Pulmonary Problems in Pregnancy

Edited by

Ghada Bourjeily, MD
Karen Rosene-Montella, MD

Humana Press

Pulmonary Problems in Pregnancy

Respiratory Medicine

Sharon R. Rounds, MD, Series Editor

Pulmonary Problems in Pregnancy, edited by Ghada Bourjeily and Karen Rosene-Montella, 2009

Pulmonary Problems in Pregnancy

Edited by

Ghada Bourjeily, MD
Assistant Professor of Medicine
The Warren Alpert Medical School of Brown University
Department of Medicine
Pulmonary and Critical Care Medicine
Women and Infants Hospital of Rhode Island

Karen Rosene-Montella, MD
Professor of Medicine and Ob/Gyn
The Warren Alpert Medical School of Brown University
Chief of Medicine
Department of Medicine
Women and Infants Hospital of Rhode Island

Humana Press

Editors
Ghada Bourjeily
Assistant Professor of Medicine
The Warren Alpert Medical School of Brown University
Department of Medicine
Pulmonary and Critical Care Medicine
Women and Infants Hospital of Rhode Island
Providence, RI
gbourjeily@wihri.org

Karen Rosene-Montella
Professor of Medicine and Ob/Gyn
The Warren Alpert Medical School of Brown University
Chief of Medicine
Department of Medicine
Women and Infants Hospital of Rhode Island
Providence, RI
Karen_Rosene_Montella@brown.edu

ISBN 978-1-934115-12-1 e-ISBN 978-1-59745-445-2
DOI 10.1007/978-1-59745-445-2

Library of Congress Control Number: 2008938362

Cover Illustration: Figure 1, Chapter 22

Printed on acid-free paper

springer.com

Preface

Pregnancy is associated with physiologic changes that help compensate for the increasing demands of the fetus and placenta. Clinically, pregnancy acts as a stress test that unmasks maternal disease and may have long term implications for maternal and fetal health. General obstetricians are often hesitant to care for complex medical problems, and internists to care for pregnant patients, which may create a gap into which sick pregnant women will fall at a time when they are most vulnerable.

Investigation and treatment of pregnant patients with pulmonary disorders is often hindered by both a fear of doing harm to the fetus and by the paucity of data needed to make recommendations. At Women and Infants Hospital, the tertiary women's teaching hospital at Brown University, 10,000 deliveries occur every year. The editors of this textbook are members in the division of obstetric and consultative medicine, a group of obstetric internists and medical specialists that provide consultation to obstetricians on complex medical and pulmonary problems. Most pulmonary and critical care training programs provide little exposure to this population. Despite this, pulmonologists and intensivists are often called upon to provide consultation to critically ill pregnant women.

As editors, our hope was to gather pulmonologists, intensivists, obstetric internists, high risk obstetricians and obstetric anesthesiologists from across the globe to shed light on some common or complex pulmonary issues occurring in pregnancy. The book is divided into three parts. The first few chapters introduce the reader to the normal physiologic changes that occur during pregnancy. The chapter on high altitude is included to illustrate the consequences of chronic hypoxia on maternal and fetal outcomes, to help extrapolate to the effects of chronic pulmonary conditions. The second part reviews general management principles, including diagnostic imaging and prescribing in pregnancy. The final, longest part includes multiple chapters on specific pulmonary disorders. The specific chapters are intended to summarize the available literature, linking science to bedside, and make management recommendations whenever possible. Our goal is that the careful reading of this text will stimulate further investigation into this fascinating and under explored area of medicine.

Ghada Bourjeily, MD
Karen Rosene-Montella, MD

Contents

Acknowledgments

Ghada Bourjeily. My heartfelt gratitude and deepest appreciation to my husband Fadlo, and my children Christopher and Naya for their tremendous support and understanding through the time it took to get this work to completion; to my mother and late father, for their encouragement and nurturing; Gwen Lariviere for her technical and secretarial assistance with this textbook.

I am also indebted to Dr. Michael Paglia, a high risk obstetrician at Women and Infants Hospital of Rhode Island and Brown University and Dr. Matthew Sermer, a high risk obstetrician at Mount Sinai Hospital and University of Toronto for their assistance with obstetrical and fetal issues.

Last but not least, I am deeply grateful to Dr. Abraham Rudolph, a perinatologist and fetal physiologist at the University of California, San Francisco, for his invaluable guidance and help with fetal matters.

Karen Rosene-Montella. My most sincere gratitude to my husband Mark, and my children Brian and Julia who have shared me with academic medicine for many years; Dr. Alan Leff for his support and encouragement; Doreen Hoogasian for her secretarial and technical assistance.

Contributors

Muhanned Abu-Hijleh, MD, FCCP, Interventional Pulmonology and Special Procedures Unit, The Division of Pulmonary, Critical Care and Sleep Medicine, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

Kathleen Akgun, MD, Pulmonary and Critical Care Section, Yale School of Medicine, New Haven, CT

Alejandro C. Arroliga, MD, Division of Pulmonary Medicine and Critical Care Medicine, Scott and White Hospital & Clinic, Texas A&M University Health and Science Center, Temple, TX

John Robert Bach, MD, Department of Physical Medicine and Rehabilitation, The New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark NJ

Venkata DP Bandi, MD, Department of Medicine, Pulmonary and Critical Care, Baylor College of Medicine, Houston, TX

John B. Bass, Jr., MD, Department of Internal Medicine, College of Medicine, University of South Alabama, Mobile, AL

Ghada Bourjeily, MD, Department of Medicine, The Warren Alpert Medical School of Brown University, Women & Infants Hospital, Pulmonary and Critical Care Medicine, Providence, RI

Marie M. Budev, DO, MPH, The Cleveland Clinic, Cleveland, OH

James N. Byrd, Jr., MD, Division of Pulmonary Medicine, University of South Alabama, Mobile, AL

Brian Casserly, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI

Kristen Cotter, MD, MPH, Department of Obstetrics and Gynecology, Women and Infants Hospital of Rhode Island

Carolyn M. D'Ambrosio, MD, MS, DABSM, The Center for Sleep Medicine, Tufts-New England Medical Center, Tufts University School of Medicine, Boston, MA

Peter G. Gibson, MD, Department of Respiratory and Sleep Medicine, Level 3, John Hunter Hospital Locked Bag 1, HRMC, Newcastle NSW, Australia

Michael A. Gropper, MD, PhD, Department of Anesthesia and Perioperative Care, Critical Care Medicine, University of California San Francisco, San Francisco, CA

Jesse Hall, MD, Department of Medicine, Pulmonary and Critical Care Medicine, The University of Chicago, Chicago, IL

D. Kyle Hogarth, MD, Department of Medicine, Pulmonary and Critical Care Medicine, University of Chicago, Chicago, IL

Shirley F. Jones, MD, Scott and White Hospital and Clinic, The Cleveland Clinic, Texas A & M University Health Science Center, Temple, TX

Samar Khan, DO, Hudson Valley Critical Care Group, Pulmonary and Critical Care, Vassar Brothers Medical Center, Poughkeepsie, NY

James R. Klinger, MD, Respiratory Care Unit, Division of Pulmonary Sleep and Critical Care Medicine, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

Kelvin Lam, MD, Tufts-New England Medical Center, Boston, MA

Lucia Larson, MD, Division of Obstetric and Consultative Medicine, Department of Medicine, Women and Infants Hospital of Rhode Island

Alan R. Leff, MD, Department of Medicine, The University of Chicago, Chicago, IL

Samir Malhotra, MD, James Hogg iCAPTURE Center for Cardiovascular & Pulmonary Research, St. Paul's Hospital, Department of Medicine (Respiratory Division), Vancouver, BC, Canada

Meredith C. McCormack, MD, MHS, Johns Hopkins University School of Medicine, Baltimore, MD

Niharika Mehta, MD, Department of Obstetric & Consultative Medicine, Women & Infants Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

Nuala J. Meyer, MD, Department of Medicine, University of Chicago, Chicago, IL

Margaret Miller, MD, Division of Obstetric and Consultative Medicine, Department of Medicine, Women and Infants Hospital of Rhode Island

Vahid Mohsenin, MD, Yale Center for Sleep Medicine, Yale University School of Medicine, New Haven, CT

Uma Munnur, MD, Department of Anesthesiology, Baylor College of Medicine, Houston, TX

Vanessa E. Murphy, BMedChem(Hons), PhD, Department of Respiratory and Sleep Medicine, Hunter Medical Research Institute, Port Waratah Coal Services, John Hunter Hospital, Newcastle NSW, Australia

Jill Newstead-Angel, MD, FRCP, General Internal Medicine, Obstetrical Medicine, Department of Medicine, Royal University Hospital, University of Saskatchewan, Saskatoon, SK, Canada

Michael S. Niederman, MD, Department of Medicine, Winthrop University Hospital, Mineola, NY

Stéphanie Pouwels-Fry, MD, Clinique des Maladies Respiratoires, Hôpital Albert Calmette, Boulevard du Pr. Jules Leclercq, Lille Cedex, France

Raymond O. Powrie, MD, Division of Obstetric and Consultative Medicine, Department of Medicine, Women and Infants Hospital of Rhode Island

Karen Rosene-Montella, MD, Department of Medicine, Women & Infants Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

Francoise J. Roux, MD, PhD, Pulmonary Critical Care, Yale University School of Medicine, New Haven CT

Jesús Sancho, MD, Respiratory Care Unit, Respiratory Medicine Department, Hospital Clínico Universitari, Universitat de Valencia, Valencia, Spain

Gregory A. Schmidt, MD, Division of Pulmonary Diseases, Department of Internal Medicine, Critical Care and Occupational Medicine, University of Iowa Healthcare, Iowa, IA

Mathew Sermer, MD, FRCSC, Mount Sinai Hospital, Toronto, ON Canada

Isabelle Tillie-Leblond, MD, PhD, Clinique des Maladies Respiratoires, Hôpital Albert Calmette, Lille Cedex, France

Benoît Wallaert, MD, Allergy and Clinical Immunology Department, Clinique des Maladies Respiratoires, Hôpital Albert Calmette, Lille Cedex, France

Pearce G. Wilcox, MD, Respiratory Division, The James Hogg iCAPTURE Center for Cardiovascular, St. Paul's Hospital, University of British Columbia, and Pulmonary Research, Vancouver, BC, Canada

Robert A. Wise, MD, Johns Hopkins Asthma and Allergy Center, Baltimore, MD

Richard N. Wissler, MD, PhD, Associate Professor of Anesthesiology and Obstetrics & Gynecology, Obstetric Anesthesiology, University of Rochester, School of Medicine and Dentistry, Rochester, NY

Part I

Normal Pregnancy

1

Physiological Transition from Fetal to Neonatal Life in Pregnancy

Alan R. Leff

Keywords: gestation, fetal circulation, lung growth and development, surfactant, embryology, fetal respiration, fetal hemoglobin

Evolution of Air-Breathing Respiration

More than 3 billion years after the formation of the earth, vertebrate life first originated in the sea. Jawless eel-like vertebrates and placoderms (primitive fish, now extinct) evolved initially, and 100 million years later in the Devonian period of the Paleozoic era, cartilaginous fish (the shark families) and boney fishes first appeared in the sea. By the end of the 40 million year Devonian period, boney fishes similar in many ways to the lungfish of today first crawled onto land. These evolved into the crossopterygian fishes, which had some capacity to breath air and use their fins to move across the remaining one third of the world not previously inhabited by vertebrates—dry land *(1, 2)*.

Instead of surviving on the paltry amounts of oxygen dissolved in the sea, air contained more than 20% oxygen. The prospects for improved energy utilization were boundless. Full air breathing was slow to evolve; in all, more than 100 million years passed between the first land-visitation boney fishes and the first fully air breathing mammals, the reptiles. Reproduction on land is a remarkable adaptation. Progeny born to non-mammalian aquatic species still extract oxygen from water. In land mammals that retain their fetuses in utero until the moment of birth, conversion of respiration for non-aquatic life must occur in a matter of minutes. Fetuses receiving their oxygen supply by placental diffusion from the maternal circulation change their entire mode of cardiovascular circulation, expand their lungs, and become air-breathing neonates. The process is as flawless as it is spectacular, and the mechanisms enabling this transformation remain incompletely understood. Some of the physiological events, however, can be described. This information is useful in understanding not only fetal survival during gestation, but also in understanding mechanisms of disease later in life, e.g., cor pulmonale and pulmonary hypertension during hypoxemia in adults. These events are outlined in brief detail in this chapter. Much of this work is taken from several chapters of a textbook written by the author and a colleague *(3)*. Considerations of lung regeneration in disease are derived in large part from the *Proceedings of the American Thoracic Society: Lund Conference VI on Lung Growth and Regeneration in Human Disease (4)*.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_1

Fetal Respiration

The embryo grows from a single cell to a fully formed fetus during a 40-week intrauterine life. The fetal metabolic rate exceeds substantially that of the mother, and fetal oxygen consumption provides the energy for growth and development. Gas exchange occurs in the fetus solely through diffusion. There is no physiological admixture of maternal and fetal blood. In cases where potential admixture in Rh blood groups might have occurred during pregnancy, immunoglobulin directed at Rh incompatibilities is administered immediately postpartum to the mother to prevent immune processing and development by the mother of blood type incompatibility in subsequent pregnancies.

As well as immune globulins, nutrients, e.g., glucose, essential minerals, and vitamins, and amino acids, also diffuse across the placenta. Hemoglobin in fetal blood derives its iron stores from the mother. All of this exchange occurs through the placenta, which is made by the fetus, and through large sinusoids at the uterine-placental interface. Finger-like chorionic villi aid the exchange process (Figure 1.1), and oxygen is transferred from the mother to the fetus by gas exchange across fetal and maternal capillary membranes. An astonishing cascade of hypoxemic events develops in the oxygen exchange process from the fetus to the mother (Figure 1.2). The uterus receives fully oxygenated maternal blood containing 20 ml O_2/100 ml blood (vol.%). The uterus consumes approximately 5 vol.% arterial blood, reducing venous oxygen content to 15 vol.%. This corresponds to a decrease in PO_2 to about 40 mmHg in the umbilical vein. Accordingly, the maternal contribution to fetal arterial blood oxygenation is blood for gas exchange having a PaO_2 of < 40 mmHg. At the same time, the umbilical artery having a fetal venous saturation of 20 mmHg equilibrates with the placenta to produce a PaO_2 in the fetus of slightly

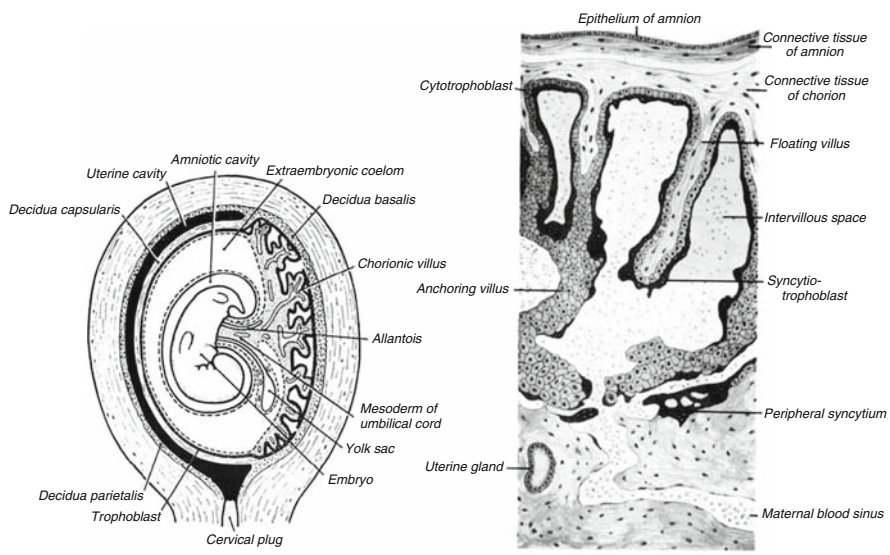


Figure 1.1 Aquatic respiration in fetal life. Gas exchange occurs across maternal and fetal membranes. There is no intermixing of blood. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 10 (137–148). By release of copyright to the authors

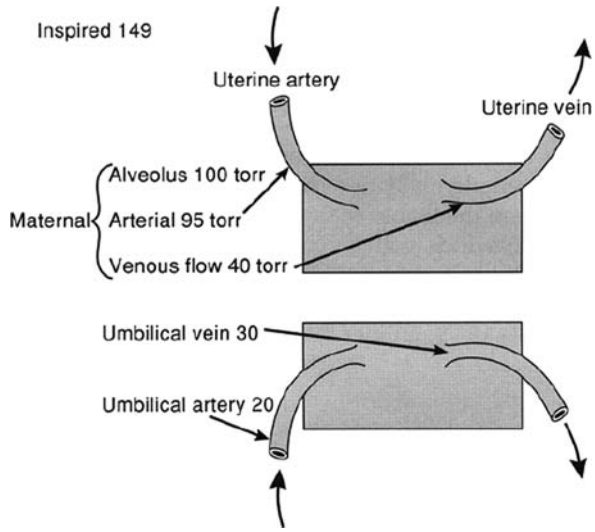


Figure 1.2 Cascade of hypoxemia from maternal to fetal circulation. Uterine extraction accounts for the greatest decrease in PO_2, which falls to 40 torr before equilibration with fetal umbilical arterial blood, which has a PO_2 of 20 torr following tissue extraction and admixing of non-reoxygenated blood From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 10 (137–148). By release of copyright to the authors

greater than 30 mmHg, which is delivered into the umbilical vein of the fetus through the ductus venosus as it joins the inferior vena cava (Figure 1.3).

Blood returning from the superior (fully non-oxygenated) and inferior vena cavas returns to the right heart and is shunted away from the fetal lung, which is not engaged in the process of respiration. Most of the blood going to the pulmonary arteries of the fetus through the right ventricle is shunted directly into the aorta through the ductus arteriosus. The ductus arteriosus closes shortly after birth, but occasionally remains patent, requiring a relatively minor surgical intervention. The hypoxic content of the fetal blood is sensed by the pulmonary arteries as well, which through an elaborate mechanism initiates pulmonary hypoxic vasoconstriction and increases the hydrostatic pressure within the right heart. This causes shunting of blood flow away from the lungs, e.g., from the right atrium into the left atrium through the foramen ovale, a flap-like window in the atrial septum. After birth, when the fetus develops adult-level PaO_2, pulmonary vasodilation occurs and the system pressure of the left circulation exceeds that on the right, closing the window that was the patent foramen ovale.

The hypoxemic response of the pulmonary arterial circulation is retained for life. Under circumstances of significant hypoxemic events ($PaO_2 < 50$ mmHg), pulmonary vasoconstriction returns. This may cause selective right heart failure (cor pulmonale). In most cases, the foramen ovale has sealed itself over the years between fetal and adult life, but occasionally the foramen does not seal—it merely remains closed because left heart pressure exceeds right heart pressure in normal circumstances. Under circumstances of extreme pulmonary hypertension, non-reoxygenated blood may be shunted directly into the adult pulmonary circulation. In primary pulmonary hypertension, an idiopathic disease of pulmonary vascular sclerosis, right heart pressures may become quite high because of a pathological (obliterative) increase in the pulmonary resistance. In the presence of a patent

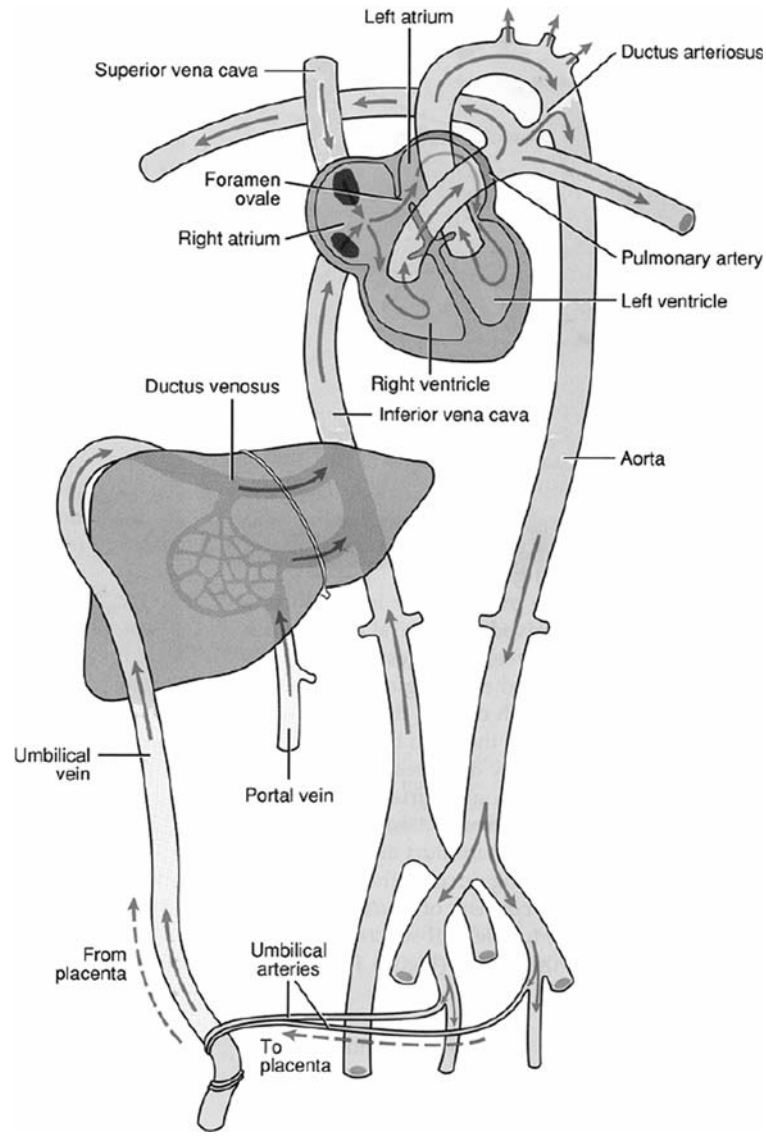


Figure 1.3 The fetal circulation. Blood returning from the placenta with a PO_2 of barely more than 30 torr is shunted into the inferior vena cava where it mixes with fully unoxgenated blood returning from the superior vena cava. Shunted away from the lung by the foramen ovale and ductus arteriosus, this "arterial" blood is sufficient nonetheless to meet fetal oxygen demands because of the contour of the oxygen-hemoglobin dissociation curve, which is determined by fetal hemoglobin (Figure 1.4). From: Leff A and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 10 (137–148). By release of copyright to the authors

foramen ovale, the high pressure also may cause shunt of venous blood directly into the arterial circulation.

In the fetus, the right atrium also receives blood that has supplied all organs returning venous blood from the superior vena cava, but which never circulates through the placenta for re-oxygenation (Figure 1.3). Consequently, the PaO_2 of the fetus never significantly exceeds 30 mmHg.

The situation is quite chaotic even upon close study. Poorly or non-reoxygenated blood delivered into the fetal equivalent is mixed with already poorly oxygenated blood that is derived from a venous maternal PaO_2 by the anatomical arrangement by which the placenta begins its equilibration with the maternal venous blood from the uterus. [By analogy to adult circulation, the umbilical artery brings deoxygenated blood to the placenta and is the maternal equivalent of the pulmonary artery, which sends venous blood to be oxygenated by the lung; and the uterine vein is the maternal equivalent of the pulmonary vein, returning oxygenated blood (however poorly accomplished) through this fetal equivalent of the adult pulmonary vein.]

The process of oxygen diffusion is also more complex in the fetus than in the air-breathing neonate. Diffusion is generally measured for carbon monoxide, but the same principles apply for oxygen. The equation for the diffusing capacity for carbon monoxide is written as the inverse of the conductance (i.e., as resistance), so that serial diffusion barriers are additive. Diffusing capacity for carbon monoxide, which is purely flow limited, is

$$1/DL_{CO} = 1/D_M + 1/\varphi \cdot 1/Vc$$

where DL_{CO} is the total diffusing capacity, D_M is the the diffusing capacity of the alveolo-capillary membrane, $1/\varphi$ is the diffusion constant, and $1/Vc$ is the blood hemoglobin concentration. Assuming the diffusion constant remains roughly the same in both circumstances (i.e., the affinity of hemoglobin for CO), any increase in DM will increase the resistance to diffusion. For the mother, diffusion barriers include the alveolar epithelium + the common basement membrane shared by the epithelium of alveolar type I cells + the endothelium of the pulmonary capillary + the maternal red blood cell membrane. For the fetus, all of the same barriers are present, but there is transfer across the maternal red cell + the epithelial basement membrane and chorionic membrane capillary + the fetal red blood cell membrane. Although never specifically measured, it may be assumed that, unlike any human condition in health or disease, fetal gas exchange is partially diffusion-limited for oxygen to a degree that adult gas exchange is not. All of this serves to ensure that fetal hemoglobin will never have greater than a $PO_2 > 30$ mmHg to supply the mightily metabolic fetus in its growth and development demands.

Carbon dioxide also must be cleared by the same circulatory arrangement, which is far less complicated by the situation by which it is transported. Most CO_2 is carried by plasma bicarbonate and equilibrates in the absence of the cascade caused by uterine oxygen extraction by diffusion across the placenta to the maternal circulation.

Returning to the fetal oxygen requirement, the critical question is how the fetus extracts sufficient oxygen to survive, even to prosper and grow. This is accomplished by the differences in contour of the maternal and fetal oxygen–hemoglobin dissociation curve. These curves are represented schematically in Figure 1.4. When the mother extracts 5 vol.% oxygen, the corresponding PvO_2 is between 30 and 40 mmHg. The slope of the fetal oxyhemoglobin desaturation curves is extremely friendly to these plasma concentrations of oxygen. Having a steeper slope and a great oxygen-carrying capacity, fetal hemoglobin, which is retained throughout gestation and for a while after delivery, is highly receptive to a PaO_2 of 30–35 mmHg. Its steep dissociation slope allows a mere change of 10 mmHg to supply 4.6 vol.% oxygen to fetal tissues. The fetus may be very busy at the process of gestation, but it has no other demands to meet, floating weightlessly in a

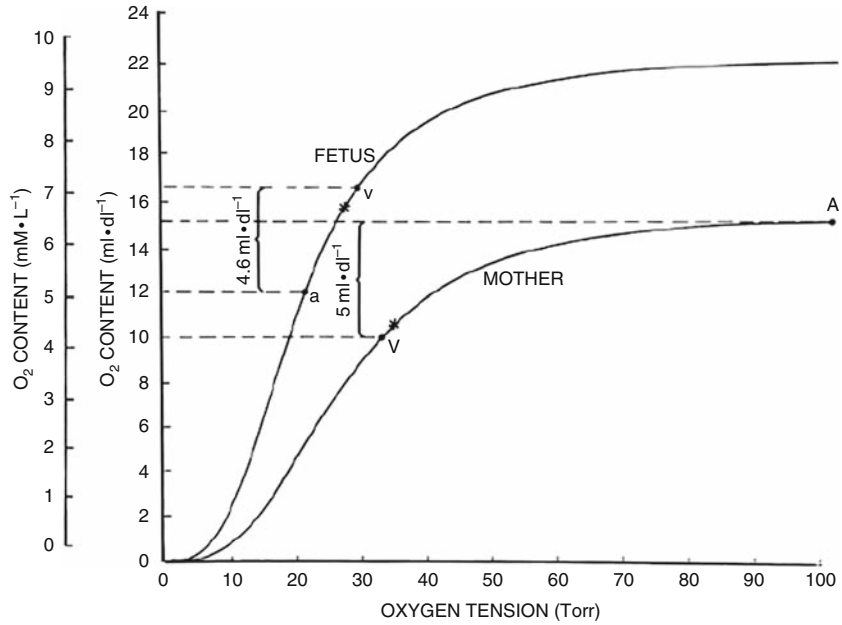


Figure 1.4 Maternal and fetal oxygen-hemoglobin dissociation curve. Maternal blood gives up only 5 volumes per cent (vol%) oxygen with a decrease of 60 torr in oxygen tension. By contrast, fetal blood, with it steeper slope and greaer oxygen carrying capacity is able to provide 4.6 vol% oxygen with a decrease of only 10 torr in oxygen tension. Thus, equilibration with the venous blood of the mother and the incremental placental barrier to diffusion do not impair adequate oxygen uptake to the fetus. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 10 (137–148). By release of copyright to the authors

non-exercising state in utero. This delivery of oxygen to tissues is thus most suitable for growth and development. By comparing the fetal oxyhemoglobin curve to the adult curve, it is clear that this curve is also highly suitable for survival in air breathing. As the neonate exercises relatively little at birth, the persistence of fetal hemoglobin suffices until it is replaced by adult hemoglobin, which has a contour more suited to meet the metabolic demand of metabolism and locomotion in an air-breathing world *(5)*.

Lung Growth and Development

The lung buds from the foregut during the sixth week of fetal development. The proximal portion develops as the larynx and trachea, which separate from the esophagus. The initial bud from the terminal bronchus to the pleura is within 1 mm of the pleura. As development continues, each branch sacrifices itself to become a daughter branch and is precisely choreographed in time and space by a selective genetic expression of appropriate growth and vascular-generating cytokines *(6)*. Stem cells in each budding generation respond to these signals, and the lung begins a process of differentiation that will last $>$ 8 years. Terminal bronchioles retreat from the pleural margin as they are systematically replaced by respiratory bronchioles and then respiratory saccules by the 28th week of gestation (Figure 1.5). The evolution to alveolar growth starts at about 20 weeks.

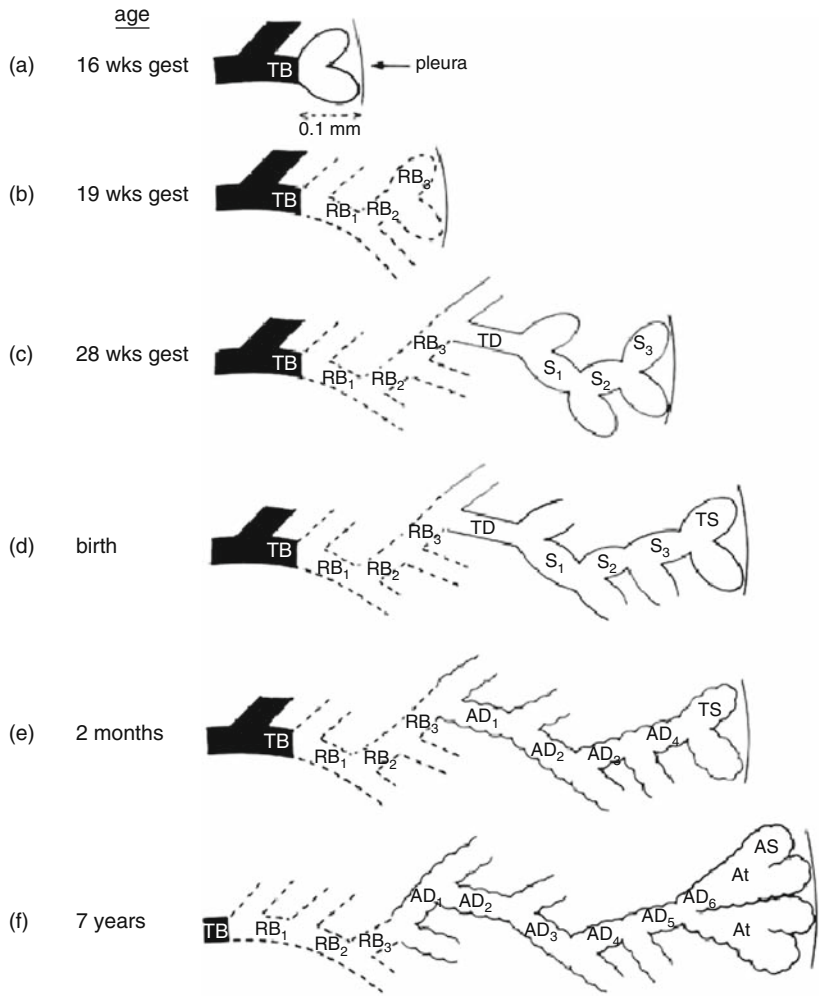


Figure 1.5 Development of gas exchange units. At 6 weeks, a primitive bud already approaches the pleural surface. In morphogenesis, each parent unit develops advancing daughter units that create successive generations of airways. As the daughter units multiply and advance to become terminal saccules, the terminal bronchiole retreats from the pleura to become a more central airway. Note that fetuses are born without alveoli and full morphogenesis into adult units does not occur until about 8 years after birth. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 10 (137–148). By release of copyright to the authors

At birth, neonates do not have alveoli. Rather, they have terminal saccules, which evolve over the next 8 or so years into the "cluster of grape" architecture that characterizes the adult arrangement of alveoli. Alveoli are connected to each other by microscopic pores of Kohn, which may play some role in preventing atelectasis if there is proximal obstruction, although some dispute this role of the pores. By the 25th week of gestation, rapid division and growth of lung units involved in gas exchange begins. At this time, the total number of collagenous airways and mucous gland is fully differentiated. Maturation of the lung is fully determined hereafter by

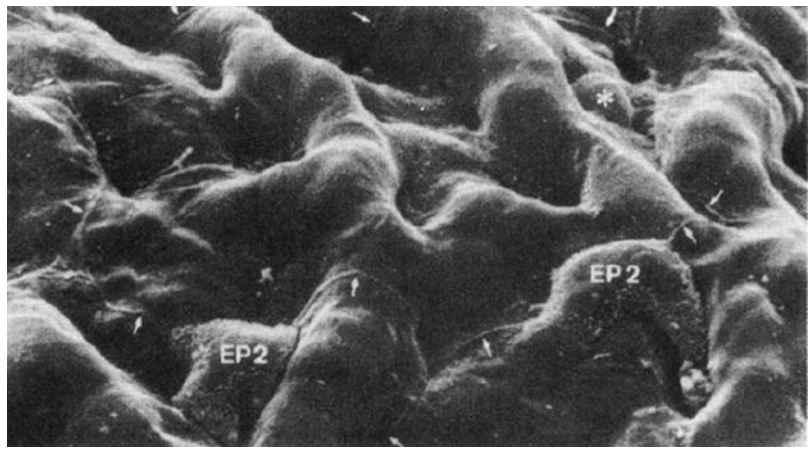


Figure 1.6 Scanning electron photomicrograph of an alveolus. Note that the vast amount of surface area is take up by Type I alveolus, which functions to exchange gas. Type II alveoli (2 are shown) are <1% of the total surface area, but these cells synthesize the all-important surfactant. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 12 (155–184). By release of copyright to the authors

the rate of saccular development and maturation of type II alveolocytes. Type I alveolocytes eventually occupy 99% of the surface area of an alveolus; type II cells occupy 1%, but these cells produce the all-important pulmonary surfactant that is essential for respiration (Figure 1.6).

Importance of Surfactant

Surfactant overcomes surface cell forces that allow for lung expansion at birth and allows the neonate to overcome the surface-active force for tidal respiration. The ability of a pre-mature neonate to survive depends on both the maturation of lung units and the maturation of surfactant production to permit ventilation. Without surfactant, lung units close at tidal volume and cannot be reopened. This circumstance produces a shunt, whereby non-ventilated lungs are fully perfused. Venous blood thus enters the arterial circulation. Unlike circumstances whereby ventilation/perfusion mis-matching can be obviated by an increase in oxygen concentrations, the closed ventilatory units of a shunt cannot be oxygenated at any concentration of oxygen. Prior to the development of exogenous surfactant and mechanical ventilation, premature infants could be treated only with pure oxygen. Survival was poor, and many infants developed retrolental hyperplasia, a condition of ocular fibrosis causing permanent blindness that results from high sensitivity of neonates to 100% oxygen.

Surface Tension

The lung is a "wet organ." The layer of liquid lining the epithelial surface of the alveolus produces surface tension. Distention of the lung for inspiration requires overcoming the normal elastic recoil of the lung inherent in lung elastic tissues and the additional contribution of lateral surface tension forces imposed by the mutual attraction that polar hydrogen (+) and oxygen (–) molecules have for each other.

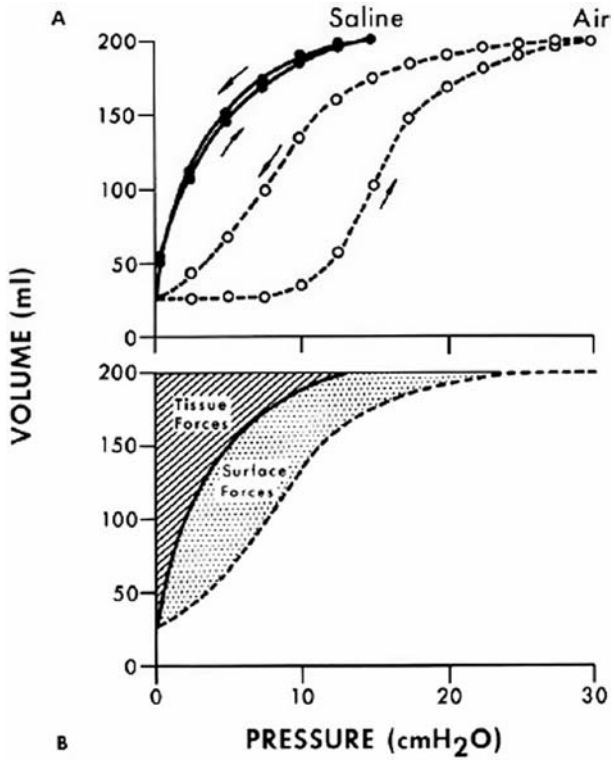
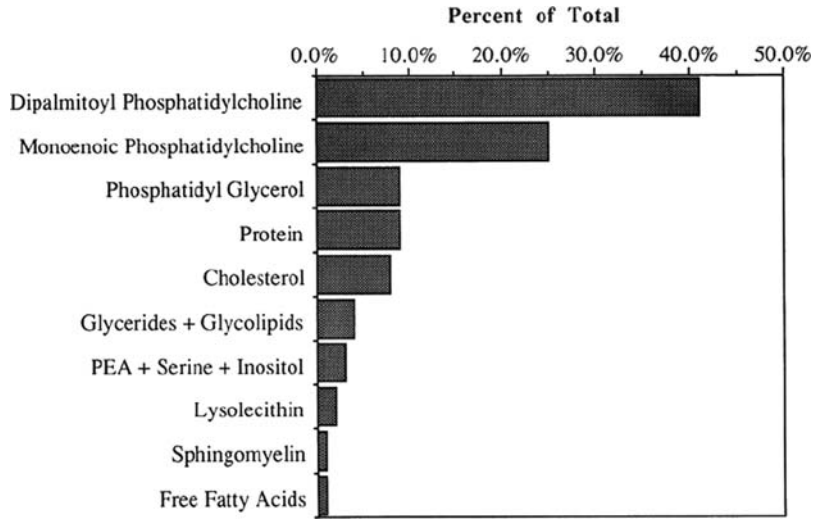


Figure 1.7 Compliance curve of a mouse lung in vivo. A: Comparison of compliance in a lung fully immersed in saline and an excised lung having an air-water interface, as in life. There are no surface tension forces in the fully immersed lung, which has considerably greater compliance than the lung inflated in air. Note also the hysteresis of the inflation-deflation curve of the air-water interface lung [see text for explanation]. B: Intergrated area (equal to work of breathing) of the saline lung (representing work to overcome tissue elastance; hatched area) and the average pressure-volume curve of the lung inflated or deflated in air (representing the work to overcome surface tension forces; dotted area). Note that surface tension force comprises at least 50% of the work of breathing overall. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 1 (3–23). By release of copyright to the authors

With a thin layer of fluid at the alveolar surface, there are lateral forces that impose upon each other based on this polarity to make the lung even more elastic, i.e., less distensible. Figure 1.7 demonstrates the difference between the compliance curves of a mouse lung immersed in saline and one having an air–water interface. Total submersion of an excised lung during inflation requires substantially less distending pressure than the same tissue having an air–water interface, as it occurs in nature. The incremental forces distending are those of surface tension. In Figure 1.7, the work of breathing is the integrated area of each plot of the lower portion of the figure. Work is derived as follows: Volume is expressed in cubic units, e.g., cm^3; pressure is force/unit area (e.g., force/cm^2). The integrated areas for each curve (tissue forces; surface forces) of Figure 1.7 are expressed in units of volume $\times$ pressure $=$ $cm^3 \times$ force/cm^2 $=$ force $\times$ distance $=$ work. This figure illustrates that at least half of the work of breathing, especially at low lung volumes, is work required to overcome surface tension forces.



Figur 1.8 Composition of surfactant. The phosphatidyl cholines are the predominant components and account for detergent effect of surfactant. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 1 (3–23). By release of copyright to the authors

Investigations performed approximately 50 years ago demonstrated that the natural surfactant (Figure 1.8) was composed predominantly of phosphatidyl choline. Other products taken from airway lavage fluid appear to play no critical role in the surface tension breaking (i.e., detergent) properties of surfactant. Surfactant also works best when its molecules are compacted. Figure 1.9 demonstrates a Clements' frame, which is used to measure surface tension when surface fluid molecules are compacted or decompacted at different surface areas. By moving the barrier inward, surfactant molecules floating on the top are compressed, and the effect of compacting water molecules on surface tension can be

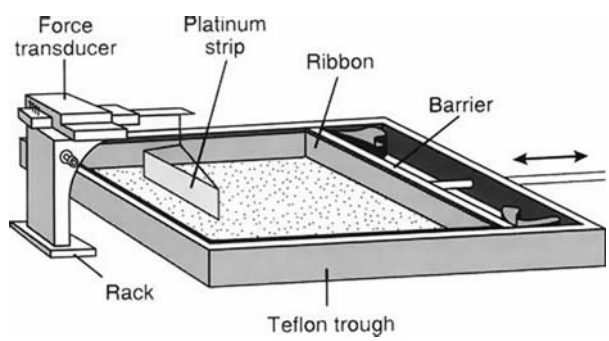


Figure 1.9 A Clements' Frame. Surface tension is measured by the force transducer attached as the platinum blade interfaces with the first molecular layer at the surface. The ribbon compresses or decompresses surface molecules to mimic the action of the lung during inspiration and exhalation. From: Leff A. and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993. Chapter 1 (3–23). By release of copyright to the authors

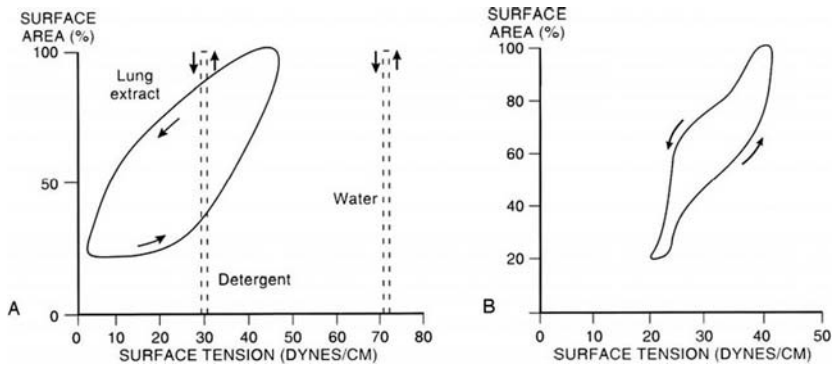


Figure 1.10 (A) Area-Surface tension diagram of water, commercial laundry detergent and lung extract as a detergent (surfactant). Note that at low areas, comparable to deflated lung volumes, surface tension is practically reduced to zero. Commercial detergent is much less effective than naturally occurring surfactant. The natural surfactant curve also has hysteresis as does the pressure-volume curve of the lung in real-life [see text for explanation]. (B) The pressure-volume curve of a premature fetus, which lacks maturation of type II alveolocytes to produce surfactant. Chapter 1 (3–23). By release of copyright to the authors

measured. Water has a surface tension of 70 dynes/cm (Figure 1.10). Because water molecules are already maximally compacted by their polar attraction to each other, changing the surface area has no effect—the molecules cannot be either compacted or decompacted by change in surface area. As shown in Figure 1.10, adding a commercial laundry detergent allows the compound to get between some of the surface hydrogen bonds and thus lessens surface tension, in this case to 30 dynes/cm. However, adding surfactant obtained from bronchial washings causes near-total abolition of surface tension.

The detergent properties of surfactant are highly area dependent. The more compacted the molecules, the more effective the detergent force of surfactant. At maximally compacted areas, naturally occurring surfactant is unsurpassed as a detergent. Note the hysteresis in the expansion/compression curves of surfactant, which corresponds to the hysteresis in Figure 1.7 for the lung having an air–water interface. This reflects the initial difficulty in breaking surface tension forces at low lung volumes, as distending pressure is applied; the detergent forces of surfactant molecules begin to lower surface tension. Correspondingly, the deflation curve has relatively lower surface tensions at the same corresponding pressures. Without surfactant, distension of lung units is greatly impaired. Figure 1.10 (right) is a schematic curve showing that surface tension forces are increased over the full range of areas as a result of defective production of surfactant in a premature neonate. These are the biophysical correlates of the shunts that premature infants develop—infants who lack alveolar type II cells or surfactant product. Artificial surfactants and treatment of the mother prior to birth with corticosteroids that cross the placental barrier contribute hugely to the salvage of infants born during the critical phase of gas exchange units. Overall, survival is possible even before the 28th week with modern technology, which includes mechanical ventilation. Prognosis improves greatly with each week that the neonate ages toward term. At 32 weeks, prognosis may be quite encouraging; by 36 weeks, prognosis is not significantly different than for term infants.

Cellular Morphology and Morphogenesis

Cells Derived from Entoderm

Goblet and serous cells are cells that line the conducting airways of the lung. Together, these cells determine the nature of the ciliary blanket of mucus that lines the conducting airways of the lung. This lining exists in a sol–gel state, which must be optimal. Mucus secretions that are too thick will trap foreign particles from reaching the delicate small airways of the lung, but cannot be swept to the mouth by the mucociliary escalator because the cilia cannot propel mucus of high viscosity. Such is the case in cystic fibrosis (CF), where infection is constant as bacteria are trapped in excessively viscous mucus. Ultimately, most CF patients succumb to respiratory failure and severe infection from the genetic transport defects in the CFTR. Mucus is rarely too thin to be effective; but in such cases, transport also would be ineffective, as the cilia would just wave through liquid without sufficient ability to produce a watery agent. Goblet cells and mucous glands, which are autonomically innervated, exist in the epithelium of the large conducting airways of the lung. In these units there is no gas exchange. Conditioning of air to proper temperature and cleansing the airways of infectious agents and particulates are the functions of these airways (Figure 1.11). There is a gradual transition, with loss of mucus-producing cells and cartilaginous support structures from the conducting airways to the alveolus, which is the thinnest of all possible membranes, designed to dialyze the alveolar gas by removing carbon dioxide and replenishing oxygen.

Ciliated cells are seen first at the 13th week. These cells follow one of the oldest morphologically conserved patterns in nature. In all tissues of all species from all ages, cilia are arranged in a 9 + 2 pattern (Figure 1.12). The central dynein arms contain ATPase, which is essential for contraction. These tubules thus are

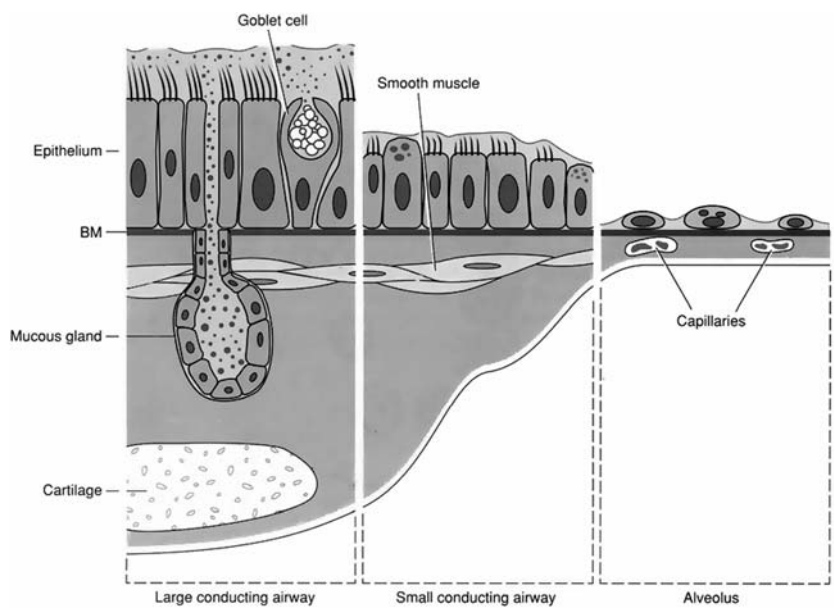


Figure 1.11 Schema of the anatomical reorganization of the airway from conducting airways, which are supportive structures that trap particulates and infectious agents from reaching delicate alveoli, to the ultra-thin and fragile alveolar-capillary membrane. Chapter 12 (155–184). By release of copyright to the authors

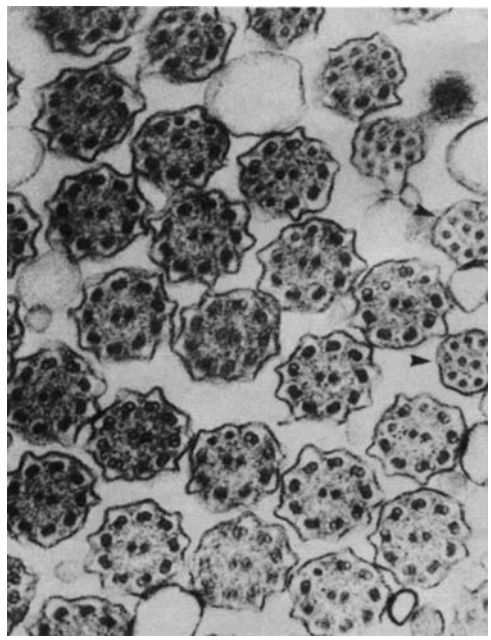


Figure 1.12 The highly conserved 9 + 2 pattern of airway cilia. The identical pattern is seen in flagella on one-cell organisms. Chapter 12 (155–184). By release of copyright to the authors

likely responsible as well for coordination of the ciliary beat, the coordinated wave that propels continuously the secretions of the lung away from the helpless alveoli and toward the mouth. In the absence of the dynein arms, cilia are dysfunctional and cannot beat. Best known among inherited syndromes of ciliary motility is Kartagener's syndrome. This mutation is often associated with partial or complete situs inversus, which may have its attendant problems, especially in cases of partial situs inversus. Kartagener's syndrome is associated with the development of bronchiectasis over life and reproductive sterility, due to lack of ciliary motility in the sperm.

Clara cells remain more of a curiosity and lack a fully defined function. It is believed that Clara cells may be important in the regeneration of injured epithelial cells in the bronchi.

Kulchitsky cells are neuroendocrinological elements, which appear by week 15 in the fetus and become less numerous in adult life. These cells produce some bioactive amines, the significance of which is not established. Kulchitsky cells are the parent cells in bronchial carcinoid tumors, where secretion of bioactive amines is thought to cause the characteristic symptoms of carcinoid syndrome in adults. Kulchitsky cells are more abundant in the gastrointestinal tract, as is the origin of carcinoid syndrome.

Alveolocytes have been covered in detail in preceding sections and are listed for the sake of embryological completeness. To summarize, the massive area of the type I alveolocytes is the gas exchange surface of the lung. The 1% of the alveoli dedicated to type II cells is the site of surfactant production.

Cells Derived from Mesoderm

Smooth muscle cells. Smooth muscle in airways is the likely evolutionary vestige of the swim bladder. Some degree of basal smooth muscle tone exists in all persons,

largely due to tonic parasympathetic activity. Parasympathetic nerves innervate human airway smooth muscle to the very distal conducting airways. Parasympatholysis causes a decrease in airway resistance. Airway resistance after morphogenesis is complete, is 1–2 cm H_2O/l/s. Airway resistance is greater in normal infants. The decrease in resistance with maturation has been attributed both to enlargement of conducting airways (80–90% of the resistance to airflow in the lung is derived from the first six generations of airways) and to progressive branching, which occurs until 8 years of age.

As airway smooth muscle has no known function in humans, there has been little evolutionary pressure to eliminate it. Smooth muscle contraction causes asthma, but humans are the only species that get true asthma. The reason for this remains unclear. If there is an evolutionary advantage to this polygenomic syndrome, such evidence has not been presented.

Smooth muscle also exists *in pulmonary blood vessels* and is responsible for the distribution of blood flow in the lung. This has been discussed in detail earlier. Development of vascular smooth muscle in the fetus is nearly complete by week 14 of gestation.

Vascular endothelium is the rough functional homolog of airway epithelium. It is the single cell layer lining the vessel. Capillary endothelial cells are about 50% of the cells lining the lung and have an intimate association with type I pneumocyte in alveolar gas exchange. Both endothelium and epithelium have numerous complex physiological and signaling functions in adults, a discussion beyond the purview of this review.

Fibroblasts. These cells of the interstitium secreted collagen and elastin. The collagenous skeleton of the lung is the limiting factor determining the elastic limit of lung distensibility.

Cartilage is the supporting structure of the larger conducting airways. Rigidity of these airways prevents collapse during expiration.

Cells Derived from Ectoderm make up the neural components of the lung. Neural ganglia develop as early as week 7 in fetal life. Autonomic innervation of airways includes at least four different systems: the parasympathetic nervous system, which directly innervates and promotes contraction of airway smooth muscle and mucous gland secretion; the sympathetic nervous system, which, in humans, does not innervate airway smooth muscle but likely controls the liquidity of airway secretions; the non-adrenergic, non-cholinergic inhibitory system, which relaxes airway smooth muscle, but has no known physiological stimulus; and the non-adrenergic, non-cholinergic stimulatory system, which likely acts through antedromal transmission of neurokinins through dorsal root ganglia and may play a role in exercise and/or cold-induced bronchoconstriction.

Material for this section of this chapter is largely taken from the textbook of Leff and Schumacker *(3)*, where considerably more detail for each of these components may be found.

Summary of Lung Development In Utero and Beyond

Table 1.1 is a temporal summary of the stages of growth and development, which are summarized schematically in Figure 1.13. In short summary, preparation for air-breathing life requires development of gas exchange airways, which commences

Table 1.1 Anatomical development of the lung.

Time	Event
Prenatal	
Day 26	Tracheoesophageal septum develops.
Day 28	Buds of mainstem bronchi appear.
Day 33	Buds of lung lobes appear.
Day 41	Bronchopulmonary segments develop; lung becomes lobulated.
Day 52	Pleural cavity is closed.
Week 8	Pseudoglandular phase occurs.
Week 16	Canalicular phase occurs.
Week 24	Saccular phase occurs and continues until birth.
BIRTH	
Postnatal	
2 months	Alveolar development begins.
2 years	Regular growth begins in place of septal formation.
7 years	Lung architecture is remodeled to adult pattern.
8 years	Alveolization ends; no further alveoli are formed during growth.
15 years	Normal growth is complete.

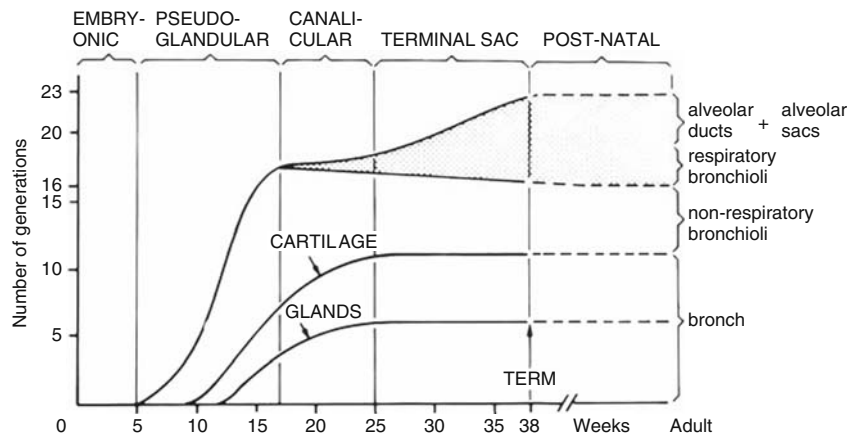


Figure 1.13 Schematic representation of lung maturation in its various stages. By 25 weeks, all generations of glandular and support tissues are differentiated. However, differentiation of gas exchange units is barely begun at this point. Hence, survival at this stage is much challenged By 36 weeks, sufficient numbers of gas exchange units have developed to virtually ensure that air-breathing respiration will be successful. The critical period between 28-and 34 weeks defines increasing likelihood for an uneventful post-natal period. Note that adult architecture of the lung is not completed until the 8th year of life

after the 25th week of gestation, at which time all other critical structures of the lung are formed. Development of respiratory saccules provides the lung units and surfactant-producing cells by rapid division and differentiation from the 27th week onward to birth. The process is completed in post-natal life and adult architectural changes are completed by the eighth post-natal year.

References

1. Colbert C. Evolution of Vertebrates. New York: John Wiley & Sons, 6th Ed. 1966; 479.
2. Smith H. From Fish to Philosopher. New York: Little Brown and Company, 1959; 304.
3. Leff A and Schumacker P. Respiratory Physiology: Basics and Applications. Philadelphia: Saunders, 1993; 198.
4. VI Lund Conference. Lung Growth and Regeneration. Proc Amer Thoracic Soc 2006; 3:(8),645–736.
5. Leff A. (Ed). Cardiopulmonary Exercise Testing. New York: Harcourt Brace Jovanovich (Grune and Stratton, Inc), 1986; 273.
6. Warburton D. Lung development and susceptibility to chronic obstructive pulmonary disease. Proc Amer Thoracic Soc 2006;3:668–672.

2

Respiratory Physiology in Pregnancy

Meredith C. McCormack and Robert A. Wise

Keywords: lung mechanics, oxygenation, ventilation, respiratory physiology, pregnancy

Introduction

Pregnancy is a normal but altered physiologic state that results in significant hormonal, mechanical, and circulatory changes. The increases in progesterone and estrogen associated with pregnancy contribute to vascular and central nervous system effects, changes in the balance of bronchoconstrictor and bronchodilator prostanoids, and increases in peptide hormones that alter connective tissue characteristics. The course of pregnancy is accompanied by structural changes to the ribcage and abdominal compartments as a consequence of the hormonal changes and the enlarged uterus. Cardiac output, pulmonary blood flow, and circulating blood volume are all increased due to increased metabolic demands. This increase in blood volume without an increase in red cell mass results in a decreased hemoglobin concentration. There is a reduction in plasma oncotic pressure due to both increased blood volume and a decrease in albumin concentration. The combination of increased pulmonary blood flow, increased pulmonary capillary blood volume, and decreased oncotic pressure all promote the formation of edema in the periphery and in the lung. Given the dramatic physical and hormonal alterations of pregnancy, perhaps the most remarkable aspect of respiratory physiology is the relatively minor impact that pregnancy has on the function of the lung. To be able to accurately identify and diagnose respiratory abnormalities in pregnant patients, the clinician must first understand normal physiologic changes of pregnancy. Over the years, there have been several excellent reviews of the effects of pregnancy on the respiratory system in health and disease *(1–6)*. This chapter provides an updated overview of respiratory physiology in healthy pregnant women *(6)*.

Chest Wall and Lung Mechanics in Pregnancy

During pregnancy, the ribcage undergoes structural changes in response to hormonal changes *(7)*. Progressive relaxation of the ligamentous attachments of the ribs cause the subcostal angle of the rib-cage to increase from 68° to 103° early in

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_2

pregnancy before the uterus is substantially enlarged. This change persists for months after the end of pregnancy when the uterus returns to normal size. The increased elasticity of the rib-cage is probably the result of the same factors that induce changes in the elastic properties of the pelvis. One of the important mediators is thought to be the polypeptide hormone relaxin which is increased during pregnancy. This substance is responsible for the softening of the cervix and the relaxation of the pelvic ligaments *(8, 9)*.

Pregnancy causes the diaphragm to elevate about 4 cm and the circumference of the lower rib-cage to increase about 5 cm *(10)*. The lower end-expiratory lung volume leads to an increased area of apposition of the diaphragm to the chest wall, which improves the coupling of the diaphragm and chest wall *(11)*. Thus, the increased tidal volume in pregnancy is achieved without an increase in the respiratory excursion of the diaphragm. The enlarging uterus results in increasing abdominal pressure which decreases chest wall compliance, which falls about 35–40% *(12)*.

The decrease in chest wall compliance causes a reduction in functional residual capacity (FRC). Reductions in the FRC and the expiratory reserve volume are the most consistent changes in static lung volumes with pregnancy. As the uterus enlarges, FRC falls by 10–25% of the previous value, starting about the 12th week of pregnancy *(13)*. The normal reduction in FRC in the supine position is further accentuated in pregnancy *(14, 15)*. By contrast, the total lung capacity is usually preserved or minimally decreased as a result of the mild increase in the inspiratory capacity. The residual volume tends to fall slightly, leading to a small increase or stability of the vital capacity *(16, 17, 10, 13, 18–21)*. The lung compliance remains normal during pregnancy but chest wall compliance is slightly reduced because of the effect of the enlarging uterus leading to a distention of the abdominal cavity. Expiratory muscle strength is in the low-normal range *(19)*.

Airflow Mechanics

Pregnancy has no significant effect on FEV_1 or the FEV_1/FVC ratio *(22, 23, 24)*. Peak expiratory flow rates remain close to the normal range and do not change during pregnancy *(25)*. The shape of the flow-volume curve and absolute flow rates at low lung volumes are normal in pregnant women *(17, 26)*. Thus, it is possible to use non-pregnant reference values to evaluate lung function in pregnant women. A reduction in FEV_1 or FVC should not be attributed to pregnancy alone. This is important for clinicians to understand, particularly as they are following patients with underlying lung diseases, such as asthma *(27, 28)*. Measurement of airway conductance by several methods demonstrates normal or increased large airway conductance *(19, 23)*. A relatively recent epidemiologic study has raised the possibility that pregnancy may induce changes in the lung that improve airway function and persist throughout life *(29)*. Small airway function as measured by closing volume is normal *(30–32)*. However, because the FRC is low, airways may close during tidal breathing and increase the alveolar-arterial oxygen gradient in the supine position.

Ventilation and Gas Exchange

Resting minute ventilation increases during pregnancy *(33–35)*. This is primarily due to an increase in tidal volume with a relatively constant breathing rate and pattern. Because the dead space-tidal volume ratio remains normal during

pregnancy, the increased tidal volume leads to increased alveolar ventilation *(36)*. Dead space may be decreased in pregnancy because of increased cardiac output and better perfusion to the apices, so ratio of VD/VT is even more advantageous.

Most studies find that this hyperventilation (increase in tidal volume) is a progesterone effect that occurs early in pregnancy during the first trimester, and stays constant or increases slightly as pregnancy progresses *(37)*. Typically, resting minute ventilation is increased about 30% during pregnancy compared to the postpartum value. This primary increase in minute ventilation is enhanced secondarily, by an increase in metabolic rate and carbon dioxide production. During pregnancy, carbon dioxide production at rest increases by about 30–300 ml/min. Despite this increase in production, overcompensation results in a low to normal CO_2 during pregnancy.

The increase in minute ventilation exceeds that which is required to maintain a normal arterial carbon dioxide level. As a result, the arterial $PaCO_2$ falls from 40 mmHg in the non-pregnant state to 32–34 mmHg in pregnancy *(38)*. The kidney excretes excess bicarbonate to compensate for the respiratory alkalosis and maintains a serum bicarbonate level of about 15–20 meq/L to preserve a normal arterial pH. Likely contributes to a rightward shift in the oxyhemoglobin dissociation curve the chronic alkalosis stimulates 2,3-diphosphoglycerate synthesis and this, in conjunction with anemia, that favors the unloading of oxygen in the periphery, presumably aiding oxygen transfer across the placenta *(39)*. There is general agreement that the main cause of the increased respiratory drive that causes the hyperpnea of pregnancy is the elevation of serum progesterone, a direct respiratory stimulant. The progesterone-induced increase in chemosensitivity results in an increase in the slope and a leftward shift of the CO_2 ventilatory response curve. The increase in chemosensitivity occurs early in pregnancy and remains constant up until delivery. The respiratory center output, which integrates both chemical and mechanical stimuli, is measured by the mouth pressure 100 ms following airway occlusion ($P_{0.1}$). This measure increases progressively throughout pregnancy, compatible with the idea that the hyperpnea of pregnancy is the result of both increased chemosensitivity and the metabolic and mechanical loads imposed by the gravid state. Shortly after delivery, the respiratory drive returns to normal with the fall in progesterone levels and the reduction in metabolic and mechanical loads induced by pregnancy.

The evidence that progesterone is a respiratory stimulant is strong *(40)*. When administered to non-pregnant individuals, progesterone increases minute ventilation, CO_2 chemosensitivity, and airway occlusion pressure *(41–43)*. It has been debated whether progesterone acts through a direct stimulatory effect on the respiratory center or through an increase in the gain of the chemoreceptors *(44)*. The most recent evidence shows that both the threshold for hypercapnic ventilation as well as the gain in ventilation is increased in pregnancy, suggesting that both intrinsic and chemically-driven responses are more sensitive in the pregnant hormonal milieu *(45)*.

The hypoxic ventilatory response is increased in pregnancy to about twice the normal level *(46)*. This occurs despite the blood and cerebrospinal fluid alkalosis that tends to suppress hypoxic drive. In contrast to the response to carbon dioxide, the hypoxic ventilatory response in pregnancy is not well correlated with progesterone levels. It is thought that the increased sensitivity to hypoxia is due to the increases in both estrogen and progesterone *(47, 48)*.

Arterial oxygen tensions are slightly increased in pregnancy as a result of the pregnancy-induced hyperpnea, with a normal pregnant level of 100–105 mmHg

(36). This high level of oxygen tension may facilitate oxygen transfer across the placenta by diffusion. However, the increased metabolic rate and the low oxygen reservoir in the lung at end-expiration make the pregnant woman particularly susceptible to develop hypoxemia in the presence of respiratory depression or apnea *(49, 50)*. In some women, the low end-expiratory lung volume may predispose them to decreasing oxygen tensions in the supine position in the late stages of pregnancy *(51)*.

The overall effect of pregnancy on diffusing capacity for carbon monoxide (Dco) is determined by the relative contributions of opposing physiologic changes. Pulmonary blood volume and cardiac output are increased in pregnancy, which should recruit capillary surface area and thereby increase Dco. This is offset by the dilutional reduction in hemoglobin concentration that occurs, leading to a constant or slightly diminished Dco in the majority of pregnant patients *(22)*. The normal increase in Dco that occurs in the supine position is absent in pregnancy, which might indicate that the gravid uterus prevents the normal increase in systemic venous return, or that the pulmonary capillary bed is already fully recruited *(26)*. The latter explanation is less plausible because exercise causes a normal increase in Dco in pregnant people *(52)*. One study suggests that there are different effects of pregnancy on Dco in high-altitude dwellers. Pregnant women dwelling at high altitude have a higher Dco than those at sea-level, but during the third-trimester they have a lower Dco than non-pregnant altitude dwellers. At sea-level, the Dco is similar throughout pregnancy compared to non-pregnant controls *(53)*. High altitude also acts additively with progesterone and ventilation is increased to a greater extent in high altitude residents compared to low altitude residents. The increase in ventilation, along with increased hemoglobin concentrations, appears to raise arterial oxygen saturation to levels similar to those of low altitude dwellers *(54)*.

Physiologic Dyspnea of Pregnancy

The increase in minute ventilation that accompanies pregnancy is often perceived as shortness of breath. About 75% of pregnant women have exertional dyspnea by 30 weeks of gestation *(55–58)*. Shortness of breath at rest or with mild exertion is so common that it is often referred to as "physiologic dyspnea." The proposed causes of dyspnea are the increased drive to breathe and the increased respiratory load. The increase in minute ventilation and the load imposed by the enlarging uterus cause an increase in the work of breathing. Other factors that are thought to contribute to the sensation of dyspnea include increased pulmonary blood volume, anemia, and nasal congestion. Studies of the psycho-physiology of dyspnea in pregnancy indicate that the dyspnea can be accounted for by the increased effort of breathing rather than an increased sensitivity to mechanical loads *(59)*.

The cardiovascular response to endurance exercise in late pregnancy is relatively unchanged compared to the post-partum state *(60)*. Similarly, exercise efficiency (change in oxygen consumption per change in work load) is unchanged *(61, 62)*. However, ventilation at any level of oxygen consumption or carbon dioxide production is increased in pregnancy which leads to increased perception of respiratory effort. This excess exercise ventilation and sensation of breathlessness can be somewhat reduced by aerobic training *(63)*. In general, fetal responses to short duration of exercises are usually

moderate and return to baseline in the post-exercise state and moderate prenatal physical conditioning does not significantly affect fetal growth *(6)*.

It can be challenging for a physician to differentiate the normal dyspnea of pregnancy from that due to disease pathology. Findings that raise the question of pathologic dyspnea include: increased respiratory rate greater than 20 breaths per minute, arterial PCO_2 less than 30 or greater than 35, hypoxemia or abnormal measures on forced expiratory spirometry, or cardiac echocardiography. The time course of symptoms is also helpful in differentiating pathologic conditions. Abrupt or paroxysmal episodes of dyspnea suggest an abnormal condition.

Summary and Conclusions

In summary, an understanding of the normal changes that occur in respiratory physiology during pregnancy (Table 2.1) is fundamental to recognizing how the presentation of lung diseases is altered by pregnancy. Although these changes in cardiovascular and respiratory physiology are remarkably well tolerated, there is diminished reserve capacity to deal with intercurrent respiratory insults. Thus, prompt recognition and treatment of altered respiratory function is needed to protect the health of the mother and fetus.

Table 2.1 Normal respiratory physiologic changes in pregnancy.

Chest Wall/Lung Mechanics	
Chest wall compliance	Decreased
Thoracic diameter	Increased
Diaphragm	Elevated
Lung compliance	Unchanged
Lung Volumes	
Total Lung Capacity	Unchanged or slightly decreased
Vital capacity	Unchanged or slightly increased
Inspiratory capacity	Slightly increased
Functional residual capacity	Decreased
Residual volume	Slightly decreased
Expiratory reserve volume	Decreased
Spirometry	
FEV_1	Unchanged
FVC	Unchanged
FEV_1/FVC	Unchanged
Gas Exchange	
D_{CO}	Unchanged or slightly decreased
Ventilation	
Minute ventilation	Increased
Tidal volume	Increased
Respiratory rate	Unchanged
Blood gas	
pH	Normal (7.39–7.42)
PaO_2	Slightly elevated (100–105 mmHg)
$PaCO_2$	Slightly decreased (32–34 mmHg)
Bicarbonate	Slightly decreased (15–20 meq/L)

Abbreviations

cm	Centimeters
Dco	Diffusing capacity for carbon monoxide
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
RV	Residual volume
TLC	Total lung capacity

References

1. Chesnutt AN. Physiology of normal pregnancy. Crit Care Clin 2004;20:609–15.
2. Fishburne JI. Physiology and disease of the respiratory system in pregnancy. A review. J Reprod Med 1979;22:177–89.
3. Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med 1995;152:427–55.
4. Pereira A, Krieger BP. Pulmonary complications of pregnancy. Clin Chest Med 2004;25:299–310.
5. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Respir Dis 1980;121:559–81.
6. Wise RA, Polito AJ, Krishnan V. Respiratory physiologic changes in pregnancy. Immunol Allergy Clin North Am 2006;26:1–12.
7. Oddoy A, Merker G. Lung mechanics and blood gases in pregnant guinea pigs. Acta Physiol Hung 1987;70:311–5.
8. Goldsmith LT, Weiss G, Steinetz BG. Relaxin and its role in pregnancy. Endocrinol Metab Clin North Am 1995;24:171–86.
9. Sherwood OD, Downing SJ, Guico-Lamm ML, Hwang JJ, O'Day-Bowman MB, Fields PA. The physiological effects of relaxin during pregnancy: studies in rats and pigs. Oxf Rev Reprod Biol 1993;15:143–89.
10. Cohen ME, Thomson KJ. Studies on the circulation in pregnancy. I. The velocity of blood flow and related aspects of the circulation in normal pregnant women. J Clin Invest 1936;15:607–25.
11. Gilroy RJ, Mangura BT, Lavietes MH. Rib cage and abdominal volume displacements during breathing in pregnancy. Am Rev Respir Dis 1988;137:668–72.
12. Marx GF, Murthy PK, Orkin LR. Static compliance before and after vaginal delivery. Br J Anaesth 1970;42:1100–4.
13. Cugell DW, Frank NR, Gaensler EA, Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc 1953;67:568–97.
14. Blair E, Hickam JB. The effect of change in body position on lung volume and intrapulmonary gas mixing in normal subjects. J Clin Invest 1955;34:383–9.
15. Schneider KT, Deckardt R. The implication of upright posture on pregnancy. J Perinat Med 1991;19:121–31.
16. Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. Br J Obstet Gynaecol 1978;85:518–24.
17. Baldwin GR, Moorthi DS, Whelton JA, MacDonnell KF. New lung functions and pregnancy. Am J Obstet Gynecol 1977;127:235–9.
18. Gazioglu K, Kaltreider NL, Rosen M, Yu PN. Pulmonary function during pregnancy in normal women and in patients with cardiopulmonary disease. Thorax 1970;25:445–50.
19. Gee JB, Packer BS, Millen JE, Robin ED. Pulmonary mechanics during pregnancy. J Clin Invest 1967;46:945–52.

20. Goucher D, Rubin A, Russo N. The effect of pregnancy upon pulmonary function in normal women. Am J Obstet Gynecol 1956;72:963–9.
21. Ihrman K. A clinical and physiological study of pregnancy in a material from northern Sweden. II. Body weight during and after pregnancy. Acta Soc Med Ups 1960;65:137–46.
22. Milne JA. The respiratory response to pregnancy. Postgrad Med J 1979;55:318–24.
23. Milne JA, Mills RJ, Howie AD, Pack AI. Large airways function during normal pregnancy. Br J Obstet Gynaecol 1977;84:448–51.
24. Mokkapatti R, Prasad EC, Venkatraman, Fatima K. Ventilatory functions in pregnancy. Indian J Physiol Pharmacol 1991;35:237–40.
25. Brancazio LR, Laifer SA, Schwartz T. Peak expiratory flow rate in normal pregnancy. Obstet Gynecol 1997;89:383–6.
26. Norregaard O, Schultz P, Ostergaard A, Dahl R. Lung function and postural changes during pregnancy. Respir Med 1989;83:467–70.
27. Bhatia P, Bhatia K. Pregnancy and the lungs. Postgrad Med J 2000;76:683–9.
28. Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. Am J Obstet Gynecol 2006;194:120–6.
29. Harik-Khan R, Wise RA, Lou C, Morrell CH, Brant LJ, Fozard JL. The effect of gestational parity on FEV1 in a group of healthy volunteer women. Respir Med 1999;93:382–8.
30. Bevan DR, Holdcroft A, Loh L, MacGregor WG, O'Sullivan JC, Sykes MK. Closing volume and pregnancy. Br Med J 1974;1:13–5.
31. Garrard GS, Littler WA, Redman CW. Closing volume during normal pregnancy. Thorax 1978;33:488–92.
32. Russell IF, Chambers WA. Closing volume in normal pregnancy. Br J Anaesth 1981;53:1043–7.
33. Knuttgen HG, Emerson K Jr. Physiological response to pregnancy at rest and during exercise. J Appl Physiol 1974;36:549–53.
34. Pernoll ML, Metcalfe J, Kovach PA, Wachtel R, Dunham MJ. Ventilation during rest and exercise in pregnancy and postpartum. Respir Physiol 1975;25:295–310.
35. Rees GB, Broughton Pipkin F, Symonds EM, Patrick JM. A longitudinal study of respiratory changes in normal human pregnancy with cross-sectional data on subjects with pregnancy-induced hypertension. Am J Obstet Gynecol 1990;162:826–30.
36. Templeton A, Kelman GR. Maternal blood-gases, PAo_2–Pao_2), hysiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976;48:1001–4.
37. Liberatore SM, Pistelli R, Patalano F, Moneta E, Incalzi RA, Ciappi G. Respiratory function during pregnancy. Respiration 1984;46:145–50.
38. Prowse CM, Gaensler RA. Repsiratory and acid-base changes during pregnancy. Anesthesiology 1965;26:381–92.
39. Tsai CH, de Leeuw NK. Changes in 2,3-diphosphoglycerate during pregnancy and puerperium in normal women and in beta-thalassemia heterozygous women. Am J Obstet Gynecol 1982;142:520–3.
40. Lyons HA AR. The sensitivity of the respiratory center in pregnancy after the administration of progesterone. Trans Assoc Am Phys 1959;72:173–180. Abstract.
41. Schoene RB, Pierson DJ, Lakshminarayan S, Shrader DL, Butler J. Effect of medroxyprogesterone acetate on respiratory drives and occlusion pressure. Bull Eur Physiopathol Respir 1980;16:645–53.
42. Sutton FD Jr, Zwillich CW, Creagh CE, Pierson DJ, Weil JV. Progesterone for outpatient treatment of Pickwickian syndrome. Ann Intern Med 1975;3:476–9.
43. Zwillich CW, Natalino MR, Sutton FD, Weil JV. Effects of progesterone on chemosensitivity in normal men. J Lab Clin Med 1978;92:262–9.
44. Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. J Appl Physiol 1978;44:393–44.
45. Jensen D, Wolfe LA, Slatkovska L, Webb KA, Davies GA, O'Donnell DE. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol 2005;288:R1369–75.

46. Moore LG, McCullough RE, Weil JV. Increased HVR in pregnancy: relationship to hormonal and metabolic changes. J Appl Physiol 1987;62:158–63.
47. Bayliss DA, Cidlowski JA, Millhorn DE. The stimulation of respiration by progesterone in ovariectomized cat is mediated by an estrogen-dependent hypothalamic mechanism requiring gene expression. Endocrinology 1990;126:519–27.
48. Hannhart B, Pickett CK, Moore LG. Effects of estrogen and progesterone on carotid body neural output responsiveness to hypoxia. J Appl Physiol 1990;68:1909–16.
49. Archer GW Jr, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth 1974;46:358–60.
50. Awe RJ, Nicotra MB, Newsom TD, Viles R. Arterial oxygenation and alveolar arterial gradients in term pregnancy. Obstet Gynecol 1979;53:182–6.
51. Ang CK, Tan TH, Walters WA, Wood C. Postural influence on maternal capillary oxygen and carbon dioxide tension. Br Med J 1969;4:201–3.
52. Bedell GN, Adams RW. Pulmonary diffusing capacity during rest and exercise. A study of normal persons and persone with atrial septal defect, pregnancy, and pulmonary disease. J Clin Invest 1962;41:1908–14.
53. McAuliffe F, Kametas N, Rafferty GF, Greenough A, Nicolaides K. Pulmonary diffusing capacity in pregnancy at sea level and at high altitude. Respir Physiol Neurobiol 2003;134:85–92.
54. Jean D, Leal C, Kriemler S, Meijer H, Moore LG. Medical recommendations for women going to altitude. High Alt Med Biol 2005;6:22–31.
55. Gilbert R, Auchincloss JH Jr. Dyspnea of pregnancy. Clinical and physiological observations. Am J Med Sci 1966;252:270–6.
56. Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol 1978;85:260–3.
57. Tenholder MF, South-Paul JE. Dyspnea in pregnancy. Chest 1989;96:381–8.
58. Zeldis SM. Dyspnea during pregnancy. Distinguishing cardiac from pulmonary causes. Clin Chest Med 1992;13:567–85.
59. Field SK, Bell SG, Cenaiko DF, Whitelaw WA. Relationship between inspiratory effort and breathlessness in pregnancy. J Appl Physiol 1991;71:1897–902.
60. Lotgering FK, Spinnewijn WE, Struijk PC, Boomsma F, Wallenburg HC. Respiratory and metabolic responses to endurance cycle exercise in pregnant and postpartum women. Int J Sports Med 1998;19:193–8.
61. Spaaij CJ, van Raaij JM, de Groot LC, van der Heijden LJ, Boekholt HA, Hautvast JG. No changes during pregnancy in the net cost of cycling exercise. Eur J Clin Nutr 1994;48:513–21.
62. Wolfe LA, Charlesworth SA, Glenn NM, Heenan AP, Davies GA. Effects of pregnancy on maternal work tolerance. Can J Appl Physiol 2005;30:212–32.
63. Ohtake PJ, Wolfe LA. Physical conditioning attenuates respiratory responses to steady-state exercise in late gestation. Med Sci Sports Exerc 1998;30:17–27.

3

High Altitude, Chronic Hypoxia, and Pregnancy

Ghada Bourjeily

Keywords: high altitude, chronic hypoxia, preeclampsia, low birth weight, growth restriction, uteroplacental circulation

Although placental and pregnancy physiology are not the focus of this book, many patients and their providers have concerns about the potential impact of altitude on fetal oxygenation. Understanding the effect of high altitude on the placenta and the potential adverse effects on the pregnancy and the fetus may help the clinician appreciate the potential effects of some advanced lung diseases and chronic hypoxia on the pregnancy and the fetus. This chapter is a succinct review of the effect of high altitude on lung function in pregnancy and placental complications.

The most obvious effect of high altitude on pregnancy outcomes is chronic hypoxia. High altitude associated chronic hypoxia affects 140 million persons in the world living at 8,000 feet or higher. This makes hypoxia at high altitude in pregnancy the most common etiology of maternal-fetal hypoxia *(1)*.

Respiratory Physiology at High Altitude

Given the high morbidity and mortality associated with pregnancy and fetal complications, an understanding of the respiratory physiology at high altitude as well as the mechanisms affecting oxygen delivery is essential. Lung function changes in pregnancy have been discussed under respiratory physiology in Chapter 2. Respiratory function in pregnancy has been studied at high altitude and compared to that of pregnant women at sea level and non-pregnant controls both at sea-level and high altitude *(2)*. Total lung capacity (TLC), residual volume (RV), expiratory reserve volume (ERV), inspiratory capacity (IC), and functional residual capacity (FRC) were greater in pregnant women at high altitude than pregnant women at sea level. In addition, forced expiratory volume in 1's (FEV_1) and forced vital capacity (FVC) were also significantly higher in gravidas at high altitude but the FEV_1/FVC was lower. Peak expiratory flow rates were not significantly different *(2)*. In a similar study, McAuliffe found that diffusion capacity was significantly higher in pregnant and non-pregnant women living at high altitude compared to their sea-level counterparts *(3)*.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_3 © Humana Press, a part of Springer Science+Business Media, LLC 2009

Studies of alveolar ventilation and oxygenation in pregnancy at high altitude have shown that pregnant women hyperventilate even further than pregnant women at sea level. A study by Hellegers et al. *(4)* of three healthy pregnant women living at high altitude examined patients tested periodically in the second and the third trimesters. In this study, it is not known whether pregnant women were smokers or not, but the authors mention that the subjects refrained from smoking one hour prior to testing. The mean $PaCO_2$ in the pregnant patients in 13 measurements was 22.93 ± 0.64 mmHg compared to 27.94 ± 0.44 mmHg in 12 measurements on four non-pregnant controls. The mean PaO_2 in that same study was found to be 59.01 ± 0.77 mmHg in pregnancy compared to 50.71 + 0.68 mmHg in the non-pregnant controls. These findings are consistent with prior reports of lower $PaCO_2$ in pregnant women living at high altitude. PaO_2 measured at term in other studies at an altitude of 4,000 m was 60.75 ± 2.2 mmHg *(5)*. Another study has evaluated pregnant women at high altitude for ABG values, oxygen content, and minute ventilation and showed significant differences between pregnant women at high altitude and at sea level (see Table 3.1). This rise of the mean PaO_2 of 9 mmHg in pregnancy compared to non-pregnant controls likely carries a more significant effect at high altitude than at sea level since the oxygen saturation is lower in pregnancy at high altitude than at sea level. It is noteworthy though, that despite a significantly lower PaO_2 and oxygen saturation, oxygen content in pregnant women at high altitude is significantly higher than at sea level. This rise in oxygen content is related to the higher hemoglobin associated with the stimulation of erythropoietin in relation to the chronic hypoxic state. In addition, the final PO_2 achieved in mixed venous blood of subjects at high altitude is not greatly diminished *(6)*. Despite these compensatory mechanisms that improve oxygen content at high altitude, a significant obstacle to oxygen delivery is the fact that cardiac output is lower at high altitude in pregnancy. In fact, a study of cardiac parameters by echocardiography in high altitude pregnancies showed

Table 3.1 Mean (SD) blood gases and ventilation in pregnant and non-pregnant women at sea level and at high altitude. (Used with permission.)

	Non-pregnant		Pregnant	
Variables	**Sea level**	**High altitude**	**Sea level**	**High altitude**
PO_2 (mmHg)	93 (9)	48 (4)[a]	98.5 (10)	53 (3)[a]
PCO_2 (mmHg)	40 (2.5)	27 (2.0)[a]	32 (3.0)	23 (1.6)[a]
pH	7.43 (0.02)	7.48 (0.03)[a]	7.45 (0.02)	7.495 (0.03)[a]
Saturation (%)	98 (0.8)	88 (3.0)[a]	98.5 (0.7)	89.9 (2.4)[a]
Haemoglobin (gr/dl)	14 (1.6)	16 (1.7)[a]	11.8 (1.4)	14.3 (1.5)[a]
HCO_3 (mMol/L)	25.3 (1.2)	19.9 (1.3)[a]	21.7 (1.6)	17.5 (1.2)[a]
Base Excess	1.37 (0.9)	−0.7 (1.4)[a]	−0.69 (1.3)	−2.06 (1.3)[a]
O_2 content (ml/100 ml whole blood)	1.82 (0.2)	1.89 (0.2)	1.58 (0.2)	1.75 (0.2)[a]
Minute ventilation (L/min)	10.5 (4)	12.4 (4)	13.3 (3.8)	16.7 (7)[a]
Respiratory rate/min	15.7 (4.8)	18.9 (5.3)	18.6 (5.9)	20.9 (6.6)[b]
Tidal volume (L)	0.7 (0.3)	0.7 (0.2)	0.8 (0.3)	0.8 (0.4)

[a] $P < 0.01$.
[b] $P < 0.05$.

values that were significantly lower than sea level pregnancies for cardiac output, stroke volume, heart rate, and ejection fraction *(7)*. All of these parameters increased progressively during gestation to a peak at about 22–25 weeks. However, the percent increase in cardiac output compared to non-pregnant controls was lower at high altitude than at sea level (17% versus 41%) *(7)*. The smaller increase in cardiac output, left atrial diameter, and end diastolic diameter suggests that the intravascular space does not expand as well in pregnancy at high altitude. The rise in systemic vascular resistance (SVR) at high altitude likely contributes to this limitation as well.

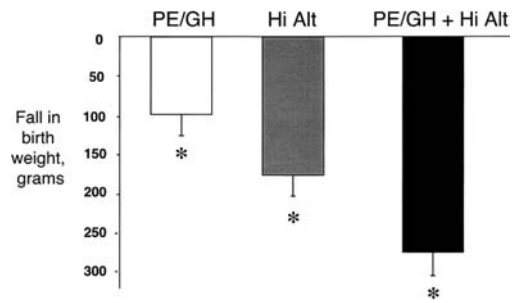
Pregnancy Outcomes Associated with High Altitude

Outcomes proposed to be related to altitude and likely to chronic hypoxia include effects on birth weight, preeclampsia, and stillbirths.

Many studies have shown that in pregnant women who reside at high altitudes, infant birth weight falls an average of 100 g for every 1,000 m of altitude gain *(8, 9)*. In Colorado, the effect of altitude on birth weight is at least as great as the effect of low maternal weight gain, preeclampsia, or smoking *(8)*. Low birth weight (LBW) and small for gestational age occurred in 10.2% and 13.7%, respectively in a study of 1,121 vaginal deliveries in Tibet *(10)*. Timing of growth limitation is, however, delayed in the course of gestation and only becomes apparent starting at 25–29 weeks of gestation *(11)*.

Although earlier reports suggest that neonatal and infant mortality is lower in LBW babies born at high altitude than LBW babies born at low altitudes *(12, 13)*, more recent reports seem to show that high altitude does not have a protective effect against significant morbidity in LBW newborns born at 2,500 m or above *(14)*.

Another important outcome that seems to be observed more often at high altitudes is preeclampsia. The rate of preeclampsia/gestational hypertension occurred in 18.9% of vaginal deliveries in Tibet *(10)*. Reports of a twofold to a fourfold increase in the incidence of preeclampsia have been described using both strict (primiparas, hypertension, and proteinuria that resolve post-partum) and less strict diagnostic criteria (hypertension with evidence of other organ involvement such as thrombocytopenia, abnormal liver function tests, or neurological



Graph 3.1 High altitude and PE decrease birth weitht. Contributions of hypertensive complications of pregnancy and altitude to reduction in birth weight in grams, controlling for gestational age, parity, and maternal weight. *$p < 0.01$
(From: ref. *(14)*, with permission from Wolters Kluwer Health/Lippincott Williams & Wilkins)

symptoms) *(15)*. This increase in the prevalence of preeclampsia may contribute, in turn, to the development of intra-uterine growth restriction (IUGR) *(8, 14, 16)* (see Graph 3.1).

Other effects of high altitude, likely combined with the higher incidence of preeclampsia, include an increased frequency of stillbirths *(14)*. In a study that consisted of a large chart review of women residing in Bolivia at 300 versus 3,600 m, higher rates of all pregnancy, fetal, and newborn complications surveyed were encountered *(14)*. Of note, fetal distress and newborn respiratory distress occurred much more frequently at high altitude (see Table 3.2).

Interestingly, however, the effects of altitude on pregnancy and fetal outcomes are not consistently encountered. Outcomes were found to vary significantly by population studied. For instance, populations that had originated at high altitudes were less likely to develop altitude-related complications such as growth restriction than populations that had emigrated to high altitudes (Andeans versus Europeans and Tibetans versus Han) *(17, 18)*. After accounting for the influences of maternal hypertensive complications of pregnancy, parity, body weight, and number of prenatal visits, European ancestry increased the frequency of small for gestational age babies at high altitude nearly fivefold when compared to Andean ancestry *(18)*. Other factors that likely affect the heterogeneity in the effect of altitude on these outcomes may be genetic. Many methods of genetic testing used have suggested that the degree of protection that a Tibetan or Andean background offers to the offspring may be secondary to different phenotypic adaptive responses to high-altitude hypoxia. Four traits have been described in a review by Beall *(19)* and include resting ventilation, hypoxic ventilatory response, oxygen saturation, and hemoglobin concentration. In fact, an autosomal dominant major gene for oxygen saturation was found in the Tibetan population and is associated with higher offspring survival, strongly suggesting a natural selection process *(20)*.

Despite that, further studies in Andean residents of high altitude have shown that there are factors that are unrelated to oxygen content that could be protective *(21, 22)*.

Table 3.2 Maternal, fetal, and neonatal complications. (From: ref. *(14)*, with permission from Wolters Kluwer Health/Lippincott Williams & Wilkins)

	Low altitude	*n*	High altitude	*n*
Bleeding first-third trimester (%)	0.1 (–0.1 to 0.4)	1476	3.1 (2.2–4.0)*	801
Premature rupture of membranes (%)	0.4 (0.0–0.8)	1518	4.0 (3.0–4.9)*	802
Preterm labor (%)	3.6 (2.3–4.8)	1494	6.5 (5.3–7.7)*	765
Oligo or polyhydramnios (%)	0.2 (–0.1 to 0.6)	1488	2.2 (1.6–3.0)*	800
Placental abruption or previa (%)	0.4 (0.0–0.8)	1494	1.7 (1.1–2.3)*	800
Fetal distress (%)	1.6 (0.7–2.5)	1275	13.2 (11.6–14.9)*	787
Nuchal cord (%)	0.4 (0.0–0.8)	1275	3.4 (2.5–4.2)*	787
Newborn respiratory distress (%)	1.4 (0.6–2.1)	1518	9.1 (7.7–10.5)*	802
Congenital anomalies (%)	0.1 (–0.1 to 0.4)	1499	1.4 (0.8–2.0)*	801

Values are mean = SEM or proportions with 95% Cl (in parentheses).
*$p < 0.01$ compared with low altitude.

Uteroplacental Circulation and Oxygen Transport

The human placenta is hemochorial, meaning that the chorion is in direct contact with maternal blood. Oxygen transport in human placentae occurs by diffusion from the maternal blood in the intervillous space to fetal blood in capillaries of the terminal villi. Maternal spiral arteries enter the myometrial wall and then turn into flaccid uteroplacental vessels that have the ability to dilate to accommodate the increased blood flow. The maternal blood bathes the chorionic villi, enters the intervillous space, and flows toward the chorionic plate. After running through a fetal lobule, maternal blood drains into the uterine vein. Oxygen diffuses across placental microvilli into the superficial capillaries of the fetus and then converges to drain into the umbilical vein, which delivers oxygenated blood to the fetus (see Figure 3.1 and Table 3.3).

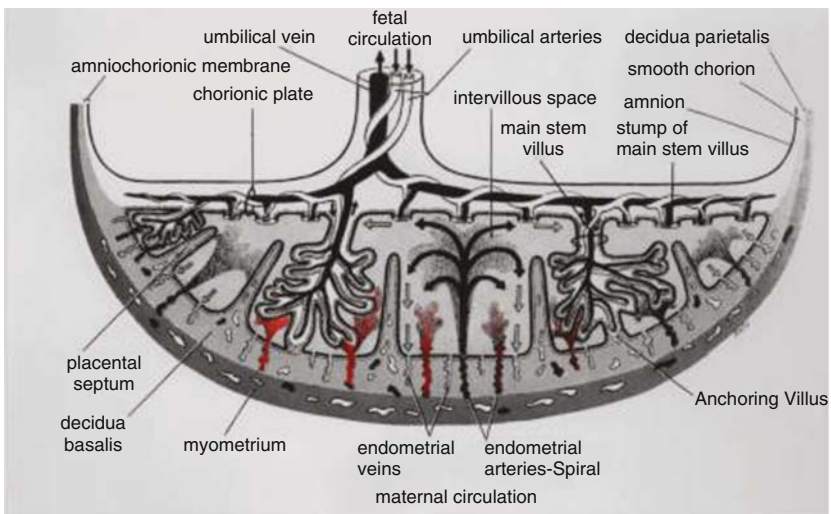


Figure 3.1 Uteroplacental circulation. With permission from S. Ramanathan, http://ramanathans.com/uteroplacental%20circulation.htm

Table 3.3 Oxygen transport. SaO2: arterial oxyhemoglobin saturation; PaO2: arterial oxygen tension; SvO2: mixed venous oxyhemoglobin saturation; PvO2: venous oxygen tension; Q: cardiac output.

Arterial oxygen content: CaO2 (mL O2/dL) = (1.34 × hemoglobin concentration × SaO2) + (0.0031 × PaO2)
Venous oxygen content: CvO2 (mL O2/dL) = (1.34 × hemoglobin concentration × SvO2) + (0.0031 × PvO2)
Oxygen delivery: DO2 (mL/min) = Q × CaO2
Oxygen consumption: VO2 (mL O2/min) = Q × (CaO2-CvO2)
Oxygen extraction: CaO2-CvO2/CaO2

Chronic Hypoxia and Effect on the Placenta

Normal pregnancy affects all oxygen determinants to the uteroplacental circulation. Because of increasing demands of the growing fetus and the conception products, oxygen consumption and delivery are increased in pregnancy. However, the increase in oxygen delivery is not related to a higher oxygen content, since oxygen content is actually lower in pregnancy because of lower hemoglobin and a relatively stable oxygen saturation. This increase is rather due to a rise in blood flow to the uteroplacental circulation (an increase of about 35-fold). Many mechanisms are responsible for this increase and include a higher nitric oxide (NO) production *(23)*, a decline in sympathetic tone, and the vasoconstrictor endothelin-1 *(24)*. Vascular endothelial growth factor (VEGF) also plays an important role in endothelial cell survival.

At high altitude, compensatory mechanisms occur during pregnancy such as a rise in minute ventilation that results in higher oxygen saturation and an oxygen content that is at least at sea-level values *(25, 26)*. For that reason, growth restriction is thought to be related to the reduced flow rather than oxygen content in hypoxia-induced IUGR.

Chronic hypoxia and the reduced flow affect fetal outcomes by different mechanisms. A systemic effect may be secondary to the fact that cardiac output is lower at high altitudes than at sea level, likely because of a lower blood volume but also a higher SVR. A change in the balance of vasoconstrictors and vasodilators may be a factor in this increase. This reduction in cardiac output contributes to a reduction in overall oxygen delivery at high altitude, despite a higher oxygen content. This decline in oxygen delivery has been observed irrespective of ancestry in a study that compared Andeans at sea level and high altitude to Europeans at sea level and high altitude *(27)*. Although minute ventilation and arterial oxygenation are certainly important, there are data supporting the overall conclusion that oxygen delivery does not cause the progressive reduction in fetal growth observed after 24 weeks of pregnancy at high altitude *(11)*. Other studies support the presence of other factors that would be protective against the development of LBW that are not related to arterial oxygen content *(21)*. Rather, fetal extraction of oxygen, increased substrate delivery related to greater blood flow, placental transport, or the fetomaternal utilization of substrate may be more important than oxygen delivery to maintain fetal growth in high altitude pregnancies.

Consequently, the uteroplacental circulation itself is likely a major culprit in maternal/fetal outcomes. Both short term and long term hypoxia lead to higher catecholamine levels. In fact, blood flow velocities in fetal arterial circulation are lower in all vessels studied at high altitude than at sea level *(28, 29)*. The effect is most prominent in the umbilical artery flow. In addition, Andean residents of high altitude in La Paz, Bolivia, were shown to have a greater uterine artery diameter, cross-sectional area, and blood flow near term and thus a 1.6-fold greater uteroplacental oxygen delivery than residents of the same altitude who had European ancestry *(22)*.

The inhibition of the NO-induced vasorelaxation to acetylcholine as well as the inhibition of the pregnancy-associated endothelial nitric oxide synthase protein in whole vessel homogenates has been proposed as a possible mechanism for the reduction in blood flow under hypoxic conditions *(30)*. More so, experiments in rats have shown that blocking endothelin-A receptor prevents the development of IUGR, suggesting a role of endothelin-A in the development of growth restriction *(31)*. However, when endothelial function was assessed by flow-mediated dilation

of the brachial artery at high altitude in pregnancy, there was no evidence to suggest endothelial function impairment *(32)*.

On the other hand, in conditions such as preeclampsia, which is more commonly found in altitude-associated chronic hypoxia, elevated levels of the membrane bound VEGF receptor (better known as sFlt-1) bind VEGF and placental-like growth factor (PlGF) and therefore inhibit endothelial cell proliferation and reduce vasorelaxation response *(33)*. However, it is not clear whether hypoxia directly affects vasodilators such as VEGF or PlGF. One study has shown that placental sFlt-1 (VEGF receptor-1) expression is increased by both physiologic and pathologic low levels of oxygen *(34)*. This oxygen-induced effect is mediated via the nuclear transcription factor HIF-1 (hypoxia inducible factor) *(34)*. In addition to mediating the effect of hypoxia on placental sFlt-1, HIF-1 may also facilitate placental oxygen transport at high altitude by increasing erythropoiesis and placental angiogenesis *(35)*.

In addition to low velocity in the uteroplacental circulation, pregnant women residing at high altitude were found to have a higher blood viscosity than their sea-level counterparts *(7)*. Hyperviscosity and an elevated hematocrit have been suggested to be associated with preeclampsia and growth restriction *(36)*.The combination of the hyperviscosity associated with the high hemoglobin *(7)* may lead to cell aggregation and affect fetal perfusion.

In summary, chronic hypoxic conditions such as high altitude have been associated with adverse fetal and maternal outcomes. Mechanisms responsible for these outcomes relate mainly to the uteroplacental circulation. High altitude is the most studied chronic hypoxic condition in pregnancy and extrapolation from these data may help understand the consequences of chronic hypoxia in pregnancy and direct the management of certain conditions.

References

1. Moore LG, Niermeyer S, Zamudio S. Human adaptation to high altitude: regional and life-cycle perspectives. Am J Phys Anthropol 1998;Suppl 27:25–64.
2. McAuliffe F, Kametas N, Espinoza J, Greenough A, Nicolaides K. Respiratory function in pregnancy at sea level and at high altitude. BJOG 2004;111(4):311–5.
3. McAuliffe F, Kametas N, Rafferty GF, Greenough A, Nicolaides K. Pulmonary diffusing capacity in pregnancy at sea level and at high altitude. Respir Physiol Neurobiol 2003;34(2):85–92.
4. Hellegers A, Metcalfe J, Huckabee WE, Prystowsky H, Meschia G, Barron DH. Alveolar PCO_2 and PO_2 in pregnant and nonpregnant women at high altitude. Am J Obstet Gynecol 1961;82:241–5.
5. Sobrevilla LA, Cassinelli MT, Carcelen A, Malaga JM. Human fetal and maternal oxygen tension and acid-base status during delivery at high altitude. Am J Obstet Gynecol 1971;111(8):1111–8.
6. Krampl E. Pregnancy at high altitude. Ultrasound Obstet Gynecol 2002;19(6):535–9.
7. Kametas NA, Krampl E, McAuliffe F, Rampling MW, Nicolaides KH. Pregnancy at high altitude: a hyperviscosity state. Acta Obstet Gynecol Scand 2004;83(7):627–33.
8. Jensen GM, Moore LG. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? Am J Public Health 1997;87(6):1003–7.
9. Giussani DA, Phillips PS, Anstee S, Barker DJ. Effects of altitude versus economic status on birth weight and body shape at birth. Pediatr Res 2001;49(4):490–4.
10. Miller S, Tudor C, Nyima, Thorsten VR, Sonam, Droyoung, Craig S, Le P, Wright LL, Varner MW. Maternal and neonatal outcomes of hospital vaginal deliveries in Tibet. Int J Gynaecol Obstet 2007;98(3):217–21.

11. Krampl E, Lees C, Bland JM, Espinoza Dorado J, Moscoso G, Campbell S. Fetal biometry at 4300 m compared to sea level in Peru. Ultrasound Obstet Gynecol 2000;16(1):9–18.
12. Beall CM. Optimal birthweights in Peruvian populations at high and low altitudes. Am J Phys Anthropol 1981;56(3):209–16.
13. Haas JD, Balcazar H, Caulfield L. Variation in early neonatal mortality for different types of fetal growth retardation. Am J Phys Anthropol 1987;73(4):467–73.
14. Keyes LE, Armaza JF, Niermeyer S, Vargas E, Young DA, Moore LG. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. Pediatr Res 2003;54(1):20–5.
15. Zamudio S. High-altitude hypoxia and preeclampsia. Front Biosci 2007;12:2967–77.
16. Palmer SK, Moore LG, Young D, Cregger B, Berman JC, Zamudio S. Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado. Am J Obstet Gynecol 1999;180(5):1161–8.
17. Moore LG. Human genetic adaptation to high altitude. High Alt Med Biol 2001;2(2):257–79.
18. Julian CG, Vargas E, Armaza JF, Wilson MJ, Niermeyer S, Moore LG. High-altitude ancestry protects against hypoxia-associated reductions in fetal growth. Arch Dis Child Fetal Neonatal Ed 2007;92(5):F372–7.
19. Beall CM. Tibetan and Andean patterns of adaptation to high-altitude hypoxia. Hum Biol 2000;72(1):201–28.
20. Beall CM. Detecting natural selection in high-altitude human populations. Respir Physiol Neurobiol 2007;158(2–3):161–71.
21. Vargas M, Vargas E, Julian CG, Armaza JF, Rodriguez A, Tellez W, Niermeyer S, Wilson M, Parra E, Shriver M, Moore LG. Determinants of blood oxygenation during pregnancy in Andean and European residents of high altitude. Am J Physiol Regul Integr Comp Physiol 2007;293(3):R1303–12.
22. Wilson MJ, Lopez M, Vargas M, Julian C, Tellez W, Rodriguez A, Bigham A, Armaza JF, Niermeyer S, Shriver M, Vargas E, Moore LG. Greater uterine artery blood flow during pregnancy in multigenerational (Andean) than shorter-term (European) high-altitude residents. Am J Physiol Regul Integr Comp Physiol 2007;293(3):R1313–24.
23. Cadnapaphornchai MA, Ohara M, Morris KG Jr, Knotek M, Rogachev B, Ladtkow T, Carter EP, Schrier RW. Chronic NOS inhibition reverses systemic vasodilation and glomerular hyperfiltration in pregnancy. Am J Physiol Renal Physiol 2001;280(4):F592–8.
24. Furuhashi N, Kimura H, Nagae H, Yajima A. Maternal plasma endothelin levels and fetal status in normal and preeclamptic pregnancies. Gynecol Obstet Invest 1995;39(2):88–92.
25. Moore LG, Jahnigen D, Rounds SS, Reeves JT, Grover RF. Maternal hyperventilation helps preserve arterial oxygenation during high-altitude pregnancy. J Appl Physiol 1982;52(3):690–4.
26. McAuliffe F, Kametas N, Krampl E, Ernsting J, Nicolaides K. Blood gases in pregnancy at sea level and at high altitude. BJOG 2001;108(9):980–5.
27. Zamudio S, Postigo L, Illsley NP, Rodriguez C, Heredia G, Brimacombe M, Echalar L, Torricos T, Tellez W, Maldonado I, Balanza E, Alvarez T, Ameller J, Vargas E. Maternal oxygen delivery is not related to altitude- and ancestry-associated differences in human fetal growth. J Physiol 2007;582(Pt 2):883–95.
28. Krampl E, Lees C, Bland JM, Espinoza Dorado J, Moscoso G, Campbell S. Fetal Doppler velocimetry at high altitude. Ultrasound Obstet Gynecol 2001;18(4):329–34.
29. Zamudio S, Palmer SK, Droma T, Stamm E, Coffin C, Moore LG. Effect of altitude on uterine artery blood flow during normal pregnancy. J Appl Physiol 1995;79(1):7–14.
30. White MM, McCullough RE, Dyckes R, Robertson AD, Moore LG. Chronic hypoxia, pregnancy, and endothelium-mediated relaxation in guinea pig uterine and thoracic arteries. Am J Physiol Heart Circ Physiol 2000;278(6):H2069–75.
31. Thaete LG, Neerhof MG, Caplan MS. Endothelin receptor A antagonism prevents hypoxia-induced intrauterine growth restriction in the rat. Am J Obstet Gynecol 1997;176(1 Pt 1):73–6.

32. Kametas NA, Savvidou MD, Donald AE, McAuliffe F, Nicolaides KH. Flow-mediated dilatation of the brachial artery in pregnancy at high altitude. BJOG 2002;109(8):930–7.
33. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111(5): 649–58.
34. Nevo O, Soleymanlou N, Wu Y, Xu J, Kingdom J, Many A, Zamudio S, Caniggia I. Increased expression of sFlt-1 in in vivo and in vitro models of human placental hypoxia is mediated by HIF-1. Am J Physiol Reg Integr Comp Physiol 2006;291(4):R1085–93.
35. Zamudio S, Wu Y, Ietta F, Rolfo A, Cross A, Wheeler T, Post M, Illsley NP, Caniggia I. Human placental hypoxia-inducible factor-1alpha expression correlates with clinical outcomes in chronic hypoxia in vivo. Am J Pathol 2007;170(6):2171–9.
36. Knottnerus JA, Delgado LR, Knipschild PG, Essed GG, Smits F. Haematologic parameters and pregnancy outcome. A prospective cohort study in the third trimester. J Clin Epidemiol 1990;43(5):461–6.

4

Sleep Physiology in Pregnancy

Ghada Bourjeily and Vahid Mohsenin

Keywords: sleep, pregnancy, hormones, cytokines, nocturnal oxygen saturation

Sleep Physiology in Pregnancy

Sleep is a universal behavior that has been convincingly shown to occur in mammalian, avian and reptilian species. Sleep is also one of the most important of human behaviors, occupying roughly over one third of human life. Although the exact functions of sleep are poorly understood, the antiquated idea that sleep is a purely passive state and simply reflects fatigue is now strongly refuted. Sleep is currently thought to be as complex as wakefulness. The functions of mammalian sleep remain unclear.

Most theories suggest a role for non-rapid eye movement (NREM) sleep in energy conservation and in nervous system recuperation, and for rapid eye movement (REM) sleep with periodic brain activation, localized recuperative processes, and emotional regulation. Protein synthesis in the brain is increased during slow-wave sleep and new neurons are generated in adult animals. Short-term (2- to 3-day) total sleep deprivation blocks subsequent proliferation of cells in some parts of the brain.

Sleep is also clearly necessary for survival, since prolonged sleep deprivation leads to severe physical and cognitive impairment and, finally, death. Deprivation of a part of the sleep cycle known as REM sleep has also been shown to be fatal in rats after a few weeks *(1)*. In humans, sleep deprivation is associated with daytime sleepiness and fatigue, lack of concentration, cognitive dysfunction, poor work performance, impaired immunity, and perturbed neuroendocrine function—insulin resistance, glucose intolerance, and possibly obesity.

Overview of Sleep Stages

Since 1968, sleep has been divided into two main stages: rapid eye movement stage (REM) and non-rapid eye movement (NREM) *(2)*. NREM sleep is further divided into four sub-categories.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_4

Rapid eye movement sleep recurs every 90–120 min of sleep and is characterized by rapid eye movement, generalized muscle atonia with inactivity in all voluntary muscles except the ocular muscles, and low-voltage, fast wave EEG pattern resembling that of the awake stage.

Non-rapid eye movement sleep stage 1 consists of relatively fast EEG waves (theta), 4–7 Hz, and is the transition between wakefulness and the deeper stages of sleep, occupying 2–5% of total sleep time. Stage 2 sleep is characterized by slowing and an increase in the amplitude of EEG waves and accounts for about 40–50% of total sleep time. Stages 3 and 4 are known as slow wave or deep sleep stages and typically show slow delta waves on EEG. Both stages occupy no more than 20% of total sleep time.

Sleep stages occur in cycles of 90–120 min with 4–5 cycles occurring in a typical night. Sleep architecture changes with age with lighter sleep and less time spent in the deep sleep stages.

The Sleep-Wakefulness Cycle

The sleep-wakefulness cycle follows a circadian rhythm that is mainly controlled by the ventral-anterior region of the hypothalamus, more specifically the suprachiasmatic nuclei. The suprachiasmatic nucleus is sensitive to both melatonin and the light-dark cycle and helps regulate the sleep-inducing neurons in the absence of sensory stimuli. Sleep initiation may begin with the emergence of inhibitory signals directed caudally toward the brainstem reticular core and posterior hypothalamus. The preoptic nucleus inhibits the histaminergic posterior hypothalamic tuberoinfundibular region *(3)* through γ aminobutyric acid (GABA) neurons *(4)* and probably acetylcholine.

Rapid eye movement sleep is generated by mesencephalic and pontine cholinergic neurons *(5)*. As REM sleep initiates, monoadrenergic locus ceruleus and serotonergic raphe neurons become inactive *(6)*.

The sleep-wake cycle also influences the hypothalamic structures responsible for the release of certain hormones resulting in a circadian rhythm. Some of these circadian hormones in fact affect sleep.

Overview of Sleep in Pregnancy

Sleep is notoriously disturbed in pregnancy for many obvious reasons. This fact has been known for decades. In fact Hippocrates' pregnancy test consisted of giving hydromel (a drink consisting of a mixture of honey and water) at sleep initiation to women suspected of being pregnant. Women who woke up because of an abdominal discomfort were diagnosed as being pregnant and those who slept through the night were thought to be non-pregnant. These findings suggest that sleep disturbances related to pregnancy were recognized centuries ago.

More recently, sleep was recognized as a common issue in pregnant women and the American Academy of Sleep Medicine has introduced "pregnancy-associated sleep disorder" as a separate entity *(7)*. This disorder includes both insomnia and excessive sleepiness that develop in the course of the pregnancy.

Sleep depth is reduced in the third trimester making women more likely to be woken up by noise in the environment *(8)*. In addition, many of the physiologic

changes that occur in pregnancy predispose to the development of sleep changes, interruptions, and disturbances. These include mechanical, anatomical, and hormonal factors that develop at different stages of pregnancy.

Mechanical and Somatic Factors Affecting Sleep Initiation and Sleep Maintenance

Gastroesophageal Factors

Gastroesophageal reflux starts early in pregnancy and is related to multiple factors. The increased levels of progesterone have a muscle-relaxing effect on the lower esophageal sphincter making it less competent. Gastric emptying is also delayed in pregnancy predisposing to reflux. In addition, as the pregnancy progresses, the enlarging uterus exerts pressure on the stomach causing it to be displaced and leading to a disadvantaged gastroesophageal angle predisposing to reflux. During sleep, the recumbent position adds to the factors causing reflux and may lead to awakening.

Urinary Factors

Urine excretion is usually decreased during sleep. However, nocturia is a common occurrence in pregnancy. The major cause of nocturnal frequency of micturition in the first and second trimesters of gestation is an increase in overnight urine flow; the increment of nocturnal micturition is large when compared with the change in the 24 h output *(9)*. Overnight sodium excretion is also augmented and is mainly responsible for the increase in urine flow *(9)*. In addition, decreased bladder capacity secondary to the effects of the growing uterus on the bladder is another cause for frequent nocturnal micturition. Sleep interruptions are therefore inevitable *(10)*.

