic Issues

Miscarriage or fetal loss is a devastating event for any family, irrespective of how early in gestation the loss occurs. Parents go through a multiple-stage grieving process: initial shock and disbelief, searching and yearning for their dead baby, and then confusion and disinterest with eventual resolution.[144] After the diagnosis of fetal death is established by real-time ultrasound, it should be openly discussed with the mother and her support person.

It is important to allow and encourage parents to express their feelings. Many women have feelings of guilt and self-blame for the loss, and it is essential to assist them in verbalizing and dealing with these feelings appropriately. It is possible that some mothers and family may express their grief as anger toward medical and nursing staff; this should not be confronted immediately but discussed at a later time.

There should be regular communication between attending physicians, residents, nursing staff, and social workers involved in these cases to ensure that conflicting information is not given to grieving parents. Early supportive therapy is advisable, with referral and access to a 24-h perinatal bereavement counseling service. Religious support should be made available if requested.

The process of labor should be fully explained to the family, so they can psychologically prepare themselves for the impending delivery. Following delivery, couples often gain comfort in seeing and holding their baby; this opportunity should be extended openly. Parents often name their baby. Social workers and staff should encourage parents to compile a memory package of photographs, a lock of hair, a copy of baby footprints, a crib card, a hat, and an identity band. Memorial services and burial or cremation ceremonies can aid in resolution of grief; therefore, such options should be discussed with parents. Support for the family's children should also be considered. Referral to parent, volunteer, and support groups and genetic counseling services should be offered.

Further Causative Diagnosis

Performance of an autopsy and pathologic examination of the placenta aid in establishing the diagnosis of IUFD, helping the family find closure, and possibly providing information on which to base future plans for pregnancy. The benefit of autopsy should be discussed with the parents, their choices outlined, and their individual wishes respected. If they do not want a full autopsy, an alternative may be a limited examination of major organs or a less invasive needle biopsy examination of key organs.[145] Nonetheless, an autopsy is important in identifying the presence of malformations and/or inherited or acquired conditions that may indicate a cause for fetal death. Negative findings may be suggestive of a cord accident, which is equally important in counseling parents about future pregnancy.[146] The placenta should be carefully examined for significant placental lesions, infection, or umbilical cord abnormalities that may have caused the fetal death. However, placental changes observed at autopsy might not be indicative of the true cause of the IUFD but may be secondary to fetal demise.[147]

Follow-up office visits in the weeks after discharge from the hospital enable the obstetrician to discuss postmortem findings and possible causes of the IUFD with the woman and her family. The likelihood of a recurrence of loss should be addressed for each abnormality found, as this is often the question that continues to plague the family. Ongoing support and counseling should be available from a local perinatal bereavement support group.

Summary

There are several important causes of IUFD. The anesthesiologists are involved in most of the cases. Because of the expected grief, special care is necessary while looking after these women.

References

1. WHO. Manual of the International Statistical Classification of Diseases, Injuries and causes of deaths, 9th revision, vol 1. Geneva: WHO, 1977.
2. NCHS. Medical and lifestyle risk factors affecting fetal mortality 1989–90. Washington, DC: NCHS/DHSS, 1996:96–1859.
3. Alberman E, Blatchley N, Botting B, et al. Medical causes on stillbirth certificates in England and Wales: distribution and results of hierarchical classifications tested by the Office for National Statistics. Br J Obstet Gynaecol 1997;104:1043–1049.
4. WHO. Making pregnancy safer: report of the Secretariat Document No. GB107/26. Geneva: World Health Organization, 2000.
5. Saraiya M, Berg CJ, Shulman H, et al. Estimates of the annual number of clinically recognized pregnancies in the United States, 1981–1991. Am J Epidemiol 1999;149:1025–1029.
6. Huang DY, Usher RH, Kramer MS, et al. Determinants of unexplained antepartum fetal deaths. Obstet Gynecol 2000;95:215–221.
7. Kliman L. Drug dependence and pregnancy: antenatal and intrapartum problems. Anaesth Intensive Care 1990;18:358–360.