Musculoskeletal Factors

As the pregnancy progresses, the musculoskeletal system undergoes many changes. The polypeptide hormone relaxin, which is increased during pregnancy, is responsible for the softening of the cervix and the relaxation of the pelvic ligaments *(11, 12)*. The symphysis pubis widens to prepare for a larger outlet. The width of the pelvis is also increased and the hips are outwardly displaced. In the late stages of pregnancy, women complain of back aches and a discomfort in the pelvic area related to these changes and many have difficulties finding a comfortable position at night.

Leg cramps are also common in pregnancy and tend to occur mostly at night adding to the factors that result in sleep interruptions.

Restless legs are a frequent complaint in pregnancy and can occur in as many as 15–27% of patients *(13–15)* and can result in significant sleep disruption. Restless legs in pregnancy are discussed in more detail in Chapter 10.

Obstetric Factors

In the late stages of pregnancy, women start complaining of uterine contractions which may occur on a daily basis and may start at any time during the day or night leading to awakening. However, given the fact that oxytocin

usually peaks at night, uterine contractions usually coincide *(16)*. Starting at about 20 weeks of gestation, the uterus is close enough to the abdominal wall that fetal movements are felt. Again, these movements may occur at any point during the day or at night leading to awakening. Abdominal discomfort may occur frequently in pregnancy and may be related to many benign factors including ligament stretching or simply pressure from the growing uterus during position changes at night.

More so, pregnant women are encouraged to avoid sleeping in the supine position in the late stages of pregnancy to avoid postural vena caval compression and are naturally unable to sleep in the prone position, limiting their ability to get comfortable which may affect sleep initiation and maintenance.

Anatomic Changes Predisposing to Sleep-Disordered Breathing

Upper airway Changes

Pregnancy is associated with hyperemia and glandular hyperactivity of the upper airway and nasal mucosa. Increased edema and friability of the airway has also been reported *(17)*. These changes are likely to be related to the direct effects of the increased plasma volume and the indirect effects of the elevated levels of estrogens. Pharyngeal dimensions have been evaluated in pregnancy using the Mallanpati scoring system and were found to be reduced *(18)*. In a more sophisticated study, Izci et al. *(19)* used the acoustic reflectance method to measure upper airway size in pregnant women and compared those to non-pregnant controls. The study found that the oropharyngeal junction is smaller in pregnant compared to non-pregnant women. These findings resolved after delivery. In another study, Izci *(20)* showed that pregnant women with pre-eclampsia have a narrower airway than pregnant women without pre-eclampsia and non-pregnant women. The above findings are particularly important since upper airway patency is an important predictor of sleep-disordered breathing.

Hormonal Factors Affecting Sleep in Pregnancy

As discussed above, many hormones follow a circadian rhythm and some of those have various effects on sleep. In addition, hormones such as progesterone, estrogen, cortisol, and others are increased in pregnancy and have been shown to have an effect on sleep.

Progesterone

Progesterone is one of the main hormones in pregnancy. Progesterone starts increasing following ovulation in a normal menstrual cycle (Figure 4.1) and continues to increase throughout pregnancy (Figure 4.2). Progesterone has sleep inducing properties and has been repeatedly shown to increase REM sleep. Subcutaneous injection of pregnenolone (a precursor of progesterone) in rats was shown to enhance slow wave sleep (SWS) as well as increased the amount of REM sleep *(21)*. In addition, pregnenolone increased the amount of SWS without a change in cortisol or growth hormone (GH) *(22)*. When administered to male

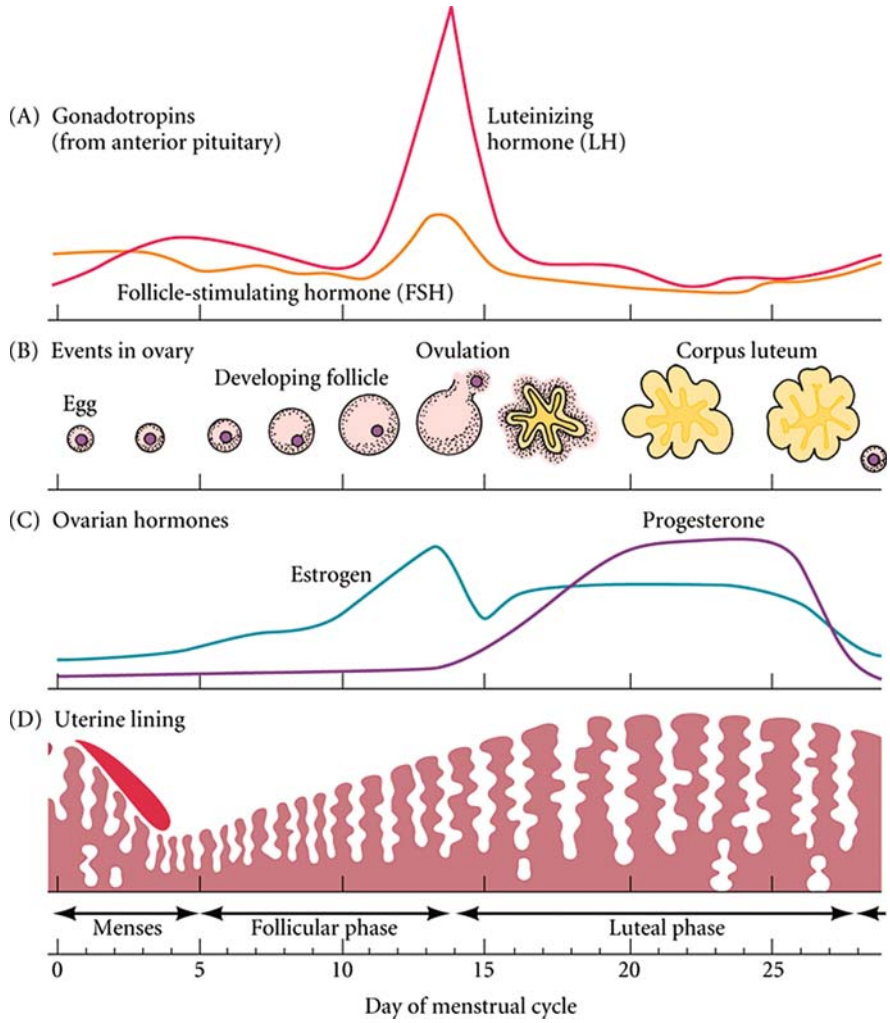


Figure 4.1 The human menstrual cycle. The coordination of (B) ovarian and (D) uterine cycles is controlled by (A) the pituitary and (C) the ovarian hormones. During the follicular phase the egg matures within the follicle and the uterine lining is prepared to receive a blastocyst. The mature egg is released around day 14. If a blastocyst does not implant in the uterus the uterine wall begins to break down, leading to menstruation (Permission was received from Sinaur Associates-the publisher. The source was Gilbert, Developmental Biology, Eighth Edition, Chapter 19, Hormones and Mammalian Egg Maturation.)

subjects in a double-blind placebo-controlled crossover study, progesterone led to an increase in non-REM sleep, a decrease in slow wave frequency EEG activity (0.4–4.3 Hz), and an increase in the higher frequency activity (>15 Hz) *(23)*. The effects of progesterone on REM latency and other measures of sleep architecture have not been consistent in the literature. One study of polysomnographic measures throughout the menstrual cycle showed no significant variation across the menstrual cycle for objective measures of total sleep time, sleep efficiency, sleep latency, REM sleep latency, and SWS *(24)*. Results from another study *(25)* indicated that REM latency was significantly shorter during the postovulatory (luteal) phase compared to the preovulatory (follicular) phase, but there was no significant difference in latency to sleep onset or the percentage of REM sleep.

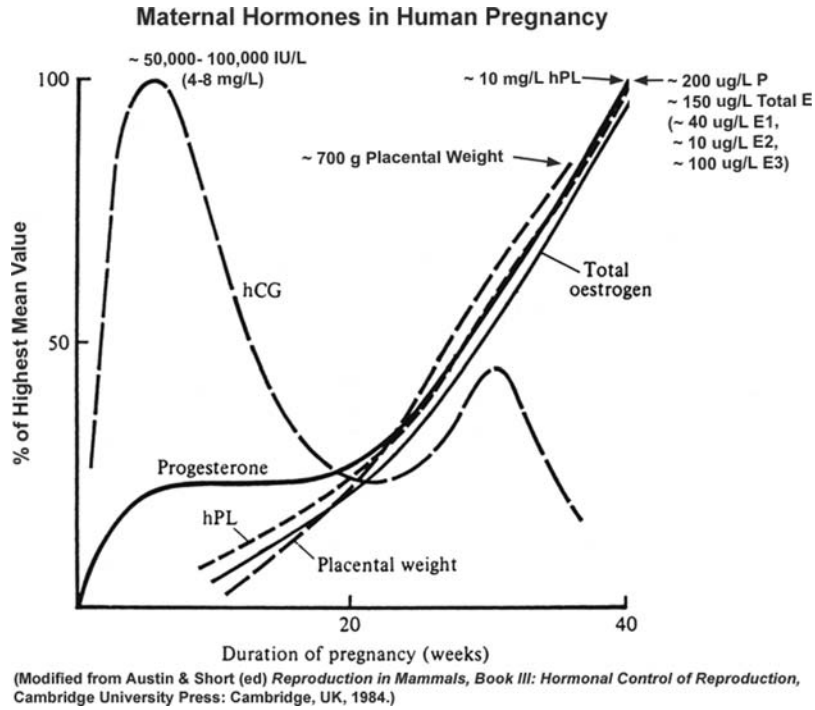


Figure 4.2 Changes in hormonal levels and placental weight during pregnancy. (Permission was received from Kenneth L. Campbell, Phd who previously published this information.)

On the other hand, progesterone has a stimulating effect on the ventilatory drive and increases upper airway dilator muscle electromyographic activity *(26)*. The respiratory stimulating properties of this hormone also enhance the responsiveness of the upper airway dilator muscles to chemical stimuli during sleep *(27, 28)* theoretically protecting against the development of sleep-disordered breathing.

A study of upper airway resistance of premenopausal women throughout the menstrual cycle *(29)* showed that during wake and stage 2 sleep, upper airway resistance was significantly higher in the follicular phase than in the luteal phase, as was the overall upper airway resistance combined for wake and across all sleep stages. In another study of 11 premenopausal women through their menstrual cycle, there was a trend toward less obstructive events in the "high progesterone periods" of the cycle in patients without any history of sleep disturbances at baseline *(30)*, suggesting a possible protective effect of progesterone.

On the other hand, it has been suggested that the strong ventilatory drive may result in a suction effect on the edematous upper airway and may lead to further obstruction *(31)*. Furthermore, it is plausible that the enhanced sensitivity of the respiratory center to CO_2, which occurs in pregnancy may predispose to central sleep apnea *(32)*.

It is possible that the effects of progesterone on breathing during sleep may be dose dependent. A study by Yamazaki *(33)* has shown that a low dose of progesterone significantly decreased the number but not the duration of spontaneous apneas and the post-sigh apneas in male rats. However, a higher dose (30 mg/kg) of progesterone had no effect on the number of spontaneous apneas and post-sigh apneas, while it prolonged the duration of post-sigh apneas.

Estrogen

Ample evidence has shown that estrogen reduces REM sleep *(34, 35, 36)*. Studies have shown that REM is enhanced in rats following ovariectomy *(37)* and reduced again following estrogen replacement. In humans, estrogen replacement has been shown to increase SWS in postmenopausal women *(38)* and improve sleep in women without hot flashes *(39)*. Estrogen replacement therapy was also shown to significantly reduce the apnea/hypopnea index in patients with mild to moderate sleep-disordered breathing *(40)*. The percent of total sleep time and of total NREM sleep time with oxygen saturation less than 90% was reduced on estrogen treatment relative to baseline but those results did not reach statistical significance. This trend was not present for estrogen and progesterone treatment relative to baseline *(40)*. This effect on sleep-disordered breathing cannot be explained on the basis of changes in sleep architecture or the effect on REM sleep since the time spent in REM and NREM sleep was not different in the estrogen group compared to baseline. On the other hand, D'Ambrosio et al. *(41)* administered Leuprolide acetate to 12 healthy volunteers and evaluated patients with sleep questionnaires and polysomnograms. The study showed no evidence of sleep fragmentation or any significant change in the apnea/hypopnea index in sex-hormone deficient subjects. The studied subjects reported increased snoring after Leuprolide administration; those symptoms were, however, not confirmed by polysomnography.

Corticotropin Releasing Hormone (CRH) and Cortisol

Corticotropin releasing hormone (CRH) is a hypothalamic hormone that leads to the stimulation of cortisol secretion. Intracerebroventricular administration of CRH in rats leads to a reduction in SWS *(42)*. Furthermore, pulsatile administration of intravenous CRH to young healthy males results in a decrease of the SWS by means of an increase in cortisol secretion and blunting of GH secretion *(43)*. In another study, pulsatile cortisol injections enhanced the slow wave activity on EEG spectral analysis in young normal men *(44)*. On the other hand, in postmenopausal women, urinary cortisol levels seem to negatively correlate with measures of NREM sleep but not with REM sleep *(45)*. In addition to its circadian variation, cortisol has been shown to be associated with depression *(46)*, which may contribute to sleep disturbances *(47)*.

In pregnancy, cortisol levels have been shown to progressively increase. For instance, in the third trimester, levels are double those in the pre-pregnant state. Levels rise to four times the pre-pregnancy state around labor and delivery. This rise in serum cortisol may contribute to the reduction in SWS seen in pregnancy. However, no studies have been directly performed to show a causal effect.

The interaction of cortisol with pregnancy hormones was evaluated in one study *(45)*. Sleep and urinary free cortisol levels were compared in two groups of post-menopausal women—one on estrogen replacement therapy (ERT) and an untreated group. This study found that under mildly stressful situations, women on unopposed ERT had greater time in stages 2, 3, and 4 and lower cortisol levels. Although both estrogens and cortisol are increased in pregnancy, no studies are available to examine the interaction of these hormones under these conditions.

Growth Hormone (GH)

Growth-hormone-releasing hormone (GHRH), also known as growth-hormone-releasing factor (GRF or GHRF), is a 44-amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus**.** GHRH is carried by the hypothalamo-hypophysial portal circulation to the anterior pituitary gland where it stimulates GH secretion and production. GHRH is released in a pulsatile manner, stimulating similar pulsatile release of GH.

Sleep promoting effects of GHRH are well established. Intracerebroventricular and intravenous administration of GHRH in rats and rabbits results in an increase in SWS *(42, 48)*. Studies in humans have shown that pulsatile administration of GHRH resulted in a surge in GH coupled with an increase in SWS *(49–51)*.

Growth hormone is also increased in pregnancy and may contribute to the somnolence associated with pregnancy *(52)*.

Melatonin

Melatonin is a hormone produced by the pineal gland, which modulates the sleep-wake cycle. Production of melatonin by the pineal gland is under the influence of the suprachiasmatic nucleus of the hypothalamus, which receives information from the retina about the daily pattern of light and darkness. Normally, the production of melatonin by the pineal gland is inhibited by light and permitted by darkness. The secretion of melatonin peaks in the middle of the night and gradually falls during the second half of the night.

Many melatonin users have reported an increase in the vividness or frequency of dreams. High doses of melatonin (50 mg) dramatically increased REM sleep time and dream activity in both narcoleptics and normal people *(53)*. A study by Lewy et al. *(54)* found that melatonin may ameliorate seasonal affective disorder and circadian misalignment. Other authors *(55)* still raise concerns about the effect of exogenous melatonin on the timing of endogenous production, raising the risk of exacerbating both clinical depression and seasonal affective disorder.

Melatonin has been well studied in pregnancy and not shown to be any different than the non-pregnant state *(56–58)*. In addition, concentrations of melatonin in the serum and the amniotic fluid of pregnant women in labor were found to follow a diurnal rhythm similar to that of non-pregnant women *(57)*.

Prolactin

Prolactin has been shown to promote REM sleep in rabbits *(60)* and may be responsible for the increase in REM sleep in early pregnancy in rats *(61)*. In humans with prolactinoma, SWS (but not REM sleep) seems to be enhanced when compared to matched controls *(62)*. The additional effect of luteinizing hormone may contribute to the increase in NREM sleep seen throughout pregnancy *(61)*. In a small study of pregnant patients, episodic secretion of prolactin was demonstrated and became augmented during nocturnal sleep *(63)*. The same study showed that higher levels of prolactin during pregnancy were related to increased secretion per secretory episode and concluded that the sleep-related secretory control of prolactin was maintained at a higher set-point during pregnancy *(63)*. A different study compared breastfeeding women to a group of age matched controls and a group of postpartum women who were bottle feeding *(64)*. Breast feeding women demonstrated a marked increase in SWS (182 ± 41 min)

compared with controls (86 ± 22 min, $P < 0.001$) and bottle feeding subjects (63 ± 29 min, $P < 0.001$).

Oxytocin

Oxytocin has been shown to peak at night in pregnancy and coincides with the onset of uterine contractions *(16)*. This factor may contribute to insomnia in the third trimester of pregnancy and possibly to arousals.

Human Gonadotropic Hormone (HCG)

Human gonadotropic hormone starts increasing about 2 weeks following conception in humans. HCG administration was shown to affect sleep-wake phases and other associated behaviors in rats which can collectively be described as longer sleeping time and decreased activity *(65)*. While administration of indomethacin alone had no effect, co-administration inhibited the effects of HCG, suggesting that the effects of HCG are probably mediated by increasing PGD_2 and decreasing PGE_2 in the areas of the brain which control these activities. After central HCG treatment, rats were less active and showed less exploratory behavior in an open-field box than the control animals *(66)*. Although no specific studies of the effect of HCG on sleep in humans are available, there is reason to believe that the same effects may apply to human pregnancy. The effects of these hormones are summarized in Table 4.1.

Cytokines

The most studied cytokines in their role in sleep are tumor necrosis factor α (TNF-α) and interleukin 1-β (IL-1). Injection of TNF-α or IL1 has been shown to induce physiological sleep but also enhance the amount of time spent in NREM sleep *(67)*. However, at high doses, IL-1 inhibits sleep rather than promotes it *(68)*. This sleep inhibition may result from an upregulation of the CRH-glucocorticoid axis *(68)*. Induction of the synthesis of IL-1 and TNF production by microbial substances such as viral double-stranded RNA for instance, also results in enhancement of NREM sleep *(69)*. IL-1 and TNF receptor knockout mice were shown to

Table 4.1 Effect of pregnancy hormones on sleep architecture.

	Levels in pregnancy	Effect on sleep architecture
Estrogen	Increased	Decreases REM in rats Increases SWS in humans
Progesterone	Increased	Increases REM in rats Increases NREM in humans
Prolactin	Increased	Increases REM in rabbits and rats Increases SWS in humans
CRH/ Cortisol	Increased	Decreases SWS in humans
GHRH/GH	Increased	Increases SWS in rats, rabbits and humans
Oxytocin	Increased, peaks at night	Likely causes arousals
BetaHCG	Increased	Longer sleep time and reduced activity in rats
Melatonin	Unchanged	Increases REM in humans

have altered physiological NREM sleep, suggesting that these cytokines play a role in sleep regulation in the absence of inflammation *(70, 71)*.

A few studies have been done linking IL-1 and TNF-α to pregnancy and pre-eclampsia. No direct studies have been done to evaluate the effect of these cytokines on sleep in pregnancy per se. IL-1 has been found in the uterus of mice on days 2 and 3 post-mating *(72)*. In addition, both IL-1 and TNF were found to be elevated in the second half of the pregnancy in the mouse uterus *(73)*. Moreover, elevated levels of IL-1 and TNF-α have been associated with pre-eclampsia in pregnant ewes *(74)*. On the other hand, sleep apnea is thought to be associated with an upregulation of TNF *(75)*. Furthermore, pregnant women with pre-eclampsia were shown to have smaller upper airways potentially predisposing them to the development of sleep-disordered breathing *(19)*. Further studies need to be done to study the effect of cytokines on pre-eclampsia and the likelihood of the development of sleep-disordered breathing.

Interleukin-6 (IL-6) is possibly a NREM-sleep inducing cytokine that is an active sleep modulator in certain disease states. Total sleep time and the amount of SWS seem to negatively correlate with daytime levels of IL-6 *(76)*, whereas increased secretion of IL-6 is related to stages 1 and 2 and REM sleep *(77)*. There are no studies that have evaluated the effect of IL-6 on sleep in pregnancy; however, maternal serum IL-6 has been suggested to be a possible biomarker for the development of preterm premature rupture of the membranes *(78)* (Figure 4.3).

Nitric oxide

Like IL-1 and TNF-α, nitric oxide (NO) enhances NREM sleep *(71)*. Further studies have shown that nitric oxide synthase-2 (NOS-2) knockout mice have more REM sleep and less NREM sleep than control mice *(79)*. On the other hand, NOS-1 knockout mice have manifested less REM sleep than controls *(79)*. NO has been implicated in the GHRH-induced pituitary release of GH, raising the possibility that NO may be involved in GHRH-induced sleep.

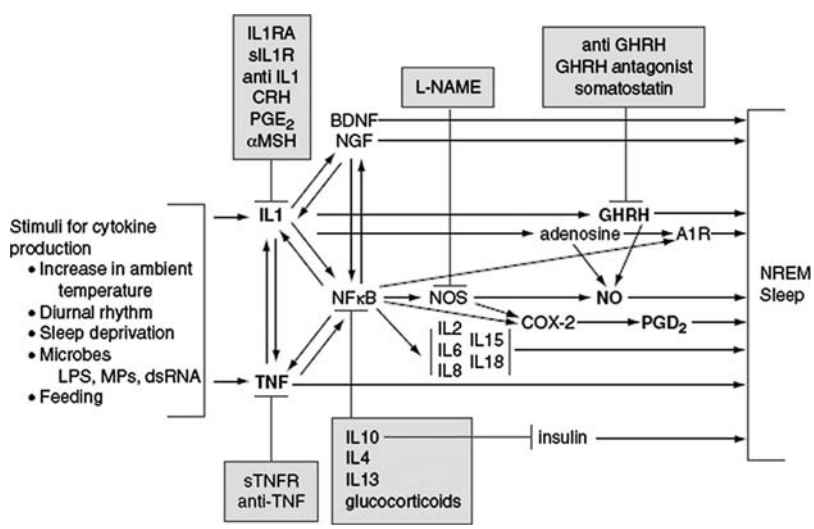


Figure 4.3 Potential roles of cytokines and hormones in inducing NREM sleep. (Permission was received from Wolters Kluwer Health/Lippincott Williams & Wilkins-the publisher. The source was Current Opinion in Pulmonary Medicine-Figure 1, Page 483.)

In pregnancy, NO may participate in the modulation of pressure and norepinephrine-induced tone of myometrial arteries of women with pre-eclampsia *(80)*. More so, in established pre-eclampsia, production of NO was higher in the uteroplacental, fetoplacental, and peripheral circulation than in normotensive pregnancies *(81)*. Plasma levels of NO were also higher in preeclamptic women suggesting an increased production in the setting of unchanged renal clearance *(82)*. Again, further studies need to be done in human pregnancy to study the role of NO and sleep in pregnancy and pre-eclampsia.

Oxygenation During Sleep in Pregnancy

Many respiratory physiologic changes occur in pregnancy affecting minute ventilation, ventilatory and oxygen reserve, oxygen tension, and carbon dioxide levels. The resting oxygen uptake in pregnancy (VO_2) is increased early in pregnancy and continues to gradually increase until term *(83–86)* (Table 4.2). This increase occurs as a result of the oxygen demands of the fetus and other products of conception as well as the increased oxygen demands by other maternal organs. Oxygen reserve is therefore reduced in pregnancy and is thought to be related to a reduced functional residual capacity *(87)* and an increase in metabolic rate. Progesterone helps counterbalance some of the above effects by stimulating the ventilatory drive leading to a higher minute ventilation. The end result is an increased PaO_2 in the resting, awake state. However, in the supine position, women in their late stages of pregnancy have been shown to have a significant drop in their oxygen saturation while awake *(88)* attributed to early closing volume.

While respiratory physiology in pregnancy has been studied somewhat, little is known about respiratory physiology during sleep in pregnancy. Cheun *(89)*

Table 4.2 Changes in sleep during pregnancy.

	Mechanical factors interrupting sleep	Ventilation	Oxygenation
First trimester	Micturition Gastroesophageal reflux Abdominal discomfort Leg cramps Restless legs	Increase in minute ventilation	+/–
Second trimester	Musculoskeletal discomfort Fetal movement Gastroesophageal reflux Abdominal discomfort Leg cramps Restless legs	Further increase in minute ventilation	+/–
Third trimester	Musculoskeletal discomfort Micturition Nocturnal contractions Fetal movement Gastroesophageal reflux Abdominal discomfort Leg cramps Restless legs	Additional increase in minute ventilation	Decrease in oxygen saturation in the supine position due to early closing volume and reduced cardiac output

studied pregnant patients admitted for cesarean section and matched them with non-pregnant controls admitted for gynecologic surgery. Anesthetized, paralyzed, ventilated patients in both groups were placed on 100% FiO_2 and then subjected to investigator-induced apneas. Pregnant patients showed a more rapid increase in their carbon dioxide levels than the non-pregnant controls (2.8 ± 1.2 mmHg/min in the non-pregnant group versus 6.8 ± 1.8 mmHg/min in the parturient group). In addition, pregnant patients desaturated much more quickly than non-pregnant controls (7.5 ± 0.9 min in the non-pregnant group compared to 3.6 ± 0.8 min in the pregnant group). Oxygen content was also significantly lower at 90% saturation versus 100% oxygen saturation in the pregnant group.

Normal values of nocturnal oxygen saturation in the general population have been established in a validation study by Gries in1996 *(90)*. Nocturnal oximetry has been evaluated in a few small studies in pregnancy but the results of those are conflicting. Authors of a few small studies have suggested that nocturnal saturation is unchanged in pregnancy *(91, 92)*. Nikkola et al. *(91)* reported mean saturations of 96.4% in 10 patients with multiple gestations and a minimum mean saturation of 92.9%. The authors concluded that nocturnal oxygenation was not affected in gravidas with multiple pregnancies. Trakkada et al. *(92)* have found a significant difference in the mean PaO_2 in the supine position between their pregnant and postpartum measurements on the same patients. There was, however, no difference between sleep stages or mean saturation in different sleep stages between the pregnant and the postpartum measurements. Others *(93)* have noted no difference in saturation in six patients tested at 36 weeks of gestation and six weeks post-partum. The mean saturation in that study was 95.64% ± 0.29 for the postpartum night and 95.42 ± 0.74 for the pregnant night. Minimal saturation was about 92% for the pregnant and the postpartum studies and was not considered abnormal. Another limitation of that study is the fact that sleep duration was different for each subject on each study night and there was a slight reduction in REM sleep on both nights. In addition, patients' weights were reported in the study but not the body mass index (BMI) and desaturations of 4% or more were not scored.

On the other hand, a study by Bourne *(94)* compared pregnant women with and without hypertension, late in their third trimester (>35 weeks gestation) to normal non-pregnant females. Mean nocturnal oxygen saturation was significantly lower in both pregnant groups compared with the non-pregnant group but as expected, BMI was significantly higher in the pregnant group. Seven of 28 patients (25%) in that study spent at least 20% of the night with saturations less than 90%. Feinsilver reported a small but significant decrease in nocturnal oxygen desaturation in 12 near-term healthy women compared to 10 age-matched controls *(95)*.

The difference in these data is in part related to the small number of patients recruited in each of these studies. Another factor is the different definitions of desaturations, the equipment used in the earlier studies providing suboptimal data, and the level of oxygen desaturation that would be considered significant in pregnancy. Another confounding factor could be the fact that the controls could not be matched for weight to the pregnant patients.

Control of Breathing During Sleep in Pregnancy

Progesterone is one of the two hormones responsible for maintaining pregnancy and circulating levels increase very early in gestation. However, progesterone has a significant impact on the respiratory system and has been shown to be a strong

respiratory stimulant. Progesterone upregulates the ventilatory drive by stimulating the chemoreceptors located on the ventrolateral surface of the medulla *(96, 97)*. In response to this stimulation, arterial carbon dioxide pressure ($PaCO_2$) is reduced to about 27–32 mmHg. Respiratory alkalosis ensues with a mean arterial pH of about 7.44 during pregnancy. This respiratory alkalosis is likely to result in instability of the respiratory control system during sleep *(98)*. In the non-pregnant population, hypocapnia and respiratory alkalosis may lead to central apneas during NREM sleep *(32)*. One small study of pregnant women showed that the frequency of hypopneas and apneas was less common in patients in late pregnancy compared to postpartum *(93)*. No conclusive evidence currently exists to establish whether respiratory alkalosis seen in pregnancy is associated with central apneas.

Sleep Measures in Normal Pregnancy

Few studies have been done to investigate changes in polysomnography that may occur during sleep in pregnancy. The most consistent findings in many studies have been increased awakenings after sleep onset and decreased sleep efficiency *(99–103)*. Changes in REM and NREM sleep in pregnancy and the postpartum period have been debated in the literature and the results vary depending on the testing site (laboratory or in the home), on the equipment used and on the inherent limitation of the night to night variability. Kimura *(104)* found that pregnancy increases NREM sleep in rats throughout gestation and enhanced REM sleep only in the first half of gestation.

A few studies have been performed in human pregnancies, some including actigraphy without polysomnography, others with polysomnography. Signal et al. *(105)* performed actigraphy studies on healthy pregnant women in the second trimester, one week before delivery, 1 week postpartum, and 6 weeks postpartum. Sleep efficiency was best in the second trimester and at six weeks postpartum when compared to the other periods. Total sleep duration was significantly lower (1.5 h less) in the first week postpartum than in the ante-partum period. When compared to multiparas, nulliparas had less efficient sleep, spent more time in bed and had greater wake after sleep onset (WASO) in the second trimester. Nulliparas also spent less time in bed and had fewer sleep episodes at one week postpartum *(105)*. Another study *(106)* has shown that sleep efficiency is lower in the postpartum period up to 3 months when compared to late gestation. As expected based on a newborn's needs, WASO was also shown to be longer in the entire three months postpartum period studied.

Schorr et al. *(107)* studied four pregnant women without known medical illnesses longitudinally during the course of the pregnancy and compared them to four healthy non-pregnant controls matched for age and weight. The study did not specify which pregnancy weight the controls were matched to. Significant differences were found between the two groups mainly in the SWS and those differences persisted in all trimesters. Normal delta wave sleep was identified in the control, non-pregnant subjects, whereas alpha intrusions were seen in the pregnant group. Despite the fact that this abnormal-appearing delta sleep was still included as stage 3/4 sleep, pregnant women spent less time in SWS than the control group.

Another study *(108)* compared polysomnographic findings of 14 pregnant patients with a history of affective disorder and 20 pregnant patients without any

medical or psychiatric history. Both groups were studied in their own homes. In the normal childbearing group, there was a progressive reduction in sleep efficiency as pregnancy progressed but sleep efficiency was most reduced in the first month postpartum. Repeated measures analysis of variance (ANOVA) showed significant effects of time were also observed for NREM sleep stages 2, 3, and 4 and REM activity in the normal childbearing group. There was a divergence in REM sleep latency between the normal and the affective disorder group at 36 weeks where REM latency decreased in the latter and remained reduced until eight months postpartum. Brunner *(99)* has also found a reduction in the power density of NREM sleep in the course of pregnancy. The changes in REM sleep with time in pregnancy were not as reliable in that study since there was a significant night to night variability in the study done in the second trimester *(99)*.

Summary

Pregnancy is associated with a multitude of factors that could result in sleep disruption and a change in sleep architecture. Mechanical factors vary according to the stage of the pregnancy. Hormones that have an effect on sleep in pregnancy like estrogen, progesterone, beta HCG, prolactin, and others generally start increasing early in pregnancy.

In a normal pregnancy, these changes result in complaints of sleep disruption and daytime hypersomnolence. However, patients with preexisting disorders may be affected more severely by these changes. Obstructive sleep apnea may worsen during pregnancy because of the anatomic and physiologic changes. Patients with chronic pulmonary disease may drop their oxygen saturation further during sleep in pregnancy, especially in the late stages given the drop in functional residual capacity associated with late pregnancy and the relative hypoventilation that occurs during normal sleep. Neuromuscular disorders affecting respiratory muscles may worsen in pregnancy. It is likely that those patients hypoventilate further during sleep.

Implications for the fetus of sleep changes in mothers with chronic lung or neuromuscular disease are related to the development of fetal hypoxemia and/or hypercapnia. Maternal PaO_2 levels of 70 mmHg or lower are poorly tolerated by the fetus and sustained hypoxemia results in fetal metabolic acidemia. Elevated maternal $PaCO_2$ levels also result in fetal acidosis and changes in placental perfusion. The effects of intermittent desaturations on fetal wellbeing such as those occurring in patients with sleep apnea are not well studied in pregnancy.

References

1. Rechtschaffen A, Bergmann BM, Everson CA, et al. Sleep deprivation in the rat: X. Integration and discussion of the findings. Sleep 1989;12:68.
2. Rechtshaffen A, Kales A (Eds). A manual of standardized terminology and scoring system for sleep stages of human subjects. U.S. Government Printing Office, Washington, DC: NIH Publication No. 204, 1968.
3. Sherin JE, Shiromani PJ, McCarley RW, Saper CB. Activation of ventrolateral preoptic neurons during sleep. Science 1996;271:216–9.

4. Jones BE. Basic mechanisms of sleep wake states. In: Kryger MH, Roth T, Dement WC (Eds). Principles and Practice of Sleep Medicine. 3rd ed. Philadelphia: Saunders; 2000:134–54.
5. Shouse MN, Siegel JM. Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. Brain Res. 1992;571:50–63.
6. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 1975;189:55–8.
7. American Academy of Sleep Medicine. International Classification of sleep disorders, revised: Diagnostic and coding manual, Westchester (IL): American Academy of Sleep Medicine, 2000, 114–5.
8. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mother's sleep. Sleep Med 2002;3:37–42.
9. Parboosingh J, Doig A. Studies of nocturia in normal pregnancy. BJOG 1973;80(10), 888–95.
10. Baratte-Beebe KR, Lee K. Sources of midsleep awakenings in childbearing women. Clin Nurs Res 1999;8(4):386–97.
11. Goldsmith LT, Weiss G, Steinetz BG. Relaxin and its role in pregnancy. Endocrinol Metab Clin North Am 1995;24:171–86.
12. Sherwood OD, Downing SJ, Guico-Lamm ML, Hwang JJ, O'Day-Bowman MB, Fields PA. The physiological effects of relaxin during pregnancy: studies in rats and pigs. Oxf Rev Reprod Biol 1993;15:143–89.
13. Ekbom KA. Restless legs syndrome. Neurology 1960;10:868–73.
14. Goodman JD, Brodie C, Ayida GA. Restless leg syndrome in pregnancy. BMJ 1988;297(6656):1101–2.
15. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology 2004;63(6):1065–9.
16. Hirst JJ, Haluska GJ, Cook MJ, Hess DL, Novy MJ. Comparison of plasma oxytocin and catecholamine secretions with uterine activity in pregnant rhesus monkeys. J Clin Endocrinol Metab 1991;73:804–10.
17. Camann WR, Ostheimer GW. Physiological adaptation during pregnancy. Intern Anesthes Clin 1990;28:2–10.
18. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallanpati score during pregnancy. Br J Anesth 1995;74:638–42
19. Izci B, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. Sleep disordered breathing and upper airway size in pregnancy and post-partum. Eur Respir J 2006;27(2):321–7.
20. Izci B, Riha RL, Martin SE, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med 2003 Jan 15;167(2):137–40.
21. Lancel M, Cronlein TA, Muller-Preuss P, Holsboer F. Pregnenolone enhances EEG delta activity during non-rapid eye movement sleep in the rat, in contrast to Midazolam. Brain Res 1994;646:85–94.
22. Steiger A, Traschel L, Guldner J, Hemmeter U, Rother B, Rupprecht R, Vedder H, Holsboer F. Neurosteroid pregnenolone induces sleep-EEG changes in man compatible with inverse agonistic $GABA_A$ –receptor modulation. Brain Res 1993;615: 267–74.
23. Friess E, Tagaya H, Trachsel L, Holsboer F, Rupprecht R. Progesterone induced changes in sleep in male subjects. Am J Physiol 1997;272:E885–91.
24. Driver HS, Dijk DJ, Werth E, Biedermann K, Borbely AA. Sleep and the sleep electroencephalogram across the menstrual cycle in young healthy women. J Clin Endocrinol Metab 1996 Feb;81(2):728–35.
25. Lee KA, Shaver JF, Giblin EC, Woods NF. Sleep patterns related to menstrual cycle phase and premenstrual affective symptoms. Sleep 1990 Oct;13(5):403–9.
26. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol 1998;84:1055–62.

27. Parisi RA, Santiago TV, Edelman NH. Genioglossal and diaphragmatic EMG responses to hypoxia during sleep. Am Rev Respir Dis 1988;138:610–6.
28. Wheatley JR, White DP. The influence of sleep on pharyngeal reflexes. Sleep 1993;16:587–9.
29. Driver HS, McLean H, Kumar DV, Farr N, Day AG, Fitzpatrick MF. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. Sleep 2005;28(4):449–56.
30. Stahl ML, Orr WC, Males JL. Progesterone levels and sleep-related breathing during menstrual cycles of normal women. Sleep1985;8(3):227–30.
31. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 1978;44:931–8.
32. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999;341:949–54.
33. Yamazaki H, Haji A, Ohi Y, Takeda R. Effects of progesterone on apneic events during behaviorally defined sleep in male rats. Life Sci 2005 Dec 12;78(4):383–8.
34. Colvin GB, Whitmoyer DI, Lisk RD, Walter DO, Sawyer CH. Changes in sleep-wakefulness in female rats during circadian and estrus cycles. Brain Res 1968; 7:173–83.
35. Branchey M, Branchey L, Nadler RD. Effects of estrogen and progesterone on sleep patterns of female rats. Physiol Behav 1971;6:743–6.
36. Fang J, Fishbein W. Sex differences in paradoxical sleep: influence of estrus cycle and ovariectomy. Brain Res 1996;734:275–85.
37. Colvin GB, Whitmoyer DI, Sawyer CH. Circadian sleep-wakefulness patterns in rats after ovariectomy and treatment with estrogen. Exp Neurol 1969;25:616–25.
38. Leproult R, Hoffmann E, Plat L, van Cauter E. Slow wave activity: effects of gender, age, and estrogen replacement therapy. Sleep 1998;21:300.
39. Polo-Kantola P, Efkkola R, Helenius H, Irjala K, Polo O. When does estrogen replacement therapy improve sleep quality? Am J Obstet Gynecol 1998;178:1002–9.
40. Manber R, Kuo TF, Cataldo N, Colrain IM. The effects of hormone replacement therapy on sleep-disordered breathing in postmenopausal women: a pilot study. Sleep 2003;26(2):163–8.
41. D'Ambrosio C, Stachenfeld NS, Pisani M, Mohsenin V. Sleep, breathing and menopause: The effect of fluctuating estrogen and progesterone on sleep and breathing in women. Gend Med 2005;2:238–45.
42. Ehlers CL, Reed TK, Henriksen SJ. Effects if corticotropin releasing factor and growth hormone releasing factor on sleep and activity in rats. Neuroendocrinology 1986;42:467–74.
43. Holsboer F, von Bardeleben U, Steiger A. Effects of intravenous corticotropin releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. Neuroendocrinology 1988;48:32–8.
44. Friess E, Tagaya H, Grethe C, Traschel L, Holsboer F. Cortisol infusion increases EEG slow wave activity within non-REM sleep in humans. J Sleep Res 1996;5 (suppl 1):69.
45. Prinz P, Bailey S, Moe K, Wilkinson C, Scanlan J. Urinary free cortisol and sleep under baseline and stressed conditions in healthy senior women: effect of estrogen replacement therapy. J Sleep Res 2001;10:19–26.
46. Sachar EJ, Roffwarg HP, Gruen PH, Altman N, Sassin J. Neuroendocrine studies of depressive illness. Pharmacopsychiatr Neuropscychopharmakol 1976;9:11–17.
47. Collop NA. Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. Clin Chest Med 2004 Jun;25(2):257–68.
48. Obal F Jr, Alfoldi P, Cady AB, Johannsen L, Sary G, Krueger JM. Growth hormone releasing factor enhances sleep in rats and rabbits. Am J Physiol 1988; 255: R310–6.
49. Steiger A, Guldner J, Hemmeter U, Rothe B, Wiedemann K, Holsboer F. Effects of growth hormone releasing factor and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. Neuroendocrinology 1992;56:566–73.

50. Kerkhofs M, van Cauter E, van Onderbergen A, Caufriez A, Thorner MO, Copinschi G. Sleep promoting effects of growth hormone releasing hormone in normal men. AM J Physiol 1993;264: E594–8.
51. Marshall L, Moelle M, Boeschen G, Steiger A, Fehm HL, Born J. Greater efficacy of episodic than continuous growth hormone releasing hormone (GHRH) administration in promoting slow wave sleep (SWS). J Clin Endocrinol Metab 1996;81:1009–13.
52. Santiago JR, Nolledo MS, Kinzler W, Santiago T. Sleep and sleep disorders in pregnancy. Ann Intern Med 2001;134:396–408.
53. Lewis A. Melatonin and the Biological Clock. New York: McGraw-Hill; 1999:23.
54. Lewy A, Sack R, Miller L, Hoban T. Antidepressant and circadian phase-shifting effects of light. Science 1987;235(4786):352–4.
55. Sankaran M, Subramanian P. Modulation of biochemical circadian rhythms during long-term melatonin treatment in rats. Singapore Med J 2006;47(1):42–7.
56. Yellon SM, Longo LD. Melatonin rhythms in fetal and maternal circulation during pregnancy in sheep. Am J Physiol 1987;252:E799–E802.
57. Zemdegs IZ, McMillen IC, Walker DW, Thorburn GD, Nowak R. Diurnal rhythms in plasma melatonin concentrations in the fetal sheep and pregnant ewe during late gestation. Endocrinology 1987;123:284–9.
58. Zarazaga LA, Malpaux B, Chemineau P. The characteristics of the melatonin secretory rhythm are not modified by the stage of pregnancy in ewes. Reprod Nutr Dev 1996;36:105–12.
59. Kivela A, Kauppila A, Leppaluoto J, Vakkuri O. Serum and amniotic fluid melatonin during human labor. J Clin Endocrinol Metab 1989;69:1065–8.
60. Obal F Jr, Opp M, Cady AB, Johannsen L, Krueger JM. Prolactin, vasoactive intestinal peptide, and peptide histidine methionine elicit selective increases in REM sleep in rabbits. Brain Res 1989;490:292–300.
61. Kimura M, Zhang SQ, Inoue S. Pregnancy associated sleep changes in the rat. Am J Physiol 1996;27:R1063–9.
62. Frieboes RM, Murck H, Stalla GK, Antonijevic IA, Steiger A. Enhanced slow wave sleep in patients with prolactinoma. J Clin Endocrinol Metab 1998;83(8):2706–10.
63. Boyar RM, Finkelstein JW, Kapen S, Hellman L. Twenty four hour prolactin secretory patterns during pregnancy. J Clin Endocrinol Metab 1975;40(6):1117–20.
64. Blyton DM, Sullivan CE, Edwards N. Lactation is associated with an increase in slow-wave sleep in women. J Sleep Res 2002;11:297–303.
65. Toth P, Lukacs H, Hiatt ES, Reid KH, Iyer V, Rao CV. Administration of human chorionic gonadotropin affects sleep-wake phases and other associated behaviors in cycling female rats. Brain Res 1994;654(2):181–90.
66. Lukacs H. Rat as model for studying behavior effects of hCG. Sem Reprod Med 2001;19(1):111–9.
67. Krueger JM, Obal F Jr, Fang J. Humoral regulation of physiological sleep: cytokines and GHRH. J Sleep Res 1999;8(Suppl 1):53–59.
68. Krueger JM, Obal F Jr, Fang J, Kubota T, Taishi P. The role of cytokines in physiological sleep regulation. Ann NY Acad Sci 2001;933:211–21.
69. Krueger JM, Majde JA. Microbial products and cytokines in sleep and fever regulation. Crit Rev Immunol 1994;14:355–79.
70. Obal F Jr, Kruger JM. Biochemical regulation of non-rapid eye movement sleep. Front Biosci 2003;8:520–50.
71. Krueger JM, Fang J, Taishi P, et al. Biochemical regulation of non rapid eye movement sleep. Ann NY Acad Sci 1998;856:148–59.
72. De M, Sanford TR, Wood GW. Expression of interleukin 1, interleukin 6 and tumour necrosis factor alpha in mouse uterus during the peri-implantation period of pregnancy. J Reprod Fertil 1993;97:83–9.
73. De M, Sanford TR, Wood GW. Detection of interleukin-1, interleukin-6, and tumor necrosis factor-α in the uterus during the second half of pregnancy in the mouse. Endocrinology 1992;131(1):14–20.

74. Yarm G, Karahan S, Nisbet C. Elevated Plasma Levels of Interleukin 1β, Tumour Necrosis Factor α and Monocyte Chemotactic Protein 1 Are Associated with Pregnancy Toxaemia in Ewes. Vet Res Commun 2007;31(5):565–73(9).
75. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metabol 2000 Mar;85(3):1151–8.
76. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. J Clin Endocrinol Metab 1999;84:2603–2607.
77. Redwine L, Hauger J, Gillin G, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol and melatonin in humans. J Clin Endocrinol Metab 2000;85:3597–3603.
78. Murtha AP, Sinclair T, Hauser ER, Swamy GK, Herbert WN, Heine RP. Maternal serum cytokines in preterm premature rupture of membranes. Obstet Gynecol 2007 Jan;109(1):121–7.
79. Chen L, Majde JA, Krueger JM. Spontaneous sleep in neuronal and inducible nitric oxide synthase knockout mice. Sleep 2002;25:A170–1.
80. Kublickiene KR, Lindblom B, Kruger K, Nisell H. Preeclampsia: evidence for impaired shear stress-mediated nitric oxide release in uterine circulation. Am J Obstet Gynecol 2000 Jul;183(1):160–6.
81. Norris LA, Higgins JR, Darling MR, Walshe JJ, Bonnar J. Nitric oxide in the uteroplacental, fetoplacental and peripheral circulations in preeclampsia. Obstet Gynecol 1999 Jun;93(6):958–63.
82. Ranta V, Viinikka L, Halmesmaki E, Ylikorkala O. Nitric oxide production with preeclampsia. Res Support, Non-U.S. Gov't Obstet Gynecol 1999 Mar;93(3):442–5.
83. Elkus R, Popovich J. Respiratory physiology in pregnancy. Clin Chest Med. 1992;13:555–65.
84. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung: state of the art. Am Rev Respir Dis 1988;137:559–81.
85. Dempsey JA, Olson EB, Skatrud JB. Hormones and neurochemicals in the regulation of breathing. In: Fishman AP, Cherniak NS, Widdicombe JG, Geiger SR (Eds). Handbook of Physiology. The Respiratory System. Control of Breathing. Section 3, Volume II. Bethesda, MD: American Physiological Society; 1986:181–221.
86. Rees GB, Pipkin FB, Symonds EM, Patrick JM. A longitudinal study of respiratory changes in normal human pregnancy with cross sectional data on subjects with pregnancy induced hypertension. Am J Obstet Gynecol 1990;162:826–830.
87. Cugell DW, Frank NR, Gaensler EA, Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc 1953;67:568–97.
88. Ang CK, Tan TH, Walters WA, Wood C. Postural influence on maternal capillary oxygen and carbon dioxide tension. Br Med J, 1969;4:201–3.
89. Cheun JK, Choi KT. Arterial oxygen desturation rate following obstructive apneas in parturients. J Korean Med Sci 1992;7(1):6–10.
90. Gries RE, Brooks LJ. Normal oxyhemoglobin saturation during sleep. How low does it go? Chest 1996;100:1489–92.
91. Nikkola E, Ekblad U, Ekholm E, Mikola H, Polo O. Sleep in multiple pregnancy: breathing patterns, oxygenation and periodic limb movements. Am J Obstet Gynecol 1996;174:1622–5.
92. Trakada G, Tsapanos V, Spiroupolos K. Normal pregnancy and oxygenation during sleep. Eur J Obstet Gynecol Repro Biol 2003:109(2):128–32.
93. Bronwell LG, West P, Kryger MH. Breathing during sleep in normal pregnant women. AJRCCM 1986:133:38–41.
94. Bourne T, Ogilvy AJ, Vickers R, Williamson K. Nocturnal hypoxemia in late pregnancy. Br. J Anaethesia 1995;75:678–82.
95. Feinsilver S, Hertz G. Respiration during sleep in pregnancy. Clin Chest Med 1992;13:637–44.

96. Lyons HA. Centrally acting hormone and respiration. Pharmacol Ther 1976;2:743–51.
97. White DP, Douglas NJ, Pickett CK, et al. Sexual influence on the control of breathing. A Appl Physiol 1983;54:874–9.
98. Edwards N, Middleton OG, Blyton DM, Sullican CE. Sleep disordered breathing and pregnancy. Thorax 2002;57(6):555–8.
99. Brunner DP, Münch M, Biedermann K, Huch R, Huch A, Borbély AA. Changes in sleep and sleep electroencephalogram during pregnancy. Sleep 1994;17:576–82.
100. Driver HS, Shapiro CM. A longitudinal study of sleep stages in young women during pregnancy and postpartum. Sleep 1992;15:449–53.
101. Hertz G, Fast A, Feinsilver SH, Albertario CL, Schulman H, Fein AM. Sleep in normal late pregnancy. Sleep 1992;15:246–51.
102. REM sleep and mood state in childbearing women: sleepy or weepy? Sleep 2000;23:877–85.
103. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstet Gynecol 2000;95:14–8.
104. Kimura M, Zhang SQ, Inoue S. An animal model for pregnancy associated sleep disorder. Psychiatry Clin Neurosci 1998;52(2):209–11.
105. Signal TL, Gander PH, Sangalli MR, Travier N, Rirestone RT, Tuohy JF. Sleep duration in healthy nulliparous and multiparous women across pregnancy and postpartum. Aust N Z J Obstet Gynaecol 2007;47:16–22.
106. Shinkoda H, Matsumoto K, Park YM. Changes in sleep wake cycle during the period from late pregnancy to puerperium identified through the wrist actigraph and sleep logs. Psychiatry Clin Neurosci 1999;53:133–5.
107. Schorr SJ, Chawla A, Meenakshi D, Sullivan CA, Naef RW III, Morrison JC. Sleep patterns in pregnancy: A longitudinal study of polysomnography recordings during pregnancy. J Perinatol 1998;18(6):(pt 1) 427–430.
108. Coble PA, Reynolds CF, Kupfer DJ, Houck PR, Day NL, Giles DE. Childbearing in women with and without a history of affective disorder. II. Electroencephalographic sleep. Compr Psychiatry 1994;35(3):215–24.

Part II

General Management Principles in Pregnancy

5

Diagnostic Imaging in Pregnancy

Margaret Miller and Lucia Larson

Keywords: radiation, teratogenicity, oncogenicity, ionizing radiation, radioisotopes

The decision to order diagnostic imaging in pregnancy is often filled with anxiety. Both the patient and provider may be fearful of the potential harmful effects of radiation on the fetus. The term radiation itself provokes images of atomic bombs and nuclear accidents. Although there is evidence that such massive doses of radiation may be associated with poor outcomes in pregnancy, it is the job of the clinician to educate women about the differences in dose and risk of radiation used in most diagnostic procedures.

In many cases, diagnostic radiography is unavoidable in the evaluation and treatment of the pregnant women. In such cases, it is important to balance the potential benefits of the testing with an accurate assessment of the risk of the procedure. In short, the test is indicated when the benefits to maternal well-being outweigh the risk of harm to the mother or the fetus. While imaging with X-ray, CT, or nuclear medicine techniques are associated with exposure to ionizing radiation, almost all of these imaging studies are associated with radiation doses that are well below the acceptable limit for pregnancy. Ultrasound and MRI do not involve ionizing radiation and may provide an alternative option in some circumstances.

Ionizing Radiation

Exposure to in utero irradiation may result in either (1) cell killing or (2) unrepaired or misrepaired DNA damage. A wide range of fetal and childhood abnormalities including death, cataracts, growth restriction, malformation, CNS abnormalities, and leukemia have been associated with high dose radiation in pregnancy. Fortunately, nearly all properly performed diagnostic procedures involve far less radiation and are associated with no measurable risk to the offspring. A number of studies have identified several specific areas of concern regarding radiation effects on the fetus. These include possible teratogenicity, genetic damage, intrauterine death, and oncogenicity.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_5

Teratogenicity

To determine the magnitude of risk of teratogenicity with the use of any diagnostic imaging procedure, it is important to consider the type of radiation, the absorbed dose of radiation, the gestational age at the time of the exposure, and the method of administration.

Radiation Dose

The absorbed dose of radiation is expressed in a number of different units of measurement (Table 5.1). These measurements reflect both the absorbed dose of radiation and the biological risk of radiation. For example, measurements of the absorbed dose include the Gray (Gy) or milligray (mGy) and the radiation absorbed dose (rad). One Gy is equivalent to 100 rad. The Sievert is a unit of measurement which reflects the biological risk of radiation and is calculated from the absorbed dose (expressed in Gy) multiplied by weighting factors including the radiation type (alpha, beta, gamma), the means of exposure (internal versus external) and the sensitivity of the organ or tissue exposed. Acceptable limits of radiation exposure are most often expressed in Sieverts. Safety legislation regarding occupational exposure to radiation recommends limits of 100 mSv/5 years for individuals who work in the presence of radiation. For a worker who becomes pregnant, recommended limits for occupational exposure to the fetus range from 2 mSv to 5 mSv for the duration of the pregnancy *(1, 2)*. Pregnant women may be exposed to radiation in a number of ways. All women have some radiation exposure in pregnancy from so-called background sources. Background radiation comes from the atmosphere, ground, and even food and beverage. The average worldwide exposure to natural radiation sources is 2.4 mSv *(3)*. Higher exposures occur at high altitudes and high latitudes. Of note, there is no consistent evidence that microwave ovens, video display terminals, cellular telephones, or other wireless networks pose a risk to the fetus.

Timing of Radiation Exposure

It is well established that ionizing radiation interferes with cell proliferation. Therefore, biological systems with a high fraction of proliferating cells show high radiation responsiveness. As a result, the embryo and fetus are highly sensitive to the effects of radiation during the entire period of prenatal development. However,

Table 5.1 Measures of radiation dose.

Quantity measured	International system	Definition	Equivalents
Dose absorbed	GRAY (Gy)	1 Gy = energy released by joule per kilogram of matter	1 Gy = 1000 mGy 1 Gy = 100 rad
	RAD (radiation absorbed dose)	1 rad = the absorption of radiation energy per gram of matter	1 rad = 0.01 Gy
Equivalent dose and effective dose	SIEVERT (SV)	Sv = Gy multiplied by weighting factor specific to each type of radiation and organ exposed.	Measurement of biologic risk. Dose limits are expressed in SIEVERTS

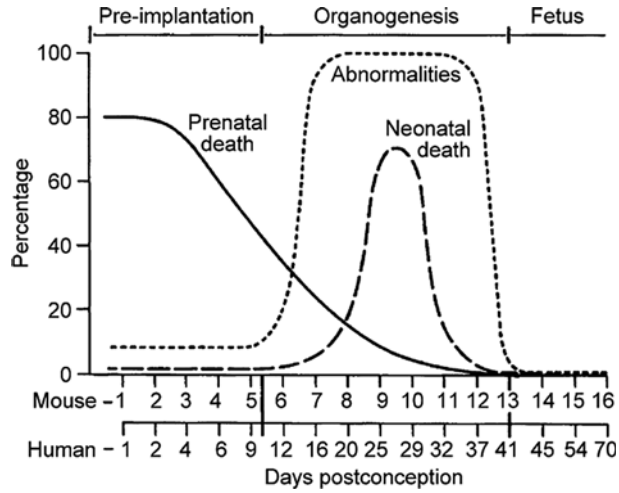


Figure 5.1 The occurrence of lethality and abnormalities in mice after a prenatal radiation exposure of about 2 Gy given at various times postconception. The two seales for the abseissa compare developmental stages in days for mice and humans (redrawn from Hall. 1994 with the permission of Hall and the publisher)

the dominant effect of radiation is highly dependent on the timing of the exposure (Figure 5.1). Prenatal development is divided into three main periods:

Pre-implantation	(0–2 weeks following conception)
Major Organogenesis	(3–8 weeks following conception)
Fetal Period	(9 weeks-term following conception)

The preimplantation stage of pregnancy most often goes unrecognized in clinical practice. As a result, human data is lacking and estimates of risk of radiation during this period are based solely on animal studies. Fortunately the process of cell proliferation and differentiation and the duration of the pre-implantation period are much the same for most mammalian species, so that generalization from animal studies is reasonable *(4)*. It is well established that the dominant effect of irradiation during this stage of gestation is early death of the conceptus *(5, 6)*. Radiation induced malformations or cancer are very unlikely. During the preimplantation period, cells are pluripotent, so the conceptus has the ability to replace cells damaged by significant radiation exposure. A number of animal studies postulate an "all or none" phenomenon with the outcome of significant radiation exposure being either a normal conceptus (one that has successfully replaced cells damaged by radiation) or complete resorption of the embryo (too many damaged cells resulting in death of the conceptus), which is usually undetectable *(7, 8)*. However, recent animal data show that although ionizing radiation in the preimplantation period may rarely induce malformations in mice, those mice were thought to originate from less vigorous embryos and are genetically predisposed for the specific malformation *(9, 10)*. This would suggest that there may be some rare exceptions to the "all or none" theory, but it would be premature to apply these experimental animal findings to clinical practice.

The lethal effect of radiation during the preimplantation period decreases rapidly during the days following the preimplantation period at which time the

risk of teratogenesis increases significantly (Figure 5.1). Based on these observations, women who are inadvertenly exposed to radiation in the preimplantation period may be counseled that, if the embryo survives, the risk of malformations, cancer, or other abnormalities is highly unlikely.

The embryo is most sensitive to the teratogenic effects of radiation during organogenesis (3–8 weeks after conception). Differences in both short and long term teratogenic effects are dependent of the developmental stage at the time of exposure (Figure 5.2). Among numerous animal studies, only a minority are able to show a complete dose-effect series. As a result, there is disagreement about the lowest teratogenic dose. Most animal data report a minimal dose that could produce teratogenic effects to be anywhere from 0.1 Gy to 0.5 Gy *(11, 12)*. The International Commission on Radiological Protection (ICRP) recommends 0.1 Gy (10 rad) at any time in gestation as a practical threshold for the induction of congenital defects *(13)*. The National Council on Radiation Protection and Measurements (NCRP) concurs that deleterious effects on the fetus are highly unlikely with exposure to less than 0.1 Gy (10 rad), but suggest that doses below 0.05 Gy (5 rad) be considered the threshold of acceptable risk *(14)*. National epidemiologic data from survivors of atomic radiation in Hiroshima and Nagasaki have been evaluated and re-evaluated over the past 50 years *(15–17)*. In these cohorts, the most common abnormalities were microcephaly, mental retardation, growth stunting, and early childhood mortality with a low rate of minor malformations. For children whose mothers were exposed in Hiroshima during weeks 6–15 postconception, a minimal dose of 50 rad was calculated for the induction of mental retardation *(18, 19)*. The minimum dose observed in Nagasaki was higher (200 rads), a difference that was attributed to the difference in neutron components of the radiation. This is 100–1,000 times the expected exposure from most simple diagnostic procedures (Table 5.2). For example, a single chest film is associated with less than 0.01 mGy or < 0.001 rad, meaning that pregnant women would need

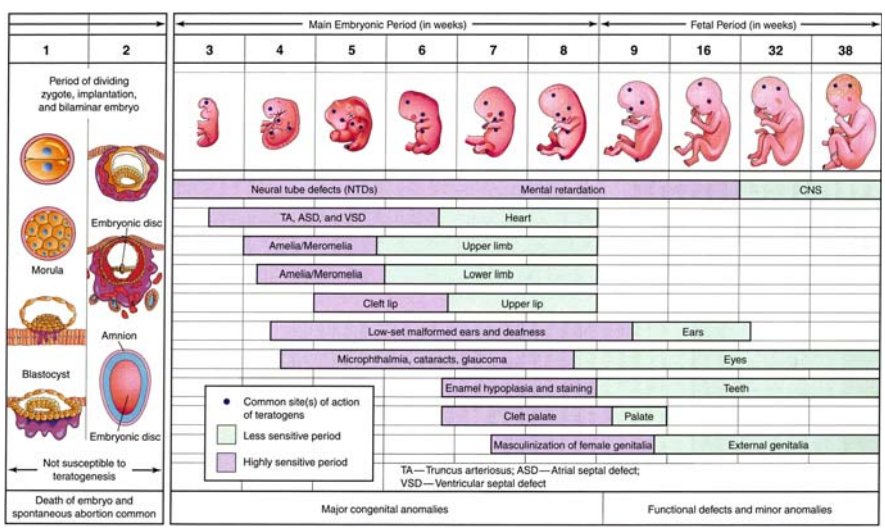


Figure 5.2 With permission from J. Valentin (Ed.) Annals of the ICRP-ICRP publication 90 2003; p.10 © Elsevier (2008)

Table 5.2 Mean ionizing radiation exposure to fetus.

Part or body region	Imaging technique	Mean radiation exposure Rads (mGy)	Other effects on pregnancy and lactation
Chest	CXR	<0.001 (<0.01)	
	CT	0.006 (0.06)	Counsel about potential risk of contrast Theoretical increased risk of breast cancer with irradiation of breast (consider use of breast sheields)
	CT pulmonary angiography (multidetector row CT)	0.00033–0.0013 (0.0033–0.013)	Counsel about potential risk of contrast Theoretical increased risk of breast cancer with irradiation of breast (consider use of breast shields)
	Ventilation Scan • Xenon 133 • Krypton 81 m	0.038–0.051 (o.38-0.51) 0.028–0.050 (0.28–0.50)	Radioisotope accumulates in bladder so hydration with frequent urination in the pregnant woman may help to minimize exposure to the fetus. Counsel about need to interrupt breastfeeding
	Perfusion Scan • Tc99-MAA • ½ dose Tc-99-MAA	0.022 (0.22) 0.014–0.025 (0.14–0.25)	
	Pulmonary angiography	<0.050 via brachial route (<0.5) 0.2–0.3 via femoral route (2–3)	
	CT venography	5 (50)	
	Conventional venography	0.6 (6)	
	MRI	No ionizing radiation	
	PET Scan with F-FDG		

to have 1,000 chest films before reaching the threshold at which there may be an increased risk to her offspring.

During the fetal period (9 weeks post-conception to term), the fetus is most sensitive to the growth-restricting effects of radiation. Malformations are unlikely, however very high doses of radiation (500–100 mGy or 50–100 rads) may have a cell-depleting effect on the central nervous system resulting in microcephaly or mental retardation. This is most evident in studies following massive radiation exposure to radiation in Hiroshima in 1945 *(20)*. Similar outcomes following the Chernobyl accident have not been reported. The ICRP advises that a threshold of 100–200 mGy is necessary to consider a risk of fetal malformation, central nervous system damage or fetal death *(21)*. All commonly used diagnostic imaging procedures are well below this threshold of radiation (Table 5.2).

Method of Administration

In addition to the dose, the radiation technique and site may affect the absorbed dose to the fetus. Procedures that require direct beam to the fetus and longer duration of exposure (such as fluoroscopy) are associated with a higher absorbed dose *(22)*. When a procedure is indicated, the dose of radiation to the fetus may be minimized by a number of techniques. Lead shielding is routinely used in chest imaging procedures that involve radiation. Although some data suggest no reduction in radiation dose to the uterus and ovaries with the use of lead shielding in chest imaging *(23)*, a number of other studies have shown significant benefit with the use of lead shields *(24)*. Kennedy et al. investigated the effects of lead shielding for fetal dose reduction in CT pulmonary angiography and found that the radiation dose is inversely proportional to the thickness of lead and the patient surface covered by the shield *(23)*. Techniques to improve dose efficiency in CT imaging include automatic tube current modulation, faster table speed, and higher pitch. The radiologists may also choose to adjust beam collimation to a very specific area of interest, increase kVp, remove the anti-scatter grid, or reduce the number of radiographs taken. In any case, good general principles of diagnostic radiology should apply, that is, that the study and technique chosen should allow for the lowest possible radiation dose without significantly reducing the quality or the diagnostic value of the examination.

Intrauterine Fetal Death

A number of studies have evaluated the effects of radiation on miscarriage and stillbirth rates. Studies following the nuclear explosion in Hiroshima and Nagasaki and after the nuclear accident in Chernobyl have not found an increase in fetal death rate *(25, 26)*. Another study looking at risks of radiologic procedures was also not associated with an increase in miscarriage or stillbirth *(27)*.

Oncogenicity

The degree to which in utero irradiation may lead to cancer induction has been a contentious issue for many years. A number of epidemiological studies in humans suggest that prenatal exposure to ionizing radiation increases the risk of leukemia and, to a lesser extent, solid tumors later in life *(28–30)*. Although it is possible that the initiating event occurs before birth, the effects are seen only after a long latency period and at a time when cancers are more likely to appear spontaneously, that is, when the individual is more "cancer-prone." Whether the crucial triggering factor was exposure to in-utero radiation is unclear and a number of other environmental and biologic factors may be playing a role.

The largest study of medical radiation exposure during pregnancy in humans is a case-control study by Stewart et al. referred to as the Oxford Survey of Childhood Cancer (OSCC) *(31)*. Results of this study indicate a relative risk (RR) for leukemia prior to the age of 10 of 1.92 for women having abdominal X-rays and 1.19 for non-abdominal examinations. Although this study provides the largest data set (included >15,000 childhood cancer cases), the timing and dose of radiation exposure relied on maternal recall of prenatal X-rays and has been criticized for other methodologic flaws. Studies of in utero exposed survivors of the atomic bomb show that the number of childhood cancers was lower than the number predicted by the OSCC study (1 observed, 8.8 predicted) *(32)*. Pooled data from seven smaller cohort studies shows a weighted average RR for total cancer of only

Table 5.3 Probability of bearing healthy children as a function of radiation does.

Dose to conceptus (mGy) above natural background	Probability of no malformation	Probability of no cancer (0–19 years)
0	97	99.7
1	97	99.7
5	97	99.7
10	97	99.6
50	97	99.4
100	97	99.1
>100	Possible, see text	Higher

1.02 *(13)*. Although cohort studies may have less potential for bias, they had relatively few childhood cancer cases and wide confidence intervals so must be interpreted with some caution. Animal studies, in general, have failed to demonstrate an increased risk in childhood leukemia, but have shown that irradiation at late fetal stages may induce solid cancers in adults *(31)*. This association is not seen with in utero radiation in the preimplantation or embryonic period.

Given the lack of clarity on this topic, counseling a patient regarding risk of oncogenicity associated with prenatal radiation can be difficult. From a public health perspective, the most prudent course is to assume that the risk of in utero radiation is not trivial and to counsel the patient accordingly. The ICRP suggests that patients should be counseled that the risk may be as high as 40% over the normal incidence if the patient is exposed to a fetal dose of 10 mGy (1 rad) or higher. It is important, however, to deliver this message in the context of the background incidence. For example, even with a dose of 10 mGy, the probability that the offspring will have no childhood cancer is 99.6% (Table 5.3). Although most diagnostic testing falls well below the 10 mGy range, procedures that result in direct beam to the fetus or therapeutic radiation may approach this level. Such procedures should not be delayed when clearly indicated, but it is reasonable to consider alternative tests/techniques in some cases.

Use of Contrast Agents

In general, contrast media are low molecular weight, water-soluble substances and, as such, are rapidly distributed throughout the extracellular space. Numerous reports show that both iodinated contrast agents and gadolinium-based MR agents cross the placenta and reach the fetus *(33, 34)* and are present in breast milk shortly after parenteral administration. Intravenous iodinated contrast agents are considered a category B drug by the US Food and Drug Administration; that is, reproductive studies in animals demonstrate no risk, but there are no controlled studies in pregnant women. Animal studies of gadolinium used for MRI procedures have shown potential fetal toxic effects when administered at doses two to seven times those used in humans *(35, 36)*. No adverse effects in humans have been reported.

The American College of Radiology (ACR) recommends that pregnant women should be counseled about both the risk of radiation exposure as well as the potential risk of contrast media *(37)*. The referring physician along with the radiologist must consider whether an alternative test that does not require contrast is reasonable (ultrasound), whether the information needed will affect the care of

the patient and fetus *during* the pregnancy, and whether it is prudent to wait until after delivery to obtain the study. Although there is a theoretical concern with iodinated contrast agents and their effects on the fetal thyroid, there are no reports in the literature to support this theory.

Occasionally the use of contrast agents is indicated for an imaging study in a breast-feeding woman. Patients and providers are often concerned about potential toxicity to the infant. An extensive review of the literature by the Committee on Drugs and Contrast Media of the ACR resulted in the following summary information and recommendations.

The plasma half-life of intravenously administered iodinated contrast agents and gadolinium is approximately 2 h and the agent is completely cleared from the bloodstream in 24 h. It is estimated that less than 1% of the administered maternal dose of contrast agent is excreted into breast milk and that less than 1% of the contrast medium in breast milk ingested by the infant is absorbed by the infant's GI tract. Therefore, the expected dose of contrast agent absorbed by the infant is extremely low, much lower, in fact, than the recommended dose for an infant undergoing an imaging study. Although theoretical risks may include toxicity or allergic sensitivity, there are no reports of adverse effects to infants as a result of these negligible amounts of contrast exposure. The ACR concludes that it is safe to continue breast feeding after receiving contrast agents *(38)*. However, if a patient remains concerned she may choose to abstain from breast-feeding for 24 h after the administration of such agents, while actively expressing and breast milk from both breasts during that time.

Ultrasound

Ultrasonography is considered safe in pregnancy and should be used as an initial imaging test when possible. Pregnant women are generally quite comfortable with ultrasonography, since it is widely used in obstetric practice for fetal evaluation. However, patients often find it reassuring to hear that ultrasound does not apply ionizing radiation and there is no evidence in animals or humans indicating that sound waves can damage a developing fetus.

Magnetic Resonance Imaging (MRI)

There is no evidence that magnetic resonance imaging poses any risk to the developing human embryo or fetus. Multiple studies have failed to show any associated abnormalities or harm *(40)*. Magnetic resonance emits radiofrequency waves and does not expose to any ionizing radiation. Any theoretical potential to cause harm to a developing fetus is likely limited to the possibility of increasing fetal temperature with MRI. For this reason, low field magnets are preferred in pregnancy if they are available. Despite a lack of data, the National Institutes of Health Consensus Development conference (1987) and the US Food and Drug Administration have recommended delaying MRI until after the first trimester *(40, 41)*. As a result, many radiology departments offer MRI after 12 weeks gestation, but reserve its use in the first trimester for patients with clinical conditions that are not amenable to other diagnostic techniques. More recently, the ACR's 2007 practice guidance document for safe MR practices recommends that MR imaging may be used if considered necessary at any time in gestation *(42)*. The ACR also

recommends obtaining a written consent to document the patient's understanding of the risks and benefits as well as possible alternative diagnostic options. These more recent guidelines recognize that certain clinical scenarios exist where the benefit of the MRI may outweigh the theoretical risk at any gestational age, for example, a pregnant woman suspected of having a cerebral vein thrombosis or other CNS vascular abnormality.

Nuclear Medicine

Nuclear medicine procedures may expose the fetus to the effects of radiation by several mechanisms. First, external irradiation of the maternal tissue will result in some level of radiation absorbed by the fetus. Second, placental transfer and fetal uptake of radiopharmaceuticals may also result in radiation exposure. In addition, with radiopharmaceuticals that are primarily excreted by the kidneys, there may be some exposure to radiation from bladder content. Fetal absorbed doses may be minimized by using the lowest effective dose, and by instituting measures to increase the rate of excretion (maternal hydration and frequent bladder emptying).

Estimation of radiation doses absorbed by the fetus from radionuclides can be difficult and imprecise. Isotopes vary quite a bit with respect to their accumulation in maternal and/or fetal target organs, ability to cross the placenta, metabolism, distribution, and half-life *(43)*. Estimation of risk requires careful consideration of the specific properties of the isotope and the dose and duration of the exposure. Most diagnostic nuclear procedures use short-acting radionuclides (such as technetium-99 m) that would not result in significant fetal doses. The exception is radioiodine, most commonly used in the evaluation and treatment of thyroid disorders. Therapeutic doses of radioiodine used in pregnancy are associated with a significant risk of fetal thyroid damage after 12 weeks gestation.

Women who are breastfeeding and require exposure to radionuclides should be counseled about potential risk to the infant and the need to interrupt breastfeeding with exposure to certain isotopes.

Informed Consent

Pregnant women and their families have a right to know the magnitude and type of radiation effect that may result from medical diagnostic procedures. Communication with the patient should be appropriate to the level of risk. For example, for most low dose procedures (<1 mGy), communication may include only a verbal reassurance that the risk is estimated to be extremely low. When the fetal dose is potentially greater that 1 mGY, then a more detailed explanation of the potential risk is appropriate. With any discussion about risk of radiation in pregnancy, it is important to include information about potential alternative modalities as well as the risk of withholding the procedure.

Summary

Thousands of pregnant women undergo medical diagnostic imaging studies every year. Much anxiety and even unnecessary terminations of pregnancy may be caused by a lack of knowledge. Patients and providers must be aware of the potential risks and benefits of any diagnostic procedure, but should also consider

that more harm than good may come from withholding the test. Although high dose radiation in pregnancy has been associated with adverse outcomes in the offspring, the weight of the evidence suggests that prenatal doses from properly done diagnostic procedures are associated with no measurable risk of fetal death, malformation, or neurological impairment that is above the background incidence.

References

1. Recommendations of the International Commission on Radiological Protection. International Commission on Radiological Protection (ICRP) Report 60. Annals of the ICRP. 1990.
2. Limitation of Exposure to Ionizing radiation. National Council on Radiation Protection (NCRP) Report 116.
3. Source and Effects of Ionizing Radiation. Annex B: Exposure from natural radiation sources. 2000 United nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) Report Volume 1, 2000.
4. Streffer C, Molls M. Cultures of preimplantation mouose embryos: a model for radiological studies. Adv Radiat Biology 1987;13:169–213.
5. Gu Y, Kai M, Kusama T. The embryonic and fetal effects in ICR mice irradiated in the various stages of the preimplantation perios. Radiat Res 1997;147:735–740.
6. Muller W-U, Streffer C. Lethal and teratogenic effects after exposure to X-rays at various times of early murine gestation. Teratology 1990;42:643–650.
7. Job TT, Leibold GJ, Fitzmaurice HA. Biological effects of roentgen rays; determination of critical periods in mammalian development with x-rays. Am J Anat 1935;56:97–117.
8. Russell LB, Russell WL. The effects of radiation on the preimplantation stages of the mouse embryo. Anat Rec 1950; 108:521.
9. Pampfer S, Streffer C. Prenatal death and malformations after irradiation of mouse zygotes with neutrons or X-rays. Teratology 1988;36:599–607.
10. Streffer C, Muller W-U. Malformations after radiation exposure of preimplantation stages. Int J Dev Biol 1996;40:335–360.
11. Kameyama Y. Low-dose radiation as an environmental agent affecting intrauterine development. Environ Med 1982;26:1–15.
12. Brent RL, Gorson RO. Radiation exposure in pregnancy. In: Moseley RD (Ed.) Current Problems in Radiology. Year Book Medical Publications Inc., Chicago, USA pp. 1–48.
13. Valentin J. Biological Effects after Prenatal Irradiation (embryo and fetus). Publication 90. Annals of ICRP. 2003;1–200.
14. Medical Radiation Exposure of Pregnant and Potentially Pregnant Women. Report of the National Council on Radiation Protection and Measurements. No. 54. 1977, July.
15. Blot WJ, Miller RW. Mental retardation following in utero exposure to the atomic bombs of Hiroshima and Nagasaki. Radiology; 1973;106:617–619.
16. Blot WJ. Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. II. Biologic effect. C. Growth and development following prenatal and children exposure to atomic radiation. J Radiat Res 1975;16:82–88.
17. Miller RW, Mulvihill JJ. Small head size after atomic irradiation. Teratology 1976;14:355–358.
18. Blot WJ, Miller RW. Mental retardation following in utero exposure to the atomic bombs of Hiroshima and Nagasaki. Radiology 1973;106:617–619.
19. Blot WJ. Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. II. Biological effect. C. Growth and development following prenatal and children exposure to atomic radiation. J Radiat Res 1975;16:82–88.
20. Miller RW, Blot WJ. Small head size after in utero exposure to atomic radiation. Lancet 1972;2:784–787.

21. Valentin J. Pregnancy and Radiation. Publication 84. Annals of the IRCP. 2000;30:1–43.
22. Osei EK, Faulkner K. Fetal doses from radiologic examinations. Br J Rad 1999;72:773–780.
23. Doshi S, Negus I, Oduko J. An assessment of fetal dose due to CT pulmonary angiography for suspected maternal pulmonary embolism. Scientific Meeting of the South West PPEM Group, 2004.
24. Kennedy EV, Iball GR, Brettle DS. Investigation into the effects of lead shielding for fetal dose reduction in CT pulmonary angiography. Br J Radiol 2007; 631–638.
25. Fry FA. International Chernobyl Project. Radiol Protect Bull 1991;124:12–18.
26. Harjulehto T, Aro T, Rita H, et al. The accident at Chernobyl and the outcome of pregnancy in Finland. Br Med J 1989;298:995–997.
27. Ginsberg JS, Hirsh J, Rainbow AJ, Caotes G. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. Throm Haemost 1989;61:189–196.
28. Stewart A, Kneale GW. Radiation doses effects in relation to obstetric X-rays and childhood cancer. Lancet 1997;1(17658):1185–1188.
29. Knox EG, Stewart A, Kneale G. Prenatal irradiation and childhood cancer. J Soc Radiol Prot 1987;7:177–189.
30. NRPB Diagnostic Medical Exposures to Ionizing Radiation During Pregnancy and Estimates of Late Radiation Risks of the UK Populations. Documents of the NRPB, 1993;4(4), National Radiological Protection Board, UK.
31. Stewart A, Webb J, Giles D, Hewitt D. Malignant disease in childhood and diagnostic irradiation in utero. Lancet 1956; 271:447.
32. Biological Effects after prenatal Irradiation (Embryo and Fetus). Annals of the ICRP. Publication 90, 2003.
33. Kanal E, Borgstede JP, Barkovich AJ, et al. American College of Radiology white paper on MR safety. Am J Roentgenol 2002;178:1335–1347.
34. Webb J, Thomsen H, Morcos SK, et al. The use of iodinated and gadolimium contrast media during pregnancy and lactation. Eur Radiol. 2005;15:12434–1240.
35. Webb JA, Thomasen HS, Morcos SK; Members of Contrast Media Safety committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol 2005;15:1234–1240.
36. DeSantis M, Straface G, Cavaliere AF, et al. Gadolinium periconceptional exposure: pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2007;86:99–101.
37. Manual on Contrast Media Version 5.0. American College of Radiology 2004;47–48.
38. American College of Radiology Committee on Drugs and Contrast media. Administration of contrast Medium to Nursing Mothers, 2004–2007.
39. Shellock FG, Crues JV. MR procedures: biologic effects, safety and patient care. Radiology 2004;232:635–652.
40. Food US, Drug Administration. Magnetic resonance diagnostic device: Panel recommendation and report on petitions for MR reclassification. Fed Regist 1998;53:7575–7579.
41. Magnetic Resonance Imaging. Statement, National Institutes of Health Consensus Development Conference (Washington, D.C., October 26–28, 1987). 1987;6(14): October 26.
42. Kanal E, Barkovich AJ, Bell C. ACR guidance document for safe MR practices: 2007. Am J Roentgenol 2007;118:1–27.
43. Radionuclide Exposure of the Embryo/Fetus. NCRP Report No. 128. Recommendations of the National Council on Radiation Protection and Measurements. 1998, September 25.

6

Prescribing in Pregnancy and Lactation

Niharika Mehta, Jill Newstead-Angel, and Raymond O. Powrie

Keywords: breast feeding, nursing, pharmacokinetics, teratogenicity, pregnancy, prescribing

Ever since the thalidomide tragedy in the 1950s, drugs have increasingly been under scrutiny for teratogenensis. Both patients and clinicians are hesitant to use medications in pregnancy because of uncertainty about fetal effects. However, with advances in medical science, as we grow more and more dependent on pharmaceuticals for disease management and prevention, medication use in pregnancy often becomes necessary.

An international survey found that 86% of the women studied took prescription medication during their pregnancy, receiving an average of 2.9 prescriptions. This pattern of medication use appeared to be almost universal and did not differ between poor and wealthy nations *(1)*. Although this data did not include herbal, alternative, or over the counter medications, the use of these agents by pregnant women is also fairly common *(2, 3)*.

This chapter aims to provide some key principles to guide clinicians when prescribing for the pregnant patient with pulmonary disease.

The Myth of the Placental Barrier

Despite the widespread belief to the contrary, no "placental barrier" exists. The clinician should assume that the fetus will be exposed to almost any medication that is given to the mother. The most notable commonly prescribed exceptions that do not cross the placenta are glyburide, heparins, and insulin. For most other medications, drug levels in the fetus may be the same, lower or even higher than in the mother. Lipophilic drugs, drugs of a low molecular weight, and drugs that are nonionized at physiologic pH generally cross the placenta more efficiently than others.

The Myth of the "Safe" Period

Traditionally, teratogenic effects of drugs have been noted as anatomic malformations and the fetus is most vulnerable to these in the first trimester. However, medications may adversely affect fetal neurological and behavioral development, fetal survival, or function of specific organs even after the first trimester. For most

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_6

drugs, it is not known whether or when an absolutely "safe" period exists when the medication can be deemed to be without effect.

The first 60 days after conception is the period of "embryonic development." The first 14 days after conception (and therefore generally the first 28 days after the first day of the last menstrual period) is often referred to as the "all or nothing period." Exposures of the pluripotential cluster of cells that exists at this point are generally believed to cause miscarriage or no effect at all. Days 14–60 after conception (the period immediately coinciding with the first missed period and/or the earliest positive home pregnancy test) are a period of cell differentiation and organogenesis. Exposures during this time probably have specific "window periods" during which the embryo is susceptible to particular toxicities. Thalidomide effects were seen only if the drug was taken between days 21 and 36. Valproic acid effects on the neural tube occur between days 14 and 27.

Drug Safety Data in Pregnancy

Definitive pregnancy safety data can only come from large, long term, and therefore expensive trials. This type of data exists for very few medications in pregnancy. Large scale pregnancy safety trials with long term follow up rarely occur for many reasons. They are difficult to conduct because the population of reproductive age women is often highly mobile. There is a lack of a financial incentive for pharmaceutical companies to conduct them and that is further complicated by their understandable concern about potential liabilities. Also, pregnant patients are considered by federal regulations for human subjects' protection to be a "vulnerable population" and their participation in clinical trials, even when no intervention is involved, is closely scrutinized by institutional review boards.

For this reason, much of the presently available pregnancy safety data comes from sources other than prospective trials. The other sources of data are as follows.

Animal Studies

Although animal studies are an important source of screening safety data, there is no information available on the sensitivity or specificity of any of the animal models of teratogenicity as applied to humans. Animal data cannot, therefore, be confidently extrapolated to humans. Some agents that have appeared to be safe in animals have subsequently been found to have fetal effects once approved for use in humans. Other drugs that appeared to be unsafe on the basis of animal studies have subsequently been shown to be well tolerated in human pregnancies. Nonetheless, drugs that have been associated with adverse fetal effects in multiple animal species at exposures similar to those expected in humans may be expected to have risks in human pregnancy as well.

Case Reports and Case Series

Although case reports and series are another resource, they suffer from the problem of recall bias as well as the inability to determine the frequency of an event because the number of exposed women with normal pregnancy outcomes is not known. Women who have a difficult pregnancy outcome are more likely to recall medication use in pregnancy and clinicians are more likely to report an adverse outcome. Case series and reports may therefore overestimate risk or raise false concerns.

Pregnancy Registries

These studies are better characterized as prospective exposed follow-up studies in which pregnant women enroll at the time of their exposure to a specific drug, but prior to the outcome of the pregnancy being known. Their prospective nature eliminates recall bias and allows an overall rate of events to be measured, since many outcomes will be normal. The utility of these studies is highly dependent on the quality of their data collection and follow-up methods. In most cases, they may be able to provide broad margins of risk, but may also identify potential risks that require further study and follow-up.

Case Control Studies

Case control studies are a commonly used tool that retrospectively compare infants with a particular adverse outcome (e.g., birth defects overall or a specific subset of defects) to normal infants and evaluates differences in exposures of each group, such as to a maternal medication. Their findings have been an essential source for identifying many important toxicities and for providing reassurance about many commonly used agents. However, these and other population-based studies suffer from the fact that they often cannot separate the effects of medication exposure from the effects of the underlying disease. An example of this issue is the difficulty that exists in distinguishing the effects of some common over the counter cold medications from the possible effects of viral illness and fever in the first trimester.

While the Food and Drug Administration (FDA) pregnancy risk classification (Table 6.1) is useful as a quick reference with regards to available safety data, it is

Table 6.1 FDA pregnancy categories.

U.S. Food and Drug Administration (FDA) Pregnancy Risk Classification
Category A "Controlled studies show no risk"
Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, nor is there any evidence of a risk in later trimester, and therefore the possibility of fetal harm appears remote.
Category B "No evidence of risk in humans"
Either animal reproduction studies have not demonstrated a fetal risk and there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimester.
Category C "Risk cannot be ruled out"
Either studies in animals have revealed adverse effect on the fetus (teratogenic) or appropriate animal data is not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D "Positive evidence of risk"
There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). There will be an appropriate statement in the "warnings" section of the labeling.
Category X "Contraindicated in pregnancy"
Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may be pregnant.

inadequate when used as the only source. There is a tendency among clinicians to view it as a "grading system" rather than a shorthand classification system summarizing what data is available. Clinicians may therefore not recognize that some drugs may receive a B or C rating simply because there is less information available as opposed to one that has a D rating. Besides, the FDA classification is unable to address the potential clinical benefit of a medication or the potential harm from withholding the medication. Several other useful resources exist in addition to the FDA classification, that may assist the clinician in the therapeutic decision making process. These are listed in Table 6.2.

Table 6.2 Resources to assess data on individual drugs.

Publication	Source and brief description
Drugs in Pregnancy and Lactation. Briggs GS, Freeman R, Yaffe S.	Lippincott Williams & Wilkins Publishers; ISBN: 0781756510; 7th edition 2005) Hardcover reference text
Catalog of Teratogenic Agents. Thomas H. Shepard	Johns Hopkins Univ Press; ISBN: 0801879531;11th edition (August 2004) Hardcover listing of 2393 agents, lactation not included
Handbook for Prescribing Medications During Pregnancy. Coustan DR and Mochizuli TK.	Lippincott Williams & Wilkins Publishers; ISBN: 0316158267 3rd edition (January 15, 1998) Convenient pocketsize paperback reference text with reliable information.
Effects of Medications on the Fetus and Nursing Infant: A Handbook for Health Care Professionals Friedman JM and Polifka JE	Johns Hopkins University Press; ISBN: 0801853451;1st edition (January 15, 1996) Paperback reference text. Succinct summaries of risk based on more comprehensive reviews in TERIS
Teratogenic Effects of Drugs Friedman JM and Polifka JE.	Johns Hopkins University Press; ISBN: 0801863872 2nd edition (July 15, 2000) Hardcover and more extensive version of text listed above.
Drugs for Pregnant and Lactating Women Weiner CP and Buhimshi C.	Churchill Livingstone; ISBN: 044306637X; 1st edition 2004 Easy to use, reader friendly hard cover text that summarizes pregnancy and lactation data for 725 generic and 2200 brand name drugs.
Medications & Mothers' Milk: A Manual of Lactational Pharmacology Thomas Hale	Hale Publishing; ISBN 0977226832 ; 12th edition (2006) Easy to use and comprehensive handbook.
http://neonatal.ama.ttuhsc. edu/lact/index.html	Useful online clinical forum. This is a helpful adjunct to Dr. Hale's reference book
Reprotox®	www.REPROTOX.org distributed in Micromedix, Inc.'s TOMES Reprorisk module. On line subscription or diskette. PDA version available

(continued)

Table 6.2 (continued)

Publication	Source and brief description
TERIS	http://depts.washington.edu/terisweb/teris/ This is also distributed in Micromedix, Inc.'s TOMES Reprorisk module Online subscription or diskette
Motherisk	www.motherisk.org . Website providing teratogen information and updates on continuing reproductive risk research
Some other useful online sources	www.aap.org/advocacy/archives/septdrugs.htm www.rxlist.com www.otispregnancy.org www.perinatology.com

Physiologic Changes of Pregnancy Affecting Pharmacokinetics

Many physiological changes that occur in pregnancy can alter the pharmacokinetics of drugs. There is a 50% increase in plasma volume which alters the volume of distribution. The dilutional hypoalbuminemia that accompanies this increased plasma volume can result in decreased protein binding and increased free drug levels. Absorption of oral agents may be affected by the slowing of gastric motility in pregnancy. There is a 50% increase in the glomerular filtration rate which may significantly decrease the half-life of renally cleared agents. Hepatic clearance of some agents is also increased in pregnancy. As an example, labetalol, an agent with both hepatic and renal clearance, has a half-life of less than 2 h in pregnancy as compared with a half-life of 6–8 h in the non-pregnant state *(4)*.

Although the above mentioned changes do not routinely warrant an adjustment in the drug dosing and administration, in some circumstances, particularly if a prescribed drug fails to achieve its desired effect, consideration should be given to increasing dose or frequency of the medication. When monitoring serum levels of medications, free rather than total drug levels should be obtained if possible.

Choosing Medication in Pregnancy

When prescribing for the pregnant patient, a key concept to bear in mind is that fetal well being is dependent on maternal well being. While definitive pregnancy safety data exists for very few drugs, the list of known teratogens is also small (Table 6.3). It is worth noting that the majority of fetuses exposed to even the most teratogenic agents are likely to be born without defects. It therefore helps to think of medication use in pregnancy as "justified or not" rather than "safe or not."

Thankfully for pulmonary physicians, most commonly prescribed respiratory agents can be readily used in pregnancy without significant concern about fetal safety. The vast majority of common antibiotics, bronchodilators, inhaled, oral,

Table 6.3 Commonly prescribed medications with known teratogenic effects in humans.

Known Human Teratogens
Warfarin
Cyclophosphamide
Diethylstilboestrol (DES)
Phenytoin, Carbamazepine, Phenobarbital, Valproic Acid
Lithium
Methimazole
Penicillamine
Thalidomide
Isotertinoin
Methotrexate

and systemic steroids appear to be more than justifiable for use throughout pregnancy when treating pulmonary disease. Table 6.4 lists some of the most commonly used medications for treating respiratory disease and classifies them as to whether available data suggest their use for this indication in pregnancy is "justifiable in most circumstances," is "justifiable in rare circumstances," or is "almost never justified." The table also provides the FDA pregnancy classification as a subscript following each medication. Table 6.5 lists medications used for sedation and neuromuscular relaxation in the same order. Medications that fall in the middle category (data suggests use justifiable in rare circumstances) are generally agents for which there is a paucity of published pregnancy data rather than presence of known fetal ill effects. These agents may be used in pregnancy but caution suggests that until more human data become available, their use should be reserved for patients in whom medications from the first column have failed or are contraindicated due to intolerance or allergy. It is best to make all decisions about medication use in pregnancy on an individual basis, after careful consideration of both the potential risks and benefits and in conjunction with the patient.

Breast Feeding and Medications

Breast feeding is the preferred method of feeding for newborns and infants and nearly every woman can breast feed her child *(5)*. Human milk is the finest source of nutrition and the only source of protective exogenous immunoglobulins available to the newborn infant *(6)*. However, both clinicians and their patients can be very wary of the impact that maternal medications may have on the breast-fed infant. Mothers with medical problems, including pulmonary conditions, often discontinue breastfeeding to take a prescribed medication. All too often, the advice to so do comes from the prescribing clinician. Cessation of breastfeeding because of maternal medication use is generally not necessary as the vast majority of medications can be considered to be compatible with breastfeeding. In fact, not only should women *not* be discouraged from breastfeeding while taking medications, the benefits of breastfeeding should lead clinicians to encourage their patients to persist with breastfeeding during medical treatment.

When prescribing medications to a nursing mother, the clinician should consider the following principles.

Table 6.4 Medications in pregnancy and lactation for the pulmonologist *(Adapted from: Drugs in pregnancy. Powrie RO, Kweder S. In: Medical Care of the Pregnant Patient. Eds Lee).*

Rosene-Montella et al. ACP Women's Health series, Second edition. In press Medication type	**Data suggests use justifiable when indicated**	**Data suggests use justifiable in rare circumstances**	**Data suggests use almost never justifiable**	**Useful review articles and comments (PMID: Pubmed ID number, for easy access to reference and abstract)**	**Breastfeeding Safety (Categories based upon Dr. Hale's book, Medications and Mother's milk. Twelfth edition.2006. Pharmasoft publishing)**
Short acting inhaled beta 2 adrenergic agonists	albuterol $_{C}$ bitolterol $_{C}$ pirbuterol $_{C}$ metaproterenol $_{C}$ terbutaline $_{C}$			Published experience with these drugs in animals and humans suggests that beta-sympathomimetics do not increase the risk of congenital anomalies. Albuterol is the most studied of these agents. Metaproterenol is the second most studied. NAEP guidelines for the management of asthma in pregnancy can be obtained through the NHLBI at http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm PMID: 16946229 PMID: 16443141 PMID: 10830999	albuterol : L1 pirbuterol : L2 terbutaline: L2
Long acting inhaled beta 2 adrenergic agonists	salmeterol $_{C}$ formoterol $_{C}$			Of the few studies that have examined pregnancy outcomes with prenatal exposure to long-acting beta2 agonists, no adverse events were found. However, due to small numbers in the studies, and because animal models have shown delayed ossification, use of this agent should be reserved for patients who have failed low potency steroids and/ or cromolyn alone.	salmeterol: L2 formoterol: L3

(continued)

Table 6.4 (continued)

Rosene-Montella et al. ACP Women's Health series, Second edition. In press Medication type	Data suggests use justifiable when indicated	Data suggests use justifiable in rare circumstances	Data suggests use almost never justifiable	Useful review articles and comments (PMID: Pubmed ID number, for easy access to reference and abstract)	Breastfeeding Safety (Categories based upon Dr. Hale's book, Medications and Mother's milk. Twelfth edition.2006. Pharmasoft publishing)
				PMID:11945116 PMID:9746382	
Xanthines	theophylline $_{C}$ aminophylline $_{C}$			These drugs do not appear to be human teratogens. The clearance of aminophylline and theophylline is increased in pregnancy but may be variable. If daily dose exceeds 700 mg, blood levels should be checked for optimal dosing. PMID: 15695974 PMID: 16443141	theophylline: L3
Inhaled corticosteroids	Low potency: beclomethasone dipropionate $_{C}$ Medium potency: trimacinolone acetonide $_{C}$ High potency: fluticasone propionate $_{C}$ budesonide $_{B}$ flunisolide $_{B}$			Beclomethasone and budenoside are the most widely studied of the inhaled corticosteroids in pregnancy and should be considered the preferred inhaled steroids in pregnancy. Relatively little of these agents are absorbed and human data has not suggested any teratogenic effects of these agents. Triamcinolone is the next most studied inhaled steroid in pregnancy with limited experience, suggesting no adverse pregnancy effects. Fluticasone has not been studied in pregnancy,	beclomethasone: L2 triamcinolone: L3 budesonide: L3 fluticasone: L3

(continued)

Table 6.4 (continued)

		however, its minimal systemic absorption and the safety of the other steroids in pregnancy make its use in pregnancy generally felt to be justifiable. PMID:16004676 PMID: 16775906	
Systemic steroids	prednisone C methylprednisolone C dexamethasone C hydrocortisone C	Most data suggests that systemic steroids do not present a teratogenic risk in human pregnancy. In doses equivalent to prednisone 25 mg/day, they do not cross the placenta because of placental metabolism (the same is not true for betamethasone or dexamethasone). Even in higher doses, the effect of hydrocortisone or prednisone on the fetus in terms of suppression of the hypothalmo-pituitary-adrenal axis is minimal. Several case control studies have found a significant association with first trimester steroid use and oral clefts, however, this was not seen in cohort studies. Even if this association is real, the risk is still small. For every 1000 embryos exposed during the susceptible days of first trimester, probably no more than 3 will develop an oral cleft. The background risk in	prednisone: L2, For chronic high dose: L4 dexamethasone: L3

(continued)

Table 6.4 (continued)

Rosene-Montella et al. ACP Women's Health series, Second edition. In press Medication type	Data suggests use justifiable when indicated	Data suggests use justifiable in rare circumstances	Data suggests use almost never justifiable	Useful review articles and comments (PMID: Pubmed ID number, for easy access to reference and abstract)	Breastfeeding Safety (Categories based upon Dr. Hale's book, Medications and Mother's milk. Twelfth edition.2006. Pharmasoft publishing)
				the general population is 1 per 1000. Therefore, the benefits of controlling a life threatening disease makes steroid use when indicated in the first trimester still generally justifiable. PMID: 15013068	
Mast cell stabilizers	cromolyn sodium $_{B}$ Nedocromil $_{B}$			Human and animal data suggest these agents are not teratogens. These agents are virtually not absorbed through mucosal surfaces and the swallowed portion is largely excreted in the feces.	cromolyn Sodium: L1
Inhaled anticholinergics	ipratropium $_{B}$			Reassuring animal studies but no published human data. Poorly absorbed by the bronchial mucosa so fetal exposure is likely minimal.	ipratropium: L2
Leukotriene inhibitors		zafirlukast $_{B}$ montelukast $_{B}$ omalizumab $_{B}$	Zileuton $_{B}$	Although these agents have reassuring animal data and are widely used in pregnancy because of the FDA category B rating, published safety data in human pregnancy is limited at this point. Their use should be limited in pregnancy to those cases in which a woman has	zafirlukast: L3 montelukast: L3

(continued)

Table 6.4 (continued)

			had significant improvement in asthma control with these medications prior to becoming pregnant that was not obtainable through other methods. Zileuton is different than other agent in this class as there is some animal data to suggest association with adverse pregnancy outcomes.	
Antihistamines	diphenhydramine $_{B}$ (but avoid in first trimester) chlorpheniramine dimenhydrinate $_{B}$	cetirizine $_{B}$ fexofenadine $_{C}$ loratidine $_{B}$	These 2003 and 2006 review articles systematically and critically review the literature on the treatment of allergic rhinitis in pregnancy. PMID: 12921487 PMID: 16579874 While the newest generation antihistaminic agents are widely used in pregnancy and have not had any concerning animal data associated with them, we still consider them to be second line agents in pregnancy, because of the lack of published human pregnancy safety data about them.	diphenhydramine: L2 chlorpheniramine: L3 cetrizine: L2 fexofenadine: L3 loratidine: L2
Cough	guaifenesin $_{C}$ dextromethorphan $_{C}$ albuterol $_{C}$ codeine $_{C}$			guaifenesin : L2 dextromethorphan : L1 codeine: L3
Nasal congestion	pseudoephedrine $_{C}$ oxymetazoline $_{C}$ nasal steroids *Beconase*™ $_{C}$		These 2006 review articles systematically and critically review the literature on the	pseudoephedrine: L3-L4 (Studies suggest significant reduction in milk production and prolactin levels

(continued)

Table 6.4 (continued)

Rosene-Montella et al. ACP Women's Health series, Second edition. In press Medication type	Data suggests use justifiable when indicated	Data suggests use justifiable in rare circumstances	Data suggests use almost never justifiable	Useful review articles and comments (PMID: Pubmed ID number, for easy access to reference and abstract)	Breastfeeding Safety (Categories based upon Dr. Hale's book, Medications and Mother's milk. Twelfth edition.2006. Pharmasoft publishing)
	Rhinocort™ C *Flonase*™ C *Nasacort*™ C nasal cromolyn B nasal ipratropium B			treatment of allergic rhinitis in pregnancy. PMID: 16443148 PMID 16579874	following exposure to pseudoephedrine)
Antibiotics	erythromycin B base, ethyl succinate or stearate (not estolate) penicillins B cephalosporins B azithromycin B vancomycin C nitrofurantoin B aminoglycosides D metronidazole B	trimethoprim C sulfonamides C	tetracycline D doxycycline D clarithromycin C fluoroquinilones C erythomycin estolate B	Despite concerning animal data, increasing human data suggests fluoroquinolones might warrant their placement in the "use may be justified in rare circumstances" category. Two recent useful review articles on use of antibiotics in pregnancy are PMID: 16648419 PMID 16076072 The Sanford guide to antimicrobial therapy (published annually by Antimicrobial Therapy, Inc., USA) includes a specific section on FDA pregnancy risk category of antivirals, antifungals, antivirals and anti-TB meds.	The following 3 part article gives an excellent review of antibiotics,antivirals and antifungals during lactation. PMID: 11155614 PMID: 11847854 PMID: 11847833
Antifungals	amphotericin B nystatin B clotrimazole B terbinafine B	Fluconazole C <400 mg per day	ketoconazole C	The following 2003 review article on antifungal use in pregnancy will be useful .PMID: 12946248	Fluconazole, ketoconazole: L2, AAP approved for use in breastfeeding nystatin: L1 amphoterecin B: L3
Anti-TB meds	isoniazid C rifampicin C		ethionamide D kanamycin D	CDC, division of TB elimination states:	PMID: 10205455. 1998 review article of breastfeeding

(continued)

Table 6.4 (continued)

	pyrizinamide $_C$ ethambutol $_C$ rifabutin $_B$		capreomycin $_C$ fluoroquinolones streptomycin $_D$	"Untreated tuberculosis (TB) represents a greater hazard to a pregnant woman and her fetus than does its treatment. Treatment of pregnant women should be initiated whenever the probability of TB is moderate to high." INH warrants monthly monitoring of liver function tests in pregnancy because of a possible increased incidence of hepatotoxicity in pregnancy. Use of PZA is supported by both WHO and British recommendations, but is not routinely recommended in the US. TB treatment regimens for HIV-infected pregnant women should include both rifamycin and PZA.	safety of antituberculosis medications. The American Academy of Pediatrics considers use of isoniazid, rifampin, ethambutol, streptomycin (first-line agents), kanamycin and cycloserine (second-line agents) compatible with breastfeeding.
Antiretroviral medications	lamivudine $_C$ zidovudine $_C$ didanosine $_B$ stavudine $_C$ nevirapine $_C$ nelfinavir $_B$ saquinavir $_B$ ritonavir $_B$	abacavir $_C$ amprenavir $_C$ (capsule only, oral solution contraindicated) lopinavir $_C$ indinavir $_C$	tenofovir $_B$ zalcitabine $_C$ delavirdine $_C$ efavirenz $_D$ atazanavir $_B$ fosamprenavir $_C$ tipranavir $_C$ emtricitabine $_B$	While human pregnancy safety data is lacking for most of the newer HIV medications, use of majority of the older antiretroviral agents is readily justifiable, efavirenz being the notable exception. Pregnancies exposed to antiretroviral therapy should be registered with the Antiretroviral Pregnancy Registry as early in pregnancy as possible in order to provide data on the risk of birth defects after	HIV infected mothers in USA are advised against breastfeeding due to risk of transmission of HIV to infants through breastmilk.

(continued)

Table 6.4 (continued)

Rosene-Montella et al. ACP Women's Health series, Second edition. In press Medication type	**Data suggests use justifiable when indicated**	**Data suggests use justifiable in rare circumstances**	**Data suggests use almost never justifiable**	**Useful review articles and comments (PMID: Pubmed ID number, for easy access to reference and abstract)**	**Breastfeeding Safety (Categories based upon Dr. Hale's book, Medications and Mother's milk. Twelfth edition.2006. Pharmasoft publishing)**
				exposure. The following article is an excellent review of HIV treatment in pregnancy. PMID: 16752931	
Antivirals	acyclovir $_{B}$ gancliclovir $_{C}$	famiciclovir $_{B}$ ganciclovir $_{C}$ foscarnet $_{C}$	amantidine $_{C}$ zanamivir $_{C}$ oseltamivir $_{C}$ PEG interferon $_{C}$ ribavirin $_{X}$	This 2003 article specifically reviews use of antiviral medications in pregnancy. PMID: 14719848	acyclovir: L2 valacyclovir: L1 Cytomegalovirus transfer into breastmilk is known but of low risk to infants born of CMV positive mothers.
Vasopressors	ephedrine $_{C}$	phenylephrine $_{C}$ epinephrine $_{C}$ norepinephrine $_{C}$		Ephedrine is felt to be the vasopressor of choice during pregnancy because it causes less reduction in uterine blood flow however based upon recent reviews either ephedrine or phenylephrine could be used in pregnancy. PMID: 16735804 PMID: 11916798	epinephrine: L1 ephedrine: L4

Subscripts $_{ABCDX}$ after each agent represents the FDA pregnancy risk classification
Breastfeeding safety categories: L1-safest, L2-safer, L3-moderately safe, L4-Possibly hazardous, L5-Contraindicated.
Disclaimers:

- This table is intended as a general guide only. It is NOT a drug safety table and for such data the reader is referred to the excellent resources listed in Table 6.4.
- All of the assignments between the three columns are value judgments and therefore somewhat arbitrary.

Table 6.5 Sedation and neuromuscular relaxation in pregnancy.

Medications Type	Commonly used agents with use justified when indicated	Comments (PMID: Pubmed ID number, for easy access to reference and abstract)
Benzodiazepines	Diazepam $_{D}$ Midazolam $_{D}$ Alprazolam $_{D}$ Lorazepam $_{D}$ Chlordiazepoxide $_{D}$	Early studies on diazepam showed an increased risk for oral clefting in both animals and in retrospective and case-control studies in humans. This has, however, been contradicted by several recent prospective and case-controlled studies and a meta-analysis that all uniformly found no association between diazepam use and clefting. Although animal studies have shown an increase in abnormal behavioral patterns after in utero exposures at levels comparable to the usual human doses, currently there is still no conclusive data regarding the possible behavioral teratogenicity of benzodiazepine use during pregnancy. Withdrawal symptoms can occur after fetal exposure late in pregnancy. One recent population based study has suggested an increased risk of congenital heart disease with concomitant serotonin reuptake inhibitor and benzodiazepine use (PMID: 18293409). Short-term diazepam treatment in usual therapeutic doses during pregnancy did not present any detectable teratogenic risk to the fetus (PMID: 17535056).
Opiates	Morphine $_{B}$ Fentanyl $_{B}$ Hydromorphone $_{B}$ Methadone $_{B}$	There are no reports linking therapeutic use of opiates with congenital malformations. With use in or close to labor, respiratory depression in the neonate has been observed. Withdrawal has been noted in neonates with prolonged in utero exposure and increased risk of neurodevelopmental problems has been found in these infants.
Antipsychotics	Haloperidol $_{C}$	Human experience in older studies has not identified an increased risk of congenital anomalies. Haloperidol is highly lipophilic and easily enters the fetal circulation Exposure during later pregnancy may cause extrapyramidal side effects in the neonate as in the adult.
Neuromuscular blockers	Mivacurium $_{C}$ Atracurium Succinylcholine $_{C}$	Based on experimental animal studies, mivacurium is not expected to increase the risk of congenital anomalies. Atracurium does not appear to cross the term placenta significantly although use of this agent at cesarean section has been associated with a brief period (15 min) of residual curarization in exposed neonates. Succinylcholine has not been associated with adverse effects on the fetus
Anesthetics and sedatives	Propofol $_{B}$ Thiopental $_{C}$	Propofol rapidly crosses the placenta. Fetal:maternal ratio is approximately 0.7. No human teratogenic data for this drug exists. Fetal exposure to propofol can vary considerably depending on maternal plasma albumin concentration; although clinical significance of this remains unclear. Propofol infusions for anesthesia in neurosurgical patients for up to 14 h resulted in no fetal adverse effects (PMID: 17198107) Thiopental readily crosses the placenta but it is taken up by the fetal liver and is slow to reach concentrations in the fetal brain sufficient to cause depression.

a. Be sure the medication is necessary. Use of medications to treat mild, self limited symptoms during breastfeeding should probably be discouraged.
b. Try to use agents for which the drug levels in breast milk are likely to be low or transient and infant absorption will be minimal.
c. It cannot be assumed that just because a medication was safe for use in pregnancy, it will be safe in breast feeding. Drug metabolism for the fetus largely is the

purview of the mother; while postpartum, the infant must metabolize any medications it is exposed to on its own. Although drug levels in breast milk for most agents are low enough that this is not generally a significant clinical issue, it may be a concern in the premature or unwell infant. A brief conversation with the neonatologist caring for the infant may help clarify these concerns in such cases.

d. If there is a possibility that a drug may present a risk to the infant, consideration should be given to measurement of blood concentrations in the nursing infant.
e. Drug exposure to the nursing infant can be minimized by having the mother take the medication during or just after she has breast fed the infant. Peak levels in breast milk generally coincide with peak levels in maternal serum and timing or breastfeeding can minimize the exposure. However, it should be mentioned that this strategy is often impractical due to the unpredictable nature of infant feeding demands and we do not generally overemphasize this approach with our patients.

How does a clinician determine which medications are the safest for breastfeeding? Almost all medications transfer into human milk to some degree. The amount of drug that transfers however is quite small in most cases, averaging less than 1% of the maternal dose. Rarely does the amount transferred into milk result in anything even close to clinically significant doses of medication being received by the infant.

Drugs enter breast milk primarily by diffusion. They are driven by equilibrium forces between the maternal plasma component and the maternal milk component. One of the most important determinants of drug penetration into the breast milk is the mother's plasma level. As the level of the medication in maternal plasma rises, the concentration in the milk rises as well. Drugs that are low in molecular weight, are highly lipid soluble, and/or have low protein binding are all more likely to be found in higher levels in breast milk. The pKa (the acid dissociation constant) of a medication will also affect its levels in breast milk, which tends to be of a lower pH than maternal serum. The pH gradient between maternal serum and milk can mean that some medications are trapped and even concentrated in human milk *(6)*.

Once medications are transferred into human milk, oral bioavailability of the medication to the infant is another important factor to consider. Many medications are neutralized by gastric acids, destroyed by the infant's gut, fail to be absorbed through the gut wall, or are sequestered in the infant's liver (first pass) and never reach the plasma where they are active. Three examples of commonly used agents that cannot be absorbed by the infant gut regardless of their level in breast milk are gentamicin, heparin, and ipratropium. Table 6.4 lists some useful resources for medication safety in pregnancy and lactation. We have found Dr. Hale's "Medication and Mothers' Milk" invaluable when caring for the nursing mother. Table 6.4 lists the lactation safety categories for some commonly used pulmonary medications, based upon his classification. The American Academy of Pediatrics (AAP) also provides information on medications and breastfeeding safety *(7)*. It reviews a small number of the medications presently available in the US and deems those agents with strong indications of safety for breastfeeding mothers as "compatible with breastfeeding." The absence of a rating by the AAP does not imply that the medication is unsafe for breastfeeding but only that the AAP has not reviewed or rendered a recommendation on the agent. A summary of the AAP's classification system

Table 6.6 Medications and breastfeeding. The American Academy of Pediatrics: Committee on drugs *(7)*. (List includes only some medications which may be of interest to the pulmonary physician. For a complete list, please see referenced article).

Cytotoxic drugs that may interfere with cellular metabolism of the nursing infant:
Cyclophosphomide
Cyclosporine
Doxorubicin
Methotrexate

Drugs of abuse for which adverse effects on the infant during breast feeding have been reported.
Amphetamine
Cocaine
Heroin
Marijuana
Phencyclidine

Drugs for which the effect on nursing infants is unknown but may be of concern
Benzodiazepines (Risk varies with specific medication)
SSRIs (Risk varies with specific medication)
Anti-psychotic medications (Risk varies with specific medication)
Metronidazole
Lamotrigine
Metoclopramide
Amiodarone

Drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution.
Sulfasalzine
Aspirin
Atenolol
Bromocryptine
Ergotamine

Medications compatible with breast feeding.

Acetaminophen	Digoxin	Inhaled steroids	Ticarcillin
Acyclovir	Dapsone	Morphine	Trimethoprim/ sulfameth
Amoxicillin	Fluconazole	Nifedipine	Oxazole
Aminoglycosides	Ibuprofen	Prednisone	Warfarin
Cephalosporins	Heparin:	Pseudoephedrine	Zolpidem
Ciprofloxacin	Unfractionated or	Sulbactam	TB Meds: INH,
Clindamycin	LMWH	Terbutaline	Rifampicin,
Codeine	Inhaled bronchodilators		Ethambutol, Streptomycin

and a list of commonly prescribed agents deemed compatible with breastfeeding are found in Table 6.6.

Conclusion

Prescribing in pregnancy will be most successful when the clinician works with the patient to make the decision about the use of a particular medication in pregnancy. It is not at all uncommon for pregnant women to take only some or none of their medications, especially if an active collaborative approach has not been established with the prescribing physician. When medication is prescribed in pregnancy to promote maternal health, the patient (and the prescribing physician) should be encouraged to think of the fetal benefit gained from optimizing maternal health.

Similarly, when caring for the lactating mother, the clinician should closely review the documentation on drugs and their levels in human breast milk prior to casually recommending discontinuation or interruption of lactation. More often than not, medical treatment is compatible with ongoing breastfeeding.

Abbreviations

NHLBI	National Heart, Lung, and Blood Institute
NAEP	National Asthma Educational Program
pH	Measure of acidity or alkalinity of a solution
SSRI	Selective Serotonin Reuptake Inhibitor
LMWH	Low Molecular Weight Heparin
CDC	Centers for Disease Control
PZA	Pyrazinamide
HIV	Human Immunodeficiency Virus
CMV	Cytomegalovirus

References

1. Medication during pregnancy: an intercontinental cooperative study. Collaborative Group on Drug Use in Pregnancy (C.G.D.U.P.) Int J Gynaecol Obstet 1992;39(3):185–96.
2. Werler MM, Mitchell AA, Hernandez-diaz S, Honein MA: Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol 2005 Sep;193(3 Pt 1):771–7.
3. Refuerzo JS,Blackewell SC, Sokol RJ, et al.: Use of over-the-counter medications and herbal remedies in pregnancy. Am J Perinatol 2005 Aug;22(6):321–4.
4. Rogers RC, Sibai BM, Whybrew WD: Labetalol pharmacokinetics in pregnancy-induced hypertension. Am J Obstet Gynecol 1990 Feb;162(2):362–6.
5. ACOG Committee Opinion No. 361: Breastfeeding: maternal and infant aspects. Obstet Gynecol 2007 Feb;109 (2 Pt 1):479–80.
6. Thomas H. Medications and Mothers' Milk. Twelfth edition. Pharmasoft Publishing, 2006.
7. The American Academy of Pediatrics: Transfer of Drugs and other chemicals into human milk: Committee on drugs. Pediatrics September 2001;108(3):776–789.

7

Monitoring Fetal Well-Being in the Critical Care Setting

Kristen Cotter and Mathew Sermer

Keywords: fetal monitoring, deceleration, cardiotocogram, fetal heart rate, non stress testing

Pregnant patients constitute a small percentage of patients in the critical care setting, but when these patients do arrive in the unit, many questions emerge regarding the need for, extent of, and interpretation of the monitoring of the fetus. Appreciating fetal heart tracings begins with an academic understanding of the terminology used for descriptions, but then requires years of experience to develop the skill in the art of interpretation. Critical care physicians cannot be expected to have a comprehensive command of the skill set needed for this task. Pregnant patients in the critical care setting therefore require an interdisciplinary approach with the participation of an obstetrician on the team, particularly if the gestational age of the fetus is beyond the limits of viability.

This chapter is not intended to provide a comprehensive guide to the assessment of fetal well-being. Rather, the aim of this chapter is to familiarize the critical care physician with some basic tools and terminology that obstetricians use in their assessments. This foundation will provide a context to aid in communication with the obstetric team and to deepen the critical care team's understanding of the second patient—the fetus—under their care.

Introduction to Electronic Fetal Monitoring

The primary tool used to assess overall fetal well-being is the cardiotocogram (CTG), which consists of electronic fetal monitoring (EFM) documented simultaneously with a recording of uterine contractions. The basic concept of EFM is that the fetus' brain modulates the heart rate; therefore a hypoxic insult to the brain will manifest itself in alterations in the fetal heart rate (FHR) patterns. Ideally, these changes will be detected and appropriate interventions will be made to interfere with the hypoxic insult before damage is permanent. The original aim of EFM, therefore, was to prevent fetal hypoxic brain injury and fetal death.

With this great promise, continuous intrapartum EFM—most commonly in the form of CTG—has been widely adopted, in spite of the lack of evidence to support its use. There is consensus that a reassuring CTG is highly predictive of a well-oxygenated fetus. On the opposite end of the spectrum, there is also consensus that

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_7

some CTG patterns indicate current or impending asphyxia *(1)*. In spite of these well-accepted ideas, there are several major limitations to CTG that make interpretation of intermediate readings challenging; these are as follows *(2)*.

First, the efficacy of EFM is uncertain. There are no randomized clinical trials of continuous monitoring versus no monitoring. The only data available compare intermittent versus continuous monitoring. A Cochrane review meta-analysis that included over 33,000 women found higher rates of cesarean delivery (RR 1.66, 95% CI 1.30–2.13) and instrumental delivery (RR 1.16, 95% CI 1.01–1.32) in the continuous monitoring group, but no difference in overall perinatal mortality (OR 0.85, CI 0.59–1.23) *(3)*. The one outcome measure that was significantly improved in the continuous monitoring group was the incidence of neonatal seizures, which was halved (RR 0.50, 95% CI 0.31–0.80). There was no evidence of benefit or harm in terms of Apgar scores, cord blood gas, admission to the neonatal intensive care unit, or hypoxic ischemic encephalopathy.

Second, the false positive rate of a non-reassuring fetal heart tracing is known to be quite high *(1)* A CTG tracing deemed "non-reassuring" (which will be discussed later in this article), while indeed alerting the obstetrician to the need to obtain reassurance or else intervene, actually has very poor specificity for predicting fetal asphyxia. The ability to predict cerebral palsy, specifically, had been called in question. One study indicated that the positive predictive value of a non-reassuring FHT for cerebral palsy for singleton fetuses weighing more than 2,500 g was only 0.14%, giving the test a 99.8% false positive rate *(4)*. These observations have contributed to a growing understanding that antepartum rather than intrapartum events likely cause cerebral palsy. Indeed, widespread use of EFM—used in 85.4% of US deliveries in 2003 *(5)*—has not changed the national incidence of cerebral palsy, even when analysis is restricted to term infants *(6)*.

Third, the reliability—or ability to reproduce consistent results on repeated application—is poor, both in terms of intra-observer *(7)* and inter-observer *(8)* interpretations. Subsequently, there is a risk of under- or over-treating due to misinterpretation.

In spite of the limitations and lack of evidence, EFM remains the standard of care as the primary method used to assess the overall tolerance of the fetus to the intrauterine environment. This is particularly the case in a critical care setting where the positive predictive value of a non-reassuring fetal heart rate pattern would be expected to be higher as compared to a similar tracing obtained in a low risk setting.

EFM Descriptions

In 1997, the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health proposed "a standardized and rigorously, unambiguously described set of definitions that can be quantitated" *(1)*. This terminology has been adopted by the American College of Obstetricians and Gynecologists *(2)*, and has made great strides in unifying the obstetric community's language in regards to EFM.

A complete description of a FHR tracing includes the following: the baseline heart rate, a description of the variability, presence or absence of accelerations, descriptions of any decelerations, and changes in trends over time. This description is then followed by an interpretation (for example, "fetal well-being reassuring") and a plan for any interventions or further assessments if needed.

The *baseline* FHR is the approximate mean FHR rounded to increments of 5 bpm (beats per minute), excluding periodic or episodic changes such as accelerations or decelerations. The observer looks for a 2-min segment where the baseline is evident within a 10-min segment (See examples in Figure 7.1). Normal baselines are between 110 and 160 bpm. Below 110 bpm is termed bradycardia and above 160 bpm is termed tachycardia.

Fetal bradycardia can be a sign of severe fetal hypoxia and compromise, such as in the setting of placental abruption or cord prolapse. Other causes include maternal hypothermia or congenital heart block. The most common cause of fetal tachycardia is fever or infection. Other causes include fetal compromise, cardiac arrhythmias, or iatrogenic administration of medications such as atropine or terbutaline *(9)*.

Fluctuations in the baseline FHR of two cycles per minute or greater is termed *variability*. It is quantitated as the amplitude of the peak-to-trough in bpm. In "absent variability," the amplitude range is undetectable. "Minimal variability" refers to a detectable range of equal to or less than 5 bpm (Figure 7.2). "Moderate variability" ranges from 6 to 25 bpm (Figure 7.3), and the range of "marked variability" exceeds 25 bpm (Figure 7.4).

Variability is traditionally considered to be the most sensitive predictor of neonatal outcome, with moderate variability representing an adequately oxygenated, responsive fetal brain and fetal heart. Variability can be helpful in interpreting other non-reassuring signs in a CTG tracing. For example, moderate variability, even in the setting of recurrent late decelerations, is highly predictive of a non-acidemic infant at birth *(10)*. In contrast, minimal or absent variability in the setting of bradycardia or tachycardia is strongly associated with fetal acidemia *(10)*.

Acceleration is defined as an abrupt increase (that is, from the onset to the peak measures <30 s) in FHR above the baseline. The peak is ≤ 15 bpm above the baseline, and the acceleration lasts ≤ 15 s (Figure 7.5). Before 32 weeks of gestation, accelerations are defined as having a peak ≤ 10 bpm above the baseline for at least 10 s.

Accelerations are frequently associated with fetal movement and are reassuring. Their presence generally confirms the absence of acidemia *(11)*. The absence of accelerations, however, does not confirm hypoxia, but rather prompts the search for reassurance by other methods.

Decelerations are transient decreases in the FHR, which occur in relation to the stress of a contraction or other physiologic events. There are a variety of different types of decelerations, each of which carries its own set of possible etiologies and implications.

Late decelerations gradually decrease (over a period of >30 s) from baseline after a contraction and then return to the baseline. When compared to the timing of the contractions, the deceleration starts after the contraction starts, the nadir occurs after the contraction's peak, and the return to baseline occurs after the contraction resolves (See Figure 7.6).

Late decelerations are considered repetitive if they occur after $>50\%$ of all contractions. They can represent the first indication of hypoxia caused by uteroplacental insufficiency and are definitely cause for clinical concern *(12)*.

Early decelerations appear in a shape that is quite similar to late decelerations, with a gradual decrease from the baseline and then return to baseline. The timing of the deceleration in relation to the contraction helps distinguish between early and late decelerations. An early deceleration and its associated contraction occur coincident in timing; that is, the onset, nadir, and recovery of the deceleration occur nearly simultaneously with the onset, peak, and ending of the contraction, respectively (See Figure 7.7).

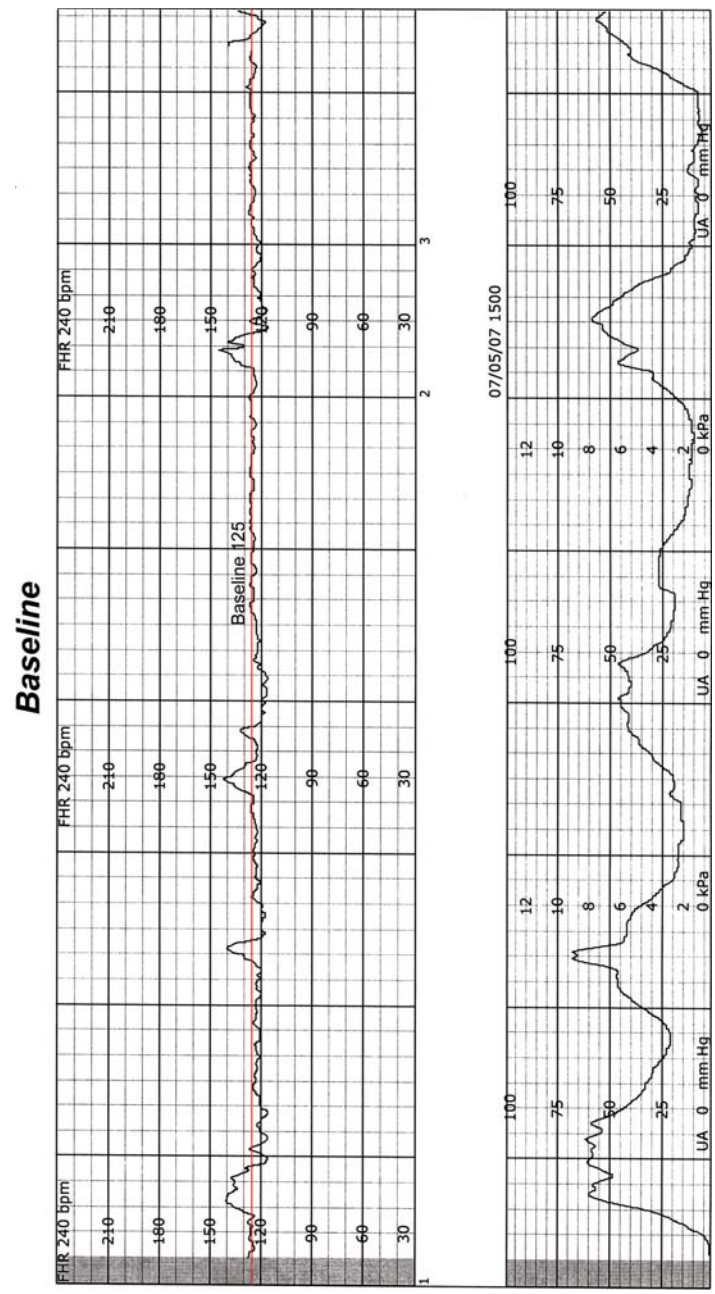


Figure 7.1 A normal baseline, here at 125 beats per minute

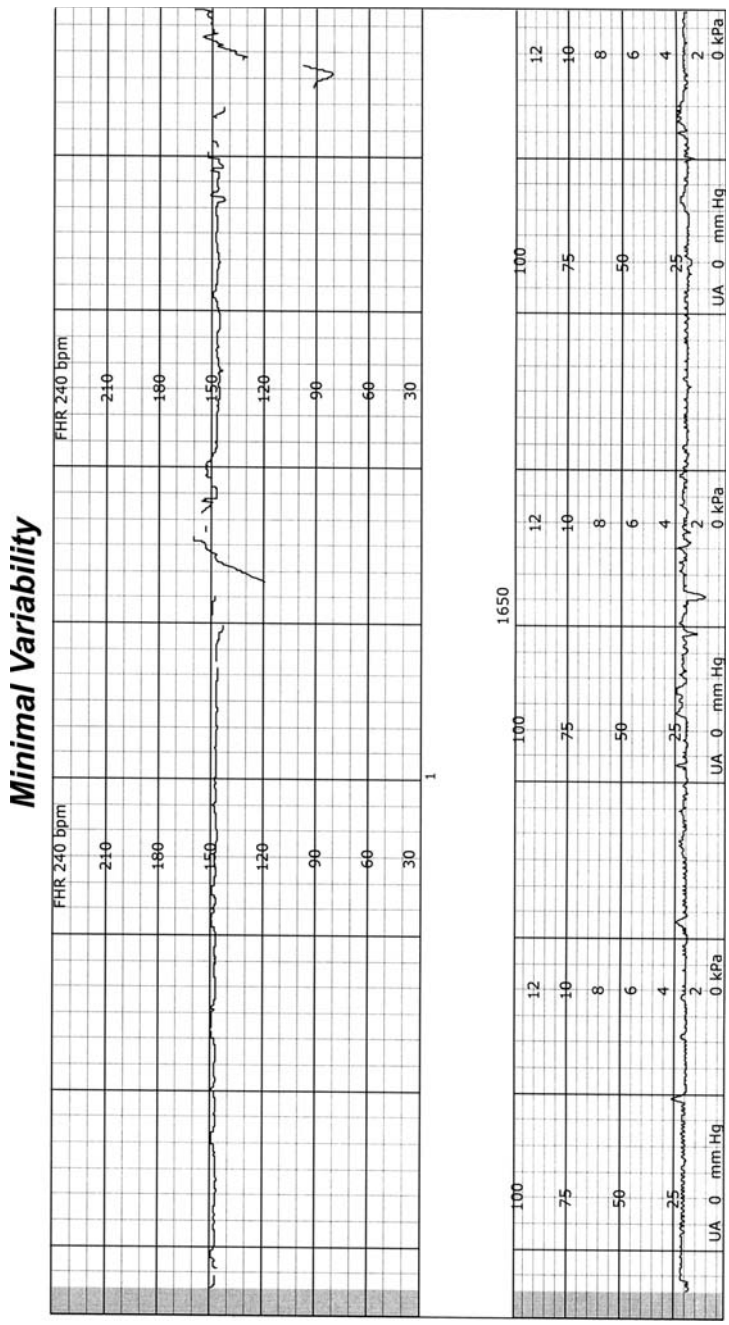


Figure 7.2 Minimal variability

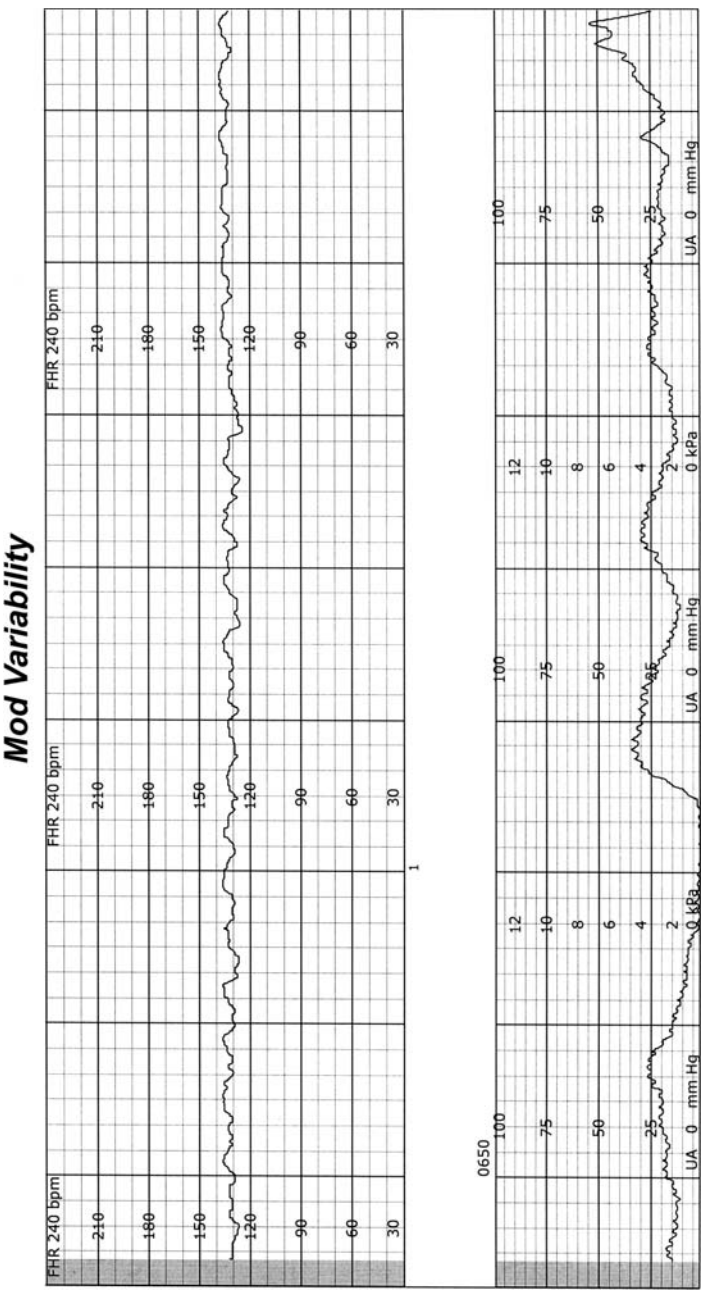


Figure 7.3 Moderate variability

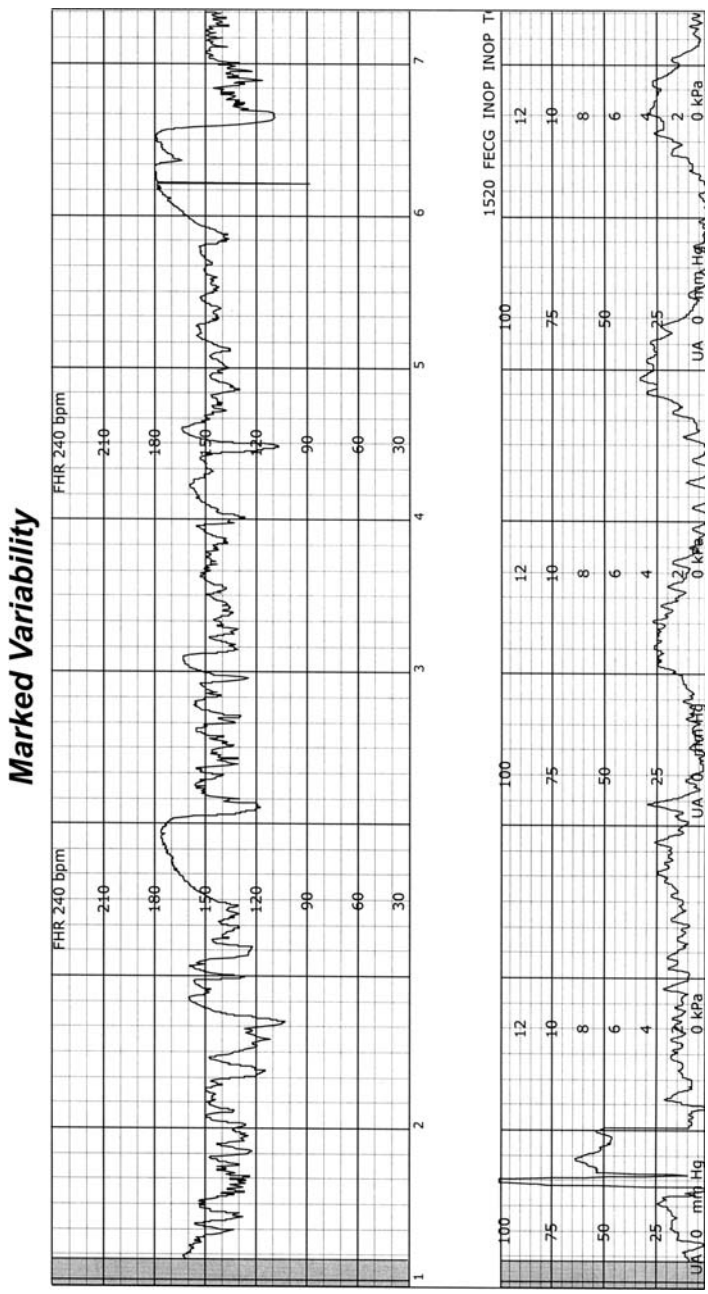


Figure 7.4 Marked variability

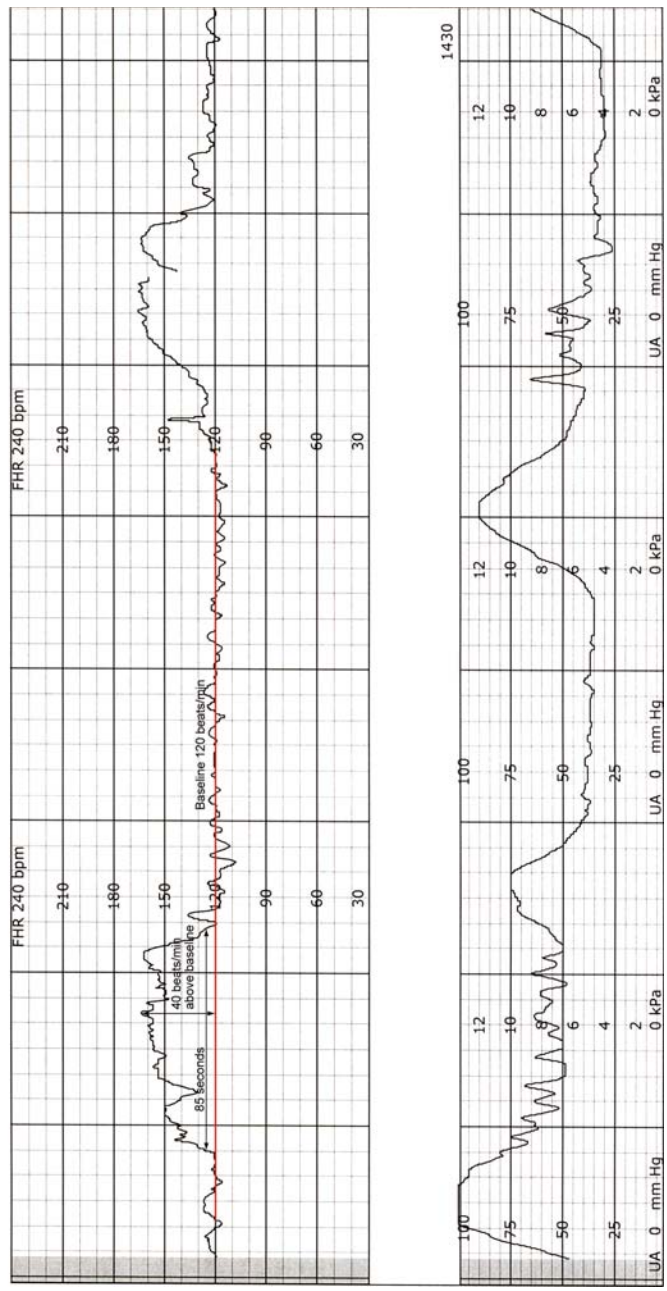


Figure 7.5 Accelerations

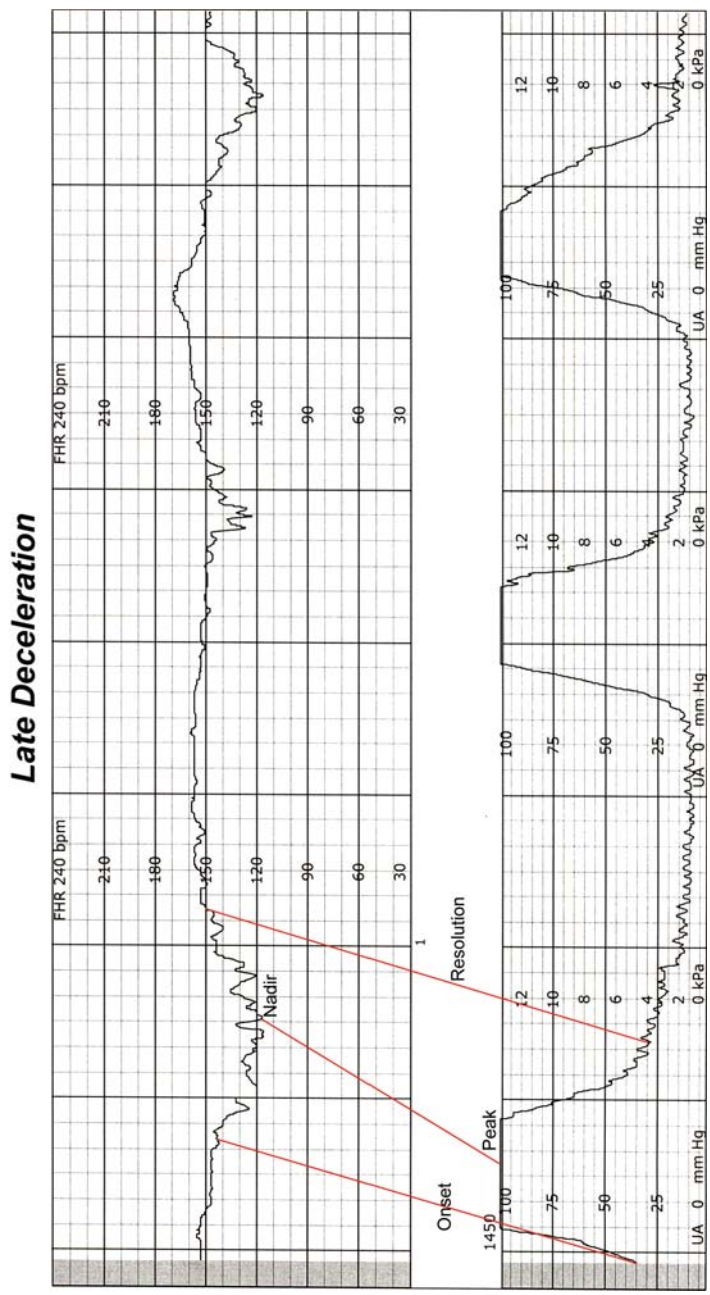


Figure 7.6 Late decelerations, where the onset, nadir, and resolution of the deceleration lags behind the onset, peak, and resolution of the contraction with which it is associated

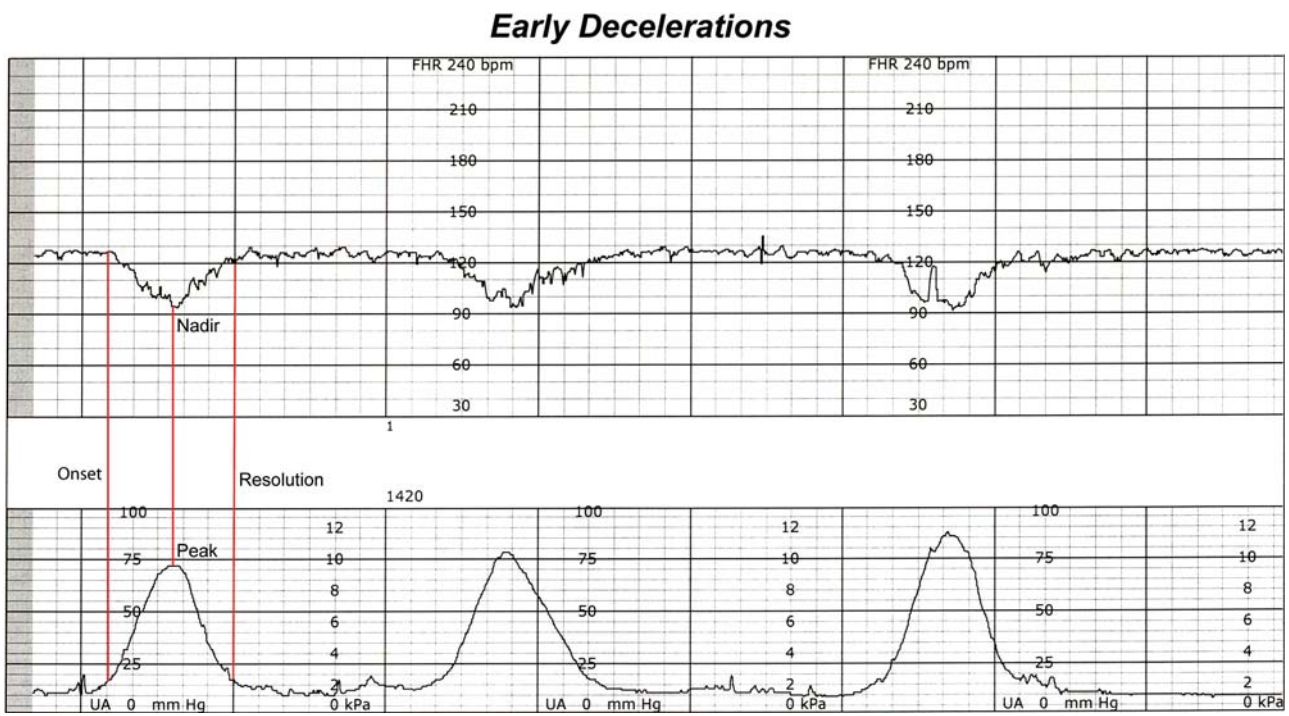


Figure 7.7 Early decelerations, where the onset, nadir, and resolution of the deceleration occur coincident with the onset, peak, and resolution of the contraction, respectively

Early decelerations are thought to be due to head compression of the fetus during contractions, likely due to a vagal response *(13)*. They are not associated with fetal hypoxia, acidemia, or low Apgar scores *(11)*.

Variable decelerations are characterized as abrupt decreases (<30 s from onset to nadir), with a nadir of at least 15 bpm below the baseline, lasting at least 15 s but not more than 2 min. A description of the variable is recorded objectively. For example, a description of Figure 7.7 might read, "Variable decelerations dropping from baseline of 140 to nadir of 65, lasting 80 s, not associated with a contraction, with abrupt recovery to baseline."

Variable decelerations are usually caused by umbilical cord occlusion. While they may occur in relationship to oligohydramnios or contractions, they frequently occur spontaneously. Fetuses are believed to have adequate physiologic mechanism to allow them to cope with occasional cord compression *(14)*, and most variable decelerations are therefore not exceptionally concerning.

Finally, *prolonged decelerations* are decreases of ≤15 bpm in the FHR below the baseline, lasting between 2 and 10 min before returning to baseline (Figure 7.8). These often prompt a stat page where the episode is emergently reported as "Low FH!," Immediate resuscitative measures by obstetric team quickly follow.

Prolonged decelerations can occur in a variety of clinical scenarios, including maternal hypotension, recent administration of epidural or spinal anesthesia, cord prolapse, uterine hyperactivity, temporary cord occlusion caused by maternal positioning, rapid descent of the presenting fetal part following sudden progression in cervical dilation, or placental abruption. Many fetuses recover spontaneously if the precipitating insult can be removed. There is, however, a risk that prolonged deceleration can lead to fetal demise, and so great clinical judgment is necessary in deciding when to await recovery versus when to delivery emergently, either by cesarean section or by operative vaginal delivery. Figure 7.9, for example, documents a prolonged fetal bradycardia that prompted a forcep-assisted vaginal delivery.

Using the above descriptions, a clinician can review a CTG to seek reassurance that the fetus is tolerating the current intrauterine environment well, without any indication of current or impending asphyxia. A "reassuring FHT"—*a term frequently used but not defined in the NICHD or any other guidelines*—is one with a baseline within normal limits, with moderate variability, with spontaneous accelerations, and without decelerations, as shown in Figure 7.5.

A CTG must always be viewed in the context of the entire maternal clinical picture. Medications such as opiates *(15)* and magnesium *(16)* can cause decreased variability and fewer accelerations. Fetal sleep cycles, which typically last about 20 min, usually produce a flat appearing tracing that revives when an awake period begins. Fetuses before the age of 32 weeks gestation are less likely to have accelerations measuring 15 bpm × 15 s, and are considered to be appropriate for gestational age if accelerations measure at least 10 bpm × 10 s.

"Non-reassuring" signs include fetal bradycardia or tachycardia, minimal variability, late decelerations, prolonged decelerations, or variable decelerations. These signs are always viewed in the context of other characteristics of the tracing. For example, occasional variable decelerations with contractions in the setting of moderate variability with spontaneous accelerations indicates an overall reassuring clinical picture. In contrast, repetitive late decelerations in the setting of minimal variability with no spontaneous accelerations requires either immediate confirmation of reassuring status by other means (to be discussed), or immediate delivery.

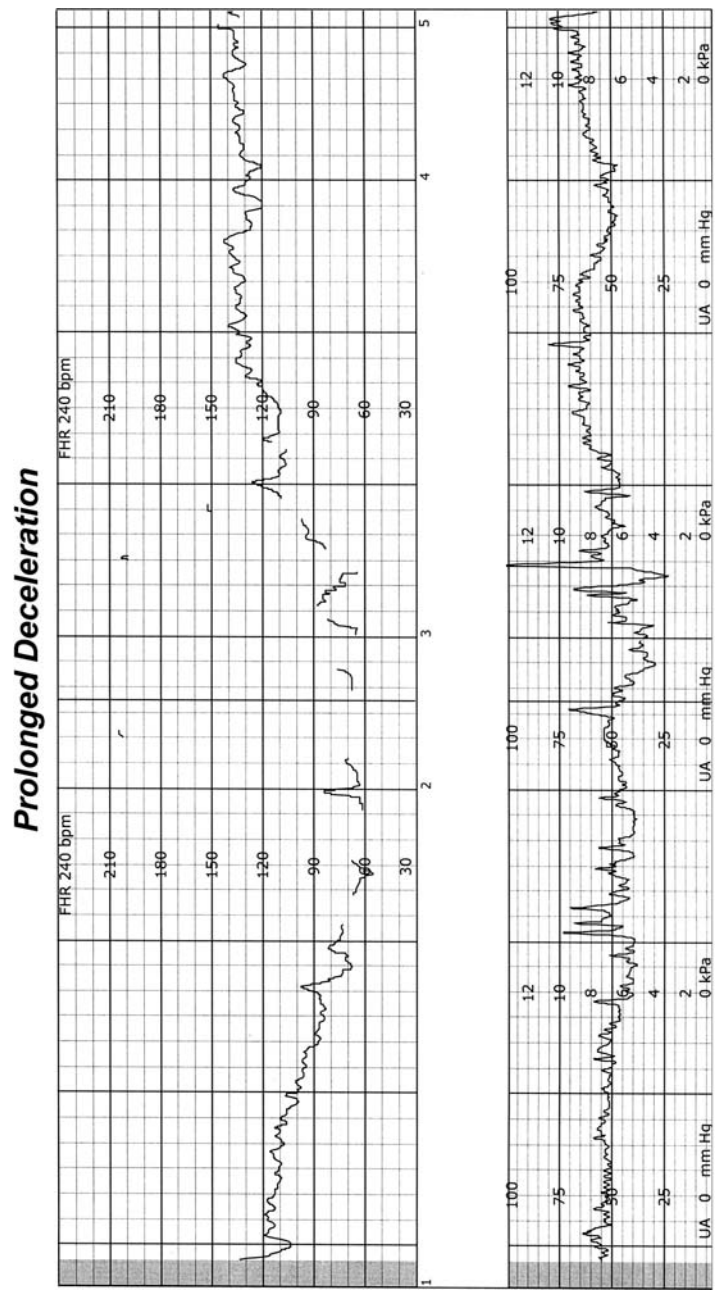


Figure 7.8 A prolonged deceleration with recovery to baseline

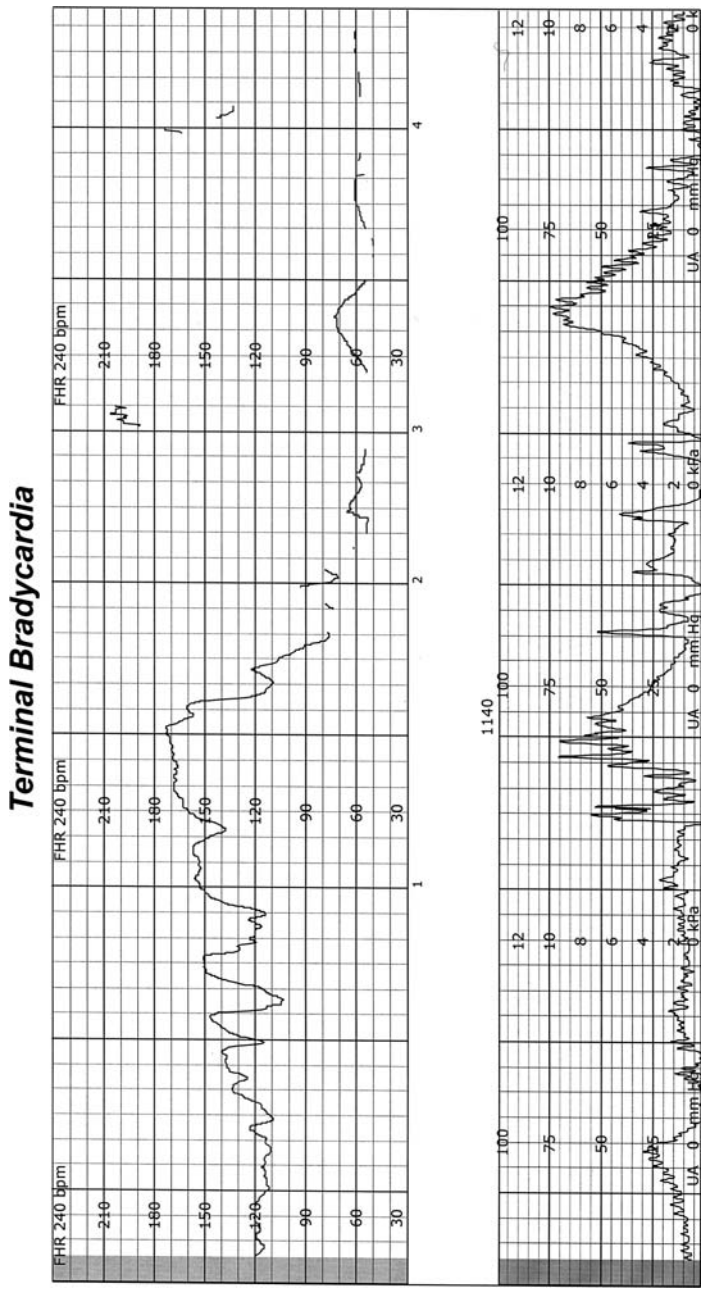


Figure 7.9 A fetal bradycardia that prompted urgent delivery by forceps

Ancillary Methods to Assess Fetal Status

The most frequently used assessment of fetal well-being, especially in the outpatient setting, is the non-stress test (NST). When there are two FHR accelerations during a 20-min interval of monitoring, with, each one rising to at least 15 bpm above the baseline and lasting for at least 15 s, the NST is described as "reactive." In pre-term fetuses, the size of the accelerations is lower, at least 10 bpm above the baseline for at least 10 s. "Non-stress" refers to the fact that contractions need not be present for this type of testing to be conducted. While the specificity is poor, the NST is among the most sensitive tools for detecting worsening hypoxemia and/or acidosis *(17)*.

Provided that the tracing is stable enough to allow time for further analysis, a non-reactive NST or a non-reassuring fetal heart tracing can prompt a number of additional diagnostic tests. First, in the absence of spontaneous accelerations, accelerations can be provoked. Early studies applied Allis clamps directly to the fetus's scalp, but the more common practice is to rub the fetal head with the provider's gloved finger. In the setting where the cervix is not dilated or the amniotic sac is not ruptured, acoustic stimulation with an external buzzer applied to the abdomen can also be used. If the fetus responds with an acceleration on the monitor, this response is widely accepted as a sign of adequate oxygenation. A recent Cochrane Review, however, notes that there is little evidence to support this practice *(18)*.

For a woman whose cervix is dilated and whose amniotic sac is ruptured, questions regarding fetal oxygenation can be resolved by directly sampling the fetal scalp blood. Most frequently, a scalp pH of >2.5 is considered reassuring, while a pH of <2.0 prompts immediate delivery, usually by urgent cesarean section. A pH between 2.0 and 2.5 warrants further sampling, usually within 30 min *(19)*.

For a woman not in labor, the Biophysical Profile Score (BPS) provides a non-invasive way to approximate fetal pH without having to obtain a fetal blood sample *(20)*. The test is performed by ultrasound, where the fetus is given a maximum of 30 min to gain 2 points in each of the following areas: NST (2 points if reactive), amniotic fluid volume (at least one pocket of fluid measuring 2×2 cm), fetal breathing movement (one episode lasting at least 30 s), gross body movements (3 discrete movements), and fetal tone (one episode of active extension with return to flexion of the limbs or trunk) *(21)*. Among structurally normal fetuses with a 10/10 BPS, the chance of intrauterine fetal demise within 7 days is 0.0748% *(22)*.

In certain cases, growth ultrasounds provide an additional method of monitoring the general well-being of a fetus. Women whose medical or obstetrical conditions place their fetus at risk for intrauterine growth restriction (IUGR), such as those with placental dysfunction, chronic hypertension, substance abuse, and others, generally begin monitoring with periodic ultrasounds starting at viability. If the fetal weight is measured at $<$ 10th percentile, the fetus is classified as having IUGR, prompting more specialized and frequent monitoring.

Timing of Monitoring

The first question to ask before ordering any medical test is almost always "Will these results change my clinical management?" In this spirit, there are times when EFM is not appropriate strictly because its findings will not prompt intervention.

In most institutions, the limit of fetal viability is defined as 24 weeks and zero days. Prior to this gestational age EFM is unhelpful, for observing even severe fetal

distress indicative of imminent demise will not prompt a cesarean section since the infant has no chance of survival outside of the uterus.

Similarly, if the mother's clinical state is too unstable to tolerate an emergent cesarean delivery for fetal indications, it is reasonable to withhold monitoring. A guiding principle in obstetrics is that the mother's health is the first priority, above that of the fetus. In these cases, fetal monitoring can be deferred until the maternal state stabilizes to the point that intervention on behalf of the fetus would be feasible. Until then, the fetal heart rate can be periodically checked by Doppler—daily, for example, or after acute events or clinical changes—to provide information regarding the survival of the fetus.

Continuous monitoring is appropriate for a viable fetus when the maternal condition is rapidly evolving or when there are active obstetric issues. Examples include following an eclamptic seizure as the timing of delivery is being debated, after a motor vehicle accident when there is a question of placental abruption, or in the setting of pre-term contractions with a question of pre-term labor.

When pregnant patients are hospitalized long-term with relatively stable medical conditions and no active obstetric complaints (that is, no contractions, leaking of fluid, or vaginal bleeding, and with adequate fetal movement), monitoring is frequently switched to intermittent. There are no guidelines to suggest what timing is most appropriate, and physician preference ranges from daily to three times per day. Monitoring usually consists of CTG until the tracing is reactive.

Interventions for a Non-Reassuring FHR

When a FHR is not reassuring, there are a number of immediate maneuvers that can be performed in an effort to resuscitate the fetus.

- Particularly important in an ICU setting where patients traditionally lie supine is the idea of uterine displacement. The pregnant patient should be placed either in the left lateral decubitus position, or at least positioned with a leftward tilt by placing a wedge under the right hip.
- Hypotension should be corrected, if possible with a bolus of intravenous fluids.
- If Pitocin is being administered, it should be turned off in the event of fetal distress. If uterine hyperstimulation is observed, a tocolytic agent such as terbutaline can be given to allow the fetus time between contractions to recover.
- Supplemental oxygen should be administered.

Perimortem Cesarean Section

A review of monitoring fetal well-being in critical care settings would be remiss to exclude a discussion of perimortem cesarean section.

In the event of maternal cardiac arrest, immediate cesarean delivery of the fetus is thought to increase the chance of survival for both the mother and the fetus. For the mother, evacuation of the uterus not only increases the effectiveness of CPR, but also results in an increased preload as the now empty uterus elevates off the vena cava. As well, there is an immediate transfusion of 500 cc of blood from the uterus as the newly emptied organ contracts down. For the fetus, there is the chance for intact survival, especially if the fetus is close to term and if the insult that prompted cardiac arrest occurred acutely, such as in the event of amniotic fluid embolism or anesthesia complications.

Case reports, which are prone to selection bias, provide the only available data for such scenarios, but it is generally accepted that delivery within 4 min of cardiac arrest provides the best hope for intact survival of the infant *(23)*. CPR should be continued throughout the surgery, and a sterile field is forgone for the sake of time.

References

1. National Institute of Child Health and Human Development Research Planning Workshop. Electronic fetal heart rate monitoring: research guidelines for interpretation. Am J Obstet Gynecol 1997;177(6):1385–90.
2. ACOG Practice Bulletin 70: Intrapartum Fetal Heart Rate Monitoring. Obstet Gynecol 2005;106:1453–60.
3. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2006;19:3.
4. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 1996;324:613–8.
5. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2003. Natl Vital Stat Rep 2005;54(2):1–116.
6. Clark SL, Hankins GD. Temporal and demographic trends in cerebral palsy–fact and fiction. Am J Obstet Gynecol 2003;188(3):628–33.
7. Devane D, Lalor J. Midwives' visual interpretation of intrapartum cardiotocographs: intra- and inter-observer agreement. J Adv Nurs 2005;52(2):133–41.
8. Ayres-de-Campos D, Bernardes J, Costa-Pereira A. Pereira-Leite L. Inconsistencies in classification by experts of cardiotocograms and subsequent clinical decision. Br J Obstet Gynaecol 1999;106(12):1307–10.
9. Creasy RK, Resnick R, Iams JD, eds. Maternal-Fetal Medicine: Principles and Practice. 5th ed. Philadelphia: WB Saunders, 2004:335–6.
10. Dawes GS, Moulden M, Redman CW. Short-term fetal heart rate variation, decelerations, and umbilical flow velocity waveforms before labor. Obstet Gynecol 1992; 80:673–678
11. Williams Obstetrics. 21st ed. New York: McGraw-Hill Professional; 2001:340.
12. Low JA, Pancham SR, Piercy WN, Worthington D, Karchmar J. Intrapartum fetal asphyxia: clinical characteristics, diagnosis, and significance in relation to pattern of development. Am J Obstet Gynecol 1977;129:857–72.
13. Paul WM, Quilligan EJ, MacLachlan T. Cardiovascular phenomena associated with fetal head compression. Am J Obstet Gynecol 1964;90:824.
14. Williams Obstetrics. 21st ed. New York: McGraw-Hill Professional; 2001:345.
15. Petrie RH: Dose/response effects of intravenous meperidine in fetal heart rate variability. J Matern Fetal Med 1993;2:215.
16. Hallak M, Martinez-Poyer J, Kruger ML, Hassan S. Blackwell SC, Sorokin Y. The effect of magnesium sulfate on fetal heart rate paramenters: A randomized, placebo-controlled trial. Am J Obstet Gynecol 1999;181:1122.
17. Morrison I, Menticoglou S, Manning FA, et al.: Comparison of antepartum test results to perinatal outcome. J Matern Fetal Med 1994;3:75.
18. East CE, Smyth R, Leader LR, Henshall NE, Colditz PB, Tan KH. Vibroacoustic stimulation for fetal assessment in labour in the presence of a nonreassuring fetal heart rate trace. Cochrane Database Syst Rev. 2005 Apr 18;(2).
19. Creasy RK, Resnick R, Iams JD, (Eds). Maternal-Fetal Medicine: Principles and Practice. 5th ed. Philadelphia: WB Saunders, 2004:432.
20. Manning FA, Snijders R, Harman CR, et al. Fetal biophysical profile scoring. VI. Correlations with antepartum umbilical venous pH. Am J Obstet Gynecol 1993;169:755.
21. Manning FA. Fetal Biophysical Profile. Obstet Gynecol Clin North Am 1999;26:557–77.

22. Dayal AK,Manning FA, Berck DJ, Mussalli GM, Avila C, Harman CR, Menticoglou S. Fetal death after normal biophysical profile score: An eighteen-year experience. Am J Obstet Gynecol 1999;18(5):1231–6.
23. Katz V, Balderston K, DeFreest M. Perimortem cesarean delivery: were our assumptions correct? Am J Obstet Gynecol 2005;192(6):1916–20; discussion 1920–1.

8

Anesthetic Considerations in Pregnant Patients with Pulmonary Disorders

Richard N. Wissler

Keywords: airway management, neuromuscular blockade, neuromuscular relaxants, general anesthesia, neuraxial anesthesia

Introduction

Anesthesia care in obstetrics includes three basic domains:

1. neuraxial blocks for labor analgesia, examples being epidural, spinal, or combined spinal-epidural (CSE) analgesia;
2. anesthesia for cesarean delivery, examples being spinal, CSE, epidural, or general anesthesia;
3. anesthesia for miscellaneous procedures such as cerclage, removal of a retained placenta, or postpartum tubal ligation.

The neuraxial blocks vary in distribution and intensity, depending on the clinical requirements. For example, the afferent pain signals for the first stage of labor (cervical dilation) enter the spinal cord through the T_{10} to L_1 spinal nerve roots (Figure 8.1). In the second stage of labor, additional afferent pain signals arrive via the S_2 to S_4 spinal nerve roots. Therefore, the ideal neuraxial labor analgesic would be distributed at and below the T10 dermatome, which corresponds to the umbilicus. Based on empiric observations, patient comfort during a cesarean delivery requires an anesthetic neuraxial block that extends cephalad to at least the T4 dermatome, which corresponds to the nipple line. Analgesic and anesthetic blocks differ in the intensity of sensory and motor effects. An analgesic block is characterized by a sensation of light touch when a sharp object is lightly applied to the block area. In contrast, an anesthetic block is "more dense" and characterized by the absence of sensation when a sharp object is lightly applied to the block area. Based on distribution and intensity, a neuraxial anesthetic for cesarean delivery is more likely to have an impact on pulmonary function compared to a neuraxial labor analgesic.

Whenever it is clinically feasible, most anesthesiologists and patients prefer neuraxial over general anesthesia in obstetrics, to maximize safety and birth experience satisfaction. For example, general anesthesia for cesarean delivery is usually limited to those situations where neuraxial anesthesia is contraindicated (Table 8.1), or when

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_8

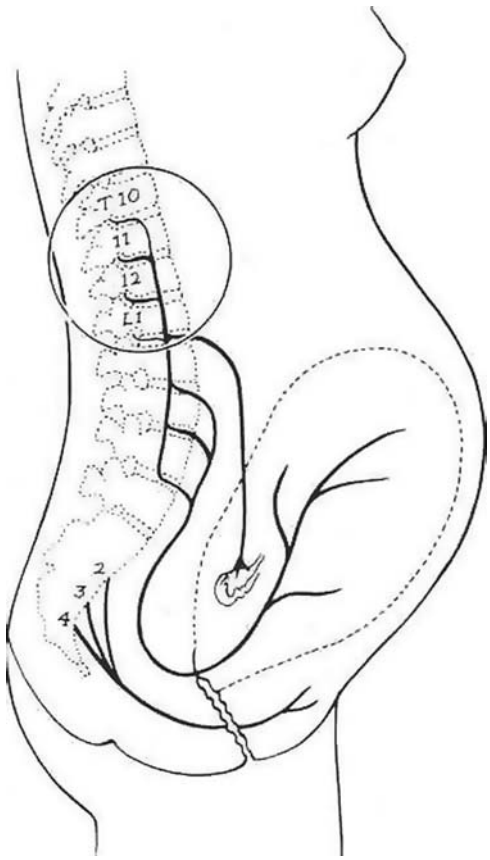


Figure 8.1 Afferent anatomic pathways for labor pain (From: Bonica JJ. Obstetric Analgesia and Anesthesia. 2nd ed. Amsterdam: World Federation of Societies of Anaesthesiologists, 1980: 44–52, with permission)

Table 8.1 (Modified from Cousins MJ and Bridenbaugh PO, 1998).

Contraindications to Neuraxial Anesthesia
1. Patient refusal
2. Shock or severe hypovolemia
3. Untreated septicemia or bacteremia
4. Increased intracranial pressure
5. Abnormal hemostasis or coagulopathy
6. Infection at the site of injection

the clinical urgency exceeds the time necessary for placement of a neuraxial block (e.g., prolapsed umbilical cord). Due to concerns about aspiration of gastric contents, general anesthesia in obstetrics usually is associated with the placement of a cuffed endotracheal tube. Many studies of safety in obstetric anesthesia have suggested that neuraxial anesthesia is safer than general anesthesia for cesarean delivery *(1, 2)*, although the lack of prospective randomized data makes this comparison vulnerable to confounding factors.

Airway Management

The term "airway management" encompasses techniques and equipment used to maintain a safe and open connection between the external world and the airway distal to the larynx. In awake and healthy patients, airway management is a normal physiologic function of the oral aperture, mouth, nose, pharynx, and larynx, with coordination provided by the nervous system.

Medications, level of consciousness, and disease processes can interfere with the normal functioning of the upper airway, necessitating a clinical airway management intervention. This intervention may be as simple as verbal stimulation of the patient or may be as complex as endotracheal intubation and positive pressure ventilation.

The decisions on airway management interventions need to be individualized. However, there are a number of basic principles for airway management in pregnancy.

1. The lower esophageal sphincter tone is decreased in pregnancy, allowing increased reflux of gastric contents into the esophagus. Symptomatic gastroesophageal reflux (GERD) is very common in pregnant women. The specific concern during clinical airway management is that gastric acid and/or food particles may be regurgitated and then aspirated into the airway. A number of adverse events can occur as a consequence of aspiration including laryngospasm, bronchoconstriction, exacerbation of underlying pulmonary dysfunction, and aspiration pneumonitis. The key clinical factors associated with fewer adverse reactions to aspiration are low volume, minimal acidity, and the absence of food particles in the aspirated fluid *(3)*. A practical approach to minimize aspiration and its effects in pregnant patients during airway management includes oral administration of a nonparticulate antacid (30 ml), cricoid pressure, intubation with a cuffed endotracheal tube, and minimal mask ventilation prior to intubation (if possible) to avoid gastric insufflation, which enhances regurgitation.
2. Gastric contents are not increased during a normal pregnancy *(4)*, except with labor or the administration of certain medications. The frequent designation of parturients as "full-stomach" patients for airway management is a misnomer, and the focus should be on the impaired barrier function between the esophagus and the stomach. Elective airway management should be delayed 6–8 h after solid food ingestion in either pregnant or nonpregnant adults, depending on the type of meal and the individual co-morbidities. Gastrointestinal transit is slower in pregnancy, possibly due to circulating progesterone. In addition, labor decreases gastrointestinal transit time in a manner analogous to trauma *(5, 6)*. Also, gastric emptying is delayed by systemic or neuraxial opioid administration *(7, 8)*. These factors should be considered in evaluating a patient for the presence of food particles in the stomach.
3. In all patients, oral intubation with direct laryngoscopy relies on a straight line of sight between the glottis and the eye of the intubating person (Figure 8.2). Prior to airway management, physical examination of the patient can identify anatomic features that will make direct laryngoscopy more challenging. These features include a small mouth opening, protruding upper incisors, small mandibular space, large tongue, thick neck, and limited neck motion. The relative size of the tongue and the mandibular space can be estimated with the Mallampati score *(9)* (Figure 8.3). During direct laryngoscopy, the blade of the laryngoscope should sweep the tongue to the side. If the tongue is large relative to the mandibular space, it may remain in the line of sight and prevent visualization of the glottis (Figure 8.2). Clinical studies suggest that the predictive value

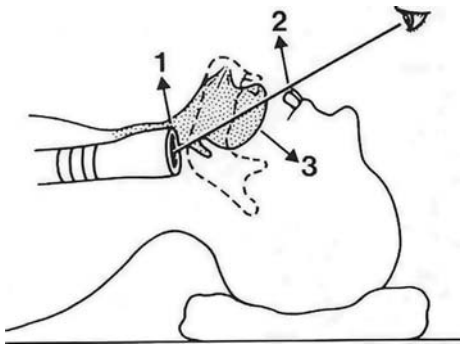


Figure 8.2 Anatomic factors affecting direct visualization of the glottis during endotracheal intubation with direct laryngoscopy. (From: Cormack RS, Lehane J. Difficult intubation in obstetrics. Anaesthesia 1984; 39:1105–11, with permission)

of the airway examination for a difficult intubation is enhanced when the Mallampati score is not used alone but in combination with other aspects of the physical exam and the history *(10, 11)*.

The physiologic changes of pregnancy may make direct laryngoscopy and intubation more challenging in parturients. These include weight gain, tongue enlargement, and mucosal swelling of the pharynx and larynx. The Mallampati score can increase for individual patients during pregnancy or labor *(12, 13)*. In preeclampsia, the mucosal swelling may be severe enough to impede intubation *(14, 15)*. In eclampsia, the patient may have bitten her tongue during the seizure leading to further swelling *(16)*. Also, breast enlargement in pregnancy may interfere with insertion of the laryngoscope into the patient's mouth.

4. Pregnant patients deplete oxygen reserves more rapidly during apnea, in comparison with nonpregnant patients *(17)*. This observation has a key impact on safe airway management during pregnancy. The physiologic basis has several components including a decreased functional residual capacity (FRC), a 15% increase in oxygen consumption by term *(18)*, and an additional 23% increase in oxygen consumption in the first stage of labor *(19)*. In many instances, general anesthesia is used for cesarean delivery in the presence of clinical circumstances that are stressful for the patient. The additional maternal catecholamine release may increase her oxygen consumption even further just prior to the induction of general anesthesia *(20)*. "Preoxygenation" is one strategy to minimize significant oxygen desaturation during airway management. The goal of preoxygenation is to maximize the fractional content of oxygen in the pulmonary gas reserves or FRC, just prior to apnea. The following factors contribute to the efficiency of

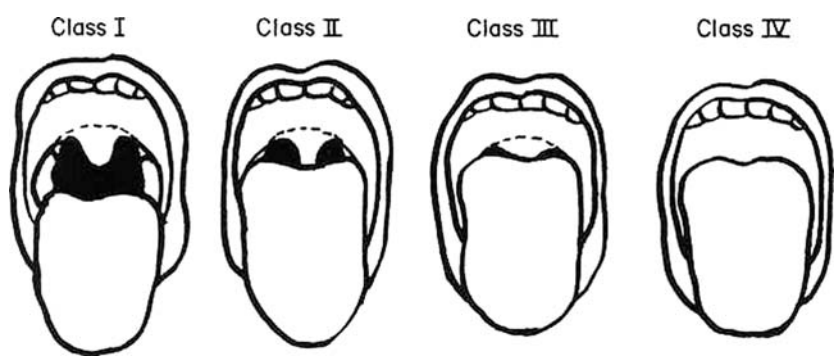


Figure 8.3 Illustration of the Mallampati scoring system for airway evaluation. (From: ref. *(9)*, with permission)

preoxygenation: tight facemask seal, high oxygen flow rate to the mask, and at least eight deep breaths by the patient *(21)*. An anesthesia breathing circuit and facemask are ideal for efficient preoxygenation. In clinical locations without an anesthesia machine, the best alternative is a high flow oxygen face mask. It is important to remember that most self-inflating positive-pressure ventilating devices used at the bedside do not have continuous oxygen flow through the mask area. In most circumstances, these devices are ineffective at preoxygenation.

5. Neuromuscular (NM) relaxant medications often are administered intravenously (IV) to allow maximum mouth opening during oral intubation with direct laryngoscopy. There are two pharmacologic categories for NM relaxants: depolarizing and nondepolarizing. Succinylcholine is the only remaining agent in the depolarizing category. All of the remaining clinically available NM relaxants, such as vecuronium, pancuronium, atracurium, or rocuronium have nondepolarizing properties. Rapid sequence induction of general endotracheal anesthesia (GETA) means that an anesthetic agent and succinylcholine are given IV, cricoid pressure is applied, and the direct laryngoscopy proceeds without any intervening positive-pressure mask ventilation. "Modified" rapid sequence induction implies that a nondepolarizing NM relaxant is used instead of succinylcholine, and positive-pressure mask ventilation through cricoid pressure proceeds while awaiting the onset of adequate NM relaxation. These two approaches have cricoid pressure in common, and are predicated on the faster onset and offset of muscle relaxation with succinylcholine compared to the nondepolarizing NM relaxants. Increasing the dose of a nondepolarizing NM relaxant may shorten the time of onset, but it also increases the duration of action. Prolonged action of a NM relaxant will delay the return of spontaneous ventilation, with safety implications if difficulty is encountered during attempted intubation.
   Succinylcholine can cause a life-threatening hyperkalemia in patients with increased numbers of acetylcholine receptors in skeletal muscle *(22)*. Clinical examples include certain types of muscular dystrophy, acquired motor denervation of skeletal muscle, and burn injuries. Hyperkalemia should be assumed if there are significant EKG changes or cardiac arrest shortly after succinylcholine administration, and it should be immediately treated with IV calcium. Succinylcholine is a potent trigger of malignant hyperthermia (MH) episodes in susceptible patients *(23)*. The Malignant Hyperthermia Association of the United States maintains a 24-h emergency hotline with immediate access to expert consultants for clinical advice (1-800-644-9737). Also, in patients with myotonic dystrophy, succinylcholine can cause a muscle contraction crisis that interferes with effective ventilation and oxygenation *(24)*. A nondepolarizing NM relaxant should be substituted for succinylcholine in airway management of patients with myotonic dystrophy, or a vulnerability to induced hyperkalemia or MH.
6. The position of the pregnant patient for airway management may need to take into consideration several different aspects of physiologic function. For example, most clinical experience with intubation occurs with nonpregnant patients in the supine position. However, pregnant patients frequently experience supine hypotension due to compression of the inferior vena cava by the gravid uterus *(25)*. One solution to this problem is to place a blanket roll under the right buttock of the pregnant patient, tipping the uterus to the left but maintaining the shoulders in a neutral position. Fortunately, many patients with upper airway obstruction during sleep or sedation have less obstruction when placed laterally, a position that is most compatible with avoidance of supine hypotension during pregnancy.

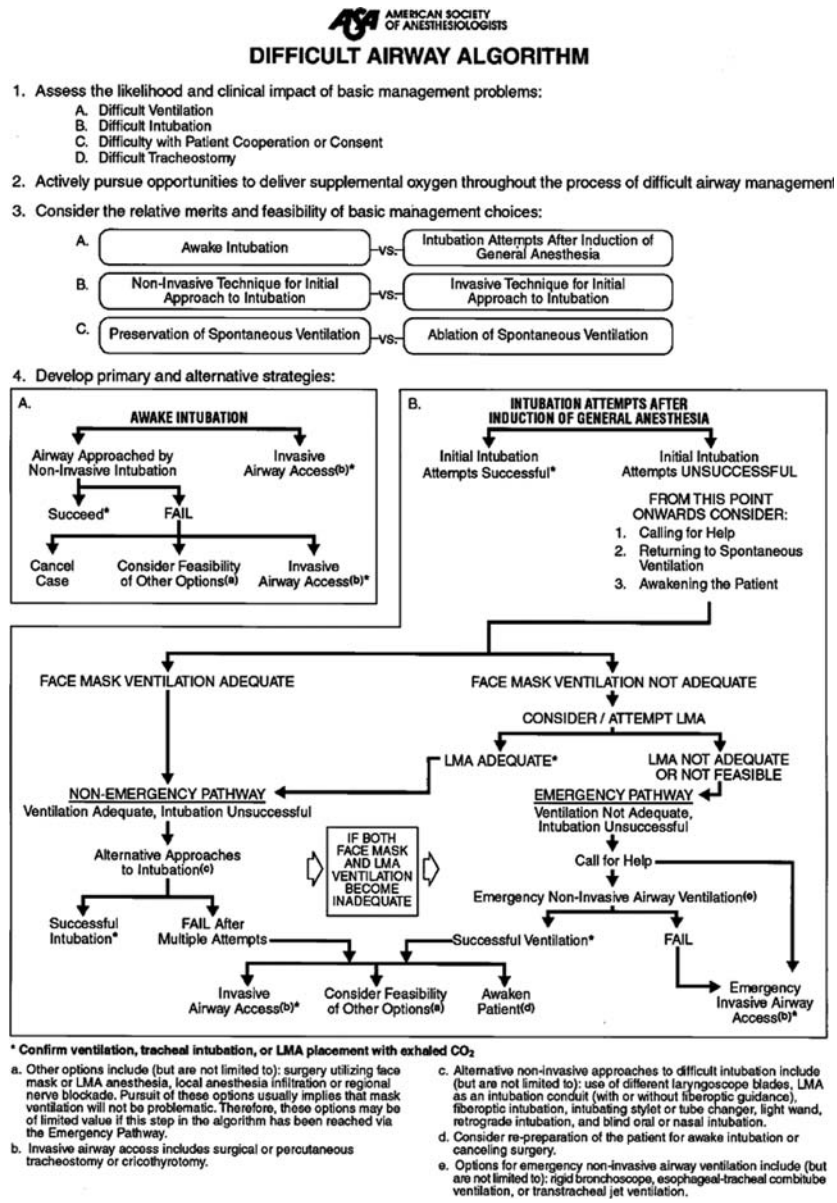


Figure 8.4 ASA Difficult Airway Algorithm (From: ref. *(11)*, with permission)

7. Failed intubation during general anesthesia for cesarean delivery occurs at a rate of approximately 1 in 250 patients *(26–28)*. These studies define intubation failure as difficulty with intubation that lasts long enough that a repeat dose of IV succinylcholine is necessary to maintain adequate NM relaxation. The observed rate of failed intubation in pregnant patients is approximately eight times greater than previous reports for nonpregnant adults *(26)*. Several authors have raised the concern that the increased popularity of neuraxial anesthesia for cesarean delivery has decreased the collective experience among anesthesiologists for the safe conduct of general anesthesia in pregnant patients *(29, 30)*. The current epidemic of obesity has safety implications for airway

management in pregnant patients. Obesity increases the difficulty of intubation during pregnancy *(31)* and is a significant factor in difficult mask ventilation after induction of general anesthesia *(32)*. Also, a recent study of anesthetic-related maternal mortality has emphasized the issue of post-extubation obstruction and hypoventilation in obese parturients *(33)*.

Every intubation attempt, in pregnant or nonpregnant patients, should have a predetermined plan to follow if difficulties are encountered. I recommend the ASA Difficult Airway Algorithm (Figure 8.4), although other reasonable "failed intubation" drills have been described. In pregnant patients, when the initial intubation attempt is unsuccessful, the immediate backup strategy is positive pressure mask ventilation through cricoid pressure. Mask ventilation may be challenging, requiring extra equipment (e.g. oral airway) and extra personnel to assist with an adequate mask seal and jaw thrust. Other available airway rescue equipment such as laryngeal mask airways (LMA), an esophageal-tracheal combitube, and fiberoptic devices should be at the bedside. Practical experience with airway rescue devices and techniques can be gained through simulation and/or airway workshops in local or regional professional meetings. The importance of prior planning for personnel and safety equipment to implement the ASA Difficult Airway Algorithm can not be overemphasized.

Neuraxial Blockade and Pulmonary Function

The primary concerns about neuraxial blockade and pulmonary function are the impact of changes in thoraco-abdominal motor function on the mechanics of breathing and coughing, and the effects of altered autonomic activity on bronchial reactivity. For cesarean delivery, anesthesia is required and the pulmonary effects of neuraxial blockade must be compared to the effects of general anesthesia. Also, postoperative recovery and analgesia are significant issues after cesarean delivery. There are many options available to patients for labor analgesia, and the pulmonary effects of neuraxial blockade must be compared to potential benefits such as decreased oxygen consumption and effectiveness of analgesia during labor.

Epidural anesthesia in the thoracic region in nonpregnant patients is associated with a clinically significant decrease in expiratory reserve volume and a smaller decrease in inspiratory capacity *(34, 35)*. As shown in Figure 8.5, these effects are proportional to the level of anesthesia with either spinal or epidural anesthesia *(34)*.

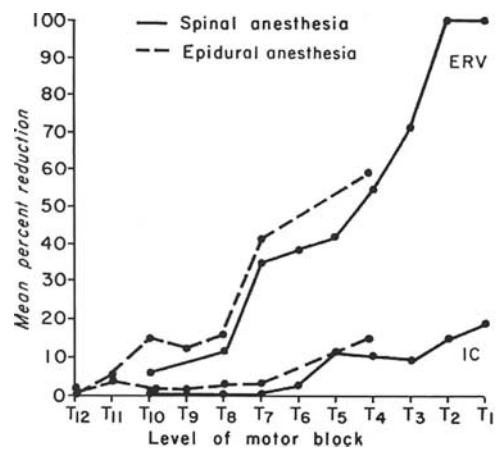


Figure 8.5 The effects of spinal and epidural motor block levels on inspiratory capacity (IC) and expiratory reserve volume (ERV). (From: ref. *(34)*, with permission)

As body mass index (BMI) increases, there is a progressive decrease in lung volumes in response to low-mid thoracic spinal anesthesia in nonpregnant women *(36, 37)*.

In pregnant women at elective cesarean delivery, epidural anesthesia to the mid-thoracic level does not significantly change the baseline peak expiratory flow rate prior to the surgical incision *(38)*. Spinal anesthesia to the upper thoracic region at elective cesarean delivery decreases vital capacity (18%), forced vital capacity (17%), FEV_1 (18%), peak expiratory flow rate (21–30%), and mid-expiratory flow (29%), prior to the surgical incision *(39, 40)*. There is a significant correlation between BMI and the magnitude of the decrease in all five of these spirometric parameters, during spinal anesthesia for cesarean delivery *(39)*. A separate study of pulmonary function with spinal anesthesia for cesarean delivery is difficult to interpret due to differences in posture during the preincisional spirometry *(41)*.

Coughing is an important pulmonary defense mechanism that may be affected by neuraxial blockade. The mechanical aspects of cough production are shown in Figure 8.6.

Decreased function of expiratory muscles in the abdomen and the thorax may significantly decrease the effectiveness of cough, by influencing both peak expiratory flow and peak intrathoracic pressure *(42)*. A study of adult men with spinal anesthesia to the mid-upper thoracic region demonstrates intact inspiratory function, but significant decreases in intra-abdominal pressure during a cough, expiratory reserve volume, and maximum expiratory pressure *(43)*. Spinal or epidural anesthesia to the mid-upper thoracic region for cesarean delivery is associated with an 18–23% decrease in the maximum expiratory pressure *(40)*. These measurements are consistent with the common clinical observation that coughing is mildly impaired during spinal anesthesia for cesarean delivery. This impairment is not clinically significant for most patients. If a patient needs to cough very frequently to clear secretions from an acute infection, elective cesarean delivery may need to be rescheduled until after treatment and symptom improvement. All patients should be advised in the preanesthetic period that neuraxial anesthesia for cesarean delivery is usually associated with a "heavy" sensation on the chest wall despite normal breathing, and a mild impairment in the effectiveness of coughing. Either one of these conditions can be frightening to patients if they are surprised by the effects of the neuraxial anesthetic, particularly those patients with chronic

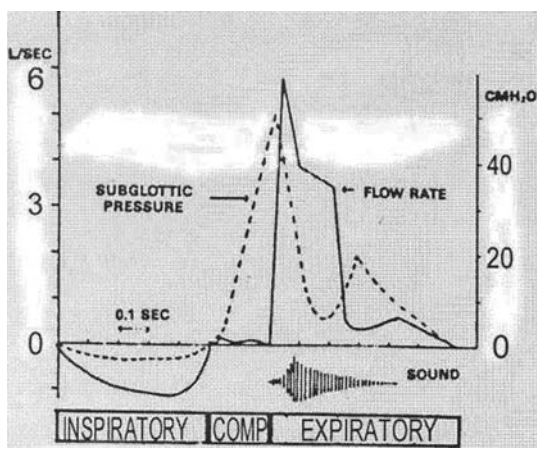


Figure 8.6 Schematic diagram of air flow and subglottic pressure during a cough. (From: ref. *(42)*, with permission)

pulmonary disease. Both the pulmonologist and the anesthesiologist play important roles in educating and reassuring patients with respiratory diseases in the preoperative and perioperative periods.

Lumbar epidural labor analgesia is associated with a minimal improvement in vital capacity (7%), forced vital capacity (4%), FEV_1 (6%), and peak expiratory flow rate (2%) in a study using a standard regimen of bupivacaine and fentanyl *(44)*. The patients were without pain for both the pre-labor and post-epidural spirometric measurements. Labor epidural analgesia decreases oxygen consumption during labor by 15% *(45)*. This effect is related to the increased oxygen consumption during painful contractions *(46)*, which is probably mediated by maternal catecholamines. When critically ill patients are in labor, effective labor analgesia can significantly lower oxygen demand and increase mixed venous oxygen concentrations *(47)*.

Although asthma and neuraxial anesthesia are common in obstetrics, and frequently coincide in the same patients, only rare case reports suggest that spinal or epidural anesthesia cause bronchospasm *(48, 49)*. In these reports, it is presumed that the sympatholytic effects of the neuraxial anesthetic adversely influence bronchial tone. A landmark prospective study of nonpregnant adults with known asthma shows that a high thoracic epidural anesthetic does not adversely affect airway resistance or lower the threshold for bronchial responses to inhaled acetylcholine *(50)*. In fact, local anesthetic administration by either the thoracic epidural or IV routes makes the asthmatic patients more resistant to bronchospasm *(50, 51)*.

General Anesthesia and Pulmonary Function

As described earlier, airway management in the pregnant patient should include endotracheal intubation. However, a series of 1,067 healthy patients for elective cesarean delivery safely underwent general anesthesia using the LMA *(52)*. One interpretation of this study is that the LMA is a reasonably safe airway rescue device for a pregnant patient in a difficult airway scenario, but a cuffed endotracheal tube is still the preferred airway safety device. The correct placement of the endotracheal tube should be verified with sustained end-tidal carbon dioxide and auscultation. Aside from the task of endotracheal tube placement, the process of direct laryngoscopy and intubation can be very stimulating to the larynx and trachea. These stimuli are potent triggers for laryngospasm and bronchospasm, as well as systemic maternal catecholamine responses. The direct airway and systemic effects both are minimized by an adequate depth of anesthesia prior to laryngoscopy. Adequate skeletal muscle relaxation may minimize direct airway responses to intubation by preventing patient movement when the endotracheal tube passes through the larynx and trachea.

General endotracheal anesthesia has a number of effects on pulmonary function in the perioperative period including a decrease in FRC that may be sustained for days, decreased mucociliary transport, altered diaphragmatic function, and altered respiratory drive to hypercapnia or hypoxia *(53, 54)*. After the surgery is completed, patients can be extubated when the NM relaxation has been reversed and verified by a nerve stimulator, spontaneous ventilation is sufficient to maintain a stable end-tidal carbon dioxide level, and the patient is awake enough to follow simple commands (such as hand squeeze and release, and breathing on request). Patients with chronic pulmonary disease or a history of sleep apnea will need to

meet additional criteria, and may require invasive ventilatory support in the early postoperative period. It is essential to discuss this openly with the at-risk patient before general anesthesia, with an emphasis on optimizing patient safety. In this way, maintaining endotracheal intubation into the postoperative period may be perceived by the patient and her family as a positive step and not a frightening setback. Hypoxemia is a common occurrence in patients after general anesthesia. The common contributing factors include the decrease in diaphragmatic function and FRC, smaller tidal volumes, decreased coughing from pain, and airway obstruction from baseline conditions plus residual anesthetic medications. Mental alertness has a significant impact on the control of breathing, and even small amounts of residual anesthesia may affect the chemical control of breathing *(53)*.

Opioids are commonly used for postoperative analgesia, usually by the IV-PCA or neuraxial routes. Both routes are effective for analgesia at rest, but neuraxial analgesia may be superior for analgesia with movement or coughing *(55)*. Opioids demonstrate a dose-dependent depression of ventilation by either route *(56, 57)*, or with medication errors *(58)*. Water-soluble opioids, such as morphine, may exhibit delayed respiratory depression at 12–24 h after neuraxial administration. In addition to respiratory depression, common side-effects of postoperative opioid administration include nausea, pruritus, and urinary retention. The main strategy to minimize opioid side-effects has been "multimodal" therapy, emphasizing the opioid dose sparing effects of nonsteroidal anti-inflammatory medications and nerve blocks *(59)*.

Anesthesia for Specific Pulmonary Disorders

In the absence of other contraindications, neuraxial labor analgesia should be appropriate for most patients with pulmonary disease. The advantages include superior pain relief and decreased oxygen consumption, without significant interference with pulmonary mechanics.

Most of the information about choices between neuraxial and general anesthesia in patients with pulmonary disease consists of individual case reports or case series. Applying the basic discussion above to the individual circumstances of your patient seems to be the best approach at this time. The following statements may help you and your patients:

1. Neuraxial anesthesia for cesarean delivery is well tolerated by most patients with chronic pulmonary disease, provided the sensations and diminished cough effectiveness are discussed with the patient before the block is placed. Patients who are in acute respiratory distress or are having difficulty clearing their airway secretions at baseline may decompensate with neuraxial anesthesia for cesarean delivery. One case report describes the use of bilevel positive airway pressure (BiPAP) during epidural anesthesia for pregnancy termination and tubal ligation in a patient with severe myasthenia *(60)*. The successful use of a respiratory adjunct depends on careful planning for equipment availability and patient acceptance. In this case, the patient was already familiar with the BiPAP device.

The neuraxial anesthetic level must be adequate for surgery to proceed, but patients with chronic pulmonary or neuromuscular diseases may be sensitive to changes in thoracoabdominal sensation and motor function. To minimize these effects, a catheter-based neuraxial anesthetic such as an epidural or CSE can be titrated to a desired level with relatively short-acting local anesthetics that can be replenished during the anesthetic as needed. Also, gravity does not have a

significant effect on the spread of epidural anesthesia but does affect most spinal anesthetics. Therefore, epidural anesthesia might allow a patient to be in a semi-upright position as opposed to the supine position for cesarean delivery, as long as the surgeon agrees.

2. Patients with asthma can be reassured that neuraxial analgesia or anesthesia will not cause bronchospasm, although it is possible that they may experience bronchospasm in the peripartum period. One of the main safety points for GETA in patients with asthma is to establish adequate depth of anesthesia prior to direct laryngoscopy and intubation. The specific choice of an anesthetic induction medication probably is less important than sufficient depth of anesthesia. The halogenated anesthetic gases have dose-dependent bronchodilating effects.

3. The choice of NM relaxants may be very important for safety during and after GETA in patients with neuromuscular diseases. Succinylcholine is a useful NM relaxant for airway management, but carries a risk of severe hyperkalemia or MH in selected patients, as described above. Nondepolarizing NM relaxants may have a longer duration in some patients with neuromuscular disease. Shorter acting anesthetic agents may have a theoretical advantage in terms of postoperative respiratory compromise, and a head-up position can assist the patient with spontaneous ventilation. Extubation following general anesthesia in these patients must be undertaken only after a thorough evaluation of respiratory strength and a careful plan for reintubation if necessary.

4. Patients with obesity, with or without obstructive sleep apnea, benefit from neuraxial anesthesia. However, the obese patients will experience more effects on pulmonary mechanics from neuraxial anesthesia than non-obese patients. General anesthesia is associated with increased postoperative hypoxemia and obstruction in patients with a history of diagnosed or suspected obstructive sleep apnea. Individual institutions are implementing local strategies for increased postoperative surveillance of these patients, based on national guidelines *(61)*.

References

1. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 1997;86:277–84.
2. Cooper GM, McClure JH. Maternal deaths from anaesthesia. An extract from Why Mothers Die 2000–2002, the Confidential Enquiries into Maternal Deaths in the United Kingdom. Br J Anaesth 2005;94:417–23.
3. Ng A, Smith G. Gastroesophageal reflux and aspiration of gastric contents in anesthetic practice. Anesth Analg 2001;93:494–513.
4. Davison JS, Davison MC, Hay DM. Gastric emptying time in late pregnancy and labour. J Obstet Gynaecol Br Commonw 1970;77:37–41.
5. Carp H, Jayaram A, Stoll M. Ultrasound examination of the stomach contents. Anesth Analg 1992;74:683–7.
6. Scrutton MJL, Metcalfe GA, Lowy C, Seed PT, O'Sullivan G. Eating in labour: a randomized controlled trial assessing risks and benefits. Anaesthesia 1999;4:329–34.
7. Kelly MC, Carabine UA, Hill DA, Mirakhur RK. A comparison of the effect of intrathecal and extradural fentanyl on gastric emptying in laboring women. Anesth Analg 1997;85:834–8.
8. Porter JS, Bonello E, Reynolds F. The influence of epidural administration of fentanyl infusion on gastric emptying in labour. Anaesthesia 1997;52:1151–6.
9. Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. Anaesthesia 1987;42:487–90.

10. 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.
11. American Society of Anesthesiologists. Practice guidelines for management of the difficult airway. Anesthesiology 2003;98:1269–77.
12. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth 1995;74:638–42.
13. Farcon EL, Kim MH, Marx GF. Changing Mallampati score during labour. Can J Anaesth 1994;41:50–1.
14. Brimacombe J. Acute pharyngolaryngeal oedema and pre-eclamptic toxaemia. Anaesth Intensive Care 1992;20:97–8.
15. Izci B, Riha RL, Martin SE, et al. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med 2003;167:137–40.
16. Saah D, Braverman I, Elidan J, Nageris B. Traumatic macroglossia. Ann Otol Rhinol Laryngol 1993;102:729–30.
17. Archer GW Jr, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth 1974;46:358–60.
18. De Swiet M. The respiratory system. In: Hytten F, Chamberlin G, Eds). Clinical Physiology in Obstetrics, Chapter 3. 2nd ed. Oxford: Blackwell, 1991;83–100.
19. Eliasson AH, Phillips YY, Stajduhar KC, Carome MA, Cowsar JD Jr. Oxygen consumption and ventilation during normal labor. Chest 1992;102:467–71.
20. Staten MA, Matthews DE, Cryer PE, Bier DM. Physiological increments in epinephrine stimulate metabolic rate in humans. Am J Physiol 1987;253:E322–30.
21. Chiron B, Laffon M, Ferrandiere M, Pittet JF, Marret H, Mercier C. Standard preoxygenation technique versus two rapid techniques in pregnant patients. Int J Obstet Anesth 2004;13:11–4.
22. Martyn JAJ, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. Anesthesiology 2006; 104:158–69.
23. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. JAMA 2005;293:2918–24.
24. Rosenbaum HK, Miller JD. Malignant hyperthermia and myotonic disorders. Anesthesiol Clin NA 2002;20:623–64.
25. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. Br Med J 1964;1:532–3.
26. Hawthorne L, Wilson R, Lyons G, Dresner M. Failed intubation revisited: 17-year experience in a teaching maternity unit. Br J Anaesth 1996;76:680–4.
27. Barnado PD, Jenkins JG. Failed tracheal intubation in obstetrics: a 6-year review in a UK region. Anaesthesia 2000;55:685–94.
28. Rahman K, Jenkins JG. Failed tracheal intubation in obstetrics: no more frequent but still managed badly. Anaesthesia 2005;60:168–71.
29. Gambling DR, Shay DC. The mother of all breathing problems. J Clin Anesth 2003;15:491–4.
30. Russell R. Failed intubation in obstetrics: a self-fulfilling prophecy? Int J Obstet Anesth 2007;16:1–3.
31. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. Anesthesiology 1993;9:1210–8.
32. Langeron O, Masso E, Hurax C, et al. Prediction of difficult mask ventilation. Anesthesiology 2000;92:1229–36.
33. Mhyre JM, Riesner MN, Polley LS, Naughton NN. A series of anesthesia-related maternal deaths in Michigan, 1985–2003. Anesthesiology 2007;106:1096–104.
34. Freund FG, Bonica JJ, Ward RJ, Akamatsu TJ, Kennedy WF Jr. Ventilatory reserve and level of motor block during high spinal and epidural anesthesia. Anesthesiology 1967;28:834–7.
35. Takasaki M, Takahashi T. Respiratory function during cervical and thoracic extradural analgesia in patients with normal lungs. Br J Anaesth 1980;52:1271–6.

36. von Ungern-Sternberg BS, Regli A, Reber A, Schneider MC. Comparison of perioperative spirometric data following spinal or general anaesthesia in normal-weight and overweight gynaecological patients. Acta Anaesthesiol Scand 2005;49:940–8.
37. Regli A, von Ungern-Sternberg BS, Reber A, Schneider MC. Impact of spinal anaesthesia on peri-operative lung volumes in obese and morbidly obese female patients. Anaesthesia 2006;61:215–21.
38. Gamil M. Serial peak expiratory flow rates in mothers during caesarean section under extradural anaesthesia. Br J Anaesth 1989;62:415–8.
39. von Ungern-Sternberg BS, Regli A, Bucher E, Reber A, Schneider MC. Impact of spinal anaesthesia and obesity on maternal respiratory function during elective caesarean section. Anaesthesia 2004;59:743–9.
40. Harrop-Griffiths AW, Ravalia A, Browne DA, Robinson PN. Regional anaesthesia and cough effectiveness: a study in patients undergoing caesarean section. Anaesthesia 1991;46:11–3.
41. Kelly MC, Fitzpatrick KTJ, Hill DA. Respiratory effects of spinal anaesthesia for caesarean section. Anaesthesia 1996;51:1120–2.
42. McCool FD. Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:48S–53S.
43. Egbert LD, Tmersoy K, Deas TC. Pulmonary function during spinal anesthesia: the mechanism of cough depression. Anesthesiology 1961;22:882–5.
44. von Ungern-Sternberg BS, Regli A, Bucher E, Reber A, Schneider MC. The effect of epidural analgesia in labour on maternal respiratory function. Anaesthesia 2004; 59:350–3.
45. Sangoul F, Fox GS, Houle GL. Effect of regional anesthesia on maternal oxygen consumption during the first stage of labor. Am J Obstet Gynecol 1975;121:1080–3.
46. Haegerdal M, Morgan CW, Sumner AE, Gutsche BB. Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 1983;59:425–7.
47. Ackerman WE, Molnar JM, Juneja MM. Beneficial effect of epidural anesthesia on oxygen consumption in a parturient with adult respiratory distress syndrome. South Med J 1993;86:361–4.
48. Mallampati SR. Bronchospasm during spinal anesthesia. Anesth Analg 1981;60:839–40.
49. Wang CY, Ong GSY. Severe bronchospasm during epidural anesthesia. Anaesthesia 1993;48:514–5.
50. Groeben H, Schwalen A, Irsfeld S, Tarnow J, Lipfert P, Hopf HB. 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;81:868–74.
51. Shono S, Higa K, Harasawa I, Sugano H, Dan K. Disappearance of wheezing during epidural lidocaine anesthesia in a patient with bronchial asthma. Reg Anesth Pain Med 1999;24:463–6.
52. Han TH, Brimacombe J, Lee EJ, Yang HS. The laryngeal mask airway is effective (and probably safe) in selected healthy parturients for elective cesarean section: a prospective study of 1067 cases. Can J Anesth 2001;48:1117–21.
53. Dahan A, Teppema LJ. Influence of anaesthesia and analgesia on the control of breathing. Br J Anaesth 2003;91:40–9.
54. Lumb AB. Nunn's Applied Respiratory Physiology. 6th ed. Philadelphia: Elsevier, 2005:297–326.
55. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery. Anesthesiology 2002;97:540–9.
56. Sarton E, Teppema L, Dahan A. Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop. Anesthesiology 1999;90:1329–38.
57. Cohen SE, Labaille T, Benhamou D, Levron JC. Respiratory effects of epidural sufentanil after cesarean section. Anesth Analg 1992;74:677–82.
58. Vicente KJ, Kada-Bekhaled K, Hillel G, Cassano A, Orser BA. Programming errors contribute to death from patient-controlled analgesia: case report and estimate of probability. Can J Anesth 2003:50:328–32.

59. Pan PH. Post cesarean delivery pain management: multimodal approach. Int J Obstet Anesth 2006;15:185–8.
60. Warren J, Sharma SK. Ventilatory support using bilevel positive airway pressure during neuraxial blockade in a patient with severe respiratory compromise. Anesth Analg 2006;102:910–1.
61. American Society of Anesthesiologists. Practice guidelines for the perioperative management of patients with obstructive sleep apnea. Anesthesiology 2006;104:1081–93.

Part III

Pulmonary Disorders in Pregnancy

9

Obstructive Sleep Apnea in Pregnancy

Kathleen Akgun and Francoise J. Roux

Keywords: Snoring, obstructive sleep apnea, pregnancy, continuous positive airway pressure therapy

Definitions of Obstructive Sleep Apnea Syndrome (OSAS)

Sleep-disordered breathing (SDB) and obstructive sleep apnea syndrome (OSAS) are defined using the apnea-hypopnea index (AHI) from overnight polysomnography (PSG). AHI is the sum of apneic and hypopneic events per hour of sleep *(1)*. Obstructive apneas are defined by more than 80% decrease in airflow for 10 s or more in the presence of thoraco-abdominal efforts. Hypopneas are defined by a decrease in airflow of at least 30% for 10 s or more accompanied by decreased oxygen saturations by 4% or more in the presence of thoraco-abdominal efforts. An AHI greater than 5 events per hour is diagnostic of OSAS and an AHI greater than 30 events per hour indicates severe disease. Percentage of sleep time spent below 90% oxygen saturation and the average number of arousals per hour of sleep aid in the assessment of SDB.

Alterations of Pregnancy and OSAS

Anatomic and Physiologic Sleep Changes During Pregnancy

Pre-menopausal women are usually protected against SDB. However, pregnancy leads to some hormonal and physical changes which might impact the development of SDB. Elevations in estrogen and progesterone affect women's risks for SDB and OSAS with some changes protective against SDB and OSAS while others may exacerbate SDB and OSAS (Table 9.1).

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_9

Table 9.1 Pregnancy and sleep disordered breathing: Risk factors and protective mechanisms.

Protective Mechanisms against OSAS in Pregnancy	Risk Factors for OSAS in Pregnancy
Increased respiratory drive (progesterone)	Weight gain
Lateral position during sleep	Upper airway narrowing
Decrease REM-stage sleep	Excessive daytime sleepiness

Changes Protective Against Sleep Disorder Breathing

Progesterone increases minute ventilation, ventilatory support, and tidal volumes *(2)* to meet increased oxygen requirements for the mother and developing fetus. Elevated progesterone also contributes to excessive daytime sleepiness and time spent in non-rapid eye movement (NREM) sleep. In addition, progesterone increases upper airway dilator muscle activity, making the upper airway less collapsible *(3)*. Estrogen and progesterone elevations decrease the total rapid eye movement (REM) stage of the sleep cycle, an additional feature protective against OSAS *(4)*.

Adverse Changes During Pregnancy Contributing to Sleep-Disordered Breathing

While progesterone has some protective mechanisms against **SDB** and OSAS, it increases suction pressure on narrowed upper airways *(5)*, predisposing to obstruction; accompanying hyperventilation may further exacerbate obstructive events *(5)*. Upward displacement of the diaphragm during pregnancy leads to thoracic cage restriction and a reduction in functional residual capacity *(6)*. Mucosal edema and hyperemia from elevated estrogen levels during pregnancy also increase upper airway resistance *(7)*, especially in the third trimester.

In a prospective cross-sectional study by Izci et al., the oropharyngeal junction was significantly smaller among pregnant women during the third trimester of pregnancy compared to non-pregnant women *(8)*. However, these changes to the upper airway resolved post-partum *(8)*. Previous studies by the same authors showed that pregnant women with pre-eclampsia had significantly narrowed upper airways compared to both non-pregnant women and pregnant women without pre-eclampsia *(9)*. These changes may further predispose to airway obstruction and worsen pregnancy-related hypertension. In addition, in a small study of 22 patients, Maasilta et al. found that obese pregnant women had higher AHI scores, increased snoring, and higher rates of respiratory arousals *(10)* compared with non-obese pregnant women.

Hypoxemia During Sleep and Pregnancy

During pregnancy, functional residual capacity (FRC) is decreased due to decreased expiratory reserve volume *(11)*. A study of 21 women in their 36th week of normal pregnancy revealed a significant difference between PaO_2 during sleep during pregnancy compared to post-partum (90.1 versus 99.2) *(12)*. The same study showed a significant difference in the supine position between pregnancy and post-partum as well (90.48 versus 97.48, respectively) *(12)*. In another study of

maternal oxygenation during late pregnancy, women beyond 32 weeks of pregnancy spent more than 20% of the nocturnal recording with an oxygen saturation less than 90%, despite experiencing a normal pregnancy *(13)*. The mean overnight oxygen saturation was much lower in the pregnant group compared to the non-pregnant group *(13)*. Other small studies have not shown any significant drops in oxygen saturation *(12, 14, 15)* but some have not considered saturations of 92% as significantly reduced, nor did they consider a 4% drop in saturation as significant *(15)*. Maasilta et al. showed greater oxygen desaturation index of 4 (ODI_4), a measure of the number of desaturation events per hour when the oxygen saturation fell by at least 4%, in obese pregnant women compared to non-obese pregnant women *(10)*.

Collectively, these changes may predispose the pregnant woman to SDB with resultant intermittent hypoxemia. These oxygenation changes contribute to reduced oxygen stores and greater sensitivity to hypoxic environments in the pregnant patient, posing serious risks to both mother and the developing child.

Incidence of Snoring and Sleep-Disordered Breathing During Pregnancy

Snoring is not common in the pre-menopausal state, affecting only 4% of non-pregnant, pre-menopausal women. In contrast, some studies showed that during pregnancy, snoring affects 14–41% of women compared to 4–17% in their matched non-pregnant controls *(8, 16)*. Among 350 pregnant women who completed self-reported snoring questionnaires, snoring was reported in 14% of pregnant women compared with 4% of non-pregnant women *(16)*. In a larger questionnaire-based survey of 502 pregnant women, 23% of participants reported snoring during the last week of pregnancy *(17)*. Guilleminault et al. monitored nocturnal sleep in an ambulatory setting with a portable recorder *(18)*. They found that snoring affected up to 44% of pregnant women *(18)*. The chronic loud snorers in that study spent between 61% and 92% of the calculated sleep time snoring *(18)*. In a case-control study by Maasilta et al., snoring was more common in obese pregnant women compared to pregnant women with normal weight *(10)*.

The prevalence of snoring seems to decrease after delivery. A study by Hedman et al. collected serial questionnaire results from 325 pregnant women and found a peak prevalence of snoring of 10.4% during the third trimester. During the postpartum period, prevalence of snoring decreased to 4.4%, a prevalence comparable to pre-pregnancy rates *(19)*. Given the higher prevalence of snoring during pregnancy, this suggests an increased likelihood of SDB and OSAS. Various studies aimed at examining this hypothesis.

Obstructive sleep apnea syndrome affects between 9–15% of women in the general population *(20, 21)*. While there are several case reports describing OSAS and pregnancy *(22–25)*, the exact prevalence of OSAS in pregnancy is still not known. Case-controlled studies using nocturnal polysomnographies demonstrated greater disturbances in SDB in obese pregnant women, especially after 30 weeks gestation, despite sleeping more in the lateral position compared with normal-weight pregnant controls *(10)*. Questionnaire results from 200 women by Pien et al. also showed increased reports of snoring and apnea symptoms through the course of pregnancy with a peak incidence around weeks 28 and 29 of pregnancy *(26)*. Significant predictors of apnea scores were increased body mass index and increased neck circumference *(20)*. However, none of these women underwent

a nocturnal PSG to adequately quantify SDB events. Edwards et al. studied 10 pregnant women using nocturnal polysomnographies and found that obstructive sleep apnea diagnosed during late pregnancy improved significantly following delivery *(27)*.

These results suggest that pregnancy may have a significant impact on the occurrence of SDB, especially in obese women. However, the exact prevalence of SDB during pregnancy cannot be assessed due to small sample size and lack of objective quantification of the SDB events. As the dose-response relationship between OSAS and hypertension has become apparent in the non-pregnant population *(28)*, it is suggestive that uncontrolled SDB and OSAS during pregnancy may predispose both mother and fetus to adverse events during pregnancy, particularly pregnancy-related hypertension and pre-eclampsia. There are no conclusive studies to date to demonstrate the above.

Complications from OSAS in Pregnancy

Risks to the Mother

The role of sleep for a healthy pregnancy has been increasingly recognized. In a prospective observational study by Lee and Gay, women who slept less than 6 h per night had longer labor *(29)*. In addition, cesarean section was required 37% of the time in women who slept less than 6 h per night compared with women who slept at least 7 h each night with an incidence of cesarean section of 11% *(29)*. Shift work also affects pregnancy. In a large Danish cohort study, women who worked fixed evening shifts had lower birth weight, full term babies *(30)*. Women who worked fixed night shifts were more likely to have post-term births, especially among industrial workers.

A recent study by Okun and Coussons-Read showed that sleep disruption can lead to an increase in inflammatory markers. Higher levels of inflammatory cytokines such as TNF-alpha in the first trimester were associated with poorer subjective report of sleep quality while decreased IL-4 in the second trimester was related to longer sleep latency times *(31)*.

Large cohort studies in the general public have demonstrated that patients with SDB have an increased risk of hypertension *(32)*. Several cardiovascular risk factors are implicated in untreated OSAS in the general population including stroke, cardiac arrhythmias, and congestive heart failure *(33)*. In a case-control study by Maasilta et al. *(10)*, polysomnographies (PSGs) recorded during early and late pregnancy in obese and normal-weight women revealed lower sleep efficiency in both groups. There were no significant differences in sleepiness or sleep architecture between the obese women and their controls. However, obese women had significant oxygen desaturations during sleep (higher ODI_4) and increased snoring compared with their non-obese pregnant controls. One obese woman with pre-eclampsia had mild obstructive sleep apnea by PSG but went into labor before nasal continuous positive airway pressure (CPAP) initiation.

Lewis et al. reported an obese woman who presented with excessive weight gain, orthopnea, and shortness of breath *(34)*. Echocardiogram revealed elevated pulmonary arterial pressures consistent with pulmonary hypertension. Overnight oximetry demonstrated significant desaturations in conjunction with apneic

episodes. After CPAP and supplemental oxygen were administered, the patient underwent spontaneous diuresis, losing over 100 pounds *(34)*, implying that SDB might have contributed to right heart failure in this pregnant patient.

In a cohort of ten women with suspected OSAS based on patient-reported snoring and excessive daytime sleepiness, AHI and arousals were elevated during the antenatal period with marked oxygen desaturations using overnight PSG *(27)*. However, AHI and minimal oxygen desaturations observed during pregnancy improved post-partum during REM and NREM sleep, independent of weight loss *(27)*. Cheun studied pregnant patients admitted for cesarean section and matched them with non-pregnant controls admitted for gynecologic surgery *(35)*. Anesthetized, paralyzed, ventilated patients on 100% FiO_2 were subjected to investigator-induced apneas. Pregnant patients showed a more rapid increase in their carbon dioxide levels than the non-pregnant controls *(35)*. Oxygen content was significantly lower at 90% saturation versus 100% oxygen saturation.

In addition, hypertensive fluctuations in blood pressure resulting from apneic episodes were significantly reduced during the postnatal period *(27)*. During pregnancy, blood pressure responses during apneas peaked between 170 and 180 mmHg, whereas postnatal peak blood pressure responses to apneas were only 130–140 mmHg. Guilleminault et al. found that chronic snorers with abnormal breathing patterns during pregnancy had increased mean systolic and diastolic blood pressure measurements *(18)* with return to baseline measurements post-partum. Further, the normal nocturnal systolic dip in blood pressure was not seen in those pregnant patients with abnormal breathing patterns.

There is considerable overlap between risk factors for pre-eclampsia and OSAS, most notably obesity. In addition, family history, patient history of pre-existing hypertension, primiparity, diabetes, advanced maternal age, and chronic kidney disease are risk factors for pre-eclampsia *(36)*. While there is no definitive role of OSAS in pre-eclampsia, there may be a link between the two disorders.

Patients with pre-eclampsia have significantly narrowed upper airways both in the seated and supine position as compared to matched pregnant patients and non-pregnant controls *(9)*. In the supine position, there is a trend toward narrower oropharyngeal orifices in patients with pre-eclampsia compared with their normotensive pregnant controls. A case-control study by Connolly et al. found inspiratory flow limitation in patients with pre-eclampsia compared with normal pregnancies and non-pregnant women *(37)*. However, whether air flow limitation contributed to the development of pre-eclampsia or was a direct result of pre-eclampsia itself could not be determined.

Characteristic edematous changes of pre-eclampsia as well as differential fat deposition likely contribute to these findings. These changes may further impair airflow and contribute to increased airway resistance and apneic events with resultant pressor responses and worsening pre-eclampsia.

In a case series of 502 women with increased snoring in pregnancy by Franklin et al. *(17)*, snoring was identified as an independent risk factor for hypertension and pre-eclampsia, even after adjusting for weight and age. SDB occurs more in patients with pre-eclampsia than controls *(38)*, as measured by increased respiratory events during sleep and desaturations. Nocturnal blood pressure is higher than daytime blood pressure readings in patients with pre-eclampsia *(39)*, a finding shared with non-pregnant snoring patients and obstructive sleep apnea patients *(40)*. In a case-control study by Edwards et al., pre-eclamptic patients demonstrate more dramatic hemodynamic pressor responses to obstructive events during overnight PSG than patients with OSAS but without hypertension *(41)*, especially

during REM sleep. The patients in the control group had 21 mmHg blood pressure variation above baseline compared to 38 mmHg seen in the patients with pre-eclampsia. Interestingly, the severity of the obstructive respiratory events did not differ between the two groups.

Impaired endothelial function is believed to contribute to pre-eclampsia and may be exacerbated by uncontrolled SDB *(38)*. Oxidative stress, perhaps from placental hypoxia and resultant endothelial dysfunction, is thought to play a role in the pathogenesis of pre-eclampsia *(42)*. In non-pregnant patients with OSAS, vascular endothelial dysfunction was demonstrated with increased blood flow resistance after sodium nitroprusside and acetylcholine infusion *(43)*.

These studies suggest that while there may be an association between SDB and hypertension during pregnancy no causal relationship has been yet demonstrated.

Risks to the Fetus

Animal models of in utero exposure to intermittent hypoxemia have yielded inconclusive results. Gozal et al. demonstrated decreased weight in rat pups exposed to intermittent hypoxia in utero compared with control rat pups. However, weight differences were resolved by 15 days of age *(44)*. Rats exposed to intermittent hypoxia demonstrated altered breathing control *(44)*; however, the authors were unable to establish that intermittent hypoxia adversely affects performance of spatial tasks in this rat model. More recent evidence demonstrated both impaired memory and decreased choline acetyltransferase by immunohistochemistry in forebrain sections of adult rats exposed to intermittent hypoxia *(45)*. Given the associations between intermittent hypoxia and impaired executive functioning, there is considerable interest in identifying neural changes related to intermittent hypoxia.

An association was found between chronically hypoxemic pregnant women living at high altitude and adverse fetal outcomes, such as intrauterine growth retardation and a higher infant mortality *(46)*. Schoenfeld et al. reported intrauterine growth retardation in eight patients with habitual snoring and nightly arousals *(47)*. A larger study in a group of 502 pregnant women by Franklin et al. *(27)* found that snoring was an independent predictor for fetal growth retardation. Additional reports of fetal growth retardation include an obese pregnant woman who spent 6% of her sleep time with an oxygen saturation less than 90% *(10)*. Another report described fetal growth retardation and fetal heart rate decelerations during maternal apneic events accompanied by hypoxemia *(48)*. Charbonneau et al. reported a case where, although normal fetal heart rate reactivity during severe apneic spells was maintained, the newborn of a woman with severe OSAS had evidence for growth retardation *(49)*.

Despite these suggested links between SDB and negative fetal outcomes, other studies have failed to support a definitive link between fetal outcomes and SDB or OSAS. Hedman et al. showed comparable sleep quality between patients with smaller babies and larger babies *(19)*. There was no connection between the children's birth weights and their mothers' sleep and snoring history during pregnancy. Guilleminault et al. also reported no significant difference in birth weights between snoring and non-snoring mothers although there was a trend toward small infants from chronic snoring mothers *(18)*. Domingo et al. reported three women with moderate SDB or OSAS who were successfully treated with CPAP whose infants were normal weight *(50)*, postulating the role of fetal hemoglobin in protecting the developing fetus from hypoxia.

As OSAS receives more attention by practitioners, the impact of untreated OSAS on fetal growth and development may become more apparent. However, taken together these results raise some concerns on the effect of SDB on fetal outcomes. Large epidemiologic studies need to be performed in order to separate fetal and pregnancy outcomes related to SDB per se from those related to comorbidities.

Screening for OSAS in Pregnancy

Although the results of theses studies are inconclusive, it is prudent for clinicians to screen pregnant women for SDB and OSAS, especially overweight or obese women, women with hypertension, pre-eclampsia, excessive weight gain, snoring, and excessive daytime somnolence. Obese pregnant women may be predisposed to more SDB and OSAS, especially during the later stages of pregnancy *(10)*. Women with gestational obstructive sleep apnea should be screened during subsequent pregnancies.

Treatment of OSAS in Pregnancy

Benefits of Treatment

In the general population, CPAP for OSAS has been shown to improve sleep architecture *(51)*, decrease nocturnal desaturation events *(52)*, decrease daytime somnolence *(51, 53, 54)*, and improve neurocognitive function *(55)*. Treatment of OSAS with CPAP also plays an important role in improving cardiovascular outcomes such as hypertension *(56)* and left ventricular function *(57)*. In addition, patients with OSAS who are treated with CPAP have decreased health care utilization and costs compared with untreated patients *(58)*.

Pregnant patients with SDB can be successfully treated with nasal CPAP *(59)*. A case by Brain et al. reported undiagnosed severe OSAS in a patient with hypertension who suffered a miscarriage in the first trimester *(60)*. Nasal CPAP was initiated and continued during her next pregnancy resulting in delivery of a live infant. In a study by Edwards et al. *(61)*, all patients with pre-eclampsia demonstrated raised nocturnal blood pressure. However, patients demonstrated a reduction of mean overnight blood pressure following treatment with nasal CPAP. While there was no frank obstructive sleep apnea, all patients demonstrated upper airway flow limitation during sleep accompanied by a 10% reduction in tidal volume *(61)*.

While there are theoretical concerns of decreased preload and decreased cardiac output from application of CPAP, physiologic changes in pregnant women may protect women against this, especially their overall increased plasma volume. In fact, Blyton et al. reported correlation between low nocturnal cardiac output and low fetal birth weight in 24 women with severe pre-eclampsia *(62)*. However, changes in cardiac output and peripheral vascular resistance improved with utilization of CPAP. There have been no studies done to evaluate the effect of positive airway pressure on placental perfusion. Until further studies are done, pregnant women should, however, be treated as aggressively as non-pregnant women.

Pregnant patients are compliant with CPAP up to 7 h per night *(59)*. CPAP pressures may need to be increased during later stages of pregnancy because of increased upper airway resistance and nasal congestion *(59)*. Collectively, these findings make a compelling argument for safely treating OSAS during pregnancy.

Conclusions

Limited clinical research identifies the impact of OSAS on pregnancy. However, the prevalence of snoring and possibly sleep disordered breathing is increased in pregnant women. Based on cohort studies in the general population, it seems cautious to have a low threshold for screening pregnant women for SDB and OSAS. Women with hypertension, snoring, or women with excessive weight gain during pregnancy should undergo PSG to evaluate for SDB.

As the physiology of OSAS is understood in the general population, consensus recommendations and case series support the routine use of nasal CPAP to treat OSAS in the pregnant population. Yet it remains controversial whether increased sleep disordered breathing in pregnancy has a negative impact on maternal-fetal outcomes.

Taken as a whole, anatomic and physiologic changes during pregnancy increase women's risk for SDB and raises suspicion for possible adverse maternal and fetal outcomes. Further studies are needed to define the effects of SDB on maternal and fetal outcomes.

References

1. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15(2):173–84.
2. Zwillich CW, Natalino MR, Sutton FD, Weil JV. Effects of progesterone on chemosensitivity in normal men. J Lab Clin Med 1978;92(2):262–9.
3. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol 1998;84(3):1055–62.
4. Santiago JR, Nolledo MS, Kinzler W, Santiago TV. Sleep and sleep disorders in pregnancy. Ann Intern Med 2001;134(5):396–408.
5. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 1978;44(6):931–8.
6. Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. Br J Obstet Gynaecol 1978;85(7):518–24.
7. Mabry RL. Rhinitis of pregnancy. South Med J 1986;79(8):965–71.
8. Izci B, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. Eur Respir J 2006;27(2):321–7.
9. Izci B, Riha RL, Martin SE, et al. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med 2003;167(2):137–40.
10. Maasilta P, Bachour A, Teramo K, Polo O, Laitinen LA. Sleep-related disordered breathing during pregnancy in obese women. Chest 2001;120(5):1448–54.
11. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Respir Dis 1980;121(3):559–81.
12. Prodromakis E, Trakada G, Tsapanos V, Spiropoulos K. Arterial oxygen tension during sleep in the third trimester of pregnancy. Acta Obstet Gynecol Scand 2004;83(2):159–64.

13. Bourne T, Ogilvy AJ, Vickers R, Williamson K. Nocturnal hypoxaemia in late pregnancy. Br J Anaesth 1995;75(6):678–82.
14. Nikkola E, Ekblad U, Ekholm E, Mikola H, Polo O. Sleep in multiple pregnancy: breathing patterns, oxygenation, and periodic leg movements. Am J Obstet Gynecol 1996;174(5):1622–5.
15. Brownell LG, West P, Kryger MH. Breathing during sleep in normal pregnant women. Am Rev Respir Dis 1986;133(1):38–41.
16. Loube DI, Poceta JS, Morales MC, Peacock MD, Mitler MM. Self-reported snoring in pregnancy. Association with fetal outcome. Chest 1996;109(4):885–9.
17. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest 2000;117(1):137–41.
18. Guilleminault C, Querra-Salva M, Chowdhuri S, Poyares D. Normal pregnancy, daytime sleeping, snoring and blood pressure. Sleep Med 2000;1(4):289–97.
19. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mothers' sleep. Sleep Med 2002;3(1):37–42.
20. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–5.
21. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med 1994;149(3 Pt 1):722–6.
22. Lefcourt LA, Rodis JF. Obstructive sleep apnea in pregnancy. Obstet Gynecol Surv 1996;51(8):503–6.
23. Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VA. Obstructive sleep apnoea during pregnancy requiring tracheostomy. Aust N Z J Obstet Gynaecol 1989;29(3 Pt 2):365–7.
24. Conti M, Izzo V, Muggiasca ML, Tiengo M. Sleep apnoea syndrome in pregnancy: a case report. Eur J Anaesthesiol 1988;5(2):151–4.
25. Kowall J, Clark G, Nino-Murcia G, Powell N. Precipitation of obstructive sleep apnea during pregnancy. Obstet Gynecol 1989;74(3 Pt 2):453–5.
26. Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. Sleep 2005;28(10):1299–305.
27. Edwards N, Blyton DM, Hennessy A, Sullivan CE. Severity of sleep-disordered breathing improves following parturition. Sleep 2005;28(6):737–41.
28. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283(14):1829–36.
29. Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. Biol Res Nurs 2004;5(4):311–8.
30. Zhu JL, Hjollund NH, Olsen J. Shift work, duration of pregnancy, and birth weight: the National Birth Cohort in Denmark. Am J Obstet Gynecol 2004;191(1):285–91.
31. Okun ML, Coussons-Read ME. Sleep disruption during pregnancy: How does it influence serum cytokines? J Reprod Immunol 2007;72(2):158–65.
32. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165(9):1217–39.
33. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003;41(9):1429–37.
34. Lewis DF, Chesson AL, Edwards MS, Weeks JW, Adair CD. Obstructive sleep apnea during pregnancy resulting in pulmonary hypertension. South Med J 1998;91(8):761–2.
35. Cheun JK, Choi KT. Arterial oxygen desaturation rate following obstructive apnea in parturients. J Korean Med Sci 1992;7(1):6–10.
36. Zhang J, Zeisler J, Hatch MC, Berkowitz G. Epidemiology of pregnancy-induced hypertension. Epidemiol Rev 1997;19(2):218–32.
37. Connolly G, Razak AR, Hayanga A, Russell A, McKenna P, McNicholas WT. Inspiratory flow limitation during sleep in pre-eclampsia: comparison with normal pregnant and nonpregnant women. Eur Respir J 2001;18(4):672–6.