8. Gottesfeld KR. The ultrasonic diagnosis of intrauterine fetal death. Am J Obstet Gynecol 1970;108:623–634.
9. Angell RR, Sandison A, Bain AD. Chromosome variation in perinatal mortality: a survey of 500 cases. J Med Genet 1984;21:39–44.
10. Poland BJ, Lowry RB. The use of spontaneous abortuses and stillbirths in genetic counseling. Am J Obstet Gynecol 1974;118:322–336.
11. Hall BD. Non-chromosomal malformations and syndromes associated with stillbirth. Clin Obstet Gynecol 1987;30:278–282.
12. Seoud MA, Toner JP, Kruithoff C, et al. Outcome of twin, triplet and quadruplet in vitro pregnancies: the Norfolk experience. Fertil Steril 1992;57:825–834.
13. Benson CB, Doubilet PM, David V. Prognosis of first-trimester twin pregnancies: Polychotomous logistic regression analysis. Radiology 1994;192:765–768.
14. Carlson NJ, Towers CV. Multiple gestation complicated by the death of one fetus. Obstet Gynecol 1989;73:685–689.
15. Cherouny PH, Hoskins IA, Johnson TRB, et al. Multiple pregnancy with late death of one fetus. Obstet Gynecol 1989;74:318–320.
16. Kilby MD, Govind A, O'Brien PS. Outcome of twin pregnancies complicated by a single intrauterine death: a comparison with viable twin pregnancies. Obstet Gynecol 1994;84:107–109.
17. Saito K, Ohtsu Y, Amano K, et al. Perinatal outcome and management of single fetal death in twin pregnancy: a case series and review. J Perinat Med 1999;27:473–477.
18. Urig MA, Clewell WH, Elliot GP. Twin-twin transfusion syndrome. Am J Obstet Gynecol 1990;163:1522–1526.
19. Randboll I, Chr P, Chr H, et al. Multiple pregnancies with single intrauterine demise. Acta Obstet Gynecol Scand 1999;78:202–206.
20. Axt R, Mink D, Hendrik J, et al. Maternal and neonatal outcome of twin pregnancies complicated by single fetal death. J Perinat Med 1999;27: 221–227.
21. Visentin L, Leo L, Alemanno MMG, et al. Management of patients with intrauterine fetal death. Clin Exp Obstet Gynecol 1996;23:263–267.
22. Incerpi MH, Miller DA, Samadi R, et al. Stillbirth evaluation: what tests are needed? Am J Obstet Gynecol 1998;178:1121–1125.
23. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intra-amniotic infection. Am J Obstet Gynecol 1991;164:1317–1326.
24. Boutonne EJ, Sierra MF. *Listeria monocytogenes*. Another look at the "Cinderella among pathogenic bacteria." Mt. Sinai J Med (NY) 1977;44: 42–59.
25. Skjoldebrand-Sparre L, Tolfrenstam T, Papadogiannallis N, et al. Parvovirus B19 infection: association with third trimester intrauterine fetal death. Br J Obstet Gynaecol 2000;107:476–480.
26. Schlesinger PA, Duray PH, Burke BA, et al. Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. Ann Intern Med 1985;103:67.
27. McDonald AB, Benach JL, Burgdorferi W. Stillbirth following Lyme disease. N Y J Med 1987;8:615.
28. Saftlas AF, Olsen DR, Atrash HK, et al. National trends in the incidence of abruptio placentae, 1979–1987. Obstet Gynecol 1991;78:1081–1086.
29. Clark SL. Placenta previa and abruptio placentae. In: Creasy RK, Resnik R (eds) Maternal-Fetal Medicine, 4th edn. Philadelphia: Saunders, 1999: 616–631.
30. Ananth CV, Berkowitz GS, Saritz DA, et al. Placental abruption and adverse perinatal outcomes. JAMA 1999;282:1646–1651.
31. Rassmussen S, Irgens LM, Bergsjo P, et al. Perinatal mortality and case fatality after placental abruption in Norway, 1967–1991. Acta Obstet Gynecol Scand 1996;75:229–234.
32. Mayer DC. Hemorrhagic obstetric emergencies. Semin Anesth 1992;11: 32–42.
33. Lester EP, Roth DG. Disseminated intravascular coagulation in pregnancy. J Reprod Med 1997;19:223–232.
34. Frederiksen MC, Glassenberg R, Stika CS. Placenta previa. A 22-year analysis. Am J Obstet Gynecol 1999;180:1432–1437.
35. Alexander JD. Vaginal bleeding associated with pregnancy. Prim Care 2000;27:137–151.