38. Yinon D, Lowenstein L, Suraya S, et al. Pre-eclampsia is associated with sleep-disordered breathing and endothelial dysfunction. Eur Respir J 2006;27(2):328–33.
39. Beilin LJ, Deacon J, Michael CA, et al. Diurnal rhythms of blood pressure, plasma renin activity, angiotensin II and catecholamines in normotensive and hypertensive pregnancies. Clin Exp Hypertens B 1983;2(2):271–93.
40. Imai Y, Abe K, Munakata M, et al. Circadian blood pressure variations under different pathophysiological conditions. J Hypertens Suppl 1990;8(7):S125–32.
41. Edwards N, Blyton DM, Kirjavainen TT, Sullivan CE. Hemodynamic responses to obstructive respiratory events during sleep are augmented in women with preeclampsia. Am J Hypertens 2001;14(11 Pt 1):1090–5.
42. Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol 1998;179(5):1359–75.
43. Carlson JT, Rangemark C, Hedner JA. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J Hypertens 1996;14(5):577–84.
44. Gozal D, Reeves SR, Row BW, Neville JJ, Guo SZ, Lipton AJ. Respiratory effects of gestational intermittent hypoxia in the developing rat. Am J Respir Crit Care Med 2003;167(11):1540–7.
45. Row BW, Kheirandish L, Cheng Y, Rowell PP, Gozal D. Impaired spatial working memory and altered choline acetyltransferase (CHAT) immunoreactivity and nicotinic receptor binding in rats exposed to intermittent hypoxia during sleep. Behav Brain Res 2007;177(2):208–14.
46. McCullough RE, Reeves JT. Fetal growth retardation and increased infant mortality at high altitide. Arch Environ Health 1977;32(1):36–9.
47. Schoenfeld A, Ovadia Y, Neri A, Freedman S. Obstructive sleep apnea (OSA)-implications in maternal-fetal medicine. A hypothesis. Med Hypotheses 1989;30(1):51–4.
48. Roush SF, Bell L. Obstructive sleep apnea in pregnancy. J Am Board Fam Pract 2004;17(4):292–4.
49. Charbonneau M, Falcone T, Cosio MG, Levy RD. Obstructive sleep apnea during pregnancy. Therapy and implications for fetal health. Am Rev Respir Dis 1991;144(2):461–3.
50. Domingo C, Latorre E, Mirapeix RM, Abad J. Snoring, obstructive sleep apnea syndrome, and pregnancy. Int J Gynaecol Obstet 2006;93(1):57–9.
51. McArdle N, Douglas NJ. Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome: a randomized controlled trial. Am J Respir Crit Care Med 2001;164(8 Pt 1):1459–63.
52. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1(8225):862–5.
53. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353(9170):2100–5.
54. Montserrat JM, 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(4):608–13.
55. Bardwell WA, Ancoli-Israel S, Berry CC, Dimsdale JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. Psychosom Med 2001;63(4):579–84.
56. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;163(2):344–8.
57. Parker JD, Brooks D, Kozar LF, et al. Acute and chronic effects of airway obstruction on canine left ventricular performance. Am J Respir Crit Care Med 1999;160(6):1888–96.
58. Bahammam A, Delaive K, Ronald J, Manfreda J, Roos L, Kryger MH. Health care utilization in males with obstructive sleep apnea syndrome two years after diagnosis and treatment. Sleep 1999;22(6):740–7.

59. Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004;5(1):43–51.
60. Brain KA, Thornton JG, Sarkar A, Johnson AO. Obstructive sleep apnoea and fetal death: successful treatment with continuous positive airway pressure. BJOG 1;108(5):543–4.
61. Edwards N, Blyton DM, Kirjavainen T, Kesby GJ, Sullivan CE. Nasal continuous positive airway pressure reduces sleep-induced blood pressure increments in preeclampsia. Am J Respir Crit Care Med 2000;162(1):252–7.
62. Blyton DM, Sullivan CE, Edwards N. Reduced nocturnal cardiac output associated with preeclampsia is minimized with the use of nocturnal nasal CPAP. Sleep 2004;27(1):79–84.

10

Restless Legs Syndrome and Periodic Limb Movement Disorder in Pregnancy

Kelvin Lam and Carolyn M. D'Ambrosio

Keywords: RLS, Restless Legs Syndrome, pregnancy, PLMD, periodic limb movement disorder, pathophysiology

Introduction

Many women have significant sleep complaints during pregnancy. One of the more frequent complaints is that of restless legs. Ekbom in 1945 was the first person to describe this in detail, labeled it as a "restless leg" condition and identified pregnancy as a common cause *(1, 2)*. Further study of patients with complaints of restless legs revealed there were patients who had limb (both legs and arms) movements during wakefulness and sleep that was disruptive. In 1980, Coleman characterized these limb movements based on the periodicity, duration, and persistence of the movements during sleep *(3)*. His work and others lead to a separate diagnostic condition referred to as Periodic Limb Movement Disorder (PLMD) *(4)*. Pregnancy is a risk factor for developing both Restless Legs Syndrome (RLS) and PLMD. Most of the available scientific literature focuses on RLS and its association with pregnancy. PLMD has an 80–90% association with RLS; however, PLMD is a distinct condition that has been associated not only with RLS but also with narcolepsy and Parkinson's disease. Unfortunately, there is very little data on PLMD in pregnancy. In this chapter, we will discuss in detail RLS during pregnancy and briefly discuss PLMD in pregnancy.

RLS Definition

Restless Legs Syndrome (RLS) is defined as a condition characterized by disagreeable leg sensations that usually occur prior to sleep onset and that cause an almost irresistible urge to move the legs *(4)*. It is considered a sensorimotor disorder in which the sensory component is the urge to move the legs. The motor component is that movement of the legs often abolishes the discomfort or relieves the urge to move. Table 10.1 shows the four necessary diagnostic features required for the diagnosis of RLS and Table 10.2 shows the most commonly associated features that may be present but not necessary in patients with RLS *(5)*. The first feature

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_10

Table 10.1 Required diagnostic criteria for Restless Legs Syndrome *(5)*.

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)

required for the diagnosis is the urge to move the legs. Patients with RLS all report some type of urge to move their legs, generally preceded by some type of unpleasant sensation such as pain, restlessness, tingling, burning, aching, or creeping feeling *(6)*. The second feature is that this urge to move the legs is worse when the patient is sedentary. Often these symptoms increase as the duration of inactivity increases *(4)*. The third feature is simply that the urge to move the legs or the abnormal sensation in the legs is partially or completely abolished when movement of the legs occurs. Massaging the legs or feet can help alleviate the symptoms for as long as that activity continues *(5)*. The fourth and final feature is that the symptoms have a circadian pattern and get worse during the evening or night. The patient must have all four features to make the diagnosis of RLS. The other features noted in Table 10.2 are common but not necessary for the diagnosis.

RLS Epidemiology and Diagnosis

The prevalence of RLS in the general population is estimated at 5–15% without any gender difference *(2, 7)*. In pregnancy, the prevalence is estimated to be as high as 15–27% *(1, 8)*. RLS that presents during pregnancy is considered secondary

Table 10.2 Supportive clinical features of Restless Legs Syndrome *(5)*.

1. Family history
   The prevalence of RLS among first-degree relatives of people with RLS is 3–5 times greater than in people without RLS.
2. Response to dopaminergic therapy
   Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson's disease. This initial response is not, however, universally maintained.
3. Periodic limb movements (during wakefulness or sleep)
   Periodic limb movements in sleep (PLMS) occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults.

RLS. It is, of course, conceivable that a patient can have idiopathic RLS that simply has its onset during a pregnancy but this is a less likely scenario. For the purposes of this chapter, secondary RLS during pregnancy will be the focus. The symptoms and diagnostic criteria are the same for both idiopathic and secondary RLS (see Table 10.1). Idiopathic RLS seems to have a genetic component and tends to occur earlier, i.e., less than 40 years of age. Studies have linked the disease to chromosomes (12 q, 14 q, 9 p) in three families. Secondary RLS is associated with iron deficiency, folate deficiency, peripheral neuropathy, end stage renal disease, pregnancy, Parkinson's disease, rheumatoid arthritis, fibromyalgia, and several other rare causes.

Because RLS is a clinical diagnosis, it is important to differentiate imitators of RLS. Nocturnal leg cramps are common in pregnancy and could potentially be confused with RLS. Nocturnal leg cramps, however, are painful and sustained contractions of the gastrocnemius and soleus muscles *(9)*. These leg cramps can be relieved with stretching and massaging the involved leg but do not resolve with movement. Hypnic jerks may also occur around sleep onset and are not associated with the urge to move the legs or relieved with movement *(4)*.

Pathophysiology

In non-pregnant patients, the most accepted prevailing hypothesis of mechanism of RLS is dopaminergic insufficiency. Evidence to support this hypothesis includes therapeutic effectiveness of dopamine agonists and brain imaging. When dopamine agonists are given to patients who have the diagnoses of RLS, the symptoms of RLS abate or reduce. Often, as supportive evidence, medication trials have been used in patients to see if the patient will have a clinical response. On the other hand, medications that have anti-dopaminergic activities such as TCA (tricyclic antidepressant) and SSRI (Serotonin Reuptake Inhibitor) can precipitate or worsen RLS symptoms. Hence, this supports the dopaminergic insufficiency theory. Iron deficiency has also been implicated in RLS pathology *(10, 11)*. Iron is required in the synthesis of dopamine and studies of CSF iron demonstrate that low CSF iron is associated with RLS symptoms. RLS symptoms also follow a circadian rhythm and the symptoms occur near the nadir of the dopamine level in the brain near the onset of sleep. Imaging studies of the brain suggests involvement of the dopamine system and iron. Autopsy evaluation of brains of patients who suffered from RLS found decreased iron content and iron transporter.

Pregnancy is a risk factor for RLS but the cause may not be entirely the same as other cases of RLS. Currently, there are three main hypotheses that attempt to explain the mechanism of pregnancy induced RLS.

One major hypothesis is related to folate which is an important cofactor for many biochemical pathways including DNA synthesis. Folate requirements increase during pregnancy. In a study of 21 pregnant women, Botez found a significant relationship between RLS symptoms and folate supplementation. In a randomized fashion, 11 women took multivitamin and folic acid supplement while the remaining 10 subjects took only the multivitamin. The author found that the prevalence of RLS in women who took a folate supplement was 9% versus 80% in the women who did not take folate supplements. Furthermore, the group that did not have RLS had higher serum folate levels *(12)*. Lee et al. *(13)* examined prospective data collected on 32 out of 45 patients during a longitudinal study of sleep patterns in healthy subjects before, during, and after pregnancy. None of the patients had RLS

before pregnancy. The authors found the prevalence of RLS to be 13% (4/32) in the first trimester, 18% (6/33) in the 2nd trimester, 23% (7/30) in the 3rd trimester, and 3% (1/31) in the 4 weeks post partum. The authors found that the mean serum folate during the third trimester was lower for RLS group compared the non-RLS group. Furthermore, the number of nights experiencing RLS symptoms in the third trimester inversely correlated with serum folate levels in this study. Interestingly, the serum folate level of all subjects was within normal limits. There were no differences in the serum ferritin level, iron, vitamin B12, or anemia indices *(13)*. These findings corroborate the findings of Botez that folate plays a role in RLS during pregnancy *(13)*.

Dopaminergic insufficiency is another potential cause of RLS in pregnancy. Iron deficiency in pregnancy is well recognized and low iron can lead to RLS symptoms as previously described. Using the revised RLS diagnostic criteria, Manconi studied 606 pregnant women who were interviewed two days post partum for a history of iron and folate intake. Blood and urinary tests were performed two days before delivery. 59.4% of patients were primiparous, and more than 75% of study subjects received iron and folate supplementation during pregnancy. One hundred and sixty-one patients reported occurrence of RLS during pregnancy. This is a prevalence rate of 26.6% for the entire group and 16.6% were new diagnosis of RLS. When the data was analyzed using a symptom occurrence of three times per week, the prevalence was 15%. The authors found that hemoglobin was lower in the new RLS group compared to healthy control. There was a mild but significant reduction in iron storage indicators in the combined RLS group compared to healthy group *(14)*. This study reinforces the theory that iron deficiency can be a cause of RLS in pregnancy.

The third hypothesis suggests that hormonal changes may affect RLS symptoms. Progesterone has been shown to increases neuronal activity and increases the sensitivity of the respiratory center to carbon dioxide. It is hypothesized that PLMD and RLS could be another manifestation of this nervous system hyperexcitability. In addition, the higher levels of prolactin in pregnancy could affect dopamine action. Prolactin decreases dopamine action and this can lead to increased RLS symptoms (dopaminergic insufficiency hypothesis.) In addition, prolactin has the same circadian rhythmicity as RLS symptoms. However, a study done by Wetter failed to support this theory, but his study was done in non-pregnant patients *(15)*. Once the change in hormonal system is restored, i.e., post delivery, RLS symptoms resolve for the majority of patients. No clinical studies are available in the literature looking at states of elevated prolactin, such as breastfeeding on RLS.

Although it is not considered the only cause, another proposed hypothesis is that anxiety and stress can often exacerbate RLS. Goodman noted that RLS prevalence decreases in the last weeks of pregnancy and suggested this may be due to limiting stress. He followed five hundred women with singleton pregnancy at 32–34 weeks in London and performed surveys and interviews on them at time of enrollment and then 4 weeks after delivery. Those with a diagnosis of RLS had follow up telephone calls. The authors found that 97 patients out of 500 studied had RLS. Of those 97 patients, 16/500 has RLS before pregnancy. After delivery, 94/97 patients had symptomatic resolution. Fifty percent of RLS patients noted some improvements in the 4 weeks before delivery, which coincided with a period of bed rest and reduced activities. Of note, activity level was based on a subjective report by the patients in that study, unfortunately limiting the use of those results. The author found that fatigue was a most common factor with development of RLS symptoms *(8)*.

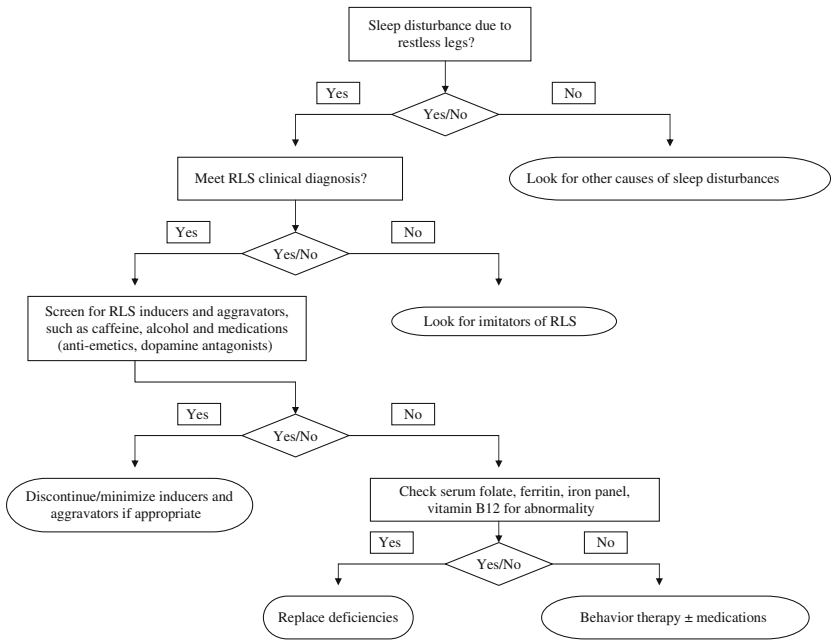


Figure 10.1 Screening and Evaluation

Clinical and Polysomnographic Evaluation

RLS is a clinical diagnosis with well-established diagnostic criteria (Table 10.1). A sleep study (polysomnogram) is not required for diagnosis. It is important to screen for potentially treatable illnesses that may cause or exacerbate RLS (See Figure 10.1). Taking a thorough history including medications is important. Some over the counter agents may have antidopaminergic activities such as the older antihistamines. Physical examination may help distinguish imitators of RLS as described above. A suggested laboratory evaluation includes: iron panel, folate, vitamin B12, thyroid function, anemia indexes, glycemia, and renal function. Although polysomnogram (PSG) is not a required diagnostic criterion for a diagnosis of RLS, PSG may uncover additional sleep disorders such as obstructive sleep apnea and PLMS. A thorough history should help in making the correct diagnosis.

Treatment

Once a diagnosis of RLS is made and a thorough work up has been performed, treatment is indicated. Treatment should be aimed at reducing or eliminating symptoms as it does not alter the course of the disease. If iron or folate deficiency is identified, appropriate therapies such as iron replacement or folate replacement can be instituted. For those patients who either do not have iron or folate deficiency or do not respond fully to replacement therapy, other agents should be considered. However, there is no reported data on using these pharmacological agents for RLS during pregnancy. The mainstay of therapy for RLS is monotherapy with dopaminergic agents. Levodopa produces adverse pregnancy outcome in experimental

animals after high-dose treatment. Although case reports in humans have not identified abnormal embryo or fetal development, this does not establish its safety in human pregnancies.

Although many benzodiazepines are category C by FDA classification, the main concern that has been associated with diazepam use in the literature is cleft lip/palate. However, since organogenesis ends around 13 weeks of gestation, the risk for those malformations is usually minimal. For that reason, the use of these drugs in the second and third trimester can be justified if patients are very symptomatic and are not responding to non-pharmacologic therapy. Opiates can also be used in pregnancy in the second and third trimester. The concern with both of these classes of medications is the risk for neonatal withdrawal when the drugs are used close to delivery.

Dopamine agonists such as Pramipexole and Ropirinole lack human data. Pramipexole has very limited reproductive data available. Ropirinole has been studied in rats and was associated with pregnancy losses. However, prolactin is a necessary hormone to maintain pregnancy in rats but not in humans and Ropirinole is associated with a decrease in prolactin levels. For that reason, the same results cannot be assumed in humans. When adding to the above the almost inexistent safety data in humans, the use of these drugs cannot be recommended. Table 10.3 outlines the current medications available for RLS and their respective category for safety in pregnancy and nursing.

Table 10.3 Selected medications used in treatment of RLS and safety in pregnancy *(17)*.

Medications		Pregnancy Category	Lactation/Nursing Mothers
Antiepileptics	Carbamazepine	D	P,U
	Gabapentin	C	P,U
Benzodiazepines	Clonazepam	D	P,N
	Triazolam	X	
Non-benzodiazepines[1]	Zaleplon	C	P,N
	Zolpidem	B	U
Dopaminergics	Carbidopa/Levadopa	C	U
	Pergolide	B*	U
	Pramipexole	C	U
	Ropinirole	C	U
Opiates	Codeine	C	P,U
	Methadone	C	P,U[2]
	Oxycodone	B	P,U

(continued)

A = Safety has been established using human studies.
B = Presumed safety based on animal studies.
C = No human studies, animal studies show an adverse effect.
D = Unsafe, evidence of risk that may in certain clinical circumstances be justifiable.
X = Highly unsafe, risk of use outweighs any possible benefits.
P = Secrete/transfer to breast milk.
U = Unknown effects on infant.
N = not recommended for use during breastfeeding.
*Pergolide has been associated with the risk of pleuralpulmonary, pleural, and retroperitoneal fibrosis.

For most patients, RLS does resolve with delivery of the baby. Therefore, non-pharmacologic treatment may be the best approach. The patient should be instructed on proper sleep hygiene such as reduced or no caffeine intake, no alcohol intake, and a calm, relaxing bedtime routine. Lower extremity massage or warm baths may provide some benefit as well. If these measures are not helpful and the patient is suffering terribly, opiates or benzodiazepines may be considered in the second trimester or later. Those should be withdrawn close to delivery in order to avoid neonatal withdrawal. Counseling of the patient should be done prior to prescribing any of the drugs and should include benefits and available data regarding safety of the drug in question.

Periodic Limb Movement Disorder

There is no specific research evaluating PLMD and pregnancy. Almost 80% of patients with RLS have Periodic Limb Movements during Sleep (PLMS) *(16)*. These periodic limb movements are defined as repetitive brief movements of the big toe and ankle dorsiflexion that occur during non-rapid eye movement (NREM) sleep. They may or may not be associated with arousals from sleep or daytime symptoms. Additionally, the knees, hips, and arms can also be involved in these periodic movements. The patient may experience insomnia, excessive daytime sleepiness, or frequent arousals from sleep. The diagnosis is often made with polysomnography during which the patient has periodic limb movements at least four in a row that last 0.5–5 seconds in duration with a 4–90 second interval between them *(4)*. These are measured by surface electromyogram during a sleep study. The number of periodic limb movements that are associated with an arousal from sleep is then calculated as the Periodic Limb Movement Arousal Index (PLMAI). A PLMAI >5 per hour of sleep is considered high. Treatment is generally given only for symptomatic patients as it does not alter the course of the disease. PLMS can be seen on polysomnography in patients with other sleep disorders such as obstructive sleep apnea, narcolepsy, and REM behavior disorder. The PLMS do not always require treatment. The pathophysiology of PLMD during pregnancy is thought to be similar to that of RLS but as yet has not been studied. Treatment is also aimed at symptomatic relief and correcting any underlying iron or folate deficiency. The standard treatment for PLMD in non-pregnant patients is the dopamine agonists. As in RLS, the potential harm to the fetus must be weighed against the benefit to the pregnant patient. There is unfortunately no data to help guide this therapeutic decision.

References

1. Ekbom KA. Restless legs syndrome. Neurology 1960;10:868–73.
2. Ekbom KA. Restless leg syndrome. Acta Med Scan 1945;158(suppl):1–123.
3. Coleman R. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome In: Guilleminault C (Ed). Sleep and Waking: Indications and Techniques. Menlo Park: Addison-Wesley; 1982.
4. The International Classification of Sleep Disorders, 2nd ed.: Diagnostic and Coding Manual. Second ed: American Academy of Sleep Medicine; 2005.
5. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4(2):101–19.

6. Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47(6):1435–41.
7. Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994;17(8):739–43.
8. Goodman JD, Brodie C, Ayida GA. Restless leg syndrome in pregnancy. BMJ 1988;297(6656):1101–2.
9. Weiner IH, Weiner HL. Nocturnal leg muscle cramps. JAMA 1980;244(20):2332–3.
10. Rich GB. Article reviewed: Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Sleep Med 2000;1(4):325–6.
11. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep 1998;21(4):371–7.
12. Botez MI, Lambert B. Folate deficiency and restless-legs syndrome in pregnancy. N Engl J Med 1977;297(12):670.
13. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med 2001;10(4):335–41.
14. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology 2004;63(6):1065–9.
15. Wetter TC, Collado-Seidel V, Oertel H, Uhr M, Yassouridis A, Trenkwalder C. Endocrine rhythms in patients with restless legs syndrome. J Neurol 2002;249(2):146–51.
16. Montplaisir J, Lapierre O, Warnes H, Pelletier G. The treatment of the restless leg syndrome with or without periodic leg movements in sleep. Sleep 1992;15(5):391–5.
17. PDR T. Physicians' Desk Reference. 61 ed. Montvale: Thompson PR; 2007.

11

Asthma in Pregnancy

Vanessa E. Murphy and Peter G. Gibson

Keywords: asthma, pregnancy, inhaled corticosteroids, fetus, exacerbation

Introduction

Asthma is one of the most common chronic medical conditions to complicate pregnancy. While there is evidence that asthma adversely impacts on some pregnancy outcomes, conversely there is evidence that pregnancy may result in a change in the clinical status of a woman with asthma. Understanding the mechanisms contributing to these events will improve the management of asthma during pregnancy. Coordinated asthma and antenatal care that combines optimal medication use with self-management skills and careful monitoring of the mother and her baby form the basis of effective management of asthma in pregnancy.

Epidemiology: The Prevalence of Asthma During Pregnancy

The prevalence of asthma among pregnant women is on the rise *(1)*. Recent estimates from the United Kingdom found that 8% of pregnant women attending antenatal clinics declared that they had asthma *(2)*. In another large study of over 280,000 pregnancies in the UK, there was a rate of asthma of 13%, similar to the rate of asthma among Australian pregnancies of approximately 12% *(3)*. In the United States, epidemiological studies suggest that between 3.7 and 8.4% of pregnant women had asthma between 1997 and 2001, an increase from 3.2% between 1988 and 1994 *(1)*. Asthma is the most common respiratory disorder to complicate pregnancy and represents a significant public health issue.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_11

Clinical Description: What Happens to Asthma During Pregnancy

It is well known and widely reported that one third of women experience a worsening of asthma during pregnancy, one third improve, and one third remain the same *(4, 5)*. The majority of data comes from subjective patient questionnaires and little is known about the mechanisms that contribute to worsening or improved asthma during pregnancy. Advances in this area may improve outcomes for both mother and baby.

Changes in Asthma Symptoms During Pregnancy

The largest study to examine changes in asthma symptoms during pregnancy followed the progression of asthma in 330 women during pregnancy and up to 12 weeks postpartum *(5)*. Women subjectively rated their asthma as having improved, remained the same, or worsened during pregnancy. Between 25 and 32 weeks gestation, there was a significant increase in asthma symptoms (wheeze, activity/sleep interference) among women whose asthma worsened, while among women who felt their asthma improved overall during pregnancy, there was a decrease in wheeze and little change in sleep/activity interference. In all women, there was a significant improvement in symptoms between 37 and 40 weeks. Improvements postpartum were observed in 58% of women who felt they had worse asthma during pregnancy, while worsening asthma postpartum was observed in 87% of women who had improvements in pregnancy *(5)*. These observations confirm the variable effect of pregnancy on asthma and indicate that asthma control (wheezing, nocturnal asthma, activity limitation) is altered in the latter stages of pregnancy.

The same study assessed some women in two successive pregnancies and only 60% followed the same course of asthma in the second pregnancy as the first *(5)*. A subsequent study from this group examined whether characteristics such as smoking, maternal body weight, fetal sex, season of delivery, and nasal symptoms in pregnancy contributed to pregnancy-associated changes in asthma *(6)*. Only the course of rhinitis during pregnancy correlated with the course of asthma during pregnancy, with rhinitis worsening or improving in more than 50% of patients whose asthma had also worsened or improved, respectively *(6)*. This suggests that systemic factors, such as IgE which can affect both the upper and lower airways, may be important in changes that occur in asthma during pregnancy *(6)*.

Changes in Lung Function During Pregnancy

A systematic review of the literature *(7)* found only three studies, of which two were published, *(8, 9)* of 54 pregnant women where asthma was assessed using objective measures. Sims et al. performed spirometry on asthmatic women during pregnancy and postpartum *(8)*. There were no pregnancy-related changes in forced expiratory volume at one second (FEV_1) to vital capacity (VC) ratio in 12 non-asthmatic and 27 asthmatic women *(8)*. In 16 subjects, Juniper et al. demonstrated an overall improvement in methacholine airway responsiveness in the second trimester compared to pre-conception, which was not related to serum progesterone or estriol concentrations *(9, 10)*. Lao and Huengsburg found that

asthmatic women who reported an improvement in the frequency or severity of asthma symptoms or exacerbations during pregnancy had significantly higher percent predicted peak expiratory flows, compared to women whose asthma did not change *(11)*.

Changes in Asthma During Labor

Labor and delivery have no major effect on maternal asthma and if an acute attack does occur at this time, normal medication use is recommended *(12)*. Stenius-Aarniala et al. found that 14% of patients with atopic asthma and 22% of patients with non-atopic asthma experienced mild asthma symptoms during labor, which were well controlled by inhaled β_2-agonists *(13)*. Similar data has been reported by other groups *(5,14, 15)*. Asthma symptoms during labor were present in 17.9% of women in a larger multi-centre study, with 46% of women with severe asthma experiencing symptoms during labor *(16)*.

Mechanisms for the Effect of Pregnancy on Maternal Asthma

Although there is little data which directly examines the mechanisms for the effect of pregnancy on maternal asthma, hormonal influences, changes in immune function, and the effects of fetal sex have all been proposed as playing a role.

Hormonal Influences

Increases in maternal hormones during pregnancy may contribute to physiological changes that result in improved asthma. For example, there is an increase in serum free cortisol during pregnancy, which may have anti-inflammatory effects *(17, 18)*. Progesterone may contribute to improved asthma via increased minute ventilation *(19)* or smooth muscle relaxation *(20)*. Alternatively, progesterone-induced changes in β_2-adrenoreceptor responsiveness and airway inflammation may contribute to worsening asthma during pregnancy *(21)*. In non-pregnant females with asthma, a desensitization and down-regulation of lymphocyte β_2-adrenoceptors following administration of medroxyprogesterone has been observed *(22)*. It has been reported that up to 40% of women experience an exacerbation around the time of menstruation when progesterone and estradiol levels are low *(23)*. However, no correlation has been found between the occurrence of premenstrual asthma and the progression of asthma during pregnancy *(17, 24)*. Studies in non-pregnant women show that a high proportion of asthmatics have an abnormal concentration of either progesterone or estradiol compared to non-asthmatics *(25)*. Such individual abnormalities possibly explain why the progression of asthma during pregnancy differs between women.

Maternal Inflammation and Immune Function

During pregnancy there are alterations in the maternal immune system, which are important to ensure a successful pregnancy, including a suppression of cell-mediated immunity and the development of a predominantly Th2 cytokine environment *(26)*. It has been shown that the placenta has a high Th2:Th1 cytokine

ratio, as demonstrated by an interleukin (IL)-5:tumor necrosis factor-α (TNF-α) mRNA ratio above 3 *(27)*. This Th2:Th1 predominance was significantly greater in placental samples collected from women with asthma who did not use inhaled corticosteroid (ICS) treatment during pregnancy *(27)*, suggesting that the Th2 environment of pregnancy may be further enhanced when the mother has asthma. This may contribute to worsening asthma in some women.

Several authors have hypothesized that Th2 cytokine polarization that is typical of allergic asthma may be heightened by the Th2 polarization of pregnancy. In a cross-sectional analysis, Tamasi et al. measured IL-4 and interferon (IFN)-γ-producing T lymphocytes and found that pregnant women with asthma had significantly increased levels of both lymphocyte subsets, compared with healthy pregnant women and non-pregnant asthmatic women *(28)*. While the authors described a negative correlation between peak expiratory flow and cell number, these correlations were weak and potentially influenced by a small number of women who developed pre-eclampsia. The number of IL-4 or IFN-γ-producing T cells was not related to whether women perceived their asthma to have improved or worsened during pregnancy *(28)*.

The Influence of Fetal Sex

It has been suggested that maternal asthma symptoms may be influenced by the fetus. Beecroft et al. found that significantly more mothers of girls reported shortness of breath, nocturnal waking, and a worsening of cough and asthma in general, while mothers of boys were more likely to report an improvement in asthma during pregnancy *(29)*. Dodds et al. reported that fewer asthmatic women pregnant with boys required steroids for treatment (14%) compared to asthmatic women pregnant with girls (20%), suggesting better managed asthma in the women pregnant with a male fetus *(30)*.

In an Australian study, there was a significant increase in dose requirements from first to third trimester, only in those pregnant with a female fetus. It was proposed that there may be an increase in maternal inflammatory pathways associated with asthma in the presence of a female fetus *(31)*. Kwon et al. also proposed worsening maternal asthma in the presence of a female fetus by examining daily peak flow variation throughout gestation *(32)*.

However, there have been recent reports which do not support a role of fetal sex in the progression of maternal asthma symptoms during pregnancy *(6, 33)*. In particular, a Canadian study of emergency department visits for asthma in over 500 women did not find any association between the frequency of asthma exacerbations during pregnancy and fetal sex. In addition, there was no relationship between emergency department visits for asthma during pregnancy and adverse pregnancy outcomes *(33)*.

Complications of Asthma During Pregnancy: Exacerbations

Exacerbations are a key feature of asthma and can be severe, requiring hospitalization. Preventing exacerbations is an important goal of asthma treatment; however, current strategies for the monitoring and management of asthma are not sufficient to prevent a large number of exacerbations of asthma during pregnancy.

Prevalence of Exacerbations

A systematic review has examined studies of asthma exacerbations during pregnancy *(34)*. Many studies have reported exacerbations requiring medical intervention such as hospitalizations or emergency department treatment for asthma during pregnancy. The median percentage of women hospitalized for asthma during pregnancy was 5.8% (2.4–8.2% interquartile range) in eight prospective cohort studies. In a large multi-centre prospective study, 20% of women had exacerbations of asthma requiring medical intervention (including hospitalization, unscheduled doctor visits, and use of emergency therapy), despite the women having actively managed asthma *(16)*. In an Australian prospective cohort study, 36% of women had a severe exacerbation requiring medical intervention for asthma during pregnancy and a further 19% had a mild exacerbation during pregnancy *(35)*.

Risk Factors for Exacerbations

Factors that increase the risk of exacerbations or worsening asthma during pregnancy include severe asthma *(16, 34)*, obesity *(36)*, inadequate prenatal care *(37, 38)*, viral infection *(35, 39)*, and rhinitis *(6)* (Figure 11.1). The use of ICS medication is clearly the most effective way of reducing the risk of exacerbations during pregnancy *(35, 40)*. The effects of maternal smoking, atopy, sinusitis, and gastroesophageal reflux on exacerbations have not been adequately investigated and require further research. However, conditions such as reflux, rhinitis, and sinusitis may worsen during pregnancy, in turn exacerbating asthma, and treatment of these conditions is recommended as a component of asthma management during pregnancy *(41)*.

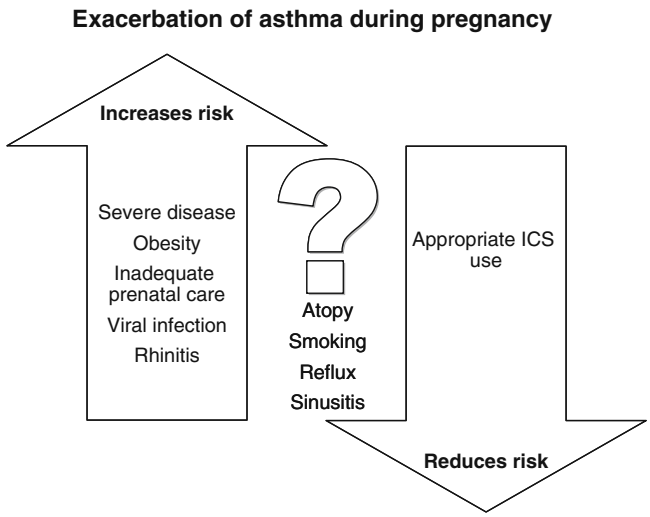


Figure 11.1 Factors associated with increased and reduced risk of exacerbations during pregnancy

Severe Asthma

The major risk factor for exacerbations of asthma during pregnancy is having severe asthma *(4, 16, 35, 42)*. Murphy et al. described exacerbations requiring medical intervention among 8% of women with mild asthma, 47% of women with moderate asthma, and 65% of women with severe asthma *(35)*.

Viral Infection

While few studies have systematically assessed the causal factors of asthma exacerbations during pregnancy, some have suggested that viral infections may be involved *(17, 35, 43, 44)*. Respiratory tract viral infections are the most common cause of asthma exacerbations requiring hospitalization in children and non-pregnant adults *(45)*. In one study, viral infection was the most common self-reported cause of severe asthma exacerbations, reported by 34% of women *(35)*. Pregnant women may be more susceptible to viral infection, due to changes in cell-mediated immunity during pregnancy *(4)*. Minerbi-Codish et al. found that pregnant women with asthma were more likely to have an upper respiratory tract or urinary tract infection during pregnancy than pregnant women without asthma, and severe asthma was associated with significantly more infections than mild asthma *(39)*. However, this was a retrospective study that relied on self-report of infection, and further evaluation using a prospective study design is required, using objective confirmation of viral infection and specific identification of the viruses responsible. A recent study from New York described an improvement in asthma symptoms during pregnancy among 50% of women who received an influenza vaccine, compared with improvement among only 15% of women who did not receive the vaccine, suggesting that prevention of infection may improve asthma symptoms among pregnant women *(46)*.

Inadequate Prenatal Care

In a low income population, Carroll et al. found that the proportion of hospital admissions, emergency department presentations, and use of rescue oral steroids for asthma during pregnancy was significantly higher among African Americans, possibly due to inadequate prenatal care *(37)*. Chung et al. also found that African American and Hispanic mothers had higher rates of asthma during pregnancy than Caucasian mothers. The multivariate analysis indicated that this finding may be a result of reduced access to health care, driven by socioeconomic disadvantage, rather than a direct effect of race itself *(38)*.

Obesity

Obesity has recently been highlighted as a significant risk factor for severe exacerbations requiring medical intervention, with 36.5% of obese subjects having an exacerbation during pregnancy, compared to 30.5% of non-obese subjects *(36)*. Overall, significantly more women with asthma (30.7%) were obese compared to women without asthma (25.5%) *(36)*.

Inadequate Medication Use

A major contributor to asthma exacerbations during pregnancy is the lack of appropriate treatment with ICS *(35, 40, 43, 47)*. Murphy et al. found that 29% of

women reported non-adherence to prescribed ICS medication prior to a severe exacerbation *(35)*. This study used self-reporting as a measure of non-adherence and may therefore underestimate the problem *(35)*. A study in Finland found that the risk of having an exacerbation was reduced by over 75% among women who were using ICS regularly *(40)*. This was supported by recent data showing an increase of asthma related emergency department and physician visits during pregnancy among women who did not use ICS prior to pregnancy *(47)*. A Japanese study described a reduction in asthma exacerbations during pregnancy and labor, concurrent with an increase in the general use of ICS for asthma treatment among pregnant women from 1995 to 2003 *(48)*. Improvements in asthma management which address the issue of ICS non-adherence and reduce the exacerbation rate are needed.

Timing of Exacerbations

Exacerbations can occur at any time during gestation, but are more common in the late second trimester *(4, 35, 43)*. A prospective cohort study of over 500 pregnant women with asthma found that the gestational age of onset of exacerbations was normally distributed, with the majority occurring between 17 and 24 weeks gestation *(40)*. Similar results were reported by Murphy et al., with exacerbations normally distributed from 9 to 39 weeks gestation around a mean of 25 weeks *(35)*. A recent study from Canada found that visits to the emergency department for asthma exacerbations peaked in the second trimester and fell as the end of pregnancy approached *(33)*. This profile was distinct from that of emergency department visits for any reason during pregnancy, which peaked at 6 weeks gestation, and decreased gradually thereafter *(33)*.

Association of Asthma with Adverse Pregnancy Outcomes

There are a large number of historical and prospective cohort studies which propose that women with asthma are at risk of poor pregnancy outcomes, particularly pre-eclampsia, Caesarean section, perinatal mortality, preterm birth, and low birth weight *(49)*. There have been three main hypotheses proposed to account for the increased risk of poor perinatal outcomes in women with asthma *(50)*. One is that there is a common pathogenesis of both severe asthma and perinatal complications *(50)*. For example, a common pathway leading to hyperactivity of the smooth muscle in both the bronchioles and the myometrium has been proposed to explain the increased incidence of preterm labor in women with asthma *(51–53)*. The second hypothesis is that asthma medications have a direct effect on the mother or fetus during pregnancy *(50)*. However, the overwhelming evidence suggests that the use of ICS treatment in particular may be protective against outcomes such as low birth weight *(49)*. Treatments and their safety will be discussed further in "Safety of Drug Treatments for Asthma". The third and most supported hypothesis is that poor asthma control during pregnancy may lead to adverse outcomes, possibly due to chronic maternal hypoxia. Maternal hypoxia could influence fetal oxygenation *(54)* with consequences for fetal growth via alterations of placental function *(27, 31, 55–59)*. The findings of Schatz et al. *(50)* indicate that reduced lung function may be a marker of poor control of asthma, which influences preterm delivery and pregnancy induced hypertension

via hypoxic mechanisms. Alternatively, the release of inflammatory mediators from the mother in response to asthma may also be involved *(49)*.

Several studies have examined the association between exacerbations of asthma during pregnancy and adverse perinatal outcomes. A meta-analysis of pregnancy outcomes among women with asthma exacerbations *(34)* has examined data from four published studies *(15, 40, 60, 61)*. The definitions of exacerbation in these studies were recurrent attacks of severe asthma or status asthmaticus *(60)*, hospitalization for asthma *(15)*, acute asthma managed in the emergency department or clinic with nebulized bronchodilators *(61)*, and attacks not controlled by the patient's usual medication and treated as an emergency *(40)*.

The Effect of Exacerbations on Low Birth Weight

In a meta-analysis *(34)*, using data from three studies *(15, 60, 61)*, women who had an asthma exacerbation during pregnancy were at significantly increased risk of having a low birth weight baby (< 2500 g) compared to women without asthma (relative risk [RR] 2.54, 95% confidence interval [CI] 1.52, 4.25). There was no increased risk for low birth weight in asthmatic women who did not have an exacerbation during pregnancy, compared to women without asthma (RR 1.12, 95% CI 0.8, 1.40). This result indicates that women with an exacerbation of asthma during pregnancy have a 2.5-fold increased odds of delivering a low birth weight baby. This relationship is significant and had a similar effect size to that of maternal smoking during pregnancy, which doubles the risk of low birth weight *(62)*. Possible mechanisms for the effect of asthma exacerbations on low birth weight include a direct effect of fetal hypoxia on fetal growth, or indirect effects of reduced utero-placental blood flow or other alterations in placental function on fetal growth *(55)*. The confounding effect of maternal smoking warrants further consideration, as only one study included in the meta-analysis matched subjects for smoking status *(61)*.

Three cohort studies have described the reduction in mean birth weight among women with asthma exacerbation during pregnancy and have found reductions of 369 g *(15)*, 434 g *(63)*, and 195 g *(64)* compared to women with no exacerbation or a control non-asthmatic group. One study was conducted at high altitude, which may have amplified the effect of asthma exacerbations on fetal hypoxia *(64)*.

The Effect of Exacerbations on Preterm Delivery

In a meta-analysis *(34)*, using data from four studies *(15, 40, 60, 61)*, women who had an exacerbation of asthma during pregnancy were not at significantly increased risk of preterm delivery compared to women without asthma (RR 1.46, 95% CI 0.77, 2.78). Likewise, women who did not have an asthma exacerbation during pregnancy were not at increased risk of preterm delivery compared to women without asthma (RR 0.93, 95% CI 0.74, 1.17).

The lack of association between exacerbations and preterm delivery in the meta-analysis may be due to the confounding effect of treatment with oral steroids, which has been associated with preterm delivery in several large prospective cohort studies *(65, 66)*. An historical cohort study of 81 women, all of whom required medication use for asthma found that oral steroid-dependent asthmatics were much more likely to have an admission for asthma (71%) than non-steroid

dependent asthmatics (30%), and were at greater risk of preterm labor and delivery *(67)*. It is difficult to separate the effect of the oral steroid medication from the effect of the severe asthma exacerbation.

The Effect of Exacerbations on Pre-eclampsia and Pregnancy-Induced Hypertension

In a meta-analysis *(34)*, using data from two studies *(40, 61)*, women who had an exacerbation of asthma during pregnancy were not at increased risk of pre-eclampsia compared to women without asthma (RR 1.37, 95% CI 0.65, 2.92). Rather, there was a significantly increased risk of pre-eclampsia in asthmatic women who did not have a severe exacerbation during pregnancy, compared to women without asthma (RR 1.48, 95% CI 1.07, 2.04).

The number of studies investigating pre-eclampsia as an outcome is small; however, a recent large case-control study identified that asthma severity and control before pregnancy may be associated with an increased risk *(68)*. Other pathogenic factors such as vascular hyperreactivtiy with asthma may contribute to alterations in uteroplacental blood flow *(42)*, affecting the development of pre-eclampsia. Changes in in vitro responses to dilator and constrictor agents in the perfused placenta from women with moderate and severe asthma have been observed *(55)* and are similar to those reported in women with pre-eclampsia *(69)*.

In a recent case-control study, Martel et al. found that there was no significant effect of exacerbations during pregnancy on the risk of pre-eclampsia or pregnancy induced hypertension *(68)*. However, women who had admissions or emergency department visits for asthma prior to pregnancy were at significantly increased risk of both pregnancy induced hypertension and pre-eclampsia *(68, 70)*, suggesting that the underlying severity of asthma may be important.

The Effect of Exacerbations on Perinatal Mortality

There are few studies adequately powered to determine the effect of asthma exacerbations during pregnancy on perinatal mortality. An early study by Gordon et al., conducted in 1970 prior to the introduction of ICS medication, studied 277 patients with actively treated asthma, of whom 16 had severe asthma characterized by regular acute attacks or status asthmaticus during pregnancy *(60)*. Six of the 16 women who had exacerbations of asthma had spontaneous abortion, fetal death, or neonatal death *(60)*.

In 2003, Hartert et al. examined acute cardiopulmonary hospitalizations during the influenza season among pregnant women and found that approximately half of the women hospitalized had asthma *(44)*. Although the effect of hospitalization on perinatal outcomes was not specifically examined in women with asthma, there were three still-births among the women who were hospitalized, all from mothers with asthma *(44)*.

Tata et al. found that women who experienced at least one exacerbation of asthma during pregnancy were significantly more likely to miscarry or have a therapeutic abortion and significantly less likely to have a live birth compared to women without asthma *(71)*. This was a large study of over 37,000 women with asthma, including 2,595 with an exacerbation *(71)*.

Management and Treatment of Asthma During Pregnancy

The goals of asthma management during pregnancy are to ensure maternal quality of life and normal fetal maturation by minimizing asthma symptoms and limitations of activity, preventing exacerbations, and maintaining near normal lung function, while minimizing reliever medication use and adverse side effects from medications *(41)*. The National Asthma Education and Prevention Program (NAEPP) released an updated expert panel report (NAEPP report) on the management of asthma during pregnancy in 2004 *(41)*. The report recommended the use of ICS for all women with persistent asthma, following a step-wise approach to therapy to achieve asthma control *(41)*. Regular medical review and monitoring of asthma is recommended during pregnancy and preferably with the involvement of the obstetrician. Education about how to self-manage asthma is an important component. Early detection of changes in lung function and asthma control is vital and women should receive education about the use of regular peak flow monitoring at home, and they should be provided with a written asthma action plan outlining how to respond to changes in their asthma and when to seek medical advice *(41, 72)*. Many studies confirm that asthma that is well controlled is less likely to result in adverse outcomes than poorly controlled asthma *(14, 15, 63, 73)*. Pregnant women should receive vigorous treatment of an exacerbation during pregnancy to reduce the risk of readmission and to improve outcomes for the fetus *(41)*. The risks of asthma exacerbations to the fetus are greater than the risks associated with the use of asthma medications during pregnancy *(41)*.

Safety of Drug Treatments for Asthma

Risk of Congenital Malformations

The data on the effect of maternal asthma or its treatment on congenital malformations is reassuring. Of the eight prospective or historical cohort studies examining congenital malformations among women with asthma *(2, 15, 40, 61, 67, 74–76)*, only one demonstrated a significantly increased odds of malformations in women with asthma compared to a control group of women without asthma (Odds Ratio [OR] 1.37, 95% [CI] 1.12, 1.68) *(74)*. This was an historical cohort study of over 2,000 women with asthma and over 9,000 controls, with adjustment made for a range of confounders including maternal age, education, parity, race, diabetes, smoking, and substance abuse during pregnancy *(74)*.

One case-control study described a significantly increased risk of cleft lip among women exposed to oral steroids during the first trimester, but was based on a very small number of cases (only 5) exposed to oral steroid during pregnancy *(77)*. A meta-analysis of four case-control studies with information on systemic steroid exposure in the first trimester found an increased risk of oral clefts (OR 3.35, 95% CI 1.97, 5.69) *(78)*. However, none of the studies were specifically conducted in women with asthma, and a variety of maternal diseases were represented, and therefore this result can not be generalized to pregnant women with asthma.

Five studies have specifically examined the effects of asthma treatment on malformations *(48,79–82)*. Two studies, exclusively in women using budesonide, found no increased risk of malformations *(79, 80)*. One study described a weak but significant increased risk of malformations in women using any drugs for asthma during pregnancy, compared to the rate of malformations in the whole population *(81)*.

A recent Canadian study of a large cohort of women with asthma further investigated the relationship between the dose of ICS used during pregnancy and congenital malformations *(82)*. The study used a prescriptions database to specifically estimate ICS dose in the first trimester in over 4,500 women with asthma and found a significantly reduced risk of malformations among users of moderate dose ICS compared to non-users. Importantly, there was also no increased risk of malformations with the use of high dose ICS, although numbers in this group were smaller and further investigation may be required *(82)*.

β_2-Agonists

The NAEPP report found that there was a significant amount of reassuring data on the safety of short-acting β_2-agonists, particularly albuterol *(41)*. A prospective cohort study published in 1988 found no significant differences in perinatal mortality, congenital malformations, preterm delivery, and low birth weight in asthmatic women who used short-acting β_2-agonists compared to women who used no treatment for asthma during pregnancy *(83)*. A recent study from this group has confirmed these findings in a larger cohort *(66)*. Recently, a case-control study found a reduced risk of pregnancy induced hypertension, but not pre-eclampsia, among users of short acting β_2-agonists compared to non-users with asthma *(70)*.

Limited data is available on the use of long-acting β_2-agonists during pregnancy and no studies have addressed the use of combined ICS and long-acting β_2-agonist preparations in asthmatic pregnant women. An epidemiological study of salmeterol use in over 15,000 patients reported that among this population, there were 65 women who used salmeterol while pregnant *(84)*. While there were no adverse outcomes reported, an assessment of outcomes was not the primary aim of the study *(84)*. The current guidelines recommend salmeterol as the preferred long-acting β_2-agonist purely on the basis of it having been available for a longer period of time in the United States *(41)*.

Inhaled Corticosteroids

A recent study using the Swedish Medical Birth Registry (1995–2004), found that 49% of women using drugs for asthma during pregnancy used ICS, and of these, 89% used budesonide *(85)*. The majority of studies concerning the safety of ICS use in pregnancy have been conducted in women using budesonide and consequently, this is the ICS of choice, recommended for use in pregnant women with persistent asthma *(41)*. However, since other ICS drugs have not been shown to be unsafe, women whose asthma was well controlled on other medications could continue to use these during pregnancy *(41, 86)*.

Several studies have indicated that the use of ICS medication for asthma during pregnancy does not result in any adverse outcomes for the fetus *(66)*. In fact, ICS use may protect against some adverse outcomes, such as low birth weight, by maintaining asthma control *(47, 49)*. An adequately powered, large multi-centre prospective cohort study, found no significant relationships between ICS use during pregnancy and outcomes such as preterm birth < 32 weeks gestation, major malformations, low birth weight, and small for gestational age infants *(66)*.

There have been few randomized controlled trials (RCTs) of asthma treatment during pregnancy, with most data derived from cohort studies. Recently data was published from a placebo-controlled RCT of low dose budesonide (400 μg/day) versus placebo among patients with recent onset mild to moderate asthma *(80)*.

The RCT included over 7,000 patients and a sub-group of 313 pregnancies were identified during the study. Pregnancies started in 219 women during the randomization phase of the trial (102 randomized to budesonide, 117 randomized to placebo), while the remaining 94 pregnancies started during the open-label phase of the trial where all participants received budesonide. The percentage of women with adverse pregnancy outcomes (including spontaneous abortion, neonatal death and congenital abnormalities) was similar among women using low dose budesonide or placebo throughout pregnancy. Results were similar when restricting the comparison to patients randomized to budesonide and patients randomized to placebo. However, other perinatal outcomes such as birth weight were not reported in this study *(80)*.

Oral Corticosteroids

A recent study found that 2.4% of pregnant women with asthma used oral corticosteroids at some time during pregnancy *(85)*. The effects of oral steroid use on pregnancy are not well described. In particular, most studies have not adequately described the dose of oral steroid used or the timing and length of use during the pregnancy. One study has found an increased risk of cleft lip in women using oral steroid during the first trimester *(77)*. There are cohort studies which find a significant association between oral steroid use and pre-eclampsia *(67, 87)*, preterm delivery *(65, 66, 76)*, and reduced birth weight *(42, 66)*. However, it is difficult to ascertain the impact of the drug itself from the impact of severe asthma exacerbations in leading to these effects. A recent study that conducted regular telephone interviews with over 113 pregnant women with asthma who used systemic steroids during pregnancy has addressed this question *(42)*. Mean birth weight was significantly reduced among oral steroid users, compared to asthmatics who did not use oral steroids and non-asthmatics. Using linear regression analysis, this study was able to differentiate between the effect of oral steroid medication and the effect of uncontrolled asthma on birth weight. Interestingly, it was the oral steroid use which was significantly associated with birth weight, while all measures of asthma control (including hospitalizations) were not significantly associated with birth weight *(42)*.

The current recommendation is that asthma be well managed so as to avoid the need for rescue oral steroid medication *(86)*. However, when required for the treatment of a severe exacerbation during pregnancy, the possible risks described are still less than the risks of severely uncontrolled asthma, which may result in maternal and/or fetal death *(41, 86)*.

Leukotriene Receptor Antagonists

Only one study has investigated the safety of leukotriene receptor antagonists (LTRAs; montelukast and zafirlukast) for asthma during pregnancy *(88)*. In this study of 96 women using LTRAs, there was no increased risk for preterm delivery, gestational diabetes, pre-eclampsia, or pregnancy loss compared to 122 women with asthma who used short acting β_2-agonists. However, there was a small decrease in birth weight among users of LTRAs and an increase in the prevalence of major structural anomalies, but the latter effect was only in comparison to the control group without asthma ($n = 346$) and should be interpreted with caution, given the small sample size *(88)*. Current guidelines do not specifically recommend the use of LTRAs during pregnancy, due to the limited data available, unless the

woman's asthma was previously well controlled on these medications prior to pregnancy *(41)*.

Treatment of Exacerbations During Pregnancy

Current guidelines on the management of asthma during pregnancy recommend treating exacerbations aggressively *(41)*. A 1999 study of women presenting to the emergency department with an exacerbation of asthma found that pregnant women were significantly less likely to be prescribed oral steroids, either in the emergency department or on discharge from hospital, compared to non-pregnant women *(89)*. The pregnant women were three times more likely to report an ongoing asthma exacerbation following discharge compared to the non-pregnant women *(89)*. Another study examined rates of hospitalization, emergency department presentation, and oral steroid courses for asthma exacerbations before and during pregnancy *(35)*. Hospitalizations were more common during pregnancy than before pregnancy, and emergency department presentations and oral steroid courses were less likely during pregnancy than before pregnancy. This data may suggest that treatment approaches for pregnant women with severe asthma exacerbations differs from those in non-pregnant women or could reflect changes in the frequency or severity of exacerbations during pregnancy *(35)*. Therapy should be maximized during any asthma exacerbation that occurs during pregnancy, as a severe asthma attack presents more of a risk to the fetus than the use of asthma medications due to the potential for fetal hypoxia *(41)*. Management of an asthma emergency during pregnancy should involve both close monitoring of lung function, and fetal activity and oxygen saturation should be maintained above 95% *(41)*. In cases of severe asthma there should be a close cooperation between the respiratory specialist and obstetrician *(41)*.

There have been two randomized controlled trials of asthma therapy during pregnancy. The first study addressed treatment of exacerbations, while the second examined treatment to prevent exacerbations. Wendel et al. studied 84 women with 105 exacerbations during pregnancy, who were randomized to receive methylprednisolone with intravenous aminophylline (n=33) or methylprednisolone alone (n=32) at the time of admission to a hospital *(90)*. Women receiving aminophylline reported more side effects, but there was no difference in the length of hospital stay between treatments *(90)*. On discharge, the women were further randomized to receive inhaled β_2-agonist with either oral steroid taper alone (n=31) or ICS plus oral steroid taper (n=34). While one third of women required readmission for subsequent exacerbations, the readmission rate was reduced by 55% with the inclusion of ICS on discharge *(90)*.

The second randomized controlled trial compared the use of inhaled beclomethasone and oral theophylline for the prevention of asthma exacerbations during pregnancy in women with moderate asthma *(91)*. The rate of severe exacerbation was 18% among women using beclomethasone and 20% among women using theophylline (not significantly different). Side effects resulting in cessation of treatment were more common in the theophylline group and these women were more likely to have an $FEV_1 < 80\%$ predicted. Maternal and fetal outcomes such as pre-eclampsia, preterm delivery, and birth weight were not different between the groups *(91)*. This trial indicated that inhaled beclomethasone was a suitable alternative to theophylline for asthma treatment during pregnancy, but compared to theophylline, the use of ICS did not reduce the exacerbation rate.

A prospective cohort study found that the risk of exacerbations of asthma during pregnancy was reduced by the use of ICS medication *(40)*. Thirty-four percent of women who had an exacerbation during pregnancy were using ICS prior to the exacerbation, while 62% of women who did not have exacerbations used ICS during pregnancy. After exacerbations, 94% of women used ICS and 74% required treatment with oral steroids *(40)*. Similar data have been reported recently by Schatz and Liebman *(47)*, suggesting the importance of women using appropriate preventer medication for asthma control during pregnancy.

Health Behavior

Cessation of Inhaled Steroid Use During Pregnancy

An Australian study found that 15% of women with severe asthma do not use inhaled steroid medication, against the advice of current guidelines *(31, 41)*. It is clear from several studies that despite numerous reports indicating the safety of ICS use for asthma treatment during pregnancy and the recommendations of clinical guidelines, a culture of apprehension about using these medications, both by pregnant women themselves *(92, 93)* and by physicians *(40, 89, 92)*, remains. In 2003, a survey of 501 asthmatic women of child-bearing age revealed that 82% of women who used ICS treatment were concerned about the effects of this medication on the fetus *(94)*. Women also felt concern about the health consequences of discontinuing medication and despite this, 36% indicated that they were likely to discontinue medication while pregnant, without first seeking advice from their physician *(94)*.

Several studies using prescription databases have identified a significant fall in prescriptions for asthma medications in early pregnancy, compared to before pregnancy *(47, 82, 95)*. Schatz and Liebman described the use of asthma medications in the 6 months prior to and 6 months after the first pregnancy claim using data from a medical insurance database, and found that while 16% of women used ICS prior to pregnancy, 52% of these women discontinued ICS after pregnancy *(47)*. Overall, the number of women using ICS during pregnancy decreased by 36% *(47)*. The use of short-acting β_2-agonists was also discontinued in 57% of subjects *(47)*. An American study found a 23% reduction in prescriptions for ICS, a 13% reduction in short-acting β_2-agonists, and a 54% reduction in oral steroid prescriptions compared to prescriptions filled in the 20 weeks prior to pregnancy *(95)*. Blais et al. also found a reduction in the use of ICS (based on prescriptions filled) from pre-pregnancy (47.2% of women) to the first trimester (40% of women) *(82)*. These data could reflect the attitudes of pregnant women themselves who may choose not to fill their prescriptions in early pregnancy, or may be related to altered prescribing practices of their physicians.

Cessation of medication during pregnancy may have adverse consequences for both the mother and the baby. Schatz and Liebman found that the number of emergency department or physician visits for asthma was higher among women who had not taken ICS medication prior to pregnancy *(47)*. Conversely, among women who were using ICS prior to pregnancy, there was a 36% decrease in the number of asthma related physician visits during pregnancy *(47)*. Similarly, Stenius-Aarniala et al. found that women who did not use ICS during pregnancy were at greater risk of exacerbations *(40)*. Using a prescription database, Olesen

et al. found that women who reduced the intensity of their asthma medications during pregnancy (e.g., ICS use to short-acting β_2-agonist use) had babies with lower mean birth weight, birth length, and gestational age, compared to women who increased the intensity of asthma treatment during pregnancy *(96)*. These data indicate that maintaining good asthma control with appropriate therapy is important for maternal and fetal health outcomes.

The release of the 2004 clinical guidelines for the treatment of asthma during pregnancy contains clear messages about the safety of medication use (especially ICS and β_2-agonists) during pregnancy and the importance of vigorous treatment of asthma exacerbations *(41)*, and may facilitate improvements in asthma management for pregnant women.

Education and Self-Management of Asthma During Pregnancy

The NAEPP report on the treatment of asthma during pregnancy indicates that individual treatment plans are required to address specific circumstances and patient needs and that self-management of asthma is an important component of care *(41)*. Pregnant women with asthma have poor asthma skills and knowledge, with an Australian study reporting that at the beginning of pregnancy, 40% of women self-reported non-adherence to ICS medication, 16% had inadequate inhaler technique, and 42% had inadequate knowledge about their asthma medications *(97)*. Only 3% were performing regular peak flow monitoring and 15% had a written action plan *(97)*. Asthma self-management education during pregnancy was subsequently provided in an antenatal clinic setting, contributing to an improvement in asthma management for pregnant women. During a 30–60 min session with an asthma educator, women received education about asthma control and management skills, including trigger avoidance and smoking cessation counselling where appropriate and inhaler technique and medication adherence were assessed. Women assessed as unstable and requiring medical review were referred to their primary care physician or to a respiratory physician for review. Each patient received an individualized written action plan as part of the program. Asthma education during pregnancy was associated with significant improvements in all aspects of self-management and with a significant increase in ICS use in women with moderate and severe asthma *(97)*. Women with severe asthma also reported fewer night time asthma symptoms and less use of reliever medications after receiving education *(97)*.

There is an expressed need for education and improved asthma management skills by women *(93)*. A 2003 survey of 501 women with asthma found that while most were concerned about the possibility of taking ICS medication while pregnant, only 19% had discussed this concern with their physician *(94)*. A multidisciplinary approach to prenatal and asthma care would be beneficial to pregnant women and is recommended by the NAEPP report *(41)*. In the 2003 survey, Chambers found that 40% of women would continue using ICS medication purely on the recommendation of their obstetrician *(94)*. A recent study has proposed that nurses have a key role to play in educating pregnant women with asthma, in a culturally sensitive way, which will empower them to alter their behavior and make lifestyle changes which control asthma symptoms *(98)*. There are significant deficiencies in asthma knowledge and self-management skills among pregnant women and these can be greatly improved by asthma education, potentially leading to better asthma control.

Smoking During Pregnancy

Smoking is more common among pregnant women with asthma than pregnant women without asthma (Table 11.1). This has been shown in the majority of studies *(3, 39, 71, 74, 85, 99–102)*. Only in two studies from Finland were smoking rates lower among women with asthma *(13, 40)*. Mihrshahi et al. also described higher rates of passive smoke exposure among pregnant women with asthma (24%) compared to non-asthmatic women (4%), but this was no longer significant when considering only the sub-group of women who were non-smokers themselves *(101)*.

There is some evidence that smoking rates are higher among women who do not use medication to treat their asthma. A study from Manchester found that smoking was more prevalent among pregnant women with asthma who did not use medication (41.1%) than among pregnant women who did use asthma medication during pregnancy (31.2%) *(2)*. Similarly, Alexander et al. found a significantly higher rate of smoking among women who did not use ICS treatment for asthma (38.2% of those with no medication, 33.9% of those using β_2-agonists only), compared to women using steroids (27.2% smokers) *(100)*. Blais et al. showed that a higher proportion of women not treated with ICS during pregnancy were smokers (54.5%) compared to women who were treated with ICS (48%) *(82)*. A recent study found that 7.4% of women who used leukotriene receptor antagonists for asthma treatment during pregnancy smoked, while 14.9% of women who used β_2-agonists smoked, compared to 8.3% of non-asthmatic women *(88)*.

Smoking is a contributor to poor perinatal outcomes, including low birth weight. The combined effects of maternal smoking and asthma have not been thoroughly investigated, but it is possible that smoking may further increase any perinatal risks associated with maternal asthma. During pregnancy, smoking cessation programs should be provided to all women, and particularly those with

Table 11.1 Rates of smoking among pregnant women with and without asthma.

Study	Country	Smoking rate in control group (%)	Smoking rate in asthma group (%)
Dombrowksi et al., 1986 *(99)*	USA	28.0	46.0
Stenius-Aarniala et al., 1988 *(13)*	Finland	16.2	8.8
Stenius-Aarniala et al., 1996 *(40)*	Finland	15.2	11.5
Alexander et al., 1998 *(100)*	Canada	27.3	34.8
Minerbi-Codish et al., 1998 *(39)*	Israel	6.5	16.8
Demissie et al., 1998 *(74)*	USA	12.1	15.3
Kurinczuk et al., 1999 *(3)*	Australia	22.3	25.3
Mihrshahi et al., 2003 *(101)*	Australia	17.0	30.0
Sheiner et al., 2005 *(102)*	Israel	4.2	11.1
Clark et al., 2007 *(2)*	United Kingdom	36.1	36.1
Kallen and Otterblad Olausson, 2007 *(85)*	Sweden	12.4	16.3
Tata et al., 2007 *(71)*	United Kingdom	31.0	34.3
Bakhireva et al., 2007 *(88)*	USA and Canada	8.3	11.5

asthma and in addition, avoidance of other triggers, including passive smoke exposure should be strongly encouraged *(41, 97)*.

Anxiety and Depression During Pregnancy

A recent study from the United Kingdom found that women with asthma have a 52% increased risk of suffering depression during pregnancy compared to women without asthma *(71)*. This finding was not dependent on the medications used by women and was further elevated (two fold increased risk) among women who had experienced exacerbations of asthma during pregnancy *(71)*. A Swedish study also reported increased use of anti-depressants among women using anti-asthmatic drugs during pregnancy *(85)*.

In non-pregnant adults it has been proposed that psychological stress and anxiety contribute to worsening of asthma. A study of university students during periods of low stress (mid-semester) and high stress (final examination week) found that sputum eosinophils following allergen challenge were increased during the high stress period, which was also characterized by significantly higher anxiety and depression scores *(103)*. This demonstrates an interaction between psychological stress and deteriorating airway inflammation in asthma.

Stress, anxiety, and depression may be contributors to worsening asthma during pregnancy. Concerns about the effects of medication use on the baby may lead to anxiety and non-adherence among pregnant women with asthma. Many women are worried about the effect their pregnancy may have on their asthma and how their asthma may affect their baby *(93, 94)*. Beckmann found that 44% of women surveyed were worried for the baby, 11% were concerned that their stress and worry could lead to asthma attacks, 7% were fearful of having an asthma attack in public, and 5% reported feeling sadness, depression, or anxiety *(93)*. A recently published RCT showed a potential benefit of relaxation techniques among pregnant women with asthma *(104)*. The women with asthma who underwent 8 weeks of training in progressive muscle relaxation showed a significant improvement in lung function (31% increase in FEV_1) over the 8 week period, compared to the control group (trained in sham exercises), who had no change in FEV_1. Other benefits of this therapy included an improvement in health-related quality of life and a reduction of anger levels *(104)*. This study suggests that improving psychological parameters may have significant effects on lung function during pregnancy.

Conclusions

Asthma is a common medical problem during pregnancy. Exacerbations of asthma can increase the risk of poor maternal and fetal outcomes during pregnancy. In particular, women who have a severe exacerbation of asthma during pregnancy are 2.5 times more likely to have a low birth weight baby than women without asthma. Being low birth weight puts the infant at greater risk of poor health later in life. Asthma that is well controlled during pregnancy is not considered to be a significant risk to the baby, and regular monitoring of maternal asthma throughout pregnancy is recommended. ICS form the cornerstone of therapy for pregnant women with persistent asthma and may protect against some adverse outcomes by controlling asthma and preventing exacerbations. Addressing health behavior issues such as maternal smoking, poor self-management skills and non-adherence to medication will be important for improving pregnancy outcomes for women with asthma.

References

1. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. Ann Epidemiol 2003;13(5):317–24.
2. Clark JM, Hulme E, Devendrakumar V, et al. Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population. Paediatr Perinat Epidemiol 2007;21:154–62.
3. Kurinczuk JJ, Parsons DE, Dawes V, Burton PR. The relationship between asthma and smoking during pregnancy. Women Health 1999;29(3):31–47.
4. Gluck JC, Gluck PA. The effects of pregnancy on asthma: a prospective study. Ann Allergy 1976;37:164–8.
5. Schatz M, Harden K, Forsythe A, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81 (3):509–17.
6. Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. Ann Allergy Asthma Immunol 2002;89 (5):463–6.
7. Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: A systematic review. Am J Obstet Gynecol 2004;190(5):1201–10.
8. Sims CD, Chamberlain GV, de Swiet M. Lung function tests in bronchial asthma during and after pregnancy. Br J Obstet Gynaecol 1976;83 (6):434–7.
9. Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Improvement in airway responsiveness and asthma severity during pregnancy. A prospective study. Am Rev Respir Dis 1989;140(4):924–31.
10. Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Effect of pregnancy on airway responsiveness and asthma severity. Relationship to serum progesterone. Am Rev Respir Dis 1991;143(3 Pt 2):S78.
11. Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990;35 (2–3):183–90.
12. Clark SL. Asthma in pregnancy. National Asthma Education Program Working Group on Asthma and Pregnancy. National Institutes of Health, National Heart, Lung and Blood Institute. Obstet Gynecol 1993;82(6):1036–40.
13. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43(1):12–8.
14. Mabie WC, Barton JR, Wasserstrum N, Sibai BM. Clinical observations on asthma and pregnancy. J Matern Fetal Med 1992;1:45–50.
15. Jana N, Vasishta K, Saha SC, Khunnu B. Effect of bronchial asthma on the course of pregnancy, labour and perinatal outcome. J Obstet Gynaecol 1995;21(3):227–32.
16. Schatz M, Dombrowski MP, Wise R, et al. Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol 2003;112(2):283–8.
17. Williams DA. Asthma and pregnancy. Acta Allergol 1967;22:311–23.
18. Nelson-Piercy C. Asthma in pregnancy. Thorax 2001;56 (4):325–8.
19. Lyons HA, Antonio R. The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. Trans Assoc Am Physic 1959;72:173–80.
20. Lye SJ, Porter DG. Demonstration that progesterone 'blocks' uterine activity in the ewe in vivo by a direct action on the myometrium. J Reprod Fertil 1978;52(1):87–94.
21. Tan KS, Thomson NC. Asthma in pregnancy. Am J Med 2000;109(9):727–33.
22. Tan KS, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of beta2-adrenoceptors by exogenous progesterone in female asthmatics. Chest 1997;111(4):847–51.
23. Tan KS. Premenstrual asthma: epidemiology, pathogenesis and treatment. Drugs 2001;61(14):2079–86.
24. Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. Thorax 1984;39(11):833–6.

25. Rubio Ravelo L, Gago Rodriguez B, Almirall Collazo JJ, Bell Heredia L, Fernandez Fernandez L. Comparative study of progesterone, estradiol and cortisol concentrations in asthmatic and non-asthmatic women. Allergol Immunopathol (Madr) 1988;16(4):263–6.
26. Chaouat G, Ledee-Bataille N, Dubanchet S, Zourbas S, Sandra O, Martal J. Reproductive immunology 2003: reassessing the Th1/Th2 paradigm? Immunol Lett 2004;92(3):207–14.
27. Clifton VL, Murphy VE. Maternal asthma as a model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. Placenta 2004;25(Suppl A):S45–52.
28. Tamasi L, Bohacs A, Pallinger E, et al. Increased interferon-gamma- and interleukin-4-synthesizing subsets of circulating T lymphocytes in pregnant asthmatics. Clin Exp Allergy 2005;35:1197–203.
29. Beecroft N, Cochrane GM, Milburn HJ. Effect of sex of fetus on asthma during pregnancy: blind prospective study. BMJ 1998;317(7162):856–7.
30. Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls. BMJ 1999;318(7189):1011.
31. Murphy VE, Gibson PG, Giles WB, et al. Maternal asthma is associated with reduced female fetal growth. Am J Respir Crit Care Med 2003;168(11):1317–23.
32. Kwon HL, Belanger K, Holford TR, Bracken MB. Effect of fetal sex on airway lability in pregnant women with asthma. Am J Epidemiol 2005;163(3):217–21.
33. Baibergenova A, Thabane L, Akhtar-Danesh N, Levine M, Gafni A. Is fetal gender associated with emergency department visits for asthma during pregnancy? J Asthma 2006;43:293–99.
34. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006;61(2):169–76.
35. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe Asthma Exacerbations During Pregnancy. Obstet Gynecol 2005;106(5):1046–54.
36. Hendler I, Schatz M, Momirova V, et al. Association of obesity with pulmonary and nonpulmonary complications of pregnancy in asthmatic women. Obstet Gynecol 2006;108:77–82.
37. Carroll KN, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, Hartert TV. Racial differences in asthma morbidity during pregnancy. Obstet Gynecol 2005;106(1):66–72.
38. Chung KD, Demissie K, Rhoads GG. Asthma in pregnancy–its relationship with race, insurance, maternal education, and prenatal care utilization. J Natl Med Assoc 2004;96(11):1414–21.
39. Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. Respiration 1998;65(2):130–5.
40. Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996;51(4):411–4.
41. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol 2005;115(1):34–46.
42. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD. Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 2005;116(3):503–9.
43. Apter AJ, Greenberger PA, Patterson R. Outcomes of pregnancy in adolescents with severe asthma. Arch Intern Med 1989;149(11):2571–5.
44. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003;189(6):1705–12.
45. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. Thorax 2002;57(7):643–8.
46. Rastogi D, Wang C, Lendor C, Rothman PB, Miller RL. T-helper type 2 polarization among asthmatics during and following pregnancy. Clin Exp Allergy 2006;36:892–8.

47. Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. Ann Allergy Asthma Immunol 2005;95(3):234–8.
48. Otsuka H, Narushima M, Suzuki H. Assessment of inhaled corticosteroid therapy for asthma treatment during pregnancy. Allergol Int 2005;54(3):381–6.
49. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. Eur Respir J 2005;25(4):731–50.
50. Schatz M, Dombrowski M, Wise R, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. Am J Obstet Gynecol 2006;194:120–6.
51. Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyperreactivity and the respiratory distress syndrome. N Engl J Med 1985;312(12):742–5.
52. Doucette JT, Bracken MB. Possible role of asthma in the risk of preterm labor and delivery. Epidemiology 1993;4(2):143–50.
53. Kramer MS, Coates AL, Michoud MC, et al. Maternal asthma and idiopathic preterm labor. Am J Epidemiol 1995;142(10):1078–88.
54. McClure JH, James JM. Oxygen administration to the mother and its relation to blood oxygen in the newborn infant. Am J Obstet Gynecol 1960;80(3):554–6.
55. Clifton VL, Giles WB, Smith R, et al. Alterations of placental vascular function in asthmatic pregnancies. Am J Respir Crit Care Med 2001;164(4):546–53.
56. Murphy VE, Zakar T, Smith R, Giles WB, Gibson PG, Clifton VL. Reduced 11beta-hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. J Clin Endocrinol Metab 2002;87(4):1660–8.
57. Murphy VE, Johnson RF, Wang YC, et al. The effect of maternal asthma on placental and cord blood protein profiles. J Soc Gynecol Investig 2005;12(5):349–55.
58. Clifton VL, Vanderlelie J, Perkins AV. Increased anti-oxidant enzyme activity and biological oxidation in placentae of pregnancies complicated by asthma. Placenta 2005;26(10):773–9.
59. Clifton VL, Rennie N, Murphy VE. Effect of inhaled glucocorticoid treatment on placental 11beta-hydroxysteroid dehydrogenase type 2 activity and neonatal birthweight in pregnancies complicated by asthma. Aust N Z J Obstet Gynaecol 2006;46(2):136–40.
60. Gordon M, Niswander KR, Berendes H, Kantor AG. Fetal morbidity following potentially anoxigenic obstetric conditions. VII. Bronchial asthma. Am J Obstet Gynecol 1970;106(3):421–9.
61. Schatz M, Zeiger RS, Hoffman CP, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995;151(4):1170–4.
62. Hammoud AO, Bujold E, Sorokin Y, Schild C, Krapp M, Baumann P. Smoking in pregnancy revisited: findings from a large population-based study. Am J Obstet Gynecol 2005;192(6):1856–62; discussion 62–3.
63. Greenberger PA, Patterson R. The outcome of pregnancy complicated by severe asthma. Allergy Proc 1988;9(5):539–43.
64. Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. Int J Gynaecol Obstet 2002;77(2):117–21.
65. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol 2003;102(4):739–52.
66. Schatz M, Dombrowski MP, Wise R, et al. The relationship of asthma medication use to perinatal outcomes. J Allergy Clin Immunol 2004;113(6):1040–5.
67. Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. Am J Obstet Gynecol 1992;167(4 Pt 1):963–7.
68. Martel MJ, Rey E, Beauchesne MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 2005;330(7485):230.

69. Read MA, Leitch IM, Giles WB, Bisits AM, Boura AL, Walters WA. U46619-mediated vasoconstriction of the fetal placental vasculature in vitro in normal and hypertensive pregnancies. J Hypertens 1999;17(3):389–96.
70. Martel MJ, Rey E, Beauchesne MF, et al. Use of short-actine beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. J Allergy Clin Immunol 2007;119(3):576–82.
71. Tata LJ, Lewis SA, McKeever TM, et al. A comprehensive analysis of adverse obstetric and paediatric complications in women with asthma. Am J Respir Crit Care Med 2007;Feb 1 Epub.
72. McDonald CF, Burdon JG. Asthma in pregnancy and lactation. A position paper for the Thoracic Society of Australia and New Zealand. Med J Aust 1996;165(9):485–8.
73. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J Allergy Clin Immunol 1986;78(2):349–53.
74. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998;158(4):1091–5.
75. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: A retrospective cohort study. Am J Obstet Gynecol 2001;184(2):90–6.
76. Dombrowski MP, Schatz M, Wise R, et al. Asthma during pregnancy. Obstet Gynecol 2004;103(1):5–12.
77. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998;58(1):2–5.
78. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385–92.
79. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999;93(3):392–5.
80. Silverman M, Sheffer A, Diaz PV, et al. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. Ann Allergy Asthma Immunol 2005;95:566–70.
81. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. Eur J Clin Pharmacol 2007;63(4):383–8.
82. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax 2007;62:320–28.
83. Schatz M, Zeiger RS, Harden KM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. J Allergy Clin Immunol 1988;82(4):686–95.
84. Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996;49(2):247–50.
85. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 1. Maternal characteristics, pregnancy and delivery complications. Eur J Clin Pharmacol 2007;63:363–73.
86. Schatz M. Breathing for two: Now we can all breathe a little easier. J Allergy Clin Immunol 2005;115(1):31–3.
87. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100(3):301–6.
88. Bakhireva LN, Jones KL, Schatz M, et al. Safety of leukotriene receptor antagonists in pregnancy. J Allergy Clin Immunol 2007;119(3):618–25.
89. Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Camargo CAJ. Acute asthma among pregnant women presenting to the emergency department. Am J Respir Crit Care Med 1999;160(3):887–92.
90. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. Am J Obstet Gynecol 1996;175(1):150–4.

91. Dombrowski MP, Schatz M, Wise R, et al. Randomized trial of inhaled beclomethasone dipropionate versus theophylline for moderate asthma during pregnancy. Am J Obstet Gynecol 2004;190(3):737–44.
92. Lipson A. Asthma and pregnancy–misleading and incorrect recommendation on the effect of medication on the foetus–and a remedy. Aust N Z J Med 1994;24(4):407–8.
93. Beckmann CA. A descriptive study of women's perceptions of their asthma during pregnancy. MCN Am J Matern Child Nurs 2002;27(2):98–102.
94. Chambers K. Asthma education and outcomes for women of childbearing age. Case Manager 2003;14(6):58–61.
95. Enriquez R, Wu P, Griffin MR, et al. Cessation of asthma medication in early pregnancy. Am J Obstet Gynecol 2006;195:149–53.
96. Olesen C, Thrane N, Nielsen GL, Sorensen HT, Olsen J. A population-based prescription study of asthma drugs during pregnancy: changing the intensity of asthma therapy and perinatal outcomes. Respiration 2001;68(3):256–61.
97. Murphy VE, Gibson PG, Talbot PI, Kessell CG, Clifton VL. Asthma self-management skills and the use of asthma education during pregnancy. Eur Respir J 2005;26(3):435–41.
98. MacMullen NJ, Tymkow C, Shen JJ. Adverse maternal outcomes in women with asthma: differences by race. MCN Am J Matern Child Nurs 2006;31(4):263–8.
99. Dombrowski MP, Bottoms SF, Boike GM, Wald J. Incidence of preeclampsia among asthmatic patients lower with theophylline. Am J Obstet Gynecol 1986;155(2):265–7.
100. Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. Obstet Gynecol 1998;92(3):435–40.
101. Mihrshahi S, Belousova E, Marks GB, Peat JK. Pregnancy and birth outcomes in families with asthma. J Asthma 2003;40(2):181–7.
102. Sheiner E, Mazor M, Levy A, Wiznitzer A, Bashiri A. Pregnancy outcome of asthmatic patients: A population-based study. J Matern Fetal Med 2005;18(4):237–40.
103. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. Am J Respir Crit Care Med 2002;165(8):1062–7.
104. Nickel C, Lahmann C, Muehlbacher M, et al. Pregnant women with bronchial asthma benefit from progressive muscle relaxation: a randomised, prospective, controlled trial. Psychother Psychosom 2006;75:237–43.

12

Tuberculosis and Pregnancy

John B. Bass and James N. Byrd

Keywords: latent TB infection, active TB infection, antituberculous drugs, pregnancy, breastfeeding

Introduction

Tuberculosis (TB) is a common infectious disease caused by *Mycobacterium tuberculosis,* which commonly attacks the lungs (as pulmonary TB) but can also affect other organ systems. Over one third of the world's population now carries the TB bacterium. Not everyone infected develops active TB, and latent (asymptomatic) infection is common. TB is a problem not only in the developing world and an increasing number of people in the developed world are contracting TB. The World Health Organization declared TB a global health emergency in 1993 *(1, 2, 3)*.

From the earliest recognition of TB, the scientific community has had widely differing beliefs about its implications for maternal and fetal health and well being. Two millennia ago, the ancient Greeks felt that women with TB who became pregnant had a much better disease course than their non-pregnant counterparts. In fact, they believed that pregnancy was so beneficial for women with active TB that these women were encouraged to become pregnant if they were not already so. This belief persisted through the Middle Ages and into the early nineteenth century. There was a drastic change in the nineteenth and twentieth centuries, when the prevailing sentiment was that women with TB did much worse after becoming pregnant. Therapeutic abortions were not only common, but were recommended and for a time were the standard of care *(4, 5)*. We now have evidence that suggests that pregnancy does not alter the course of TB. Though the studies done to support this evidence are small, they nonetheless demonstrate that women with TB who become pregnant are not at increased risk for an adverse maternal or fetal outcome *(6)*.

However, with increasing rates of TB infection in this country, partially as a result of Human Immunodeficiency Virus (HIV) infection, and partially because of larger populations of immigrants from areas of the world with high prevalence of TB, screening for and treatment of TB during pregnancy are becoming more important. In disadvantaged populations with limited access to care, often the only contact with the health care system is during pregnancy *(7, 8)*. Since screening

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_12

for TB is recommended in all such high-risk individuals, regardless of pregnancy status, health care providers should take this opportunity to screen for TB and offer HIV counseling and screening *(9, 10)*.

Though there is no definite increase in TB risk associated with pregnancy, there are several special considerations that alter the standard evaluation and treatment. These are discussed in detail below.

Evaluation

There is very little deviation from the standard approach to the evaluation for TB in pregnant women as opposed to the general population. The most common methods of determining exposure to and infection with *Mycobacterium tuberculosis* include skin testing, roentgenography, and sputum analysis. These are discussed below. Other methods are less common and are beyond the scope of this chapter.

Skin Testing

Methods and Special Circumstances

The standard skin test for the determination of previous *M. tuberculosis* exposure and latent infection is the Mantoux method. This involves injection of a standard dose of 5 Tuberculin units (0.1 mL) of Purified Protein Derivative (PPD) via a 27-guage needle into the dermis of the volar surface, and observing for local reaction 48–72 h later. This type of reaction is a Type IV, cell-mediated delayed hypersensitivity reaction. There is no evidence that pregnancy alters interpretation of the skin test *(11)*.

A circumstance that must be considered when interpreting the skin test is previous history of the Bacille Calmette-Guérin (BCG) vaccine. The BCG vaccine is a vaccine against *M. tuberculosis* that is prepared from a strain of the attenuated live bovine tuberculosis bacillus, *Mycobacterium bovis*, that has lost its virulence in humans by being specially cultured in an artificial medium for years. This is particularly important since many immigrants who are at higher risk for TB are from areas of the world where the BCG vaccine is more common. The BCG vaccine is not currently recommended for routine use in the United States, as it may interfere with future interpretation of skin testing, and has been shown to be of varying effectiveness *(12)*.

Interpretation and Guidelines

All pregnant women from populations that are recommended to have routine TB screening should have skin testing if there has not been previous testing *(13)*. The test is positive if there is greater than a 5, 10, or 15 mm induration based on certain epidemiological risk factors (Table 12.1).

Women with positive skin testing, even if they are not symptomatic, should have chest radiography performed to exclude pulmonary TB. Women who have symptoms suspicious for TB should have chest radiography even if skin testing is negative or inconclusive.

Serum Quantiferon Testing

The QuantiFERON® TB test and QuantiFERON® TB Gold test (QFT) are blood tests that measure an individual's immune reactivity to *M. tuberculosis*. The

Table 12.1 Criteria for establishing positive tuberculin skin test reactions.

≥ 5 mm	≥ 10 MM	≥ 15 MM
HIV Disease	Recent Immigrants (< 5 years) from TB Prevalent Countries	No TB Risk Factors
Recent TB Contact	Residents/Employees of High-Risk Areas	
X-ray Consistent with prior TB	Mycobacteriology Laboratory Personnel	
Organ Transplant	Children < 4	
Immunocompromised	Injection Drug Users	

test is performed by mixing blood specimens with antigens and incubated for 16–24 h. Testing should be performed within 12 h. In LTBI, the blood cells recognize the tuberculin antigen and release interferon gamma (IFNγ). Results are based on the proportion of IFNγ released. The first generation QFT (QuantiFERON® TB test) was approved by the US Food and Drug Administration (FDA) in 2001, while the second generation test (QuantiFERON® TB Gold test) was approved by the FDA in 2005.

Advantages of QFT over TST include the fact that QFT requires a single patient visit, does not cause a booster phenomenon and is subject to less reader bias than TST.

In general, the Centers for Disease Control and prevention (CDC) discourages testing for LTBI in low risk populations. The CDC also does not recommend the use of QFT in pregnant women, children under 17 years of age, or in individuals with a high risk of progression of the disease.

Roentgenography

Chest radiography with single posterior–anterior and lateral films exposes the fetus to a minimal amount of radiation. This amount of radiation is even lower in the early stages of pregnancy given that a first trimester fetus is much farther from the chest than a third trimester fetus, for instance. Susceptibility to radiation varies however with various gestational stages (refer to Chapter 5 on diagnostic imaging). Individuals who have symptoms suggestive of TB, regardless of the stage of pregnancy, should have chest radiography. Furthermore, women with positive skin testing and certain risk factors, like HIV infection, should have chest radiographs performed regardless of the stage of pregnancy. Asymptomatic women with likely latent TB, diagnosed in the first trimester, may choose to wait until the second trimester to get a radiograph. However, given that the amount of radiation exposure to the fetus is so minimal, obtaining a chest radiograph in the first trimester is an acceptable option as well.

Radiographs performed on pregnant women should be appropriately shielded. The radiation field should cover only the thorax as possible and the abdomen and gonadal regions should be shielded with the appropriate thickness of lead. The amount of radiation from standard chest radiography is less than 0.25 mRad with a maximum recommended exposure during the course of gestation being 5 Rads *(14, 15)*.

Sputum Analysis

Sputum analysis should be performed in any person with chest radiograph findings suspicious for TB. At least three sputum specimens should be collected, preferably on different days. These specimens should be stained appropriately for direct

visualization of acid-fast organisms after carbolfuchsin staining and should be cultured on appropriate growing media for 3–8 weeks, depending on the culture medium *(16)*.

Specific Treatment Situations

Preventive Therapy

Transmission of TB is by inhalation of droplet nuclei produced when a person with infectious pulmonary TB or laryngeal TB coughs, laughs, sneezes, or talks. Individuals who have close contact with persons known to have active TB, including household contacts, but who *do not have* positive skin testing are considered exposed to TB. They should have repeat skin testing in 3 months. If repeat skin testing is negative, nothing further should be done unless they develop symptoms suggestive of TB *(17)*.

Latent Tuberculosis

Individuals who have been in close contact with persons known to have active TB, including household contacts, and who have appropriately positive skin testing or positive quantiferon testing (QFT), but do not have symptoms of active tuberculosis, and who *have* negative chest radiography for active disease, are considered to have latent tuberculosis infection (LTBI). This form of TB is not considered infectious *(17)*. The treatment of choice for LTBI is oral isoniazid (INH) for 9 months *(18)*. Although INH does cross the placenta, there is no increased toxicity to the fetus and there is no known evidence of teratogenicity. However, there is evidence that there may be increased hepatotoxicity in pregnant women with this agent. This may be especially true in women from minority populations. For this reason, INH is generally held until after 2–3 months following delivery in these individuals, unless specific risk factors such as HIV infection or recent skin test conversion are present *(19)*.

Active Tuberculosis

High-risk individuals with symptoms suggestive of TB should be considered to have active tuberculosis infection (ATBI). They usually have positive skin or quantiferon testing and radiographs that are suspicious for the disease, and the organism should be easily identified in their sputum. Though unlikely, some of the above may be negative. In the absence of all the above, the diagnosis of ATBI is unlikely *(17)*.

The benefits of treating active TB in pregnancy far outweigh any potential drug toxicity, and should not be delayed *(17, 20)*. Consultation with health care professionals who commonly treat TB is recommended, as is following current CDC Guidelines for the treatment of active TB. Pregnancy does not significantly affect the response to antituberculous medications and TB is not a medical indication for abortion.

Current Guidelines

The Centers for Disease Control and Prevention (CDC) has established guidelines for the diagnosis and treatment of TB exposure, latent infection, and active infection. These guidelines vary widely based on clinical suspicion, the presence

or absence of organisms on sputum staining, the presence or absence of cavitations on chest radiography, and the antibiotic susceptibility of the specific organism recovered. They also vary in length of treatment based on certain risk factors and antituberculous medications used. A clinician familiar with these guidelines should be consulted to guide therapy.

Agents Used for the Treatment of Tuberculosis

Prescribing drugs in pregnancy is discussed in detail in Chapter 6 of this book.

First-Line Agents

Isoniazid

Isoniazid (INH) is the most commonly used antituberculous medication. Its mechanism of action in not known, but it is believed to inhibit mycolic acid synthesis, resulting in disruption of the bacterial cell wall. It readily distributes to all body tissues, including the CSF. It crosses the human placenta. Although INH is considered pregnancy category C, there are no known teratogenic effects associated with its use and its use in pregnancy is recommended when indicated (Table 12.2).

For latent infection, the (CDC) report published in 2005 recommends therapy with INH in individuals with or without HIV for 9 months *(21)*. Pregnant women at high risk for reactivation should be treated during pregnancy. In patients that are at low risk for reactivation, therapy can be delayed until the post-partum period. For active infection, it is generally given daily at 5 mg/kg/day, but can be dosed at different amounts and intervals. Smaller doses are required for severe renal impairment and severe hepatic disease. INH also interacts with many commonly prescribed medications, so a careful review of all patient medications is especially important. It should be given concomitantly with pyridoxine (discussed below) *(22)*.

Rifampin

Rifampin is another commonly used antituberculous medication, and is also used in the treatment and prophylaxis of meningococcal meningitis. It works by binding to the beta subunit of DNA-dependant RNA polymerase, thus blocking RNA

Table 12.2 Drug classifications in pregnancy.

Category	Interpretation	Evidence
A	Controlled studies show no risk	Adequate studies in pregnant women have failed to demonstrate fetal risk
B	No evidence of risk in humans	Either animal findings show risk but human findings do not, or animal studies show no risk but human studies have not been done
C	Risk cannot be ruled out	Animal studies demonstrate risk or are lacking and human studies are lacking
D	Positive evidence of risk	Data shows risk to the fetus but potential benefits may outweigh risks
X	Contraindicated in pregnancy	Data shows fetal risk which outweighs potential benefit

transcription and RNA synthesis. Rifampin is extensively protein bound and is highly lipophilic. It crosses the human placenta. Again, although rifampin is considered pregnancy class C, there no evidence to suggest teratogenicity.

For latent infection, Rifampin may be used for four months as an alternative to INH. However, the evidence for this regimen is not as strong as the evidence supporting the use of INH for 9 months. Rifampin may be used in the treatment of LTBI in patients exposed to INH-resistant TB. For active infection, it is generally given daily at 10 mg/kg/day (maximum dose 600 mg/day), but dosing intervals and amounts vary. Smaller doses are required in severe hepatic disease. Rifampin also interacts with many commonly prescribed medications, including antiemetics, calcium channel blockers, and terbinafine. Patients and medical officials should be aware that rifampin causes red-orange discoloration of all bodily fluids, including urine, feces, sweat, and tears *(23)*.

Rifampin is known to decrease the efficacy of oral contraceptives and should be used in association with another form of birth control.

Ethambutol

Ethambutol interferes with RNA synthesis, suppressing mycobacterial multiplication. It readily distributes to all body tissues and concentrates in the kidneys, lungs, saliva, and red blood cells. Ethambutol should be used in the treatment of active TB in pregnancy and is not known to be associated with teratogenicity. Although there's a theoretical concern of Ethambutol causing optic neuritis in the offspring, there have no reports of such an occurrence. The lack of such reports could be secondary to the fact that detecting optic neuritis in the newborn is difficult.

For active TB infection, Ethambutol is generally given daily at 15–25 mg/kg/day. Dose adjustments are required for renal impairment. Its absorption is decreased with aluminum containing antacids. It may cause optic neuritis and baseline and monthly visual testing is recommended *(24)*.

Pyrazinamide

Pyrazinamide is used commonly as a part of a multi-drug antituberculous regimen. Its mechanism of action in not precisely known, but it is converted to pyrazinoic acid by susceptible strains of mycobacteria, which lowers the pH of the bacterial environment. It readily distributes to all body tissues, including the CSF. It crosses the human placenta. Detailed teratogenicity data are unavailable for Pyrazinamide. However, it use is probably safe in pregnancy and is recommended by the World Health Organization and the International Union against Tuberculosis and Lung Disease (IUATLD).

For active infection, it is given daily at doses between 15 and 30 mg/kg/day. The maximum daily dose is 2,000 mg daily regardless of body weight. The dose must be adjusted for moderate to severe renal impairment and in hepatic disease. It may cause severe or even fatal hepatotoxicity when used with rifampin, so liver function must be assessed periodically. It should be used cautiously in individuals with alcoholism, gout, or porphyria *(25)*.

Streptomycin

Streptomycin was previously used commonly in the treatment of active TB, though its use is becoming less common. It is an aminoglycoside, which binds to the 30S ribosomal subunit, causing disruption of peptide sequencing. It distributes to the extracellular compartment, crosses the human placenta, and can be ototoxic and

nephrotoxic to the fetus. Streptomycin is considered pregnancy class D and should not be used during pregnancy.

For active infection, it is generally given daily at 15 mg/kg/day. Dose adjustment is required for renal impairment. Serum peaks and troughs must be monitored *(26)*.

Second-Line Agents

The second-line agents used for the treatment of TB are a widely varied group of antibiotics. Their efficacy and usefulness is varied, as are their varied risks associated with pregnancy. They should only be used for the treatment of TB when there are strong contraindications or poor response to the first-line agents. Generally, only a specialist well knowledgeable in the treatment of TB should use these medications to treat active TB.

Amikacin

Amikacin and other aminoglycosides are often avoided in pregnant women because of the theoretical concern for nephrotoxocity and ototoxicity. Histologic evidence of nephrotoxicity has been shown in kidneys and cochlear cells of the offspring of rats and mice given Amikacin. No human reports are available. These concerns should not preclude the use of Amikacin if indicated for serious infections.

Clinical studies have shown that the concentration of Amikacin in breast milk is too low to measure. In addition, aminoglycosides are poorly absorbed in the gastrointestinal tract, making adverse reactions during lactation quite unlikely *(27)*.

Capreomycin

Capreomycin sulfate has not been studied during human pregnancy. According to the manufacturer, Capreomycin produced an increase risk of birth defects in rats, when given at 3.5 times the human dose. Based on experimental animal data and general potential for ototoxicity and rib anomalies, other anti-tuberculosis medications are preferable during pregnancy *(27)*.

Clofazimine

Clofazimine was not teratogenic in rats and mice at 50 mg/kg/day or in rabbits at 15 mg/kg/day *(1)*. The drug crosses the placenta *(2)* and may produce skin pigmentation in the fetus just as it does in adults. Clofazimine enters breast milk in an amount estimated to be 22.1 +/– 1.9% of the maternal dose. Although adverse effects of human exposure by this route have not been described, animal studies have suggested an increase in bone marrow chromosomal abnormalities and skin pigmentation in sucklings *(27)*.

Cycloserine

There are no published human or animal data on the safety of use of Cycloserine in pregnancy *(27)*.

Dapsone

There has been a small number of case reports of uncomplicated pregnancies, without any adverse neonatal outcomes following exposure to Dapsone during

gestation. However, there have also been cases of hemolytic anemia in mothers and their offspring described after exposure to dapsone, both during gestation and during lactation. The anemia did resolve following discontinuation of the drug.

Given that Dapsone may compete with bilirubin, it may increase the possibility of kernicteris from hyperbilirubinemia in neonates exposed to dapsone while in utero. Some clinicians have recommended the discontinuation of dapsone therapy 1 month before the expected date of delivery, if possible, to minimize the development of neonatal kernicteris.

Dapsone and its primary metabolite, monoacetyldapsone, are both excreted in breast milk. Because toxic doses of this drug may be ingested by an exposed suckling, the WHO Working Group on Drugs and Human Lactation concluded that the use of dapsone during breastfeeding is not safe *(28)*. In contrast, the American Academy of Pediatrics classified dapsone among drugs that are usually compatible with breastfeeding *(29)*.

Ethionamide

At high doses, Ethionamide has been shown to increase the risk of certain central nervous system anomalies in certain animal species but not others. There have been reports of the same anomalies in human neonates exposed during the first trimester of gestation but no causal relationship can determined based on the available literature *(27)*.

There are no data looking at the safety of this drug during lactation.

Para-Aminosalicylic Acid

Although reports suggest an increase in the risk of malformations in neonates exposed to para-aminosalicylic acid in utero, the data does not suggest a clear malformation syndrome. In addition, there are no adequate control groups identified with these studies.

Safety data during lactation are insufficient and supports the WHO Working Group on Drugs and Human Lactation's conclusion *(28)* that no recommendation can be made.

Fluoroquinolones

Fluoroquinolones are avoided during pregnancy and lactation because of toxicity to developing cartilage in experimental animal studies. However, among the reports on human pregnancies, there have been no documented adverse effects in relation to this class of drugs.

Rifabutin

Based on experimental animal studies, rifabutin therapy during pregnancy is not expected to increase the incidence of congenital malformations. There are no available reports on its use during lactation.

Thalidomide

Thalidomide exposure during pregnancy is associated with limb reduction defects, facial hemangiomata, esophageal and duodenal atresia, tetralogy of Fallot, renal

agenesis, and anomalies of the external ear. A risk of congenital anomalies is estimated at 20% of cases exposed to Thalidomide *(27)*. Therefore the use of this agent in pregnancy cannot be justified.

Other Agents

Although these agents are not used in the treatment of TB itself, they are commonly used alongside the first- and second-line agents to augment their efficacies or to reduce their toxicities.

Pyridoxine
Pyridoxine (Vitamin B6) is given with INH to reduce possible drug-induced neuritis and peripheral neuropathy associated with that medication. It is also given in the treatment of seizures and/or coma from acute INH toxicity. It is usually given at 25 mg/day. It crosses the placenta and is pregnancy class A (Table 12.2) at this dose. It is pregnancy class C at doses greatly exceeding this *(30)*.

Dexamethasone
Dexamethasone has been used in the treatment of tuberculous meningitis. Although Dexamethasone crosses the placenta and may be associated with adverse events in pregnancy such as hyperglycemia, as well as the potential to cause fetal/neonatal adrenal suppression, it should be used as indicated in the treatment of tuberculous meningitis *(31)*.

Breast Feeding

Many mothers from this country, as well as immigrants from developing countries, prefer to breastfeed their infants after delivery. Specific knowledge of the medications used for the treatment of TB should be given to the mothers so that they may make an educated decision about this practice.

First line antituberculous medications enter the breast milk but in small amounts that are not considered to be toxic to the newborn. Breast feeding should not be withheld in mothers receiving first line therapy *(18, 22–26)*. See Table 12.3 for details.

Table 12.3 Second-line antituberculous medications.

Drug	Pregnancy class	Safe in lactation	Miscellaneous
Amikacin	D	Y	aminoglycoside
Capreomycin	C	N	aminoglycoside
Clofazimine	–	N	
Cycloserine	C	No controlled studies, moderately safe *(36)*	
Dapsone	C	N	
Ethionamide	C	N	
Para-aminosalicylic acid	C	N	
Fluoroquinolones	C	N	QT prolongation, tendon rupture
Rifabutin	B	–	
Thalidomide	X	N	phocomelia

Tuberculosis Transmission

The spread of TB from a mother to her child during the antenatal period, delivery, and the puerperium is of major concern both for the safety of the child and for public health reasons. Each of these periods has specific modes of transmission, rates of transmission, and risk factors for transmission that must be considered. Furthermore, the disease locale in the mother is also of importance when considering transmission. These scenarios are discussed below.

Pulmonary Tuberculosis

Pulmonary tuberculosis is generally spread from person to person by droplet nuclei in the modes described above. Thus, TB that is confined to the thorax or limited to lymphadenitis poses little risk to the fetus prior to delivery *(17)*. After delivery, TB can be transmitted from the mother to her infant by the usual airborne route. Therefore, the mother should be evaluated for infectious risk at the time of delivery *(32)*. Pulmonary TB cannot be spread through breast milk. However, breastfeeding should be withheld in patients with active pulmonary TB that are still considered infectious, in order to avoid close contact and spread via respiratory droplets.

Extra-Pulmonary Tuberculosis

Congenital transplacental transmission of TB is rare and occurs most commonly through hematogenous infection via the umbilical vein in mothers who have active TB infection of the placenta or genital tract. However, placental involvement does not automatically lead to congenital tuberculosis, but may also occur following fetal ingestion of infected amniotic fluid, fetal aspiration of infected amniotic fluid.

The most recent criteria for the diagnosis of congenital TB mandate that the neonate have a tuberculous lesion (e.g., infiltrates on chest X-ray or granulomas) and that at least one of the following four criteria be present: (1) onset during the first week of life; (2) primary hepatic TB complex or caseating hepatic granuloma; (3) tuberculous infection of the placenta or maternal genital tract; or (4) exclusion of the possibility of postnatal transmission by a contact investigation *(33)*.

Congenital TB is associated with a high mortality rate if left untreated. In one cases series of congenital TB, the mortality rate was 46%.The diagnosis was made postmortem, in the majority of the cases, illustrating the difficulty in recognizing maternal disease *(34)*.

The incidence of lower birthweight infants and lower infant Apgar scores (less than 7) is higher in pregnant women with extrapulmonary TB (excluding lymphadenitis) *(35)*.

References

1. www.cdc.gov/tb
2. Bass JB. Tuberculosis in pregnancy. UpToDate 2007
3. World Health Organization (WHO). Tuberculosis Fact Sheet Number 104 – Global and Regional Incidence. March 2006, Retrieved on 6 October 2006.
4. Snider DE. Pregnancy and Tuberculosis. Chest 1984;86:10–13.
5. Schwabe KH, Dobstadt HP. Lungentuberkulose und Schwangerschaft. Beitr Klin Tuberk 1966;134:75–96.

6. De March AP. Tuberculosis and Pregnancy. Five-to-ten-year review of 215 patients in their fertile age. Chest 1975;68:800–804.
7. Tuberculosis among pregnant women – New York City, 1995-1992. MMWR 1993;42:605.
8. Llewelyn M, Cropley I, Wilkenson RJ, Davidson RN. Tuberculosis diagnosed during pregnancy: A prospective study from London. Thorax 2000; 55(2):129–132.
9. Prevention and control of tuberculosis in U.S. communities with at-risk minority populations and prevention and control of tuberculosis among homeless persons. MMWR 1992;41 (No RR-5).
10. Tuberculosis among foreign-born persons entering the United States: Recommendations of the Advisory Committee for Elimination of Tuberculosis. MMWR 1990;39 (No RR-18):1.
11. http://www.cdc.gov/nchstp/tb/pubs/Mantoux/part1.htm.
12. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG Vaccine in the Prevention of Tuberculosis. JAMA1994;271:698–702.
13. Guidelines for the Investigation of Contact of Persons with Infectious Tuberculosis: Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR 2005;54 (No RR-15).
14. National Commission on Radiation Protection Report 54. Medical Radiation Exposure of pregnant and Potentially Pregnant Women. Washington, DC: National Commission on Radiation Protection; 1997.
15. Valentin J. Biological effects after prenatal irradiation-embryo and fetus. International Commission on Radiological Protection Publication 90. Ann ICRP 2003;33:1–206
16. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Official Statement of the American Thoracic Society and CDC. Am J Respir Crit Care Med 2000;161:1376–1395.
17. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. This Official Statement of the American Thoracic Society was Adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This Statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this Statement as it relates to infants and children were endorsed by the American Academy of Pediatrics (AAP), August 1999. Am J Respir Crit Care Med 2000;161:S221.
18. Centers for Disease Control and Prevention (CDC). Treatment of Tuberculosis. MMWR 2003;52 (No. RR-11).
19. Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494.
20. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. Obstet Gynecol Clin North Am 1997;24:659.
21. Centers for Disease Control and Prevention (CDC). Guide for primary health care providers: Targeted tuberculin testing and treatment of latent TB infection (2005). Publication 99-8212. http://www.cdc.gov/tb/pubs/LTBI/pdf/TargetedLTBI05.pdf.
22. Isoniazid: Drug Information. Lexi-Comp.
23. Rifampin: Drug Information. Lexi-Comp.
24. Ethambutol: Drug Information. Lexi-Comp.
25. Pyrazinamide: Drug Information. Lexi-Comp.
26. Streptomycin: Drug Information. Lexi-Comp.
27. Reprorisk System {Internet database}. Greenwood Village, Colo: Thomson Healthcare. Updated periodically.
28. The WHO Working Group, Bennet PN (Ed). Drugs and Human Lactation. Elsevier, Amsterdam, New York, Oxford, 1988. pp.275–6.
29. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 2001;108:776–89.
30. Pyridoxine: Drug Information. Lexi-Comp.

31. Dexamethasone: Drug Information. Lexi-Comp.
32. Adhikari M, Pillay T, Pillay DG. Tuberculosis in the newborn: An emerging disease. Pediatr Infect Dis J 1997;16:1108.
33. Centers for Disease Control and Prevention (CDC). Congenital pulmonary tuberculosis associated with maternal cerebral tuberculosis-Florida 2002. MMWR 2005;54:249–50
34. Hageman J, Shulman S, Schreiber M, Luck S, Yogev R. Congenital tuberculosis: critical reappraisal of clinical findings and diagnostic procedures. Pediatrics 1980;66:980–4.
35. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. N Engl J Med 1999;341:645.
36. Hale TW. In: Medications and Mother's Milk, 10th Edition. Pharmasoft Publishing, Cycloserine, 2002;190–191.

13

Pneumonia in the Pregnant Patient

Samar Khan and Michael S. Niederman

Keywords: Pneumonia, pathogenesis, viral pneumonia, fungal pneumonia, HIV, aspiration

Community acquired pneumonia is a common illness, and pneumonia and influenza serve as the seventh leading cause of death in the United States. In the pregnant patient, pneumonia is the most common cause of fatal non-obstetric infection *(1–3)*. Pneumonia can have adverse consequences for both the mother and her fetus, with certain infections (particularly viral and fungal) assuming greater virulence and mortality than in non-pregnant women of similar age *(2, 3)*. Pneumonia is a relatively common cause of respiratory failure in pregnant patients, but in contrast to older studies, newer data suggest that not all pneumonias are more common or more serious in pregnant women than in other populations. However, because pneumonia can impact both the mother and fetus, it may lead to an increased likelihood of complicated preterm delivery, compared to pregnancies in which infection is absent.

The pathogens responsible for community-acquired pneumonia (CAP) are similar in pregnant and non-pregnant patients, with *Streptococcus pneumoniae*, *Hemophilus influenzae, Mycoplasma pneumoniae, Legionella* spp., *Chlamydophila pneumoniae*, and influenza A accounting for the majority of cases *(2–4)*. However, reduction in cell-mediated immunity associated with pregnancy (especially during the third trimester) places women at an increased risk of more severe forms of pneumonia and disseminated diseases from pathogens normally contained by this type of immune response, including herpes virus, influenza, varicella, and coccidioidomycosis *(3, 5–7)*.

In this review, we discuss the epidemiology, risk factors, maternal and fetal impact of pneumonia, microbiology, clinical features, and management of pneumonia in pregnancy. Tuberculosis in pregnancy was discussed in Chapter 12.

Epidemiology

The incidence of pneumonia has varied widely in a number of published surveys, largely reflecting the types of populations that were evaluated and the era of the study. A very high incidence was reported in the series by Finland *(8)* and Hopwood *(9)* in the years before 1965 ranging from 6.3 per 1,000 deliveries to

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_13

8.5 per 1,000 deliveries *(8, 9)*. Benedetti et al. examined 89,219 deliveries in a university and county hospital setting from 1972 to 1975 *(10)* and documented a lower incidence of pneumonia (0.4 per 1,000), with only 1 in every 2,288 deliveries being affected. Madinger et al. studied 32,179 deliveries at a community hospital from 1983 to 1988 and found pneumonia to complicate 1 out of every 1,287 deliveries (0.78 per 1,000) *(11)*. Berkowitz and LaSalsa examined 1,120 case records at a large city hospital from 1988 to 1989 and found that antepartum pneumonia occurred in 1 of every 367 deliveries *(12)*. This pattern of an apparent decrease, followed by an increasing incidence of pneumonia complicating pregnancy in recent years may reflect the fact that women with chronic illnesses are now able to become pregnant, and there is also a rising prevalence of immune deficiencies (such as HIV infection) and illicit drug use in pregnant women. However, Munn and colleagues *(13)* estimated the prevalence of antepartum pneumonia to potentially be much lower, ranging from 0.78 to 2.7 per 1,000 deliveries.

Two recent Canadian studies have compared the rates of CAP in pregnant and non-pregnant women. In the first, Jin et al. found the rate to be similar to the non-pregnant population, with reported rates of hospitalization for pneumonia of 1.51 per 1,000 deliveries versus 1.47 per 1,000 in non-pregnant controls *(14)*. In a similar study, comparing the incidence of CAP in pregnant women and non-pregnant age-matched controls presenting to a hospital, the incidence was 1.1 per 1,000 and 1.3 per 1,000, respectively *(15)*. Thus, compared to earlier studies, the incidence of pneumonia in pregnancy has declined, but the rates may be higher in large urban hospitals than in community settings, reflecting the different populations at risk. In addition, the available data generally come from those who are seen in a hospital, and may not reflect milder forms of illness seen in a physician's office.

There are very few formally collected data sets about nosocomial pneumonia in the pregnant or post-partum patient, but one form of pneumonia that falls into this category is aspiration pneumonia complicating labor and delivery. In fact, Mendelson's original description of gastric acid aspiration was made in obstetric patients undergoing labor and delivery *(16, 17)*. In the 1960s, as many as 2% of all maternal deaths were due to aspiration *(17)*. The pregnant woman is physiologically predisposed to aspiration because of elevation of the intragastric pressure due to the gravid uterus, a relaxed gastroesphageal sphincter due to the circulating progesterone, and delayed gastric emptying that accompanies pregnancy. These factors, coupled with sedation and analgesia that may be given during labor, increased abdominal pressure and vigorous abdominal palpation during examinations and extraction of the baby, all increase the threat of aspiration. The incidence of this complication has declined over time, with an increased awareness of the problem and with efforts directed towards prevention. In Mendelson's original series, the incidence was 1 in 667 deliveries, but in the 1970s, the rate was as low as 1 in 6,000 vaginal deliveries, but still 1 in 430 Caesarean sections. More recent studies of Caesarean section patients report a rate of 1 in 1,431 to 1 in 1,547 *(17)*. Mortality from this complication has been very low in recent years, with one death in 9,200 pregnancies *(17)*.