36. Ramin SM, Gilstrap LC. Placental abnormalities: previa, abruption, and acreta. In: Plauché WC, Morrison JC, O'Sullivan MJ (eds) Surgical Obstetrics. Philadelphia: Saunders, 1992:193–216.
37. Manning FA. Intrauterine growth retardation. Morbidity and mortality in 1560 small-for gestational age fetuses. In: Fetal Medicine: Principles and Practice. Norwalk, CT: Appleton & Lange, 1995.
38. McCowan LM, Buist RG, North RA, et al. Perinatal morbidity in chronic hypertension. Br J Obstet Gynaecol 1996;103:123–129.
39. Bernstein PS, Divon MY. Etiologies of fetal growth restriction. Clin Obstet Gynecol 1997;40:723–729.
40. Julkunen H, Jouhikainen T, Kaaja R, et al. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. Lupus 1993;2:125–131.
41. Nielson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high-risk pregnancies. Cochrane Database Syst Rev 2000;2:CD000073.
42. Vintzileos AM. Antenatal assessment for the detection of fetal asphyxia. An evidence-based approach using indication-specific testing. Ann N Y Acad Sci 2000;900:137–150.
43. Battaglia C, Artini PG, d'Ambrogio G, et al. Maternal hyper-oxygenation in the treatment of intrauterine growth retardation. Am J Obstet Gynecol 1992;167:430–435.
44. Cunningham FG, McDonald PC, Gant NF, et al. Williams' Obstetrics, 20th edn. Stamford: Appleton & Lange; 1997:827–837.
45. Vorherr H. Placental insufficiency in relation to post-term pregnancy and fetal postmaturity. Evaluation of fetoplacental function: management of the postterm gravida. Am J Obstet Gynecol 1975;123:67–103.
46. Divon MY, Haglund B, Nisell H, et al. Fetal and neonatal mortality in the postterm pregnancy: the impact of gestational age and fetal growth restriction. Am J Obstet Gynecol 1998;178:726–731.
47. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. A clinical trial of induction of labor versus expectant management in post-term pregnancy. Am J Obstet Gynecol 1994;170:716–723.
48. Varner MW. Autoimmune disorders and pregnancy. Semin Perinatol 1991;15:238–250.
49. Mintz G, Niz J, Gutierrez G, et al. Prospective study of pregnancy in systemic lupus erythematosus. Results of a multi-disciplinary approach. J Rheumatol 1986;13:732–739.
50. Sittiwangkul S, Louthrenoo W, Vithayasai P, et al. Pregnancy outcome in Thai patients with systemic lupus erythematosus. Asian Pac J Allergy Immunol 1999;17:77–83.
51. Gimovsky ML, Montoro M, Paul RH. Pregnancy outcome in women with systemic lupus erythematosus. Obstet Gynecol 1984;63:686–692.
52. Packham DK, Lam SS, Nicholls K, et al. Lupus nephritis and pregnancy. Q J Med 1992;83:315–324.
53. Nicklin JL. Systemic lupus erythematosus and pregnancy at the Royal Women's Hospital, Brisbane, 1979–1989. Aust N Z J Obstet Gynecol 1991;31:128–133.
54. Rai R, Regan L. Antiphospholipid antibodies, infertility and recurrent miscarriage. Curr Opin Obstet Gynecol 1997;4:279–282.
55. Rai R, Cohen H, Dave M, et al. Randomized controlled trial of aspirin plus heparin in pregnant women with recurrent miscarriage associated with antiphospholipid antibodies. BMJ 1997;314:253–257.
56. Elias M, Eldor A. Thromboembolism in patients with the "lupus"-type circulating anticoagulant. Arch Intern Med 1984;144:510–515.
57. Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing the perioperative analgesia and thromboprophylaxis. Reg Anesth Pain Med 1998;23(suppl 2):164–177.
58. Ostensen M, Aune B, Husby G. Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. Scand J Rheumatol 1983;12:69–72.
59. Gabbe SG. Management of diabetes in pregnancy: six decades of experience. In: Pitkin RM (ed) Yearbook of Obstetrics and Gynecology. Chicago: Yearbook, 1980:37.
60. Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. Am J Obstet Gynecol 1981;140:730–736.

61. Reece EA, Homko CJ. Infant of the diabetic mother. Sem Perinatol 1994;18:459–469.
62. Connell FA, Vadheim C, Emmanuel I. Diabetes in pregnancy: a population based study of incidence, referral for care and perinatal mortality. Am J Obstet Gynecol 1985;151:598.
63. Landon MB, Gabbe SG. Fetal surveillance in pregnancy complicated by diabetes mellitus. Clin Obstet Gynecol 1991;34:535–543.
64. Drury MI, Greene AT, Stronge JM. Pregnancy complicated by clinical diabetes mellitus. A study of 600 pregnancies. Obstet Gynecol 1977;49: 51–60.
65. Albert TJ, Landon MB, Wheller JJ, et al. Prenatal detection of fetal anomalies in pregnancies complicated by insulin dependent diabetes mellitus. Am J Obstet Gynecol 1996;174:1424–1428.
66. Moore TR. Diabetes in pregnancy In: Creasy RK, Resnik R (eds) Maternal-Fetal Medicine, 4th edn. Philadelphia: Saunders, 1999.
67. Langer O, Hod M. Management of gestational diabetes mellitus. Obstet Gynecol Clin N Am 1996;23:137–159.
68. Mestman J. Hyperthyroidism in pregnancy. Clin Obstet Gynecol 1997; 40:45–64.
69. Davis LE, Lucas MJ, Hankins GDV, et al. Thyrotoxicosis complicating pregnancy. Am J Gynecol 1989;160:63–70.
70. Khoury JM, Becerra JE, d'Almada PJ. Maternal thyroid disease and risk of birth defects in offspring: a population based case controlled study. Pediatr Perinatol Epidemiol 1989;3:402–420.
71. Millar LK, Wing DA, Leung AS, et al. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Am J Obstet Gynecol 1994;84:946–949.
72. Phillippe HJ, Perdu M, Couderc S, et al. Isolated fetal tachycadia; a diagnostic event of Basedow's disease. Apropos of a case (in French). J Gynecol Obstet Biol Reprod 1994;23:432–434.
73. Greenman GW, Gabrielson MO, Flanders JH, et al. Thyroid dysfunction in pregnancy. Fetal loss and follow-up evaluation of surviving infants. N Engl J Med 1962;267:426–431.
74. Bussen S, Stek T. Positive thyroid autoantibodies and recurrent spontaneous abortions. Hum Reprod 1995;10:2938–2940.
75. Leung AS, Millar LK, Koonings PP, et al. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993;81:349–353.
76. Lockwood CJ, Hobbins JC. Hematological mediated recurrent pregnancy wastage. In: Bern MM, FD Frigelletto (eds). Hematologic Disorders in Maternal-Fetal Medicine. New York: Wiley-Liss, 1990: 1–23.
77. Walker W. Hemolytic disease of the newborn. In: Gairdner D, Hull D (eds) Recent Advances in Pediatrics, 4th edn. London: Church, 1971:119.
78. Cunningham FG, McDonald PC, Gant NF. Williams' Obstetrics, 20th edn. Stamford: Appleton & Lange, 1997:967–1008.
79. Kupperminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilias in women with complications of pregnancy. N Engl J Med 1999;340:9–13.
80. Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. Lancet 1996;348:913–916.
81. Gerdhardt A, Scharf RE, Beckmann MV, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med 2000;342:374–380.
82. Brenner B, Mandel H, Lanir N, et al. Activated protein C resistance can be associated with recurrent fetal loss. Br J Haematol 1997;97:551–554.
83. Ananth CV, Savitz DA, Bowes WA Jr. Hypertensive disorders and stillbirth in North Carolina, 1988 to 1991. Acta Obstet Gynecol Scand 1995;74:788–793.
84. Shah DM, Reed G. Parameters associated with adverse perinatal outcome in hypertensive pregnancies. J Hum Hypertens 1996;10:511–515.
85. Mabie WC, Pernoll ML, Biswas MK. Chronic hypertension in pregnancy. Obstet Gynecol 1986;67:197–205.
86. Jain L. Effect of pregnancy-induced and chronic hypertension on pregnancy outcome. J Perinatol 1997;17:425–427.
87. National Institute on Drug Abuse. Pregnancy & Health. Rockville, MD: NIDA, U.S. Dept. of Health & Human Services, 1994.