Risk Factors

The onset of pneumonia can be any time during gestation, with the mean gestational age at admission for pneumonia ranging from 24 to 31 weeks in the study by Yost et al. *(18)*. The same study also found that there was no significant difference

in maternal age or parity between the women who have pneumonia during pregnancy and those who do not *(18)*. In a case-control study of 59 women with pneumonia and 118 controls, using multivariate analysis, both anemia (measured as hematocrit of 30% or less) and a history of asthma were found to be independently associated with a fivefold increased risk for the development of pneumonia *(13)*. The study also reported the use of a tocolytic agent to delay labor as a risk factor for development of pneumonia. In another case-control study of 37 pneumonia patients and 74 controls, the use of antepartum corticosteroids was associated with a higher rate of infections (64.5% versus 17.5%) including four pneumonias in previously healthy women *(19)*. In one series of 71 women with CAP, 31 had underlying chronic diseases, although their presence did not lead to an adverse outcome *(20)*. In other series, women with CAP have had a high frequency of cigarette smoking and drug abuse.

A recent prospective study by Shariatzadeh et al. *(15)* compared 28 patients with pneumonia during pregnancy to 333 non-pregnant females in the same age group with pneumonia. Asthma requiring treatment was present in 46.5% of the pregnant pneumonia patients compared with 17.1% of the non-pregnant group, recognizing a large difference in sample size in the two groups. While other studies have found an association between asthma and pneumonia in pregnancy, none demonstrated an incidence as high as reported here. The accumulation of airway secretions and the presence of airway obstruction may account for the association of asthma with pneumonia, possibly accentuated by the reduction in functional residual capacity that occurs during pregnancy.

One other maternal problem associated with pneumonia is placental abruption *(21)*. Using a database of singleton births, the incidence of abruption was 0.96%, but was 2.05% (Odds ratio 2.2) in women with viral and bacterial pneumonia. The study commented only on the association but did not make clear a causative effect in either direction. It is possible that the association may be related to common risk factors (e.g., smoking, cocaine use) between pneumonia and abruption.

Pathogenesis of Pneumonia and its Complications in Pregnancy

Pneumonia can complicate pregnancy, in part because of altered host defenses in the parturient woman, and pneumonia can lead to potential adverse consequences for both the mother and the fetus adding morbidity and mortality when compared to the non-pregnant host. Particular types of pneumonia bear special significance for the pregnant woman, especially those of viral and fungal origin. In addition, pneumonia in the pregnant patient leads to an increased likelihood of complicated preterm delivery compared to pregnancies in which infection is absent.

Impact of Pregnancy on Pneumonia Risk (Table 13.1). Alterations in cellular immunity have been widely reported during pregnancy, especially in the second and third trimester, generally thought to protect the fetus from "rejection" by the mother. These include a decreased lymphocyte proliferative response, decreased natural killer cell activity, changes in T cell populations with a decrease in circulating helper T cells, reduced lymphocyte cytotoxic activity, and production of substances by the trophoblast that block maternal recognition of fetal major histocompatibility antigens *(2, 22)*. In addition, hormonal changes during pregnancy including elevation of progesterone, human chorionic gonadotropin, alpha fetoprotein, and cortisol may also inhibit cell mediated immune function *(22)*. These changes can predispose to infection with certain pathogens such as viruses, fungi, and tuberculosis.

Table 13.1 Alterations in pregnancy predisposing to an increased incidence and mortality from pneumonia.

Immunologic changes
Reduced lymphocyte proliferative response
Diminished cell-mediated cytotoxicity
Reduced number of helper T cells
Reduced lymphokine response to alloantigens
Physiologic changes
Increase in oxygen consumption
Increase in lung water
Elevation of diaphragm
Aspiration more likely in labor and delivery
Coexisting illnesses
Smoking
Anemia
Asthma
Cystic fibrosis
Illicit drug use
HIV infection
Immunosuppressive illness and therapy
Placental abruption
Labor and delivery
Increases risk for aspiration pneumonia

Catanzaro et al. *(23)* have shown that the hormonal changes lead to an increase in 17-estradiols, which can enhance the in vitro growth of *Coccidiodes immitis (17)*.

In addition to these changes, some of the physiologic changes of pregnancy can make the pregnant woman more prone to a severe pneumonia course. These include elevation of the diaphragm by up to 4 cm, decrease in functional residual capacity, an increase in oxygen consumption, and an increase in lung water *(2, 24)*. These alterations decrease the ability of the pregnant woman to clear respiratory secretions and aggravate airway obstruction associated with pulmonary infections. The elevation of the diaphragm and the associated decrease in functional residual capacity, coupled with the increase in oxygen consumption during pregnancy, make the pregnant woman less able to tolerate even brief periods of hypoxia, particularly in the third trimester.

Consequences of pneumonia on maternal outcomes. Pneumonia in pregnancy carries an increased risk of adverse outcomes when compared to pneumonia in non-pregnant women *(2, 3, 10–12, 24)*. In older data from the US Department of Health and Human Services *(1)*, 2,475 maternal deaths were examined from the years 1974–1978 and approximately 1% of these (24 deaths) were a result of pneumonia, which served as the most common non-obstetric infectious cause of mortality. Mortality data from the state of Massachusetts show that infection-related deaths in pregnancy have declined from 8.8 per 100,000 live births in the years of 1954–1957, to 0.6 per 100,000 births in 1982–1985 *(25)*. Although pneumonia is an uncommon cause of death among all pregnant women, the mortality rate can still be quite high among those who do develop pneumonia in pregnancy. In the preantibiotic era, the maternal death rate was observed to be as high as 32% of all such cases *(10)*, but in more recent series, the mortality attributable to pneumonia in pregnancy declined to 8.6% in one study *(9)*, while in another there was no maternal mortality *(10)*. Yost et al. found no deaths in 133 episodes, Jin observed no mortality in 333 pneumonia episodes in

pregnancy, and Shariatzadeh et al. observed no maternal deaths in 28 pneumonia episodes *(14, 15, 18)*. On the other hand, Richey and colleagues found 5 out of 71 pregnant women to have adverse outcomes including two maternal deaths, one early abortion, one preterm labor, and one fetal death *(20)*. These women tended to have more severe illness, with a lower initial mean oxygen tension, more diffuse radiographic pneumonia, and were more likely to be current smokers. In other more recent series, complications were also common, but mortality was not high, even when women with comorbid illnesses were evaluated. In one series, of the 25 patients studied, 40% suffered multiple complications including five requiring intubation, two developing empyema, one with pneumothorax, one with pericardial tamponade, and one with atrial fibrillation *(11)*, yet there was only one maternal death, occurring in a patient with cystic fibrosis.

While many series show low mortality rates overall from pneumonia in pregnancy *(12)*, viral lung infection and opportunistic lung infection still carry a substantial maternal mortality and morbidity *(3, 26–29)*. In one population study of eight influenza seasons, there were 297 respiratory disease hospitalizations, and seven women required ICU care, five during the third trimester. Ninety-two of these hospitalizations were for influenza or pneumonia and these women tended to have more cesarean deliveries than others, but mortality did not occur *(30)*.

Consequences of pneumonia on fetal outcomes. Although pneumonia can occur at any time during gestation, Hopwood's study found the mean time was 32 weeks *(9)*, but 17 of 23 patients developed pneumonia between weeks 25 and 36 of gestation and seven delivered during the course of their acute illness, with two mortalities among this group *(9)*. In the study by Benedetti et al., of 39 cases of pneumonia in pregnancy, 16 presented before 24 weeks gestation, 15 from weeks 25 and 36 of gestation and eight later than 37 weeks gestation *(10)*.

Significant fetal complications have been observed in all of the large studies of pneumonia in pregnancy. The majority of poor fetal outcomes occurred in mothers with underlying comorbid illnesses such as chronic respiratory disease, or other maternal disease *(11)*. A number of studies have shown that women with pneumonia in pregnancy are more likely to deliver prematurely and have babies that are small for gestational age (SGA). Berkowitz et al. noted a 12% rate of SGA babies and women had infants who weighed 400 g less than randomly selected patients without pneumonia *(12)*. In this series of 25 patients, most pneumonias were in the second and third trimesters, full-term delivery occurred in 14, one had preterm delivery, three underwent voluntary termination of pregnancy, three had term SGA babies, and four were lost to follow-up. Munn et al. found that pneumonia patients delivered babies at a significantly earlier gestational age than women without pneumonia, were more likely to deliver before 34 weeks, and their infants weighed significantly less *(13)*. Yost and colleagues reported that the women with pneumonia had babies that were 150 g smaller than seen in the overall population, and the frequency of low birth-weight infants was 16% in the pneumonia population versus 8% in the general population. In addition, they observed a trend to more preterm labor in the women with pneumonia *(18)*. In another recent series, women hospitalized with CAP had a relative risk of SGA babies of 1.86 *(14)*.

Fetal death has been reported as a complication of CAP in earlier series, but seems less common in more recent studies *(15, 18, 20)*. In one series, no maternal or fetal deaths were noted, however, an abortion at 10 weeks gestation and two preterm deliveries were observed in the pneumonia group *(15)*. Benedetti et al. reported a 2.6% rate for intrauterine fetal death and Madinger et al. noted a 12%

neonatal death rate *(10, 11)*. On the other hand, no excess fetal death was observed in recent series, including the comparison study by Yost and colleagues and in the study by Jin et al. *(14, 15, 18)*. One study found an association between drug and alcohol abuse with preterm delivery, but not with low birth-weight *(14)*. Thus, although most pregnant patients with pneumonia do well, it is important to identify patients with additional risk factors for poor perinatal outcome such as comorbid illness, smoking, and drug and alcohol abuse to intensify monitoring in an effort to avoid fetal complications.

While no congenital syndrome has been attributed to antepartum pneumonia, fever, tachypnea, and hypoxemia may be harmful to the developing fetus. Preterm labor as a complication of infection may be the result of the uterine response to certain mediators of infection and inflammation *(11, 13)*. McGregor has hypothesized that certain bacteria induce the production of phospholipases, proteases, and prostaglandins that can induce labor, although these speculations evolved with cervicovaginal infection in mind *(31)*. Lung infection is known to induce a similar compartmentalized inflammatory response, which has now been well documented in the non-pregnant patient with pneumonia *(32)*. It is quite possible that the cascade of mediators released by the active host inflammatory response to infection could exert distant effects on the uterus, leading to a high rate of labor during the course of pneumonia

Bacteriology

Any infectious agent that causes lung infection in the non-pregnant patient has been observed to complicate the course of pregnancy. The relative incidence of infection with any given agent is difficult to estimate without the use of comprehensive methodology to diagnose the etiologic pathogen for pneumonia. The available data are derived mainly from observational, and often retrospective, studies where only routine microbiological investigations have been used. Sputum and blood cultures were the main methods of diagnosis (Table 13.2) *(2)*. Hopwood *(9)* identified a responsible pathogen in only 9 of 23 cases, with a mixture of gram-positive bacteria,

Table 13.2 Bacteriology of Pneumonia in Pregnancy (in decreasing order of frequency).

Streptococcus pneumoniae (including DRSP)
Hemophilus Influenzae
No pathogens identified
"Atypical" pneumonia agents:
Legionella species (more common in severe pneumonia)
Mycoplasma pneumoniae
Chlamydophila pneumoniae
Viral agents
Influenza A
Varicella
Pseudomonas aeruginosa (with bronchiectasis, cystic fibrosis)
Aspiration
Fungi
Coccidioidomycosis
Pneumocystis jiroveci (with HIV infection)

gram-negative bacteria, and Influenza A virus being implicated. Benedetti et al. *(10)* found a bacterial pathogen in 21 of 39 patients, with pneumococcus serving as the predominant pathogen, accounting for 13 cases, and *Hemophilus influenzae* being the second most common organism isolated. Madinger et al. *(11)* also found *Streptococcus pneumoniae* (pneumococcus) to be the most common, followed by *Hemophilus influenzae* as the second most common pathogen isolated. In these studies, serologic testing was rarely performed to search for atypical pathogens such as *Mycoplasma* or *Chlamydophila*. Berdowitz's series *(12)* also found pneumococcus and *Hemophilus influenzae* as the most common pathogens.

The methodologic limitations in these studies are multiple, primarily due to incomplete and non-prospective diagnostic testing, and the absence of routine testing for atypical pathogens, which are ordinarily common in women of childbearing age. Even the recent pneumonia series are subject to the same problems, with very little etiologic data presented, and no routine diagnostic testing, with most patients doing well with empiric therapy that assumes the same bacteriology of CAP as in non-pregnant patients. Numerous case reports and selected limited series have shown a role for other etiologic agents including mumps, infectious mononucleosis, swine influenza, influenza A, *Legionella, Varicella, Chlamydophila pneumoniae*, *Coccidioidomycosis*, and other fungal pneumonias *(3*, *23*, *28*, *33–41)*. Whether infection with any of these agents is more common in pregnancy than in the non-pregnant state is unknown, but certain pathogens, such as influenza and varicella may represent a greater hazard to the pregnant woman because of her physiologic defects in cell-mediated immunity.

The overall incidence of varicella in pregnancy has been reported as 1–5 per 10,000 births and both fetal and maternal complications present several management problems for clinicians. Varicella pneumonia usually complicates primary infection in 0.3–1.8% of all cases, but as many as 9% of primary cases during pregnancy can be complicated by pneumonia *(27)*. Influenza A is a common infection in pregnant women during epidemics and carries a higher mortality than in the non-pregnant patient *(37)*, with the maternal mortality rates being as high as 30–50% in the 1918 epidemic *(2*, *3*, *42)*. In the Asian flu epidemic of 1957–1958, 10% of all deaths occurred in pregnant women and almost 50% of women of childbearing age who died were pregnant *(37*, *41)*. This increased mortality was especially noted in the third trimester.

Another viral infection documented in pregnancy was Severe Acute Respiratory Syndrome (SARS) infection, which is due to a coronavirus. One case series *(43)* described 12 patients with SARS during pregnancy, with seven in the first trimester and five in the second and third trimesters. Overall mortality was 25%, with half being admitted to the ICU and one-third requiring mechanical ventilation. Fetal complications were common with four of the seven first trimester infections leading to spontaneous abortion and most of the others leading to preterm labor and babies that were small for gestational age.

Several other new microbiologic concerns have now emerged for patients with CAP. Up to 40% of *S. pneumoniae* may be antibiotic resistant (DRSP), although it has been difficult to document an impact of relatively low level in vitro resistance on outcomes when usual therapies are used *(44)*. It is important to note that if any antibiotic has been used in the three months preceding CAP due to pneumococcus, the organism is more likely to be resistant to an agent that was recently used *(45)*. In addition to recent antibiotic therapy, another risk for DRSP is exposure to a child in daycare, a potentially common risk for women who are pregnant, so that this organism should be considered in all pregnant women *(44)*. Community-

acquired strains of methicillin-resistant *S. aureus* (CA-MRSA) are not being reported commonly, but may cause serious forms of CAP following influenza infection *(46)*. The organism can lead to a severe, bilateral necrotizing infection due to the production of a variety of toxins, including the Panton-Valentine Leukocidin (PVL). While this organism most commonly leads to skin and soft tissue infection, there is one case report of a severe necrotizing pneumonia due to CA-MRSA which seeded the lung, 9 days post-partum, from septic pelvic thrombophlebitis as a consequence of an infected episiotomy site *(47)*.

Aspiration is a form of pneumonia that can be a post-partum or an obstetrical complication, causing either a chemical pneumonitis, or a bacterial infection involving the pathogens found in the oropharynx and gastric contents, primarily anaerobes and gram-negative enteric organisms.

Clinical Features and Management of Specific Respiratory Infections

Bacterial Pneumonia

Clinical Features. Overall, the clinical presentation of pneumonia during pregnancy has not been found to differ substantially from the findings in non-pregnant adults, and include fever, cough, pleuritic chest pain, rigors, chills, and dyspnea *(8, 15)*. A report by Ramsey et al. *(48)* showed that during pregnancy 59.3% of patients with pneumonia reported a productive cough, 32.2% shortness of breath, and 27.1% pleuritic chest pain. Hopwood *(9)* reported that among 23 patients with pneumonia in pregnancy, all had preceding upper respiratory infection and 20 had cough. Fever above 101°F was present in 18 patients; only three reported dyspnea and five had chills.

Munn et al. demonstrated that 98% of patients with antepartum pneumonia had positive chest radiographs, either at admission or on repeat examination, with findings including infiltrates, atelectasis, pleural effusion, pneumonitis, or pulmonary edema *(13)*. Benedetti et al. *(10)* examined the radiographic features of pneumonia in pregnancy and found that 28 out of 39 patients had an infiltrate confined to a single lobe, while the remainder had multilobar pneumonia, and only one had a pleural effusion.

Most women with pneumonia do not have multilobar illness, but when present it correlates with a greater risk for a complicated course of illness *(18)*. There are many different methods used to define severity of illness in patients with CAP, but the Pneumonia Severity Index (PSI) is most widely used in the United States to help define the need for inpatient care and the need for ICU care *(49)*. The PSI uses an assessment of patient age, comorbidity, and laboratory and clinical data to define a patient's risk of death, with scores leading to categorization into one of five groups, each with increasing mortality risk. In its original derivation, pregnant patients were omitted, but Shariatzadeh and Marrie have observed that all pregnant patients that they evaluated fell into the low risk classes I and II, similar to age-matched controls *(15)*. However, twice as many pregnant patients were hospitalized as age-matched controls with similar PSI scores, yet they had a shorter length of stay. Thus, the PSI may either underestimate the need for inpatient care in pregnancy, or else physicians were being more cautious with admitting pregnant women, even if there was a relatively low mortality risk from pneumonia. The limits of the PSI were suggested in the study by Yost et al., with the finding that the use of the PSI would have recommended that two thirds of admitted pregnant CAP patients could have been sent home, but if this had been done, 10/79 would

likely have required later readmission because of a complicated course *(18)*. The limitations of scoring systems such as the pneumonia severity index and the APACHE score in pregnancy include the fact that some of the physiologic changes occurring in pregnancy may alter the scoring system. For instance, physiologic anemia with hematocrit as low as 30 are normally seen in pregnancy. The white cell count may be physiologically elevated in pregnancy as well and numbers as high as 14,000–15,000 may be seen. Other changes include a lower creatinine in pregnancy with a normal range being 0.5–0.7. Therefore, while a creatinine of 1.0 may be normal in the non-pregnant population, it is clearly an abnormal value in pregnancy and may contribute to inaccurate scoring.

Certain presenting signs suggest the need for ICU admission in the CAP patient and these criteria should probably be liberalized for the pregnant patient, because of a reduced physiologic reserve to tolerate hypoxemia. In addition, if certain infections are present, such as varicella-zoster, the potential for rapid progression in pregnancy is high enough that expectant ICU observation may be justified. Criteria for severe CAP, used in the new ATS/IDSA guidelines, but not specific to pregnant women, include the presence of at least one major criterion such as the need for mechanical ventilation or septic shock requiring vasopressors, or the presence of three minor criteria *(44)*. The minor criteria include the following: respiratory rate of at least 30 breaths /minute, PaO2/FiO2 ratio $\leq$ 250 mmHg, multilobar infiltrates, confusion or disorientation, BUN $\geq$ 20 mg/dL, WBC $<$ 4,000/ mm^3, platelet count $<$ 100,000/ mm^3, hypotension requiring aggressive fluid resuscitation, and hypothermia. The guidelines also suggested that criteria such as hypoglycemia, hyponatremia, asplenia (as in sickle cell disease), and unexplained acidosis be considered in deciding the need for ICU admission *(44)*.

Diagnostic Testing. When complications of pneumonia develop in the pregnant patient, they may be a consequence of a delay in recognition, leading Hopwood et al. to recommend that all women with persistent upper respiratory distress have a chest radiograph *(9)*. Madinger and colleagues reported that although all 25 patients who had pneumonia did have signs and symptoms of lung infection, the diagnosis was initially overlooked in five patients *(11)*. This may explain why respiratory failure, empyema, and other serious complications, adding to morbidity, complicated half of those diagnosed with pneumonia.

According to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines for the management of adults with CAP, all patients with suspected CAP should have a chest radiograph *(44)*. All admitted patients should also have an assessment of gas exchange (oximetry or arterial blood gas), routine blood chemistry, and blood counts. Blood cultures can give false positive results and are only recommended in patients with severe illness, especially if there has been no prior therapy with antibiotics. Two sets of blood cultures are recommended. Sputum culture and gram stain should be obtained if a drug-resistant pathogen, or an organism not covered by usual empiric antibiotic therapy is suspected. Routine serologic testing is not recommended for any population with CAP. However, for patients with severe CAP, Legionella urinary antigen and pneumococcal urinary antigen should be measured and aggressive efforts at establishing an etiologic diagnosis should be made, including consideration of bronchoscopy.

Therapy. Based on the expected organisms in pregnant women with CAP, therapy should be directed at *Streptococcus pneumoniae* (including DRSP in patients with recent antibiotic therapy, underlying chronic heart or lung disease, and those with exposure to a child in daycare), *H. influenzae* (especially in cigarette smokers), and the "atypical" pathogens such as *Chlamydophila pneumoniae, Mycoplasma pneumoniae*,

and *Legionella pneumophila* (the latter in the setting of severe CAP). In choosing an antibiotic for bacterial pneumonia, the safety of the agent in pregnancy must be considered, along with its efficacy. Pencillins, cephalosporins, and erythromycin are all safe and potentially effective antimicrobials for CAP *(50)*. Clindamycin is probably also safe, but there is limited clinical experience with this agent *(51)*. The fluoroquinolones are commonly used to treat CAP in non-pregnant patients, but should not be used during pregnancy. They pose a theoretic risk of arthropathy, malformations, and can be both mutagens and carcinogens, although sporadic reports of safe use in pregnancy have appeared, suggesting that they can be used if absolutely necessary *(52)*. Other drugs to be avoided in pregnancy include tetracyclines (the mother is at risk for fulminant hepatitis and these agents can stain and deform fetal teeth and cause bony deformities), chloramphenicol (can cause bone marrow suppression in fetus, and if given near term can cause "gray baby syndrome" with gray facies, flaccidity, and cardiovascular collapse), and sulfa compounds (can cause fetal kernicterus) *(53)*. Aminoglycosides should be used only if there is a strong clinical indication of serious gram-negative infection, as there is potential risk of ototoxicity to the fetus. Vancomycin poses a risk to the fetus of fetal nephrotoxicity and ototoxicity and similarly should only be used if absolutely necessary. Linezolid is categorized as pregnancy Category C, and there is limited experience in pregnancy, but it is a protein synthesis inhibitor, so it should also be avoided unless no other alternative therapy is available.

Current guidelines for CAP recommend that all patients be treated for pneumococcus and atypical pathogens, which can often be present as co-pathogens *(44)*. Thus, no patient should receive empiric therapy with a beta-lactam (penicillin or cephalosporin) alone (Table 13.3). For an outpatient with mild CAP, and no risks for DRSP, therapy should be with an oral macrolide such as azithromycin,

Table 13.3 Recommended empiric therapy of community-acquired pneumonia in pregnancy.

Outpatients
No comorbid illness, no recent antibiotics, no DRSP risks (including exposure to a child in daycare)
Azithromycin (or erythromycin)
Co-existing cardiopulmonary disease, recent antibiotic therapy, or DRSP risk factors
Beta-lactam (high dose amoxicillin, cefuroxime, or cefpodoxime) plus azithromycin (or erythromycin)
Inpatient, not in ICU
No comorbid illness or DRSP risks
Intravenous azithromycin or erythromycin
Co-existing cardiopulmonary disease or DRSP risk factors
Intravenous beta-lactam (cefotaxime, ceftriaxone) PLUS intravenous azithromycin (or erythromycin)
Inpatient in ICU
No Pseudomonal risks
Intravenous beta – lactam (cefotaxime, ceftriaxone) PLUS intravenous azithromcyin (or erthromycin)
Pseudomonal risks present
Intravenous anti-Pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) PLUS an aminoglycoside (amikacin, gentamycin, tobramycin) PLUS intravenous azithromycin (or erythromycin)

Clarithromycin is not recommended for use in pregnancy. Fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin) are not recommended in pregnancy, but anecdotal experience suggests possible safety if alternative therapy is not available.

which is better tolerated than erythromycin. Clarithromycin is not recommended for use in pregnancy because of adverse embryonic and fetal outcomes in animal studies. If an outpatient with mild illness is at risk for DRSP, then therapy should be given with a macrolide combined with either high dose amoxicillin (3 g per day), cefpodoxime, or cefuroxime (500 mg twice daily).

If the patient is admitted to a hospital, therapy should be initially given intravenously, with azithromycin or erythromycin if the patient has no risks for DRSP. Yost and colleagues studied 119 women with CAP who were hospitalized and 83% of them received erythromycin monotherapy, with only one having a poor clinical response, but with five requiring discontinuation because of intestinal symptoms *(18)*. Azithromycin may be better tolerated as an intravenous macrolide than erythromycin. Although tetracyclines are not recommended in pregnancy, one case report discussed that they may be necessary in certain select patients, such as those with *Chlamydophila psittac*i pneumonia and a failure to respond to macrolide therapy *(36)*. If DRSP risks are present, therapy can be with ceftriaxone or cefotaxime, with the addition of an intravenous macrolide (azithromycin or erythromycin). Intravenous cefuroxime is not recommended because some studies have reported a worse outcome if this drug is used in patients with pneumococcal bacteremia and in vitro resistance is present, while the same findings have not occurred with the cephalosporins that are recommended.

In the ICU-admitted patient with severe CAP, no patient should get monotherapy, and combination therapy should be with cefotaxime or ceftriaxone plus a macrolide (azithromycin or erythromycin) if Pseudomonal risks are not present. Pseudomonal risks include bronchiectasis, prolonged corticosteroid therapy, and cystic fibrosis. If Pseudomonal risks are present, therapy should be with an anti-Pseudomonal beta-lactam (imipenem, meropenem, cefepime, or piperacillin-tazobactam), with an aminoglycoside (amikacin, gentamycin, tobramycin), and a macrolide. Imipenem is classified as pregnancy Category C, while piperacillin with tazobactam is pregnancy Category B. Community-acquired MRSA should be considered in patients with severe CAP after influenza, but as mentioned above, the safety of vancomycin and linezolid in pregnancy is not known.

Supportive therapy of the pregnant patient with pneumonia is no different than in the non-gravid state; hydration, antipyretic therapy, and supplemental oxygen remain the key therapies. The goal of oxygen therapy is to maintain the arterial oxygen tension well above 70 mmHg, as hypoxemia is less well tolerated in the pregnant female. Importantly, respiratory alkalosis leads to reduction in uterine blood flow and thus work of breathing should be decreased whenever possible in the pregnant pneumonia patient: adequate oxygenation is mandatory for that matter. Respiratory failure mandating mechanical ventilation has occurred in pregnancy and requires close monitoring of both the mother and the fetus. Preterm labor is a well described complication of pneumonia and may also need to be treated using tocolytics if the patient can tolerate them, although tocolytics have been reported to cause maternal pulmonary edema.

Viral Pneumonias

Influenza Virus

The influenza viruses are myxoviruses of three antigenically different types, A, B, C, that can cause disease in humans, but most epidemics in humans are due to type A. First identified in 1933, influenza remains a significant cause of morbidity and

mortality from febrile respiratory illness worldwide *(42, 54)*. Pregnant women are at increased risk for both acquiring influenza, and for developing complications of infection. In one study by Neuzil et al., pregnant women were affected more often than non-pregnant women *(42)*. Influenza also led to hospitalization for acute cardiopulmonary illness more often in women during the third trimester, in those with advanced age, and in those with underlying medical conditions such as asthma *(30, 42)*. Historically, influenza in pregnancy has been associated with higher rate of morbidity and mortality *(5)*. The course of influenza was first reported during the epidemic of 1918 when 1,350 cases in pregnant women who had an influenza-like illness were evaluated, and pneumonia was a complication in 585 (43%) of these cases. In 52% of these patients, pregnancy was interrupted, and there were 308 (23%) maternal deaths. The mortality was highest in the last three months of pregnancy, and increased if influenza was complicated by pneumonia *(54)*. Overall, in the 1918 epidemic, influenza during pregnancy had a 30% maternal mortality, increasing to 50% in the presence of pneumonia *(55)*. Mortality rose in tandem with the duration of pregnancy to a maximum of 61% when influenza was contracted in the ninth month of pregnancy. In the 1957 epidemic, 50% of women of childbearing age who died were pregnant and 10% of all the influenza deaths were among pregnant women *(37)*. However since 1958, pregnancy studies have shown a variable association with an enhanced morbidity and mortality from influenza *(55)*.

The clinical presentation of influenza does not appear to be altered by pregnancy. The incubation period is one to four days, and symptoms include cough, fever, malaise, coryza, headache, and myalgias *(56)*. In an uncomplicated case, influenza may resolve in 3 days or less. If symptoms persist for more than 5 days, especially in a pregnant patient, complications such as pneumonia should be suspected. Pneumonia, due to a viral or a secondary bacterial infection, is a well-recognized complication of influenza. Influenza pneumonia occurred in 12% of 102 pregnant patients with influenza in the 2003–2004 season, and led to complications such as respiratory failure, meningitis, and myocarditis *(3)*.

When pneumonia complicates influenza in pregnancy, antibiotics should be started and should be directed at the likely pathogens that can cause secondary infection including pneumococcus, *H. influenzae*, and *S. aureus*, including MRSA. Therapy for these organisms has been discussed above, but antiviral agents should be considered if a viral pneumonia is likely, especially early in the course of illness *(2)*. Anti-viral agents such as amantadine and rimantadine can prevent illness in exposed patients and reduce the duration of symptoms if given within 48 h of the onset of illness. Amantadine is effective against Influenza A and acts by blocking the release of viral nucleic acids and can be used for prophylaxis in high-risk pregnant women or for therapy in complicated cases *(3)*. It has been found to be non-embryotoxic in mice at 25 times the dose used in humans. When used in post partum women, Amantadine is excreted in breast milk and therefore should only be used in the highest risk patient. There is little experience in pregnancy with the newer neuraminidase inhibitors, zanamivir and oseltamivir, which can also be effective for treatment and prophylaxis, if started within 48 h of the onset of symptoms.

While anti-virals can be prophylactic after exposure, the primary method of influenza prevention is vaccination. The recommendation of the Advisory Committee on Immunization Practices is that all women who will be pregnant during influenza season receive the vaccine. Vaccination can also be performed safely in any trimester of pregnancy and so should be recommended to all pregnant women who have not yet been vaccinated *(57–58)*. The inactivated form of the

vaccine is used for pregnant women as well as other high-risk groups. Breast-feeding is not a contraindication to vaccination *(58)*.

Varicella Pneumonia

Varicella has a higher incidence and severity in pregnant than in non-pregnant patients, and so has the potential to complicate the course of pregnancy and lead to congenital defects. Pneumonia is the most serious complication of varicella, but when varicella pneumonia is present in the non-pregnant individual, it leads to a mortality of 11–17%, in contrast to a rate of 35–40% in pregnant patients *(3, 27)*. Haake et al. reviewed 34 cases of varicella pneumonia in pregnancy and found a 35% mortality *(27)*. Although only 5–10% of cases occur in adults, this population accounts for 25–55% of fatal cases *(3)*.

Varicella-Zoster (VZ) is a DNA virus that usually causes a benign, self-limited illness in children, but up to 10% of the adult population is susceptible to primary infection *(3)*. Studies show that the infection rate in pregnant women is as high as 4–6.8%, but after a close exposure, the risk of infection may be as high as 70% *(59)*. Pregnancy may also increase the rate of pneumonia as a complication of primary infection, and smoking may also be a risk factor, with infected smokers having a higher rate of pneumonia than infected non-smokers *(60)*. An increased intensity of skin eruption is also cited as a risk factor for developing subsequent pneumonia, especially if there are more than 100 skin lesions *(61)*.

Pregnancy also enhances the virulence of the VZ virus, as a consequence of functional T cell abnormalities, as well as higher levels of circulating corticosteroids, increased blood volume and altered respiratory reserve. Most reports have shown that when varicella pneumonia complicates pregnancy, it is usually in the third trimester and that infection occurring at this time is more severe and complicated than if it occurs earlier *(28, 62)*. The incidence of pulmonary involvement in primary varicella infection is approximately 16% *(3)*.

The incubation period of varicella is between 14–18 days *(3, 61, 63)* but can vary from 10 days to 3 weeks. In the mother the virus is in the blood for 24–48 h before the exanthem, and during this period 24% of fetuses develop transplacental infection *(64)*, which can lead to congenital malformations in 1.2% of the exposed fetuses. Clinically, varicella pneumonia presents 2–5 days after the onset of fever, vesicular rash (chickenpox), and malaise and is heralded by the onset of pulmonary symptoms *(2, 28)* including cough, dyspnea, pleuritic chest pain, and even hemoptysis. In one series all patients with VZ pneumonia had oral mucosal ulcerations *(28)*. Severity of illness may range from asymptomatic radiographic infiltrates to fulminant respiratory failure and acute lung injury *(27, 28)*. Typically chest radiographs reveal interstitial, diffuse miliary or nodular infiltrates that resolve by 14 days unless complicated by acute lung injury and respiratory failure *(65)*. The severity of infiltrates has been described to peak with the height of the skin eruption *(66)*. One late sequela of varicella pneumonia is diffuse pulmonary calcification *(62)*.

All patients with VZ pneumonia require aggressive therapy with antiviral agents (acyclovir) and early hospitalization. Mechanical ventilation may be needed in up to half of all pregnant women with varicella pneumonia, and this group has a mortality rate of at least 25%. Multiple investigators have used acyclovir, a DNA polymerase inhibitor in the pregnant patient, demonstrating its safety in pregnancy *(3, 27, 65, 66)* and its lack of teratogenicity *(67)*. In a study of 312 pregnancies in which acyclovir was used, no increase in the number or pattern of birth defects was seen *(67)*. Haake et al. reviewed the early initiation of therapy within 36 h of

admission, and found that those receiving early therapy had an improved hospital course after the fifth hospital day, lower mean temperature, less tachypnea, and improved oxygenation, compared to those who were not treated *(27)*. The recommended dose is 7.5 mg/kg every 8 h intravenously, although doses of 3–18 mg/kg have been used. Treatment is recommended for 7 days. Some small series have suggested a benefit from adjunctive corticosteroid therapy at modest doses *(3)*.

Fetal and Neonatal Effects

The effects of varicella on the fetus are of concern, and include intrauterine infection in 10–20% *(68)*. Traditionally fetal involvement has been in three areas: "varicella embryopathy" stemming from maternal disease developing before 20 weeks gestation; congenital varicella from 20 weeks gestation until term, but more commonly close to term; and neonatal disease occurring when the pregnant patient has active lesions at the time of delivery *(69)*. Varicella embryopathy was first described in 1947 by Laforet and Lynch and has since been redefined by a number of authors *(69–72)*, but includes limb hypoplasia, skin scarring, central nervous system involvement, and other skeletal lesions. This embryopathy has been reported with infection occurring as late as 26 weeks *(69)*.

The largest series of congenital varicella reported 1,373 pregnancies complicated by VZ from 1980–1993. Fetal abnormalities occurred most commonly in the children of women infected between 13 and 20 weeks of gestation than at any other time in pregnancy *(73)*. Fetal anomalies varied from skin lesions to lethal multi-organ system involvement. Because of concern about fetal effects, the use of prophylactic immune globulin is recommended within 96 h of exposure to prevent maternal illness, in women without prior varicella infection (negative IgG titers) or immunization. Importantly the use of VZ immune globulin in a pregnant woman may not eliminate the incidence of embryopathy, but if given before maternal infection develops, it may decrease or attenuate fetal disease *(73)*. Immunoprophylaxis with zoster immune globulin should be given early after close exposure of a seronegative pregnant woman, with the aim of preventing disease in the mother, but not in the fetus. Although expensive, one analysis suggested that the use of this approach is likely to be cost-effective *(34)*. The varicella vaccine, however, is contraindicated in pregnancy because it is a live-attenuated vaccine.

Other Viruses

Pneumonia may complicate up to 50% of adult measles cases, and bacterial super-infection is common. In one report of three cases of rubeola during pregnancy, all patients had bacterial super-infection and two had preterm labor *(38)*.

Severe acute respiratory syndrome is caused by a coronavirus, which can affect pregnant women, leading to symptoms that are the same as in non-pregnant women, and include fever, chills, rigors, malaise, and myalgias *(74)*. Patients are most infectious in the second week of illness. Laboratory findings are remarkable for marked lymphopenia and thrombocytopenia. Chest radiograph findings are patchy to generalized interstitial infiltrates *(74)*. The case fatality was 25% in 12 cases that were reported in pregnancy *(43)*, and other complications included first trimester spontaneous abortions, preterm births, and intrauterine growth restriction. Treatment includes broad-spectrum antibiotics to cover super-imposed bacterial infections, high dose corticosteroids, and possibly ribavirin, which has shown teratogenic effects in animals *(43)*.

Fungal Pneumonia

Fungal pathogens that have caused pneumonia include *Cryptococcus neoformans, Histoplasma capsulatum, Sporothrix Schenkii, Blastomyces dermititidis, and Coccidioides immitis (48)*. Fungal pneumonia in pregnancy is rare and when it does occur, it usually resolves without treatment in healthy women. In contrast, disseminated disease carries a more serious prognosis and can complicate pregnancy, particularly with infection in the third trimester *(22, 33)*.

Coccidioidomycosis generally occurs in the Southwestern United States and symptoms include fever, cough, headache, malaise, weight loss, and erythema nodosum. While most patients have pulmonary involvement (including an infiltrate, pleural effusion, miliary infiltrates, or cavitation), disseminated disease includes central nervous system involvement, skin, and bony lesions. Those with erythema nodosum have a lower rate of disseminated disease and a higher rate of recovery *(33)*.

Cantanzaro examined the published experience with Coccidioidomycosis in pregnancy and looked at both maternal and fetal complications as a function of when the infection was acquired *(23)*. In one 1951 series, among five patients who had infection before pregnancy, the disease remained stable and did not disseminate. There were 12 patients who acquired infection in the first trimester leading to one fatal disseminated disease with associated fetal loss. The other 11 had pulmonary infection only and recovered without dissemination, and 10 of the pregnancies were completed successfully. Among five women who were infected in the second trimester, one developed meningitis and one died of disseminated infection. The course was much different for the 11 women who acquired infection in the final trimester. Disseminated infection developed in seven, all of whom died. Other investigators also reported high rates of dissemination and maternal mortality, especially for infection acquired in the third trimester. Stevens *(75)* reported that 20% of patients with Coccidioidomycosis pneumonia in the third trimester of pregnancy developed disseminated disease, likely as a consequence of the alteration in maternal cell-mediated immunity during late pregnancy *(2)*.

For disseminated disease or severe pneumonia treatment with intravenous amphotericin B (pregnancy category B) is recommended followed by oral fluconazole post-partum *(33, 76, 78)*. Earlier series used ketoconazole and itraconazole, but fluconazole is preferred as a more effective, more bioavailable agent, with less potential for teratogenicity *(33)*. If possible, fluconazole should not be used in the first trimester when it may be teratogenic, and it may predispose to premature birth if used in the second trimester. Thus, amphotericin B is the preferred therapy in early pregnancy, with fluconazole in the third trimester, if needed.

Other fungal infections have been reported in pregnancy such as cryptococcosis, blastomyosis, and sporotrichosis. These are rare events and the impact of pregnancy on these infections or how these infections alter the outcome of pregnancy is not clear *(2)*.

Aspiration Pneumonia

As discussed earlier, pregnancy can increase the risk of aspiration, particularly in the peri-partum period *(16)*. Aspiration may involve bacteria from the oropharynx (enteric gram-negatives or anaerobes), solid particulate matter from the stomach, or liquid stomach contents including gastric acid. The aspiration of bacteria leads to a pneumonic infection that usually begins at least 24 h after the event. When

particulate matter is aspirated, it can lead to immediate bronchospasm, cough, and possibly cyanosis. Aspiration of gastric contents leads to symptoms that begin 6–8 h after the event, at which time the patient usually is symptomatic including tachypnea, bronchospasm, pulmonary edema, and hypotension *(16)*. The risk for pneumonitis is substantially increased if the aspirated fluid has a pH of less than 2.4 *(77)*.

The major thrust of management is prevention. Regional anesthesia is preferred over general anesthesia, and if the latter is used, the patient should have nothing by mouth for 24 h, if possible. Airway protection is paramount even with regional anesthesia and cricoid pressure and rapid sequence induction at the time endotracheal intubation can reduce the risk of aspiration *(17)*. Raising gastric acid pH pharmacologically may also help avoid some of the complications of aspiration, but there are no data to document a clear benefit nor a preference for antacids over histamine-type 2 blockers and proton pump inhibitors.

Prevention of Pneumonia

Several strategies are effective in preventing pneumonia in high-risk populations and can be applied to women of childbearing ages or during pregnancy *(3)*. Vaccinations are available for Influenza, pneumococcus, and varicella. The risk of influenza related respiratory illness in pregnancy is similar to high-risk non-pregnant populations. Therefore, the influenza vaccine is recommended for all women who will be pregnant during influenza season, regardless of gestational age *(57)*. Varicella vaccination is recommended for susceptible women considering pregnancy at 1–3 months before pregnancy or post-partum. Vaccination may reduce the risk of congenital varicella syndrome and decrease morbidity from adult complications of varicella. The varicella vaccine is not recommended for use during pregnancy because it is a live-attenuated vaccine *(78)*. The current pneumococcal vaccine contains the purified capsular polysaccharide from the 23 serotypes that cause 85–90% of the infections. The vaccine is effective in decreasing the prevalence of pneumococcal pneumonia and is recommended to women with underlying medical illnesses, including immunocompromised states, asplenia, sickle cell disease, diabetes, or chronic cardiopulmonary disease *(44)*. It may be given during pregnancy in women with the listed risk factors *(79)*. For women with children at home at the time of pregnancy, it may be useful to be sure that the children have received the new pneumococcal conjugate vaccine, since it can prevent disease in the children, which in turn may reduce the risk of maternal disease and of maternal infection with DRSP.

Pneumonia Complicating Human Immunodeficiency Virus (HIV) Infection

Although a thorough discussion of this topic is beyond the scope of this review, many women with HIV infection are of childbearing age, and pregnancy can interact in a potent fashion with HIV infection *(29)*. Pregnancy can theoretically accelerate the progression of underlying HIV infection-related immune suppression, and respiratory infection can be the AIDS defining illness for some pregnant patients, leading to an increased risk of both maternal and fetal mortality *(80)*. In addition, vertical transmission of HIV infection to the newborn is a serious concern. Antiretroviral therapy may improve CD4+ count, and reduce the risk of respiratory infection, so therapy should be continued during pregnancy.

Bacterial respiratory infections are the most common respiratory complication of HIV infection, but a low CD4+ count (<200 cells/μL) predisposes not only to bacterial pneumonia, but also to pneumonia with *Pneumocystis jeroveci* (PCP), which can be a serious infection risk for both mother and fetus. In one review of 22 patients with PCP in pregnancy, 59% had respiratory failure necessitating mechanical ventilation and mortality was 50% for the mothers, and there were five intrauterine deaths and four neonatal deaths *(81)*. Women with PCP infection should receive therapy with trimethoprim-sulfa (TMP-SMX), along with corticosteroids if hypoxemia is present. These patients should be monitored for preterm labor and at the time of delivery, any woman receiving TMP-SMX or dapsone should have their baby monitored closely for hyperbilirubinemia and kernicterus. For HIV infected women, without active PCP, prophylaxis is best done when the CD4+ cell count falls below 200 cells/μL, using TMP-SMX. Because of the potential teratogenic risk of TMP in the first trimester, consideration should be given to the use of aerosolized pentamidine because of its lack of systemic absorption.

Summary

Although pregnancy is infrequently complicated by pneumonia, lung infection in the antepartum period, by bacteria, viruses, and fungi can be associated with significant maternal and neonatal morbidity. Beyond the influence of pregnancy induced changes on cell immunity, there are certain physiological changes in pregnancy that both predispose to infection and also make it more difficult for the pregnant women to sustain any type of respiratory infectious insult. Thus pregnant patients require a higher level of surveillance and early intervention, and the prognostic scoring systems used in non-pregnant patients may not apply in pregnancy. Certain types of pneumonias, particularly influenza and aspiration, can be avoided if patients at risk are identified and existing strategies for prevention are applied. The safety of antimicrobial must also be considered when a pregnant patient is being treated for pneumonia.

References

1. Kaunitz AM, Hughes JM, Grimes DA, Smith JC, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–612.
2. Rodrigues J, Niederman MS. Pneumonia complicating Pregnancy. Clin Chest Med 1992;13:679–691.
3. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005;33:S390–S397.
4. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. Thorax 2001;56:398–405.
5. Laibl VR, Sheffield JS. Influenza and Pneumonia in pregnancy. Clin Perinatol 2005;32:727–738.
6. Esmonde TF, Herdman G, Anderson G. Chicken Pox Pneumonia: An association with pregnancy. Thorax 1989;44:812–815.
7. Wack EE, Ampel NM, Gagliani JN, et al. Coccidiomycosis during pregnancy. Chest 1988;94:376–379.
8. Finland M, Dublin TD. Pneumococcal pneumonias complicating the pregnancy and puerperium. JAMA 1939;250:1027–1032.
9. Hopwood HG. Pneumonia in Pregnancy. Obstet Gynecol 1965;25:875–9.

10. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol 1982;144:413–417.
11. Madinger NE, Greenspoon JS, Elrodt AG. Pneumonia during pregnancy: Has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161:657–662.
12. Berkowitz K, LaSala A. Risk factors associated with increasing prevalence of pneumonia during pregnancy. Am J Obstet Gynecol 1990;163:981–985.
13. Munn MB, Groome LJ, Atterbury JL, Baker SL, Hoff C. Pneumonia as a complication of pregnancy. J Matern Fetal Med 1999;8:151–154.
14. Jin Y, Carriere KC, Marrie TJ, Predy G, Johnson DH. The effects of community acquired pneumonia during pregnancy ending in a live birth. Am J Obst Gynecol 2003;18:800–806.
15. Shariatzadeh MR, Marrie TJ. Pneumonia during pregnancy. Am J of Med 2006;119:872–876.
16. Baggish MS, Hooper S. Aspiration as a cause of maternal death. Obstet Gynecol 1974;43:327–336.
17. Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. Br J Anaesth 1999;83:453–460.
18. Yost NP, Bloom SL, Richey SD, Ramin SM, Cunningham FG. An appraisal of treatment guidelines for antepartum community acquired pneumonia. Am J Obstet Gynecol 2000;183:131–135.
19. Rotmensch S, Vishne TH, Celentano C, Dan M, Ben-Rafael Z. Maternal infectious morbidity following multiple courses of betamethasone. J Infect 1999;39:49–54.
20. Richey SD, Roberts SW, Ramin KD, Ramin SM, Cunningham G. Pneumonia complicating pregnancy. Obstet Gynecol 1994;84:525–528.
21. Getahun D, Ananth CV, Peitier MR, Smulian JC, Vintzileos AM. Acute and chronic respiratory diseases in pregnancy: Associations with placental abruption. Am J Obstet Gynecol 2006;195:1180–1184.
22. Lederman MM. Cell mediated immunity and pregnancy. Chest 1984;86:6S–9S.
23. Catanzaro A. Pulmonary mycosis in pregnant women. Chest 1984;86:14S–18S.
24. Rigby FB Pastorek JG II. Pneumonia during Pregnancy. Clin Obstet Gynecol 1996;39:107–119.
25. Sachs BP, Brown DA, Driscoll SG, et al. Maternal Mortality In Massachusetts: Trends And Prevention. New Engl J Med 1987;316:667–672.
26. Dinsmoor MJ. HIV Infection and Pregnancy. Med Clin North Am 1989;73:701–709.
27. Haake DA, Zakowski PC, Haake DL, et al. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: Retrospective controlled study and review. Rev Infect Dis 1990;12:788–798.
28. Harris RE, Rhoades ER. Varicella pneumonia complicating pregnancy: Report of a case and review of the literature. Obstet Gynecol 1965;25:734–740.
29. Koonin LM, Ellerbrock TV, Atrash HK, et al. Pregnancy-associated deaths due to AIDS in the United States. JAMA 1989;261:1306–1309.
30. Hartert TV, Neuzil KM, Shintani AK, et al. maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during Influenza season. Am J Obstet Gynecol 2003;2:145–55.
31. McGregor JA. Prevention of Preterm Birth: New initiatives based on microbial-host interactions. Obstet Gynecol Surv 1988;43:1–14.
32. Boutten A, Dehoux MS, Seta N, et al. Compartmentalized IL-8 and elastase release within the human lung in unilateral pneumonia. Am J Respir Crit Care Med 1996;153:336–342.
33. Spinello I, Johnson R, Baqui S. Coccidioidomycosis and pregnancy. Ann NY Acad Sci 2007;1111:358–64.
34. McKendrik MW, Lau J, Alston S, Bremmer J. VZV infection in pregnancy: A retrospective review over 5 years in Sheffield and discussion on the potential utilisation of varicella vaccine in prevention. J Infec 2007;55:64–67.
35. Biem J, Roy L, Halik J, et al. Infectious Mononucleosis Complicated by Necrotizing Epiglottitis, Dysphagia, and Pneumonia. Chest 1989;96:204–205.

36. Gherman RB, Leventis LL, Miller RC. Chlamydial Psittacosis during pregnancy; A case report. Obstet Gynecol 1995;Oct 86:648–650.
37. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. Arch Int Med 1990;150:213–215.
38. Stein SJ, Greenspoon JS. Rubeola during pregnancy. Obstet Gynecol 1991;78:925–929.
39. Tewari K, Wold SM, Asrat T. Septic shock in pregnancy associated with Legionella pneumonia: Case report. Am J Obstet Gynecol 1997;176:706–707.
40. Steyn DW, Odendaal HJ. Fetal resuscitation in a patient with varicella pneumonia and preterm labor. Int J Gynecol Obstet 1989;30:171–175.
41. Winterbauer RH, Ludwig WR, Hammar SP. Clinical course, management and long-term sequelae of respiratory failure due to influenza viral pneumonia. John Hopkins Med J 1977;141:148–155.
42. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094–1102.
43. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with SARS. Am J Obstet Gynecol 2004;191:292–297.
44. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 (Suppl 2):S27–S72.
45. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A, et al. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis 2005;40:1288–1297
46. Micek ST, Dunne M, Kollef MH. Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant Staphylococcus aureus: Importance of treatment with antimicrobials inhibiting exotoxin production. Chest 2005;128:2732–2738
47. Rotas M, McCalla S, Liu C, Minkoff H. Methicillin-resistant Staphylococcus aureus necrotizing pneumonia arising from an infected episiotomy site. Obstet Gynecol 2007;109:533–536.
48. Ramsey PS, Ramin KD. Pneumonia in pregnancy: Medical complications of pregnancy. Obstet Gynecol Clin North Am 2001;28:553–569.
49. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243–250
50. Hollingsworth HG. Pneumonia in pregnancy. Obstet Gynecol 1985;65:605–612.
51. Maccato ML. Respiratory insufficiency due to pneumonia in pregnancy. Obstet Gynecol North Am 1991;18:289–299
52. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: A multicenter prospective controlled study. Antimicrob Agents Chemother 1998;42:1336–1339.
53. Levin S, Jupa JE. Principles of antibiotic use in obstetrics and gynecology. Obstet Gynecol Ann 1976;5:293–313.
54. Harris JW. Influenza occurring in pregnant women. JAMA 1919;72:978–902.
55. Larsen JW. Influenza and pregnancy. Clin Obstet Gynecol 1982;25:599–603.
56. Cox NJ, Subbarao K. Influenza. Lancet 1999;354:1277–1282.
57. Deinard AS, Ogburn P. A/NJ/8/76 Influenza vaccination program: Effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140:240–245.
58. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, et al. Prevention and control of influenza. Recommendations of the advisory committee on immunization practices. MMWR Recomm Rep 2004;53:1–40.
59. Sauerbrei A, Sonntag S, Wutzler P. Prevalence of varicella zoster in pregnant patients. Zentralbl-Gynakol 1990;112:223–226.
60. Ellis M, Neal K, Webb A. Is smoking a risk factor for pneumonia in adults with chickenpox? BMJ 1986;294:1002.
61. Zambrano MA, Martinez A, Minguez JA, et al. Varicella pneumonia complicating pregnancy. Acta Obstet Gynecol Scand 1995;74:318–320.

62. Eder SE, Apuzzio JJ, Weiss G. Varicella pneumonia during pregnancy: Treatment of two cases with acyclovir: Am J Perinatol 1988;5:16–18.
63. Srabstein JC, Morris N, Larke RPB, et al. Is there a congenital varicella syndrome? J Pediatr 1974;84:239–243.
64. Salzman MB, Sood SK. Congenital anomalies resulting from maternal varicella At 251/2 weeks gestation. Pediatr Infect Dis 1992;11;504–505.
65. Cox SM, Cunningham FG, Luby J. Management of varicella pneumonia complicating pregnancy. Am J Perinatol 1990;7:300–301.
66. Duong CM, Munns RE. Varicella pneumonia during pregnancy. J Fam Prac 1979;8:277–280.
67. Andrews EB, Yankasas BC, Cordero JF, et al. Acyclovir in pregnancy registry: Six years experience. Obstet Gynecol 1992;79:7–13.
68. Smego RA, Asperilla MO. Use of acyclovir for varicella pneumonia during pregnancy. Obstet Gynecol 1991;78:1112–1116.
69. Katz VL, Kuller JA, McMahon MJ, Warren MA, Wells SR. Varicella during Pregnancy. Maternal And Fetal Effects. West J Med 1995;163:446–450.
70. Laforet EG, Lynch CL. Multiple congenital defects following maternal varicella: Report of a case. N Engl. J Med 1947;236:534–537.
71. Alkalay AL, Pomerance JJ, Rimoin DL. Fetal varicella syndrome. J Pediatr 1987;111:320–323.
72. Siegel M. Congenital malformations following chickenpox, measles, mumps, and hepatitis: Result of a cohort study. JAMA 1973;226:1521–1524.
73. Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: Prospective study of 1739 cases. Lancet 1994;343:1548–1551.
74. Peiris JS, Yuen KY, Osterhaus AS, Stiohr K. The severe acute respiratory syndrome. N Engl J Med 2003;349:2431–2441.
75. Stevens DA. Coccidioidomycosis. N Engl J Med 1995;332:1077–1082.
76. Ely EW, Peacock JE, Haponik EE, Washburn RG. Cryptococcus pneumonia complicating pregnancy. Medicine 1998;77:153–167.
77. Hollingsworth HM, et al. Acute respiratory failure in pregnancy. J Intensive Care Med 1989;4:11–34.
78. Lam CM, Wong SF, Leung TM, et al. A case controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with SARS. BJOG 2004;111:771–774.
79. Munoz FM, Englund JA, Cheesman CC, Maccato ML, Pinell PM, et al. Maternal immunization with pneumococcal polysaccharide vaccine in the third trimester of gestation. Vaccine 2001;20:826–837.
80. Kumar RM, Uduman SA, Khurrana AK. Impact of pregnancy on maternal AIDS. J Reprod Med 1997;42:429–434.
81. Ahmad H, Mehta NJ, et al. Pneumocystis carinii pneumonia in pregnancy. Chest 2001;120:666–671.

14

Chronic Pulmonary Disease and Pregnancy

Shirley F. Jones, Marie M. Budev, and Alejandro C. Arroliga

Keywords: lung cancer, lung transplantation, smoking, interstitial lung disease, restrictive lung disease

Respiratory Physiology of Normal Pregnancy

The gravida state causes a profound number of biochemical, anatomical, and physiological changes throughout the gestational period. These changes impact respiratory physiology in only a minor way in females with no underlying lung disease, but in an individual with chronic pulmonary disease, any alteration in the balance of their pre-pregnancy respiratory physiology can lead to devastating consequences during the pregnancy, impacting both fetal and maternal morbidity and mortality. For the care of the pregnant pulmonary patient, a clear understanding of the normal respiratory physiology is of paramount importance. Listed in Table 14.1 are some of the mechanical alterations of the respiratory tract noted during pregnancy *(1–3)*.

Changes in ventilation and gas exchange during pregnancy usually are attributed to uterine enlargement and diaphragmatic elevation that lead to a reduction in the expiratory reserve volume, residual volume, and functional residual capacity *(1)*. Total lung capacity is either unchanged or slightly decreased while forced expiratory volume in the first second (FEV_1) and peak flow are usually preserved *(4, 5)*. Diffusion capacity of carbon monoxide (DLCO) initially increases during the first trimester, then decreases to normal levels as the pregnancy progresses *(1)*. Progesterone mediated effects lead to an increase in the tidal volume by 30–50%, producing an overall rise in minute ventilation and a concomitant respiratory alkalosis and elevations in partial pressure of oxygen in arterial blood (PaO_2) *(4, 6, 7)*. On the contrary, in late pregnancy, accommodations in the supine position cause a reduction in the PaO_2 and a mild increase in the alveolar to arterial oxygen gradient (A-a gradient). The overall oxygen consumption increases by 20% during pregnancy likely due to growth of maternal and fetal tissue and increases in cardiac and respiratory work with further increases during labor *(8)*.

It is important to note that the marked increase in plasma volume in pregnancy may impact the management of the pregnant patient by altering drug

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_14

Table 14.1 Mechanical changes of the respiratory system during pregnancy *(1–3)*.

Location	Effect
Upper Respiratory Tract	Hyperemia Mucosal Edema Increased secretion production
Thoracic Cage	
Anteroposterior diameter	Increases
Transverse diameter	Increases
Subcostal angle	Increases
Chest circumference	Increases 5–7 cm
Diaphragm	Elevates up to 4 cm

pharmacokinetics, therefore affecting dose and administration of many medications. The volume of distribution is increased during gestation due in part to a 30–50% increase in plasma volume *(9)*. The plasma protein concentration is decreased in pregnancy, which can produce an increase in the unbound fraction of certain drugs, while increases in body fat, common during gestation, increase the volume of distribution for lipophilic drugs *(10)*. Increased GFR increases renal clearance of drugs, often necessitating narrowing of dosing intervals. Despite this, few studies actually incorporate the pharmacokinetic changes during pregnancy into clinical dosing guidelines *(10)*.

Introduction to Chronic Lung Disease in Pregnancy

Restrictive lung diseases, lung transplantation, tobacco use, and lung cancer, though common reasons for consultation in pulmonary medicine, are rare in the pregnant female. In addition, pregnant women are often excluded from clinical trials. Therefore, very little data exists in regards to management and treatment. We have summarized the current evidence, primarily case reports and small series, to serve as a guide to the management of the pregnant female with chronic pulmonary disease.

Lymphangioleiomyomatosis and Pregnancy

Lymphangioleiomyomatosis (LAM) is a rare interstitial lung disease affecting primarily young women of reproductive age. The disease is characterized clinically by dyspnea, cough, and airflow obstruction. Spontaneous pneumothorax is common, occurring in 50% of cases, and recurrent pneumothoraces should prompt suspicion of the disease *(11)*. High resolution computed tomography reveals thin walled cysts throughout the lung parenchyma. Ground glass opacities are seen in about 59% of cases, nodular opacities much less frequently while intrathoracic lymphadenopathy and pulmonary hypertension are unusual *(12, 13)*. The pathogenesis of LAM is not entirely clear, but estrogen is suspected to be a key factor in

the development and progression of the disease, supported by the fact that most cases involve women of reproductive age or the use of exogenous estrogen therapy *(*14, *15)*.

Little is known about the outcomes and effects of LAM on pregnancy except in case reports and series. In a retrospective review of 69 cases of pulmonary LAM, 75% of subjects had a history of pregnancy before or at the time of diagnosis *(16)*. The disease seems to accelerate with pregnancy and resolve or improve with oophorectomy *(11)*. Urban et al. reported marked exacerbation of disease during pregnancy in 14% of subjects, and in fact, complications associated with LAM during pregnancy are noted to be 11 times higher than at any other time in a woman's life *(16, 17)*. In a series from the United Kingdom of 50 women with a diagnosis of LAM *(17)*, seven got pregnant after the disease was diagnosed. One had a termination, one had an uncomplicated pregnancy and the other five had very complicated pregnancies with three lung surgeries during pregnancy and recurrent pneumothoraces. It is not clear whether the chest wall changes that occur in pregnancy including the increase in the antero-posterior diameter of the chest and the widening of the rib angle predispose to their development. Pneumothorax is usually well tolerated in pregnancy unless it is large enough to result in hypoxemia or hemodynamic compromise secondary to a reduction in cardiac output. In those cases, a high suspicion for placental insufficiency should be maintained and fetal monitoring instituted in cases of fetal viability. Management should be the same in pregnancy as in non-pregnant patients including placement of a chest tube for drainage. However, the operator should keep in mind that the diaphragm is about 4–5 cm higher in the pregnant than in the non-pregnant state. In cases of recurrent pneumothoraces, successful surgical treatment has been reported. Data regarding surgery during pregnancy is extrapolated from general surgeries. Most anesthetic agents and analgesics are classified as category C in pregnancy. However, there has been no evidence of teratogenicity described with inhaled anesthetics. With any procedures in pregnancy, it is important to keep in mind that 20% of cardiac output is dedicated to the uterine circulation and that the supine position can be associated with a 25–30% drop in cardiac output related to a reduction in preload secondary to compression of the inferior vena cava. In addition, since pregnancy is a hypercoagulable state, DVT prophylaxis should be strongly advocated in the perioperative period in patients with prolonged surgery or bed rest.

Other management considerations in a pregnant patient with LAM or other conditions predisposing to the development of pneumothoraces is avoiding Valsalva maneuver during active labor. Specific considerations need to be discussed with the obstetric team such as a passive descent or the use of forceps to avoid maternal effort. Trendelenbourg position may need to be avoided in patients with a restrictive physiology in order to avoid further drops in the functional residual capacity. An early epidural is recommended in order to avoid further increases in minute ventilation and oxygen consumption. Although successful pregnancies have been reported, the optimal management of the pregnant patient with LAM is unknown, and due to concerns that estrogen may exacerbate disease, avoidance of pregnancy is suggested. Those who desire pregnancy should be educated about maternal death from LAM before their child reaches adult age. Overall, disease is progressive and prognosis poor, with a median survival of approximately 10 years from time of diagnosis, though few cases report longer survival up to 20 years *(11, 18)*.

Pulmonary Langerhans Cell Histiocytosis and Pregnancy

Pulmonary Langerhans Cell Histiocytosis (LCH) is an uncommon interstitial lung disease seen in young adult smokers. Historically, the disease shows male predilection, but this predilection could actually be a reflection of gender related differences in smoking. The clinical presentation is variable with symptoms including cough, dyspnea, fatigue, fever, malaise, and weight loss. Pneumothorax is seen in 25% of cases and is often found on presentation *(11)*. Computed tomography reveals mid to upper lung nodules, cysts, and interstitial thickening. Extrapulmonary manifestations include cystic bone lesions and CNS involvement with diabetes insipidus. The diagnosis of diabetes insipidus may be easily missed in pregnancy, since polyuria, polydipsia, and dehydration may be signs of pregnancy itself. Unlike LAM, pulmonary hypertension is common with advanced disease *(19)*. Patients with a history of LCH of a reproductive age should be screened for the presence of pulmonary hypertension, since this may be associated with detrimental consequences in pregnancy. In a normal pregnancy, pulmonary arterial pressures remain unchanged and the increase in cardiac output that is counterbalanced by a reduction in pulmonary vascular resistance (PVR). In patients with pulmonary hypertension, the drop in PVR does not occur because of vascular smooth muscle proliferation. Consequently, pulmonary arterial pressures may increase exponentially. Little data exists regarding LCH and pregnancy, mainly in the form of case reports. Pulmonary function tests appear to stabilize during pregnancy, but this may be an individual finding *(20)*. Recurrent pneumothoraces during pregnancy can be problematic requiring surgical management *(20)*. In most reported cases, there are no adverse effects on pregnancy outcomes, however, Growden et al. reported a case of progressive multifocal involvement including genital lesions thought to be secondary to LCH temporally related to the subject's first pregnancy. Though disease was treated successfully, a subsequent pregnancy resulted in termination after signs of dissemination and local symptoms were present *(21)*. Patients with a history of pulmonary hypertension should be strongly advised against pregnancy as morbidity and mortality are significantly increased. Labor and delivery considerations are the same as for patients with LAM.

Sarcoidosis

Overview of Disease

Sarcoidosis is characterized by granulomatous lung disease that can involve multiple organs, including lung, heart, eyes, joints, liver, spleen, CNS, and skin. The disease is found worldwide, with peak incidence between 20 and 29 years old. Overall Scandanavian countries have the highest incidence of disease, whereas in the United States the incidence of sarcoidosis is 6 cases per 100,000 person-years, with a slight increase in females *(22)*.

Outcomes in Pregnancy and Sarcoidosis

In a retrospective survey, sarcoidosis was not found to affect fertility, and patients with sarcoidosis account for approximately 0.02–0.06% of normal deliveries *(23, 24)*. Sarcoidosis has not been associated with an increased risk of fetal or maternal complications and evaluation of the placenta does not reveal any evidence of

granulomatous involvement *(24)*. The effect of pregnancy on the course of disease is variable. Most studies are retrospective with small numbers, but report that for the most part pregnancy has no adverse effect on the disease. In a retrospective study by Agha et al. of 18 patients, 15 patients had stability or improvement of disease while three patients experienced deterioration *(25)*. Factors that portend a worse prognosis include lung parenchymal involvement, advanced radiographic stage, presence of extrapulmonary sarcoidosis, treatment with drugs other than steroids, older maternal age, and low inflammatory activity *(26, 27)*. However, patients with severe disease can have good outcomes. Boggess et al. reported of a pregnant patient with severe restrictive lung disease (vital capacity 38% predicted) on steroids with three successful pregnancies and deliveries despite clinical and radiographic progression of disease *(28)*. On the contrary, patients with sarcoidosis and pre-existing hypoxia or pulmonary hypertension are more likely to have worse outcomes. Usually the course of sarcoidosis in pregnancy follows the pre-pregnancy course. Patients whose disease had been quiescent prior to conception would typically not have an exacerbation of the disease during pregnancy, whereas those with active disease prior to conception will likely continue to progress during the course of the pregnancy.

Management of Sarcoidosis During Pregnancy

While the indications to treat sarcoidosis with corticosteroids are not entirely clear, treatment for the pregnant patient with sarcoidosis does not differ from the non-pregnant state. Those with cardiac and neurological involvement, hypercalcemia, and eye involvement not responsive to topical therapy warrant systemic therapy *(29)*. Close to 87% of Prednisone is metabolized by the placenta, so there is minimal transfer to the fetus and no reports of fetal adrenal suppression. Initiation of systemic corticosteroids should include a discussion of complications associated with pregnancy and steroids. The discussion should include the potential risk for the development of gestational diabetes, preeclampsia, and a possibility for premature rupture of membranes. There is limited data suggesting that first trimester exposure can increase the risk of cleft lip and cleft palate. In patients with sarcoidosis requiring corticosteroid therapy, the benefit usually outweighs the risk. Patients that are treated during the pregnancy with systemic steroids usually require stress doses of corticosteroids during labor and delivery. Methotrexate is teratogenic and should not be used. Close follow-up during and after pregnancy is warranted to evaluate for the progression of disease as some patients may worsen clinically.

Idiopathic Pulmonary Fibrosis in Pregnancy

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive scarring of the lung parenchyma and subsequent decrease in pulmonary function leading to restrictive physiology that is usually relentless leading to a median survival from the time of diagnosis of approximately 3 years *(30)*. A higher prevalence of the disease exists in males (20.2/100,000) than in females (13.2/100,000). Patients with IPF are generally elderly or middle aged with two thirds of cases diagnosed in patients older than 60 years, therefore little is known about the effect of pregnancy on the disease. It is not clear if any relationship exists between disease and exacerbation during the pregnant state. However, Prichard et al. *(31)* described a 26-year-old female with an acute flare of IPF during pregnancy while maintained on corticosteroids and supplemental oxygen prior to her pregnant state. As

mentioned, many other interstitial diseases such as sarcoidosis actually may show remission during the gravid state.

The disease is extremely uncommon in the childbearing age although a few case reports do exist that describe both successful and unsuccessful pregnancies in this age group *(32, 33)*. Usually the outcome of the pregnancy depends on the disease course through the pregnancy and the severity of the disease at the time of conception. Restrictive lung diseases such as IPF demonstrate a reduction in lung volume and an increase in the ratio of FEV_1 to forced vital capacity. Lung expansion is limited due to an alteration in the lung parenchyma and in IPF the diffusion capacity may be reduced due to effacement of the alveolar capillary units. In general, pregnancy is well tolerated by patients with mild IPF due to the large ventilatory reserve and pregnancy is advised against in these cases mostly because of the poor prognosis of the disease in general and its rapid progression even outside of pregnancy. As pregnancy progresses, minute ventilation increases and this increase is mostly secondary to an increase in tidal volume, which may reach levels that are 50% higher than baseline. In IPF as well as other restrictive lung diseases, patients usually experience breathing difficulties as the pregnancy progresses since the expected increase in tidal volume is limited by the restrictive physiology and the much needed increase in minute ventilation is then achieved by a rise in respiratory rate. It has been suggested based on respiratory changes that occur during pregnancy that if an IPF patient can demonstrate an increase in her oxygen consumption by at least three times resting level, this may predict the mother will likely tolerate the pregnancy and subsequent delivery *(34)*. This suggestion is not however based on any solid data. Patients with severe restrictive lung disease (i.e., vital capacity of <1 l) have little ventilatory reserve and will likely not be able to meet the demands required by pregnancy and should be advised to avoid pregnancy or consider termination *(26)*. There is no true cure for IPF and due to the progressive, fatal nature of the disease, cytotoxic salvage therapy is often recommended and it is the recommendation that patients avoid pregnancy all together. If a woman with IPF should become pregnant she should be closely monitored by both a pulmonary and high risk obstetrical team throughout her pregnancy and during the perinatal and postnatal period. Case reports have described both successful cesarean and vaginal deliveries in IPF pregnancies *(35)*. A restrictive physiology is not an indication for cesarean delivery and vaginal delivery should be attempted unless there are obstetrical indications for a cesarean. It is recommended to plan early epidural anesthesia to prevent further increases in minute ventilation and oxygen consumption that would occur with labor and delivery. Patients requiring a cesarean section for other reasons will typically receive anesthesia via the spinal route. In patients with a restrictive physiology, high levels of anesthesia should be avoided since respiratory muscles could then be affected, furthering restriction. The Trendelenbourg position should also be avoided since it may be associated with further reduction in FRC.

Kyphoscoliosis

Overview of Disease

Kyphoscoliosis is a disease of the spine causing curvature in both the anteroposterior (kyphosis) and lateral directions (scoliosis). The severity of spinal curvature is measured by the Cobb angle, which is the angle formed by the intersection of

perpendicular lines drawn superior to the highest vertebrae and inferior to the lowest vertebrae involved in the curve. This angle is a predictive measure of mortality and if greater than 100°, it is considered severe and associated with respiratory failure *(36)*.

Kyphoscoliosis and Effects on Pulmonary Function

When the Cobb angle is greater than 100°, the vital capacity is reduced to 50% predicted *(36)*. However, in patients with secondary kyphoscoliosis, concomitant neuromuscular disease may produce fluctuations in the predicted severity of restriction. Rarely, airflow obstruction and atelectasis will result from compression by surrounding mediastinal structures and the rib cage *(26, 36)*. Hypercapnia may be secondary to ventilation perfusion mismatching but may also be related to respiratory muscle weakness and sleep-related hypoventilation. Nocturnal non-invasive positive pressure ventilation has been shown to improve hypoxemia and exercise tolerance, reduce daytime partial pressure of carbon dioxide in arterial blood (pCO2) levels, and hospitalizations in patients with chronic respiratory failure *(37, 38)*.

Kyphoscoliosis and Pregnancy

Historically, patients with scoliosis were counseled against pregnancy. Case reports of death from congestive heart failure and abdominal laceration in pregnant patients with kyphoscoliosis appeared in the 1960's, but underlying respiratory or cardiovascular function was not known *(39)*. Siegler et al. examined respiratory function in 64 patients with thoracic scoliosis, over half of which had spinal deformities greater than 60°. In the majority of pregnancies, vaginal delivery was successful while caesarean section was performed in only two patients secondary to scoliosis *(40)*. These and other studies suggest that even patients with large degrees of spinal deformity are able to carry successful pregnancies *(40, 41)*. While these patients do have an increased risk of preterm delivery, the number of other adverse events is not significantly increased *(42)*. Even in cases of cardiorespiratory failure and hypoventilation related to pregnancy and kyphoscoliosis, noninvasive positive pressure ventilation has been used successfully *(43, 44)*. Data regarding progression of spinal deformity with pregnancy is mixed with small early studies showing some worsening of the spinal angle. However, two larger follow up studies including 389 patients both with surgically and brace treated scoliosis showed no significant change in spinal curvature *(45, 46)*. Anesthetic considerations in pregnant patients during labor and delivery follow the same principles as other patients with restrictive lung disease.

Lung Transplantation and Pregnancy

Lung transplantation is now considered a therapeutic option for end-stage pulmonary disease *(47)*. Recent improvements in the allocation of organs, overall improvements in surgical techniques, and a better fundamental understanding of transplant immunology, immunosuppression, and prophylaxis has led to improvements in overall 5-year survival which nears 50% for most lung transplant

recipients *(48)*. Naturally as the long term survival has improved, recipients begin to consider trying to deal with normal life issues including becoming pregnant or starting a family. Successful pregnancies following other solid organ transplants including kidney, liver, and heart have been described with no significant increased risk of congenital malformations or neonatal infections related to the use of maternal or paternal immunosuppression *(49)*. Pregnancy outcomes among lung transplant recipients are far less clear *(50)*. Only a limited number of cases exist and have shown variable outcomes in graft function after transplant and fetal and maternal mortality *(51)*. According to the National Transplantation Pregnancy Registry (NTPR), lung transplant recipients experience more frequent acute episodes of rejection during pregnancy when compared to other solid organ transplant recipients and have a higher incidence of chronic rejection or bronchiolitis obliterans post-partum that contributes significantly to maternal mortality *(52)*. Out of 11 lung transplant patients who became pregnant according to NTPR, 48% of the group had experienced loss of graft function within two years after pregnancy. The possible reasons for the development of acute or chronic rejection of the lung graft in relation to pregnancy include limiting surveillance for acute rejection due to theoretical risks of radiation exposure from bronchoscopy early in the pregnancy course and changes in immunosuppressive levels. It is important to know that the amount of fetal radiation exposure that occurs during a bronchoscopy performed under fluoroscopy is minimal and is in the range of a few mrads when appropriate shielding is used, with an acceptable fetal radiation amount being 5 rads during the course of the pregnancy. Other maternal complications have also been reported including the development of pregnancy induced hypertension and gestational diabetes *(50)*. Most lung transplantation centers advocate against pregnancy in lung transplant recipients but if a female transplant recipient still seeks to become pregnant, current recommendations are to postpone pregnancy for at least 2 years to assess the status of the graft and the development of bronchiolitis obliterans and for careful counseling of both the recipient and partner *(50)*. The fact that the mother may not survive to see her child grow due to the issue of rapid onset of chronic rejection after delivery must be discussed openly with potential parents.

Smoking Cessation and Pregnancy

The prevalence of reported smoking during pregnancy in developed countries is between one in every three to five pregnant women, but could actually be an underestimation *(53)*. Factors that influence prevalence rates include low socioeconomic status, lack of partner, ethnicity, maternal age, level of education, and multiparity. The pathogenesis of smoking during pregnancy is twofold: an impairment in fetal oxygen delivery and high levels of carboxyhemoglobin. Placentas from smokers have reduced capillary volume and increased thickness of villous membranes. In addition, nicotine acutely decreases intervillous perfusion, possibly by nicotine induced vasospasm. On the other hand, carboxyhemoglobin is cleared slowly from fetal circulation and competes with fetal oxyhemoglobin. A left shift of oxyhemoglobin dissociation curve also occurs. Furthermore, amniocytes from smokers have increased incidence of structural chromosomal abnormalities (deletions, translocations) compared with nonsmokers. There is evidence that nicotine can directly impair lung development due to interaction with nicotinic

acetylcholine receptors (nAChR). In rhesus monkeys, infusion of nicotine resulted in decreased lung weight and volume, and increased airway resistance. Term human infants with significant cotinine levels at delivery are not able to maximize and vary their heart rates normally during the first few hours of life. Nicotine has effects on brain neurotransmitters (acetylcholine, norepinephrine, dopamine, serotonin) and on types and density of neurotransmitter receptors.

Smoking during pregnancy has been associated with increases in low birth weight infants, preterm delivery, perinatal death, stillbirth, spontaneous pregnancy loss, placental abruption, and placenta previa. Smoking during pregnancy has also been associated with long term effects on children including the development of respiratory symptoms and infections, middle ear infections, and even the development of asthma. Smoking has also been associated with infertility. After delivery, smoking mothers are less likely to breastfeed or have a shorter duration of breast feeding than mothers who do not smoke *(54)*. Smoking in the postpartum period has been associated with an increased risk of neonatal death (RR 1.2–1.4) and with SIDS (RR 2.0–7.2).

While pregnancy is a motivational factor for some women to discontinue smoking, for others, smoking cessation remains a challenge. It is estimated that around 40–45% of women who smoked before pregnancy quit before their first prenatal visit or during the first trimester, while around 18% smoked until delivery *(55, 56)*. Those who were less likely to abstain from smoking were women who had a partner who smoked, less than 12 years of education, smoked more than 10 cigarettes per day, and had an unplanned pregnancy and did not attend antenatal classes *(57)*. It is estimated that as many as 90% of women who were smoke free throughout their entire pregnancy relapse within the first year after delivery (most within the first 6 weeks).

Anti-Smoking Interventions

Pregnancy seems to be the perfect opportunity for patients to quit smoking. Pregnant women not only are additionally concerned about the ill effects of smoking on fetal wellbeing but they also have frequent visits to their health care providers, even in a perfectly normal pregnancy. So theoretically, this would sound like the perfect time to make an intervention.

Counseling

While it is difficult to generalize the result of counseling on smoking cessation due to differences in methodology between studies, counseling sessions that exceed the minimal advice to quit are effective. If delivered by trained personnel, 5–15 min of counseling of targeted information specific for the pregnant smoker significantly increases rates of smoking cessation *(58)*. However in a survey of obstetricians and gynecologists, use of the five A's of smoking cessation (ask, advise, assess, assist, and arrange) was less than optimal. While 98% of respondents asked about smoking, only two thirds advised to quit, and compliance with the final three (assess, assist, and arrange) were even less *(59)*. Another study, however, showed that only 49% asked their patients about smoking habits and a smaller proportion 28% provided a strategy to quit smoking *(60)*

Perhaps more intense monitoring of progress within the first 2 weeks of quitting should be implemented, as pregnant women who smoke within this time period are more likely to fail *(61)*.

Pharmacologic Therapy

Maternal nicotine and cotinine are cleared more rapidly in pregnancy, likely due to accelerated metabolism but the mechanism is not entirely clear. This fact has important implications for studies using cotinine to confirm smoking status and for nicotine replacement therapy.

Nicotine replacement therapy during pregnancy is a controversial issue. While blood levels of nicotine are lower with replacement therapy compared to actual cigarette use, animal studies using nicotine have been associated with central nervous system defects *(62)*. All studies utilizing nicotine replacement therapy for smoking cessation in pregnancy have involved the patch with results demonstrating no increase in smoking cessation rates over placebo in one study and high dropout rates in another *(63, 64)*. This raises the question of whether dosing was adequate for the amounts of cigarettes smoked and the fact that nicotine clearance is faster in pregnancy. The American College of Obstetricians and Gynecologists recommend that nicotine replacement therapy should be considered only when nonpharmacologic treatments have failed, and the potential benefits of an increased chance of achieving smoking cessation outweigh the unknown risks of nicotine replacement with possibly concomitant smoking *(65)*. There is an ongoing trial in the UK on smoking, nicotine, and pregnancy that is randomizing 1,050 smoking pregnant women to the nicotine patch 15 mg versus placebo with counseling.

If nicotine replacement is being considered, we would recommend using the lowest effective dose, therapeutic drug monitoring (cotinine levels during smoking and again during therapy), and using the patch for 16 h rather than 24 h.

Buproprion is used as both an antidepressant and for smoking cessation. There has been only one published prospective study regarding its safety during pregnancy. In a study of 136 women who were exposed to bupropion during the first trimester of pregnancy, there were no increased rates of congenital malformations or differences in mean birth weight or age compared to controls. While an increased number of spontaneous abortions were reported in the buproprion group, these were not significantly increased when compared to those taking other antidepressants *(66)*. On the other hand, review of registry data, though small, indicates that use of buproprion may be associated with increased risk of congenital cardiac and skeletal malformations *(67)*. Although overall smoking cessation may be more successful in women who use buproprion versus nicotine replacement therapy *(68)*, its use for smoking cessation cannot yet be recommended in pregnancy, because of the lack of human safety data. We would encourage physicians to enroll patients on buproprion in the registry to help collect adequate information regarding safety of the drug.

Lung Cancer in Pregnancy

While lung cancer has surpassed both breast and colon cancer as the leading cause of cancer death in women, its incidence in pregnancy can be expected to rise for a number of reasons. Although the number of women who smoke in the United

States has remained relatively constant, the incidence of smoking among adolescent girls continues to increase. In addition, the choice of delayed childbearing along with modern fertilization techniques allow those with advanced maternal age to become pregnant. This produces a scenario in which rising numbers of women of reproductive age have had a significant amount of smoke exposure. Overall less than 20 cases of lung cancer during pregnancy have been reported.

Diagnosis

When malignancy is suspected during pregnancy, stress levels heighten, for the necessary decisions will affect both the mother and fetus. Unfortunately evaluation for malignancy usually does not occur until later in the gestational period as symptoms such as dyspnea, cough, and hemoptysis are misinterpreted as an infectious process while bone pain, an indication of metastatic disease, is attributed to normal changes of pregnancy. In addition, physicians are apprehensive to utilize radiography in the diagnostic evaluation for concern of fetal well-being, but pregnancy should not delay the diagnosis if malignancy is suspected. The estimated fetal exposure from radiologic diagnostics used in the evaluation of lung cancer is small and is not associated with increased risk of fetal loss or anomalies even if used in the first trimester *(69, 70)*. Additional testing may be required and may include bronchoscopy with or without fluoroscopic guidance or CT-guided needle biopsy. Reports of bronchoscopy in pregnancy are rare, however, there are numerous reports of gastrointestinal endoscopic procedures safely performed in pregnancy. In general, if the mother tolerates the procedure well, the fetus should not be at risk. Oxygen saturations should be kept at 95% or better during the procedure using supplemental oxygen *(71)*. In the unusual event of desaturations or hypoventilation, fetal distress is possible. In cases of fetal viability, fetal monitoring is suggested and delivery may be performed if needed. In addition, one should weigh the advantage and the risks of the procedure against the risks of delaying or missing the diagnosis. In cases of suspected lung cancer for instance, the diagnosis should not be delayed especially if subsequent treatment may include highly toxic drugs or radiation therapy and a decision to terminate an early pregnancy is considered. Risks from conscious sedation during bronchoscopy include drug-related fetal injury, premature labor, cardiac arrhythmia, altered mental status with resultant hypoventilation, aspiration, and respiratory distress. However, many drugs used in moderate sedation are thought to be safe for the fetus and the American Society of Gastroenterology has recently published guidelines on the use of sedating drugs during endoscopic procedures *(72)*. Opioids can be used in pregnancy and benzodiazepines can also be used after the first trimester. Bronchoscopy, moderate sedation, and fetal monitoring are discussed in detail in the chapters on interventional pulmonology *(20)*, the chapter on prescribing in pregnancy and lactation *(6)*, and the chapter on fetal monitoring *(7)*. These risks are in addition to those inherent with the procedure itself such as pneumothorax, hypoxemia, wheezing, bleeding, and blood pressure lability *(73)*.

Treatment

Unfortunately many reported cases of lung cancer in pregnancy are diagnosed once disease is locally advanced or metastatic. Of the 19 reported cases of lung cancer in pregnancy, placental metastases were found in eight *(69)*. While the infant

outcome is usually healthy, two reports describe metastasis to the infant found months after delivery, suggesting perhaps that serial follow-up and imaging be performed *(74, 75)*. Treatment depends upon the histologic cell type, gestational age at time of diagnosis, clinical stage, possibility of surgery, and desires of the patient. Generally, surgery is deferred until the second trimester when organogenesis is completed and risk of fetal loss is less unless the patient desires therapeutic abortion. The patient must consider that a delay in treatment could potentially result in malignancy progression. Though few cases report the use of radiation therapy during pregnancy with lung cancer, favorable infant outcomes can be extrapolated from cases of Hodgkin's lymphoma and breast cancer during gestation. Irradiation of the maternal chest wall or breast exposes the fetus to 0.1–0.3% of the total dose, usually 50 Gy *(76)* and the amount of exposure depends in part on the proximity of the irradiation field to the fetal structures. With appropriate shielding, fetal exposure is less than 50 mGy. Healthy fetal outcomes have been reported with radiation treatment during the second and third trimester *(77)*. Termination of pregnancy is advised with fetal doses greater than 100 mGy, however, this is based on radiation effects from Japanese bomb survivors who received a single large exposure, but less detrimental effects may be expected if the dose is given over a course of multiple treatments *(76)*. The use of intrapartum chemotherapy with cisplatin and vinorelbine for lung cancer has been reported by Jänne et al. Fetal outcome in this case was a premature infant at 26 weeks *(78)*. Most data on the use of intrapartum chemotherapy in gestation are extrapolated from other malignancies. Cisplatin utilized for ovarian cancer during pregnancy has been associated with mainly healthy outcomes, but some reports of prematurity and CNS abnormalities *(78)*. Healthy fetal outcomes have been reported with the use of vinorelbine though the number of cases is small *(78)*. The timing of chemotherapy is important as drug induced leukopenia and thrombocytopenia may produce negative consequences and should be avoided as delivery date nears. Overall chemotherapy is best reserved for use in the second and third trimester if necessary. In certain instances, early delivery may be considered in case the amniocentesis suggests lung maturity, if antepartum treatment is deemed inadequate or if mother refuses to expose the fetus to chemotherapeutic drugs or radiation.

Summary

Treatment of the pregnant female with chronic pulmonary disease should be based on knowledge of respiratory physiology of pregnancy and the specifics of the underlying chronic disease. Medical management varies depending on respiratory illness but in many cases, successful outcomes in pregnancy can be expected.

References

1. Elkus R, Popovich J Jr. Respiratory physiology in pregnancy. Clin Chest Medicine 1992;13(4):555–565.
2. Contreras G, Guittierrez M, Beroiza T. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144:837–841.
3. Bonica JJ. Maternal respiratory changes during pregnancy and parturition. In: Marx GF, ed. Parturition and Perinatiology. Philadelphia: FA Davis, 1973:2–19.
4. Fishburne JI. Physiology and disease of the respiratory system in pregnancy. J Reprod Med 1979;22:177–189.

5. ACOG technical bulletin Pulmonary disease in pregnancy. Int J Gynaecol Obstet 1996;54:187–196.
6. Pernoll ML,Metcalfe J, Dovach PA. Ventilation during rest and exercise in pregnancy and postpartum. Respir Physiol 1975;25:295–310.
7. Templeton A, Kelman GR. Maternal blood gases, (PAO2-PaO2), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976;48:1000–1004.
8. Novy MJ, Edwards MJ. Respiratory problems in pregnancy. Am J Obstet Gynecol 1967;99:1024–1045.
9. Maternal Physiology. In: Cunningham ed. Williams obstetrics, 22nd ed. New York: McGraw-Hill, 2005.
10. Little B. Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. Obstet Gynecol 1999;93:858–868.
11. King TE, Crausman RS. Pulmonary lymphangioleiomyomatosis. In: Fishman AP, ed. Fishman's Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1998:1171–1178.
12. Kitaichi M, Nishimura K, Itoh H, et al. Pulmonary lymphangioleiomyomatosis: A report of 46 patients including a clinicopathologic study of prognostic factors.Am J Respir Crit Care Med 1995;151:527–533.
13. Boehler A.Lung transplantation for cystic lung disease: Lymphangioleiomyomatosis, histiocytosis X and sarcoidosis. Semin Respir Crit Care med 2001;22:509–516.
14. Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous estrogen used for infertility treatment. Thorax 2002;57:1085–1086.
15. Baldi S, Papotti M, Valente MI, et al. Pulmonary lymphangioleiomyomatosis in postmenopasual women: Report of two cases and review of the literature.Eur Respir J 1994;7:1013–1016.
16. Urban T, Lazor R, Lacronique J, et al. Pulmonary Lymphangioleiomyomatosis: A study of 69 patients. Medicine. 1999;78:321–337.
17. Johnson SR,Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 2000;55:1052–1057.
18. Sawicka EH, Morris AJ. A report of two long-surviving cases of pulmonary hymphangioleiomyomatosis and the response to progesterone therapy. Br J Dis Chest 1985;79:400–406.
19. Fartoukh M, Humber M, Capron F, et al. Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med 2000;161:216–223.
20. Sharma R, Maplethorpe R, Wilson G, et al. Effect of pregnancy on lung function in adult pulmonary Langerhans cell histiocytosis. J Matern Fetal Neonatal Med 2006;19:67–68.
21. Growdon WA, Cline M, Tesler A, et al. Adverse effects of pregnancy on multifocal eosinophilic granuloma. Obstet Gynecol 1986;67(3 Suppl):2S–6S.
22. Henke CE, Henke G, Elveback LR. The epidemiology of sarcoidosis in Rochester, Minnesota: A population based study of incidence and survival. Am J Epidemiol 1986;123:840–845.
23. Cohen R, Talwar A, Efferen LS. Exacerbation of underlying pulmonary disease in pregnancy. Crit Care Clin 2004;20:713–730.
24. Selroos O. Sarcoidosis and pregnancy: A review with results of a retrospective survey. J Intern Med 1990;227:221–224.
25. Agha FP, Vade A, Amendola MA. Effects of pregnancy on sarcoidosis. Surg Gynecol Obstet 1982;155:817–822.
26. King TE. Restrictive lung disease in pregnancy. Clin Chest Med 1992;13:607–622.
27. Haynes R. Sarcoidosis and pregnancy. Obstet Gynecol 1987;70:369–372.
28. Boggess KA,Easterling TR, Raghu G. Transactions of the fifteenth annual meeting of the Society of Perinatal Obstetricians. Management and outcomes of pregnant women with interstitial and restrictive lung disease. Am J Obstet Gynecol 1995;173:1007–1014.
29. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors

and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736–755.
30. Chapman JT, Farver CF. Idiopathic Interstitial Lung Disease: A review of recent classifications. Clin Pulm Med 2004;11:17–24.
31. Prichard MG, Musk AW. Adverse effect of pregnancy on familial fibrosing alveolitis. Thorax 1984;39:319–320.
32. Sholapurkar SL, Vasishta K, Dhall GI, et al. Idiopathic pulmonary fibrosis (IPF) necessitating therapeutic mid trimester abortion: A case report. Asia Oceania J Obstet Gynaecol 1991;17:303–306.
33. Sharma CP, Aggarwal AN, Vashisht K, et al. Successful outcome of pregnancy in idiopathic pulmonary fibrosis. J Assoc Physicians India 2002;50:1446–1448.
34. Ratto D, Balmes J, Boylen T, et al. Pregnancy in a woman with severe pulmonary fibrosis secondary to hard metal disease. Chest 1988;93:663–665.
35. Boggess KA, Easterling TR, Ragu G. Management and outcome of pregnant women with interstitial and restrictive lung disease. Am J Obstet Gynecol 1995;173:1007–1014.
36. McCool FD, Rochester DF. The lungs and chest wall disease. In: Murray JF, ed. Textbook of Respiratory Medicine, 3rd ed., vol 2. Philadelphia: Saunders, 2000:2357–2376.
37. Zaccaria S, Ioli F, Lusuardi M. Long-term nocturnal ventilation in patients with kyphoscoliosis. Monaldi Arch Chest Dis 1995;50:433–437.
38. Fuschillo S, De Felice A, Gaudiosi C. Nocturnal mechanical ventilation improves exercise capacity in kyphoscoliotic patients with respiratory impairment. Monaldi Arch Chest Dis 2003;59:281–286.
39. Mannin CW. Pregnancy and scoliosis. Lancet 1967;2(7520):792–795.
40. Siegler D, Zorab PA. Pregnancy in thoracic scoliosis. Br J Dis Chest 1981;75:367–370.
41. Yim R, Kirschner K, Murphy E. Successful pregnancy in a patient with spinal muscular atrophy and sever kyphoscoliosis. Am J Phys Med Rehabil 2003;82:222–225.
42. Visscher W, Lonstein JE, Hoffman DA. Reproductive outcomes in scoliosis patients. Spine 1988;13:1096–1098.
43. Reddy R, Evans E, Khoo O. Pregnancy in kyphoscoliosis: Benefit of non-invasive ventilatory support. J Obstet Gynaecol 2005;25:267–268.
44. Restrick LJ, Clapp BR, Mikelsons C. Nasal ventilation in pregnancy: Treatment of nocturnal hypoventilation in patient with kyphoscoliosis. Eur Resp J 1997;10: 2557–2658.
45. Orvomaa E, Hiilesmaa V, Poussa M. Pregnancy and delivery in patients operated by the Harrington method for idiopathic scoliosis. Eur Spine J 1997;6:304–307.
46. Danielsson AJ, Nachemson AL. Childbearing, curve progression, and sexual function in women 22 years after treatment for adolescent idiopathic scoliosis; a case control study. Spine 2001;26:1449–1456.
47. Minai OA, Budev MM. Referral for lung transplantation: A moving target. Chest 2005;127:705–707
48. http://www.ishlt.org/registries/slides.asp? slides = heartLungRegistry (accessed last 11/06)
49. Radomski JS, Ahlswede BA, Jarrell BE, et al. Outcome of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc 1995;27:1089–1090.
50. Budev MM, Arroliga AC, Emery S. Exacerbation of underlying pulmonary disease in pregnancy. Crit Care Med 2005;33:S313–S318.
51. Gyi KM, Hodson ME, Yacoub MY. Pregnancy in cystic fibrosis lung transplant recipients: Case series and review. J Cyst Fibros 2006;5:171–175.
52. Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. Clin Transpl 2000;10:123–134.
53. Lumley J, Oliver SS, Chamberlain C. Interventions for promoting smoking cessation during pregnancy (Review). Cochrane Database of Syst Rev 2004;4:CD001055.

54. Giglia R, Binns CW, Alfonso H. Maternal cigarette smoking and breastfeeding duration. Acta Paediatr 2006;95:1370–1374.
55. Quinn VP, Mullen PD, Ershoff DH. Women who stopped smoking spontaneously prior to prenatal care and predictors of relapse before delivery. Addict Behav 1991;16:29–40.
56. Grange G, Borgne A, Ouazana A. Prevalence of smoking cessation during pregnancy according to trimester. Gynecol Obstet Fertil 2006;34:1126–1130.
57. Giglia RC, Binns CW, Alfonso HS. Which women stop smoking during pregnancy and the effect on breastfeeding duration. BMC Public Health 2006;6:195–203.
58. Melvin CL, Dolan-Mullen P, Windsor RA. Recommended cessation counseling for pregnant women who smoke: a review of the evidence. Tob Control 2000;9S3:III80–84.
59. Jordan TR, Dake JA, Price JH. Best practices for smoking cessation in pregnancy: Do obstetrician/gynecologists use them in practice? J Womens Health 2006;15:400–441.
60. Orleans CT, Barker DC, et al. Helping pregnant smokers quit: Meeting the challenge in the next decade. Tob Control 2000;9(Suppl 3):iii6–iii11
61. Higgins ST, Heil SH, Dumeer AM. Smoking status in the initial weeks of quitting as a predictor of smoking cessation outcomes in pregnant women. Drug Alcohol Depend 2006;85:138–141.
62. Dempsy DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf 2001;24(4):277–322.
63. Wisborg K, Henriksen TB, Jespersen LB. Nicotine patches for pregnant smokers: A randomized controlled study. Obstet Gynecol 2000;96:967–971.
64. Hothem ED, Gilbert AL, Atkinson ER. A randomized pilot control study using nicotine patches with pregnant women. Addict Behav 2006;31:641–648.
65. ACOG Committee Opinion 316: Smoking Cessation During Pregnancy. Obstet Gynecol 2005;106:883.
66. Chun-Fai-Chan B, Koren G, Fayez I. Pregnancy outcome of women exposed to buproprion during pregnancy: A prospective comparative study. Am J Obstet Gynecol 2005;192:932–936.
67. No authors listed. Buproprion (amfebutamone): Caution during pregnancy. Prescrire Int 2005;14:225.
68. Chan B, Einarson A, Koren G. Effectiveness of buproprion for smoking cessation during pregnancy. J Addict Dis 2005;24:19–23.
69. Mujaibel K, Benjamin A, Delisle M, Williams K. Lung cancer in pregnancy: Case reports and reviw of the literature. J Matern Fetal Med 2001;10:426–432.
70. American College of Obstetricians and Gynecologists. Guidelines for diagnostic imaging during pregnancy. Int J Gynaecol Obstet 1995;51:288–291.
71. Kammerer WS. Nonobstetric surgery during pregnancy. Med Clin North Am 1979;63:1157–1164.
72. ASGE Guideline: Guidelines for Endoscopy in pregnant and lactating women. Gastrointest Endosc 2005;61(3):357–362.
73. Bahhady IJ, Ernst A. Risks of and recommendations for flexible bronchoscopy in pregnancy: A review. Chest 2004;126:1974–1981.
74. Harpold TL, Wang MY, McComb JG, et al. Maternal lung adenocarcinoma metastatic to the scalp of a fetus. Case report. Pediatr Neurosurg 2001;35:39–42.
75. Teksam M, McKinney A, Short J, et al. Intracranial metastasis via transplacental (vertical) transmission of maternal small cell lung cancer to fetus: CT and MRI findings. Acta Radiol 2004;45:577–579.
76. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: Poena magna, not anymore. Eur J Cancer 2006;42:126–140.
77. Nisce LZ, Tome MA, He S, et al. Management of coexisting Hodgkin's disease and pregnancy. Am J Clin Oncol 1986;146–151.
78. Jänne PA, Rodriguez-Thompson D, Metcalf D, et al. Chemotherapy for a patient with advanced non-small cell lung cancer during pregnancy: A case report and a review of chemotherapy treatment during pregnancy. Oncology 2001;61:175–183.

15

Neuromuscular and Chest Wall Diseases in Pregnancy

John Robert Bach and Jesús Sancho

Keywords: pregnancy, ventilatory failure, neuromuscular diseases, chest wall disease, non-invasive ventilation, assisted cough

Introduction

Patients with severe respiratory muscle impairment, in particular when vital capacity is below 60% of the predicted normal values, are often discouraged from becoming pregnant for fear of respiratory complications and the need for tracheostomy and invasive mechanical ventilation *(1)*. A growing fetus can impair the functioning of weak diaphragms resulting in lower vital capacity and respiratory reserve and impair cough function. In addition, there is increased oxygen consumption and ventilation requirement. Complications in pregnancy and the need for analgesics and anesthesia during labor and delivery can also cause or exacerbate ventilatory failure.

Neuromuscular Diseases

Neuromuscular diseases (NMD) are those affecting motor unit (upper and lower motor neuron, neuromuscular junction, and muscle) (Table 15.1). These processes are characterized by a progressive muscle weakness. The main causes of morbidity and mortality in neuromuscular patients are respiratory problems due to respiratory muscles weakness *(2)*. Inspiratory, expiratory, and upper airway (bulbar) muscles are involved, resulting in a progressive alveolar hypoventilation, decrease in cough capacity, and swallowing dysfunction with episodes of aspiration *(3)*.

Alveolar hypoventilation initially occurs during rapid eye movement (REM) sleep when respiratory muscle inhibition and a decrease in respiratory output occur in patients with a weak diaphragm. As the disease progresses, hypoventilation extends to non-REM sleep and finally to wakefulness *(4)*. The progressive decline in respiratory muscle function also produces a decrease in cough capacity, which can become ineffective. This results in atelectasis, increased work of breathing due to impairment in lung compliance because of retained respiratory secretions, and repetitive chest infections *(5)*.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_15

Table 15.1 Most common neuromuscular diseases.

Motor neuron diseases
– Amyotrophic lateral sclerosis
– Primary lateral sclerosis
– Spinal Atrophy
– Post-polio syndrome
Spinal Chord
– Spinal chord injury (trauma, tumors, ischemic lesions...)
– Multiple sclerosis
Neuropathies
– Guillain-Barre syndrome
Neuromuscular junction diseases
– Myasthenia gravis
Muscular diseases
– Duchenne muscular dystrophy
– Becker muscular dystrophy
– Myotonic muscular dystrophy (Steinert)
– Limb-girdle muscular dystrophy
– Fascioscapulohumeral muscular dystrophy
– Inflammatory myopathies such as polymyositis
– Metabolic myopathies such as acid maltase deficiency or mitochondrial myopathy
– Congenital myopathies such as nemaline myopathy, centronuclear myopathy

During an acute chest episode, such as a common chest cold, respiratory failure can be precipitated due to a reduction in respiratory muscle strength produced during a respiratory tract infection *(6)*. This reduction in respiratory muscle strength can cause an effective cough capacity at baseline to become ineffective during an acute respiratory episode, and change a banal chest cold into a life-threatening situation.

Chest Wall Diseases

The main conditions that cause chest wall diseases are idiopathic kyphoscoliosis, those secondary to neuromuscular disease, and the mutilating consequences of tuberculosis. Other rarer etiologies are kyphosis secondary to spinal tuberculosis, abnormal spine development, ankylosing spondylitis, pectus excavatum, and pectus carinatum.

In chest wall diseases, the asymmetric deformity of the thoracic cage produces a restrictive ventilatory defect affecting total lung capacity and functional residual capacity. These abnormalities compromise respiratory muscle function due to a disadvantageous position on the length-tension curve *(7)*. Moreover, a decrease in dynamic lung and thoracic cage compliance generates an increase in the work of breathing. To maintain minute ventilation with less work of breathing, patients adopt a rapid shallow breathing pattern. However, this pattern increases the fraction of dead space ventilation and induces alveolar hypoventilation *(8)*. This state worsens during sleep, when central respiratory output and muscle tone decrease, and during exercise, when the work of breathing increases due to the rise in metabolic demands.

Complications in Neuromuscular and Chest Wall Diseases During Pregnancy

The physiological effects of pregnancy on respiratory function may precipitate respiratory failure in patients with neuromuscular or chest wall disease.

Pregnancy

The rise in estrogen produced by pregnancy generates an increase in upper airway resistance due to hyperemia, with nasal mucosa edema, increased secretions, and occasionally the development of nasal polyps. These changes predispose to obstructive sleep apneas *(9, 10)*. Moreover, in those patients with bulbar dysfunction, these facts, together with the laxity of ligaments induced by a rise in progesterone, may increase the instability of the upper airway resulting in an increased risk of obstructive apneas, choking episodes, and impaired cough capacity *(11)*.

The progressive enlargement of the uterus during pregnancy produces a progressive increase in abdominal pressure that generates a situation in which the diaphragm has a better fulcrum to lift and expand the rib cage *(12)*. However, if movement of the rib cage is limited, as happens in neuromuscular and chest wall diseases, the generated negative intrathoracic pressure may induce a paradoxical movement of the rib cage. This enlargement of the uterus leads to an alteration of the rib cage configuration with a 50% increase of the subcostal angle and an increase in diameter of the lower rib cage due to ligament laxity induced by progesterone, resulting in a greater radius of curvature of the diaphragm *(13)*. This occurrence is partially opposed to the enlargement of zone of apposition as a result of the diaphragm rising by 4–5 cm due to increased intra-abdominal pressure *(11)*. In this situation, if the diaphragm is weak or paralyzed, it rises still further in the supine position and breathlessness and respiratory failure may develop.

Despite the elevation of the diaphragm, muscular strength remains unchanged and there is no alteration in rib cage compliance because the length of its muscle fibers does not cause significant reduction in their contractility *(14, 15)*.

The raised intra-abdominal pressure that elevates the diaphragm produces an impairment of the restrictive pattern characteristic in neuromuscular and chest wall diseases due to a decrease by about 18% of functional residual capacity (300–500 mL); this diminution is divided almost equally between the expiratory reserve volume and the residual volume. Increased pulmonary blood volume is present in pregnancy and may contribute to the reduced functional residual capacity *(16)*. These changes are accompanied by worsening ventilation and perfusion matching resulting in PaO_2 falls, especially during sleep (loss of muscle tone, supine position, and possible obstructive apneas). The reduction in functional residual capacity is clinically associated with rapid desaturation during hypopnea *(17)*. Hypercapnia may develop later in pregnancy as the uterus enlarges.

Pregnancy produces an increase in the metabolic rate and respiratory drive; oxygen consumption increases 20–33% owing to both maternal and fetal metabolic demands. The consequence is an increase in minute ventilation that is due to a 30% increase in tidal volume; the respiratory rate rises only about 10% later in pregnancy *(14)*. These changes involve an extra demand on the respiratory system that can be limited by underlying neuromuscular and chest wall disease. Patients with respiratory muscle weakness and restrictive pattern cannot assume the required increase in tidal volume and a respiratory failure will develop.

During pregnancy, the altered hormonal balance causes estrogen-related capillary congestion and mucous hypersecretion; in those neuromuscular patients with expiratory muscle weakness, complications related to retained secretions may appear if cough capacity decreases.

The rise in progesterone produced during pregnancy increases the laxity of ligaments that might worsen spinal deformities and muscular strength could be affected *(11)*. Moreover, worsening of underlying neuromuscular disease with an increase in

muscle weakness has been described during pregnancy, such as myotonic dystrophy *(18)*, facioscapulohumeral dystrophy *(19)*, or myasthenia gravis *(20)*.

Several risk factors for developing ventilatory failure during pregnancy in neuromuscular and chest wall diseases have been argued: bilateral diaphragm paralysis, Cobb angle greater than 100°, vital capacity lower than 1 L, and hypercapnia *(11)*.

Labor

In neuromuscular and chest wall diseases, ventilatory failure can be precipitated during labor because the ventilatory requirements, cardiac output, and venous return increase due to muscular activity. During the expulsive phase, maximal isometric diaphragmatic contractions are sustained for around 15 s with a reduction in perfusion of the diaphragm during these contractions, which can precipitate muscle fatigue and lead to ventilatory failure *(21)*.

Patients with a spinal deformity can have cephalopelvic disproportion, making a cesarean necessary. However, it is technically more difficult to carry out a cesarean section on those patients with severe spinal curves due to anteflexion of the uterus in the abdominal cavity, with the result that the lower uterine segment is inaccessible *(22, 23)*.

Sedatives and analgesics used during labor or cesarean section can precipitate a hypercapnic respiratory failure in theses patients due to depression of the respiratory center.

Postpartum

During the postpartum period, the pain induced by labor or cesarean produces a diminution in coughing effort intensity, resulting in a decrease in cough capacity. This can be fatal in those patients with expiratory muscle weakness as it increases the risk of atelectasis or superinfection due to retained secretions. In this phase, sedatives and analgesics must be used carefully due to the risk of depression of the respiratory center resulting in ventilatory failure.

A decrease in cough capacity, effectiveness resulting in atelectasis has been reported after use of spinal and epidural anesthesia for cesarean in normal pregnant woman *(24)*. This risk increases in neuromuscular patients due to the respiratory muscle weakness of the underlying disease.

Management of Pregnancy in Neuromuscular and Chest Wall Diseases

While there are reports of women with restrictive pulmonary syndromes secondary to neuromuscular and chest wall diseases who have had successful pregnancies without ventilatory support *(1, 25–30)* (and one case in which a pregnancy was supported by intermittent positive pressure ventilation delivered via an indwelling tracheostomy tube), in many cases the deliveries were induced once respiratory symptoms developed. In none of the cases were symptoms relieved or pregnancy extended by non-invasive ventilatory support. However, full-term gestation is possible even for women without functional respiratory muscles *(31–35)*. Such patients need to be made aware of the inspiratory and expiratory muscle aids that can be used to maintain alveolar ventilation and airway secretion clearance

throughout gestation, labor, and delivery. These aids should be introduced at the first signs of alveolar hypoventilation or ineffective cough capacity.

The three goals of optimal respiratory management for patients with neuromuscular and chest wall diseases are to maintain alveolar ventilation as normal as possible around-the-clock, to expand the lungs to maintain pulmonary compliance, and to maximize clearance of airway secretions when necessary *(36)*.

Monitoring During Pregnancy

Women with neuromuscular or chest wall diseases should be studied before becoming pregnant in order to know their baseline situation and their respiratory muscle function. A spirometry is carried out to measure vital capacity (FVC) and maximal inspiratory (PImax) and expiratory pressures (PEmax) at the mouth. A nocturnal pulse oximetry and arterial blood gas is performed when the patient awakes. With the aid of these procedures and with the evaluation of the patient's symptoms, indication for inspiratory muscles aids can be assessed. Cough capacity must be evaluated carefully. During a cough effort, the initial high flows in the expulsive phase have been shown to be essential for mucus clearance *(37)*; thus peak cough flow (PCF) measurement, which is largely dependent on the intensity of the cough, has been proposed specifically for evaluation of cough effectiveness. Measurement of PCF is readily available for neuromuscular patients: it does not need sophisticated equipment, it is easy and quick to determine, and it does not make the patient suffer. Moreover, when values are still not very decreased, PCF can be measured using a portable device used to measure peak expiratory flows by asthmatic patients *(38)*. Assisted PCF (PCF generated with assisted coughing techniques) both manually (PCF_{MIC}) and mechanically ($PCF_{MI\text{-}E}$) must be measured in order to assess efficacy of expiratory muscles aids *(39)*. Depending on age and gender, PCF can range from 5 to 14 L/s. At any age, risk for pneumonia increases when PCF are less than 5 L/s and it is almost inevitable when less than 2.7 L/s; such flows are generally ineffective to clear any airway debris *(40, 41)*.

When vital capacity is lower than 1.5 L, measurement of maximum insufflation capacity (MIC) must be performed. This parameter is the maximum volume of air that can be held with a closed glottis and then expelled; it can be obtained by insufflating air via an inflatable bag or a volumetric ventilator, coordinating insufflations with glottic closure to keep air from escaping *(40)*. Patients whose bulbar dysfunction prevents effective glottic closure cannot achieve this. Attaining a much higher MIC than vital capacity has proved to be an essential condition for successfully maintained, non-invasive management in the medium term. Consequently, MIC is a better prognostic factor than vital capacity in NMD. Moreover, patients with a MIC of less than 1.5 L have diminished spontaneous and assisted PCFs, which increases morbidity and mortality. It is necessary to obtain a minimum MIC of 1 L for manually assisted coughing to achieve flows that avoid mucous accumulation *(41)*.

During pregnancy, patients should be closely monitored and symptoms of hypoventilation (breathlessness, orthopnea, morning headache, and somnolence), oxyhemoglobin saturation (SpO_2), $PaCO_2$ (non-invasively with transcutaneous CO_2 or end-tidal CO_2 or invasively with arterial blood gasometry), and PCF should be regularly measured.

Respiratory Muscles Aids

Inspiratory and expiratory muscle aids are manual or mechanical devices that assist inspiratory or expiratory muscle function by applying forces to the body or intermittent pressure changes to the airway. The aim is to assist or replace the function of the respiratory muscles; these aids do not require training or invasion of the airway (non-invasive) in order to maintain an adequate alveolar ventilation and removal of respiratory secretions. Inspiratory muscles are assisted in order to maintain alveolar ventilation with non-invasive mechanical ventilation, and manual or mechanical assisted coughing techniques are applied to the expiratory muscles *(42, 43)*.

Inspiratory Muscle Aids: Non-invasive Ventilation

Non-invasive ventilation (NIV) provides mechanical ventilation without accessing the airway. Devices that provide intermittent positive pressure ventilation (IPPV) are more effective and more comfortable than the other alternatives, such as negative pressure body ventilation (iron lung, chest shell-style ventilators, and wrap-style ventilators) and intermittent abdominal pressure ventilation. The NIV technique is applied through an interface and delivered by pressure-cycled or volume-cycled ventilators *(42)*. This technique is considered when symptoms of hypoventilation (such as fatigue, dyspnea, morning headache, and somnolence) are present together with certain physiologic criteria *(44)* (Table 15.2). These criteria should even be looser in the pregnant patient since the fetal oxygenation and ventilation are closely related to maternal oxygenation and ventilation. Initially, NIV is used during sleep, when signs of hypoventilation are more apparent, but as the NMD disease progresses the number of hours of NIV use increases. Nowadays, around-the-clock NIV can be used if different interfaces are alternated.