88. Chastoff IJ. Drug use and women: establishing a standard of care. Ann N Y Acad Sci 1989.
89. Birnbach DJ, Stein D, Grunebaum A, et al. Cocaine screening of parturients without prenatal care: an evaluation of a rapid screening assay. Anesth Analg 1997;84:76–79.
90. Chastoff IJ, Burns WJ, Schnoll SH, et al. Cocaine use in pregnancy. N Engl J Med 1985;313:666–669.
91. Orser B. Thrombocytopenia and cocaine abuse. Anesthesiology 1991; 74:195–196.
92. Jatlow P, Barash DG, Van Dyke C, et al. Cocaine and succinylcholine sensitivity: a new caution. Anesth Analg 1979;58:235–238.
93. Birnbach DJ, Stein DJ, Thomas K, et al. Cocaine abuse in the parturient: what are the anesthetic implications? Anesthesiology 1993;79: A288.
94. Ramoska E, Sachetti A. Propanolol induced hypertension in the treatment of cocaine intoxication. Ann Emerg Med 1983;14:1112–1113.
95. Harlap S, Shiono PH. Alcohol, smoking and the incidence of spontaneous abortions in the first trimester. Lancet 1980;2:173–176.
96. Feng T. Substance abuse in pregnancy. Curr Opin Obstet Gynecol 1993; 5:16–23.
97. Kistin N, Handler A, Davies E, et al. Cocaine and cigarettes: a comparison of risks. Pediatr Perinatol Epidemiol 1996;10:269–278.
98. Meyer MB, Toniascia JA. Maternal smoking, pregnancy complications and perinatal mortality. Am J Obstet Gynecol 1977;128:494–502.
99. Pastore LM, Hertz-Picciotto I, Beaumont JJ. Associations between stillbirth and 14 medical exposures. Pediatr Perinatol Epidemiol 1999;13: 421–430.
100. Gold EB, Tomich E. Occupational hazards to fertility and pregnancy outcome. Occup Med 1994;9:435–469.
101. Ericson HA, Kallen AJB. Hospitalization for miscarriage and delivery outcome among Swedish nurses working in operating rooms 1973–78. Anesth Analg 1985;64:981–988.
102. Hemminki K, Kyyronen P, Lindbohm M. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs and other potential hazards based in hospitals, based on registered information of outcome. J Epidemiol Community Health 1985;39:141–147.
103. Goulet L, Theriault G. Stillbirth and chemical exposure of pregnant workers. Scand J Work Environ Health 1991;17:25–31.
104. Wilson JG. Environment and Birth Defects. New York: Academic Press, 1973.
105. Cordero JF. Effect of environmental agents on pregnancy outcomes: disturbances of pre-natal growth and development. Med Clin N Am 1990;74:279–290.
106. Mighty H. Trauma in pregnancy. Crit Care Clin 1990;10:623–634.
107. Fildes J, Reed L, Jones N, et al. Trauma: the leading cause of maternal death. J Trauma 1992;32:643–645.
108. Farmer D, Adzick S, Crombleholme W, et al. Fetal trauma: relation to maternal injury. J Pediatr Surg 1990;25:711–714.
109. Connolly AM, Katz VL, Bash KL, et al. Trauma and pregnancy. Am J Perinatol 1997;6:331–336.
110. Shah KH, Simons RK, Holbrook T, et al. Trauma in pregnancy: maternal and fetal outcomes. J Trauma Inj Infect Crit Care 1998;45:83–86.
111. Esposito TJ. Trauma during pregnancy. Emerg Med Clin N Am 1994; 12:167–199.
112. Rogers FB, Rozycki GS, Osler TM, et al. A multi-institutional study of factors associated with fetal death in injured pregnant patients. Arch Surg 1999;134:1274–1277.
113. Curet MJ, Schermer CR, Demarest GB, et al. Predictors of outcome in trauma during pregnancy: identification of patients who can be monitored for less than six hours. J Trauma Inj Infect Crit Care 2000;49:18–24.
114. Ali J, Yeo A, Gana TS, et al. Predictors of fetal mortality in pregnant trauma patients. J Trauma Inj Infect Crit Care 1997;42:782–785.
115. Kissinger DP, Rozycki GS, Morris JA Jr, et al. Trauma in pregnancy: predicting pregnancy outcome. Arch Surg 1991;126:1079–1086.
116. Ma OJ, Mateer JR, Ogata M, et al. Prospective analysis of rapid ultra-