An interface passes pressurized air from the ventilator to the patient's upper airway. The selection of the right mask is crucial for the success of NIV *(42)*. Interfaces for NIV include nasal masks, oronasal masks, and mouthpieces depending on the area of the patient's face it is to be applied; nose, nose and mouth, or mouth, respectively. Nasal or oronasal masks are usually used during sleep and mouthpieces during wakefulness. Nasal masks are tolerated better than oronasal masks, with lower dead space but can produce greater air leaks through the mouth. Nasal pillows are a type of nasal mask that consist of soft cone-shaped rubber pledgets that are inserted into each nostril and connected to the ventilator via a plastic tubing assembly. Oronasal masks are used instead of nasal masks if air leaks through the mouth are excessive, compromising the efficacy of ventilation; however, oronasal interfaces produce greater claustrophobia and may interfere with coughing. Nasal prongs/lipseal interfaces provide a closed system of ventilatory support with minimal skin pressure and are increasingly popular. Mouthpieces can

Table 15.2 Indications for noninvasive ventilation in neuromuscular and chest wall diseases *(44)*.

– Symptoms of hypoventilation (fatigue, morning headache, somnolence, dyspnea)
– Physiologic criteria:
– $PaCO_2 \geq 45$ mmHg
– Nocturnal oximetry with $SpO_2 \leq 88\%$ during five consecutive minutes
– PImax < 60 cmH_2O
– FVC $< 50\%$ predicted value

be used during sleep if inserted through lip seals and strapped in place so that oral retention is possible.

The two main complications related to NIV are oxygen desaturation due to air leaks and complications related to interfaces. By definition, NIV is ventilation with air leaks. These leaks may be at the point of contact of the mask with the skin or through mouth or nose, according to the kind of mask. With pressure-cycled ventilators the leaks are compensated by the ventilator itself increasing delivery of air volume to achieve the set pressure; with volume-cycled ventilators, leaks must be compensated by increasing the tidal volume set. If air leaks are much greater and cannot be compensated, another kind of mask must be used. The principal complication related to interfaces is skin redness or ulceration due to the pressure of the mask on the underlying skin. These lesions are frequent over the nasal bridge.

IPPV Mouthpiece

An NIV mouthpiece is the most commonly used method of daytime ventilatory support for patients who need continuous ventilation, and following extubation of patients who are unable to breathe autonomously *(45)*. Most commonly, simple flexed mouthpieces are grasped by the patient's lips and teeth for deep insufflations as needed. Some patients keep the mouthpiece between their teeth all day. Most patients prefer to have the mouthpiece held near the mouth. A metal clamp attached to a wheelchair can be used for this purpose or the mouthpiece can be fixed onto motorized wheelchair controls, most often, sip and puff, chin, or tongue controls. The ventilator is set for large tidal volumes, often 1,000–2,000 mL. The patient grasps the mouthpiece with the mouth, thereby supplementing or substituting inadequate autonomous breath volumes. The patient varies the volume of air taken from ventilator cycle to ventilator cycle and breath-to-breath to vary tidal volume, speech volume, and cough flows, as well as to stack air to expand the lungs fully to maintain lung and chest wall compliance *(46)*.

To use IPPV mouthpieces effectively and conveniently, adequate neck rotation and oral motor function are necessary to grasp the mouthpiece and receive IPPV without insufflation leakage. To prevent the latter, the soft palate must move posteriocaudally to seal off the nasopharynx. In addition, the patient must open the glottis and vocal cords, dilate the hypopharynx, and maintain airway patency to receive the air.

Since it is often impossible to turn off the low pressure alarms of volume-cycled ventilators, to prevent their sounding during routine daytime IPPV when not every delivered volume is received by the patient, a flexed 15 mm mouthpiece for IPPV or an in-line regenerative humidifier can be used. These create 2–3 cm H_2O back pressure, which is adequate to prevent the low pressure alarm sounding.

IPPV Nasal

Patients prefer to use IPPV mouthpieces for daytime use *(47)*, so nasal IPPV is more practical for nocturnal use only. Daytime nasal IPPV is indicated for those who cannot grasp or retain a mouthpiece because of oral muscle weakness, inadequate jaw opening, or insufficient neck movement. It is also useful during labor when a woman is supine and concentrating on her contractions, as she may not want to think about grasping a mouthpiece. Twenty-four-hour nasal IPPV is, therefore, a viable and desirable alternative to intubation or tracheostomy for some patients with severe lip and oropharyngeal muscle weakness and also for

labor provided that the woman is not too sedated. Nasal IPPV users learn to close their mouths or seal off the oropharynx with their soft palates and tongues to prevent oral insufflation leakage.

Expiratory Muscle Aids and Assisted Coughing

Patients with weak inspiratory muscles almost invariably have at least as weak expiratory (cough) muscles *(48)*. Non-invasive mechanical ventilation cannot be used long-term unless the woman is taught and equipped to be able to cough effectively during intercurrent upper respiratory tract infections or during any periods of profuse airway secretions *(49, 50)*. The patient must be taught manual and mechanical assisted coughing. PCF values lower than 2.7 L/s has been proposed as indicating an ineffective cough on the basis of flows below this level resulting in extubation failure *(51)*. PCF values lower than 4.5 L/s in a medically stable condition have also been reported to be associated with a high risk for pulmonary complications during respiratory tract infections because the pressure generated by expiratory muscles is reduced during chest infections and, consequently, PCF decrease and become ineffective *(52)*. Therefore, patients with PCF lower than 4.5 L/s must be taught assisted coughing techniques (manual and mechanical) and be monitored regularly to ensure these maneuvers are effective.

Manually Assisted Coughing

PCF generated by manually assisted coughing are much greater than those attained with an unassisted cough effort *(43)*. If the VC is under 1.5 L, insufflating the patient to greater than maximum inspiratory capacity (to the maximum insufflation capacity or MIC) is especially important to optimize cough flows *(40)*. Once the patient takes a breath to at least 1.5 L, maximally air stacks by being delivered volumes of air that are consecutively held with a closed glottis, or is maximally insufflated, an abdominal thrust is timed to glottic opening as the patient initiates the cough. Typically, one can increase PCF from ineffective (less than 160 L/m) to very effective (greater than 300 L/m) levels by manually assisted coughing *(41)*.

Manually assisted coughing requires a cooperative patient without severe bulbar dysfunction, good coordination between the patient and caregiver, and adequate physical effort and often, frequent application by the caregiver. It is usually ineffective in the presence of severe scoliosis because of a combination of restricted lung capacity and the inability to effect diaphragm movement by thrusting because of severe rib cage and diaphragm deformity. It has been used by all of the women ventilator users who had normal full-term deliveries so having a gravid uterus does not appear to be a contraindication to its use. A thoracic thrust can also be applied instead *(53)*. Chest compressions must be applied with caution in the presence of an osteoporotic rib cage. Thrusts should not be applied aggressively for 1 or 1.5 h following a meal to avoid aspiration of food. When manually assisted coughing is ineffective or inadequate, the most effective alternative for generating optimal PCF and clearing airway secretions is the use of mechanical assisted coughing.

The inability to generate over 2.7 L/s or 160 L/m of assisted PCF despite having a vital capacity or MIC greater than 1 L usually indicates fixed upper airway obstruction or severe bulbar muscle weakness and hypopharyngeal collapse during coughing attempts *(43)*. Vocal cord adhesions or paralysis may have resulted from

a previous translaryngeal intubation or tracheostomy *(54)*. Since some lesions, especially the presence of obstructing granulation tissue, can be corrected surgically, laryngoscopic examination is warranted. If not correctable, such severe bulbar-innervated muscle dysfunction that prevents manually assisted cough flows from exceeding 160–200 L/m would make pregnancy a high risk irrespective of the extent of need for ventilator use.

Mechanically Assisted Coughing

Mechanically assisted coughing (MAC) is an expiratory muscle aid technique in which cough is assisted by mechanical insufflation-exsufflation (MI-E). This involves a deep insufflation by a positive pressure blower followed immediately by a forced exsufflation in which high expiratory flow rates and a high expiratory pressure gradient are generated between the mouth and the alveoli. This increased gradient established between the positive pressure of the insufflated lungs and the negative pressure applied during the exsufflation cycle is responsible for air being expelled from the lungs at a great flow rate allowing airway clearance *(41, 43)*.

The MI-E (Cough-Assist^{TM}) is applied non-invasively through an oronasal mask and no collaboration from the patient is needed. The insufflation and exsufflation pressures and delivery times are independently adjustable. Set pressures lower than 30 cm H_2O have been reported ineffective ($PCF_{MI-E} < 2.7$ L/s) *(55)*. Insufflation to exsufflation pressures of +40 to –40 cm H_2O are usually the most effective and preferred by most patients. If a thoracic thrust is applied during the exsufflation cycle the generated PCF_{MI-E} will be greater. However, when the mechanical properties of the lungs and chest wall are abnormal, such as in the case of reduced chest wall compliance due to obesity or increased airway resistance due to respiratory secretions or atelectasis, the usual MI-E settings may not generate effective PCF_{MI-E} and must be increased.

The Cough-Assist^{TM} can be manually or automatically cycled. Manual cycling facilitates caregiver-patient coordination of inspiration and expiration with insufflation and exsufflation, respectively, but it requires hands to deliver an abdominal thrust, to hold the mask on the patient, and to cycle the machine.

One treatment consists of about five cycles of MI-E or MAC followed by a short period of normal breathing or ventilator use to avoid hyperventilation. While insufflation and exsufflation pressures when used via the upper airway are almost always from +35 to +60 cm H_2O to –35 to –60 cm H_2O, it must be kept in mind that the goal is for rapid maximal chest expansion followed immediately by rapid lung emptying, each in about 2–4 s. Pauses between cycles are unnecessary. Most patients use 35–45 cm H_2O pressures for insufflations and exsufflations via the upper airway. In experimental models, +40 to –40 cm H_2O pressures have been shown to provide maximal forced deflation VCs and flows. In a recent study in a lung model with normal human compliance, insufflation volumes exceeded 90% of predicted inspiratory capacity when insufflation times were over 3 s *(55)*. In reality, because of lung inertial factors, pressures of 40 cm H_2O (via an interface with adequate caliber) can take a whole minute to inflate lung tissues fully.

When MI-E is used for airway secretion clearance, multiple treatments are given in one sitting until no further secretions are expulsed and any secretion or mucus-induced $dSpO_2$ are reversed. Use can be required as frequently as every few minutes around-the-clock during severe chest infections. Although no medications are usually required for effective MI-E in neuromuscular ventilator users, liquefaction

of sputum using heated aerosol treatments may facilitate mucus elimination when secretions are inspissated.

The principal factor that limits the efficacy of MI-E is the severity of bulbar dysfunction. In those patients with severe bulbar dysfunction, a collapse of the upper airway during an exsufflation cycle occurs generating ineffective PCF_{MI-E}.

Glossopharyngeal Breathing

Glossopharyngeal breathing (GPB) or "frog breathing" assists both inspiratory and, indirectly, expiratory muscle function. It can provide an individual with weak inspiratory muscles and no measurable vital capacity with a ventilator-free breathing time with normal alveolar ventilation and perfect safety when not using a ventilator, or in the event of sudden ventilator failure day or night. Moreover, GPB allows patient to achieve MIC for assisted coughing or for assisted speaking.

The technique involves the use of the glottis to add to an inspiratory effort by projecting (gulping) boluses of air into the lungs. The glottis closes with each "gulp." One breath usually consists of 6–9 gulps of 40–200 mL each *(57)*. During the training period, the efficiency of GPB can be monitored with a spirometer, measuring the milliliters of air per gulp, gulps per breath, and breaths per minute. Approximately 60% of ventilator users with no autonomous ability to breathe and good bulbar muscle function can use GPB for autonomous breathing from minutes to up to all day *(58)*. Inability to use the soft palate to seal off the nose can stop some patients from using this technique. The safety and versatility afforded by GPB are key reasons to eliminate tracheostomy in favor of non-invasive aids.

Pregnancy in Bulbar Neuromuscular Patients

The main limitation and cause of failure of non-invasive respiratory muscle aids in NMD patients is severe bulbar dysfunction *(39, 59)*. Some neuromuscular disorders, such as amyotrophic lateral sclerosis, can involve function of bulbar-innervated muscles. The bulbar-innervated muscles are required for speaking, swallowing food, and ultimately for protecting the airway from aspiration of food and saliva; another important function of this muscle is to stabilize the upper airway.

Severe bulbar dysfunction can produce glottic collapse during NIV that turns it ineffective. Failure to close the glottis impedes air stacking, thus decreasing effectiveness in manually assisted coughing. MAC for patients with severe bulbar involvement produces a collapse of the upper airway during the exsufflation cycle generating an ineffective PCF_{MI-E} *(39)*. Bulbar-innervated muscle dysfunction can result in saliva aspiration with a persistent decrease in SpO_2 baseline below 95%. There are no non-invasive techniques to assist or support bulbar-innervated muscle function. Pregnancy should be advised against in these cases.

Complications During Pregnancy that Can Affect Respiratory Function

Problems that could arise to destabilize a pregnant woman include asthma, venous thromboembolism, infections, bleeding, complications of labor, and unrelated medical illnesses or need for surgical interventions. These complications can necessitate general anesthesia or involve the temporary loss of the ability to cooperate

with non-invasive methods and necessitate invasive ventilatory support and airway management. Users of continuous NIV are intubated for general anesthesia and acute medical illnesses; they are subsequently extubated back to non-invasive aids. However, this requires the understanding and cooperation of intensive care physicians and access to specific extubation protocols. Any pregnant woman with limited ventilatory reserve who has not required ventilator use but who will undergo general anesthesia must be trained in NIV and MAC pre-operation to facilitate extubation to NIV and MAC post-operation.

Abbreviations

FVC	Forced vital capacity
GPB	Glossopharyngeal breathing
IPPV	Intermittent positive pressure ventilation
MAC	Mechanical assisted coughing
MIC	Maximum insufflation capacity
MI-E	Mechanical insufflation-exsufflation
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
PCF	Peak cough flow
PCF_{MIC}	Manually assisted PCF
PCF_{MI-E}	Mechanically assisted PCF
PEmax	Maximum expiratory pressure at mouth
PImax	Maximum inspiratory pressure at mouth
REM	Rapid eye movement
SpO_2	Oxyhemoglobin saturation

References

1. Yim R, Kirschner K, Murphy E, et al. Successful pregnancy in a patient with spinal muscular atrophy and severe kyphodcoliosis. Am J Phys Med Rehabil 2003;82:222–25.
2. Lechtzin N, Wiener CM, Clawson, MSN, et al. Hospitalization in amyotrophic lateral sclerosis: causes, costs and outcomes. Neurology 2001;56:753–57.
3. Schiffman PL, Blesh JM. Pulmonary function at diagnosis of amyotrophic lateral sclerosis: rate of deterioration. Chest 1993;103:508–13.
4. Andersen PM, Borasio GD, Dengler R, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. Eur J Neurol. 2005;12:921–38.
5. Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory aids. Chest 2002;122:92–8.
6. Szeinberg A, Tabachnik E, Rashed N, et al. Cough capacity in patients with muscular dystrophy. Chest 1988;94:1232–5.
7. Pehrsson K, Bake B, Larsson S, et al. Lung function in adult idiopathic scoliosis: 20 year follow up. Thorax 1991;46:474–8.
8. Kafer E. Idiopatic scoliosis. Gas exchange and the age dependence of arterial blood gases. J Clin Invest 1976;58:825–33.
9. Schatz M, Zieger RS. Diagnosis and management of rhinitis during pregnancy. Allergy Proc 1988;9:545–54.
10. Charbonneau M, Falcone T, Cosio M, et al. Obstructive sleep apnea during pregnancy. Am Rev Respir Dis 1991;144:461–3.

11. Shneerson JM. Pregnancy in neuromuscular and skeletal disorders. Monaldi Arch Chest Dis 1994;49:227–30.
12. Gilroy RJ, Mangura BT, Lavietes MH. Rib cage and abdominal volume displacements during pregnancy. Am Rev Respir Dis 1988;137:668–72.
13. Weinberg SE, Weiss ST, Cohen WR, et al. Pregnancy and the lung: State of the art. Am Rev Respir Dis 1980;121:559–81.
14. Contreras G, Gutierrez M, Beroiza T, et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144:837–41.
15. Elkus R, Popovich J. Respiratory physiology in pregnancy. Clin Chest Med 1992;13:555–65.
16. Cugell DW, Frank NR, Gaensler EA. Pulmonary function in pregnancy. Serial observations in normal women, Am Rev Tuberc 1953;67:568–72.
17. Rizk NW. The lungs in obstetric and gynecology disease. In: Murray, Nadel, Mason, Boushey eds. Textbook of Respiratory Medicine 3rd Ed. Saunders Company. Philadelphia. 2000:2317–27.
18. Rudnik-Schöneborn S, Schneider-Gold C, Raabe U, et al. Outcome and effect of pregnancy in myotonic dystrophy type 2. Neurology 2006;66:579–80.
19. Ciafaloni E, Pressman EK, Loi AM, et al. Pregnancy and birth outcomes in women with facioscapulohumeral muscular dystrophy. Neurology 2006;67:1887–89.
20. Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis. Consequences for pregnancy, delivery and the newborn. Neurology 2003;61:1362–66.
21. Nava S, Zanotti E, Ambrosino N, et al. Evidence of acute diaphragmatic fatigue in a "natural" condition. The diaphragm during labor. Am Rev Respir Dis 1992;146: 1226–30.
22. Gupta S, Singariya G. Kyphoscoliosis and pregnancy. A case report. Indian J Anaesth 2004;48:215–20.
23. Phelan JP, Dainer MJ, Cowherd DW. Pregnancy complicated by thoracolumbar scoliosis. South Med J 1978;71:76.
24. Harrop-Griffiths AW, Ravalia A, Browne DA, et al. Regional anaesthesia and cough effectiveness. A study in patients undergoing caesarean section. Anaesthesia 1991;46: 11–3.
25. Dufour P, Berard J, Vinatier D, et al. Myotonic dystrophy and pregnancy: a report of two cases and a review of the literature. Europ J Obstet Gynecol Reprod Biol 1997;72:159–64.
26. Carter GT, Bonekat HW, Milio L. Successful pregnancy in the presence of spinal muscular atrophy: two case reports. Arch Phys Med Rehabil 1994;75:229–31.
27. Rudnik-Schoenborn S, Breuer C, Zerres K. Stable motor and lung function throughout pregnancy in a patient with infantile spinal muscular atrophy type II. Neuromuscul Disord 2002;12:137–40.
28. Weston LA, DiFazio CA. Labor analgesia and anesthesia in a patient with spinal muscular atrophy and vocal cord paralysis. Reg Anest 1996;21:350–4.
29. Wilson RD, Williams KP. Spinal muscular atrophy and pregnancy. Br J Obstet Gynecol 1992;99:516–7.
30. Bergofsky EH. Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis 1979;119:643–69.
31. Bach JR. Successful pregnancies for ventilator users. Am J Phys Med Rehabil 2003;82:226–9.
32. Díaz-Lobato S, Gomez Mendieta M, Moreno García M, et al. Two full-term pregnancies in a patient with mitochondrial myopathy and chronic ventilatory insufficiency. Respiration 2005;72:654–6.
33. Pieters Th, Amy JJ, Burini D, et al. Normal pregnancy in primary alveolar hypoventilation treated with nocturnal nasal intermittent positive pressure ventilation. Eur Respir J 1995;8:1424–7.
34. Reddy R, Evans E, Khoo O, et al. Pregnancy in kyphoscoliosis: Benefit of noninvasive ventilatory support. J Obstet Gynaecol 2005;25:267–8.

35. Restrick LJ, Clapp BR, Mikelsons C, et al. Nasal ventilation in pregnancy: treatment of nocturnal hypoventilation in a patient with kyphoscoliosis. Eur Respir J 1997;10:2657–8.
36. Servera E, Sancho J, Zafra MJ. [Cough and neuromuscular disease. Noninvasive secretion management]. Arch Bronconeumol 2003;39:418–27.
37. King M, Brock G, Lundell C. Clearance of mucus by simulated cough. J Appl Physiol 1985;58,1776–82.
38. Sancho J, Servera E, Díaz J, et al. Comparison of peak cough flows measured by pneumotachograph and a portable peak flow meter. Am J Phys Med Rehabil 2004;83:608–12.
39. Sancho J, Servera E, Díaz J, et al. Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. Chest 2004;125:1400–5.
40. Kang SW, Bach JR. Maximum insufflation capacity. Chest 2000;118:61–5.
41. Bach JR. Mechanical insufflation-exsufflation: comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. Chest 1993;104:1553–62.
42. Bach JR. Update and perspectives on noninvasive respiratory muscle aids: Part 1–the inspiratory muscle aids. Chest 1994;105:1230–40.
43. Bach JR. Update and perspectives on noninvasive respiratory muscle aids: Part 2–the expiratory muscle aids. Chest 1994;105:1538–44.
44. Consensus Conference. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—A Consensus Conference Report. Chest 1999;116:521–34.
45. Bach JR, Alba AS, Saporito LR. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. Chest 1993;103:174–82.
46. Bach JR, Alba AS. Noninvasive options for ventilatory support of the traumatic high level quadriplegic. Chest 1990;98:613–19.
47. Bach JR, Alba AS. Management of chronic alveolar hypoventilation by nasal ventilation. Chest 1990;97:52–57.
48. Polkey MI, Lyall RA, Green M, et al. Expiratory muscles function in amyotrophic lateral sclerosis. Am J Respir Crit Care Med 1998;158:734–41.
49. Gomez-Merino E, Bach JR. Duchenne muscular dystrophy: prolongation of life by noninvasive respiratory muscle aids. Am J Phys Med Rehabil 2002;81:411–15.
50. Bach JR, Rajaraman R, Ballanger F, et al. Neuromuscular ventilatory insufficiency: the effect of home mechanical ventilator use vs. oxygen therapy on pneumonia and hospitalization rates. Am J Phys Med Rehabil 1998;77:8–19.
51. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. Chest 1996;110:1566–71.
52. Bach JR, Ishikama Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest 1997;112:1024–8.
53. Hilling L, Bakow E, Fink J, et al. Directed cough. American Association Respiratory Care Clinical Practice Guideline. Respir Care 1993;38:495–9
54. Richard I, Giraud M, Perrouin-Verbe B, et al. Laryngotracheal stenosis after intubation or tracheostomy in patients with neurological disease. Arch Phys Med Rehabil 1996;77:493–96.
55. Gómez-Merino E, Sancho J, Marín J, et al. Mechanical insufflation-exsufflation: pressure, volume, and flow relationships and the adequacy of the manufacturer's guidelines. Am J Phys Med Rehabil 2002;81:579–83.
56. Bach JR, Baird JS, Plosky D, et al. Spinal muscular atrophy type 1: Management and outcomes. Pediatr Pulmonol 2002;34:16–22.
57. Bach JR, Alba AS, Bodofsky E, et al. Glossopharyngeal breathing and non-invasive aids in the management of post-polio respiratory insufficiency. Birth Defects 1987;23:99–113.

58. Bach JR. New approaches in the rehabilitation of the traumatic high level quadriplegic. Am J Phys Med Rehabil 1991;70:13–20.
59. Bach JR, Bianchi C, Aufiero E. Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis. Chest 2004;126:1502–7.

16

Pregnancy and the Cystic Fibrosis Patient

Samir Malhotra and Pearce G. Wilcox

Keywords: pregnancy, cystic fibrosis, fertility, nutritional, metabolic, lung transplant

Introduction—Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder with an incidence of roughly 1 in 3,200 live births in North America *(1)*. Outcomes have steadily been improving in a magnitude that has been largely unparalleled for genetic disorders. In the last 30 years the median age of survival has moved from 14 to 32 years *(2)* and it is projected that an individual born today with CF, in developed countries, can expect to live into their forties *(3, 4)*.

In the 2000 Cystic Fibrosis Foundation Patient Registry Annual Data Report, more than 35% of CF patients were over the age of 18 *(2)*. With these increases in longevity, many CF patients have the opportunity to make reproductive decisions. To highlight this, the most recent projection is that 4% of women with CF become pregnant each year *(5)*.

The understanding of the pathophysiology of CF has moved expeditiously with the relatively recent discovery that it occurs because of a defect in the chloride channel resulting from mutations in the CFTR gene. The number of CFTR mutations continues to increase with well over a thousand identified to date. While the preeminent role for impairing chloride transport has been well established, it is recognized that CFTR has many other functions, which continue to be elucidated and will likely contribute to the disease process. Even with knowledge of the gene defect, there remains some uncertainty as to how it leads to the disorder we recognize as CF and to how we can account for considerable genotypic/phenotypic variability.

The cardinal feature of CF is chronic lung disease, which is in large part related to chronic airway inflammation/infection with recurrent exacerbations. This is manifest as a chronic obstructive disorder, which, as it progresses, leads to more parenchymal destruction and ultimately in many cases to chronic respiratory failure. In advanced stages it can produce pulmonary hypertension (PH) and cor pulmonale. Other common findings include exocrine pancreatic insufficiency, congenital absence of the vas deferens in males, liver disease, osteopenia/osteoporosis, gastroesophageal reflux and GI motility disorders,

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_16

and diabetes mellitus. Each of these manifestations has the potential to negatively impact on maternal and fetal health.

Sexual Health

Sexual health is an integral aspect of the care of the adolescent and adult CF patient. The CF clinic and team are the primary source for many CF patients for disease related longitudinal information. This responsibility, shared with other caregivers, often extends now into support with their sexual health. CF patients have a trend to a delayed puberty by 2 years in young women and 1.5 years in young men *(6)*. Despite this, there is no difference in onset of sexual activity in CF and non-CF individuals *(7, 8)*. Timely education around aspects of sexuality and fertility are being sought by CF patients and their families. In a study by Roberts et al. *(9)* 56% of young men, 57% of young women and 92% of parents of CF adolescents preferred to know the issues regarding their sexual health before the age of 16.

Fertility

Reproductive decision making has become a reality for many CF patients, with most now reaching their reproductive years. The impact of CF on fertility is very gender specific.

In male CF patients, only approximately 2% are fertile *(10, 11, 12)*. The vast majority are infertile secondary to the congenital absence or atresia of the vas deferens, leading to azoospermia. The azoospermia does not reflect severity of CF disease in other organ systems such as the respiratory or gastrointestinal system *(13, 14)*. There is evidence to establish that the vas deferens is the organ most sensitive to abnormal CFTR production. CFTR mutations can lead to infertility without any other CF manifestations *(15)*.

Sperm production and maturation are not adversely impacted by CF. Reproductive options for male CF patients are limited by the challenges of sperm retrieval and relative immotility of the sperm. Retrieval of sperm is possible through testicular sperm extraction (TESA) or percutaneous epididymal sperm aspiration (PESA). Due to the sperm's defective motility, it must be placed in the recipient oocyte by intracytoplasmic sperm injection (ICSI). Palermo et al. *(16)* have achieved fertilization and live birth rates of 15–55% with ICSI. In comparison, non-CF ICSI can yield a fertilization rate of 52–64% *(17)*.

Women with CF have normal reproductive anatomy with unaffected oocyte production. Despite this, early studies have suggested a fertility rate of < 20 % in CF women *(18)* as compared to non-CF women who have $> 80\%$ fertility rate *(19)*. This number is clearly misleading as current evidence would support minimal CF impact on fertility. It is their overall systemic health that most influences pregnancy. Illustrative of this, the CF patient's menarcheal age is directly related to the general health of the patient. The health in turn is influenced by height, weight, and achievement of body fat (ideal of 18%). If these parameters are achieved, inception of a near normal menstrual cycle is to be expected *(6)*. The pulmonary status of women with CF has a strong association with their reproductive physiology. The objective measure of FEV_1 has been shown to be a marker for amenorrhea. Amenorrhea is more commonly seen with a $FEV_1 < 55\%$ *(6)*.

When a fertility issue does exist, in an otherwise healthy CF woman, it can be due to the quality of the cervical mucus *(20)*. The CFTR gene plays an integral role

in homeostasis of water content in the cervical mucus. It is thought to be hormonally regulated to coincide with the menstrual cycle, peaking at ovulation *(21)*. However, this is not seen in CF patients. The mucus becomes more tenacious and mucoid as a result of the CFTR mutation and its impact on chloride, sodium, and water transport. Studies have shown that in CF patients, there is a greater risk of mucus plugging in the endocervix and cervical os *(20, 22)*, inhibiting the natural passage of sperm and leading to infertility.

Bioethics and Pregnancy in the CF Patient

Prior to conception, an integral part of the reproductive decision making process involves an awareness of the medical and psychosocial aspects of having a child. In doing so, a multidisciplinary approach is required, often with the involvement of a genetic counselor. It is imperative that the CF physician integrate the patient's social, religious, and cultural context in their proceedings.

With CF patients desiring pregnancy biomedical ethical issues may arise. To address these and other issues in a systematic fashion, the CF physician may consider using a clinical approach such as the "Staged Model-shared treatment decision making model" *(23)*. This model for interaction with the CF patient desiring pregnancy includes four steps: (a) defining the physician-patient relationship, (b) a process of information exchange, (c) dialogue and deliberation, and (d) consensual agreement to proceed. By using a "Staged Model-shared treatment decision making model" *(23)*, the construct of medical ethics will be upheld and consolidation of the physician-patient relationship retained.

Potential parents must be informed of the long-term care of the child. The global and holistic issues of a healthy physical and psychosocial upbringing for the child is paramount in the decision making process to proceed with pregnancy. There is a possibility that the CF parents may have an early death, and a single parent or other individuals will be responsible for the child. It has been estimated that 20% of mothers will have died before their child reaches the age of 10, a number that increases to 40% if the pre-gravid FEV_1 is $< 40\%$ predicted.

Further, the long term consequences for the women with CF having a pregnancy need to be discussed. Aspects of how pregnancy affects CF and the converse are reviewed in the subsequent sections. Of particular note, there is evidence that pregnant CF patients may produce panel reactive antibodies. Whether these antibodies adversely affect lung transplantation is unclear.

How Cystic Fibrosis Exerts Changes on Pregnancy

Perinatal Mortality

In patients with CF, perinatal mortality rates have varied amongst studies. This could be reflective of several issues including standard of care and access to care for the pregnant CF patient, which may differ appreciably between jurisdictions.

A Canadian study by Gilljham et al *(24)* examined a prospective cohort of CF patients from 1963–1998. Of the 79 pregnant CF patients, 11 had miscarriages and 7 had medical terminations. Of note, three terminations were secondary to psychological reasons. Four neonates were born preterm (< 37 weeks), four were small for gestational age, and three had a low birth weight. In this same study, the mean gestational age and birth weight on an average were 40 weeks and 3.2 kg,

respectively. These statistics were comparable to offspring of non-CF mothers for the province as a whole over a contemporary period. Gillet et al *(25)* in a retrospective study from 1980–1999 in France, identified 90 pregnancies in 80 women with CF. There were 64 live births, one maternal death, and 11 interruptions. Kent et al *(26)* has suggested a stillbirth rate of 4% and an abortion rate 24%. In comparison, in the United States in 2003, the abortion rate was 52% in those younger than 25 years of age *(27)*.

The relative differences between the registries and study results make it difficult to draw definitive conclusions. However, it seems that of those women who have successful live births, the neonates are in general healthy. The rates of successful pregnancy are very similar to that in the non-CF population. This may reflect a selection of pregnancy by CF individuals with a relatively milder disease and might not apply if pregnancy occurs in a cohort of more severely affected individuals. Long term follow up of these neonates are required to further understand if they are at risk to any untoward physiological changes by virtue of being born to a mother with CF.

Maternal Morbidity and Mortality

Maternal outcomes during pregnancy have markedly improved over the past three decades. Early studies highlighted what were often adverse results including often precipitous declines in pulmonary status and high maternal mortality. Cohen and colleagues *(28)* reported 18% mortality within 2 years of pregnancy, which seemed to be largely accounted for by pre-pregnancy advanced lung disease. Several retrospective studies had also drawn attention to the role of lung disease *(6)* with other factors including pancreatic insufficiency, poor nutritional status, diabetes mellitus, and *B. cepacia* infection. Recommendations were that only those with mild CF disease (Taussig score > 80) should consider pregnancy.

More recent experience, however, would support pregnancy as a viable option for a much broader CF cohort. Gilljam and colleagues *(24)* found no differences in survival between 54 pregnant CF women compared to non-CF controls. Goss et al *(29)* used a parallel cohort study design matching 680 pregnant CF women (out of a total of 8,136 $>$ age 12 from 1985–1997) with 3,327 controls. Ten-year data showed that survival was actually greater in the pregnant group although this likely related to less severe disease in those becoming pregnant. When matched for relevant clinical factors, there were comparable survival rates for both groups. In this study survival was not affected by more severe lung disease ($FEV_1 < 40\%$) or the presence of diabetes.

Despite the improved outcomes, an uneventful gestational course cannot be assured. Limitations in the numbers evaluated and in the study designs to date handicap our ability to provide clinical useful guidelines for our patients who might be considering pregnancy. Gilljam et al *(24)* reported that 6/7 patients who died within 15 years of pregnancy had a $FEV_1 < 40\%$. We believe it reasonable to extrapolate from the non-pregnant CF population when appraising risks. In addition to this FEV_1 threshold, other parameters might include CO_2 retention, meeting the criteria for domiciliary O_2, marked nutritional deficiency, and *Burkholderia cepacia* infection. Identification of those who may be at increased risk of poor outcomes through the pregnancy clearly requires further study, as factors denoting a poor long-term outcome are paramount in the informed decision making process of a CF patient desiring pregnancy.

How Pregnancy Exerts Changes on CF

Lung Function

There is no contemporary compelling evidence that pregnant women with stable CF will have worsening of their disease in peripartum period. However, CF patients with a $FEV_1 < 50\%$, colonization of *Burkholderia cepacia*, diabetes, and poor nutrition have been shown to have poor outcomes *(30)*. The majority of previous studies investigating this question have been case-control studies or retrospective matched pair cohort studies. There is a significant amount of variability in results due to this, and consensus is difficult to establish.

A study by Nakilena *(31)* reviewed a small sample of CF pregnant women to matched CF non-pregnant controls. In comparing their respective lung function, the study did not demonstrate any significant deterioration in lung function throughout pregnancy. This result has been replicated in a study by McMullen et al *(32)*, in which there was a non-significant decline in FEV_1 between pregnant and non-pregnant CF women (6.8% versus 4.7%, $p = 0.61$, and baseline FEV1 74.5% versus 66.4%, respectively). These results are reassuring for the CF physician in prenatal and perinatal counseling. However, caution must be kept in mind as the large proportion of the CF patients in both studies had mild lung disease *(31, 32)*. Further studies must be done to further qualify the results of the aforementioned studies.

Nutritional and Metabolic Changes

The metabolic effects that are encountered in pregnancy consist mainly of changes in nutritional demand. A CF patient's predisposition to diabetes and pancreatic insufficiency augments this nutritional demand.

In a pregnancy not influenced by CF, there is enhanced insulin secretion and near normal insulin sensitivity in the first trimester. In late pregnancy a decrease in insulin sensitivity with an increased insulin secretion manifests. Throughout pregnancy there is an increase in hepatic glucose production, yet despite this there is a further hyper-metabolic state with a relative net balance favoring protein catabolism.

The metabolic profile of a pregnant CF patient is altered and the normal pregnant metabolic physiology becomes an issue that needs to be observed carefully. Notably, there is decreased insulin secretion and an increased level of hepatic glucose production *(33)*. In the CF patient this lends itself to a higher risk of gestational diabetes. The CF pregnant patient is in a hyper metabolic state and due to this, there is a greater net negative protein balance *(34)*. The combination of these physiological changes can negatively impact the pregnancy for both mother and fetus. For the fetus, there is a higher risk of preterm labor and delivery *(24)*, prematurity, and birth defects, while for the mother there is a higher risk of deterioration in the postpartum period.

Gastrointestinal (GI) changes occur in the normal pregnancy. In particular, the gall bladder tends to empty slower than in the non-pregnant state *(35)*. The CF patient has a baseline pre-pregnancy predisposition to bile stasis, and therefore during pregnancy this can cause an exacerbation of further cholestasis *(36)*.

Secondary to the increased volume retention, weight gain, pressure from the growing gravid uterus on abdominal contents, and decreased gastric motility, many CF pregnant patients develop or exacerbate gastroesophageal reflux. Other

factors that cause or exacerbate gastroesophageal reflux include high levels of progesterone that lead to a decrease in the tone of the lower esophageal sphincter. Further changes that can be seen are persistent periods of constipation. This is thought to be due to the water retention and decreased motility *(35)*. Constipation may be more apparent in the CF patient as they may already have underlying GI motility problems.

In general, nutritional requirements increase during pregnancy. It has been suggested the increases are at least 300 kcal/day. The CF patient already has high caloric needs because of less efficient absorption, the exaggerated work of breathing, and the hyper-metabolic systemic state relating to the inflammatory effects of the illness. Therefore the metabolically taxed pregnant CF patient may find difficulty in attaining and maintaining the additional nutritional requirements to meet the demands of the stress of pregnancy, pregnancy effects on CF, and basal calorie requirement for CF disease. This can put undue physiological stress on both mother and fetus and may cause harmful perinatal issues. Very low body weight should be considered a relative contraindication to pregnancy, secondary to the increase risk of premature delivery *(37)* and maternal mortality.

To ensure that nutritional demands are met, the patient must be counseled by the CF physicians and allied health members regarding the need and rationale for augmented nutritional support. In some cases, access to resources to maintain this extra nutritional requirement may be required. The therapeutic options to address nutritional issues are discussed in detail in "Lung Transplant and the Pregnant CF Patient".

Cardiopulmonary Changes

Special consideration is required in pregnant women with moderate to severe CF lung disease, particularly in those who exhibit PH. Pregnancy impacts lung volumes, although with limited significance in a normal pregnant patient. There are reductions in expiratory reserve volume, residual volume, and to some extent functional residual capacity (FRC). Minute ventilation increases appreciably, in part because of an increased VO_2 and also because of augmented progesterone. Hemodynamic perturbations in the pregnant patient include increases in blood volume of up to 40% (predominantly in the last half of pregnancy), a concomitant increase in cardiac output of 40–45%, a physiological response of an increase pulmonary blood flow, and the reflex recruitment of pulmonary blood vessels to meet the demand of increased pulmonary blood flow.

In the CF patient with PH, there is a limited ability to compensate for these physiological changes with a finite ability to recruit pulmonary vessels. This may in turn cause maternal hypoxemia, fetal hypoxia, and intrauterine growth retardation *(38)*. A cycle of worsening PH, reduction of cardiac output, reduced mixed venous-oxygenation, and increasing left heart compromise can lead to overt right ventricular failure and cardiac arrest. Because of these risks, PH is viewed as a relative contraindication to pregnancy *(39)*. Patients with PH need to be counseled on the risks and benefits to both potential mother and fetus. If a patient with moderate to severe PH or alternatively marked ventilatory compromise decides to continue with pregnancy, it may be appropriate to hospitalize the patient at 20 weeks, when the cardiac output is peaking, for close monitoring *(38)*. Early involvement of an Obstetrician, PH expert, and a Maternofetal physician is critical in optimizing maternal and fetal outcomes.

Immunity

Immunity changes with a shift from a cellular response to more humoral response in pregnancy *(40)*. Theoretically, this could make a pregnant CF woman more susceptible to certain infections *(41)*. There is no clear consensus in the literature, however, as to whether there is an increase in CF pulmonary exacerbations during pregnancy. Most studies have shown similar exacerbation rates and outcomes compared to non-pregnant women. This could relate to the more frequent follow up and therapeutic adherence during pregnancy *(32)*. Further basic science and clinical trials are needed to explore the balance between the pro-inflammatory pregnancy state and the resultant anti-inflammatory response.

Factors in the Care of the Pregnant CF Patient

Nutritional and Metabolic Aspects

A CF woman not gaining the weight expected during pregnancy through traditional means is at an increased risk for premature delivery and intrauterine growth retardation. Once recognized by the multidisciplinary team it is imperative that prompt action take place to ensure nutritional supplementation. Consultation with a dietician throughout pregnancy is recommended. Further interventional methods may be required, including enteral tube feeding or percutaneous endoscopic gastrostomy feeding *(42)*. In the non-pregnant CF women, once the ideal body weight drops below 85%, nocturnal enteral feeding may need to be considered. With the knowledge that gastroesophageal reflux is very common, it is prudent to consider the overall trend of the mother's and fetus weight gain/growth when establishing the optimal time to intervene with enteral feeding.

Whether the pregnancy is or is not complicated by CF, vitamin supplementation is important. Supplementation with folate to decrease the risk of neural tube defects is the current standard of care. Special consideration for further supplementation is required for women with CF, as they also may also be deficient in the fat soluble vitamins. Therefore supplementation of Vitamin A, D, E, and K are required throughout pregnancy.

Gestational diabetes mellitus is an issue in many non-CF and CF pregnancies. Given the already burdened metabolic system in the pregnant CF patient, the addition of gestational diabetes may cause further problems. To ensure prompt treatment and referral to an endocrinologist, the 1998 CF Foundation consortium recommends that all CF patients who are pregnant be screened pre-pregnancy and at the end of each trimester with an oral glucose tolerance test until diabetes develops.

Labor and Delivery

The most common obstetrical issue in the pregnant CF women is premature delivery, occurring in up to 24% of the CF pregnancies *(38)*. Otherwise as long as the health of the CF pregnant women is stable throughout the pregnancy, obstetrical complications match that of the non-CF pregnant women.

Despite that, a detailed labor and delivery plan should be developed in conjunction with the obstetricians and the obstetric anesthesiologist. If the pregnancy has been uncomplicated, the patient should be encouraged to proceed with a vaginal delivery *(26)*. Caesarian section is an alternative but it does not offer any

advantages over vaginal delivery in a CF patient. In addition, given that it is a surgical procedure with need for anesthetic agents, it may pose a problem for the already compromised pulmonary status of the pregnant CF patient. When a local spinal anesthesia is used, as an alternative to general anesthetic, there still is a risk of restrictive ventilatory physiology *(44)*, especially if high levels of anesthesia are used and affect the lower thoracic roots. Other measures needed to avoid further restriction include avoiding the Trendelenbourg position that may reduce FRC further. Several case reports stress the importance of using minimal sedation, analgesics in order to avoid ventilatory failure, and emphasize the adjuvant use of bronchodilators and post-delivery chest physiotherapy to optimize the labor and delivery for both mother and neonate *(45, 46)*. In general, an early epidural can help minimize the increase in oxygen consumption and the ventilatory requirements associated with labor. However, in patients with associated PH, precipitous drops in blood that may be associated with epidural or spinal anesthesia should be avoided in order to avoid acute right ventricular failure.

Breastfeeding and Postpartum Care

An integral art of the post partum care is to ensure health of the neonate. There is a 1 in 2,500 chance that the neonate will be a carrier of the CF gene, with the chances of manifesting the disease depending on the paternal genotype. Testing of the infant may be appropriate depending on clinical circumstances. Increasingly, jurisdictions are including CF testing as a routine.

For the mother, the approach is clearly to optimize pulmonary status and other manifestations of CF. This may include intensifying chest physiotherapy, starting antibiotics that are safe for breastfeeding for CF exacerbations, stress steroids as needed, and continued use of bronchodilators.

Breast feeding allows for neonate nutrition and bonding with mother and is generally encouraged. However, breastfeeding may pose extra physiological stress on the CF patient. This is secondary to breast feeding increasing metabolic demands, especially if the mother with CF has a tenuous post-partum respiratory status. In unusual instances it may be counseled that these extra demands and the resultant risks are not to be assumed.

Breast milk from a mother with CF has the same energy content compared to non-CF mothers *(47)*. However, specific lipid fractions have been suggested to be altered linoleic and arachidonic *(48)*.

There does not seem to be any significant deleterious long-term impact of breast feeding on the mother *(49)*. Currently the evidence is not conclusive for either a negative or positive impact of breast feeding for neonates/infants. Further studies are required to help the patient and multidisciplinary team make an informed decision.

Pharmacological Aspects and the Pregnant CF Patient

Pregnancy impacts considerably on medication pharmacokinetics and pharmacodynamics. A larger volume of distribution occurs as a result of intravascular expansion. There is a greater glomerular filtration rate associated with pregnancy and faster clearance of renally excreted drugs. The P450 system and hepatic metabolism does not seem to be altered in pregnancy.

The majority of commonly used CF drugs do not pose a teratogenic effect on the fetus. Some notable exceptions include ciprofloxacin, which can cause joint

arthropathy. Non-steroidal anti-inflammatories can cause early constriction of the ductus arteriosus and should be avoided. There are no studies investigating the specific pharmocodynamic and pharmacokinetic changes in pregnant CF patients. Due diligence must be sought by reviewing the introduction of any new medication and questioning whether dosage requirements are needed with preexisting medications.

Lung Transplant and the Pregnant CF Patient

For many CF patients lung transplant is the only option to curtail morbidity and mortality with advanced complications associated with CF. With advances in transplant medicine, the overall 5-year survival rate can be greater than 50%. The medications used in lung transplant patients do not preclude them from considering pregnancy as an option, making it possible for CF lung transplant patients to consider post lung transplant pregnancies.

There are several case reports of both successful and unsuccessful pregnancies in CF lung transplant patients *(50)*. Compared to other solid organ transplant patients having pregnancies, lung transplant patients have a higher proportion of rejection (40% versus 4%) and graft failure (30% versus 13%) postpartum *(51)*. Factors that influence the success of pregnancy in this patient population include the number of rejections prior to pregnancy and known acute rejection *(51)*. Less than two rejections is purported to confer a better pregnancy outcome *(51)*. Given the small numbers of cases reported, it is difficult to make definitive conclusions for this patient population. Therefore until further studies are completed with long term data, it must be with trepidation that CF physicians encourage pregnancy for the post CF lung transplant patient.

Summary

With scientific developments and a clearer understanding of the molecular aspects of CF, the scope of disease has changed in the last three decades. Technological advancements have revealed new genotypes and detection of CF in traditionally held unaffected populations.

With more aggressive nutritional intervention and the advent of newer pharmacotherapeutics, longevity has been promoted in the CF patient. This has lead to greater optimism of leading a healthier life. For more CF patients, there exists the option to become pregnant.

Amongst caregivers the traditional held belief of "concern" has shifted to one of reserved enthusiasm. In most instances pregnancy will lead to a normal fetal outcome with limited, if any, adverse effects on the mother.

Despite the aforementioned clinical, pharmacological, and scientific developments, concentrated efforts are required to research and stratify women with CF into low, intermediate, and high risk for pregnancy. Further insight is required into the issues that face women with CF in the immediate and long term post-partum period. The pregnant CF patient is becoming a common clinical scenario; therefore it is paramount that physicians caring for these individuals become comfortable with both the pulmonary and holistic aspects of the pregnant CF patient.

References

1. Rosenstein BJ, Cutting JR. The Diagnosis of Cystic Fibrosis: A consensus statement; cystic fibrosis foundation consensus panel. J Pediatr 1998;132:589–595.
2. Cystic Fibrosis Foundation. Patient Registry 2000 Annual data report. Bethesda, MD. Cystic Fibrosis Foundation, 2001;1–2.
3. MacLusky I, Levison H. Cystic fibrosis. In: Kendig's Disorder's of the Respiratory Tract in Children. Sixth Edition. Chernick V, Boat TF (Eds). Philadelphia, PA, WB Saunders, 1998; 838–882.
4. Yankaskas J, Marshall B, Sufian B, Simon R, Rodman D. Cystic Fibrosis Adult Care: Consensus Conference Report. Chest 2004;125:1–39.
5. Fitzsimmons S, Fitzpatrick S, Thompson B. A longitudinal study of the effects of pregnancy on 325 women with cystic fibrosis. Pediatr Pulmonol 1996;Suppl 13: 99–101. 10th North American Cystic Fibrosis Conference.
6. Edenbourough FP. Women with CF and their potential for reproduction. Thorax 2001;56:649–656.
7. Sawyer SM, Bowes G, Phelan PD. Reproductive health in young women with CF. J Adolesc Health 1995;17:46–50.
8. Sawyer SM, Tully MA, Dovey M, Colin AA. Reproductive health in males with CF. Pediatr Pulmonol 1998;25:226–30.
9. Roberts S, Green P. The sexual health of adolescents with cystic fibrosis. J R Soc Med 2005; 98 (Suppl 45):7–16.
10. Gaillard DA, Carre-Pigeon F, Lallemand A. Normal vas deferens in fetuses with cystic fibrosis. J Urol 1997;158:1549–1552.
11. Philipson G. Cystic Fibrosis and reproduction. Reprod Fertil Dev 1998;10:113–119.
12. Heaton ND, Pryor JP. Vas aplasia and cystic fibrosis. Br J Urol 1990;66:538–540.
13. Denning CR, Sommers SC, Quigley HJ. Infertilty in male patients with CF. Pediatrics 1968;41:7–17.
14. Kaplan E, Schwachman H, Perlmutter AD. Reproductive failure in males with CF. N Eng J Med 1968;270:65–69.
15. Schulz S., Jakubiczka S., Kropf S., Nickel I., Muschke P., Kleinstein J. Increased frequency of cystic fibrosis transmembrane conductance regulator gene mutations in infertile males. Fertil Steril. 2006 Jan;85(1):135–8.
16. Palmero G, Joris H, Devroey P, Van Steirteghem A. Pregnancies after intracytoplasmic injection single spermatozoon into an oocyte. Lancet 1992;340: 17.
17. Tarlatzis BC, Bili H., Survey on intracytoplasmic sperm injection: report from the ESHRE ICSI Task Force. European Society of Human Reproduction and Embryology. Hum Reprod. 1998 Apr;13; Suppl 1:165–177.
18. Rodgers H, Knox A, Toplis P, Thornton S. Successful pregnancy and birth after IVF in women with cystic fibrosis. Hum Reprod 2000;15(10):2152–2153.
19. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996 Mar;65(3):503–509.
20. Kopito LE, Kosasky HJ, Shwachman H. Water and electrolytes in cervical mucus from patients with cystic fibrosis. Fertil Steril 1973;24:512–516.
21. Shawker TH, Hubbard VS, Reichert CM, et al. Cystic ovaries in cystic fibrosis: an ultrasound and autopsy study. J Ultrasound Med 1983;2:439–444.
22. Oppenheimer EA, Case AL, Esterly JR, et al. Cervical mucus in cystic fibrosis: a possible cause of infertility. Am J Obstet Gynecol 1970;108:673–674.
23. Wexler I, Johannesson M, Edenborough FP, Sufian BS, Kerem E. Pregnancy and chronic progressive pulmonary disease. Am J Respir Crit Care Med 2007;175: 300–305.
24. Gilljham M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis E. Pregnancy in cystic fibrosis: fetal and maternal outcome. Chest 2000;118;85–91.
25. Gillet D, Braekleer M, Bellis G, Durieu I. Cystic fibrosis and pregnancy. Report from French data (1980–1999). BJOG 2002; 109:912–918.
26. Kent N, Farquharson D. Cystic fibrosis and pregnancy. Can Med Assoc J 1993; 149:809–813.

27. Strauss L, Gamble S, Parker W, Cook D, Zane S, Hamdan S. Abortion Surveillance – United States, 2003. MMWR 2006; 55(SS11): 1–32.
28. Cohen LF, di Sant'Agnese PA, Friedlander J. Cystic fibrosis and pregnancy. A national survey. Lancet 1980 Oct 18;2(8199):842–844.
29. Goss C, Rubenfeld GD, Otto K, Aitken ML. The effect of pregnancy on survival in women with cystic fibrosis. Chest 2003;124:1460–1468.
30. Kotoloff R, Fitzsimmons S, Fiel S. Fertility and pregnancy in patients with cystic fibrosis. Clin Chest Med 1992;13:623–35.
31. Frangolias DD, Nakielna EM, Wilcox PG. Pregnancy and cystic fibrosis: a case controlled study. Chest 1997;111: 963–969.
32. McMullen Ann H., Pasta David J., Frederick Paul D., Konstan Michael W., Morgan Wayne J., Michael S, Wagener Jeffery S, for the investigators and coordinators of the epidemiologic study of cystic fibrosis. Chest 2006;129:706–711.
33. Peraldo M, Fasulo A, Chiappani E, Milio C, Marianelli L. Evaluation of glucose tolerance and insulin secretion in cystic fibrosis patients. Horm Res 1998;49:65–71.
34. Hardin DS, Rice J, Cohen R, Ellis KJ, Nick JA. The metabolic effects of pregnancy in cystic fibrosis. Obstet Gynecol 2005;106:367–75.
35. McFayden IR. Maternal changes in normal pregnancy. In: Turnball, SA, Chamberlin G. editors. Obstetrics. Livingstone, Edinburgh, London, Melbourne and New York: Churchill, 1989.
36. Eggermont E. Gastrointestinal manifestation in cystic fibrosis. Eur J Gastrol Hepatol 1996;8:731–738.
37. Edenborough FP, Mackenzie WE, Stableforth DE: The outcome of 72 pregnancies in 55 women with Cystic Fibrosis in the United Kingdom. 1977–1996. Br J Obstet Gynaecol 2000;107:254–261.
38. Budev, M., Arroliga Alejandro C., Emery S. Exacerbation of underlying pulmonary disease in pregnancy. Crit Care Med 2005;33(10 suppl).
39. Edenborough FP: pregnancy in women with cystic fibrosis. Acta Obstet Gynecol Scand 2002;81:689–692.
40. Wegmann TG, Lin H., Guilbert L, Mossman TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th2 phenemonon? Immunol Today 1993;14:353–356.
41. Brabin B. Epidemiology of infection in pregnancy. Rev Infect Dis 1985;7:579–603.
42. Conway SP, Morton A, Wolfe S. Enteral tube feeding for cystic fibrosis. Cochrane Database Syst Rev 2000;(2).
43. Williams SGJ, Ashworth F, McAlweenie A, Poole S, Hodson ME, Westaby D. Percutaneous endoscopic gastrostomy feeding patients with cystic fibrosis,. Gut 1999;87–90.
44. Kelly MC, Fitzpatrick KTJ, Hill DA. Respiratory effects of spinal anaesthesia for Caeserian section. Anaesthesia 1996;51:1120–1122.
45. Cameron AJD, Skinner TAJ. Management of parturient with respiratory failure. Anaesthesia 2005; pp 77–80.
46. Muammar M., Marshall P, Skelton Wyatt. Caeserian section in a patient with cystic fibrosis. Int J Obstet Anaesth 2005;14:70–73.
47. Bitman J, Hamosh M, Wood DL, Freed LM, Hamosh P. Lipid composition of milk from mothers with cystic fibrosis. Pediatrics 1987;80:927–932.
48. Mueller DH, Tulp O, Michael SH. Cholesterol and macronutrient composition of breast milk from cystic fibrosis mothers. Am J Clin Nutr 1991;53:25. Abstract.
49. Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis and their infants: a review of five cases. J Am Diet Assoc 1994;159(7).
50. Armenti AR, Radomski JS, Moritz MJ, Gaughan WJ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Ch 9. Clin Transpl 2004;103–114.
51. Gyi, K, Hodson M, Yacoub M. Pregnancy in cystic fibrosis lung transplant recipients: case series and review. J Cyst Fibros 2006;5(3):171–175.

17

Pulmonary Complications of Collagen Vascular Disease in Pregnancy

Stéphanie Pouwels-Fry, Isabelle Tillie-Leblond, and Benoît Wallaert

Keywords: rheumatoid arthritis, Sjögren's syndrome, polymyositis and demrmatomyositis, systemic sclerosis, systemic lupus erythematosus, antiphospholipid antibody syndrome

Collagen vascular diseases (CVD) are a heterogeneous group of chronic autoimmune diseases frequently complicated by pulmonary involvement. The respiratory system may be involved in any of its components: airways, pleura, parenchyma, vessels, or respiratory muscles. However, interstitial lung disease and pulmonary hypertension (PH) are the most severe complications. CVD often affects childbearing women, thus management of pregnant women with collagen vascular disease is likely to occur. The presence of underlying pulmonary disease can present a significant challenge during the pregnancy and postpartum period. However, few studies or case reports describing pulmonary diseases associated with CVD are reported during pregnancy. The manifestations most frequently reported are related to vascular involvement, mainly thrombosis and PH. The effect of pregnancy on respiratory manifestations is often controversial. However, pulmonary involvement during CVD is rarely responsible for acute respiratory distress or for deleterious fetal or maternal outcomes. Patients with CVD and with severe interstitial lung disease (vital capacity < 1 L) or with PH should be advised to avoid pregnancy or consider therapeutic termination for maternal indications.

Immunity and Pregnancy

The pregnancy is characterized by maternal tolerance of the semi-allogenic fetus. The process involved in this tolerance remains unknown, although several mechanisms adapting the maternal immunity have been postulated. Pregnancy produces an environment of immune suppression with depressed immune function of natural killer cells, phagocytic cells, and some cells implicated in cytotoxicity. However, antibody-dependent cellular cytotoxicity function remains normal *(1, 2)*. On the other hand, maternal T cells acquire a transient state of tolerance during pregnancy specifically for fetal antigens inherited from the father *(3–5)*, protecting against the rejection. In rheumatoid arthritis (RA), some beneficial effects of pregnancy have been described. One possible hypothesis is that

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_17

maternal dendritic cells present fetal human leukocyte antigens (HLA) derived from apoptotic syncitiotrophoblast under non-inflammatory conditions, leading to tolerogenic signals and remission of the inflammatory disease as a consequence *(6)*. During the pregnancy, interleukin-10, an anti-inflammatory mediator, is elevated in the blood, and enhances the tolerogenic potential of dendritic cells in vitro *(7, 8)*. In RA, there is also a strong contribution of B cells. During the pregnancy, a contribution of autoreactive B cells to disease in women with RA may be lessened by the fact that CD4, CD25, and T_R cells kill activated B cells in the maternal peripheral blood *(9)*. Another important adaptation leading to tolerance during pregnancy is a switch from T-helper (Th) 1 dominance to Th2 dominance *(10)*. Nevertheless, clinical observations showed that the effect of CVD on pregnancy outcome and the effect of pregnancy on CVD are variable.

Respiratory Physiology During Pregnancy

The airways, thoracic cage, respiratory muscles, and cardiovascular system are all affected by normal pregnancy, with anatomic, functional, and hormonal changes. Dyspnea is common during normal pregnancy. About 50% of pregnant women complain of dyspnea before 20 weeks of gestation and 75% by 31 weeks *(11)*. To understand the development of pathologic dyspnea, clinicians have to understand normal respiratory and cardiovascular changes during pregnancy.

Because of the enlarging uterus, the diaphragm is elevated by 4–5 cm, without any muscle dysfunction but diaphragmatic excursion remains normal *(12)*. The elevated diaphragm causes a decrease in lung volumes and microatelectasis in the lower lobes *(13)*. There is also an increase in the antero-posterior and transverse diameter of the thoracic cage. This is the result of the relaxation of the ligamentous attachments of the ribs and broadening of subcostal angle.

The pregnancy is characterized by a progressive decrease of 8–40% in expiratory reserve volume and of 7–22% in residual volume due to the elevation of the diaphragm. Consequently, the functional residual capacity decreases about 10–25% after the fifth month of pregnancy *(14)*. However, the inspiratory capacity increases significantly and therefore, total lung capacity remains unchanged. Forced expiratory volume, forced vital capacity, and peak flow rates are unchanged in pregnancy. Because of decreased functional residual capacity, airway resistance should theoretically be increased. However, airway resistance is lower during pregnancy due to a relaxation of bronchial smooth muscles as a result of increased levels of cortisol and progesterone. Tidal volume increases from 450 to 600 mL and is facilitated by thoracic cage changes and is caused by an increase in the respiratory drive that is secondary to elevated levels of progesterone. Minute ventilation is consequently increased without any significant contribution from the respiratory rate *(15)*. Diffusing capacity of the lungs for carbon monoxide (DLCO) is quite similar to non-pregnant levels. Some studies show an increase during the first trimester with a decrease until 24–27 weeks of gestation with normalization occurring after delivery *(16)*. Despite hyperventilation, pregnant women have a drop in their oxygen levels in the supine position late in pregnancy. Resting oxygen consumption increases by 20% during pregnancy as a consequence of fetal growth and demands from other conception products as well as the increase in cardiac and respiratory work of the mother. With exercise, because of the increase in oxygen consumption and decrease in functional residual capacity,

ventilatory reserves are reduced *(17)*. Therefore, restrictive pulmonary disorders associated with hypoxemia and/or PH may pose significant risks to both mother and fetus during pregnancy.

Systemic Sclerosis

Pulmonary involvement in systemic sclerosis is very common and bears a poor prognosis. Interstitial lung disease is the most common respiratory manifestation, followed by PH. Alveolar hemorrhage, pleural involvement, and respiratory muscle weakness are less common.

The Effect of Pregnancy on Systemic Sclerosis

Steen et al. followed 59 women with systemic sclerosis who had 91 pregnancies. These patients were compared to control subjects. Scleroderma symptoms, mainly those of Raynaud's syndrome were unchanged or improved. Most women had no change in their symptoms in the post-partum period *(18)*. The increase in intra-abdominal pressure during pregnancy might increase pulmonary symptoms associated with gastro-esophageal reflux due to esophageal involvement in systemic sclerosis (Figure 17.1).

Lambe et al. examined associations between childbearing and the risk of systemic sclerosis: nulliparity was associated with an increased risk of systemic sclerosis and the risk decreased with the number of births. Among parous women, younger age at first birth was associated with an increased risk of systemic sclerosis. These findings suggest that pregnancy may have a protective effect through an unknown mechanism *(19)*.

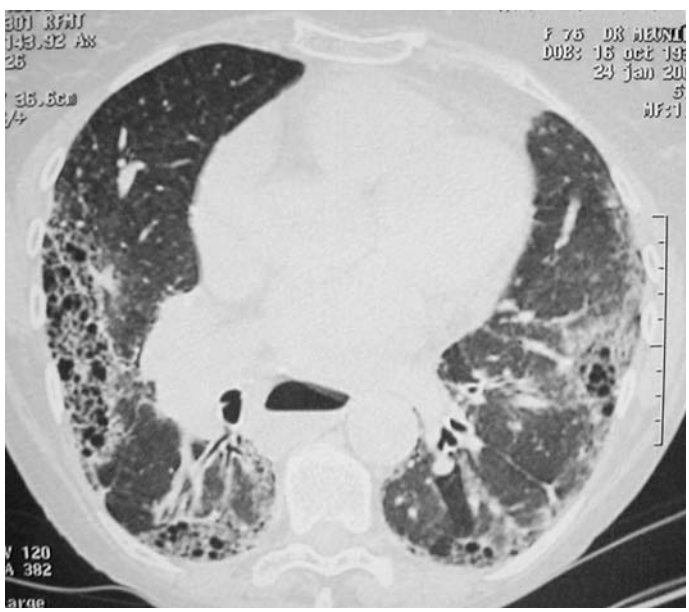


Figure 17.1 High resolution CT-scan at the lower lobes level. Severe interstitial lung disease and esophageal dilatation in a patient with systemic sclerosis

The Effect of Systemic Sclerosis on Pregnancy and Fetal Outcome

The effect of systemic sclerosis on pregnancy remains controversial. Old studies reported poor outcomes for the mother and fetus with fetal loss, and preterm delivery. Several retrospective studies showed fewer complications *(20, 21)*. In other studies *(18)*, miscarriages were more common in women with long-standing diffuse systemic sclerosis. The frequency of preterm births was higher in the systemic sclerosis pregnant group than in controls (about 30% of pregnancies compared with 5% in controls). Preterm births were also significantly higher in the diffuse scleroderma group compared to other types of the disease. Factors affecting preterm birth were thought to be related to hypertension or mild preeclampsia in four patients, premature rupture of the membranes in four, and placental bleeding in two patients. In 7 out of the 19 patients with preterm births, no fetal or maternal cause was identified *(18)*.

Steen et al. *(18)* reported five patients who had pulmonary fibrosis, none of whom required oxygen. Three patients had preterm deliveries and children were reported to be healthy without significant details on prematurity and need for neonatal intensive care. One patient developed aspiration pneumonia and adult respiratory distress syndrome (ARDS) and therefore had a therapeutic abortion at 20 weeks. One patient with a vital capacity of 55% of predicted had two elective abortions.

Pulmonary hypertension is a frequent and severe complication of systemic sclerosis. Although there is no clear data in the literature on the course of PH associated with systemic sclerosis during pregnancy, PH associated with systemic sclerosis shares similarities with idiopathic PH. PH primarily endangers pregnant women *(22)*. Maternal death rate is increased (30–52%) and so is fetal/neonatal mortality (fetal and neonated demise 12%). Death of the patient most often occurs after delivery due to acute or progressive right sided heart failure. Late hospital admission, operative delivery, and pulmonary vasculitis were identified as factors contributing to maternal death *(22)*. During the pregnancy and the post-partum period, there may be a need for selective pulmonary vasodilators such as epoprostenol, inhaled NO, inhaled iloprost, or prostacyclin. A poor response to nitric oxide and maternal post-partum death was reported in a case of scleroderma associated with PH *(23)*. Aerosolized PGI2 or its analog iloprost is currently used as the drug of choice for patients with secondary vascular PH. Iloprost does not have any human pregnancy safety data. Data in different animal species has shown that Iloprost is not teratogenic in monkeys or rabbits at doses of 0.5 and 0.43 mg/kg. Teratogenic effects were, however, seen in rats at doses of 0.01, 0.1, and 1 mg/kg/day and a high rate of fetal death (50%) was observed at the highest doses *(24)*. Risks and benefits of selective pulmonary vasodilators should be weighed prior to their use in any pregnant patients. Safety of other drugs is discussed in more detail in the chapter on PH in pregnancy (Chapter 19).

When seen in preconception counselling, women with significant PH should be advised against pregnancy as the disease seems to progress rapidly during pregnancy and maternal and fetal mortality are both quite elevated *(25)*. Termination in the late stages of pregnancy (second trimester or beyond) is also associated with a great deal of morbidity and mortality, since cardiac output seems to peak half way through the second trimester and pulmonary pressures have likely increased significantly by that time.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic auto-immune disease that occurs predominantly in women of childbearing age. Almost any organ can be involved in SLE. Pulmonary manifestations mainly include pleural effusions and interstitial lung disease. PH is rare. Antiphospholipid antibodies are present in 20–40% of patients with SLE and may be responsible for alveolar hemorrhage, and other complications discussed below. Antiphospholipid antibody syndrome may also occur as an individual entity in patients who do not have SLE.

The Effect of Pregnancy on SLE

The effect of pregnancy on SLE remains controversial. Lupus flares can occur during any trimester and in the post-partum period, but the majority (46%) occurs during late pregnancy or the post-partum period *(26)*. However, most flares are mild and respond to low-doses of systemic steroids. The risk for lupus flare increases when the disease is active before pregnancy, and when low albumin level, proteinuria or elevated anti-double-stranded DNA antibody titers are detected during pregnancy. The use of prophylactic prednisolone during pregnancy is quite controversial. At doses above 10 mg/day, systemic steroids may also increase the risk of pregnancy-induced hypertension, preeclampsia, infection, as well as gestational diabetes *(27–30)*. Steroids should be kept at the minimum dose required to control active lupus. Bacterial pneumonia may occur during pregnancy, and differentiating infection from SLE activity is sometimes difficult, especially in case of acute lupus pneumonitis *(31)*. Bacterial pneumonia may be severe in SLE, and antibiotic therapy should be tailored to the most likely pathogens (usual pathogens, mycobacteria and nocardia).

Fulminant lupus pneumonitis may occur during pregnancy, often associated with pericarditis and/or pleuritis *(32)*. Dyspnea and/or hemoptysis may be secondary to alveolar hemorrhage, a rare and potentially fatal manifestation of SLE *(33)*, related to intravascular thrombosis of veins and arteries. In most of these cases, antiphosphoipid antibodies are present (anticardiolipin antibodies, lupus anticoagulant or B2 glycoprotein are detected). Treatment with high-dose corticosteroids remains the mainstay of therapy. Chang et al. reported diffuse alveolar hemorrhage in 8 of 1,541 patients with SLE in Taiwan: among the eight patients, two were pregnant and successfully treated with combined plasmapheresis, veno-venous hemofiltration, and high dose steroids *(34)*.

The Effect of SLE on Pregnancy and Fetal Outcome

In clinical practice, it is difficult to differentiate SLE manifestations from pregnancy-related hypertensive complications. Indeed, preeclampsia and eclampsia can mimic lupus, presenting with edema, hypertension, anemia, thrombocytopenia, proteinuria, and renal impairment. In Singapore, maternal mortality rate was evaluated among 26,173 deliveries. Nine maternal deaths were reported. The causes of death were related to systemic lupus in three cases complicated by pulmonary embolism, antiphospholipid syndrome (APS), or interstitial pneumonitis *(35)*.

Pulmonary hypertension has a significant impact on pregnancy outcome and represents a significant cause of indirect maternal deaths *(36)*. Thus, in patients with PH, pregnancy should be considered high risk for both mother and fetus. However, stable patients treated with epoprostenol or nebulized prostacyclin

analogue iloprost may successfully complete pregnancy *(37, 38)*. A case of pulmonary metastasis of choriocarcinoma with PH secondary to tumor emboli has been reported during the course of SLE *(39)*.

The risk of adverse fetal outcome is increased in SLE. The most common predisposing factor to prematurity in SLE is antiphospholipid antibodies.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies (aPLs) are a group of autoantibodies that recognize negatively charged phospholipids, phospholipid-associated proteins, or phospholipid–protein complexes. Although numerous aPLs have been identified, the ones that are most widely accepted and best characterized are lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti beta 2 glycoprotein 1. Table 17.1 summarizes the criteria for APS diagnosis.

Antiphospholipid syndrome is diagnosed when specific clinical features are identified in addition to specific levels of antiphospholipids. APS is associated with obstetric and thrombotic complications and its association with SLE increases maternal and fetal morbidity and mortality.

Table 17.1 Criteria for antiphospholipid antibody syndrome.

Antiphospholipid syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical Criteria:

(1) Vascular thrombosis: one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated criteria.
(2) Pregnancy morbidity
  (a) One or more unexplained deaths of a morphological normal fetus at or beyond the 10th week of gestation, or
  (b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of
    (i) eclampsia or severe preeclampsia, or
    (ii) recognized features of placenta insufficiency, or
  (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory:

(1) Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid dependent antibodies [4●●]).
(2) ACL antibody of IgG or IgM isotype in serum or plasma, present in medium or high titer, i.e., above 40 G phospholipid units or M phospholipid units, or above the 99th percentile, on two or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA) [4●●].
(3) Anti-β_2GPI antibody of IgG or IgM isotype, present in serum or plasma (in titer above the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures [4●●].

Adapted from: Pierangeli SS, Chen PP, Gonzalez EB. Antiphospholipid antibodies and the antiphospholipid syndrome: an update on treatment and pathogenic mechanisms. Current Opinion in Hematology. 2006;13:366–375.

Obstetric Complications

Numerous obstetric complications are thought to be secondary to APS. Prospective studies *(40–47)* have established a strong association between aPL and pregnancy loss; a large proportion of these losses occur in the second or third trimester. While fetal deaths usually make up only a small percentage of all pregnancy losses in the general population *(48)*, 50% of pregnancy losses in a large cohort of women with APS were related to fetal deaths *(48)*. Recurrent spontaneous abortions are also associated with aPL *(49, 50, 51, 52–58)*. Abnormal placentation is a characteristic of certain obstetric complications that are secondary to APS. These disorders include preeclampsia, which may occur in up to 48% of patients with APS *(59)*, intrauterine growth restriction complicating 15–30% of pregnancies in women with APS *(44, 59, 60, 61)*. Antiphospholipids are found to be present in a significant proportion of pregnant patients with severe preeclampsia occurring before 34 weeks of gestation *(62–65)*. Other complications include abnormal fetal heart rate tracings occurring in up to 50% of APS pregnancies *(44, 59)* and preterm birth occurring 12–35% of women with aPL *(44, 59, 43, 65)*. Indications for testing for aPL are discussed in Table 17.2.

Thrombosis

Thrombosis is the most important medical complication associated with aPL. About 2% of patients with an episode of unexplained venous thrombosis are found to have aPL *(66)*. Deep venous thrombi of the legs and pulmonary embolus are certainly the most common thromboses associated with aPL *(67)*, but thromboses may occur in unusual sites such as the cerebral circulation in pregnant women *(67–70)*.

Estimation of the increase in risk associated with aPL beyond the baseline incidence thrombosis associated with pregnancy is difficult to make because of lack of data on patients not receiving prophylactic anticoagulation. A meta-analysis estimated the odds ratio for venous thrombosis to be 3.2 (95% CI, 1.10–9.28) when only high titers of aCL were considered and 11.1 (95% CI, 3.8–32.3) in patients with LA *(71)*. This ratio may be even higher when antibodies to B2 Glycoprotein are present as well. Apparently, patients with APS with a

Table 17.2 Indications for antiphospholipid antibody testing.

Recurrent spontaneous abortion*
Unexplained fetal death in the second or third trimester
Severe preeclampsia before 34 weeks of gestation
Unexplained venous thrombosis
Unexplained arterial thrombosis
Unexplained stroke
Unexplained transient ischemic attack or amaurosis fugax
Systemic lupus erythematosus or other connective tissue disease
Autoimmune thrombocytopenia
False-positive result on serologic test for syphilis
Unexplained prolongation in clotting assay
Unexplained severe intrauterine growth restriction

*Three or more spontaneous abortions with no more than one live birth.

history of an obstetric complication of APS have a 60% chance of developing a venous thromboembolism (VTE) in the ensuing 10 years *(72)*.

The Catastrophic aPL Syndrome

The catastrophic aPL syndrome is a serious and often fatal complication in patients with aPL that results from widespread platelet thrombi in the microvasculature and large vasculature. This phenomenon is usually triggered by an inflammatory insult, such as surgery, delivery, or sepsis. A high index of suspicion should be kept when an acute pulmonary syndrome, HELLP, or multisystem disorder/SIRS occurs post-partum, especially in patients with known aPL.

Treatment of Pregnant Women with Antiphospholipid Syndrome

Heparin anticoagulation is the mainstay of treatment of patients with APS with the combination of heparin and low dose aspirin likely being the more effective regimen *(73, 74)*. A recent review summarizes all of the treatment trials to date that include heparin, low dose aspirin, steroids, or immunoglobulin therapy *(75)*. Patients without active or recurrent thrombosis, or another indication for lifelong anticoagulation, need only prophylactic levels of heparin anticoagulation but those should be administered throughout pregnancy.

Intravenous infusions of gamma globulin have been used for other indications, such as previous failure of heparin for the treatment of APS, severe placental insufficiency, and early-onset preeclampsia, but no evidence exists for or against efficacy in these circumstances *(76)*.

Unfortunately, the risk of complications related to aPL is not eliminated with delivery. Women with APS should be counseled about their risks for the development of nonobstetric disorders associated with aPL post-partum *(77)*. Long-term anticoagulation with coumadin should be considered in women with previous thromboses *(78)*. It is uncertain whether patients with APS but no previous thromboses should receive thromboprophylaxis, despite a clearly increased risk for thrombosis in this group.

Cases of neonatal lupus, caused by the transplacental passage of maternal IgG anti-Ro/SS-A and anti-La/SS-B antibodies to the fetus, have been described. Although it may be a benign syndrome with only cutaneous manifestations, there is risk for significant neonatal morbidity and mortality due to myocarditis and congenital complete heart block *(79)*.

Nevertheless, important advances in the obstetric care and medical evaluation and treatment of women with SLE have improved its complications in pregnancy.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common CVD. RA affects preferentially women. Pulmonary manifestations include pleural effusions, rheumatoid nodules, interstitial lung disease, bronchiectasis, and airway obstruction. Although PH is a rare manifestation of RA, alveolar hemorrharge related to pulmonary vasculitis may occur.

The Effect of Pregnancy on RA

RA improves in pregnancy. Remission is common and improvement occurs in 75% of cases during the first trimester. On the other hand, relapse in the post-partum period is frequent (90% of cases), most frequently 2 months after child birth. A quarter of patients with RA do, however, continue to have active disease or even worsening of arthritis. Modification of inflammatory and of anti-inflammatory mediators, as well as the increase in IL-10 and the Th2 cell activation may explain the clinical improvement *(6–9)*.

In patients with RA, deterioration or appearance of respiratory manifestations has not been reported during pregnancy. The risk of arthritis flare or the risk to develop RA is increased up to 6 months following delivery *(80, 81)*.

Interestingly, a study by Yan et al. investigated whether maternal serum levels of fetal DNA correlated with disease activity in 25 patients with RA and juvenile idiopathic arthritis. This study used quantitative polymerase chain reaction panel targeting unshared, paternally transmitted HLA sequences, or an insertion sequence within the glutathione S-transferase M1 gene was used to measure cell-free fetal DNA. This study found that maternal fetal DNA levels inversely correlated with disease activity both pregnancy and the post-partum period *(82)*.

The Effect of RA on Pregnancy and Fetal Outcome

Most pregnant women with RA have an uneventful pregnancy, with no significant complication.

Spondyloarthropathies (SA):
SA follow a similar course to RA during pregnancy. Patients with SA have not been reported to have pulmonary manifestations develop or worsen. However the risk of flares or the development of arthritic symptoms exists in those patients until 6 months post-partum *(80, 81)*. In addition, although the peripheral arthritis and uveitis improve in patients with spondyloarthropathy, spinal disease may deteriorate in about 25% of patients. Spinal manifestations may be difficult to manage, especially when high doses of corticosteroids may be required.

Sjögren's Syndrome

Severe respiratory manifestations during Sjögren's syndrome are rare. Dry cough and bronchiolitis are the most frequent manifestations, when bronchiectasis, interstitial lung disease, PH, lymphocytic alveolitis, and pulmonary lymphoma are rare.

The Effect of Pregnancy on Sjögren's Syndrome

In primary Sjögren's syndrome, pregnancy does not appear to influence the course of the disease *(83)*.

The Effect of Sjögren's Syndrome on Pregnancy and Fetal Outcome

A case-control study evaluated 58 patients with primary Sjögren's syndrome in Norway and compared them to a group of 157 controls *(84)*. These controls were selected randomly by a computerized method from the Birth and Population Registries of Norway and were matched for age and same area of residence.

Judging by the number of pregnancies in the Sjögren group, fertility was not thought to be affected. However, a significantly higher number of patients in the Sjögren group had 3 months or more of amenorrhea and the patient group also had higher rates of intervention for endometriosis. In addition, the study showed a higher risk of congenital atrioventricular block (with presence of anti-SSa antibodies) with a high neonatal morbidity and mortality *(85)*. Being based on a survey, this study is unfortunately somewhat limited by recall bias especially that the mean age of the patients was 55.

Polymyositis and Dermatomyositis

Pulmonary involvement is common in inflammatory myopathies, including respiratory muscle dysfunction, interstitial lung disease, lung cancer, aspiration pneumonia, and PH.

The Effect of Pregnancy on Myositis

Pregnancy outcomes and disease activity of polymyositis and dermatopolymyositis are not well defined with few case reports and retrospective studies being published. Older studies reported relapses of disease activity *(86)*. In more recent studies, no increase in activity of the disease was found during pregnancy *(87, 88)*. Few recent case reports described successful treatment with intravenous immunoglobulin therapy in women who had a flare of disease despite moderate-dose steroid therapy *(89, 90)*. No data about respiratory involvement during pregnancy and myositis were reported.

The Effect of Myositis on Pregnancy and Fetal Outcome

The effect of dermatopolymyositis on pregnancy is frequent and severe: miscarriage, prematurity, and fetal death in 50% of the cases *(86)*. In more recent studies, fetal mortality has improved but morbidity seems to be dependent on the degree of disease activity at the time of conception. In fact, in a recent retrospective study, 173 patients with dermatopolymyositis were followed: Nine patients had 14 pregnancies after the disease onset. Five women with disease in remission had uneventful pregnancies and delivered healthy babies. Among the four women (eight pregnancies) with active disease at the time of pregnancy, two had preterm birth, four had spontaneous abortions, and two had induced abortions. Only one woman had a healthy baby *(88)*.

Conclusion

Pulmonary involvement is common in CVD. Pregnancy and maternal outcome in CVD appear to be closely correlated with the health status of the mother. Pregnancies occurring during an inactive phase of disease show a positive outcome. Pregnancy is contraindicated in few respiratory complications such as PH or severe interstitial lung disease (vital capacity < 1 L and or DLCO $< 50\%$). Patients with ILD may require supplemental oxygen therapy early in pregnancy to avoid hypoxemic episodes, which may be dangerous for the fetus. During labor, maternal effort should be limited and oxygen saturation must be monitored. In cases of PH,

invasive pulmonary hemodynamic monitoring should be discussed. Care of these patients should be coordinated between chest physicians with expertise in pulmonary hypertension and the high risk obstetrician.

References

1. Doria A, Cutolo M, Ghirardello A, et al. Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. Arthritis Rheum 2002;47:202–209.
2. Weetman AP. The immunology of pregnancy. Thyroid 1999;9:643–646.
3. Tafuri A, Alferink J, Moller P, et al. T cell awareness of paternal alloantigens during pregnancy. Science 1995;270:630–633.
4. Jiang SP, Vacchio MS. Multiple mechanisms of peripheral T cell tolerance to the fetal "allograft". J Immunol 1998;160:3086–3090.
5. Zhang LI, Martin DR, Fung-Leung WP, et al. Peripheral deletion of mature CD8 + antigen-specific T cells after in vivo exposure to male antigen. J Immunol 1992; 148:3740–3745.
6. Adams KM, Yan Z, Stevens AM, et al. The changing maternal "self" hypothesis: a mechanism for maternal tolerance of the fetus. Placenta 2007;28:378–382.
7. Holmes VA, Wallace JM, Gilmore WS, et al. Plasma levels of the immunomodulatory cytokine interleukin-10 during normal human pregnancy: a longitudinal study. Cytokine 2003;21:265–269.
8. Steinbrink K, Jonuleit H, Muller G, et al. Interleukin-10-treated human dendritic cells induce a melanoma-antigen-specific anergy in CD8(+) T cells resulting in a failure to lyse tumor cells. Blood 1999;93:1634–1642.
9. Zhao DM, Thornton AM, DiPaolo RJ, et al. Activated CD4 + CD25 + T cells selectively kill B lymphocytes. Blood 2006;107:3925–3932.
10. Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. JAMA 2005; 294:2751–2757.
11. Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol 1978;85:260–263.
12. Contreras G, Gutierrez M, Beroiza T, et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144:837–841.
13. Boggess KA, Easterling TR, Raghu G. Management and outcome of pregnant women with interstitial and restrictive lung disease. Am J Obstet Gynecol 1995;173:1007–1014.
14. Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. Br J Obstet Gynaecol 1978;85:518–524.
15. Fishburne JI. Physiology and disease of the respiratory system in pregnancy. A review. J Reprod Med 1979;22:177–189.
16. Milne JA, Mills RJ, Coutts JR, et al. The effect of human pregnancy on the pulmonary transfer factor for carbon monoxide as measured by the single-breath method. Clin Sci Mol Med 1977;53:271–276.
17. Artal R, Wiswell R, Romem Y, et al. Pulmonary responses to exercise in pregnancy. Am J Obstet Gynecol 1986;154:378–383.
18. Steen VD. Pregnancy in women with systemic sclerosis. Obstet Gynecol 1999;94:15–20.
19. Lambe M, Bjornadal L, Neregard P, et al. Childbearing and the risk of scleroderma: a population-based study in Sweden. Am J Epidemiol 2004;159:162–166.
20. Steen VD, Conte C, Day N, et al. Pregnancy in women with systemic sclerosis. Arthritis Rheum 1989;32:151–157.
21. Chung L, Flyckt RL, Colon I, et al. Outcome of pregnancies complicated by systemic sclerosis and mixed connective tissue disease. Lupus 2006;15:595–599.
22. 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; 31:1650–1657.
23. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 4-1999. A 38-year-old woman with increasing pulmonary hypertension after delivery. N Engl J Med 1999;340:455–464.

24. Battenfeld R, Schuh W and Schobel C. Studies on reproductive toxicity of iloprost in rats, rabbits and monkeys. Toxicol 1995;letters 78:223–234.
25. Weiss BM, Hess OM. Pulmonary vascular disease and pregnancy: current controversies, management strategies, and perspectives. Eur Heart J 2000;21:104–115.
26. Cervera R, Font J, Carmona F, et al. Pregnancy outcome in systemic lupus erythematosus: good news for the new millennium. Autoimmun Rev 2002;1:354–359.
27. Petri M, Howard D, Repke J, et al. The Hopkins Lupus Pregnancy Center: 1987–1991 update. Am J Reprod Immunol 1992;28:188–191.
28. Lockshin MD, Reinitz E, Druzin ML, et al. Lupus pregnancy. Case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. Am J Med 1984;77:893–898.
29. Wong KL, Chan FY, Lee CP. Outcome of pregnancy in patients with systemic lupus erythematosus. A prospective study. Arch Intern Med 1991;151:269–273.
30. Khamashta MA, Ruiz-Irastorza G, Hughes GR. Systemic lupus erythematosus flares during pregnancy. Rheum Dis Clin North Am 1997;23:15–30.
31. Leikin JB, Arof HM, Pearlman LM. Acute lupus pneumonitis in the postpartum period: a case history and review of the literature. Obstet Gynecol 1986;68:29S–31S.
32. Comer M, D'Cruz D, Thompson I, et al. Pneumonitis in a lupus twin pregnancy: a case report. Lupus 1996;5:146–148.
33. Gaither K, Halstead K, Mason TC. Pulmonary alveolar hemorrhage in a pregnancy complicated by systemic lupus erythematosus. J Natl Med Assoc 2005;97:831–833.
34. Chang MY, Fang JT, Chen YC, et al. Diffuse alveolar hemorrhage in systemic lupus erythematosus: a single center retrospective study in Taiwan. Ren Fail 2002;24:791–802.
35. Loh FH, Arulkumaran S, Montan S, et al. Maternal mortality: evolving trends. Asia Oceania J Obstet Gynaecol 1994;20:301–304.
36. McMillan E, Martin WL, Waugh J, et al. Management of pregnancy in women with pulmonary hypertension secondary to SLE and anti-phospholipid syndrome. Lupus 2002;11:392–398.
37. Elliot CA, Stewart P, Webster VJ, et al. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J 2005;26:168–173.
38. Bendayan D, Hod M, Oron G, et al. Pregnancy outcome in patients with pulmonary arterial hypertension receiving prostacyclin therapy. Obstet Gynecol 2005;106:1206–1210.
39. Bologna C, Jorgensen C, Anaya JM, et al. Association of systemic lupus erythematosus and choriocarcinoma: a role of hormonal immunomodulation? Clin Exp Rheumatol 1994;12:59–61.
40. Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. Am J Obstet Gynecol 1989;161:369–373.
41. Lynch A, Marlar R, Murphy J, et al. Antiphospholipid antibodies in predicting adverse pregnancy outcome. Ann Intern Med 1994;120:470–475.
42. Pattison NS, Chamley LW, McKay EJ, et al. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations. Br J Obstet Gynaecol 1993;100:909–913.
43. Yasuda M, Takakuwa K, Tokunaga A, Tanaka K. Prospective studies of the association between anticardiolipin antibody and outcome of pregnancy. Obstet Gynecol 1995;86:555–559.
44. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80:614–620.
45. Rai RS, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. Hum Reprod 1995;10:3301–3304.
46. Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone to low-dose heparin treatment. Am J Obstet Gynecol 1992;166:1318–1327.

47. Out HJ, Bruinse HW, Godlieve CML, et al. A prospective, controlled multicenter study on the obstetric risks of pregnant women with antiphospholipid antibodies. Am J Obstet Gynecol 1992;167:26–32.
48. Goldstein SR. Embryonic death in early pregnancy: a new look at the first trimester. Obstet Gynecol 1994;84:294–297.
49. Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW. Antiphospholipid antibodies and fetal death. Obstet Gynecol 1996;87:489–493.
50. Rai RS, Regan L, Clifford K, et al. Antiphospholipid antibodies and beta2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Hum Reprod 1995;10:2001–2005.
51. Yetman DL, Kutteh WH. Antiphospholipid antibody panels and recurrent pregnancy loss: prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. Fertil Steril 1996;66:540–546.
52. Petri M, Golbus M, Anderson R, Whiting-O'Keefe Q, Corash L, Hellmann D. Antinuclear antibody, lupus anticoagulant, and anticardiolipin antibody in women with idiopathic habitual abortion. Arthritis Rheum 1987;30:601–606.
53. Barbui T, Cortelazzo S, Galli, et al. Antiphospholipid antibodies in early repeated abortions: a case-controlled study. Fertil Steril 1988;50:589–592.
54. Parazzini F, Acaia B, Faden D, Lovotti M, Marelli G, Cortelazzo S. Antiphospholipid antibodies and recurrent abortion. Obstet Gynecol 1991;77:854–857.
55. Parke AL, Wilson D, Maier D. The prevalence of antiphospholipid antibodies in women with recurrent spontaneous abortion, women with successful pregnancies, and women who have never been pregnant. Arthritis Rheum 1991;34:1231–1235.
56. Out HJ, Bruinse HW, Derksen RHWM. Antiphospholipid antibodies and pregnancy loss. Hum Reprod 1991;6:889–897.
57. MacLean MA, Cumming GP, McCall F, Walker ID, Walker JJ. The prevalence of lupus anticoagulant and anticardiolipin antibodies in women with a history of first trimester miscarriages. Br J Obstet Gynaecol 1994;101:103–106.
58. Balasch J, Creus M, Fabregues F, et al. Antiphospholipid antibodies and human reproductive failure. Hum Reprod 1996;11:2310–2315.
59. Lima F, Khamashta MA, Buchanan NMM, et al. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumatol 1996;14:131–136.
60. Caruso A, DeCarolis S, Ferrazzani S, et al. Pregnancy outcome in relation to uterine artery flow velocimetry waveforms and clinical characteristics in women with antiphospholipid syndrome. Obstet Gynecol 1993;82:970–977.
61. Kutteh WH. Antiphospholipid antibody associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low dose aspirin alone. Am J Obstet Gynecol 1996;174:1584–1589.
62. Sletnes KE, Wislof F, Moe N, Dale PO. Antiphospholipid antibodies in preeclamptic women: relation to growth retardation and neonatal outcome. Acta Obstet Gynecol Scand 1992;71:112–117.
63. Moodley J, Bhoola V, Duursma J, Pudfin D, Byrne S, Kenoyer DG. The association of antiphospholipid antibodies with severe early onset preeclampsia. S Afr Med J 1995;85:105–107.
64. Branch DW, Andres R, Digre KB, Rote NS, Scott JR. The association of antiphospholipid antibodies with severe preeclampsia. Obstet Gynecol 1989;73:541–515.
65. Milliez J, Lelong F, Bayani N, et al. The prevalence of autoantibodies during third trimester pregnancy complicated by hypertension or idiopathic fetal growth retardation. Am J Obstet Gynecol 1991;165:51–56.
66. Badacarro MH, Vessey M. Recurrence of venous thromboembolic disease and the use of oral contraceptives. Br Med J 1974;1(5901):215–217.
67. Rosene-Montella K. Hypercoagulable states in pregnancy. Curr Obstet Med 1993; 2:141–161.
68. Schafer AI. The hypercoagulable states. Ann Intern Med 1985;102:814–828.

69. Hughes GRV. The antiphospholipid syndrome: ten years on. Lancet 1993: 342:341–344.
70. Toubi E, Khamashta MA, Panarra A, Hughes GR. Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. Am J Med 1995:99:397–401.
71. Wahl DG, Guillemin F, de Maistre E, et al. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. Lupus 1998;7:15–22.
72. Sammaritano LR. Therapy insight: guidelines for selection of contraception in women with rheumatic diseases. Nat Clin Pract Rheumatol 2007;3(5):273–281.
73. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997;314:253–257.
74. Kutteh WH. Antiphospholipid antibody associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low dose aspirin alone. Am J Obstet Gynecol 1996;174:1584–1589.
75. Petri M, Qazi U. Management of antiphospholipid syndrome in pregnancy. Rheum Dis Clin N Am 2006;32:591–607.
76. Kochenour NK, Branch DW, Rote NS, Scott JR. A new postpartum syndrome associated with antiphospholipid antibodies. Obstet Gynecol 1987;69:460–468.
77. Silver RM, Draper ML, Scott JR, Lyon JL, Reading J, Branch DW. Clinical consequences of antiphospholipid antibodies: a historic cohort study. Obstet Gynecol 1994;83:372–377.
78. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995;332:993–997.
79. Ruiz-Irastorza G, Khamashta MA. Systematic lupus erythematosus and antiphospholipid syndrome during pregnancy. Z Rheumatol 2006;65:192–194, 196–199.
80. Ostensen M, Ostensen H. Ankylosing spondylitis – the female aspect. J Rheumatol 1998;25:120–124.
81. Barrett JH, Brennan P, Fiddler M, et al. Breast-feeding and postpartum relapse in women with rheumatoid and inflammatory arthritis. Arthritis Rheum 2000; 43:1010–1015.
82. Yan Z, Lambert NC, Ostensen M, et al. Prospective study of fetal DNA in serum and disease activity during pregnancy in women with inflammatory arthritis. Arthritis Rheum 2006;54:2069–2073.
83. Picone O, Alby C, Frydman R, et al. Sjogren syndrome in Obstetric and Gynecology: literature review. J Gynecol Obstet Biol Reprod (Paris) 2006;35:169–175.
84. Haga HJ, Gjesdal CG, Irgens LM, et al. Reproduction and gynaecological manifestations in women with primary Sjogren's syndrome: a case-control study. Scand J Rheumatol 2005;34:45–48.
85. Costedoat-Chalumeau N, Amoura Z, Le Thi Hong D, et al. Neonatal lupus syndrome: review of the literature. Rev Med Interne 2003;24:659–671.
86. Gutierrez G, Dagnino R, Mintz G. Polymyositis/dermatomyositis and pregnancy. Arthritis Rheum 1984;27:291–294.
87. Silva CA, Sultan SM, Isenberg DA. Pregnancy outcome in adult-onset idiopathic inflammatory myopathy. Rheumatology (Oxford) 2003;42:1168–1172.
88. Vancsa A, Ponyi A, Constantin T, et al. Pregnancy outcome in idiopathic inflammatory myopathy. Rheumatol Int 2007;27:435–439.
89. Williams L, Chang PY, Park E, et al. Successful treatment of dermatomyositis during pregnancy with intravenous immunoglobulin monotherapy. Obstet Gynecol 2007; 109:561–563.
90. Mosca M, Strigini F, Carmignani A, et al. Pregnant patient with dermatomyositis successfully treated with intravenous immunoglobulin therapy. Arthritis Rheum 2005; 53:119–121.

18

Venous Thromboembolism in Pregnancy

Karen Rosene-Montella and Ghada Bourjeily

Introduction

Pregnancy is a hypercoagulable state accompanied by changes in maternal physiology that also contribute to an increased risk of thrombosis. Diagnosis and treatment of venous thromboembolism (deep venous thrombosis and pulmonary embolism) during pregnancy present unique challenges. In non-pregnant patients, there is ample clinical research upon which recommendations are based, but there is a paucity of data in pregnancy resulting in difficulties in establishing specific recommendations. Management of pregnancy associated venous thromboembolism (VTE) is further complicated by the potential effects of diagnostic testing and therapy on the fetus, the lack of validation of therapeutic interventions in pregnancy, and by patient and provider fears.

Untreated pulmonary embolism carries an in-hospital mortality rate close to 30%, which falls to 8% when pulmonary embolism is appropriately diagnosed and treated *(1)*. Although mortality in the obstetric population from VTE is decreasing in some parts of the world *(2, 3)*, PE continues to be a major cause of mortality in many other parts *(4, 5)*. Thus, it is imperative when thromboembolism is suspected, to provide diagnosis and treatment that are both immediate and effective. Hesitancy to use standard diagnostic and therapeutic tools in pregnant women may delay the diagnosis and contribute to maternal mortality. Failure to diagnose pulmonary embolism because of mistaken fears that the testing required would harm the fetus was responsible for the majority of cases of fatal maternal PE in the UK Confidential Inquiry into Maternal Mortality *(6)*. This chapter will review the epidemiology, pathogenesis, diagnosis, prophylaxis, and treatment of pregnancy associated venous thromboembolism and thrombophilias. Recommendations for approaches to patients with suspected and confirmed pregnancy associated VTE and/or thrombophilia based on available data and consensus recommendations will be made, and suggestions for areas of further research will be discussed.

Epidemiology

Pulmonary embolism remains the leading cause of non-obstetric maternal mortality in the developed world *(7–9)*. Fifty percent of VTE in women under the age of 40 occurs in association with pregnancy and VTE is 10 times more common in

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_18

pregnant women than non-pregnant women of comparable age. Retrospective cohort studies using population-based administrative databases suggest that the incidence of VTE is 5–12 per 10,000 pregnancies in the antenatal period and 3–7 per 10,000 deliveries in the post-partum period *(10–13)* in contrast to an age and sex-adjusted incidence of 1.6 per 10,000 women and 0.2 per 10,000 women respectively in comparable time frames *(14)*. Obesity, smoking, preeclampsia, cesarean section, or thrombophilia may further increase the incidence of VTE in association with pregnancy.

Sixty-five percent of VTE occur ante-partum and in a recent study, the majority of these occurred in the first trimester. *(15)* A meta-analysis demonstrated that ante-partum VTE can occur in any trimester but found a higher incidence in later trimesters than individual studies that have demonstrated the highest incidence in the first *(12, 15)* and second trimesters *(16)*. More than a third of pregnancy-related VTE occur during the post-partum period, highlighting the increased daily risk of thrombosis in the 6–12 week post-partum period compared to the 40-week ante-partum period.

Pregnancy is a case study for Virchow's thrombosis triad: hypercoagulability, venous stasis, and vascular damage are all present during normal pregnancy and the puerperium. Hypercoagulability is a result of increased levels of procoagulant factors (increased factor V and VIII levels) and decreases in fibrinolytic and anticoagulant activity (decreased protein S levels and increased activated protein C resistance) *(17)* (Table 18.1). Venous stasis is a consequence of progesterone-induced smooth muscle relaxation and vasodilatation; so stasis is present early in the first trimester and peaks at 36 weeks, as a result both of increasing vein distensibility and compression of pelvic vessels by the enlarging gravid uterus *(18)*. Compression of the left iliac vein by the right iliac artery may account for

Table 18.1 Normal hematology values.

Test	Reference intervals	Change in pregnancy
CBC		
Leucocytes (WBC)	3.00–10.5 × 109/L	↑to 10–16 × 109/L
Hemoglobin (Hgb)	115–155 g/L	↓100–130 g/L
Platelet count	125–400 × 109/L	↓near term to as low as 115 × 109/L
PTT	24–36s	↔
INR	0.9–1.2	↔
Fibrinogen	>2.0 g/L	↑↑
Von Willebrand factor antigen (vWF)	*Group O:* 0.40–1.75 U/mL *Non-group O:* 0.70–2.10 U/mL	↑
Factor VIII	0.6–1.95 U/mL	↑
D-Dimer	<300 ug/L	↑
Protein C	*Functional:* 0.75–1.60 *Antigen:* 0.70–1.20 U/mL	↔
Protein S	*Functional:* 0.50–1.00 *Antigen:* 0.57–1.20 U/mL	↓
Antithrombin (AT)	0.80–1.25 U/mL	↔
Homocysteine	<10 umol/L	↑

Adapted from: Rodger M: Normal hematologic changes in pregnancy. In: Rosene-Montella K, Keely E, Barbour LA, Lee RV, eds. Medical Care of the Pregnant Patient. 2nd ed. Philadelphia, PA: American College of Physicians; 2008:423–425.

the marked propensity for left leg deep vein thrombosis in pregnancy *(19)*. The majority (over 90%) of DVTs in pregnancy develop in the left leg *(12)*. Vascular endothelial damage of pelvic vessels by either vaginal or operative delivery likely adds to the risk of post-partum venous thrombosis.

Pregnancy associated DVT or PE causes immediate morbidity from the acute event and its treatment as well as long term morbidity. Eighty percent of pregnant women with VTE go on to develop post-thrombotic syndrome despite treatment and 65% will have objectively confirmed deep venous insufficiency *(20)*. Risk benefit analyses of preventive measures need to take into account not only PE-related mortality, but the long term morbidity associated with chronic venous insufficiency as well.

Preconception Counseling

Thrombosis specific preconception counseling is required for all women at potentially high risk of pregnancy associated VTE. These include patients with previous thrombotic events, patients with family history of VTE, and patients with thrombophilias or other risk factors. Counseling should include an assessment of risk, recommendations for prophylaxis, and consideration for the need for ante-partum and post-partum anticoagulation. The maternal and fetal risks associated with anticoagulants, the signs and symptoms of recurrent DVT, and/or PE and a plan should these symptoms arise needs to be reviewed. Pregnant women are counseled to contact their physician in case they develop leg swelling, calf, thigh, groin, or buttock pain (especially unilateral) or if they develop chest pain (especially pleuritic) and/or shortness of breath that lasts longer than 15 min at rest, impairs functional ability or is of sudden onset. Women are also counseled to maintain adequate hydration, avoid prolonged immobilization, and consider prophylactic measures for prolonged air travel. Considerations for prophylaxis according to risk category are reviewed in the section below on prophylaxis and in Table 18.3.

Risk Factors

Risk factors for VTE that have been studied in pregnancy include prolonged bed rest, maternal age, family history of thrombosis, parity, previous thrombosis, thrombophilia, previous superficial phlebitis, pre-eclampsia, tobacco use, and operative delivery (C-section) (see Table 18.2). Studies of bed rest are conflicting with both negative and positive studies. In a recent, adequately powered case control study, prolonged bed rest during pregnancy was not demonstrated to be an independent risk factor for VTE *(21)*. However, in the RIETE registry, 19% of the 72 VTE events that occurred ante-partum followed 4 or more days of bedrest *(22)*. In a small case control study, family history of thrombosis (1st degree relatives) was demonstrated to be a risk factor for pregnancy-associated VTE *(23)*. In a large population based retrospective cohort study of pregnant women, cesarean section, parity greater than 3, pre-eclampsia, and tobacco consumption were all demonstrated to be risk factors for pregnancy-associated VTE while maternal age was not an independent risk factor *(24)*. However, in another retrospective cohort study higher VTE rates were observed with maternal age over 35 *(25)*. Women with pregnancy-associated VTE are more likely to have factor V Leiden (FVL) or prothrombin gene mutation than pregnant controls without VTE

Table 18.2 Risk factors for venous thromboembolism in pregnancy.

Well established risk factors	Less clear evidence is a risk factor
Thrombophilia	Prolonged bed rest
Family history of thrombosis	Maternal age
Previous VTE	Parity
Previous superficial phlebitis	Tobacco use
Operative delivery (C-section)	Pre-eclampsia

Adapted from: Rodger M, Rosene-Montella K, Barbour LA: Acute thrombeombolic disease. In: Rosene-Montella K, Keely E, Barbour LA, Lee RV, eds. Medical Care of the Pregnant Patient. 2nd ed. Philadelphia, PA: American College of Physicians; 2008:426–444.

(26, 27). Recent studies have demonstrated that the expected ante-partum VTE rates in thrombophilic women with prior idiopathic VTE are at least 10% (95% confidence intervals –0.25 to –44.5%) *(28)*. Thrombophilic women with prior secondary proximal VTE are estimated to have a 6% (95% confidence intervals –0.17 to –31.9%) risk of ante-partum VTE recurrence in subsequent pregnancies *(28)*. Superficial venous thrombosis has also been shown to be an independent risk factor for VTE in pregnancy (odds ratio of 9.4) in case-control studies *(24)*.

Risk estimates vary, based on the type of thrombophilia, with the highest recurrence risk associated with antithrombin deficiency, FVL and prothrombin Gene mutation homozygotes, compound heterozygotes (patients with more than one thrombophilia), and patients with true antiphospholipid antibody syndromes.

Activated Protein C Resistance and Factor V Leiden

Activated protein C (APC) dampens the activated coagulation and forms a complex, along with protein S and factor V, that deactivates two activated coagulation factors, factor Va and factor VIIIa. *(29–32)*. APC resistance (APCR) results in an imbalance of the coagulation cascade increasing the propensity for pathological thrombosis. This has been thought to be secondary, in most cases, to factor V Leiden (FVL), a mutated factor V *(30–33)*. FVL is inherited in an autosomal dominant fashion and is found in over 90% of patients with APCR *(34)*. Currently, APCR is the most common inherited hypercoagulable state in both pregnant and non-pregnant patients *(35)*. However, even in the absence of the FVL mutation, the frequency of APCR is increased in pregnancy with a significant fall in the activity of APC in the second and third trimesters. This is likely related to increased factor VIII and decreased free protein S levels *(36)*.

Obstetric complications with FVL are common and women with FVL are more than twice as likely to have severe preeclampsia *(37)*; have almost a threefold higher risk of IUGR *(38)*; more than a sixfold higher risk of placental abruption *(39)*; and are twice as likely to have repeated pregnancy loss *(40)*, especially losses in the second trimester.

Prothrombin Gene Variant

Prothrombin is the precursor to thrombin, and thrombin cleaves fibrinogen to form fibrin. Presence of the G20210A allele is associated with increased prothrombin levels and a predisposition to venous thromboembolic disease. G20210A allele

is now being implicated as a common cause of DVT in the lower extremities in both the non-pregnant and pregnant populations *(41, 42)*. Recent meta-analyses also suggest that prothrombin gene variant is associated with approximately a doubling of the risk for placenta mediated pregnancy complications.

Protein C, Protein S, and Antithrombin Deficiencies

Like APCR, these deficiencies have autosomal-dominant inheritance with variable penetrance. However, unlike FVL and PGV, where a single gene mutation is identified, Protein S, Protein C, and antithrombin are associated with hundreds of rare insertions, deletions, and point mutations. These proteins all have an inhibitory effect on coagulation and when they are deficient there is a substantially increased risk of venous thrombosis.

Patients with antithrombin deficiency appear to have the highest risk for thrombosis during pregnancy. Obstetric complications include an increased risk for fetal loss, with an estimated fivefold increase in the rate of stillbirth *(43)*.

Protein C deficiency and protein S deficiency have, on the other hand, been less often associated with thrombosis during pregnancy. However, because these deficiencies are rare, limited data are available for pooling in meta-analyses, resulting in imprecise estimates of risk with wide confidence intervals.

Antiphospholipid Antibodies

Antiphospholipid antibodies (aPLs) are a heterogeneous group of autoantibodies that recognize negatively charged phospholipids, phospholipid-associated proteins, or a phospholipid–protein complex. Although a number of aPLs have been described, lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti beta 2 glycoprotein 1 are best characterized and most widely accepted for clinical use.

These antibodies have been associated with numerous clinical problems, including arterial, venous, and small vessel thrombosis and recurrent pregnancy loss *(44–47)*. However, only those patients who have specific clinical features in addition to specific aPL levels are considered to have the antiphospholipid syndrome (APS). Other autoimmune conditions, especially systemic lupus erythematosus (SLE), often coexist with APS *(45)*.

In addition to fetal loss, aPL has been associated with several obstetric disorders. Pregnancies that result in surviving infants in women with aPLs are often complicated by early severe preeclampsia, intrauterine growth restriction (IUGR), placental insufficiency, and preterm birth *(48,49)*.

On the other hand, the most important medical complication associated with aPL is thrombosis, with DVT and PE being the most common. However, complications may occur at unusual sites such as the cerebral circulation *(50–53)*. APS is discussed in greater detail in the chapter on pulmonary complications of collagen vascular disease.

Hyperhomocysteinemia

Hyperhomocystinemia is an inborn error of metabolism and is an important cause of hypercoagulability and a risk factor for VTE and arterial thrombosis. In the severe form of hyperhomocystinemia, both arterial and venous thrombosis can occur. However, more recently it was discovered that mild acquired hyperhomocystinemia resulting from folic acid, vitamin B6, or vitamin B12 deficiency, renal failure or certain drugs was also associated with an increased risk for thrombosis *(54)*. Hyperhomocystinemia has also been associated with spontaneous abortion, placental infarction, and placental abruption.

The common C677T mutation for methylenetetrahydrofolate reductase (MTHFR) is associated with hyperhomocysteinemia; however, meta-analyses have failed to find an association between VTE and homozygosity for MTHFR C677T *(55)*. Likewise, this mutation has not been clearly implicated with placenta-mediated complications. Homocysteine levels decrease in pregnancy probably related to increased circulating volume, decreased albumin levels *(56)*, and to the use of prenatal vitamins containing folic acid.

Elevated Factor VIII

Elevated Factor VIII levels have been identified as a risk factor for a first VTE and a predictor of recurrent VTE in those that have had VTE. However, the appropriate upper limit for defining a factor VIII thrombophilia is debated, currently limiting the clinical utility of this test *(57)*. Furthermore, there are limited data in the literature evaluating the association of elevated FVIII levels and placenta-mediated pregnancy complications. Since normal pregnancy increases Factor VIII levels, it is possible that elevated Factor VIII will be an important cause of pregnancy associated thrombosis.

Compound Heterozygotes

The coexistence of risk factors has recently gained attention in the literature. In one study *(35)*, approximately 15% of patients with protein C deficiency and 39% of patients with protein S deficiency were positive for the FVL mutation greatly increasing the likelihood of expression of thrombosis. Similarly, coinheritance of hyperhomocystinemia and the FVL mutation may manifest as severe thrombotic events. The coexistence of aPLs and any of the other defects further increases the likelihood of both thrombosis and fetal loss.

Diagnosis

Clinical assessment of non-pregnant patients has been demonstrated to be useful in classifying patients into low, moderate and high pre-test probabilities *(58, 59)*. These classifications have been widely used in the general population. However, these studies do not specifically address pregnant patients. Moreover, the physiologic changes associated with pregnancy affect both the clinical presentation and the reliability of diagnostic testing. Cardiovascular physiologic changes include a rise in cardiac output by about 45% in singleton pregnancies and about 52% in twin pregnancies. This increase in cardiac output is due in part to an increase in heart rate (20%) and stroke volume. Plasma volume is about 50% higher by 32 weeks of gestation *(60–62)*. In late pregnancy, the diaphragm is raised by 4–5 cm particularly in the latter part of the pregnancy *(60, 63, 64)* and the functional residual capacity is reduced by about 20% *(60, 63)*.

Physiologic dyspnea is a common complaint in pregnancy and is partly related to the increase in minute ventilation. In addition, weight gain, anemia, and deconditioning are significant contributors to dyspnea, which may occur with exertion.

On the other hand, arterial oxygen tension is increased to about 105 mmHg during pregnancy and late in pregnancy, the alveolo-arterial gradient is slightly elevated *(60, 63, 65)*.

Clinical Predictors

A few studies have reported on the sensitivity and specificity of individual signs and symptoms in non-pregnant patients *(66–69)*. Overall, individual presenting symptoms do not reliably differentiate between patients with and without pulmonary embolism. One study confirms that the presence of chest wall tenderness in patients with pleuritic chest pain does not exclude pulmonary embolism *(70)*. However, that study did not include pregnant patients. In addition, one or more risk factors was present in over 96% of patients in a population of 1,231 non-pregnant patients treated for confirmed VTE *(71)*. Furthermore, in the PIOPED study, the presence of one or more risk factors was more common in patients with PE compared to those without a diagnosis of PE *(72)*. In that study, experienced clinicians were able to separate a cohort of non-pregnant patients with suspected pulmonary embolism into high, moderate, and low probability groups without using specific clinical decision tools. Another study by Perrier et al. also used clinical assessment alone to stratify patients into different risk categories *(73)*. Since those studies, clinical decision tools have been developed and validated for use in the non-pregnant population *(74–76)*.

Unfortunately, given that pregnancy is an independent risk factor for thrombosis, it is difficult to know how models of clinical prediction of pulmonary embolism could be applicable to a pregnant population. In addition, clinical prediction is complicated by the fact that a large proportion of pregnant women complain of dyspnea that is thought to be physiologic and have a physiologic increase in heart rate. More so, it is very likely that certain risk factors as well as the distribution of physical findings (e.g., left leg swelling) would be different in pregnant women. Consequently, the performance of clinical assessment may differ in this sub-population. Furthermore, historical risk factors, such as family or personal history of VTE, thrombophilia, or obstetric complications thought to be associated with thrombophilia (such as recurrent miscarriages, placental abruption) may be important determinants of pretest probability in the pregnant population.

In addition, the diagnostic value of a clinician's overall diagnostic impression has not been specifically studied in pregnant women with suspected PE. Consequently, clinical pretest probability cannot at this time be used in the management of pregnant women with suspected PE, whether or not it is based on prediction tools or clinician's "gestalt." However, this is an important area to consider for future research.

Diagnostic Procedures

Diagnostic assessment of PE in pregnant women is certainly complicated by the physiologic changes in pregnancy that affect the diagnosis of VTE. Understanding those changes helps alert clinicians to the limitations associated with diagnostic imaging techniques.

Arterial Blood Gases

In a small study by Powrie et al., the alveolo-arterial gradient was found to be normal in 10 out of 17 patients with confirmed pulmonary embolism compared to $<20\%$ in the general population *(77)*.

Electrocardiography

The electrocardiogram may show some minor changes in a normal pregnancy. Although the mean QRS axis has been reported to be deviated to the left because of the elevated hemidiaphragm, there are reports of no axis changes and right axis deviation as well. An elevated heart rate is not an unusual finding in a normal pregnant woman. While understanding that the changes mentioned may occur in normal pregnant women, electrocardiographic signs associated with PE may still be identified.