sound performed by emergency physicians. J Trauma Inj Infect Crit Care 1995;38:879–885.
117. Pearlman MD, Tintinelli JC, Lorenz RP. A prospective controlled study of outcome after trauma during pregnancy. Am J Obstet Gynecol 1990; 162:1502–1510.
118. Paull J, Ziccone S. Halothane, enflurane and methoxyflurane and isolated human uterine muscle. Anaesth Intensive Care 1980;8:397.
119. Hall JE, Ng WS, Smith S. Blood loss during first trimester termination of pregnancy: comparison of two anaesthetic techniques. Br J Anaesth 1997;78:172–174.
120. Nathan N, Peyclit A, Lahrimi A, et al. Comparison of sevoflurane and propofol for ambulatory anaesthesia in gynecological surgery. Can J Anaesth 1998;45(12):1148–1150.
121. Kumarasinghe N, Harpin R, Stewart AW. Blood loss during suction termination of pregnancy with two different anaesthetics. Anaesth Intensive Care 1977;25:48–50.
122. American College of Obstetricians and Gynecologists. Clinical management guidelines for obstetrician-gynecologist. Induction of labor. Practice Bulletin N. 10. ACOG, 1999.
123. Veber B, Gauthe M, Michel-Cherqui M, et al. Severe hypertension during postpartum hemorrhage after iv administration of prostaglandin E_2. Br J Anaesth 1992;68:623–624.
124. Caldeyro-Barcia R, Poseiro JJ. Physiology of the uterine contraction. Clin Obstet Gynecol 1960;3:386–408.
125. Zorlu CJ, Yalcin HR, Caglar T, et al. Conservative management of twin pregnancies with one dead fetus: is it safe? Acta Obstet Gynecol Scand 1997;76:128–130.
126. Enbom JA. Twin pregnancy with intrauterine death of one twin. Am J Obstet Gynecol 1985;152:424–429.
127. Randboll I, Chr P, Chr H, et al. Multiple pregnancies with single intrauterine demise. Acta Obstet Gynecol Scand 1999;78:202–206.
128. Visentin L, Leo L, Alemanno MMG, et al. Management of patients with intrauterine fetal death. Clin Exp Obstet Gynecol 1996;23:263–267.
129. Peterson IR, Nyholm HC. Multiple pregnancies with single intrauterine demise. Description of 28 pregnancies. Acta Obstet Gynecol Scand 1999;78:202–206.
130. Santema JG, Swaak AM, Wallenburg HG. Expectant management of twin pregnancies with single fetal death. Br J Obstet Gynaecol 1995; 102:26–30.
131. Dudley DKL, D'Alton ME. Single fetal death in twin gestation. Semin Perinatol 1986;10:65–72.
132. Chestnut DH, Vincent RD Jr, McGrath JM, et al. Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are receiving intravenous syntocin? Anesthesiology 1994;80:1193–2000.
133. Lurie S, Blickstein I, Feinstein M, et al. Influence of epidural anesthesia on the course of labour in patients with antepartum fetal death. Aust NZ J Obstet Gynaecol 1991;31:227–228.
134. Hawkins JL, Koonin LM, Palmer SK, et al. Anesthesia related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–284.
135. Weiner AE, Reid De, Roby CC, et al. Coagulation defects with intrauterine death from Rh isosensitization. Am J Obstet Gynecol 1950;60:1015.
136. Maslow AD, Breen TW, Sarna M, et al. Prevalence of coagulation abnormalities associated with intrauterine fetal demise. Can J Anaesth 1996;43:1237–1243.
137. Parasnis H, Raje B, Hinduja IN. Relevance of plasma fibrinogen estimation in obstetric complications. J Postgrad Med 1992;38:183–185.
138. Peterson IR, Nyholm HC. Multiple pregnancies with single intrauterine demise. Description of 28 pregnancies. Acta Obstet Gynecol Scand 1999;78:202–206.
139. Baglin T. Disseminated intravascular coagulation: diagnosis and treatment. BMJ 1996;312:683–687.
140. Phillips LL, Skrodelis V, King TA. Hypofibrinogenemia and intrauterine fetal death. Am J Obstet Gynecol 1964;89:903–914.
141. Pritchard JA. Fetal death in utero. Am J Obstet Gynecol 1959;14:573–580.
142. Weiner CP. The obstetric patient and disseminated intravascular coagulation. Clin Perinatol 1986;13:705–717.
143. American Society of Anesthesiologists Taskforce on Blood Component Therapy. Practice guidelines for blood component therapy. Anesthesiology 1996;84:732–747.
144. Leon IG. Psychodynamics of perinatal loss. Psychiatry 1986;49:312–324.
145. Fox R, Pillai M, Porter H, et al. The management of late fetal death: a guide to comprehensive care. Br J Obstet Gynaecol 1997;104:4–10.
146. Rushton DI. Prognostic role of the perinatal postmortem. Br J Hosp Med 1994;52:450–454.
147. Chambers DM. The perinatal autopsy: a contemporary approach. Pathology 1992;24:45–55.

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