Imaging Procedures

Misuse or lack of use of adequate diagnostic procedures may affect diagnostic accuracy, and in the case of pulmonary embolism, it likely impacts mortality rates in pregnant women. Radiation exposure in pregnancy discussed in detail in the chapter on diagnostic testing (Chapter 5).

Radiation Exposure and Fetal Safety

The need to make an accurate diagnosis and adequately treat pulmonary embolism certainly outweighs the risk of fetal radiation exposure that diagnostic testing for VTE entails *(77–80)*. According to a report by the national commission on radiation protection, an exposure to less than 5 rads is considered acceptable in the course of a given pregnancy *(81)*.

Protocol modification as well as the use of physical barriers help reduce the amount of radiation but should only be applied in a way that would not affect diagnostic accuracy. Frequent voiding in the case of radioactive material may help avoid excessive radiation exposure. Physical barriers can be used to minimize exposure. A discussion between the radiologist, medical physicist, and the treating physician should take place to decide on ways to minimize radiation without compromising the accuracy of the diagnosis.

Chest Radiography

Chest radiographs are an important tool in the evaluation of patients with suspected pulmonary embolism. Chest roentgenograms help exclude other causes of symptoms including pulmonary edema, pneumonia, or pneumothorax and may identify findings that may be due to PE such as pleural effusions, atelectasis, or peripheral opacities. Chest radiographs will most likely be normal in gravidas suspected of having pulmonary embolism, since those patients are young and rarely have chronic lung disease that would cause abnormal radiographic findings *(82)*. Although finding another diagnosis does not always preclude using other imaging procedures in the work-up of pulmonary embolism, it may potentially offer an alternative diagnosis avoiding further radiation exposure and unnecessary testing without adding a significant amount of radiation (0.001 rad or less) *(79)*.

Ventilation-Perfusion Scans

Accuracy studies of ventilation perfusion scans have shown that a high probability scan has a positive predictive value (PPV) of 96% when associated with a high clinical likelihood. A low probability or normal/near normal scan have a negative predictive value of 96–98% when combined with a low clinical likelihood *(72)*.

Unfortunately, these accuracy studies did not include pregnant patients *(72)*. However, NPV and PPV of high or low probability readings are, in fact, significantly different when associated with high versus low clinical likelihood, illustrating the importance of interpreting VQ scan results concomitantly with clinical pretest probability. This fact is very important in the pregnant population since, as discussed above, there are no clinical prediction tools that are validated in pregnancy and a provider's clinical assessment has not been studied in terms of predicting the presence or absence of PE. For that reason, the predictive values of VQ scans is likely different in the pregnant compared to the general population, especially that, theoretically, pregnant patients would fall at least in the moderate risk category given that they have a risk factor. There are no accuracy data on VQ scans in pregnancy available for the pregnant population.

Outcome studies of the non-pregnant patients with negative VQ scans show less than 0.5% rate of fatal PE *(72)*. The outcome data available in the pregnant population are those based on small retrospective studies *(83, 84)*. Anticoagulation was withheld in 81 patients with a normal scan in one study *(83)* with one resultant death within 2 days. In the other study, anticoagulation was held in 52 patients with either normal or low probability scans and no VTE developed at follow up (3–60 months, mean 25 months) *(84)*.

Diaphragmatic elevation in pregnancy leads to a reduced FRC and may theoretically result in false positive interpretation of compressed areas. However, the rate of non-diagnostic or intermediate scans is significantly lower *(83, 85)* and that of normal scans significantly higher (73–83%) *(83, 85)* in pregnancy than in the general population *(72)*. This is likely a reflection of the general wellbeing and young age of the pregnant population but may also mirror the poor predictive power of the clinical presentation resulting in physicians ordering many normal tests.

CT Pulmonary Angiograms

Computed tomography (CT) has been used for the detection of pulmonary embolism for close to a decade. Although single-slice scanners frequently miss small peripheral emboli in the upper and lower lobes and horizontal emboli in the middle lobe and lingula, meta-analyses involving mostly single detector CT scanners showed good outcome data *(86)*.

The addition of detection rows has helped significantly in detecting small peripheral emboli. In general, CTPAs offer an alternative diagnosis in 25–40% of patients, provide information on the location and the extent of emboli, supply prognostic clues to the diagnosis *(87)*, and are cost-effective *(88, 89)*.

CTPA and Pregnancy

Some physiologic changes that occur in pregnancy such as the increase in plasma volume, cardiac output, and heart rate may affect the time between the injection and appearance of contrast in the main pulmonary artery, subsequently impacting vessel opacification. Poor opacification may make the interpretation of poor flow or no flow more challenging.

In the general population, the rate of inconclusive tests in the general population ranges between 1.9–9% *(86, 90, 91)* but is much higher in the pregnant population *(92)*. No accuracy or outcome data are available to date on CTPAs in pregnancy. Retrospective studies, published only in abstract form so far, of a total of 78

patients who had technically adequate, negative CTPA with leg dopplers performed within 48 h of CTPA, showed 2 positive dopplers out of 78 negative CTPAs *(93)*. There are, however, ongoing studies looking at outcomes following CTPA both retrospectively and prospectively. Accuracy studies of imaging tests are harder to perform in pregnancy given the obvious concern about radiation exposure to the fetus.

Fetal Radiation Exposure

The amount of fetal radiation exposure following a CT angiogram is likely lower than the amount that follows a ventilation perfusion scan *(94)* even when a perfusion scan alone is performed. Radiation exposure varies by protocol used. For instance, the addition of detection elements in multidetector scanners likely increases the amount of radiation absorbed by the fetus. However, some experts argue that the addition of elements improves tube utilization output and reduces the ratio of excess radiation dose that does not contribute to image generation *(95)*. Although collimation thickness increases the amount of radiation exposure *(96)*, the enhanced image resolution leading to an augmented accuracy in detecting pulmonary emboli with the thinner slices outweigh the risks of fetal radiation exposure.

Breast Radiation Exposure

Another concern in using CT angiograms in young female patients is the amount of breast radiation exposure. Extrapolation of data from atomic bomb survivors suggests that exposure of the breasts before age 20 to a radiation dose of 1 Sv or higher was associated with an estimated RR of cancer of 14.6% *(97–101)*. A CT of the chest done without breast shielding exposes the breast to an average of 2–5 rads *(102, 103)*. Bismuth breast shields were shown to reduce the amount of radiation exposure from an average of 2.2 to 1.0 rad *(102)* but unfortunately those are not routinely used in the US. More recent reports using BEIR VII calculations suggest a relative risk of breast cancer following CT coronary angiography was estimated at 1 in 143 at age 20 and a lifetime relative risk of 0.7% after exposure to an average of 0.0005–0.0008 Gy *(104)*, which is higher than the amount of exposure to the breasts from a CT pulmonary angiogram. Although there are no convincing data to suggest that pregnant women's breasts are more susceptible to radiation compared to the non-pregnant population, it would be prudent to use breast shields during chest CTs in this young patient population.

Isolated Subsegmental Emboli

The clinical significance of subsegmental emboli is debated in the literature and management of those emboli has been individualized based on patient's risk factors and overall status. A report from the Fleishner society *(105)* as well as other experts *(106)* suggests treating emboli if (1) there's evidence of DVT, (2) poor cardiopulmonary reserve, and (3) hypercoagulable state placing patients at risk for recurrence. Given that pregnant patients are hypercoagulable, it may be prudent to work them up further or even treat them for subsegmental emboli until further evidence supports withholding anticoagulation.

Pulmonary Angiography

Pulmonary angiograms have been considered the gold standard in the diagnosis of PE for many years. In recent years, they are performed much less often and they seem to be slowly replaced by CTPA. The disadvantage of this test in the pregnant population is the relatively high radiation dose, especially if the femoral route is being used. However, this amount remains significantly lower than 5 rad (the upper limit of radiation considered acceptable in pregnancy).

Magnetic Resonance Imaging

Magnetic resonance (MR) imaging allows both an anatomical and a physiologic definition of thrombi. Thrombi are visualized as intravascular filling defects but their impact on the regional ventilation and perfusion is also provided by MR.

Multiple techniques may be used in the diagnosis of PE but the gadolinium enhanced MRA is the most common. Although MR may be as sensitive as a CTPA in detecting proximal, lobar, and segmental emboli *(107–109)*, its limited resolution does not allow a reliable detection of subsegmental emboli. When this technique was compared to pulmonary angiography, it detected all lobar and segmental pulmonary emboli but its sensitivity for subsegmental clots was only 40%. Some experts argue that a lower detection rate of subsegmental emboli may in fact be an advantage of this technique. Other techniques include real time MR (RT-MR), which is gated to the patient's respiration and shows emboli on T2 weighted images, without necessitating the use of gadolinium. In a study by Kluge et al. *(110)*, the sensitivity of RT-MR was higher than Gd-MR when both were compared to 16-row MDCT. This technique is particularly attractive in the pregnant population since it does not involve the use of gadolinium. MR perfusion studies require the use of a contrast agent (usually gadolinium) and does not show direct evidence of clot. Instead, like nuclear study imaging, it generates a signal based on the volume of blood in a specific region. Although MR appears like an appealing alternative, its use cannot be routinely recommended until further studies are available. A multicenter trial (PIOPED III) is underway to evaluate the use of MR in diagnosing pulmonary embolism. Unfortunately, this study excluded pregnant patients.

The placental transfer of gadolinium has been studied in rabbits *(111)* and found to cross the rabbit placenta. The concentrations found in the placenta and the fetal urinary tract are thought to have a potential for rabbit fetal toxicity. Very limited studies are found in human pregnancies. Case reports of exposure to gadolinium in pregnancy report no adverse events but those certainly do not establish safety *(112, 113)*. Therefore, given the limited data regarding the use of gadopentetate in pregnancy, its use is limited to circumstances in which additional data provided by its use outweigh potential unknown risks.

Gadopentetate dimeglumine is found in small quantities in breast milk *(114)*. It is estimated that 0.009% of the maternal intravenous dose is transferred to the newborn *(114)*, which is less than 1/100th the dose used in neonates. Therefore many experts argue that nursing need not be held following the administration of gadolinium.

Imaging of the Lower Extremities

Impedence Plethysmography

Impedence plethysmography is another technique that has been validated in pregnancy by a study by Hull et al. *(115)* and this test was later shown to be inferior to

compression ultrasounds *(116, 117)*. Impedence plethysmography is no longer being used in most centers in North America.

Compression Ultrasonography

In both the non-pregnant and pregnant population the diagnostic imaging procedure of choice for the diagnosis of lower extremity venous thrombi is venous compression ultrasound (CUS) imaging. Venous ultrasound imaging is non-invasive and is not associated with fetal radiation exposure. (Figure 18.1)

Serial venous ultrasound imaging has been validated in clinical management studies to safely exclude DVT in unselected patients and to have high sensitivity and specificity for proximal DVT in accuracy studies in non-pregnant populations *(118)*. Leg venous ultrasound imaging is insensitive to calf DVT, which may propagate in pregnancy, hence the recommendation for serial CUS. If no DVT is detected by day 14, then DVT can be considered excluded. The only study that has evaluated the use of a single ultrasound in pregnancy is a retrospective study that included both pregnant and post-partum women *(119)*. Although this study has shown that initial ultrasounds are associated with a low rate of VTE at 3 months, the use of this strategy cannot be justified based on those numbers alone obviating the need for further prospective studies *(119)*.

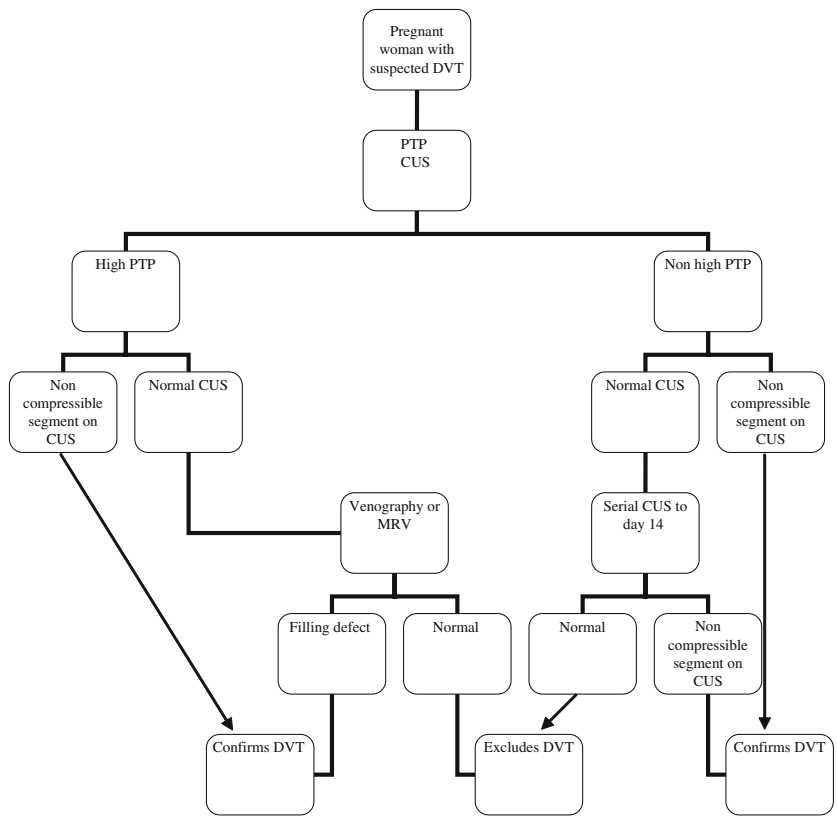


Figure 18.1 Management of suspected deep venous thrombosis in pregnancy. DVT: deep venous thrombosis; PTP: pretest probability; CUS: compression ultrasonography; MRV: magnetic resonance venography. Adapted from Rodger MA, Walker MC, Wells PC. Diagnosis and treatment of venous thromboembolism in pregnancy. Best Pract Res Clin Haematol. 2003;16:279–296.

Limitations of ultrasound testing include venous stasis, which progresses throughout pregnancy secondary to increases in vein diameter and compression from the gravid uterus *(18)*. These physiologic changes in pregnancy may affect the diagnostic accuracy of venous ultrasound imaging in pregnant women. In addition, there is increasing evidence that isolated pelvic thrombi can be found in pregnant and post-partum patients *(120)* and localized in the pelvic and iliac veins. Although a complete evaluation of the proximal venous system including the iliac veins and the distal inferior vena cava (IVC) is attempted in some institutions in the pregnant population, pelvic veins may be obscured by the enlarged uterus and are often difficult to fully assess by ultrasounds.

Therefore, in patients with significant leg swelling and negative ultrasound studies, evaluation of the iliac and the pelvic veins with magnetic resonance venography may be warranted, especially in patients with very proximal symptoms.

The evidence behind the use of leg studies in the work-up of pulmonary embolism is more complicated. Wells et al. have demonstrated that in non-pregnant patients with non-high probability VQ scans and initial normal ultrasonography, the performance of three additional venous ultrasound imaging tests over a 2-week period (serial ultrasound testing) can be used to safely exclude the diagnosis of pulmonary embolism *(121)*. However, the use of leg ultrasounds as an initial test to evaluate for PE is recommended in symptomatic non-pregnant patients by some societies *(122)* but not others *(123)*. It is not recommended to use CUS as a first choice in asymptomatic non-pregnant patients as this approach is not validated, CUS have a low PPV in asymptomatic patients and the percentage of patients with PE that have concomitant documented DVT on CUS is only in the range of 23–52% *(124–127)*. However, despite the lack of evidence to support the use of CUS in gravidas without DVT symptoms, many authors suggest their use as an initial test in the work-up of PE *(128–132)*. Disadvantages of this approach in pregnancy include (1) the NPV and PPV of a single ultrasound is not known in the pregnant population as the use of a single CUS has not been validated in the pregnant population; (2) Slow flow situations and the fact that pelvic thrombi are more common in pregnancy complicate the use if this test; (3) this approach has not been validated neither in the pregnant nor in the non-pregnant population; (4) data from the non-pregnant population suggest that although this test may improve diagnostic efficiency, this is achieved on the basis of diagnostic accuracy.

Further studies are needed to evaluate this approach in terms of diagnostic accuracy, cost-effectiveness, and radiation protection.

For all those reasons, we suggest chest imaging as an initial test in patients without leg symptoms suggestive of DVT.

Lower Extremity Venograms

Conventional Venograms

Conventional venograms have been considered the gold standard in the diagnosis of deep venous thrombi *(133)* but are rarely used in pregnancy because of their invasive nature and the amount of fetal radiation exposure associated with the test (close to 0.6 rad). The use of conventional venograms in the general population is now quite limited because of the wide availability of less invasive testing. In many centers, contrast venograms are only used in specific scenarios such as very swollen or obese legs, calf DVT where management may change based on the findings, and before placement of IVC filters or thrombolysis *(134)*.

CT Venograms

More recently, CT venograms became available and could be performed at the same time as the CTPA and with the same contrast bolus. In the PIOPED II trial, the addition of CT venograms showed an improvement in the sensitivity and specificity of CT angiograms (4, 8, and 16 row scanners) from 83 to 90% *(91)*.

The amount of fetal radiation exposure in CT venograms is estimated to be close to 5 rads, greatly affecting its use in pregnancy *(128, 135)*. Another disadvantage is the fact that CT venograms have not been studied in pregnancy. It is possible that the same physiologic changes that affect image resolution in CT angiograms of the chest would affect the technical adequacy of this test. More so, the fact that venous stasis increases in pregnancy and venous return is hindered by the enlarged uterus may affect the accuracy of the reading. Therefore, the routine use of CT venograms in pregnancy cannot be justified.

MR Venograms

MR venography is being increasingly used in the work-up of pelvic DVT in pregnancy, despite limited studies in pregnancy. Both time of flight angiography and true FISP can be used and neither one of those techniques involve the use of contrast. MR direct thrombus imaging (MRDTI) is another technique that relies on the detection of methemoglobin in an acute thrombus without the use of gadolinium. A superior advantage of MRDTI over other diagnostic modalities is its consistent sensitivity in the detection of clots anywhere in the lower extremities (above or below the knee and in the pelvis) *(136)*. MRDTI has been evaluated in the diagnosis of pulmonary embolism in small studies and has shown high sensitivity and specificity *(137)*. Further studies are needed to determine the right technique and inter-reader agreement, given the difficulties related to reading the slower flow associated with the gravid uterus.

2-D Echocardiography

Echocardiography helps assess right ventricular function and provides prognostic clues relating to in-hospital mortality from massive PE *(138, 139)* but is thought to be less predictive in hemodynamically stable patients *(140)*.

Echocardiography is, however, an insensitive tool in the diagnosis of pulmonary embolism *(141)*.

In the setting of acute PE, echocardiography helps evaluate right ventricular dilation, right atrial dilation, pulmonary hypertension, tricuspid regurgitation as well as paradoxical septal motion. Nonetheless, the hyperdynamic state of pregnancy may affect its interpretation. For instance, both the systolic and the diastolic dimensions are slightly increased in pregnancy and so is systolic function. Moreover, a moderate increase in the size of the right chambers and the left atrium is seen as well as a progressive dilation of pulmonary, tricuspid, and mitral valve annuli resulting in a mild degree of pulmonary, tricuspid, and mitral regurgitation *(142)*. Therefore, interpretation of 2D-echocardiograms should preferably be carried out by a cardiologist experienced in reading those in pregnancy

Laboratory Tests

D-Dimers

D-dimers have been evaluated in the workup of PE in the non-pregnant population mostly in those with a low clinical suspicion for PE and was shown to have a NPV

of 94% or better *(141, 143, 144)*. Recently, new D-dimer measurements emerged (VIDAS and latex agglutination assays (MDA)) that help in ruling out PE in patients with even a moderate suspicion *(145)*.The use of D-dimers in pregnancy is, however, complicated by the fact that D-dimers increase progressively in pregnancy and there are no established reference values for D-dimers in the pregnant population nor are there data evaluating the use of D-dimers in "filtering" patients with low or moderate clinical suspicion.

D-dimer levels rise during pregnancy *(146–148)* and are significantly higher at 26 and 34 weeks than 16 weeks and controls *(148)*. In addition, Bombeli evaluated serial D-dimers in pregnant women with thrombophilias or a family history of thrombosis *(149)*. Overall, in this study, D-dimer levels seem to increase as pregnancy progressed. However, when the thrombosis group was analyzed separately, levels seem to decrease in the first trimester then gradually increase. This study fails to mention the gestational age at which the clot occurred making it difficult to draw conclusions regarding the relationship of Dimers and the clot.

A study by Chan *(150)* using the qualitative SimpliRED assay showed a NPV of 100% in a cohort of 149 pregnant patients evaluated for DVT. The confidence interval in this study was at 95–100%.

In summary, there are no defined reference values for D-dimers in pregnancy and the negative predictive value of this test in this setting is not well known. In addition, the British Thoracic Society *(122)* recommends the use of D-dimers only in association with clinical pre-test probability, which has not been tested in the pregnant population. Hence, until further studies are done to establish normal D-dimer levels in pregnancy and their predictive power in the diagnosis of venous thromboembolism, the use of this test to exclude the diagnosis of pulmonary embolism cannot be recommended.

Prognostic Biomarkers

Troponins carry a good negative predictive value for death or in-hospital deterioration in the general population *(151–153)*. However, troponins have not been studied in pregnancy and no information is available regarding their correlation with clot burden in pregnancy.

Plasma brain natriuretic peptide (BNP) and N-terminal pro-BNP carry a good negative predictive value for in-hospital mortality in the general population *(154–157)*. Barker et al. evaluated 70 pregnant patients and found a weak but significant correlation between the log BNP and the cardiac power output *(158)* in patients with cardiac disease. This correlation was much weaker in the pregnant population than the non-pregnant population. Other small studies have found these markers to be significantly elevated in patients with severe pre-ecclampsia *(159,160)*, suggesting left ventricular dysfunction but were not studied in the setting of venous thromboembolism and right heart dysfunction. Therefore, biological markers need to be evaluated further in the pregnant population.

Other Thromboses

The search for a source of thrombi in pregnancy should consider some sites that would be quite uncommon in the non-pregnant population. *(161)*. Ovarian vein thrombosis, presents with flank, back, or groin pain, is often seen in the setting of post-partum endometritis with persistent fever and occurs more frequently on the right side *(16)*. Because propagation into the IVC and embolization has been seen

with this thrombosis, ovarian vein thrombosis should be viewed as a true DVT and treated accordingly *(162)*. More so, a clinical diagnosis of septic pelvic thrombophlebitis is no longer acceptable and imaging of the pelvic veins should be considered using MRI, MRV, or CT.

Patients with ovarian hyperstimulation have an unusually high incidence of subclavian vein thrombosis in the absence of intravenous catheters. The ovarian hyperstimulation syndrome, which results from high levels of serum estradiol (E2) and progesterone concentrations (greater than 1,500 pg/mL and greater than 30 ng/mL, respectively) is characterized by ascites, pleural effusions, and azotemia and often includes DVT.

Management

The absence of randomized controlled trials specific to pregnancy complicates VTE treatment recommendations. Additional factors that need to be considered during pregnancy management include the ongoing increased risk of VTE from pregnancy, the need for reversal of anticoagulation at the time of delivery, and the possible need for dosing alterations, given the increased volume of distribution and renal clearance of heparins in pregnancy. These factors lead to the need for individualized treatment recommendations that should be made in conjunction with a physician specializing in the care of VTE during pregnancy. Treatment recommendations often must be extrapolated from therapies based on evidence from studies of non-pregnant patients and tailored to pregnancy.

Treatment

Pharmacologic Therapy

Pharmacokinetics, Dosing, and Monitoring

Intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) are the mainstay of initial therapy both in the pregnant and the non-pregnant population. Both drugs enhance the action of antithrombin, preventing further thrombus formation and allowing time for fibrinolysis to dissolve the established clot.

Unfractionated heparin should be administered intravenously for the management of a new acute VTE (5–10 days; minimum 5 days) and can be used subcutaneously for the subacute management of DVT (after 5–10 days). Adjusted-dose subcutaneous heparin is given every 8–12 h to prolong the PTT into the therapeutic range or to achieve a mid-interval therapeutic heparin level (0.2–0.4) or heparin anti-Xa level of 0.35–0.67 (Table 18.3). Many laboratories do not report heparin levels or heparin anti-Xa levels but report corresponding therapeutic PTT ranges.

One caveat in long term anticoagulation in pregnancy is the fact that heparin requirements are increased and the difficulty maintaining anticoagulation with subcutaneous heparin. Some patients need up to 40,000 U/d to prolong the activated partial thromboplastin time (aPTT); with subcutaneous administration, dosages as high as 20,000 U every 8 h may be required to maintain adequate levels *(163)*. This decrease in bioavailability, seen especially with subcutaneous heparin, is due to pregnancy-related changes in pharmacokinetics. Increases are seen in heparin-binding proteins (such as von Willebrand factor [vWF]), plasma volume, renal clearance, and heparin breakdown by the placenta. Moreover, the

Table 18.3 Treatment of venous thromboembolism in pregnancy.

Ante-partum anticoagulation					
	Prophylaxis		Aggressive prophylaxis		
Drug	**First 20 weeks**	**20–37 weeks****	**First 20 weeks**	**20 weeks to term*****	**Full treatment***
Dalteparin	5000 U/d	5000 U q12h	100 U/kg/d	100 U/kg/d	100 U/kg q12h with antiXa monitoring
Enoxaparin	30 mg /d	30 mg q12h	1 mg/kg/d	1 mg/kg/d	1 mg/kg q12h with antiXa monitoring
Tinzaparin	4500 U/d	4500 U q12h	88 U/kg/d	88 U/kg/d	88U/kg q12h with antiXa monitoring
Heparin	Alternative if LMWH unaffordable 7,500 bid first 20 weeks 10,000 bid 20–37 weeks		Alternative if LMWH unaffordable 10,000 bid to achieve antiXa level of –0.1 to 0.3 U/ml		Adjusted to mid-interval anti-Xa 0.35–0.67 with q12h SC injections

Prophylaxis post partum anticoagulation			
	Prophylaxis	**Aggressive prophylaxis**	**Full treatment**
Dalteparin	5000 U/d	100 U/kg/d	100 U/kg q12h with antiXa monitoring
Enoxaparin	30 mg /d	1 mg/kg/d	1 mg/kg q12h with antiXa monitoring
Tinzaparin	4500 U/d	88 U/kg/d	88 U/kg q12h with antiXa monitoring
Warfarin	INR 2-3	INR 2-3	INR 2-3

*Anti Xa monitoring is recommended; target pre 0.2–0.3 and post 0.5–1.0.** Consider discontinuing at 37 weeks to allow uncomplicated delivery (use of epidural analgesia and reduce bleeding risk). ***Consider planned induction or elective C-Section.
U = units; /d = per day; q12h = every twelve hours; /kg=per kilogram
Adapted from: Rodger M, Rosene-Montella K, Barbour LA: Acute thromboembolic disease. In: Rosene-Montella K, Keely E, Barbour LA, Lee RV, eds. Medical Care of the Pregnant Patient. 2nd ed. Philadelphia, PA: American College of Physicians; 2008:426–444.

pregnancy-related increase in factor VIII levels may prevent prolongation of the PTT, even at adequate heparin levels. Therefore, when pregnant patients have unusually high heparin requirements, aPTT may be less than optimal in assessing dose requirements. When anti-Xa levels were used instead of aPTTs in monitoring a similar non-pregnant group *(163)*, lesser doses were required and unnecessary dose escalation was avoided.

LMWH administration has become standard therapy in the treatment of most VTE in non-pregnant patients, given its almost complete bioavailability, obviating the necessity of laboratory monitoring and dose adjustments *(164)*. However, LMWH should be avoided in patients with renal failure and in situations where urgent reversal of anticoagulation may be required (e.g., high bleeding risk or imminent surgery or delivery).

Long term LMWH use in pregnancy is more complex than the short term use in the non-pregnant population. Pharmacokinetic studies of LMWH in pregnancy show that drug clearance is dependent on gestational age *(165, 166)* and that prolonged use may result in an accumulation of dose effect *(167)*. Hence, treatment with full dose LMWH in pregnancy may best be done by monitoring target anti-Xa levels of 0.5–1.1, 3–6 h post dose. We recommend weekly anti-Xa

monitoring in patients on full treatment dose LMWH until the level is therapeutic and then patients are to be monitored monthly.

Complications

Although short term use of heparin use may be associated with some complications, prolonged therapy raises different concerns. The rate of major bleeding with prolonged UFH is estimated to be 2% *(168)*. Long term UFH therapy may cause osteoporosis and can lead to symptomatic fractures *(168)*. Heparin-induced decreases in bone density of >10% occurred in 30% of patients studied and was at least partly reversible. Post-partum bone density measurements should be considered in pregnant patients exposed to heparin, with recommendations for calcium, vitamin D, and weight-bearing exercise if osteopenia is detected. Heparin induced thrombocytopenia (HIT) is estimated to occur in 3–5% of patients treated with UFH, necessitating careful platelet monitoring daily in the first 5–7 days, then less frequently (weekly for a month then monthly).

Several meta-analyses of randomized controlled trials have shown that LMWH is as safe and effective as UFH in the treatment of acute VTE in the general population *(169, 170)*. The only randomized controlled trial comparing LMWH to UFH in the treatment of pregnancy associated VTE was only adequately powered to determine that LMWH causes less bone loss when compared to UFH *(171)*. Long term LMWH can result in osteoporosis and osteoporotic fractures; an osteoporotic fracture was reported in one patient (0.04%) in Greer's systematic review *(172)*. No adequately powered pregnancy studies examining differences in efficacy and other maternal safety parameters have been published; however, this study and a small series suggest equivalence *(173)*.

Although complications of LMWH for the parturient are likely uncommon, no studies examining its use in pregnancy have been adequately powered to accurately estimate the incidence of HIT or that of clinically significant bleeding after prolonged LMWH therapy in pregnancy. A recent systematic review including 64 reports documenting 2,777 pregnancies concluded that LMWH is safe during pregnancy *(172)*; there were no deaths reported in that study and the incidence of serious side effects was low.

Heparin induced thrombocytopenia results from the development of platelet activating anti-PF4/heparin complex antibodies. The diagnosis is made with HIT antibody formation in addition to other features such as unexplained thrombocytopenia, skin lesions at heparin injection sites, or acute systemic reactions after administration of an IV heparin bolus *(174)*. A careful review of the literature reveals two cases of HIT in pregnancy *(175, 176)*. Allergic skin reactions to LMWH were reported in 50 women (1.80%), some of which may be associated with HIT antibodies *(177)*. In Greer's systematic review *(172)*, significant bleeding was present (1.98% overall; 55 events), with 12 (22%) cases of significant antenatal bleeding, 26 (47%) cases of post-partum hemorrhage, and 17 (31%) wound hematomas.

In addition, therapy with LMWH near the time of delivery has been shown to reduce the likelihood of obtaining epidural anaesthesia *(178)* mainly because of the risk of epidural hematomas and hemiplegia in non-obstetric patients on anticoagulants undergoing epidural anaesthesia. Furthermore, the American Society of Regional Anaesthesia recommends withholding regional anaesthesia in parturients who have had LMWH injections in the 12–24 h prior to the procedure. Thus, analgesic options can be severely limited in patients receiving LMWH close to term.

Fetal Safety

LMWHs do not cross the placenta, making them safe for the fetus when administered during pregnancy. A small study has specifically examined the teratogenic potential of LMWH and found no difference in congenital malformations between women receiving LMWH and those receiving low-dose aspirin *(179)*. Greer's systematic review had limited data on fetal outcomes; in that study, successful fetal outcomes were defined as live births and were reported in 94.7% *(172)*. LMWH is only minimally secreted in the breast milk *(180)* and is not absorbed orally; hence, any LMWH in the breast milk would not be absorbed in the infant's GI tract and LMWH is safe to use in the nursing mother.

Warfarin should be avoided in pregnancy as it crosses the placenta and is associated with congenital malformations (especially with exposure from 6–12 weeks) and fetal and neonatal hemorrhage *(181)*. An embryopathy similar to chondromalacia punctata (stippled epiphyses and nasal and limb hypoplasia) has been reported in at least 5–10% of infants exposed to warfarin in that time period *(182)*. Although exposure after the first-trimester may prevent skeletal embryopathy, the risk for fetal bleeding persists throughout gestation, potentially leading to fetal loss. In addition, warfarin exposure at any point in gestation may result in fetal central nervous system (CNS) abnormalities that are probably secondary to bleeding (including dorsal and ventral midline dysplasias and midline cerebellar atrophy). These conditions present as microcephaly, optic atrophy, or mental retardation.

Moreover, the use of warfarin toward term is further contraindicated, when the combination of delivery-induced trauma and anticoagulation can cause serious bleeding in the neonate. Warfarin use during pregnancy is usually restricted to patients with mechanical heart valves between 12 and 34 weeks of gestation. Its use in pregnancy in this patient population is justified because of the high failure rates seen with therapeutic doses of standard heparin.

Duration of Therapy

Recognizing the above considerations, it is the practice of most centers in the US to treat acute VTE in pregnancy with full dose LMWH for 3–6 months and then either continue full therapeutic doses or reduce the dose to half of the full treatment dose throughout the remainder of pregnancy and at least throughout the post-partum period.

The total duration of therapy, after the post-partum period is over, should be long enough to complete a full course of therapy. Indications for longer term or lifetime anticoagulation should be the same as in the non-pregnant population (recurrent idiopathic VTE, antiphospholipid antibody associated VTE, high risk or combined thrombophilias).

Management of Anticoagulation Around Labor and Delivery

Other considerations to be taken into account include the management of anticoagulation around labor and delivery. Given that labor can occur at any time once patients are at term (37 weeks), our practice recommends changing patients over from LMWH to UFH around 36 weeks, since UFH is easier to reverse than LMWH and has a shorter half life in the event of an unexpected labor.

If the VTE is diagnosed near term (over 37 weeks) then consideration should be given to placement of a temporary IVC filter and a planned induction after reversal of anticoagulation. Reversal of anticoagulation without IVC filter protection is strongly discouraged in the 4-week period after the diagnosis of the VTE, given the

high mortality of untreated thromboembolism during this period *(183)*. When VTE occurs more remotely from term, longer unanticoagulated periods are acceptable. A discussion with the treating obstetrician should occur close to term to discuss ways to avoid an anticoagulant effect of subcutaneous heparin or LMWH at delivery. One way would be to replace subcutaneous heparin therapy with intravenous heparin therapy near term and induce labor 12–24 h later, usually according to the obstetrician's preference, which is usually based on history of parity and the status of the cervix. After delivery, heparin therapy (full-dose intravenous or adjusted-dose subcutaneous) should be resumed as soon as hemostasis is achieved and warfarin therapy should be started. Heparin therapy can be discontinued once a therapeutic international normalized ratio (INR) of 2.0–3.0 is achieved and warfarin should be continued at least until 8 weeks post-partum. In cases of complicated labor or after cesarian sections, it may be prudent to avoid overlapping both drugs immediately post-partum in order to avoid bleeding complications.

In patients receiving prophylactic doses of anticoagulation, LMWH should be substituted to UFH close to term. According to the recommendations of the American Society of Regional Anesthesia, no special considerations are to be made prior to the administration of regional anesthesia. Patients receiving prophylactic doses of LMWH may be denied regional anesthesia if they have received their last dose 12–24 h prior to the procedure.

Non-pharmacologic Therapy

Graduated compression stockings providing 30–40 mmHg should be considered in patients with pregnancy associated DVT to help reduce the risk of long term postphlebitic syndrome.

Thrombolytic Therapy

A total of 172 cases of thrombolytic therapy in pregnant patients have been reported worldwide. When these cases are combined, the maternal mortality rate is 1.2%, the bleeding rate is 8.1%, and the incidence of fetal loss is 5.8% *(184)*. Streptokinase at therapeutic doses was not associated with a fibrinolytic effect in cord blood and neither streptokinase nor urokinase seems to be teratogenic. When hemorrhagic complications occur, they are most frequently encountered intrapartum or post-partum when fibrinolytic therapy has been given near delivery. Tissue plasminogen activator is being used with increasing frequency, is not teratogenic, and seems to be the safest fibrinolytic drug in pregnancy. Indications for the use of thrombolysis is not different in the pregnant population and thrombolytic drugs should be considered in the presence of a life threatening PE or in case of thrombosis of a prosthetic heart valve. Thrombolysis is not indicated for DVT because of increased hemorrhagic complications, potential fetal risk, and an absence of proven efficacy in decreasing the incidence of the postphlebitic syndrome.

Prophylaxis for Thromboembolic Disease

Normal Pregnant Women

Although pregnancy and the puerperium result in an increased relative risk to develop VTE, preventative therapy is not currently recommended because absolute risks are very low (less than 1 in 1,000 pregnancies). In situations of greater risk, such as following urgent cesarean section, cesarean section in high risk patients

(i.e., those with well established risk factors [see Table 18.2]), and in patients with prolonged bed rest, thromboprophylaxis may be considered.

Thrombophilic Women with No Prior History of VTE or Prior Obstetric Complication

Ante-Partum Period

Although thrombophilic women are at greater relative risk of developing VTE and pregnancy complications in the ante-partum period, that risk remains low *(185)* and does not justify the use of thromboprophylaxis in these cases. The current standard of care in these patients is to observe without prophylaxis as little data is available about absolute risks. Further, even less is known about whether the benefits of prophylaxis (e.g., heparin) outweigh the known absolute risks of prophylaxis. The patients in this group with the highest risk are those with positive family history, homozygotes, compound heterozygotes, or antithrombin deficiency. Therefore, our recommendation are consistent with the ACCP consensus recommendations advocating that thromboprophylaxis be considered in this group.

Post-Partum Period

Post-partum prophylaxis is advised in all women with known thrombophilia. As described above, the daily relative risk of VTE is high in the post-partum period and it is expected that in thrombophilic women the absolute risks will be found to be significant. A choice of either warfarin with a target INR of 2–3 or prophylactic dose LMWH for 6 weeks should be instituted. Both cross into the breast milk to a small extent but do not alter the newborn's coagulation. In our experience, many mothers of newborn children prefer LMWH over warfarin in order to avoid the inconvenience of lab monitoring.

Women with Previous VTE

Patients with Previous History of VTE

In women with previous VTE (proximal DVT or PE) who are no longer on anticoagulants, risk stratification is required to determine the level of ante-partum VTE prophylaxis. A study of 125 women with a single previous VTE demonstrated that the lowest risk of recurrent VTE was in a subgroup of patients with a previous VTE that was secondary to a temporary risk factor without an identifiable thrombophilia *(28)*. The authors of this study concluded that it was safe to withhold ante-partum prophylaxis from this group, despite the small sample size and wide confidence interval. Based on these data, the ACCP does not recommend the use of anticoagulation if the prior event is secondary to a reversible risk factor *(186)*. However, most providers, including the authors, still use prophylaxis in this group, particularly if there is a positive family history, the index clot was in pregnancy or on oral contraceptives or an additional risk factor is present, especially since data from other studies demonstrates a higher risk in this group. *(187)* (Table 18.4). According to the same study by Brill-Edwards *(28)*, there is clear agreement that ante-partum prophylaxis should be recommended (1/10 women had ante-partum

Table 18.4 Rate of recurrent venous thromboembolism (VTE) during the recorded pregnancies and puerperium periods according to the presence or absence of thrombophilia and the circumstances of the first event.

	No. of women	No. of recurrent VTE/ no. of pregnancies% (95% CI)	No. of recurrent VTE/ no. of postpartum periods% (95%CI)
Thrombophilia			
Yes (all types)	35	5/63 7·9 (3·4–17·2)	4/45 8·8 (3·5–20·7)
Yes (factor V Leiden only)	19	2/39 5·1 (1·4–16·8)	4/28 14·2 (5·7–31·4)
No	53	4/92 4·3 (1·7–10·6)	6/75 8·0 (3·7–16·3)
Risk factors at first VTE			
None	21	2/47 4·2 (1·1–14·2)	1/32 3·1 (0·5–15·7)
Oral contraceptive use	14	2/21 9·5 (2·6–28·9)	0/15
Pregnancy/puerperium	33	5/51 9·8 (4·2–20·9)	7/45 15·5 (7·7–28·7)
Other transient risk factors	20	0/36	2/28 7·1 (1·9–22·6)

Permission Granted: De Stefano V, Martinelli I, Rossi E, Battaglioli T, Za T, Mannuccio Mannucci P, Giuseppe L: The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. British Journal of Haematology 2006;135, 386–391.

recurrences [10%, 95% CI 0.3–44%]) in women with unprovoked VTE and thrombophilia. Thromboprophylaxis should be considered in all women with a prior VTE and an identifiable thrombophilia (2/21women had ante-partum recurrences [10%, 95% CI –1% to 30%]. The risk of post-partum recurrence was 2.4% (3/125) (95%CI –0.5 to 7.0%) despite all study participants being recommended post-partum prophylaxis, suggesting a clear need for post-partum prophylaxis. Two of the three events occurred after hospital discharge arguing in favor of longer post-partum prophylaxis (6–8 weeks).

For ante-partum prophylaxis we recommend prophylactic dose LMWH with an empiric dose increase at or near 20 weeks (see Table 18.3) and post-partum prophylactic dose anticoagulation (See Table 18.3).

Patients with Current or Recent VTE, Currently on Treatment

In women on oral anticoagulants with a current or recent VTE, those drugs should be discontinued as soon as they become pregnant (missed menses and/or positive urine pregnancy test). In women who become pregnant and have had a recent VTE, full dose therapeutic LMWH is to be immediately initiated to complete a full course (6 months) of therapeutic anticoagulation. After 6 months of therapeutic anticoagulation aggressive prophylaxis in the form of half treatment dose LMWH, or, if the VTE is older than 6 months, standard prophylaxis should be offered. All patients should be continued on a prophylactic regimen once their treatment has been completed. (See treatment section for full discussion of therapeutic options and monitoring) (Table 18.3).

Conclusion

Clinicians and patients are hampered by the lack of specific evidence to guide the management of suspected and confirmed VTE in pregnancy. Further research is required to confidently make recommendations in this area. Nevertheless, these are common problems in pregnancy so evidence must be borrowed from non-pregnant populations and individualized diagnostic and treatment approaches applied to these patients.

References

1. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326:1240–1245.
2. Samuelsson E, Hellgren M, Hogberg U. Pregnancy related deaths due to pulmonary embolism in Sweden. Acta Obstetrica et Gynecologia 2007;86:435–443.
3. Biaggi A, Paradisi G, Ferrazzani S, De Carolis S, Lucchese A, Caruso A. Maternal mortality in Italy, 1980–1996. Eur J Obstet Gynecol Repro Biol 2004;114:144–149.
4. Panting-Kemp A, Geller SE, Ngyen T, Simonson L, Nuwayhid B, Castro L. Maternal deaths in an urban perinatal network, 1992–1998. Am J Obstet Gynecol 2000;183(5):207–1212.
5. Sullivan EA, Ford JB, Chambers G, Slaytor EK. Maternal mortality in Australia, 1973–1996. Aust N Z J Obstet Gynaecol 2004; 44:452–457.
6. Why mothers die 2000–2002. The Sixth Report of the confidential enquiries into maternal deaths in the United Kingdom. Gwyneth Lewis (Director and Editor), James Drife, MD (Clinical Director), RCOG Press of the Royal College of Obstetricians and Gynaecologists, London, CEMACH November 2004.
7. Atrash HK, Koonin LM, Lawson HW, Franks AL, Smith JC. Maternal mortality in the United States, 1979–1986. Obstet Gynecol 1990;76:1055–1060.
8. de Swiet M. Maternal mortality: confidential enquiries into maternal deaths in the United Kingdom. Am J Obstet Gynecol 2000;182:760–766.
9. Rochat RW, Koonin LM, Atrash HK, Jewett JF. Maternal mortality in the United States: report from the Maternal Mortality Collaborative. Obstet Gynecol 1988;72:91–97.
10. Andersen BS, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. The cumulative incidence of venous thromboembolism during pregnancy and puerperium. An 11 year Danish population – based study of 63,300 pregnancies. Acta Obstet Gynecol Scand 1998;77:170–173.
11. Treffers PE, Huidekoper BL, Weenink GH, et al. Epidemiologic observations of thromboembolic disease during pregnancy and in the puerperium in 56,022 women. Int J Gynaecol Obstet.1983;21:327–331.
12. Gherman RB, Goodwin TM, Leung B, Byrne JD, Hethumumi R, Montoro M. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999;94:730–734.
13. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. Br J Obstet Gynecol 2001;108:56–60.
14. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester study. Arch Intern Med 1991;151:933–938.
15. James AH, Tapson VF, Goldhaber SZ. Thrombosis during pregnancy and the postpartum period. Am J Ostet Gynecol 2005;193:216–219.

16. Rutherford SE, Phelan JP. Deep venous thrombosis and pulmonary embolism in pregnancy. Obstet Gynecol Clin North Am 1991;18:345–370.
17. Clark P, Brennand J, Conkie JA, McCall F, Greer IA, Walker ID. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. Thromb Haemost 1998;79:1166–1170.
18. Macklon NS, Greer IA, Bowman AW. An ultrasound study of gestational and postural changes in the deep venous system of the leg in pregnancy. Br J Obstet Gynaecol 1997;104:191–197.
19. Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. Obstet Gynecol Surv 1999;54:265–271.
20. Bergqvist A, Bergqvist D, Matzsch T, Lindhagen A. Late symptoms after pregnancy-related deep vein thrombosis. Br J Obstet Gynaecol 1990;97:338–341.
21. Carr MH, Towers CV, Eastenson AR, Pircon RA, Iriye BK, Adashek JA. Prolonged bed rest during pregnancy : Does the risk of deep vein thrombosis warrant the use of routine Heparin prophylaxis? J Mat Fet Med 1997;6:264–267.
22. Blanco-Molina A, Trujillo-Santos J, Criado J, Lopez L, Lecumberri R, Gutierrez R, Monreal M, for the RIETE Investigators*. Venous thromboembolism during pregnancy or postpartum: findings from the RIETE Registry. Thromb Haemost 2007;97(2):186–190.
23. McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997;78:1183–1188.
24. Danilenko-Dixon DR, Heit JA, Silverstein MD, Yawn BP, Petterson TM, Lohse CM et al. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post-partum: a population-based, case-control study. Am J Obstet Gynecol 2001;184:104–110.
25. Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scott Med J 1996;41:83–86.
26. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M 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.
27. Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost 2002;87:791–795.
28. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows RF, Kearon C et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med 2000;343:1439–1444.
29. Dahlback B. Inherited thrombophilia: resistance to activated protein C as a pathogenic factor of venous thromboembolism. Blood 1995;85:607–614.
30. Dahlback B. Factor V gene mutation causing inherited resistance to activated protein C as a basis for venous thromboembolism. J Intern Med 1995;237:221–227.
31. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 1994;330:517–522.
32. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, De Ronde H et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64–67.
33. Voorberg J, Roelse J, Koopman R, Buller HR, Berends F, ten Cate JW et al. Association of idiopathic venous thromboembolism with single point- mutation at Arg506 of factor V. Lancet 1994;343:1535–1536.
34. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood 1996;87:3531–3544.
35. Florell SR, Rodgers GM. Inherited thrombotic disorders: an update. Am J Hematol 1997;54:53–60.
36. Walker MC, Garner PR, Keely EJ, Rock GA, Reis MD. Changes in activated protein C resistance during normal pregnancy. Am J Obstet Gynecol 1997;177:162–169.

37. Lin J, August P. Genetic thrombophilias and preeclampsia: a meta-analysis. Obstet Gynecol 2005;105:182–192.
38. Howley HE, Walker M, Rodger MA. A systematic review of the association between factor V Leiden or prothrombin gene variant and intrauterine growth restriction. Am J Obstet Gynecol 2005;192:694–708.
39. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. Eur J Obstet Gynecol Reprod Biol 2002;101:6–14.
40. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss. A meta-analysis. Arch Intern Med 2004;164:558–563.
41. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M 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.
42. McColl MD, Ellison J, Reid F, Tait RC, Walker ID, Greer IA. Prothrombin 20210 G–>A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. Br J Obstet Gynecol 2000;107:565–569.
43. Brenner B, Mandel H, Lanir N, Younis J, Rothbart H, Ohel G et al. Activated protein C resistance can be associated with recurrent fetal loss. Br J Haematol 1997;97:551–554.
44. Asherson RA, Khamashta MA, Ordi-Ros J, et al. The "primary" antiphospholipid syndrome: major clinical and serologic features. Medicine (Baltimore) 1989;68:366–374.
45. Alarcon-Segovia D, Perez-Vasquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. Semin Arthritis Rheum 1992;21:275–286.
46. Pierangeli SS, Chen PP, Gonzalez EB. Antiphospholipid antibodies and the antiphospholipid syndrome: an update on treatment and pathogenic mechanisms. Curr Opin Hematol 2006;13:366–375.
47. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006:4:295–306. (This paper summarizes evidence-based revision of the preliminary consensus criteria of 1999).
48. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80:614–620.
49. Lima F, Khamashta MA, Buchanan NMM, et al. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumatol 1996;14:131–136.
50. Rosene-Montella K. Hypercoagulable states in pregnancy. Curr Obstet Med 1993;2:141–161.
51. Schafer AI. The hypercoagulable states. Ann Intern Med 1985;102:814–828.
52. Hughes GRV. The antiphospholipid syndrome: ten years on. Lancet 1993:342:341–344.
53. Toubi E, Khamashta MA, Panarra A, Hughes GR. Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. Am J Med 1995:99:397–401.
54. Bakker RC, Brandjes DP. Hyperhomocysteinaemia and associated disease. Pharm World Sci 1997;19:126–132.
55. Ray JG, Shmorgun D, Chan WS. Common C677T polymorphism of the methylenetetrahydrofolate reductase gene and the risk of venous thromboembolism: meta-analysis of 31 studies. Pathophysiol Haemost Thromb 2002;32:51–58.
56. Walker MC, Smith GN, Perkins SL, Keely EJ, Garner PR. Changes in homocysteine levels during normal pregnancy. Am J Obstet Gynecol 1999;180:660–664.
57. Wells PS, Langlois NJ, Webster MA, Jaffey J, Anderson JL. Elevated factor VIII is a risk factor for idiopathic venous thromboembolism in Canada – is it necessary to define a new upper reference range for factor VIII? Thromb Haemost 2005;93:842–846.
58. Wells PS, Hirsh J, Anderson DR, Lensing AWA, Foster G, Kearon C et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995;345:1326–1330.

59. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997;350:1795–1798.
60. Elkus R, Popovich J. respiratory physiology in pregnancy. Clin Chest Med 1992;13:555–565.
61. Hytten F. Blood volume changes in normal pregnancy. Clin Haematol 1985;14:601–612.
62. Lee W. Cardiorespiratory alterations during pregnancy. Crit Care Clin 1991;7:763–775.
63. Weinberger SE, Weiss ST, Cohen WR et al. Pregnancy and the lung: state of the art. Am Rev Respir Dis 1980;121:559–581.
64. Crapo RO. Normal cardiopulmonary physiology during pregnancy. Clin Obstet Gynecol 1996;39(1): 3–16.
65. Templeton A, Kelman GR. Maternal blood gases (PAO2-PaO2), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976;48:1001–1004.
66. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598–603.
67. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. Am J Cardiol 1991;68:1723–1724.
68. Susec O, Jr., Boudrow D, Kline JA. The clinical features of acute pulmonary embolism in ambulatory patients. Acad Emerg Med 1997;4:891–897.
69. Manganelli D, Palla A, Donnamaria V, Giuntini C. Clinical features of pulmonary embolism. Doubts and certainties. Chest 1995;107:25S–32S.
70. Hull RD, Raskob G, Carter CJ, Coates G, Gill GJ, Sackett DL et al. Pulmonary embolism in outpatients with pleuritic chest pain. Arch Intern Med 1988; 148:838–844.
71. Anderson FA, Jr., Wheeler HB. Venous thromboembolism. Risk factors and prophylaxis. Clin Chest Med 1995;16:235–251.
72. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263:2753–2759.
73. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999;353:190–195.
74. Wicki J. Perneger TV. Junod AF. Bounameaux H. Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med 2001;161(1):92–97.
75. Wells PS, Anderson DR, Rodger MA, Stiell I, Dreyer JF, Barnes D et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001;135:98–107.
76. Wells PS, Anderson DR, Rodger MA, Ginsberg JS, Kearon C, Gent M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000; 83:416–420.
77. Powrie RO. Larson L. Rosene-Montella K. Abarca M. Barbour L. Trujillo N. Alveolar-arterial oxygen gradient in acute pulmonary embolism in pregnancy. [erratum appears in Am J Obstet Gynecol 1999 Aug;181(2):510]. Am J Obstet Gynecol 1998 Feb;178(2):394–396.
78. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996; 335:108–114.
79. Ginsberg JS, Hirsh J, Rainbow AJ et al. Risks to the fetus of radiologic procedures used in the diagnosis of venous thromboembolic disease. Thromb Haemost 1989; 61:189–96.
80. International Commission on Radiological Protection Publication 84. Pregnancy and medical radiation. Ann ICRP 2000;30:1–43.

81. National Commission on Radiation Protection Report #54. Medical Radiation Exposure of pregnant and Potentially Pregnant Women. Washington, DC: National Commission on Radiation Protection; 1997.
82. Fidler JL, Patz Jr EF, Ravin CE. Cardiopulmonary complications of pregnancy: radiographic findings. AJR Am J Roentgenol 1993;161:937–942.
83. Chan WS. Ray JG. Murray S. Coady GE. Coates G. Ginsberg JS. Suspected pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. Arch Intern Med 2002;162(10):1170–1175.
84. Balan KK, Critchley M, Vedavathy KK, Smith ML, Vinjamuri S. The value of ventilation-perfusion imaging in pregnancy. Br J Radiol 1997;70(832):338–340.
85. Yoo D, Lazarus E, Khalil H, Bourjeily G, Noto RB, Mayo-Smith WW. Diagnostic Yield of Ventilation Perfusion (V/Q) Scans in Pregnancy: Review of the Findings in 315 Consecutive Pregnant Patients from 1999 through 2006. Presented at RSNA meeting November 2007.
86. Quiroz R, Kucher N, Zou K, Kipfmueller F, Costello P, Goldhaber S and Schoepf UJ Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: A systematic review. JAMA 2005;293(16):2012–2017.
87. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber S. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation 2004;110(20):3276–3280.
88. van Erkel AR. van Rossum AB. Bloem JL. Kievit J. Pattynama PM. Spiral CT angiography for suspected pulmonary embolism: a cost-effectiveness analysis. Radiology 1996 Oct;201(1):29–36.
89. Doyle NM. Ramirez MM. Mastrobattista JM. Monga M. Wagner LK. Gardner MO. Diagnosis of pulmonary embolism: a cost-effectiveness analysis. Am J Obstet Gynecol 2004;191(3):1019–1023.
90. Moores LK, Jackson WL, Shorr AF, Jackson JL. Metaanalysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. Ann Intern Med 2004;141:866–874.
91. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, Leeper KV, Popovich J Jr, Quinn DA, Sos TA, Sostman HD, Tapson VF, Wakefield TW, Weg JG, Woodard PK, for the PIOPED II investigators. Multidetector computed tomography for acute pulmonary embolism, N Eng J Med 2006;354(22):2317–2327.
92. Khalil H, Bourjeily G, Lazarus E, Yoo D, Mayo-Smith W. Multidetector CT Pulmonary Angiograms in Pregnant Patients: The "Limited, No Central PE" – How Limited? Presented at RSNA meeting, November 2007.
93. Bourjeily G, Khalil H, Habr F, Miller M, Rosene-Montella K. Multidetector-row computed tomography in the detection of pulmonary embolism in pregnancy. Chest 2007;132(4):500S.
94. Winer-Muram HT. Boone JM. Brown HL. Jennings SG. Mabie WC. Lombardo GT. Pulmonary embolism in pregnant patients: fetal radiation dose with helical CT. Radiology 2002;224(2):487–492.
95. Schoepf UJ, Costello P. CT angiography for the diagnosis of pulmonary embolism: state of the art. Radiology 2004;230:329–337.
96. Schoepf UJ, Holzknecht N, Helmberger TK, Crispin A, Hong C, Becker C, Reiser M. Subsegmental pulmonary emboli: improved detection with thin collimation multidetector row spiral CT. Radiology 2002;222:483–490.
97. Land CE, Tokunaga M, Tokuoka S, Nakmura N. Early onset breast cancer in A-bomb survivors. Lancet 1993;342:237.
98. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimated risk of radiation-induced fatal cancer from pediatric CT. AJR 2001;176:289–296.
99. Tubiana M. Carcinogenic effects of low radiation doses. Cancer Radiother 1999;3:203–214.
100. American Cancer Society. Cancer facts and figures. Atlanta, Ga: Am Cancer Society, 1994.

101. Tokunaga M, Land CE, Tokuoka S, Nishimori I, Soda M, Akiba S. Incidence of female breast cancer among atomic bomb survivors, 1950–1985. Radiat Res 1994; 138:209–223.
102. Hopper KD. King SH. Lobell ME. TenHave TR. Weaver JS. The breast: in-plane x-ray protection during diagnostic thoracic CT – shielding with bismuth radioprotective garments. Radiology 1997;205(3):853–858.
103. Parker MS, Hui FK, Camacho MA, Chung JK, Broga DW, Sethi NN. Female breast radiation exposure during CT pulmonary angiography. AJR 2005;185:1228–1233.
104. Einstein AJ, Hanzlova MJ, Rajagopalan S. Estimating the risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007;298(3):317–323.
105. Remy-Jardin M, Pistolesi M, Goodman LR et al. Management of suspected acute pulmonary embolism in an era of CT angiography: a statement of the Fleischner Society. Radiology 2007;245(2):315–329.
106. Goodman LR. Small pulmonary emboli: what do we know? Radiology 2005; 234(3):654–658.
107. Hatabu H, Uematsu H, Nguyen B, Miller WT, Jr, Hasegawa I, Gefter WB. CT and MR in pulmonary embolism: a changing role for nuclear medicine in diagnostic strategy. Semin Nucl Med 2002;32:183–192.
108. Gupta A, Frazer CK, Ferguson JM, et al. Acute pulmonary embolism: diagnosis with MR angiography. Radiology 1999;210:353–359.
109. Meaney JF, Weg JG, Chenevert TL, Stafford-Johnson D, Hamilton BH, Prince MR. Diagnosis of pulmonary embolism with magnetic resonance angiography. N Engl J Med. 1997;336:1422–1427.
110. Kluge A, Luboldt W, Bachmann G. Acute pulmonary embolism to the subsegmental level: diagnostic accuracy of three MRI techniques compared with 16-MDCT. AJR Am J Roentgenol. 2006;187:W7–W14.
111. Novak Z, Thurmond AS, Ross PL, Jones MK, Thornburg KL, Katzberg RW. Gadolinium-DTPA transplacental transfer and distribution in fetal tissue in rabbits. Invest Radiol 1993;28:828–830.
112. Marcos HB, Semelka RC, Worawattanakul S. Normal placenta: gadolinium-enhanced dynamic MR imaging. Radiology 1997;205:493–496.
113. Barkhof F, Heijboer RJ, Algra PR: Inadvertent i.v. administration of gadopentetate dimeglumine during early pregnancy [letter]. Am J Roentgenol 1992;158:1171.
114. Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, Seifert B, Puchert E, Wittek S, Debatin JF: Gadopentetate dimeglumine excretion into human breast milk during lactation. Radiology 2000;216:555–558.
115. Hull RD, Raskob GE, Carter CJ. Serial impedance plethysmography in pregnant patients with clinically suspected deep-vein thrombosis: clinical validity of negative findings. Ann Intern Med 1990;112(9):663–667.
116. Anderson DR, Lensing AW, Wells PS, Levine MN, Weitz JI, Hirsh J. Limitations of impedance plethysmography in the diagnosis of clinically suspected deep-vein thrombosis. Ann Intern Med 1993 Jan; 1;118(1):25–30.
117. Wells PS, Hirsh J, Anderson DR, et al. Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. Thromb Haemost 1995 Dec; 74(6):1423–1427.
118. Cogo A, Lensing AWA, Koopman MMW, Piovella F, Siragusa S, Wells PS et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. Br Med J 1998; 316:17–20.
119. Le Gal G, Prins AM, Righini M et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant and post-partum women: a retrospective hospital based study. Thromb Res 2006;118:691–697.

120. Rodger MA. Avruch LI. Howley HE. Olivier A. Walker MC. Pelvic magnetic resonance venography reveals high rate of pelvic vein thrombosis after cesarean section. Am J Obstet Gynecol 2006;194(2):436–437.
121. Wells PS, Anderson DR, Ginsberg JS. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and non-invasive diagnostic tests. Semin Thromb Hemost 2000;26:643–656.
122. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003;58:470–484.
123. ATS Guidelines: The diagnostic approach to acute venous thromboembolism. Am J Respir Crit Care Med 1999;160:1043.
124. Torres JA, Aracil E, Puras E et al. Role of venous duplex imaging of lower extremity for pulmonary embolism diagnosis. Angiologia 1999;51:71–76.
125. Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 1997;126(10):775–781.
126. Barrelier M, Lezin B, Landy S et al. Prevalence of duplex ultrasonography detectable venous thrombosis in patients with suspected or acute pulmonary embolism. J Mal Vac 2001;26:23–30.
127. MacGillavry M, Sanson B, Buller H et al. Compression ultrasonography of the leg veins in patients with clinically suspected pulmonary embolism: is a more extensive assessment of compressibility useful? Thromb Haemost 2000;884:973–976.
128. Scarsbrook AF, Evans AL, Owen AR, Gleeson FV. Diagnosis of suspected venous thromboembolic disease in pregnancy. Clin Radiol 2006 Jan;61(1):1–12.
129. Chan WS, Ginsberg JS. Diagnosis of deep venous thrombosis and pulmonary embolism in pregnancy. Thromb Res 2002;107:85–91.
130. PIOPED II investigators. Diagnostic pathways in acute pulmonary embolism: Recommendations of the PIOPED II investigators. Radiology 2007;242:15–21.
131. Patel SJ, Reede DL, Katz, DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: Algorithms and radiation dose considerations. RadioGraphics. 2007;27:1705–1722.
132. Kearon C. Diagnosis of pulmonary embolism. CMAJ 2003;168(2):183–194.
133. Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation 1981;64:622–625.
134. Katz DS, Hon M. Current DVT imaging. Techn Vasc Interv Radiol 2004;7(2): 55–62.
135. Rademaker J. Griesshaber V. Hidajat N. Oestmann JW. Felix R. Combined CT pulmonary angiography and venography for diagnosis of pulmonary embolism and deep vein thrombosis: radiation dose. J Thorac Imaging 2001;16(4):297–299.
136. Moody AR. Magnetic resonance direct thrombus imaging. J Thromb Haemost 2003;1:1403–1409.
137. 137. Moody A, Wastie M, Gregson R, Whitaker S. Diagnostic accuracy of direct MR imaging of pulmonary emboli compared to conventional pulmonary angiography. Radiol 1997;268(Suppl):205.
138. Sukhija R. Aronow WS. Lee J. Kakar P. McClung JA. Levy JA. Belkin RN. Association of right ventricular dysfunction with in-hospital mortality in patients with acute pulmonary embolism and reduction in mortality in patients with right ventricular dysfunction by pulmonary embolectomy. Am J Cardiol;2005;95(5): 695–696.
139. Binder L. Pieske B. Olschewski M. Geibel A. Klostermann B. Reiner C. Konstantinides S. N-terminal pro-BNP or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism.Circulation 2005;112(11):1573–1579.
140. Ten Wolde M. Sohne M. Quak E. Mac Gillavry MR. Buller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. Arch Intern Med 2004;164(15):1685–1689.

141. Roy PM. Colombet I. Durieux P. Chatellier G. Sors H. Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. Br Med J 2005;331(7511):259.
142. Elkhayam U, Gleicher N. Cardiac evaluation during pregnancy. In: Cardiac problems in pregnancy. Eds Elkhayam U and Gleicher N, 3rd edition, Wiley-Liss, 1998.
143. Kline JA, Runyon MS, Webb WB, Jones AE, Mitchell AM. Prospective study of the Simplify D-dimer assay for pulmonary embolism in emergency department patients. Chest 2006;129:1417–1423.
144. Writing group for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing and computed tomography. JAMA 2006;295(2):172–179.
145. Perrier A. Roy PM. Sanchez O. Le Gal G. Meyer G. Gourdier AL. Furber A. Revel MP. Howarth N. Davido A. Bounameaux H. Multidetector-row computed tomography in suspected pulmonary embolism.N Engl J Med 2005;352(17):1760–1768.
146. Eichinger S. D-dimer testing in pregnancy. Pathophysiol Haemost Thromb 33(5–6):327–9, 2003 Sep–2004 Dec.
147. Boehlen F. Epiney M. Boulvain M. Irion O. de Moerloose P. Changes in D-dimer levels during pregnancy and the postpartum period: results of two studies. Medicale Suisse 2005;1(4):296–298.
148. Morse M. Establishing a normal range for D-dimer levels through pregnancy to aid in the diagnosis of pulmonary embolism and deep vein thrombosis. J Thromb Haemost 2004;2:1202–1204.
149. Bombeli T. Raddatz-Mueller P. Fehr J. Coagulation activation markers do not correlate with the clinical risk of thrombosis in pregnant women. Am J ObstetGynecol 2001;184(3):382–389.
150. Chan WS, Chunilal S, Lee A, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. Ann Intern Med 2007;147:165–170.
151. Meyer G. Roy PM. Sors H. Sanchez O. Laboratory tests in the diagnosis of pulmonary embolism. Respiration 2003;70(2):125–132.
152. Meyer, T, Binder, L, Hruska, N, et al. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000;36:1632–1636.
153. Giannitsis, E, Muller-Bardorff, M, Kurowski, V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102,211–217.
154. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low probrain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 2003;107:1576–1578.
155. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107:2545–2547.
156. Pruszczyk P, Kostrubiec M, Bochowicz A, Styczynski G, Szulc M, Kurzyna M, Fijalkowska A, Kuch-Wocial A, Chlewicka I, Torbicki A. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. Eur Resp J 2003;22:649–653.
157. Ten Wolde M, Tulevski II, Mulder JW, Sohne M, Boomsma F, Mulder BJ, Buller HR. Brain natriuretic peptide as a predictor of adverse outcome in patients with acute pulmonary embolism. Circulation 2003;107:2082–2084.
158. Barker D, Williams S, Mason G, McLoughlin H, Schlosshan D, Tan L. Plasma brain natriuretic peptide may not be useful to assess possible cardiac symptoms during pregnancy: 248. Am J Obstet Gynecol 2006;193(6):79.
159. Kale A, Kale E, Yalinkaya A, Akdeniz N, Canoruc N. The comparison of amino-terminal probrain natriuretic peptide levels in preeclampsia and normotensive pregnancy. J Perinat Med 2005;33(2):121–124.

160. Resnik JL. Hong C. Resnik R. Kazanegra R. Beede J. Bhalla V. Maisel A. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol 2005;193(2):450–454.
161. Kaunitz AM, Hughes JM, Grimes DA, Smith JC, Rochat RW, Kafrissen ME. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–612.
162. DHSS. Report on confidential inquiries: maternal deaths in England and Wales 1986–1988. 1991. London, Her Majesty's Station Office.
163. Levine MN, Hirsh J, Gent M, Turpie AGG, Cruickshank M, Weitz J et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 1994;154:49–55.
164. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost 2001;86:980–984.
165. Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol 1999;181:1113–1117.
166. Hunt BJ, Doughty HA, Majumdar G, Copplestone A, Kerslake S, Buchanan N et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. Thromb Haemost 1997;77:39–43.
167. Brieger D, Dawes J. Long-term persistence of biological activity following administration of Enoxaparin sodium (clexane) is due to sequestration of antithrombin- binding low molecular weight fragments – comparison with unfractionated heparin. Thromb Haemost 1996;75:740–746.
168. Ginsberg JS, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 1998;114:524S–530S.
169. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight Heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000;160:181–188.
170. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight Heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A Meta-analysis of randomized, controlled trials. Ann Intern Med 1999;130:800–809.
171. Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 2002;87:182–186.
172. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005;106:401–407.
173. Malcolm JC, Keely EJ, Karovitch AJ, Wells PS. Use of low molecular weight heparin in acute venous thromboembolic events in pregnancy. J Obstet Gynaecol Can. 2002;24:568–571.
174. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:311S–337S.
175. Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. Br J Obstet Gyncol 2001;108:1134–1140.
176. Huhle G, Geberth M, Hoffmann U, Heene DL, Harenberg J. Management of heparin-associated thrombocytopenia in pregnancy with subcutaneous r-hirudin. Gynecol Obstet Invest 2000;49:67–69.
177. Payne SM, Kovacs MJ. Cutaneous dalteparin reactions associated with antibodies of heparin-induced thrombocytopenia. Ann Pharmacother 2003;37:655–658.

178. Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. Br J Obstet Gynaecol 1983;90:1124–1128.
179. Bar J, Cohen-Sacher B, Hod M, Blickstein D, Lahav J, Merlob P. Low-molecular-weight heparin for thrombophilia in pregnant women. Int J Gynaecol Obstet 2000;69:209–213.
180. Richter C, Sitzmann J, Lang P, Weitzel H, Huch A, Huch R. Excretion of low molecular weight heparin in human milk. Br J Clin Pharmacol 2001;52:708–710.
181. Chan WS, Anand SS, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves. Arch Intern Med 2000;160:191–196.
182. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980;68:122–140.
183. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997;336:1506–1511.
184. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. Obstet Gynecol Surv 1995;50:534–541.
185. Lindqvist PG, Svensson PJ, Marsaal K, Grennert L, Luterkort M, Dahlback B. Activated protein C resistance (FV:Q506) and pregnancy. Thromb Haemost 1999; 81:532–537.
186. Bates SM, Greer IA, Hirsh JA, Ginsberg JS. Use of antithrombotic agents during pregnancy. The seventh ACCP conference on antithrombotics and thrombolytics in pregnancy. Chest 2004;126:627–644.
187. DeStefano, et al. Pregnancy Related Venous thromboembolism. Br J Hem 2006; 135:386–391.

19

Pulmonary Arterial Hypertension in Pregnancy

Brian Casserly and James R. Klinger

Keywords: pulmonary arterial hypertension, pulmonary circulation, pulmonary vascular resistance, right ventricle

Introduction

Pulmonary arterial hypertension (PAH) is a disease of unknown etiology that affects young and middle-aged woman with greater frequency than the rest of the population *(1)*. It is characterized by an elevation in pulmonary vascular resistance (PVR) and a decrease in cardiac output (CO) that results in right-sided heart failure and reduced exercise capacity. Without treatment, it usually progresses to right heart failure and death. Recently developed therapies have improved exercise capacity and prolonged survival, but a cure for this debilitating disease does not yet exist. Fortunately, the disease is extremely rare. Unfortunately it usually strikes without warning and occurs most often in women who are otherwise healthy.

Pregnancy causes profound changes in the pulmonary circulation. During the first trimester, the right ventricle (RV) and pulmonary vasculature must rapidly adapt to marked increases in circulating blood volume and CO. The stress of labor further heightens cardiovascular demand followed by substantial and rapid fluid shifts postpartum. Whether or not these stresses on the pulmonary circulation can precipitate the development of PAH is unknown. Patients who seemingly develop PAH during their pregnancy may have had early disease before becoming pregnant that did not manifest clinically until their lungs were subjected to the increase in blood flow. On the other hand, increased pulmonary blood flow is a recognized precipitant of pulmonary vascular disease and many of the vascular growth factors that are up-regulated during pregnancy have been implicated in the pathogenesis of PAH in non-pregnant patients. To fully appreciate the impact of pulmonary vascular disease on a woman's pregnancy, a thorough understanding of the pulmonary circulation is needed along with an appreciation of the normal changes in pulmonary blood flow that occur during pregnancy.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_19

The Pulmonary Circulation in Healthy Adults

Pressure flow characteristics of the pulmonary circulation differ markedly from that of systemic vessels. The systemic circulation is a high pressure system that contains a series of high resistance vessels that step down intravascular pressure from a mean of about 90 mmHg in the aorta to approximately 10 in the tissue capillaries (Figure 19.1). This decrease in pressure is accomplished by heavily muscularized arteries and arterioles. Vascular tone in these vessels is mediated by the autonomic nervous system and adrenergic receptors that respond to circulating catecholamines. These vessels constrict and dilate in response to local stimuli in order to direct blood flow to those vascular beds that require increased oxygen delivery. The systemic circulation is often described as having a baseline vascular tone, the net effect of sympathetic and parasympathetic activity on the different vascular beds. This tone can be further affected by circulating catecholamines released from the adrenal glands as part of a physiological response or by pharmacologic manipulation. In particular, adrenergic agonists and antagonists can profoundly increase or decrease vascular tone in arterial resistance vessels, resulting in marked changes in systemic vascular resistance (SVR). Dramatic reductions in systemic vascular tone can also be accomplished with other non-selective vasodilators such as calcium channel antagonists (CCB) and nitric oxide (NO) donors.

In contrast, the pulmonary circulation is a low-pressure system with mean pulmonary arterial pressure (PAP) only about 17 mmHg and a total pressure drop from arterial to venous vessels of just over 10 mmHg (Figure 19.1). Thus, mean PAP is only about a fifth of mean arterial pressure in the systemic circulation and PVR is only about one eighth of SVR. Because the pressure differential across the pulmonary circulation is so small, heavily muscularized vessels are not needed and resting vascular tone is low. Pulmonary arteries in humans do have adrenergic, cholinergic, and muscurinic receptors and respond to sympathetic or parasympathetic stimulation by increasing or decreasing pulmonary vascular tone *(2)*. However, these responses are small compared to the systemic circulation and circulating adrenergic agonists or antagonists have little effect on normal pulmonary vascular tone. In fact, only under circumstances of increased vascular tone do pulmonary vasodilators become effective.

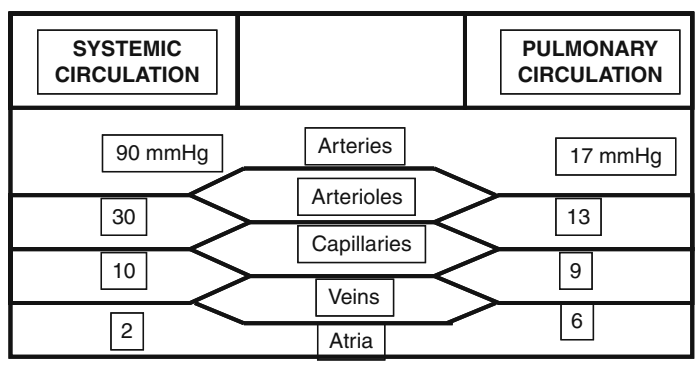


Figure 19.1 Changes in intravascular pressure across the systemic and pulmonary circulations. In: Lumb AB ed. Nunn's Applied Respiratory Physiology. New York: Elsevier Limited, 2005

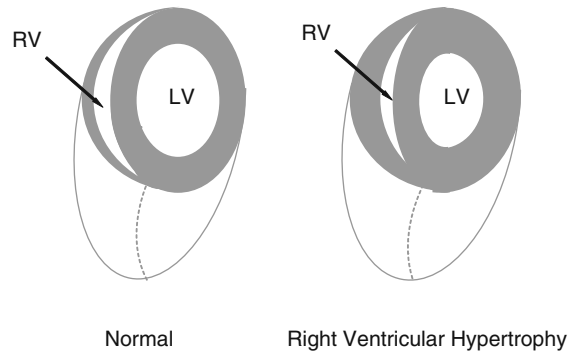


Figure 19.2 Changes in right ventricular free wall thickness during right ventricular hypertrophy. Under normal conditions, the right ventricular free wall is thin and compliant, but with chronic pressure overload hypertrophies and more closely resembles the left ventricular free wall. See text for discussion

Blood flow through the lungs is provided primarily by the RV, a low-pressure pump designed to work against a fraction of the afterload experienced by the LV. With its thin, compliant lateral free wall, the RV responds well to increases in venous return, but tolerates acute increases in afterload poorly (Figure 19.2). The limited systolic function of the RV prevents acute increases in PAP of more than 20–40 mmHg above baseline regardless of how high resistance across the pulmonary circulation becomes. The inability of the RV to maintain CO in response to sudden increases in PVR is the primary cause of syncope or death in pulmonary embolism. On the other hand, the RV is capable of adapting to gradual elevation of PVR via hypertrophy of its lateral free wall and the intraventricular septum. Perhaps the best example of RV adaptation to increased afterload is seen in Eisenmenger's syndrome where congenital intracardiac shunting greatly increases RV workload from infancy. Under these conditions, the RV hypertrophies to a point where it more closely resembles the LV and PAP approaches that of systemic arterial pressure (Figure 19.2).

Another area where the healthy pulmonary circulation differs from the systemic is its response to exercise. In a healthy adult, it is not unusual for CO to increase up to fivefold and systemic arterial pressure to increase 50% or more during vigorous exercise *(3)*. In contrast, PAP remains unchanged with exercise or increases only slightly. The lack of a rise in PAP occurs because healthy lung has a much greater capacity for accommodating increases in blood flow than the systemic circulation. Increased flow across the pulmonary vascular endothelium induces the synthesis and release of endogenous NO, and possibly other pulmonary vasodilators that decrease pulmonary vascular tone and resist platelet aggregation and intravascular thrombosis *(4)*. Flow-induced dilation of patent vessels and recruitment of under perfused pulmonary vessels results in substantial decrease in PVR and an increase in pulmonary blood flow with little change in PAP.

Pulmonary Hypertension

Pulmonary hypertension (PH) refers to an abnormal elevation of PAP. In healthy individuals, PAP at rest is about 25/10 mmHg with a mean PAP of 17 mmHg. Although the upper limit of normal is not uniformly agreed upon, most

professional organizations and consensus panels including the World Health Organization international conference on primary pulmonary hypertension accept the definition of PAH as mPAP greater than 25 mmHg at rest or greater than 30 mmHg with exercise and a pulmonary capillary wedge pressure (PCWP) $\leq$15 mmHg *(5)*.

Pulmonary hypertension can occur as a normal physiologic response or in association with chronic disease. Perhaps the best known cause of increased PAP is hypoxic pulmonary vasoconstriction. Unlike systemic vessels that dilate in response to a fall in oxygen tension, pulmonary vascular smooth muscle constricts in response to hypoxia. The reasons for this differential response to oxygen tension between the pulmonary and systemic circulations remains an area of active research. It appears to be due in large part to differences in the oxygen response of voltage gated potassium channels in the cell membranes of pulmonary versus systemic vascular smooth muscle *(6)*. Hypoxic pulmonary vasoconstriction is potentiated by hypercapnea and acidosis. Continued exposure to hypoxia, as occurs during residence at high altitude or chronic hypoxic lung disease, results in hypertrophy and hyperplasia of pulmonary vascular smooth muscle, medial thickening of normally muscularized vessels, and muscularization of more peripheral, normally non-muscularized vessels. These changes, known as pulmonary vascular remodeling, produce fixed increases in PVR and PAP that are accompanied by RV hypertrophy.

Elevation of pulmonary venous pressure due to left sided heart disease causes a compensatory increase in PAP. The effect of congestive heart failure on PAP is often under appreciated. Considering that mean PAP in the healthy lung is not much more than 15 mmHg, an increase in PCWP from 10 to 25 can nearly double mPAP. The greatest increase in PAP from left sided heart disease is seen in mitral stenosis. With chronic disease, PCWP can approach 30 mmHg and a mean PAP greater than 45 is not uncommon *(7)*. Mitral valve replacement can restore pulmonary venous pressure to near normal values, but chronic remodeling of the pulmonary circulation often results in sustained increases in PAP.

Pulmonary hypertension associated with chronic heart and lung disease is often referred to as secondary PH, meaning that the increase in PAP is a normal and necessary result of disease outside of the pulmonary circulation. Secondary PH is the more common type of PH and usually results in only moderate elevations of PAP that parallel the severity of the underlying disease.

Pulmonary hypertension that occurs without any underlying heart or lung disease is frequently referred to as primary pulmonary hypertension (PPH) and represents a true pulmonary vasculopathy that is progressive and severe resulting in marked elevation of PAP to near systemic values, RV failure, and death. This disease was probably first described in 1891 by the German physician Ernst von Romberg, who termed the pulmonary vascular lesions he discovered at autopsy as "pulmonary vascular sclerosis" *(8)*. The term PPH was used by Dresdale et al. *(9)* to describe a series of patients with RV failure associated with severe vasculopathy of the pulmonary circulation and no other identifiable pulmonary or cardiac disease. This type of pulmonary vasculopathy is also seen in several systemic diseases such as scleroderma, liver cirrhosis, HIV infection, and congenital left to right intracardiac shunts. Confusion over whether these types of PH should be considered primary or secondary prompted the development of new terminology for pulmonary hypertensive diseases. In 1998, a World Health Organization (WHO) sponsored world symposium on primary pulmonary hypertension proposed a new categorization of PH that was revised at the next international

conference in Venice, Italy, 2003 *(10)* (Table 19.1). Under this system, all diseases in Group I are termed PAH. PPH is referred to as idiopathic PAH and divided into sporadic and familial cases. PH associated with connective tissue disease, portal hypertension, HIV infection, congenital left to right shunts, use of anorectic drugs, and pulmonary veno-occlusive disease are all considered various forms of PAH. Group II is PH associated with elevations in pulmonary venous pressure from left sided heart disease and is termed pulmonary venous hypertension (PVH). Group III describes PH associated with chronic lung disease, group IV is PH associated

Table 19. 1 World Health Organization classification of pulmonary hypertensive diseases.

1.0 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic pulmonary arterial hypertension
  - Sporadic
  - Familial
- 1.2 Pulmonary arterial hypertension related to:
  - Collagen vascular disease
  - Congenital systemic to pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs/toxins
- 1.3 Associated with venous or capillary involvement
  - Pulmonary veno-occlusive disease
  - Pulmonary capillary hemangiomatosis

2.0 Pulmonary venous hypertension (PVH):
- 2.1 Left sided atrial or ventricular HD
- 2.2 Left sided valvular heart disease

3.0 Pulmonary hypertension associated with lung disease or hypoxia
- 3.1 COPD
- 3.2 Interstitial lung disease
- 3.3 Sleep disordered breathing
- 3.4 Alveolar hypoventilation syndrome
- 3.5 High altitude

4.0 Chronic thromboembolic disease
- 4.1 Obstruction of proximal pulmonary arteries
- 4.2 Obstruction of distal pulmonary arteries
- 4.3 Other emboli
  - –tumor
  - –parasites
  - –foreign material

5.0 Miscellaneous
- Sarcoidosis
- Histiocytosis X
- Lymphangiomatosis
- External compression of pulmonary arteries
  - – tumor
  - – adenopathy
  - – fibrosing mediastinitis

with acute and chronic thromboembolic disease, and the last group is reserved for parasitic diseases, sarcoidosis, and other miscellaneous causes of elevated PAP. The WHO classification system has the advantage of lumping all of the major pulmonary vasculopathies into the first class. Despite likely differences in etiologies, the different types of PH in Group I have similar clinical presentations and progressive elevation in PAP that if untreated usually progress to RV failure and death from the pulmonary vascular disease itself.

Although the etiology is not well understood, the histopathologic changes of pulmonary vessels in patients with PAH have been well described. Typical changes include hypertrophy of pulmonary smooth muscle cells and increased production of extracellar matrix causing medial thickening and narrowing of the vessel lumen. Proliferation of pulmonary vascular smooth muscle results in muscularization of smaller normally non-muscularized arteries. In addition, proliferation of pulmonary vascular endothelial cells further narrows the vessel lumen (Figure 19.3A). Some vessels develop the characteristic plexiform lesion consisting of near obliteration of the vessel lumen from monoclonal proliferation of pulmonary vascular endothelial cells and small channels for blood flow formed by re-cannulization *(11)* (Figure 19.3B). Although it is easy to see how these grossly obliterated vessels would increase resistance to pulmonary blood flow, histologic studies have not been able to demonstrate a good correlation between the extent of plexiform

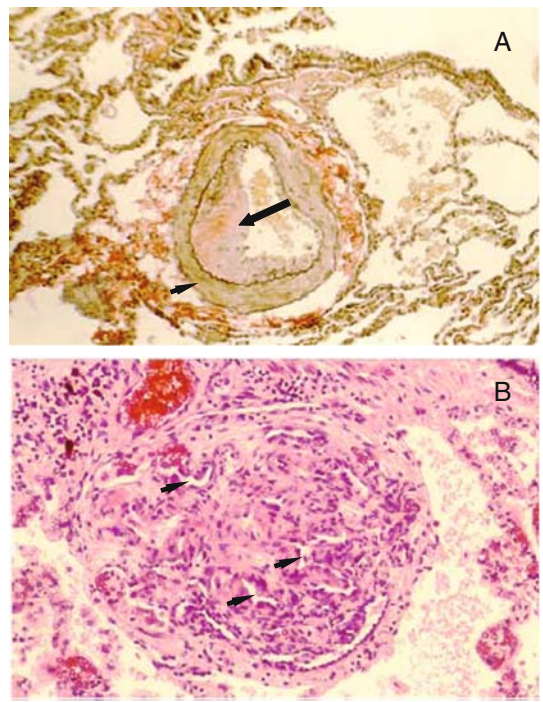


Figure 19.3 Photomicrographs of lung section from a patient with pulmonary arterial hypertension. (A) Medial and intimal thickening are caused by hypertrophy of pulmonary vascular smooth muscle cells (*small arrow*) and proliferation of pulmonary vascular endothelial cells (*large arrow*), respectively. (B) Marked proliferation of pulmonary vascular endothelial cells causing near complete obliteration of the vascular lumen, characteristic of the plexiform lesion of pulmonary arterial hypertension. Blood flow is limited to narrow passageways caused by recannulization of the lumen (*arrows*). (Photomicrographs were provided by Charles Kuhn III, MD)

lesions and the severity of PH or response to vasodilators *(12)*, suggesting instead that plexifrom lesions may be simply a marker of pulmonary vasculopathy or the result of increased shear stress caused by narrowing of the upstream vessels.

The Pulmonary Circulation in Pregnancy

Increased metabolic demands from the placenta and developing fetus increase oxygen consumption throughout pregnancy, peaking at 15–30% above baseline by full term *(13)*. Increased O_2 delivery is accomplished by an increase in erythrocyte mass and a corresponding rise in intravascular blood volume that must be oxygenated by the maternal lungs. The increase in blood volume begins soon after conception. Circulating blood volume increases 10% by the end of the second month and continues to increase throughout most of the pregnancy peaking at about 40–50% greater than the pre-pregnant value by 32–36 weeks *(14)*. The increase in blood volume is accompanied by an increase in CO and circulating levels of vasodilators. CO increases and SVR decreases by 20–30% within the first 5–8 weeks of pregnancy *(14)*. The increase in CO is accomplished by both an increase in left ventricular end diastolic volume and an increase in stroke volume *(14)*. Systolic function is maintained throughout most of the pregnancy due to an increase in filling volume and decreased afterload.

A considerable reduction in vascular resistance also occurs in the pulmonary vascular bed. In an early study by Robson et al. *(15)*, PAP, pulmonary blood flow, and calculated PVR were assessed by Doppler echocardiography in 13 pregnant women at monthly intervals. Pulmonary blood flow increased on average 47% throughout the pregnancy, yet no change in PAP was seen. The lack of elevation in PAP was explained in part by a 24% reduction in PVR by 8 weeks of pregnancy that persisted until delivery. All pulmonary hemodynamic values returned to baseline values by 6 months post-partum.

Association of Pulmonary Hypertension with Pregnancy

The true incidence of PAH presenting during pregnancy is unknown. Approximately 4–8% of patients develop their PAH either during their pregnancy or in the post-partum period. Dawkins et al. *(16)* found six cases of PAH associated with pregnancy out of 73 PAH patients referred for heart-lung transplantation. However, one patient had a family history of PAH and lived at high altitude. In a large study published nearly 40 years ago *(17)*, Wagenvoort and Wagenvoort found 27 cases of PPH that were associated with the onset of pregnancy out of 602 cases of PPH reported in the literature. In their study, they found no gender preference for PPH in children but nearly a 4:1 female to male ratio in adults. They concluded that pregnancy might be one of the causes for the predilection of PAH in adult as compared to pre-adolescent females. The incidence of PAH in the general population has been estimated to be as low as two per million *(18)* and even a several fold increase in the incidence of PAH would be difficult to detect in the obstetric population without assessing hundreds of thousands of patients. Idiopathic PAH occurs most commonly in the third and fourth decades of life and more frequently in women than in men by about 2–1. Thus, fertile women represent a subpopulation of patients that have the highest incidence of PAH regardless of whether or not they are pregnant. Maternal death rates in developed countries are estimated to be

about 10–15 per 100,000 pregnancies with about 20% of these deaths attributed to cardiovascular disease *(19)*. Assuming a death rate of 30% in patients with PAH who carry their pregnancy to term *(19)*, only one case of PAH per 100,000 pregnancies would be expected even if all of the maternal cardiovascular deaths were due to this disease. Furthermore, one study *(20)* found that less than 10% of the cases of heart disease complicating pregnancy were acquired during the pregnancy. Thus, cardiovascular mortality rates do not suggest that the overall incidence of PAH in pregnant women is significantly greater than in the general population. However, without larger population based studies that examine the incidence of PAH in pregnancy it is not possible to determine if pregnancy itself is a risk factor for PAH.

It may not be surprising that many women who develop PAH are diagnosed during their pregnancy. Women may become more concerned with their overall health during the time that they are carrying and they may be more likely to report moderate symptoms such as dyspnea or chest heaviness with exertion and easy fatigability. Similar symptoms such as ankle edema or exertional lightheadedness might be disregarded until discussed during a prenatal visit. In addition, patients have frequent visits to their providers improving the chances of detection of symptoms. Finally, the increased stress placed on the respiratory system during pregnancy may make symptoms of mild to moderate PH more pronounced.

On the other hand, it is entirely possible that physiologic changes in the pulmonary circulation during pregnancy actually contribute to the development of PAH or to worsening of preexisting disease. Increased flow through the pulmonary circulation is a well-established mechanism for producing pulmonary vascular disease in animals. Unilateral pneumonectomy followed by administration of the alkaloid monocrotaline causes pulmonary capillaritis and PH in rodents and produces the classical plexiform lesions seen in human disease *(21)*. Aortopulmonary shunts consistently produce PH in newborn lambs *(22)*. Furthermore, congenital left to right cardiac shunts frequently result in PAH that is believed to be due primarily to the increase in blood flow through the pulmonary circulation. The reason PH does not occur in the maternal lung despite as much as a 50% increase in blood flow is uncertain, but likely due to increased expression of pulmonary vasodilators that allow the lung to accommodate the increase in blood flow.

Aside from increased pulmonary blood flow, a variety of other hemopoietic and angiogenic events occur during pregnancy that could contribute to the development of pulmonary vasculopathy. Although the role of intravascular thrombosis in the development of PH remains somewhat controversial, numerous coagulation abnormalities have been described in PAH and intravascular thrombosis is apparent in most histologic studies of lungs from PAH patients *(23–26)*. These thrombi do not appear to be pulmonary emboli, but rather represent intravascular thrombosis in situ. Decreased expression of prostaglandin synthase and a lower ratio of plasma prostaglandin to thromboxane levels may also contribute to in situ thrombosis in PAH *(27, 28)*.

Similarly, a mild coagulopathy has been well described in pregnant women and venous thromboembolism has been found to complicate 0.1–0.2% of all pregnancies *(29–32)*. Chronic thromboembolic PH occurs within a year of acute pulmonary embolism in approximately 5% of cases *(33)* and could contribute to the development of PAH in pregnancy.

Perhaps most intriguing are the vast changes in expression of vasogenic and angiogenic growth factors that occur during pregnancy for development of the placental fetal circulation and maturation of the fetal pulmonary circulation. Many

investigators have speculated whether expression of these growth factors, many of which have been implicated in the development of PAH, can induce the development of PH in the maternal lung. A variety of vascular growth factors have been shown to be upregulated in animal models that develop PH by increased pulmonary blood flow. For example, fetal lambs with PH induced by aortopulmonary shunt have increased pulmonary expression of vascular endothelial growth factor (VEGF) and its receptors Flt-1 and KDR/Flk-1, transforming growth factor-beta (TGFß), fibroblast growth factor-2 (FGF-2), and endothelin converting enzyme-1 *(34–37)*. Increased expression of these and other vascular growth factors occurs within 4 weeks of increasing pulmonary blood flow and likely play a role in the development of PH in these animal models. Whether or not the increase in pulmonary blood flow that occurs during pregnancy is enough to induce up-regulation of these growth factors is uncertain. However, expression of the soluble VEGF receptor sFlt-1 is increased in the placenta and in peripheral blood mononuclear cells of pregnant women *(38)* and circulating levels of VEGF increase fourfold during the first trimester and remain elevated for up to 20 weeks *(39, 40)*. A considerable body of data suggests that growth factors such as these play important roles in the development of PAH *(41–44)*.

In addition to vasoactive substances that may be induced by increased pulmonary blood flow, expression of numerous growth factors is up-regulated in the placenta during development of the fetoplacental vasculature *(45)*. One of the most important of these may be hypoxia inducible factor 1 (HIF-1). HIF-1 is expressed in low oxygen environments and responsible for the induction of a variety of proteins involved in erythropoesis and angiogenesis. Cellular expression of HIF-1 in human trophoblasts occurs early in pregnancy and is thought to play a major role in regulating placental morphogenesis, angiogenesis, and trophoblast differentiation *(46, 47)*. Interestingly, HIF-1 has also been shown to promote the proliferative response of human pulmonary artery vascular smooth muscle cells to FGF-2, platelet derived growth factor (PDGF), and epidermal growth factor (EGF) *(48)* and to increase VEGF expression in human pulmonary artery endothelial cells *(49)*. Other growth factors that have been implicated in the development of PH such as insulin like growth factor and interleukin-6 are also expressed by the placenta *(50–53)*.

Whether or not pregnancy actually induces the onset of PAH is yet to be determined. Presently, there are no studies that strongly link the onset of pregnancy to development of PAH, but it is not difficult to see how such a link could be made. Furthermore, it seems entirely possible that hemodynamic changes and alteration in pulmonary vascular expression of angiogenic factors that occur during pregnancy have the potential to facilitate the progression of pulmonary vascular disease in patients with pre-existing PAH.

Evaluation of Pulmonary Hypertension in the Pregnant Patient

Exertional dyspnea is the most common symptom in PAH, usually manifesting well before chest pain or symptoms of right heart failure. Unfortunately, this complaint is common in many medical conditions and the differential diagnosis is quite broad unless other suggestive symptoms or physical signs are available to guide the practitioner. Most physicians will order appropriate tests to exclude common diseases such as asthma, emphysema, pulmonary fibrosis, coronary artery disease, and anemia. When a thorough work up for these diseases turns up negative, the patient's symptoms are often attributed to deconditioning. The lack of a plausible diagnosis can

lead to frustration and agitation causing some providers to conclude that the patient's dyspnea is due to an anxiety disorder. The lack of any symptoms that are uniquely characteristic of PAH is one of the reasons why patients in the NIH registry were symptomatic on average 1–2 years before being diagnosed.

As the disease progresses, functional capacity deteriorates. Patients often learn to avoid stairs and inclines, park closer to where they have to go, and give up recreational activities. By the time ordinary physical activity becomes difficult, signs of right heart failure may be present. Patients may notice ankle edema, puffiness, mild weight gain, or other signs of volume overload. The pulmonic component of the second heart sound, heard best over the left sternal border, intensifies and the second heart sound may split as the RV enlarges. Tricuspid regurgitation manifests as holosystolic murmur over the left or right sternal border and jugular venous distension can be seen. Strenuous activity now causes additional symptoms such as chest tightness, angina, and exertional lightheadedness. By this point, most patients have sought medical attention and will be referred for cardiac evaluation where the diagnosis is usually found by echocardiography. In the final stages, patients become essentially bed bound, unable to walk even short distances without becoming short of breath. Elevated right-sided pressures result in passive liver congestion causing anorexia, abdominal discomfort, hepatomegaly, and ascites. Without treatment, patients slowly progress to a moribund state before dying. Alternatively, RV failure can occur suddenly in the final stages of disease resulting in cardiogenic shock, circulatory collapse, and sudden death. Mortality increases sharply as exercise capacity declines. For this reason, early diagnosis of PAH is important. The WHO sponsored symposium on pulmonary hypertension developed a four-staged grading system of functional capacity based on the NYHA functional class for congestive heart failure (Table 19.2).

Early diagnosis of PAH can be challenging in the pregnant patient. A mild respiratory alkalosis manifested by an increase in tidal volume is physiologic in pregnancy *(13)*. This, coupled with the increased workload of carrying a gravid uterus frequently leads to exertional dyspnea. Physical signs of PAH may also be masked during pregnancy. Ankle edema occurs frequently during pregnancy due to increases in intravascular volume and compression of the IVC by the gravid uterus. Splitting of the second heart sound occurs as the RV expands to accept the increase in circulating blood volume. More suggestive signs of right heart failure such as jugular venous distension or hepatomegaly may suggest the diagnosis, but occur late in the disease. Mild jugular venous distention may also be seen in a normal pregnancy in relation to the increased blood volume. The task of the physician is to determine when dyspnea and signs of right heart failure are out of proportion to the stage of pregnancy.

Table 19.2 World Health Organization functional classification for patients with pulmonary arterial hypertension.

Class I	Symptoms do not limit physical activity. Ordinary physical activity does not cause undue discomfort
Class II	Slight limitation of physical activity. The patient is comfortable at rest, yet experiences symptoms with ordinary physical activity
Class III	Marked limitation of physical activity. The patient is comfortable at rest, yet experiences symptoms with minimal physical activity
Class IV	Inability to carry out any physical activity. The patient may experience symptoms even at rest. Discomfort is increased by any physical activity. These patients manifest signs of right heart failure

Few simple tests are available for the evaluation of PAH. Plasma BNP and troponin levels rise as the RV fails, but are usually only mildly elevated in early to moderate PH. Plasma BNP levels have been shown to correlate less with LV dysfunction in the pregnant patient than in non-pregnant patients *(54)*, but the ability of BNP to predict the presence of PAH in pregnancy has not been studied. Patients with PAH more commonly have elevations in ANA titer and uric acid levels, but these tests are non-specific. PA and lateral CXR may detect cardiomegaly, but mild enlargement of the cardiac silhouette during pregnancy is not uncommon due to upward and lateral displacement of the heart caused by the expanding uterus. Barring any abnormalities that would explain the patient's dyspnea, chest radiograph (CXR), routine blood work, and pulmonary function tests should be considered to exclude asthma or other airways disease. Pulmonary emboli should be excluded. Exercise oximetry can be helpful. A fall in oxygen saturation strongly suggests pulmonary vascular disease especially in the absence of parenchymal lung disease. However, a normal test has a low negative predictive value for excluding PAH. If no explanation for the patient's dyspnea is forthcoming, transthoracic echocardiography (TTE) should be performed. In addition to assessing PAP, the echocardiogram provides important information about RV and LV function and valvular insufficiency. Mitral regurgitation, LV hypertrophy with diastolic dysfunction, decreased LV systolic function, and segmental wall motion defects suggestive of coronary artery disease are all possible findings to explain a patient's dyspnea and occur at least as frequently as PAH in the pregnant patient *(19)*.

A reasonably accurate assessment of PAP can be made using Doppler ultrasound during echocardiography. This technique depends on the presence of an identifiable regurgitant jet across the tricuspid valve. The speed of this jet is measured and the ventricular pressure necessary to produce it is calculated using a modification of the Bernoulli equation:

$$\begin{aligned}\text{Systolic PAP} = \text{RV systolic pressure} &= 4\,(\text{tricuspid regurgitant velocity})^2 \\ &+ \quad \text{right atrial pressure (RAP)}\end{aligned}$$

In the absence of any RV-PA gradient, such as pulmonary stenosis, RV, and PAP systolic pressures are considered to be equal. The RAP is generally assigned a value of 10 cm H_2O or can be estimated by examining the degree of inferior vena cava (IVC) collapse during inspiration *(55)*.

Once a diagnosis of PH is made by echocardiogram, a search for known causes of PH should begin. As mentioned earlier, venous thromboembolism needs to be excluded, as the risk for this disease is increased during pregnancy and because pulmonary embolism is a common cause of PH. If lower extremity ultrasound and CT pulmonary angiogram are negative, acute PE is unlikely; however, if there is any history of previous venous thrombosis or hypercoagulopathy, a ventilation perfusion lung scan should be considered to exclude chronic thromboembolic PH. A baseline sleep study to exclude significant central or obstructive sleep apnea should also be considered, especially in patients with symptoms of chocking arousals, heavy snoring, or daytime hypersomnolence. Laboratory tests for connective tissue disease, liver cirrhosis, HIV infection, and hypothyroidism should be considered. These are low yield tests, but the incidence of idiopathic PAH is so small that uncommon diseases with a known association with PH need to be considered.

If evaluation reveals a correctable cause for the patients PH, such as chronic hypoxemia or thromboembolic disease, the underlying cause should be treated and the patient followed by serial echocardiography and standardized measurement of

exercise capacity such as 6 min walking distance. The 6-min walk test measures distance walked in a 6-min period without assistance or encouragement along with vital signs, pulse oximetry, and the Borg dyspnea score. If no correctable cause of a patient's PH is discovered, pulmonary artery catheterization (PAC) should be performed. PAC confirms the diagnosis, determines the severity of PAP elevation, and provides important measurements of RV function. Elevated RAP, RV end diastolic pressure, or reduced CO identify a compromised RV and are associated with worse prognosis *(56)*. Sufficient data are lacking to determine if hemodynamic measurements can predict outcome in parturient patients with PAH, but it follows that patients with decreased CO and elevated right-sided pressures are at increased risk of hemodynamic instability during labor and delivery.

A PAC also allows for assessment of acute hemodynamic response to selective pulmonary vasodilators such as prostacyclin, adenosine, or NO. Nonselective vasodilators, such as calcium channel blockers (CCB) should not be used unless a patient first demonstrates a positive vasodilator response to a selective pulmonary vasodilator. Pulmonary vasodilator responsiveness is assessed by both the change in PAP and the final PAP achieved. The fall in PAP in response to pulmonary vasodilators represents the portion of PAP elevation that is due primarily to pulmonary vasoconstriction. The difference between the mPAP after receiving vasodilators and normal PAP values represents the increase in PVR that is likely due to pulmonary vascular remodeling. A positive vasodilator response is defined as a decrease in mean PAP of >10 mmHg and a post vasodilator mean PAP of < 40 mmHg *(57)*. These patients typically respond well to CCBs with a favorable long-term survival *(58)*. Unfortunately, less than 10% of PAH patients are found to have a positive pulmonary vasodilator response and therefore, most will require treatment with one of several recently approved medications for PAH.

Treatment of Pulmonary Hypertension

Three classes of medications are currently FDA approved for the treatment of PAH in adults. These include prostacyclin (PGI_2) analogues, frequently referred to as prostanoids, endothelin receptor antagonists (ERA), and phosphodiesterase inhibitors (PDEI) (See Table 19.3).

Table 19.3 Drugs available for treatment of pulmonary arterial hypertension.

Drug class	Drug name	FDA approval	Trade name	Category	Admin route	WHO class indication
Prostanoid						
	Epoprostenol	1995	Flolan	B	IV	III, IV
	Treprostinil	2001	Remodulin	B	IV, sc,	III, IV
	Iloprost	2005	Ventavis	C	Inhaled	III
ERA						
	Bosentan	2001	Tracleer	D	Oral	II–III
	Ambrisentan	2007	Letairis	D	Oral	II–III
	Sitaxsentan	Pending		D	Oral	II–III
PDEI					L	
	Sildenafil	2005	Revatio	B	Oral	II–III
	Tadalafil	In clinical trials		B	Oral	II–III

Epoprostenol. This drug was the first medicine to receive FDA approval for PAH and remains one of the most effective therapies. Unfortunately, all prostanoid therapies require either continuous infusion or frequent inhalations that limit their usefulness. Oral prostacyclin preparations have been shown to be effective in clinical trials, but have not yet been approved for treatment in the US *(59)*. Epoprostenol was used initially as a bridge to lung transplant in patients with advanced disease *(60)*, but was found to prolong survival and improve functional class in many of these patients. Randomized controlled trials in the mid 1990s showed that epoprostenol infusion in patients with PAH improved 6 min walking distance, WHO functional class, and survival over 12 weeks of therapy compared to patients treated with conventional medical therapy alone *(61, 62)*. Long-term open label studies have shown improved 1 and 3 year survival compared to historical controls *(63)*. Epoprostenol has a half-life of less than 6 min in human blood and is unstable at room temperature. It is delivered by continuous intravenous infusion using a battery operated pump and secure IV access site such as a Hickman catheter. An ice pack is needed to keep the medicine cassette cool because epoprostenol is unstable at room temperature. Patients often become symptomatic within 5 min of drug interruption and require a backup pump and loaded drug cassette always available in case of sudden pump or tubing failure. Patients are usually treated through a specialized center for PH and must be able to take care of all aspects of pump function, drug preparation, and administration on their own with the assistance of a dedicated individual willing to step in if the patient becomes incapacitated. The rate of catheter infection is approximately 1% per 1,000 catheter days and infection with unusual organisms has been described *(64, 65)*. Despite these challenges, epoprostenol has been used effectively for many patients with PAH and has improved functional class and survival considerably. It is presently considered one of the most efficacious therapies for patients with PAH and is the preferred therapy for patients with WHO Class IV disease *(66)*.

Treprostinil. This prostacyclin analogue is similar to epoprostenol but its prolonged half-life and greater stability at room temperature allow it to be delivered as a subcutaneous infusion under the skin of the abdomen, upper thigh, buttock, or upper arm. Infusion is accomplished via a small needle similar to a thumbtack inserted perpendicularly to the skin. The needle is taped in place and connected via small diameter tubing to a battery operated insulin pump. Its longer half-life, close to 4 h, reduces the risk of side effects in the event infusion is interrupted and its stability at room temperature allows for drug to be delivered for up to 3 days before reloading the cassette. The lack of a central line eliminates catheter related infection, but discomfort at the site of subcutaneous infusion necessitates discontinuation in about 10% of patients. Overall, treprostinil therapy offers significant advantages over epoprostenol, but there is some concern about whether it is as efficacious *(67, 68)* and epoprostenol remains the drug of choice for patients with advanced disease in WHO functional class IV *(66)*. Treprostinil is also approved for intravenous infusion.

Iloprost. This short acting prostacyclin derivative was developed for inhalational therapy in Europe and approved for use in the US in 2005. It is administered via a portable battery operated ultrasonic nebulizer 6–9 times daily. Each treatment takes about 15 min to complete. In clinical trials, it appears to be as effective as continuous infusion therapy with epoprostenol or treprostinil over a 3 month period, although clinical deterioration has been reported after 1–2 years in up to

40% of patients using iloprost as monotherapy *(69)*. The freedom from continuous infusion makes this prostanoid an attractive alternative to epoprostenol or treprostinil, however many patients have found the need for such frequent treatments inconvenient and lack of compliance with this rigorous treatment schedule can be an issue.

Bosentan. Bosentan was the first orally active agent approved by the FDA for the treatment of PAH. It is non-selective ERA that blocks the effect of endothelin, a potent vasoconstrictor secreted by the vascular endothelium that causes pulmonary vasoconstriction, and hypertrophy and proliferation of adjacent vascular smooth muscle. In patients with PAH, circulating levels of endothelin are increased and its expression in pulmonary vessels and plexiform lesions is up regulated *(41)*. Endothelin acts on two receptors. The A receptor (ER_A) located on vascular smooth muscle mediates the vasoconstrictive effect of endothelin. The B receptors (ER_B) located on vascular endothelial cells has been shown to release NO in response to ligand binding. Bosentan has an ER_A:ER_B affinity ratio of about 4:1. Highly selective ER_A antagonists such as sitaxsentan and ambrisentan have been developed for treatment of PAH and have recently completed clinical trials *(70, 71)*. Ambrisentan received FDA approval for the treatment of PAH in 2007. All three ER antagonists are oral agents and have been shown to decrease mPAP and PVR in patients with idiopathic PAH and PAH associated with connective tissue disease. Although this class of drugs improves survival compared to historical controls *(72)*, nearly a third of patients deteriorate within 2 years of treatment and require additional therapy, change of therapy, or lung-transplantation.

ERAs cause serious fetal defects and increase the metabolism of birth control pills. Women should be counseled not to become pregnant while taking these medications and a double method of birth control is indicated for fertile women who are sexually active. ERAs are also associated with marked elevation of liver transaminases in as many as 10% of patients. This adverse effect can occur at any time, but is nearly always reversible provided the dose is reduced or the drug stopped. Patients taking these agents are required by the FDA to have liver function tests monitored monthly. The ERAs also affect the metabolism of many medications that are hepatically cleared and cause a mild anemia. Hemoglobin levels should be followed while on therapy.

Phosphodiesterase Inhibitors. Pulmonary vasodilators such as NO, prostacyclins, and natriuretic peptides relax constricted vascular smooth muscle by increasing intracellular levels of cAMP and/or cGMP. These cyclic nucleotides activate downstream protein kinases that modulate intracellular calcium levels *(73)*. Both nucleotides are degraded by a family of enzymes known as phosphodiesterases. In pulmonary vascular smooth muscle, cGMP is degraded primarily by PDE-5, the same isotype that degrades intracellular cGMP in vascular smooth muscle of the corpus cavernosum. Several selective PDE-5 inhibitors have been approved for the treatment of erectile dysfunction. These agents have acute pulmonary vasodilator effects as well *(74)*. Presently, sildenafil is the only PDEI approved for treatment of PAH in the US, although clinical trials with the longer acting tadalafil are ongoing. In an international multicenter randomized controlled trial sildenafil was shown to improve pulmonary hemodynamics and functional capacity over 12 weeks compared to placebo *(75)*. The average improvement in 6 min walking distance was maintained for at least a year. In the US, sildenafil is marketed under the trade name Viagra for treatment of erectile dysfunction and under the trade name Revatio for treatment of PAH. Its onset of

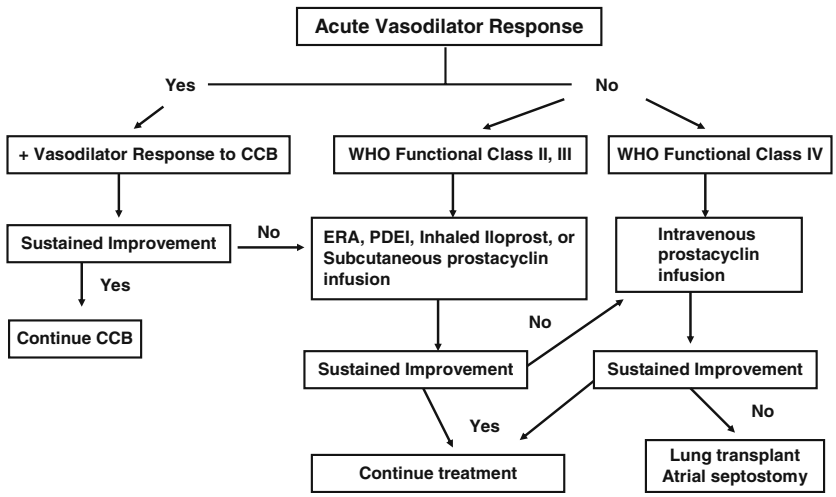


Figure 19.4 Treatment algorithim for medical management of patients with pulmonary arterial hypertension. A positive vasodilator response is defined in the text. CCB—calcium channel blocker, WHO—World Health Organization, ERA—endothelin receptor antagonist, PDEI—phosphodiesterase inhibitor. Adapted from the American College of Chest Physicians evidence-based clinical practice guidelines (see ref. *64*)

action peaks about an hour after ingestion and the half-life is about 4 h. Side effects include headache and visual blurriness.

Initial therapy for managing PAH is determined by the patient's hemodynamics, response to pulmonary vasodilators, and functional class. Guidelines to medical management have been published by the American College of Chest Physicians and by the American College of Cardiology *(65, 76–78)*. Patients who have a positive vasodilator response and reasonable functional capacity (WHO Class I–III) can be managed with a CCB if shown to respond to these agents acutely. Patients with a negative vasodilator response are usually treated with an ERA or PDEI if they are in WHO functional class II or III. Inhaled or subcutaneous infusion of prostacyclin is also used as initial monotherapy for these patients or added to oral therapy if they fail to improve. Patients in WHO functional class IV should be treated with continuous intravenous infusion of epoprostenol or treprostinil (Figure 19.4).

Management of Pulmonary Hypertension in the Pregnant Patient

The first step in managing PH in the pregnant patient is to insure that the diagnosis is correct. Given the low incidence of PAH and the seriousness of its consequences during pregnancy, a certain diagnosis is imperative. Pulmonary arterial catheterization and pulmonary vasodilator testing should be done at the time of diagnosis as is true of all patients with newly diagnosed PAH *(79)*. Once the diagnosis is secure, it is important to have a careful discussion with the patient and her partner about the diagnosis, short and long term prognosis, and implications for the pregnancy. A discussion of treatment options should start with serious consideration of terminating the pregnancy depending on the gestational age and severity of the PH. This may seem to be a harsh recommendation, but the risk of death in a parturient with PAH cannot be overstated. Data prior to the development of

modern treatments for PAH suggest a maternal mortality rate of nearly 50–60% *(80–82)*. More recent studies have reported mortality rates of 30% or lower in patients with idiopathic PAH *(19, 83)*, but these data come from studies of substantially smaller numbers of patients. The reluctance to report patients who did not survive delivery likely makes the true mortality rate higher. Furthermore, PAH has been associated with significant fetal morbidity and mortality. In fact, intrauterine growth restriction has been reported in up to a third of infants born to mothers with Eisenmenger's Syndrome *(84)*, a pulmonary hypertensive disease with a better prognosis than idiopathic PAH. Mothers who present early in their pregnancy with mild PAH can be followed initially, but a careful plan should be developed for interval assessment of PA pressure and RV function. Right heart catheterization may be necessary to accurately assess the severity of disease. Any indication that PAH is progressing should elicit consideration of ending the pregnancy. PAPs may rise with the rising CO; the latter peaks at about 26–30 weeks of gestation. However, following this peak, the next physiological insult occurs during labor and delivery. For that reason, decisions to terminate are ideally finalized prior to the peak CO. Once that peak is reached, a termination carries as high a risk to the mother as delivery, and in that case it would make sense to postpone delivery at least until fetal maturity is achieved. However, some patients with a potential for third trimester complications that may affect CO would likely benefit from an earlier delivery. Individualized, multidisciplinary team decisions should then be made depending on how advanced the pregnancy is and how well the mother's right heart is tolerating the PH.

A question that frequently arises in the treatment of fertile women who are diagnosed with PAH before they become pregnant is whether it will ever be safe for them to conceive. Prior to the advent of modern treatments, the risks to the mother and child of completing a pregnancy were so high that surgical sterilization was recommended at the time that PAH was diagnosed *(85, 86)*. Whether or not new therapies for PAH can reverse the disease to a point where the risks of pregnancy are acceptable is uncertain. Easterling et al. *(87)* described two patients with PAH who safely delivered three infants after being treated with prostacyclin for a year prior to conceiving. Both patients had a positive vasodilator response initially and had normalization of RV function after a year of therapy. These encouraging results provide hope to some women with newly diagnosed PAH, but they are applicable only to a small minority of PAH patients who have favorable vasodilator responses acutely and are able to sustain that response in the long-term. Unfortunately, for the great majority of women with PAH, pregnancy will remain too great a risk to assume even with the availability of more modern treatments.

If a pregnant woman with PAH decides to carry a fetus to term despite the known risks, treatment should begin immediately with the goal of reducing PVR and RV size to as close to normal as possible. A team approach that incorporates a high risk obstetrician, anesthesiologist and a cardiologist or pulmonologist experienced in managing PAH has been advocated *(88)*. Pregnant patients with PAH are candidates for all of the treatments described above except for the ERAs that have been shown to cause severe fetal defects in animal studies. Few data are available regarding the outcome of fetuses from women who became pregnant inadvertently while taking ERAs. At least three women are known to have delivered healthy fetuses after becoming pregnant while taking bosentan and stopping the drug in the first trimester *(89, 90)*. Sildenafil, treprostinil, and epoprostenol are Pregnancy Category B because there are no known adverse effects but there are minimal data

available. Iloprost is Pregnancy category C because it has been shown to cause shortened phalangeal structures in fetal rats *(91)*.

Goals of treatment may need to be more aggressive than in non-pregnant patients with PAH because profound increases in pulmonary blood flow and intravascular volume are likely to worsen pulmonary hemodynamics and RV function as the pregnancy progresses. Furthermore, the compromised RV and pulmonary circulation may be subjected to complications such as bleeding, infection, thromboembolism, or even general anesthesia at the time of delivery. Finally, the RV will need to handle large shifts in intravascular volume in the post-partum period even in patients who have an uncomplicated course and normal delivery. Thus, pulmonary hemodynamics and RV function should be improved as much as possible prior to the onset of labor.

Most pregnant patients with PAH should be considered for prostanoid infusion therapy at the time of diagnosis. Consensus opinion is that prostanoids are the most effective therapy in PAH and are likely to provide the greatest hemodynamic improvement in the limited window available prior to delivery. In patients who have moderate PAH on oral therapy prior to becoming pregnant, it may be reasonable to continue therapy with a PDEI, but close monitoring of RV function and exercise capacity is vital and clinicians should have a low threshold for transitioning to or adding prostanoid therapy. Patients who become pregnant while on ERAs must be transitioned immediately to an alternative class of drugs because of the high risk of fetal defects. Transition to a prostanoid is probably prudent, although a PDEI could be used if the patient's disease is moderate and well controlled.

In addition to pulmonary vasodilators, anticoagulation with unfractionated or low molecular weight heparin should be considered to prevent in situ thrombosis in the diseased pulmonary artery and to guard against venous thromboembolism. Although studies demonstrating a survival effect of low level anticoagulation in patients with idiopathic PAH have not been well designed, most practitioners favor low level anticoagulation in patients with PAH unless the patient is at risk of developing significant hemorrhagic complication *(64)*.

Management of Labor and Delivery in the Pulmonary Hypertensive Patient

The primary concern in bringing the pregnant patient with PAH to delivery is that the demand for increased CO during labor will outstrip the circulatory systems ability to maintain flow through the diseased pulmonary circulation. CO increases an average of 12% above pre-labor values during uterine contractions and up to 34% at full dilation of the cervix *(92)*. This can be 60–80% greater than CO prior to the start of pregnancy. Uterine contractions can each increase intravascular blood volume as much a 500 ml during labor and blood volume may increase 1,000–1,500 ml immediately after delivery *(93, 94)*. The RV must keep up with this marked increase in flow despite several factors that combine to impede right ventricular performance. Increased pulmonary blood flow raises PAP and RV afterload *(95)*. Marked increases in intrathoracic pressure from pushing maneuvers and compression of the IVC by the gravid uterus impede venous return to the RV. Analgesics and sedatives used to ease the discomfort of labor can decrease catecholamine release, but also impede systemic venous tone and further decrease right sided filling pressures. The result of all of these factors can be a rise in central venous pressure (CVP), PAP, and PVR and subsequent decrease in CO *(96)* (Figure 19.5).

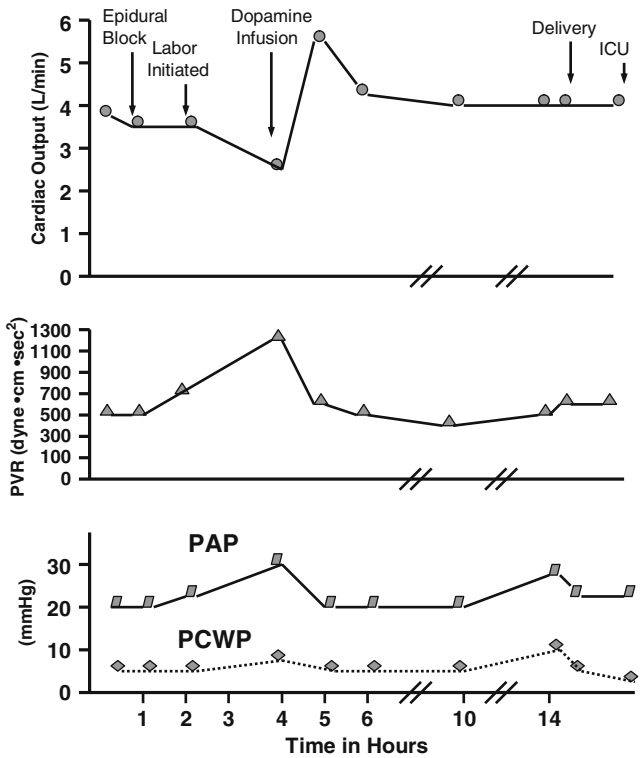


Figure 19.5 Cardiopulmonary hemodynamics during labor and delivery in a patient with pulmonary arterial hypertension. At the onset of labor, pulmonary arterial pressure rises (PAP, *bottom panel*) as cardiac output falls (CO, *upper panel*) causing a rise in pulmonary vascular resistance (PVR, *middle panel*). Cardiac output improved with dobutamine infusion and PAP fell, but rose again shortly before delivery. See text for explanation. Used with permission from Robinson DE and Leicht CH. Anesthesiology. 1988;68:285–8 (ref. *96*)

Formal guidelines for management of labor and delivery in patients with PAH have not been forthcoming. Most practitioners advocate forceps or vacuum assisted vaginal delivery using epidural anesthesia *(97, 98)*. This approach limits the degree of cardiovascular stress caused by pain during labor, avoids sudden decreases in right sided filling pressures by limiting pushing by the mother during labor, and minimizes the vasodilator effects of anesthesia. Cesarean section may be indicated in patients with obstetrical complications that would prolong labor or increase the stress of delivery and this approach has been used successfully to deliver pregnant women with PAH *(99–102)*. However, the increased anesthesia and increased risk of thrombosis can worsen pulmonary hemodynamics and the procedure has been associated with increased mortality in women with pulmonary vascular disease compared to vaginal delivery *(19)*.

A general approach to delivering the parturient with PAH was proposed by Mangano et al. *(103)* over 20 years ago and still holds true today. First, the degree of PH and the reactivity of the vascular bed should be determined prior to delivery. Use of a PAC to monitor filling pressures, PAP, and CO during delivery is somewhat controversial. Some practitioners argue against the routine use of PAC in the parturient with PAH citing the potential risk of complications such as thromboembolic events, arrhythmias, misleading data, and difficulty of catheter insertion in the setting of elevated right sided pressure and tricuspid regurgitation *(85, 98)*.

Others point to small case series suggesting that the routine use of invasive cardiac monitoring has not improved the outcome of the parturient with severe PH *(104)*. However, these opinions hail from a time before modern treatments for PAH were widely available. Catheterization of the pulmonary artery is entirely feasible in the pregnant patient and in experienced hands will yield important information regarding the severity of the patient's disease, central filling pressures, and response to vasodilators. The greater acceptance of PAC to help manage labor and delivery in women with PAH is reflected in its use in numerous case reports since the turn of the century *(94, 97, 105, 106)*.

Second, factors that worsen PH such as hypoxemia, hypercarbia, acidemia, and pain should be minimized. Adequate ventilation and oxygenation should not be problematic in a patient with no other underlying lung disease. If other co-morbidities exist, or if PAH has advanced to hypoxemia that cannot be easily corrected with supplemental oxygenation, intubation and mechanical ventilation of the patient may be warranted. The relief of pain and stress of labor are important. Although catecholamines in general have only minimal effect on pulmonary vascular tone, the increase in CO that they cause due to chronotropic effects can raise PAP and RV afterload considerably. General anesthesia is generally avoided due to its depressant effects on vascular tone and myocardial contractility. However, lumbar segmental epidural anesthesia with low dose bupivacaine/fentanyl mixtures *(96)* has been used successfully to control the discomfort of labor with minimal systemic hemodynamic effects *(95)*.

Third, large changes in RV preload and LV afterload should be avoided. RV output relies heavily on preload and monitoring of CVP is essential to ensure adequate venous return, especially in patients receiving positive pressure ventilation and/or heavy anesthesia. Patients who require mechanical ventilation should be ventilated with moderate to low lung volumes. Supine position should be avoided to prevent aortocaval compression. Finally, the need for early diagnosis and a team wide approach to management of these difficult patients cannot be overemphasized. Careful planning with the obstetrician, anesthesiologist, and pulmonary or cardiology specialist experienced in the management of PAH is needed to optimize the patients chance of survival.

Few guidelines exist regarding the use of pulmonary vasodilators during labor and delivery. Prior to the development of selective pulmonary vasodilators, medical management relied on oxygen, diuretics, and CCB. Calcium channel blockers have poor selectivity for the pulmonary circulation and in the great majority of patients with pulmonary vascular disease cause greater vasorelaxation of systemic than pulmonary resistance vessels. Furthermore, the doses often needed to produce any significant pulmonary vasodilatory effect can result in significant myocardial depression. These effects can lead to severe hypotension. In fact, some attempts to transition pregnant patients with PAH from intravenous prostacyclin therapy to oral calcium channel antagonists have resulted in maternal death postpartum *(93, 107)*. Although successful management of PAH with CCB during pregnancy and post-partum has been described *(108, 109)*, their use should generally be avoided in the pregnant patient with PAH. The advent of more pulmonary selective vasodilators has made the use of CCB obsolete except for the rare patient that has been shown to demonstrate an acute favorable hemodynamic response *(13)*.

The greatest experience with pulmonary vasodilator therapy during labor has been with the prostacyclins. Intravenous epoprostenol, iloprost, and inhaled epoprostenol have all been used to successfully manage labor. Several case reports have described successful management of labor and delivery with intravenous

epoprostenol *(100, 105)*. Inhaled iloprost has also been used successfully to manage PAH during pregnancy and the post-partum period *(89)*. Some authors have suggested that inhaled prostacyclin is more efficacious or safer than intravenous therapy because it avoids systemic hypotension and has less anti-platelet activity. However, systemic hypotension and increased bleeding have not been reported with intravenous therapy. Although no studies have directly compared intravenous to inhalational therapy, one patient treated with inhaled iloprost 7–9 times per day developed progressive disease that cumulated in cardiac arrest and required initiation of intravenous iloprost after successful cardiac resuscitation *(89)*.

Inhaled NO has also been used successfully to deliver mothers with PAH *(110)*. This drug has the advantages of rapid onset, virtually no systemic hemodynamic or anti-platelet effects and rapid elimination after discontinuation. The disadvantage is its difficulty to administer because FDA-approved devices that can deliver the drug by nasal cannula are not readily available. Thus, patients usually require transition to other therapies after iNO is initiated.

Although primary vasoactive therapy should be aimed at reducing RV afterload, the possibility of RV failure from abrupt increase in preload cannot be ignored. As discussed earlier, the RV is more tolerant of preload than the LV. However, at full term the dilated RV of a PAH patient may already be near full capacity. At this point, additional increases in intravascular volume from uterine contraction or post-partum fluid shifts may overdistend the RV free wall or impede LV filling by further shifting of the intraventricular septum. Either effect can cause a precipitous fall in CO and cardiogenic shock. Diuretics and acute veno-dilators such as intravenous nitroglycerin have been used to improve pulmonary hemodynamics during delivery. The use of vasoactive agents to reduce preload requires careful hemodynamic monitoring and should be employed only in patients with PACs.

Management of Pulmonary Hypertension in the Post-partum Patient

Successful delivery of the pulmonary hypertensive patient is often greeted with relief and a sense that the worst is over when in fact the most dangerous period may just be beginning. In fact, most of the mortality associated with PAH in pregnancy occurs during the month following delivery with the highest risk in the first 10 days post partum *(19)*. Worse still is that post-partum death from PAH often occurs suddenly from irreversible cardiovascular collapse many days after successful delivery in patients who had appeared to be relatively stable *(78, 80, 95, 111)*.

The cause of cardiovascular collapse after delivery is not well understood. Considerable redistribution of extra vascular fluid to the intravascular space occurs during the first 2 weeks post-partum. Sudden increases in PVR have been described *(112)*. Although the mechanisms responsible for the increase in PVR are uncertain, the sudden onset of deterioration has raised concern of amniotic fluid embolism or thrombosis of small pulmonary arteries *(95, 113)*. It is not unreasonable to expect that some degree of occlusion of the pulmonary microcirculation normally occurs after delivery due to amniotic debris and small blood clots. This is likely well tolerated by the healthy lung, but may cause hemodynamic compromise in the post-partum patient with a diseased pulmonary circulation. At the same time, significant changes in myocardial contractility occur. Decreased LV systolic function occurs late in pregnancy and reaches a nadir in the post-partum period. Thus, increases in RV preload and afterload occur at a time when the myocardium of the RV is poorly prepared to handle it. Easterling et al. *(85)* described a patient who

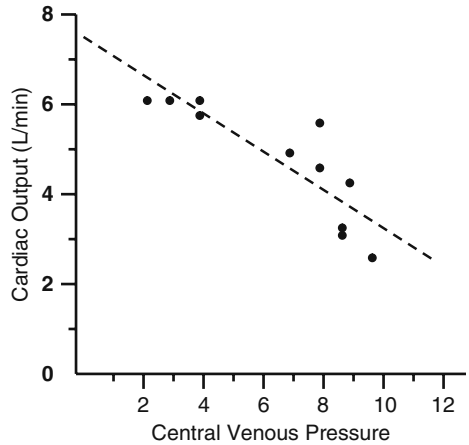


Figure 19.6 Cardiac output (CO) response to central filling pressures. CO remains within normal over a range of CVP from 2 to 8. Elevation of CVP above 8 is accompanied by a fall in CO. See text for further discussion. Used with permission from Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: treatment with Obstet Gynecol. 1999;93:494–8 (ref. *87*)

developed sudden dyspnea after receiving a blood transfusion post-partum. RV failure was characterized by falling CO in the face of rising CVP (Figure 19.6). The patient improved with careful diuresis over the next 24 h and an increase in her prostacyclin dose.

Careful observation of cardiovascular stability and volume status is crucial for at least 1–2 weeks after delivery. Although no formal recommendations have been made, it is imperative to keep the mother hospitalized for at least several days until she is hemodynamically stable and able to ambulate without difficulty. Many practitioners hospitalize the patient for longer periods up to several weeks after delivery to ensure complete recovery.

Management of PAH and RV failure in the post-partum patient does not differ significantly from that of the non-pregnant PAH patient, except that more attention may need to be given to intravascular fluid shifts. Echocardiography can be used to assess RV size and estimate PAP. Rising plasma BNP and troponin levels may signal worsening RV strain and alert the physician to a deteriorating situation. Diuretics may need to be increased to reduce RV preload. Patients should be continued on the regiment of anti-pulmonary hypertensive medications that was used to control their PAH before or during labor. Changes in the dose of pulmonary vasodilators post-partum will depend to some degree on the known vasodilator response of the patient. Patients who are unresponsive to pulmonary vasodilators are unlikely to benefit from empirically increasing the dose of these agents post-partum over concern of increasing RV demand. Those who have demonstrated acute vasodilatory response should likely be considered for treatment with these agents if they show signs of worsening RV compromise on echocardiogram or clinical signs of RV failure.

Ionotropic agents may improve RV function and help the patient survive this difficult period. Right heart catheterization may be needed to monitor central filling pressures and CO. In general, post-partum patients with PAH who show signs of clinical deterioration should be considered class IV patients and treated with prostacyclin. Concerns about platelet dysfunction and bleeding can be minimized by use of inhaled agents if necessary.

Summary and Conclusions

Despite recent advances in the treatment of PAH, its presence during pregnancy significantly increases the risk of maternal death. Due to the small number of cases that have been reported since the advent of modern treatments, the absolute risk of carrying a fetus to term and surviving delivery remains uncertain. Physicians today have more options for manipulating pulmonary hemodynamics during the pregnancy and after delivery, but the effectiveness of even the most recent medications is limited. Patients with PAH should be advised not to become pregnant because of the risk to both mother and child during the pregnancy and the likelihood of exacerbating their underlying PAH. It may be appropriate to reconsider pregnancy in the event of an unusually favorable response to treatment, but PAP pressure and CO need to return to near normal levels before proceeding. Patients who develop PAH during their pregnancy should be treated aggressively, preferably with a prostacyclin derivative. A team approach that incorporates obstetrician, anesthesiologist, and a physician experienced in the management of PAH should be utilized. Pulmonary artery catheterization should be performed as early in the pregnancy as possible to assess disease severity and response to selective pulmonary vasodilators and again at the time of delivery to monitor hemodynamic responses and guide management of fluids, pressors, and pulmonary vasodilators if the need arises. Maternal mortality rates are highest in the post-partum period and patients should be kept in hospital for careful observation of fluid shifts and RV failure for the first several days to weeks after delivery. Greater experience with the use of modern anti-pulmonary hypertensive medications in the pregnant patient with PAH may produce more specific recommendations regarding postpartum care in this difficult patient population.

Acknowledgements: This paper was supported in part by NIH grant HL-088328-01 (JRK)

References

1. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216–223.
2. Barnes PJ, Liu SF. Regulation of pulmonary vascular tone. Pharmacol Rev 1995;47:87–131.
3. Michelsen S, Otterstad JE. Blood pressure response during maximal exercise in apparently healthy men and women. J Intern Med 1990;227:157–163.
4. Hakim TS. Flow-induced release of EDRF in the pulmonary vasculature: site of release and action. Am J Physiol 1994;267: H363–H369.
5. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216–223.
6. Weir EK, Olschewski A. Role of ion channels in acute and chronic responses of the pulmonary vasculature to hypoxia. Cardiovasc Res 2006;71:630–641.
7. Tandon HD, Kasturi J. Pulmonary vascular changes associated with isolated mitral stenosis in India. Br Heart J 1975;37:26–36.
8. Romberg E. Uebere Sklerose Der Lungenarterien. Dtsch Arch Klin Med 1981;48:197–206.
9. Dresdale DT, Schultz M, Michtom RJ. Primary pulmonary hypertension. I. Clinical and hemodynamic study. Am J Med 1951;11:686–705.

10. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5S–12S.
11. Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF, Tuder RM. Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. J Clin Invest 1998;101:927–934.
12. Palevsky HI, Schloo BL, Pietra GG, Weber KT, Janicki JS, Rubin E, Fishman AP. Primary pulmonary hypertension. Vascular structure, morphometry, and responsiveness to vasodilator agents. Circulation 1989;80:1207–1221.
13. Lumb AB. Pregnancy, neonates and children. In: Lumb AB ed. Nunn's Applied Respiratory Physiology. New York: Elsevier Limited, 2005:229–230.
14. Weiss BM, Maggiorini M, Jenni R, Lauper U, Popov V, Bombeli T, Spahn DR. Pregnant patient with primary pulmonary hypertension: inhaled pulmonary vasodilators and epidural anesthesia for cesarean delivery. Anesthesiology 2000;92:1191–1194.
15. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial changes in pulmonary haemodynamics during human pregnancy: a non-invasive study using Doppler echocardiography. Clin Sci 1991;80:113–117.
16. Dawkins KD, Burke CM, Billingham ME, Jamieson SW. Primary pulmonary hypertension and pregnancy. Chest 1986;89:383–388.
17. Wagenvoort CA and Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. Circulation 1970;42: 1163–1182.
18. Rubin LJ. Primary pulmonary hypertension. Chest 1993;104:236–250.
19. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31: 1650–1657.
20. Bitsch M, Johansen C, Wennevold A, Osler M. Maternal heart disease. A survey of a decade in a Danish university hospital. Acta Obstet Gynecol Scand 1989;68:119–124.
21. Okada K, Tanaka Y, Bernstein M, Zhang W, Patterson GA, Botney MD. Pulmonary hemodynamics modify the rat pulmonary artery response to injury. A neointimal model of pulmonary hypertension. Am J Pathol 1997;151:1019–1025.
22. De Canniere D, Stefanidis C, Brimioulle S, Naeije R. Effects of a chronic aortopulmonary shunt on pulmonary hemodynamics in piglets. J Appl Physiol 1994;77:1591–1596.
23. Karmochkine M, Cacoub P, Dorent R, Laroche P, Nataf P, Piette JC, Boffa MC, Gandjbakhch I. High prevalence of antiphospholipid antibodies in precapillary pulmonary hypertension. J Rheumatol 1996;23:286–290.
24. Welsh CH, Hassell KL, Badesch DB, Kressin DC, Marlar RA. Coagulation and fibrinolytic profiles in patients with severe pulmonary hypertension. Chest 1996;110: 710–717.
25. Hassell KL. Altered hemostasis in pulmonary hypertension. Blood Coagul Fibrinolysis 1998;9:107–117.
26. Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. Mayo Clin Proc 1985;60:16–25.
27. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992;327:70–75.
28. Tuder, RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, Badesch DB, Voelkel NF. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159:1925–1932.
29. Redman CW. Coagulation problems in human pregnancy. Postgrad Med J 1979;55: 367–371.
30. Beller FK, Ebert C. The coagulation and fibrinolytic enzyme system in pregnancy and in the puerperium. Eur J Obstet Gynecol Reprod Biol 1982;13:177–197.
31. Rutherford S, Montoro M, McGehee W, Strong T. Thromboembolic disease associated with pregnancy: an 11-year review. Am J Obstet Gynecol 1991;164:286–286.

32. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996; 335:108–114.
33. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography Doppler and five-year survival analysis. Circulation 1999;99:1325–1330.
34. Mata-Greenwood E, Meyrick B, Soifer SJ, Fineman JR, Black SM. Expression of VEGF and its receptors Flt-1 and Flk-1/KDR is altered in lambs with increased pulmonary blood flow and pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2003;285:L222–L231.
35. Mata-Greenwood E, Meyrick B, Steinhorn RH, Fineman JR, Black SM. Alterations in TGF-beta1 expression in lambs with increased pulmonary blood flow and pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2003;285:L209–L221.
36. Wedgwood S, Devol JM, Grobe A, Benavidez E, Azakie A, Fineman JR, Black SM. Fibroblast growth factor-2 expression is altered in lambs with increased pulmonary blood flow and pulmonary hypertension. Pediatr Res 2007;61:32–36.
37. Black SM, Bekker JM, Johengen MJ, Parry AJ, Soifer SJ, Fineman JR. Altered regulation of the ET-1 cascade in lambs with increased pulmonary blood flow and pulmonary hypertension. Pediatr Res 2000;47:97–106.
38. Rajakumar A, Michael HM, Rajakumar PA, Shibata E, Hubel CA, Karumanchi SA, Thadhani R, Wolf M, Harger G, Markovic N. Extra-placental expression of vascular endothelial growth factor receptor-1,(Flt-1) and soluble Flt-1 (sFlt-1), by peripheral blood mononuclear cells (PBMCs) in normotensive and preeclamptic pregnant women. Placenta 2005;26:563–573.
39. Evans PW, Wheeler T, Anthony FW, Osmond C. A longitudinal study of maternal serum vascular endothelial growth factor in early pregnancy. Hum Reprod 1998;13:1057–1062.
40. Wheeler T, Evans PW, Anthony FW, Godfrey KM, Howe DT, Osmond C. Relationship between maternal serum vascular endothelial growth factor concentration in early pregnancy and fetal and placental growth. Hum Reprod 1999;14:1619–1623.
41. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Stewart DJ. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732–1739.
42. Sturrock A, Cahill B, Norman K, Huecksteadt TP, Hill K, Sanders K, Karwande SV, Stringham JC, Bull DA, Gleich M, Kennedy TP, Hoidal JR. Transforming growth factor-beta1 induces Nox4 NAD(P)H oxidase and reactive oxygen species-dependent proliferation in human pulmonary artery smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 2006;290: L661–L673.
43. Hirose S, Hosoda Y, Furuya S, Otsuki T, Ikeda E. Expression of vascular endothelial growth factor and its receptors correlates closely with formation of the plexiform lesion in human pulmonary hypertension. Pathol Int 2000;50:472–479.
44. Benisty JI, McLaughlin VV, Landzberg MJ, Rich JD, Newburger JW, Rich S, Folkman J. Elevated basic fibroblast growth factor levels in patients with pulmonary arterial hypertension. Chest 2004;126:1255–1261.
45. Rajakumar A, Conrad KP. Expression, ontogeny, and regulation of hypoxia-inducible transcription factors in the human placenta. Biol Reprod 2000;63:559–569.
46. Cowden Dahl KD, Fryer BH, Mack FA, Compernolle V, Maltepe E, Adelman DM, Carmeliet P, Simon MC. Hypoxia-inducible factors 1alpha and 2alpha regulate trophoblast differentiation. Mol Cell Biol 2005;25:10479–10491.
47. Fryer BH, Simon MC. Hypoxia, HIF and the placenta. Cell Cycle 2006;5:495–498.
48. Schultz K, Fanburg BL, Beasley D. Hypoxia and hypoxia-inducible factor-1alpha promote growth factor-induced proliferation of human vascular smooth muscle cells. Am J Physiol Heart Circ Physiol 2006;290: H2528–H2534.
49. Yamakawa M, Liu LX, Date T, Belanger AJ, Vincent KA, Akita GY, Kuriyama T, Cheng SH, Gregory RJ, Jiang C. Hypoxia-inducible factor-1 mediates activation of cultured vascular endothelial cells by inducing multiple angiogenic factors. Circ Res 2003;93:664–673.

50. Holmgren L, Glaser A, Pfeifer-Ohlsson S, Ohlsson R. Angiogenesis during human extraembryonic development involves the spatiotemporal control of PDGF ligand and receptor gene expression. Development 1991;113:749–754.
51. Street ME, Seghini P, Ziveri MA, Fieni S, Volta C, Neri TM, Viani I, Bacchi-Modena A, Bernasconi S. Interleukin-6 and insulin-like growth factor system relationships and differences in the human placenta and fetus from the 35th week of gestation. Growth Horm IGF Res 2006;16:365–372.
52. Balasubramaniam V, Le Cras TD, Ivy DD, Grover TR, Kinsella JP, Abman SH. Role of platelet-derived growth factor in vascular remodeling during pulmonary hypertension in the ovine fetus. Am J Physiol Lung Cell Mol Physiol 2003;284: L826–L833.
53. Humbert M, Monti G, Brenot F, Sitbon O, Portier A, Grangeot-Keros L, Duroux P, Galanaud P, Simonneau G, Emilie D. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. Am J Respir Crit Care Med 1995;151:1628–1631.
54. Barker D, Williams S, Mason G, McLoughlin H, Schlosshan D, Tan L. Plasma brain natriuretic peptide may not be useful to assess possible cardiac symptoms during pregnancy: 248. Am J Obstet Gynecol 2006;193, (6):79.
55. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735–740.
56. D'Alonzo GE, Barst RJ, Ayers SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991;115: 343–349.
57. World Symposium on Primary Pulmonary Hypertension (Venice, Italy 2003).
58. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76–81.
59. Galie N, Humbert M, Vachiery JL, Vizza CD, Kneussl M, Manes A, Sitbon O, Torbicki A, Delcroix M, Naeije R, Hoeper M, Chaouat A, Morand S, Besse B, Simonneau G. Arterial Pulmonary Hypertension and Beraprost European (ALPHABET) Study Group. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2002;39:1496–502.
60. Higenbottam TW, Spiegelhalter D, Scott JP, Fuster V, Dinh-Xuan AT, Caine N, Wallwork J. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. Br Heart J 1993;70:366–370.
61. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296–302.
62. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA Jr. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000;132:425–434.
63. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–1482.
64. Yap RL, Mermel LA. Micrococcus infection in patients receiving epoprostenol by continuous infusion. Eur J Clin Microbiol Infect Dis 2003;22:704–705.
65. MMWR Centers for Disease Control and Prevention (CDC). Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension-seven sites, United States, 2003–2006. MMWR Morb Mortal Wkly Rep. 2007;56:170–172.

66. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV. American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35S–62S.
67. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ; Treprostinil Study Group. 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;165:800–804.
68. Gomberg-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitz AC, Barst RJ. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med 2005;172:1586–1589.
69. Opitz CF, Wensel R, Winkler J, Halank M, Bruch L, Kleber FX, Hoffken G, Anker SD, Negassa A, Felix SB, Hetzer R, Ewert R. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Eur Heart J 2005;26:1895–1902.
70. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N. STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006;47:2049–2056.
71. Galie' N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, Zwicke D, Naeije R, Shapiro S, Olschewski H, Rubin LJ. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005;46:529–535.
72. McLaughlin VV. Survival in patients with pulmonary arterial hypertension treated with first-line bosentan. Eur J Clin Invest 2006;36:10–15.
73. Klinger JR. The nitric oxide/cGMP signaling pathway in pulmonary hypertension. Clin Chest Med 2007;28:143–167.
74. Ghofrani, HA, Voswinckel, R, Reichenberger, F, et al. Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. J Am Coll Cardiol 2004;44:1488–1496.
75. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148–2157.
76. Badesch DB, McLaughlin VV, Delcroix M, Vizza CD, Olschewski H, Sitbon O, Barst RJ. Prostanoid therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:56S–61S.
77. Channick RN, Sitbon O, Barst RJ, Manes A, Rubin LJ. Endothelin receptor antagonists in pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:62S–67S.
78. Ghofrani HA, Pepke-Zaba J, Barbera JA, Channick R, Keogh AM, Gomez-Sanchez MA, Kneussl M, Grimminger F. Nitric oxide pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:68S–72S.
79. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE. American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:14S–34S.
80. Mccaffrey RM, Dunn LJ. Primary pulmonary hypertension in pregnancy. Obstet Gynecol Surv 1964;19:567–591.
81. Breen TW, Janzen JA. Pulmonary hypertension and cardiomyopathy: anaesthetic management for caesarean section. Can J Anaesth 1991;38:895–899.
82. Martinez JM, Comas C, Sala X, Gratacos E, Torres PJ, Fortuny A. Maternal primary pulmonary hypertension associated with pregnancy. Eur J Obstet Gynecol Reprod Biol 1994;54:143–147.
83. Carro-Jimenez EJ, Lopez JE. Primary pulmonary hypertension and pregnancy. Bol Asoc Med P R 2005;97:328–333.

84. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34:721–741.
85. Sinnenberg RJ Jr. Pulmonary hypertension in pregnancy. South Med J 1980;73: 1529–1531.
86. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy – a lethal combination. Anaesth Intensive Care 1990;18:366–374.
87. Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: treatment with pulmonary vasodilators. Obstet Gynecol 1999;93:494–498.
88. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth 1994;41:502–512.
89. Elliot CA, Stewart P, Webster VJ, Mills GH, Hutchinson SP, Howarth ES, Bu'lock FA, Lawson RA, Armstrong IJ, Kiely DG. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J 2005;26:168–173.
90. 3rd TRAX PMS Data Report to CPMP for the period from 24 May 2002–19 February 2003 (Actelion Pharmaceuticals, data on file).
91. Battenfeld R, Schuh W, Schobel C. Studies on reproductive toxicity of iloprost in rats, rabbits and monkeys. Toxicol Lett 1995;78:223–234.
92. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy.Br Heart J 1992;68:540–543.
93. Monnery L, Nanson J, Charlton G. Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. Br J Anaesth 2001;87:295–298.
94. Bildirici I, Shumway JB. Intravenous and inhaled epoprostenol for primary pulmonary hypertension during pregnancy and delivery. Obstet Gynecol 2004;103:1102–1105.
95. Slomka F, Salmeron S, Zetlaoui P, Cohen H, Simonneau G, Samii K. Primary pulmonary hypertension and pregnancy: anesthetic management for delivery. Anesthesiology 1988;69:959–961.
96. 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;68:285–288.
97. Lam GK, Stafford RE, Thorp J, Moise KJ Jr, Cairns BA. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. Obstet Gynecol 2001;98:895–898.
98. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth 1994;41:502–512.
99. Olofsson C, Bremme K, Forssell G, Ohqvist G. Cesarean section under epidural ropivacaine 0.75% in a parturient with severe pulmonary hypertension. Acta Anaesthesiol Scand 2001;45:258–260.
100. Badalian SS, Silverman RK, Aubry RH, Longo J. Twin pregnancy in a woman on long-term epoprostenol therapy for primary pulmonary hypertension. A case report. J Reprod Med 2000;45:149–152.
101. O'Hare R, McLoughlin C, Milligan K, McNamee D, Sidhu H. Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth 1998;81:790–792.
102. Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, Krivosic-Horber R. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. Can J Anaesth 2001;48:584–587.
103. Mangano DT. Anaesthesia for the pregnant cardiac patient, In: Shnider SM, Levinson G, eds. Anaesthesia for Obstetrics, 3rd Edn. Baltimore: Williams and Wilkins, 1983: 502–508.
104. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy – a lethal combination. Anaesth Intensive Care 1990;18:366–374.
105. Hill LL, De Wet CJ, Jacobsohn E, Leighton BL, Tymkew H. Peripartum substitution of inhaled for intravenous prostacyclin in a patient with primary pulmonary hypertension. Anesthesiology 2004;100:1603–1605.
106. Stewart R, Tuazon D, Olson G, Duarte AG. Pregnancy and primary pulmonary hypertension: successful outcome with epoprostenol therapy. Chest 2001;119:973–975.

107. Vonk Noordegraaf A, Roeleveld RJ. Primary pulmonary hypertension in pregnancy. Br J Anaesth 2002;88:151.
108. Kiss H, Egarter C, Asseryanis E, Putz D, Kneussl, M. Primary pulmonary hypertension in pregnancy: a case report. Am J Obstet Gyn 1995;172:1052–1054.
109. Nootens M, Rich S. Successful management of labor and delivery in primary pulmonary hypertension. Am J Cardiol 1993;71:1124–1125.
110. Robinson JN, Banerjee R, Landzberg MJ, Thiet MP. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. Am J Obstet Gynecol 1999;180:1045–1046.
111. Nelson DM, Main E, Crafford W, Ahumada GG. Peripartum heart failure due to primary pulmonary hypertension. Obstet Gynecol 1983;62:58S–63S.
112. Sullivan JM, Ramanathan KB.Management of medical problems in pregnancy–severe cardiac disease. N Engl J Med 1985;313:304–309.
113. Weir EK. Diagnosis and management of primary pulmonary hypertension: In: Weir WK, Reeves JT eds. Pulmonary Hypertension. New York: Futura, 1984:142–143.

20

Pulmonary Procedures During Pregnancy

Muhanned Abu-Hijleh

Keywords: interventional pulmonology, pregnancy, bronchoscopy, conscious sedation, pleural procedures, monitoring, thoracentesis, chest tube

Introduction

Pulmonary procedures during pregnancy are frequently needed for the evaluation and management of primary pulmonary conditions as well as systemic disorders with pulmonary manifestations. The interactions between the expected pulmonary physiological and anatomical adaptations to pregnancy, the procedure itself, and the use of conscious sedation (or general anesthesia) during pregnancy can result in overall risks that are different from similar procedures in non-pregnant patients, heightening both patient and physician anxiety and concern. The literature that deals with pulmonary procedures during pregnancy is limited to a few reviews *(1, 2)* and case reports. Some data can be extrapolated from the literature that deals with endoscopy during pregnancy *(3–6)*. Until more specific literature addresses pulmonary procedures during pregnancy is available, general recommendations will be suggested during this overview.

Pregnancy is associated with well-documented adaptations in pulmonary physiology and anatomy *(7–9)* (Chapter 2). The size and pressure effects of the gravid uterus on pulmonary mechanics result in cephalad displacement of the diaphragm and an increase in the anterior–posterior diameter of the chest *(10, 11)*. The vital capacity remains unchanged, although the functional residual capacity and the residual volume are usually reduced. The respiratory system compliance is usually reduced toward term.

Hormonal changes during pregnancy can affect the mucosal lining of the airways. Estrogen induces capillary dilation with hyperemia and edema of the upper airways, potentially increasing the risk of bleeding and airway obstruction during bronchoscopy. Pulmonary flows do not change significantly during pregnancy *(8)*, but the respiratory center response appears to be exaggerated *(12)*. This is probably related to the effect of progesterone on the respiratory center sensitivity to carbon dioxide *(13)*. The tidal volume usually increases during pregnancy without significant change in the respiratory rate. This leads to higher baseline minute ventilation and a lower baseline carbon dioxide set level. Production of carbon dioxide increases

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_20

during pregnancy due to the relatively high baseline metabolic rate (of the mother and the fetus). Although oxygen consumption increases significantly during pregnancy, this increase in minute ventilation and overall alveolar ventilation results in a higher baseline partial pressure of arterial oxygen *(7, 14)*. Sedation that affects such adaptations can result in hypoventilation with significant effects on the mother and the fetus. Such changes can predispose pregnant patients to rapid oxyhemoglobin desaturation during pulmonary procedures and related conscious sedation.

As the cardiac output increases and the pulmonary vascular resistance decreases during pregnancy, the overall pulmonary artery pressure remains generally unchanged *(15–17)*. This has important implications and confirms the overall safety of transbronchial pulmonary parenchymal biopsies during pregnancy in the appropriate settings. The supine position can result in compression of the inferior vena cava, which decreases the cardiac output and leads to the "supine hypotension syndrome" during pregnancy *(18)*. Therefore, careful positioning of pregnant patients during bronchoscopy is necessary. Maternal hypotension related to position of the pregnant patient or sedation can result in significant reduction in the fetal blood flow.

It is important for physicians who perform procedures and administer conscious sedation to pregnant patients to understand that the magnitude of the described anatomical, mechanical, and hemodynamic physiological changes of pregnancy can be exaggerated or blunted during pulmonary procedures and related sedation. It is also important to be aware that some anatomical changes occur in pregnancy, possibly affecting the procedure. For instance, nasal mucosa and the upper airway may be more edematous than the non-pregnant, and Mallampati scores higher. Pre-procedure evaluation, strict monitoring, and the availability of skilled operators who anticipate pregnancy related changes and potential risks are all essential. Understanding the effects of conscious sedation medications on the maternal and fetal physiology is a cornerstone.

Interventional Pulmonology

Interventional pulmonology is a relatively new sub-specialty encompassing a wide variety of diagnostic and therapeutic interventions for benign and malignant disorders of the airways, the lung parenchyma, and the pleura *(19–21)*. The exposure of interventional pulmonologists to pulmonary procedures during pregnancy continues to grow, especially in large institutions. The majority of interventional procedures remain diagnostic in nature with a focus on bronchoscopy, pleural space sampling and drainage *(20)* (Table 20.1). Rigid bronchoscopy is reserved for limited diagnostic procedures and a variety of advanced therapeutic procedures. Other procedures performed by some interventional pulmonologists include percutaneous tracheostomy and transtracheal oxygen catheters.

The availability of more advanced technology should theoretically improve the safety of interventional pulmonary procedures during pregnancy. Examples include the utility of endobronchial ultrasound for image guided sampling of the mediastinal lymph nodes that should improve the diagnostic yield. The availability of transthoracic ultrasound to the interventional pulmonologist should improve the safety and accuracy of pleural procedures during pregnancy.

The growing experience of interventional pulmonologists with pulmonary procedures during pregnancy should provide further data about the safety and specific recommendations in the future. The following discussion will involve extrapolation of data from the larger experience of gastro-esophageal interventions during pregnancy.

Table 20.1 Interventional procedures offered by interventional pulmonologists.

Bronchoscopy	Pleural procedures
Diagnostic: – Endobronchial wash, cytology brush specimens, forceps biopsy and needle aspiration – Bronchoalveolar lavage specimens – Transbronchial lung biopsy, brush specimens for microbiology and cytology, and needle aspiration – Transbronchial mediastinal and hilar needle aspiration – Endobronchial ultrasound – Autofluorescence bronchoscopy – CT fluoroscopy guided bronchoscopy Therapeutic: – Removal of foreign bodies – Airway dilation: balloon or rigid dilation – Endobronchial resection and recanalization techniques using mechanical debulking, laser, electrocautery and argon plasma coagulation – Placement of stents (silicone, metallic or dynamic) – Brachytherapy – Photodynamic therapy – Cryotherapy	Diagnostic thoracentesis Therapeutic thoracentesis Pleural manometry Closed pleural biopsy Chest tube placement Chemical pleurodesis through chest tubes Placement of tunneled pleural catheters Medical thoracoscopy (Medical pleuroscopy) Transthoracic ultrasound to guide pleural procedures

Multidisciplinary Approach

The decision to perform pulmonary procedures on pregnant patients depends on close collaboration and planning that should involve interventional pulmonologists, obstetricians, maternal-fetal medicine specialists, neonatologists, pharmacologists, intensivists, radiologists, and anesthesiologists as necessary. Thoracic surgeons may provide important insight into the potential for thoracic surgical alternative interventions in some patients.

Pre-procedure Considerations

The indication to perform any pulmonary procedure or intervention should be clear to the physician and the patient. Alternative approaches that include empiric management, radiographic studies and procedures under general anesthesia should be explored. However, higher morbidity may be associated with inaccurate diagnosis, which may lead to inadequate treatment. The potential benefits and risks of postponing the procedure temporarily until further stage of pregnancy (e.g., after the first trimester), or after delivery should be considered. However, the decision to proceed with the intervention should not only focus on the maternal and fetal risks of the procedure itself, but also on the risks associated with the lack of an accurate diagnosis affecting appropriate management of the pregnant patient. The treating physician should be fully aware of the physiology of labor and delivery and keep in mind that labor and delivery are situations that place the respiratory system under a significant amount of stress and are

associated with increased demands (minute ventilation increases significantly and so does oxygen consumption). Consequently, accurate diagnosis and adequate management of certain conditions during pregnancy and in anticipation of labor could be of paramount importance.

An appropriate consent documenting a discussion of the potential known and unknown risks of the procedure itself, diagnostic or therapeutic intervention, and conscious sedation or anesthesia medications should be obtained.

Obviously, patients should be stabilized prior to elective procedures. If the procedure is deemed necessary despite relative instability of the patient, the urgent need should be clearly documented and discussed with the patient and appropriate representatives. In situations where airway compromise or lung collapse with resulting respiratory distress and failure are complicating factors, it may be necessary to perform the procedure to optimize maternal and fetal outcome. Stabilizing the patient by administering blood products, intravenous fluids, appropriate medications, mechanical ventilation, adequate oxygenation, and intensive monitoring in a critical care setting should be attempted while preparing the patient for such emergent procedures. Close collaboration with obstetricians to monitor the fetus, anesthesiologists for full airway control and appropriate anesthesia or sedation, and thoracic surgical back up when necessary would all be ideal.

For elective procedures, appropriate pre-procedure evaluation of the airway should be performed *(1, 4)*. This includes documentation of the appropriate airway Mallampati class, oral cavity, and teeth condition to anticipate any potential challenges or complications.

The pulmonologist performing the procedure should be fully aware of the safety and hemodynamic effects of anesthestic drugs commonly used for sedation during pregnancy. Consultation with an anesthesiologist is recommended if more complex or prolonged procedures are anticipated. Although obstetrician involvement for fetal monitoring should be considered and discussed with individual obstetricians, we will provide some general guidelines in this chapter on the need and timing for fetal monitoring.

Positioning of the Patient

The pregnant patient with gravid uterus (especially >20 weeks gestation) is at risk for supine hypotension *(15, 18)* that results from compression of the inferior vena cava by the gravid uterus. This can lead to reduction in the preload, reducing the patient's cardiac output and blood pressure. The medications used for conscious sedation can also result in maternal hypotension. The combination of conscious sedation and the supine position can cause abrupt hypotension, reduced blood flow to the fetus, and related complications. Placing the patient in the left lateral position (if possible) to avoid supine hypotension during bronchoscopy and other pulmonary procedures is reasonable. The left lateral position should be adopted if supine hypotension develops while the pregnant patient is in another position during bronchoscopy or other pulmonary procedures. The semi-seated position (if there are no signs or symptoms of hemodynamic compromise) is also adequate during pulmonary procedures. The procedure room, table, fluoroscopy equipment, lead shielding, and other equipment should be arranged to accommodate such positions.

Topical Anesthesia and Conscious Sedation

Topical Anesthesia

The Food and Drug Administration classified medications during pregnancy into five categories. Unfortunately, this classification system is in large part based on either animal data or a lack of data. Teratogenicity can be species specific, which may be misleading in the interpretation of drug effects. Categories A and X are the most helpful suggesting that category A drugs do have human data to support their safe use in pregnancy and category X drugs should be avoided because of the known teratogenic effects. However, information on categories B and C is certainly less informative and therefore, benefit and risk of the medication should be weighed on an individual basis and reproductive data on the drugs reviewed individually. For instance, many category B drugs may actually be drugs for which there are no data and many C and some D drugs may have a better risk/benefit ratio and could be used. The available medications for conscious sedation and topical anesthesia are generally category B or C (Table 20.2).

Topical Lidocaine is administered for topical anesthesia of the central airways to improve patients' tolerance of the procedure by temporarily decreasing the gag reflex and cough. The total dose of Lidocaine should be limited to 8.2 mg/kg in adults (approximately 29 mL of 2% Lidocaine solution for a 70-kg adult) *(22)*. Neither systemic nor local Lidocaine has been associated with any significant malformations or teratogenic effects. However, similar to the non-pregnant patients, the minimum amount necessary should be used without exceeding the recommended limits. Potential complications include arrhythmias and convulsions. Methemoglobinemia related to Lidocaine can rarely develop.

Conscious Sedation

Anxiolysis and moderate sedation are usually used during bronchoscopy and can be used carefully in pregnant patients. The goal with the use of sedatives is comfort and relaxation, not deep sedation. A lower medication dose is usually used since the ventilatory response and, therefore desaturations could be exaggerated in pregnancy. Such levels of sedation can be administered by (or under the supervision of)

Table 20.2 Medications that can be used during pulmonary procedures in pregnancy.

Category B medications:
Lidocaine (topical / local anesthesia)
Meperidine
Propofol (deep sedation)
Ketamine (deep sedation)
Naloxone (reversal agent)
Category C medications:
Fentanyl
Morphine
Flumazenil (reversal agent)
Category D medications:
Midazolam (use after the first trimester if needed) *(80)*

the interventional pulmonologist. Deep sedation usually requires evaluation, administration, and monitoring under the supervision of an anesthesiologist *(4)*.

Meperidine, an opiate analgesic, is a category B medication used for conscious sedation during procedures that involve pregnant patients *(23)*. It is metabolized to a long half life derivative, which can accumulate after repetitive high doses and can lead to maternal respiratory depression and seizures. Meperidine crosses the placenta and diminished fetal heart beat variability can be noted after administration. This is usually transient and is not associated with poor outcomes. The dose of this medication should be titrated to obtain relaxation and analgesia without somnolence, using the lowest possible dose that achieves such effect (usually 50–75 mg) *(4)*.

Other medications without known contraindications in pregnancy include Propofol and Ketamine. Both medications are usually administered under the supervision of an anesthesiologist. Propofol is a short acting intravenous anesthetic that is usually administered for deep sedation during the induction of anesthesia. The safety, short time of onset, short recovery time, and the depth of sedation *(24)* make this option attractive for performing bronchoscopy during pregnancy. Administration by nurses under the supervision of endoscopists has been reported *(25)*. However, we recommend using this medication under the supervision and monitoring of an anesthesiologist during pregnancy. Furthermore, the experience with this medication during the first trimester of pregnancy is limited *(26)*. The experience with Ketamine use for endoscopic procedures during pregnancy is even more limited, especially during the first trimester of pregnancy. The anesthesiologist should be aware of the potential oxytocic effect with the possibility of increasing the uterine tone and contractions *(27)*. Increased maternal blood pressure is also possible. Both Ketamine and Propofol can cause neonatal neurological depression and maternal respiratory depression.

There is somewhat more experience with Fentanyl (FDA category C), which is a synthetic narcotic agonist that can cause maternal and neonatal respiratory depression and decreased fetal heart rate variability *(28)*. It is generally safe, although embryocidal effects were reported in mice *(29)*. The rapid onset of action and rapid recovery time relative to Meperidine make this medication attractive. Low doses during pregnancy appear to be effective.

Morphine use has been associated with reduced growth and behavioral abnormalities in animal studies, but not in humans. Neonatal withdrawal syndromes have been reported with prolonged maternal use near term *(30)*.

Of the benzodiazepines, Diazepam is rarely used in conscious sedation since Midazolam is preferred. This is related to Midazolam's more rapid onset of action and recovery, in addition to its significant amnestic effects. In addition, Diazepam may be associated with congenital abnormalities although the risk of association with oral clefts has been challenged in recent studies *(31, 32)*. Midazolam was not reported to cause oral clefts or major fetal malformations. However, given the lack of controlled studies that evaluate its use in the first trimester, we cannot recommend the use of Midazolam during early pregnancy, as it has similar mechanism of action to Diazepam *(4, 33, 34)*. Maternal and neonatal respiratory depression is possible. Transient fetal neurobehavioral depression is also possible.

Agents used to reverse medications' effects during conscious sedation include Naloxone (FDA category B) and Flumazenil (FDA category C). Naloxone is a rapidly acting opiate antagonist. This medication is not recommended for routine use after conscious sedation. It should be reserved for patients with signs of narcotic toxicity that include hypotension, unresponsiveness, and respiratory

depression. Naloxone should be administered in small graded doses until the desired effect is obtained *(4)*. Flumazenil is used to reverse the central effects of benzodiazepines that include respiratory depression and unresponsiveness. The effects of this medication on the fetus are not clear. Using Flumazenil is reserved for maternal benzodiazepine toxicity where the benefits to the mother outweigh potential maternal or fetal risks. Seizures are a potential complication especially in mothers who use benzodiazepines chronically *(35)*.

Patient and Fetal Monitoring

Routine monitoring (Table 20.3) of pulse oximetry *(36)*, intermittent non-invasive blood pressure, heart rate, and rhythm is essential *(22)*. The pregnant patient should have an adequate intravenous access for administration of medications and for resuscitation with intravenous fluid if necessary. Endotracheal intubation and cardio-pulmonary resuscitation equipment, anesthesia, and obstetric services should be readily available.

The patient should be monitored for hypotension and other side effects related to conscious sedation, deep sedation, and topical anesthetics. At the end of the procedure, the patient should be transferred to a close recovery facility, or recover in the procedure room with continuous monitoring in the left lateral position, until the effects of the conscious sedation medications and topical anesthetic resolve. Special attention to aspiration risk and postural hypotension should always be a routine practice. The procedure should be terminated if an adequate level of sedation cannot be achieved and poor patient tolerance becomes an issue. Similarly, the procedure should be terminated at any point if the interventional pulmonologist feels that the goals of the procedure cannot be safely achieved.

The fetal oxygen supply depends on the maternal oxygen content and delivery. Oxygen supplementation to maintain the pulse oximetry at higher levels (greater than 95%) than what is routinely practiced in non-pregnant patients should be used *(1)*. This is essential as oxyhemoglobin desaturation is frequent during bronchoscopy and conscious sedation *(37)*. Oxygen supplementation using a face mask, laryngeal mask intubation, or endotracheal intubation should be considered if adequate oxyhemoglobin saturation cannot be maintained using a regular nasal cannula. The routine monitoring of arterial blood gases or capnography is not

Table 20.3 Patient monitoring during and after pulmonary procedures that involve pregnant patients and require conscious sedation.

Standard monitoring:
Continuous pulse oximetry
Continuous respiratory rate
Intermittent non-invasive blood pressure
Continuous pulse and electrocardiographic monitoring
Non-standard (recommended):
Fetal Heart monitoring (after 24 weeks)
Document fetal heart rate before and after the procedure (before 24 weeks)
Non-standard (optional):
Capnography

recommended. Although capnography monitoring to detect hypoventilation that is not detected by pulse oximetry appears promising, it is not routinely available or recommended at this point *(1, 38, 39)*. Pregnant patients should receive bronchodilators for the same indications as non-pregnant patients. This is especially true for asthmatic patients where pre-procedure bronchodilators should be considered *(22)*.

Monitoring the fetus prior to 24 weeks of gestation is difficult and is not routinely recommended. Finding a fetal heart rate prior to 24 weeks of gestation during the whole procedure may be very challenging and an intervention is not usually indicated prior to viability. The interpretation of fetal heart monitors during sedation is controversial since it is likely that fetal heart rate variability will be diminished or absent until the effect of the sedative wears off. This effect is not usually associated with poor outcomes. In addition, many experts argue that fetal monitoring is neither accurate nor informative prior to 28 weeks of gestation *(40)*. Finally, when the fetus is not viable, delivery is not an option. For these reasons, many high risk pregnancy experts recommend documenting a heart rate prior to the procedure and immediately after the procedure is terminated when the fetus has not reached viability (prior to 24 weeks). It can be safely assumed at this stage that if the mother is tolerating the procedure well, the fetus should not be in any distress. Once the fetus is viable (after 24 weeks of gestation), fetal heart monitoring during endoscopic procedures becomes more appealing and more reliable. In addition, in the unlikely event that the mother is in distress in relation to the procedure, an intervention can then be made and the fetus can be delivered if necessary. Despite that, many high risk obstetricians recommend obtaining a strip of fetal heart rate prior to the procedure and about 30 min after the procedure is completed to allow time for the fetus to "wake up," unless the mother is experiencing complications related to the procedure, such as significant hypoxemia or hypoventilation. One caveat in fetal non-stress testing is that non-reassuring tracing is not always predictive of fetal compromise. We recommend that every institution with the potential to treat pregnant patients has a separate conscious sedation and fetal monitoring policy.

Bronchoscopy

Flexible bronchoscopy is generally a routine and safe procedure in non-pregnant patients. The reported mortality rate is 0.01–0.04% with major complications rate in the range of 0.08–0.5% *(22, 41–45)*. The indications for bronchoscopy *(20)* during pregnancy are similar to non-pregnant patients (Table 20.4: indications, contraindications, and complications *(22, 46, 47)*). Diagnostic bronchoscopy includes inspection of the airways for evaluation of unexplained pulmonary symptoms or findings on radiographic studies related to a variety of infectious, malignant, and inflammatory conditions. Evaluation of the airway after trauma, inhalational injury, suspected airway stenosis, and suspected aspiration of a foreign body are other indications. This includes airway inspection and a variety of sampling techniques that involve endobronchial washing, brushing, forceps biopsy, and needle aspiration or biopsy. Bronchoalveolar lavage, tranbronchial forceps biopsies, brush sampling, needle aspiration, and forceps biopsy are other sampling techniques. Mediastinal and hilar transbronchial needle aspiration and biopsy are other routine diagnostic procedures. The samples can be analyzed for microbiological findings, cytology, pathology, cell count with differential, and other tests.

Therapeutic indications involve removal of foreign bodies, airway dilation, and re-canalization procedures using various dilation techniques, laser therapy, electrocautery, argon plasma coagulation, cryotherapy, brachytherapy, photodynamic

Table 20.4 Bronchoscopy: indications, contraindications and potential complications.

Indications	Contra-indications	Potential Complications
Diagnostic bronchoscopy: Pulmonary symptoms Hemoptysis Cough Wheezing and stridor Abnormal radiographic studies Pulmonary infections Diffuse lung disease Lung mass Mediastinal or hilar lymphadenopathy Positive or suspicious sputum cytology Staging of lung cancer Follow up of lung cancer after treatment Esophageal and mediastinal tumors Inhalational injuries Thoracic trauma Vocal cord paralysis Hoarseness Diaphragmatic paralysis Pleural effusion and chylothorax Tracheo-esophageal fistula Broncho-pleural fistula Superior vena cava syndrome Potential foreign body aspiration Lung abscess Endotracheal tube placement Endotracheal tube related injuries Postoperative assessment of anastomosis **Therapeutic bronchoscopy:** Foreign body Retained secretions Mucous plugs Blood clots Necrotic debris Endotracheal tube placement Hemoptysis Benign strictures and stenoses Airway obstruction Benign tumors Malignant tumors Extrinsic compression Lung abscess Mediastinal and bronchogenic cysts Tracheo-esophageal fistula Broncho-pleural fistula Therapeutic lavage Thoracic trauma	Lack of patient cooperation Lack of skilled personnel Lack of appropriate facilities Absence of appropriate consent from patient or representative Unstable angina Uncontrolled arrhythmia Refractory hypoxia not responsive to oxygen Hemodynamic instability Severe coagulopathy (for biopsies) High positive end-expiratory pressure Severe, uncontrolled and unstable systemic illness **Additional contraindications for rigid bronchoscopy:** Cervical spine instability Maxillofacial trauma Marked diminished range of motion of the head and neck Head and neck deformity	**Related to conscious sedation and local anesthesia:** Respiratory depression Hypotension Tachycardia Lidocaine shock Syncope Hyperexcitable state Seizures Laryngospasm Dizziness Nausea and vomiting Anaphylaxis Bradycardia Methemoglobinemia Cardiac or respiratory arrest **Related to the procedure:** Epistaxis Pulmonary hemorrhage Pneumothorax Fever Hypoxemia Hypercarbia Dyspnea Bronchospasm Laryngospasm Hemodynamic instability Myocardial ischemia and infarction Arrhythmia Pneumonia Bacteremia Pulmonary infiltrates Vasovagal reactions Hoarseness of voice and aphonia Airway obstruction Cardiac or respiratory arrest **Additional complications related to rigid bronchoscopy:** Injury to the gums, lips, teeth or throat Laryngeal edema Sore throat Neck stiffness and injury Airway disruption Risks related to general anesthesia

therapy, and the use of the microdebrider. Assistance during endotracheal intubation, removal of retained secretions, mucous plugs, and blood clots are other indications. The risks of most of the therapeutic procedures during pregnancy were not adequately studied.

The experience of bronchoscopists with advanced diagnostic procedures during pregnancy is limited. This is especially true with the newer advanced diagnostic and therapeutic techniques. The procedure is generally preserved for a clear indication, in the absence of a reasonable alternative and definitive contraindication, when the immediate results make a significant difference in the overall management of the patient, and the procedure benefits are deemed to outweigh potential maternal and fetal risks. Emergent procedures are performed with clear indications and consent to maximize the maternal and fetal outcomes.

Specific complications include those related to the procedure itself, sedation, anesthesia, sampling techniques (e.g., biopsy), and intubation with mechanical ventilation if necessary.

Fluoroscopy

Fluoroscopy during bronchoscopy is frequently used in non-pregnant patients to guide biopsies from localized or diffuse abnormalities appreciated on the chest imaging studies. Although it is a common practice to use fluoroscopy during transbronchial biopsies and other transbronchial invasive sampling techniques, the use of fluoroscopy may not increase the yield of transbronchial biopsies especially in diffuse pulmonary disease *(48)*. This is important to keep in mind when performing bronchoscopic procedures on pregnant patients. The effects of ionizing radiation related to fluoroscopy during bronchoscopic procedures performed on pregnant patients were not specifically studied.

The available data is related to general recommendations and extrapolated data about fetal exposure to radiation. Endoscopic procedures shed some light on this issue.

The effect of radiation exposure during pregnancy is greatest prior to the completion of organogenesis. Ionizing radiation at high dose has well-known teratogenic effects on the fetus and should be avoided and at least minimized to the recommended safe levels *(49)*.

Collaboration with the medical physics department of each institution should be done prior to procedures on pregnant patients that involve radiation. Medical physicists can assist with technique modification and appropriate shielding *(50)* that would minimize the risk of radiation. The average amount of fetal radiation during fluoroscopy exposure is in the order of a few mRads especially when appropriate shielding is used. This amount of fetal radiation is minimal and unlikely to be associated with ill-effects, even during the first trimester. Necessary procedures with clear indications should not be postponed because of concerns for fetal radiation from fluoroscopy. However, elective procedures involving fluoroscopy may be reserved to the second trimester and third trimester but only if the pregnant patient's condition allows and there is no need for a timely diagnosis, keeping in mind that the fetus will be closer to the radiation source at that time but will be past organogenesis.

The amount of fetal radiation exposure depends on the site exposed to radiation and its proximity to the fetus, the type of radiation, gestational age, and the technique used. Other factors include the energy and size of the X-ray beam, the skin surface exposure to the mother, the size of the patient, and the depth of the

fetus. The fetus is still at risk of exposure even if it is not in the radiation field. This is related to the internal scatter of the radiation after it enters the mother *(51)*. In the first trimester, it is recommended that fetal exposure not exceed 1 mSv of radiation. Over the entire gestation, the maximum permitted exposure is 5 mSv (1 Sv = 1 Gy = 100 R) *(52)*.

Pleural Procedures

Pleural Effusion

Pleural effusion is a common problem that is frequently encountered during medical practice. The etiology of pleural effusions is related to a variety of conditions that includes altered hydrostatic and oncotic forces, infectious, inflammatory, and malignant disorders. Imbalance between pleural fluid formation and absorption can lead to pleural fluid accumulation *(53)*. Direct extension of the fluid from the peritoneal cavity is also possible *(54)*. Small amounts of pleural fluid can be visualized by chest sonography in healthy pregnant women. This finding, if isolated, should not be taken as a sign of occult thoracic disease *(55)*.

Analysis of the pleural fluid by thoracentesis (if clinically indicated) can help in understanding the etiology of pleural effusion and designing specific management options *(56)*. Pleural effusions can be divided into exudative effusions or transudative effusions based on specific criteria to narrow the differential diagnoses and complement the pre-procedure clinical diagnosis.

The analysis of pleural fluid and simultaneous serum levels of LDH and protein using Light's criteria remains the most important and widely used method to differentiate exudative from transudative effusions *(57)*. For exudative effusions, this includes pleural fluid protein to serum protein ratio >0.5, pleural fluid LDH to serum LDH ratio >0.6 and pleural fluid LDH greater than two thirds the upper limits of normal serum LDH. Any one of the three criteria is adequate to classify the fluid as an exudate. Other criteria that utilize pleural fluid analysis without simultaneous serum tests to diagnose exudative effusions include a pleural fluid protein level >2.9 gm/dL, pleural fluid cholesterol >45 mg/dL and a pleural fluid LDH >60% of the upper limits of normal serum value *(58)*. Other tests of the pleural fluid include cell count with differential, glucose, pH, albumin, amylase, cytology, microbiological stains, microbiological cultures among others. Such tests are important to further evaluate the etiology of the pleural effusion to narrow the differential diagnosis, predict potential complications including pleural fibrosis with restriction, assess the need for pleural space drainage and evaluate the need for further evaluation and treatment including the potential need for pleural biopsies or surgical intervention *(59)*. For example, pleural fluid lymphocytosis carries a narrow differential diagnosis that includes tuberculosis and malignancy. Table 20.5 presents an overview of common etiologies of exudative and transudative pleural effusions.

Thoracentesis

Diagnostic and therapeutic thoracentesis are safe procedures that are performed at the bedside after proper positioning under local anesthesia. Anxiolytics or pain medications are rarely necessary. Potential complications include pneumothorax, bleeding, infection, inadvertent puncture of the liver or spleen, and vasovagal reactions *(60)*. Such complications are not common and the safety of the

Table 20.5 Overview of the etiologies of exudative and transudative pleural effusions.

Exudative pleural effusions	Transudative pleural effusions
– Infectious etiologies: Pulmonary infections Pleural infections including tuberculosis Sub-pleural infections – Malignancy – Inflammatory disorders Connective tissue disorders Pnacreatitis and pancreatic pseudocyst Uremic pleuritis Sarcoidosis Postcardiac injury syndrome Radiation therapy – Pulmonary embolism – Drug-induced – Hemothorax – Chylothorax – Lymphangioleiomyomatosis – Esophageal rupture – Ovarian hyperstimulation syndrome – Meigs' syndrome – Hypothyroidism – Iatrogenic etiologies: Feeding tube in the pleural space Central venous catheter in the pleural space – Yellow nail syndrome – Benign asbestos pleural effusion – Negative intrapleural pressure: Atelectasis Trapped lung – Diuretic treated congestive heart failure	– Congestive heart failure – Hypoalbuminemia – Nephrotic syndrome – Hepatic hydrothorax – Urinothorax – Constrictive pericarditis – Peritoneal dialysis – Superior vena cava obstruction – Atelectasis and trapped lung (can be exudative) – Ovarian hyperstimulation syndrome (can be exudative) – Meigs' syndrome (can be exudative) – Hypothyroidism (can be exudative) – Pulmonary embolism (usually exudative) – Sarcoidosis (usually exudative) – Malignancy (usually exudative)

procedure is well established. The rate of potential pneumothorax is generally <12%. The safety of this procedure can be significantly enhanced if ultrasound guidance is used *(61–63)*. A low rate of pneumothorax (1.3%) was reported even in critically ill patients on mechanical ventilation when ultrasound guidance is used *(64)*.

Although the safety, diagnostic yield, and other aspects of this procedure were not specifically studied in pregnant patients, ultrasound use is generally recommended. The pregnancy related adaptations with cephalad displacement of the diaphragm by 4–5 cm can limit the clinical examination guidance to perform this procedure. The safety of ultrasound during pregnancy and the portability of this modality make it appealing for the bedside use to guide thoracentesis and other pleural procedures in pregnant patients. This can be performed by radiologists and interventional pulmonologists or intensivists with adequate experience in this modality. Chest radiographs expose the fetus to a minimal amount of radiation (0.001 mSv) and should not be withheld when indicated.

Table 20.6 Indications for pleural space drainage in pregnant patients.

Pneumothorax:
Symptomatic pneumothorax of any size
Large* primary or secondary spontaneous pneumothorax in stable patients
Large* iatrogenic pneumothorax
Progressive or symptomatic iatrogenic pneumothorax of any size
Pneumothorax of any size in unstable patients
Evidence of tension pneumothorax
Pneumothorax in patients on mechanical ventilation
Anticipation of large air-leak or broncho-pleural fistula
Pleural effusions:
Hemothorax
Empyema
Complicated parapneumonic effusions
Chylothorax
Pleural effusions causing significant symptoms or restriction
Penetrating chest trauma
Post-operative management after thoracic surgery

* Large pneumothorax defined as $\geq$2 cm between the lung margin and the chest wall or $\geq$3 cm apex-to-cupola distance.

Pleural Space Drainage

Pleural space drainage is frequently needed for patients with primary or secondary pneumothoraces (Table 20.6) *(65–67)*. Primary spontaneous pneumothorax has been reported in >50 cases during pregnancy, but the true incidence is largely unknown *(68)*. Rupture of small bullae has been suggested as one cause for primary spontaneous pneumothorax. Secondary spontaneous pneumothorax develops in the setting of pre-existing lung disease such as chronic obstructive pulmonary disease (COPD), tuberculosis, pneumonia (including pneumocystis pneumonia), cystic fibrosis, lung malignancies, Langerhans cell histiocytosis, tuberous sclerosis, lymphangioleiomyomatosis, and interstitial lung disease. It is not clear whether the anatomic changes that occur during pregnancy including the increase in the antero-posterior diameter of the chest and the widening in the rib angles predispose patients to the development of these pneumothoraces in the course of pregnancy. Small bore chest tubes (10–22 F) appear to be as effective as large bore tubes for draining pneumothoraces *(65, 66, 69, 70)*. Although simple aspiration for pneumothoraces was recommended as the initial modality for large primary spontaneous pneumothoraces and small secondary spontaneous pneumothoraces *(65)*, this approach was not systematically studied in pregnant patients. Until further data is available, we recommend drainage in pregnant patients using small bore chest tubes. Further surgical intervention for the management of persistent air-leak was reported *(71)*.

Pleural effusions that fail to respond to the initial medical management and cause significant symptoms, hypoxemia, or restriction of effective ventilation should be drained. This is true for pleural effusions of any etiology, as the primary goal of management should be to stabilize the patient and ensure adequate oxygenation and ventilation. Empyema defined as aspiration of pus from the pleural space and positive pleural fluid microbiological stains or cultures should be drained. Complicated parapneumonic effusions should also be drained. This

includes effusions with evidence of low pleural fluid pH (or very low glucose), thickened pleural surfaces (split pleura sign by imaging), loculated effusions, large effusions occupying half or more of a hemithorax, and parapneumonic effusions with high LDH (more than three times the upper serum normal limit of LDH) *(72, 73)*. The small bore chest tubes appear to be as effective as large bore chest tubes for most of the indications including malignancy, empyema, and parapneumonic effusions *(70, 73, 74)*. Appropriate surgical intervention should be considered within the initial 10–14 days if conservative medical management and chest tube drainage fails. This approach should be considered earlier in selected patients including those with deterioration despite initial management and sepsis. Small non-complicated parapneumonic effusions in stable patients can be observed closely while the patient is receiving medical management. Such effusions should be drained with the development of any sign of complication or suspicion of the development of empyema.

Pleural Biopsy

Further evaluation of pleural disorders with pleural biopsy is frequently needed. The common indications for pleural biopsy include the need to confirm or rule out tuberculosis or malignancy in exudative pleural effusions of unclear etiology. Closed pleural biopsy has a modest yield for the diagnosis of malignancy and tuberculosis *(75)*. A combination of pleural fluid adenosine deaminase, differential cell count (with high lymphocytic percentage), and closed needle biopsy has a high diagnostic yield in undiagnosed exudative pleural effusions in areas with high incidences of tuberculosis. This may substitute thoracoscopic biopsies at a considerably lower expense in countries with poor resources where the incidence of tuberculosis is relatively high *(76)*. Image guided pleural biopsies and thoracoscopy (pleuroscopy) are superior to closed pleural biopsy in the diagnosis of malignancy *(77–79)*. Thoracoscopy is also superior to closed pleural biopsy in the diagnosis of tuberculosis *(77)*. Potential complications of various pleural biopsy techniques include bleeding, infection, pneumothorax, pain, and discomfort. Pleural biopsy techniques during pregnancy were not adequately studied. Medical thoracoscopy (pleuroscopy) is a safe procedure that is routinely practiced by interventional pulmonologists under local anesthesia and moderate or deep conscious sedation on spontaneously breathing patients (compared to general anesthesia and single lung ventilation that are practiced during video assisted thoracoscopic surgery by thoracic surgeons). However, the safety of this procedure under conscious sedation during pregnancy remains largely unknown.

References

1. Bahhady IJ, Ernst A. Risks of and recommendations for flexible bronchoscopy in pregnancy: a review. Chest 2004;126(6):1974–81.
2. Betti A, Cavaliere S, Bergonzini R. Bronchoscopy in pregnancy... Radiol Med (Torino) 1999;97(4):327–30.
3. Gilinsky NH, Muthunayagam N. Gastrointestinal endoscopy in pregnant and lactating women: emerging standard of care to guide decision-making. Obstet Gynecol Surv 2006;61(12):791–9.
4. Cappell MS. Sedation and analgesia for gastrointestinal endoscopy during pregnancy. Gastrointest Endosc Clin N Am 2006;16(1):1–31.

5. Bruno JM, Kroser J. Efficacy and safety of upper endoscopy procedures during pregnancy. Gastrointest Endosc Clin N Am 2006;16(1):33–40.
6. Qureshi WA, Rajan E, Adler DG, et al. ASGE Guideline: guidelines for endoscopy in pregnant and lactating women. Gastrointest Endosc 2005;61(3):357–62.
7. Liberatore SM, Pistelli R, Patalano F, Moneta E, Incalzi RA, Ciappi G. Respiratory function during pregnancy. Respiration 1984;46(2):145–50.
8. Milne JA, Mills RJ, Howie AD, Pack AI. Large airways function during normal pregnancy. Br J Obstet Gynaecol 1977;84(6):448–51.
9. Elkus R, Popovich J, Jr. Respiratory physiology in pregnancy. Clin Chest Med 1992;13(4):555–65.
10. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Respir Dis 1980;121(3):559–81.
11. Gilroy RJ, Mangura BT, Lavietes MH. Rib cage and abdominal volume displacements during breathing in pregnancy. Am Rev Respir Dis 1988;137(3):668–72.
12. Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol 1978;85(4):260–3.
13. Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. J Appl Physiol 1978;44(6):393–44.
14. Artal R, Wiswell R, Romem Y, Dorey F. Pulmonary responses to exercise in pregnancy. Am J Obstet Gynecol 1986;154(2):378–83.
15. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv 1994;49(12 Suppl):S1–14.
16. Bridges EJ, Womble S, Wallace M, McCartney J. Hemodynamic monitoring in high-risk obstetrics patients, II. Pregnancy-induced hypertension and preeclampsia. Crit Care Nurse 2003;23(5):52–7.
17. Bridges EJ, Womble S, Wallace M, McCartney J. Hemodynamic monitoring in high-risk obstetrics patients, I. Expected hemodynamic changes in pregnancy. Crit Care Nurse 2003;23(4):53–62.
18. Kinsella SM, Lohmann G. Supine hypotensive syndrome. Obstet Gynecol 1994;83(5 Pt 1):774–88.
19. Bolliger CT, Mathur PN, Beamis JF, et al. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J 2002;19(2):356–73.
20. Wahidi MM, Herth FJ, Ernst A. State of the art: interventional pulmonology. Chest 2007;131(1):261–74.
21. Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures: guidelines from the American College of Chest Physicians. Chest 2003;123(5):1693–717.
22. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax 2001;56 Suppl 1:i1–21.
23. Mattingly JE, D'Alessio J, Ramanathan J. Effects of obstetric analgesics and anesthetics on the neonate: a review. Paediatr Drugs 2003;5(9):615–27.
24. Lazzaroni M, Bianchi Porro G. Preparation, premedication, and surveillance. Endoscopy 2005;37(2):101–9.
25. Rex DK. The science and politics of propofol. Am J Gastroenterol 2004;99(11):2080–3.
26. Gin T.Propofol during pregnancy. Acta Anaesthesiol Sin 1994;32(2):127–32.
27. Marx GF, Hwang HS, Chandra P. Postpartum uterine pressures with different doses of ketamine. Anesthesiology 1979;50(2):163–6.
28. Rayburn W, Rathke A, Leuschen MP, Chleborad J, Weidner W. Fentanyl citrate analgesia during labor. Am J Obstet Gynecol 1989;161(1):202–6.
29. Martin LV, Jurand A. The absence of teratogenic effects of some analgesics used in anaesthesia. Additional evidence from a mouse model. Anaesthesia 1992;47(6):473–6.
30. Levy M, Spino M. Neonatal withdrawal syndrome: associated drugs and pharmacologic management. Pharmacotherapy 1993;13(3):202–11.
31. Czeizel A. Lack of evidence of teratogenicity of benzodiazepine drugs in Hungary. Reprod Toxicol 1987;1(3):183–8.

32. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol 1994;8(6):461–75.
33. Cappell MS, Colon VJ, Sidhom OA. A study of eight medical centers of the safety and clinical efficacy of esophagogastroduodenoscopy in 83 pregnant females with follow-up of fetal outcome with comparison control groups. Am J Gastroenterol 1996;91(2):348–54.
34. Cappell MS, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. Dig Dis Sci 1996;41(12):2353–61.
35. Brogden RN, Goa KL. Flumazenil. A reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. Drugs 1991;42(6):1061–89.
36. Berg JC, Miller R, Burkhalter E. Clinical value of pulse oximetry during routine diagnostic and therapeutic endoscopic procedures. Endoscopy 1991;23(6):328–30.
37. Maranetra N, Pushpakom R, Bovornkitti S. Oxygen desaturation during fibreoptic bronchoscopy. J Med Assoc Thai 1990;73(5):258–63.
38. Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 1996;84(2):459–71.
39. Nelson DB, Freeman ML, Silvis SE, et al. A randomized, controlled trial of transcutaneous carbon dioxide monitoring during ERCP. Gastrointest Endosc 2000;51(3):288–95.
40. Schwartz N, Young BK. Intrapartum fetal monitoring today. J Perinat Med 2006; 34(2):99–107.
41. Zavala DC. Diagnostic fiberoptic bronchoscopy: Techniques and results of biopsy in 600 patients. Chest 1975;68(1):12–9.
42. Credle WF, Jr., Smiddy JF, Elliott RC. Complications of fiberoptic bronchoscopy. Am Rev Respir Dis 1974;109(1):67–72.
43. Suratt PM, Smiddy JF, Gruber B. Deaths and complications associated with fiberoptic bronchoscopy. Chest 1976;69(6):747–51.
44. Simpson FG, Arnold AG, Purvis A, Belfield PW, Muers MF, Cooke NJ. Postal survey of bronchoscopic practice by physicians in the United Kingdom. Thorax 1986;41(4):311–7.
45. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. Chest 1995;107(2):430–2.
46. Prakash UB, Cavaliere S. Bronchoscopy. In: Gold WM, Murray JF, Nadel JA, eds. Atlas of procedures in respiratory medicine: a companion to Murray and Nadel's Textbook of Respiratory Medicine. Philadelphia: Saunders; 2002:216–7.
47. Lamb CR, Beamis JF. Rigid Bronchoscopy: An interventional tool with a history and a future. In: Beamis JF, Mathur PN, Mehta AC, eds. Interventional pulmonary medicine. New York: M. Dekker; 2004:15–7.
48. Anders GT, Johnson JE, Bush BA, Matthews JI. Transbronchial biopsy without fluoroscopy. A seven-year perspective. Chest 1988;94(3):557–60.
49. Timins JK. Radiation during pregnancy. N J Med 2001;98(6):29–33.
50. Ben Farhat M, Gamra H, Betbout F, et al. Percutaneous balloon mitral commissurotomy during pregnancy. Heart 1997;77(6):564–7.
51. Kahaleh M, Hartwell GD, Arseneau KO, et al. Safety and efficacy of ERCP in pregnancy. Gastrointest Endosc 2004;60(2):287–92.
52. Menees S, Elta G. Endoscopic retrograde cholangiopancreatography during pregnancy. Gastrointest Endosc Clin N Am 2006;16(1):41–57.
53. Lai-Fook SJ. Pleural mechanics and fluid exchange. Physiol Rev 2004;84(2):385–410.
54. Lieberman FL, Peters RL. Cirrhotic hydrothorax. Further evidence that an acquired diaphragmatic defect is at fault. Arch Intern Med 1970;125(1):114–7.
55. Kocijancic I, Pusenjak S, Kocijancic K, Vidmar G. Sonographic detection of physiologic pleural fluid in normal pregnant women. J Clin Ultrasound 2005;33(2):63–6.
56. Collins TR, Sahn SA. Thoracocentesis. Clinical value, complications, technical problems, and patient experience. Chest 1987;91(6):817–22.

57. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77(4):507–13.
58. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. Chest 1997;111(4):970–80.
59. Heffner JE. Discriminating between transudates and exudates. Clin Chest Med 2006;27(2):241–52.
60. Grogan DR, Irwin RS, Channick R, et al. Complications associated with thoracentesis. A prospective, randomized study comparing three different methods. Arch Intern Med 1990;150(4):873–7.
61. Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? Chest 2003;123(2):418–23.
62. Raptopoulos V, Davis LM, Lee G, Umali C, Lew R, Irwin RS. Factors affecting the development of pneumothorax associated with thoracentesis. AJR Am J Roentgenol 1991;156(5):917–20.
63. Feller-Kopman D. Ultrasound-guided thoracentesis. Chest 2006;129(6):1709–14.
64. Mayo PH, Goltz HR, Tafreshi M, Doelken P. Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. Chest 2004;125(3):1059–62.
65. Henry M, Arnold T, Harvey J. BTS guidelines for the management of spontaneous pneumothorax. Thorax 2003;58 Suppl 2: ii39–52.
66. Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest 2001;119(2):590–602.
67. Baumann MH. Management of spontaneous pneumothorax. Clin Chest Med 2006;27(2):369–81.
68. Sills ES, Meinecke HM, Dixson GR, Johnson AM. Management approach for recurrent spontaneous pneumothorax in consecutive pregnancies based on clinical and radiographic findings. J Cardiothorac Surg 2006;1:35.
69. Tsai WK, Chen W, Lee JC, et al. Pigtail catheters vs large-bore chest tubes for management of secondary spontaneous pneumothoraces in adults. Am J Emerg Med 2006;24(7):795–800.
70. Horsley A, Jones L, White J, Henry M. Efficacy and complications of small-bore, wire-guided chest drains. Chest 2006;130(6):1857–63.
71. Wong MK, Leung WC, Wang JK, et al. Recurrent pneumothorax in pregnancy: what should we do after placing an intercostal drain. Hong Kong Medical J 2006;12(5):375–80.
72. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. Chest 2000;118(4):1158–71.
73. Light RW. Parapneumonic effusions and empyema. Proc Am Thorac Soc 2006;3(1):75–80.
74. Shankar S, Gulati M, Kang M, Gupta S, Suri S. Image-guided percutaneous drainage of thoracic empyema: can sonography predict the outcome? Eur Radiol 2000;10(3):495–9.
75. Chakrabarti B, Ryland I, Sheard J, Warburton CJ, Earis JE. The role of Abrams percutaneous pleural biopsy in the investigation of exudative pleural effusions. Chest 2006;129(6):1549–55.
76. Diacon AH, Van de Wal BW, Wyser C, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J 2003;22(4):589–91.
77. Loddenkemper R. Thoracoscopy – state of the art. Eur Respir J 1998;11(1):213–21.
78. Harris RJ, Kavuru MS, Mehta AC, et al. The impact of thoracoscopy on the management of pleural disease. Chest 1995;107(3):845–52.
79. Hansen M, Faurschou P, Clementsen P. Medical thoracoscopy, results and complications in 146 patients: a retrospective study. Respir Med 1998;92(2):228–32.
80. Qureshi WA et al.ASGE Guideline: guidelines for endoscopy in pregnant and lactating women. Gastrointest Endosc 2005;61(3):357–362.

21

Critical Illness in Pregnancy

D. Kyle Hogarth and Jesse Hall

Keywords: placenta previa, uterine atony, uterine rupture, septic shock, hypovolemic shock, preeclampsia, HELLP

Introduction

The gravid patient will typically experience few difficulties during the course of her pregnancy. A small but significant number of pregnant patients will become ill enough to require the intensive care unit for both obstetrical and non-obstetrical problems. Therefore, the obstetrical physician must have an understanding of how to monitor and manage the critically ill pregnant patient and how to approach emergencies unique to pregnancy. In a report of ICU utilization during hospital admission for delivery in the United States in one state, 822,591 admissions from 1984 to 1997 were analyzed. There were 1,023 admissions to the intensive care unit, with mortality in the ICU of 3.3% *(1)*. Predictors for ICU admission in this retrospective analysis included: age greater than 35 (Odds Ratio [OR] 1.4), African-American ethnicity (OR 1.8), race other than black or white (OR 5.9), treatment in minor teaching hospital (OR 2.0), and transfer to a higher-level hospital for care (OR 2.51) *(1)*. The most common indication for ICU admission involved obstetrical related complications. These included complications of cesarean section, preeclampsia or eclampsia, and peripartum hemorrhage *(1–4)*. The most common risk factors associated with ICU mortality included pulmonary complications, shock, cerebrovascular events, and drug dependence*(1)*. In another study looking at 74 obstetric patients admitted to an ICU over 7 years, the most common reason for admission was respiratory insufficiency *(5)*. Outside of the United States, a much smaller study of ICU admissions in the United Arab Emirates demonstrated similar mortality rates *(6)*. In another series, a majority of obstetric patients admitted (71%) to the ICU required ventilatory support *(7)*. About 65% of obstetric patients admitted to the ICU experience failure of one or more organ systems *(5, 8)*. Eighty-two percent of antepartum admissions to the ICU results in delivery, a majority (78%) via cesarean section *(9)*. These observations underline the need for a high level of coordination between obstetrical and critical care physicians to assure appropriate coordinated care of the critically ill pregnant patient. Frequent and detailed communication between these care

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_21

providers can reduce the usual anxiety that arises from the challenges of managing "both patients" (i.e., mom and baby) and the relative low frequency of ICU admission for obstetrical patients.

While concern was raised in the past that severity of illness scoring systems commonly used in the ICU to help predict mortality and guide management are not calibrated for the pregnant patient *(10, 11)*, case-control series have demonstrated similar performance for APACHE II, SAPS II, and MPM II in matched pregnant and non-pregnant patients. *(12)* Thus, being pregnant does not independently increase the risk of mortality in the ICU per se. However, the pregnant patient in the intensive care unit does provide unique challenges to the critical care team.

This chapter will focus on general principles of critical care for pregnant patients, while expanding on unique obstetric urgencies and emergencies. Please review the chapter by Meyer and Schmidt (Chapter 22) regarding pulmonary management of the critically ill gravid patient. We will review the physiology of pregnancy in the context of critical illness, address invasive monitoring, and discuss current therapeutic principles and medications for the gravid patient. Future areas of research will be highlighted throughout. Ultimately, the care of the critically ill gravid patient requires not just the skill of one lone doctor, but also the skills of a multidisciplinary team consisting of intensivists, high-risk obstetricians, anesthesiologists, neonatologists, and other consultants. This combined, thorough approach has reduced the general obstetrical mortality rate to 4–20 per 100,000 deliveries in developed countries. Unfortunately, the rate is 55–920 per 100,000 deliveries in countries lacking the resources to provide prenatal, peri-partum, and post-partum comprehensive care, and may be higher owing to potential lower reporting from non-urban underdeveloped areas *(4)*.

The Physiology of Pregnancy

A thorough understanding of the adaptive physiologic changes of pregnancy is important when managing a critically ill gravid patient. The critical care physician has to "reset" their baseline parameters as to what is normal. Many findings on examination of a critically ill non-gravid patient are normal in the context of the altered physiology of pregnancy. To adequately assess and monitor a pregnant patient and determine which changes are adaptive and which are pathologic, the physician must understand the normal changes that occur in respiration, cardiac function, and acid-base physiology during pregnancy. Please see Chapter 2 for a detailed discussion of the respiratory physiology of pregnancy.

Expansion of extracellular fluid volume accounts for 6–8 kg of the total weight gained during pregnancy. Expansion of plasma volume starts around 6 weeks of gestation with a total maternal blood volume increased by 25–52%, with a peak at 32 weeks of gestation. Heart rate increases about 20–30% and stroke volume increases 20–50%, resulting in a 50% increase in cardiac output that starts by 8–11 weeks of gestation. The increment is greater in multiple pregnancies compared to singleton pregnancies. Peripheral vascular resistance is reduced. Myocardial contractility is likely increased in pregnancy. Colloid osmotic pressure is also reduced. As a result of these physiologic changes, peripheral edema, jugular venous distention, displaced ventricular apex, S3, early or midsystolic murmur at the left lower sternal border are commonly seen in a normal gravida.

Labor is typical for cyclic increments in heart rate and volume and dramatically alters cardiovascular loading conditions and demands. Pain, particularly

Table 21.1 Changes in physiology of the pregnant patient.

Parameter	Direction of change
Blood volume	Increase
Albumin	Decrease
Hematocrit/hemoglobin	Decrease
Blood pressure	Decrease
Heart rate	Increase
Stroke volume	Increase
Cardiac output	Increase
Systemic vascular resistance	Decrease
Pulmonary vascular resistance	Decrease
Minute ventilation	Increase
Oxygen consumption	Increase
PCO_2	Decrease
HCO_3	Decrease
Acid–base state	Compensated respiratory alkalosis

associated with the second stage of labor, and Valsalva maneuver during pushing leads to stimulation of the sympathetic nervous system resulting in dramatic increases in heart rate, blood pressure, and myocardial oxygen consumption. Every contraction is associated with autotransfusion and diversion of close to 500 cc of blood from the uterine to the maternal circulation. This leads to a higher cardiac output and mean arterial blood pressure. The use of epidural anesthesia helps minimize the sympathetic response to pain and helps in attenuating the increase in cardiac output by causing vasodilatation. The effects of autotransfusion can only be avoided by eliminating labor by performing a surgical delivery. Understanding these physiological changes helps plan a less complicated delivery, since the increase in preload stresses patients with cardiomyopathy or mitral regurgitation; sudden blood loss is less tolerated in patients with aortic stenosis and the increased heart rate may decompensate patients with mitral stenosis.

For a quick review, Table 21.1 summarizes the changes in respiratory physiology associated with pregnancy.

General ICU Assessment

The general changes associated with pregnancy have many implications for the assessment and management of the critically ill pregnant patient. The assessment of maternal blood flow, whether invasive or non-invasive, must take into account the baseline elevation in maternal cardiac output. Ensuring adequate venous return requires that the gravid patient be maintained in the left lateral decubitus position. Venous return principles are paramount in maintaining the increased cardiac output the placenta requires. Optimizing delivery of oxygen to the feto-placental unit should focus on managing any degree of hypoxemia in the mother, as the fetus/placenta has no method of autoregulation to increase oxygen delivery if oxygen content diminishes to a critical level. Elective intubation and mechanical ventilation of the critically ill pregnant patient can help to achieve the goal of adequate oxygen delivery if the circulation is not compromised by mechanical ventilation. (See Meyer and Schmidt Chapter 22) Recall that positive pressure ventilation, especially with the application of positive end-expiratory pressure (PEEP), may decrease venous return

and could decrease tissue oxygen delivery. Maintenance of an adequate blood pressure is crucial to preserve fetal well-being, as auto-regulation of blood flow by the uterine circulation is limited. Anemia sometimes needs to be corrected in this population if oxygen delivery is compromised.

Circulatory Disorders in the Gravid Patient

Shock is the hypoperfusion of end-organ tissues. The approach to the hypoperfused pregnant patient is essentially the same as for the non-pregnant shock patient, with the additional nuance of the potential compression of the IVC by of the gravid uterus causing a decrease in venous return, as noted above. The initial management of shock includes distinguishing between low flow and high flow states and assessing the intravascular volume status of the patient, keeping in mind the normal changes in pregnancy. If necessary, invasive monitoring using central venous catheterization, and even right-heart catheterization, may be required. Complications of central venous access can occur during insertion or after prolonged placement. Complications occur at a rate of up to 5% during and after placement of central lines, and include arterial puncture, pneumothorax, infection, cardiac arrhythmia, and thrombosis *(2)*. Therefore, a careful assessment of the risk and benefits of invasive monitoring must be weighed for each patient. A careful bedside assessment, history, and routine labs can typically allow a determination of the adequacy of intravascular volume in a vast majority of cases. Non-invasive portable imaging, such as echocardiography, may also provide valuable information to help determine a patient's intravascular volume status. Echocardiographic findings seem to correlate with more invasive monitoring such as placement of pulmonary artery catheters in critically ill obstetric patients *(13, 14)*.

On the other hand, fractional excretion of sodium was found to poorly correlate with pulmonary artery catheter readings in one small study of pregnant patients with preeclampsia *(15)*.

If invasive monitoring is required, subclavian or internal jugular locations are preferred due to lower infection rates *(16)*. However, the safest location to place a central venous catheter is in the location the operator is most experienced and comfortable performing. If a right heart catheter must be placed, then the femoral position is relatively contraindicated secondary to vena caval obstruction by the gravid uterus and the possible need for emergent delivery of the fetus. The PA catheter is increasingly falling out of favor in the critical care of non-gravid patients as it has continuously failed to demonstrate a mortality benefit, and is associated with increased complications *(17, 18)*.

Table 21.2 lists the relative indications for right heart catheterization in the gravid patient *(2)*.

Hypovolemic Shock

Efforts should focus on rapid detection and correction of the underlying cause of hypovolemia, while rapidly replacing the volume that has been lost. Hypovolemic shock will occur secondary to profound dehydration or via large volume blood loss. Table 21.3 lists common causes of massive bleeding in the pregnant patient. While assessing for causes of hemorrhage related to the gravid state, care must be taken to evaluate for non-gravid causes of blood loss. Furthermore, critically ill

Table 21.2 Relative indications for right heart catheterization in the gravid patient.

Routine operative or labor/delivery monitoring if:
Severe pulmonary hypertension
Significant valvular disease (mitral/aortic)
Class III or IV congestive heart failure
Hypertension or preeclampsia complicated by:
Pulmonary edema
Heart failure
Oliguric renal failure
Shock, if
Etiology obscure
Volume resuscitation fails
Elevated central venous pressure
Vasoactive drugs are required
Acute respiratory failure
Accompanied by shock
Requiring mechanical ventilation and PEEP
With pulmonary edema of unknown etiology

gravid patients can frequently develop disseminated intravascular coagulation (DIC), so any massive bleeding should prompt a coagulopathy workup.

No matter what the cause of blood loss, intravenous access with two large bore (16 gauge or larger) intravenous catheters is required. If peripheral access cannot be secured, central venous catheterization will be needed, but should utilize a short length, wide bore catheter (e.g., a "triple lumen" catheter is not adequate, owing to small individual channel diameter, as well as length, creating unacceptable resistance to rapid infusion of fluids). Resuscitation with crystalloid or colloid should be instituted until blood can be administered. In cases of massive hemorrhage, the administration of unmatched type-specific blood may be required. Supplemental oxygen should always be applied and the patient should be placed in the left lateral decubitus position to maximize venous return. In patients receiving massive transfusions, a survey for resultant DIC should be undertaken. The massively transfused patient is also at risk for hypothermia, which can aggravate bleeding by inhibiting clotting/coagulation. If possible, a blood warmer should be utilized during massive transfusion, and warming blankets should be applied to the patient. Patients should also be monitored for a secondary thrombocytopenia resulting from consumption, and hypocalcemia due to the citrate utilized in blood storage. Hypocalcemia from massive transfusion can inhibit coagulation, as calcium is required for the enzymatic reactions of coagulation.

Table 21.3 Etiology of hemorrhagic shock in pregnancy in descending order of incidence.

Early pregnancy	Late (3rd trimester)	Post-partum
Trauma	Trauma	Uterine atony
Ectopic pregnancy	Placenta previa	Surgical trauma
Abortion	Placental abruption	Uterine inversion
Disseminated intravascular coagulation	Disseminated intravascular coagulation	Disseminated intravascular coagulation
Hydatidiform mole	Uterine rupture	Retained placenta
	Marginal sinus rupture	

Causes of Hypovolemic Shock Unique to Pregnancy

Placental Abruption

Placental abruption occurs in 1/77–1/250 pregnancies, with an increased incidence in patients with hypertension, high parity, cigarette smoking, cocaine use, thrombophilias, and history of previous abruption *(19–21)*. Massive hemorrhage can occur, with 2–3 L of blood typically lost in cases where the fetus dies. Maternal mortality from abruption ranges from 0 to 5% while fetal mortality is 5–36% *(20, 21)*. Placental abruption is thought to occur secondary to rupture of the spiral arteries of the placenta with formation of a hematoma that separates the placenta from the uterine wall. The diagnosis is made clinically based on abdominal pain and vaginal bleeding, though ultrasound may assist the clinician. Management should focus on surgical control of the bleeding by dilation and curettage. Uterine artery embolization or emergent hysterectomy can be utilized when all other bleeding control attempts have been made and failed.

Placenta Previa

Placenta previa occurs in approximately 1/200 pregnancies and normally does not cause massive hemorrhage. However, if vaginal examination of the patient results in disruption of the placenta over the cervical os, massive hemorrhage can ensue. Rarely, invasion of trophoblastic tissue into the myometrium (*placenta previa et accreta*) occurs and the patient is at risk for massive hemorrhage during delivery *(22)*. The diagnosis is made with ultrasound and delivery should be managed surgically. With good prenatal care, placenta previa should be managed expectantly and a planned surgical delivery can occur.

Uterine Rupture

Uterine rupture occurs in roughly 1 in 2,000 pregnancies and accounts for 5% of maternal deaths *(22, 23)*. Multiparous patients with prolonged labor are most at risk for this complication. Other risk factors include uterine scars, uterine anomalies, forceps delivery, fetal anomaly, and excessive uterine stimulation *(24)*. There is also a small but significant risk of rupture in women attempting vaginal delivery after having a prior surgical delivery (Vaginal Birth after Cesarean Section [VBAC]) *(25, 26)*. In overt rupture, the patient may have peritoneal signs, but a recent study of 99 uterine ruptures demonstrated only 13 patients reporting pain, and 11 with vaginal bleeding *(27)*. Significant vaginal blood loss can occur in the absence of physical findings as well, and should prompt an evaluation for rupture. Fetal distress is the most reliable sign, but is not specific *(27)*. Ultrasound aids in the diagnosis. Management involves emergent surgical delivery of the baby. The patient will need to undergo surgical exploration of the abdomen, and may require a hysterectomy *(27, 28)*. Maternal death is not common, except in cases of rupture occurring outside a hospital *(27)*.

Uterine Atony

In a study of 23,390 pregnancies, uterine atony occurred in 1,416 women (6%). In a multivariable model, several variables were independently associated with atony. These included multiple gestation, maternal Hispanic race, induced or augmented labor for >18 h, infant birth weight >4,500 g, and clinically diagnosed chorioamnionitis. It is important to note that half of the cases of atony in the study were associated with women lacking a given risk factor or combination of risk factors *(29)*.

Atony of the myometrium can be managed with uterine massage, intramuscular methylergonivine, and intravenous oxytocin *(30)*. Methylergonivine should be avoided in patients with hypertension. Oxytocin may lead to hyponatremia secondary to its antidiuretic effect. Prostaglandins can be used to increase uterine tone *(30)*.

Septic Shock

Introduction

One contribution to shock in sepsis is a "relative hypovolemia." Though the patients total body water/volume may be normal, or even elevated, the intravascular volume and pressure are commonly reduced on presentation. When intravascular volume has been repleted—as after early volume resuscitation—the patient typically exhibits high output hypotension. This places the patient within the spectrum of Systemic Inflammatory Response Syndromes, which are defined in Table 21.4 *(31)*. These four entities are a spectrum of increasing severity and signal a need for accelerated yet focused assessment, especially in the gravid patient. Sepsis is an important cause of hypoperfusion in pregnancy, as it accounts for up to 15% of all maternal deaths *(32)*. The circulation in normal pregnancy can resemble early sepsis, with a high cardiac output and low vascular resistance so sepsis can be difficult to diagnose in the febrile gravid patient. An understanding of the common causes of sepsis in pregnancy may help the clinician in making the diagnosis.

Typical causes of sepsis (lung, genito-urinary tract) occur in the gravid patient in a manner similar to the non-gravid individual. Localizing symptoms to the infected organ and physical signs of infection are similar. Physical findings of warm, flushed extremities with brisk capillary refill, bounding peripheral pulses, absent jugular venous distension, and signs of end-organ hypoperfusion (decreased urine production or mental status) are the same in pregnant and non-pregnant women.

Management

General Principles

The management of the septic gravid patient is similar to the non-gravid patient. Cultures of blood, urine, and pelvic sites should be obtained. Empiric coverage with broad-spectrum antibiotics for polymicrobial infection should be initiated and then narrowed as cultures and sensitivities are ultimately obtained. Consultation with infectious disease specialists and pharmacy specialists is recommended to aid in proper antibiotic selection, dosage, and monitoring. Although there is a theoretical concern that aminoglycosides may increase the risk of fetal nephrotoxicity and ototoxicity, this has not been demonstrated in human pregnancies.

Cardiovascular support of the septic gravid patient should follow the general principles of assuring adequate venous return, cardiac filling pressures, and mixed venous oxygen saturation. Though the major studies of management of critically ill septic patients have excluded pregnant patients, there are no practical reasons to believe that the general principles outlined in these studies should not be applied to the gravid patient. The ICU physician should essentially manage the gravid patient in a manner similar to the non-gravid patient except for some minor principles that will be highlighted in this chapter.

Table 21.4 Definitions of sepsis Syndromes.

Infection,[a] documented or suspected, and some of the following: [b]
General variables
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate > 90 min^{-1} or > 2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12,000 μL^{-1})
Leucopenia (WBC count <4000 μL^{1})
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Arterial hypotension [b] (SBP <90 mm Hg. MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
$S\bar{v}o_2 > 70\%$ [b]
Cardiac index >3.5 $L \cdot min^{-1} \cdot M^{-23}$
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 <300)
Acute oliguria (urine output <0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$ or 45 mmol/L for at least 2 h)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion variables
Hypelactatemia (>1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; $S\bar{v}o_2$, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

[a]Infection defined as a pathologic process induced by a microorganism: [b]Svo_2 at >70% is normal in children (normally, 75-80%), and CI 3.5-5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children; [c] diagnostic criteria for sepsis in pediatric population are signs and symptoms of inflammation plus infection with hype- or hypothermia (rectal temperature >38.5 or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
Table from: Levy et al. *(31)*.

Early Goal Directed Therapy

Septic shock should be managed with early goal directed therapy (EGDT) *(33)*. The landmark paper by Rivers et al. did list pregnancy as an exclusion criterion, but the principles outlined by the study are consistent with the goals of management of the critically ill pregnant patient and should be applied. In non-gravid patients, EGDT was demonstrated to decrease mortality by 16% *(33)*. Though the exact parameters used in the paper have not been objectively tested and published in the gravid patient, our own anecdotal experience using EGDT for pregnant patients has demonstrated benefit and safety.

After obtaining central access above the diaphragm, intravenous crystalloid should be used to maintain a central venous pressure (CVP) of at least 10 mmHg, and transfusion of packed red blood cells (pRBCs) to ensure a hematocrit (Hct) of at least 30%. Measurement of a central venous saturation at the level of the superior vena cava (ScVO2), with a goal of at least 70%, is the other guiding principle of EGDT. For saturations less than 70%, Dobutamine should be added to ensure adequate cardiac output and adequate mixed venous saturation. Vasoconstrictive medications (e.g., Norepinephrine) should be added only if systemic hypotension persists after the goals for CVP, Hct, and ScVO2 are met. See Figure 21.1 for the algorithm utilized for EGDT *(33)*. Vasoconstrictors should only be employed once the intravascular volume is deemed adequate and the above therapy has not resulted in reversal of systemic hypotension. Risks of vasoconstrictors should be weighed against their benefits in improving tissue perfusion by improving hemodynamics. Twenty to thirty percent of cardiac output is directed to the uterine arteries to supply a flow of about 500 mL/minute. Placental blood flow is proportional to uterine perfusion pressure (uterine arterial pressure minus uterine venous pressure) which is directly proportional to systemic blood pressure and cardiac output. Uterine perfusion pressure is inversely proportional to uterine vascular resistance and uterine blood flow usually functions at its maximal capacity at baseline. Vasoactive drugs should be instituted only after restoration of an adequate intravascular volume status. This is particularly important for the fetus as utero-placental flow is especially likely to be compromised if

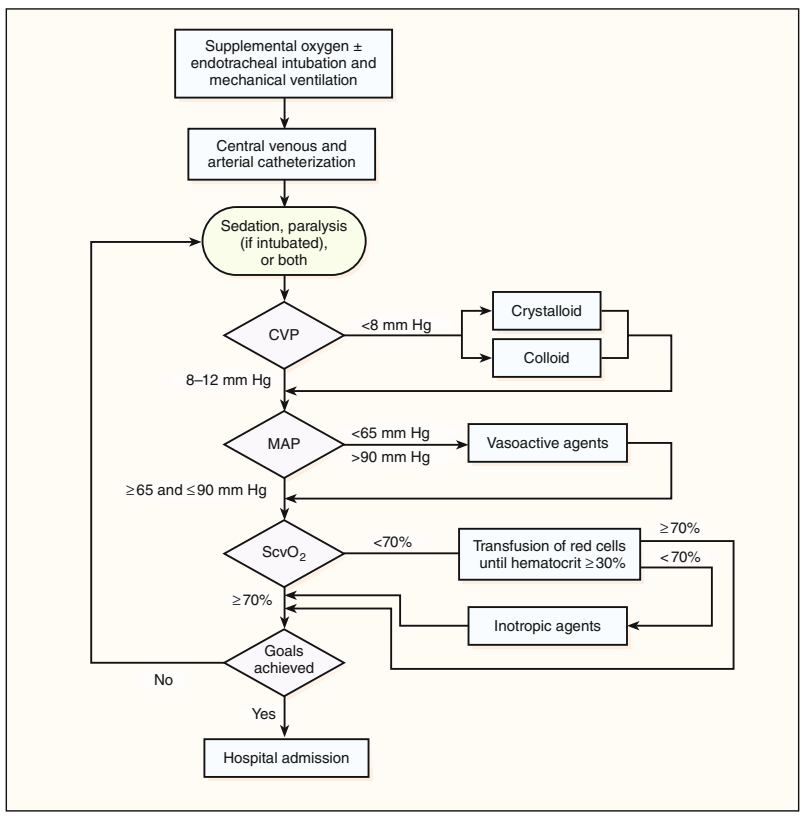


Figure 21.1 Algorithm for early goal directed therapy *(33)*

vasoconstriction is imposed on an insufficient circulating volume. All vasoactive agents have the potential to decrease uterine perfusion so fetal monitoring will be an important component of care. Vasoactive medications have not been well studied in pregnancy. Ephedrine is a sympathomimetic agent frequently used near term to reverse hypotension induced by spinal or epidural anesthesia. Ephedrine has not been associated with adverse fetal outcomes and does not seem to affect intervillous blood flow and is considered the drug of choice in pregnant patients with circulatory collapse *(34, 35)*. In cases where patients are not responding or not tolerating Ephedrine, phenylephrine could be a second choice. However, given that the advantages of one vasopressor over another in pregnancy are not clearly demonstrated by human data, an additional consideration in the choice of a vasopressor is the physicians comfort level with using the medication.

Insulin Therapy for "Tight" Glucose Control

In patients with diabetes experiencing an acute myocardial infarction (MI), aggressive glycemic control through titrated intravenous insulin lead to an 11% reduction in mortality *(36)*. In a randomized, prospective study of critically ill patients undergoing primarily cardiothoracic surgery, aggressive glucose control through the infusion of continuous insulin to maintain glucose levels between 80 and 110 mg/dL decreased overall mortality by 34%, and reduced mortality from sepsis by 76% *(37)*. Importantly, these results were seen in patients without diabetes who exhibited the common hyperglycemia related to the stress of critical illness. Symptomatic hypoglycemia developed in 5% of patients. Neither study involved pregnant patients, but pregnancy does induce a relative state of insulin resistance. It is also known that long-term control of glucose in pregnant diabetics leads to improved fetal outcomes by lowering the incidence of stillbirths, macrosomia, congenital anomalies, and neonatal hypoglycemia. Therefore, though tight insulin therapy has not been tested in the critically ill pregnant patient, the benefit demonstrated in other critically ill states should be achievable in the gravid patient.

Drotrecogin Alpha (Activated Protein C)

Activated Protein C (APC) is a normal circulating anticoagulant. APC stimulates fibrinolysis, and inactivates factors Va and VIIIa, thereby inhibiting the formation of thrombus. Decreased thrombus formation may lead to decreased inflammation in some states by inhibiting platelet activation, neutrophil recruitment, and mast cell degranulation *(38, 39)*. Patients with sepsis have reduced levels of APC, and have formation of microthrombi that may contribute to microvascular dysfunction in sepsis, as well as to propagate ongoing inflammation *(40)*. The PROWESS study was a multi-centered randomized trial that demonstrated APC administration in patients with severe sepsis resulted in an absolute mortality reduction by 6.1% and a 13% reduction in the group with the highest predicted mortality. Pregnancy was an exclusion criterion. In the PROWESS study, 3.5% of patients receiving APC had significant hemorrhage, compared to 2% in the placebo group. The role of drotrecogin alpha (infused APC) has not been defined in the pregnant population with sepsis *(41, 42)*. These patients were excluded in the original PROWESS study. Case reports of the safe use of Drotrecogin alpha in pregnancy have been reported in the medical literature *(42, 43)*, but we cannot advocate its use on that basis because of the lack of safety information.

Corticosteroids

General administration of corticosteroids for the management of sepsis does not improve outcomes *(44, 45)*. However, the administration of steroids for selected populations may be associated with improved outcomes in critically ill patients. The normal physiologic response to stress is to increase corticosteroid secretion from the adrenal glands. In sepsis, some patients exhibit a minimal adrenal stress response, a condition coined "relative" hypoadrenalism. One prospective randomized trial of 300 septic patients (pregnancy again an exclusion criterion) used low-dose hydrocortisone and fludrocortisone for those patients demonstrating blunted adrenal response to exogenous ACTH administration, even though the patients had baseline elevated levels of cortisol. The study demonstrated improved survival (47% versus 37%), and shortened the length of time requiring vasoactive support *(46)* in subset analysis. A recent multicenter prospective randomized trial has been completed (CORTICUS), which should shed further light on this topic; however, pregnancy was again an exclusion criterion. As of writing this text, CORTICUS data is not available. Although the use of corticosteroids and mineralocorticoids is justified in pregnancy in many situations, long term use has been associated with the development of gestational diabetes and even preeclampsia. Patients who would necessitate the use of steroids if they had not been pregnant should not be denied treatment on the basis of pregnancy alone.

Chorioamnionitis

Chorioamnionitis or intra-amniotic infection occurs in 1–4% of pregnancies and most commonly occurs after prolonged rupture of membranes, prolonged labor, or post-invasive procedures such as amniocentesis or cervical cerclage *(47)*. Patients typically have fever, tachycardia, uterine tenderness, and foul smelling amniotic fluid. Management should focus on therapy for *Enterococcus, Enterobacter*, and Group B streptococcal organisms and otherwise follow general principles for monitoring and management of sepsis. The need for surgical extirpation and complicating septic thrombophlebitis should be considered in all patients.

Cardiogenic Shock

Introduction

Hypoperfusion secondary to cardiac dysfunction during pregnancy can be divided into two broad categories: cardiac conditions acquired during pregnancy, and non-pregnant cardiac conditions worsened by the adaptive physiology of pregnancy (e.g., valvular abnormalities) *(48)*. Ultimately, the general management principles of cardiogenic shock should focus on quickly determining the underlying cause of the cardiogenic shock while providing appropriate general support and specific therapies toward the underlying cause (e.g., fix a valvular abnormality, treat an underlying MI). Consultation with cardiology, invasive monitoring of central pressures, and echocardiographic imaging of the myocardium are recommended.

ECG interpretation in the gravid patient must take into account the changes seen with pregnancy. The heart rate will be increased by about 20% in the late stages of gestation, the PR and QT will shorten, there will be left axis deviation, and some non-specific ST segment changes can occur. Right axis deviation has also been described in pregnancy. Development of chamber dilation is sometimes seen and is usually secondary to the 50% increase in plasma volume. The development of a new arrhythmia during pregnancy should institute a search for the inciting

event (i.e., thyroid disease, electrolyte abnormality, illegal drugs, etc.) although chamber dilation itself likely predisposes to the development of arrythmias during pregnancy. Another effect of the hyperdynamic state of pregnancy is the fact that it may affect the interpretation of 2D echocardiograms. Therefore, interpretation should be done by a cardiologist that is experienced with the physiologic changes of pregnancy. For instance, both the systolic and the diastolic dimensions are slightly increased in pregnancy and so is systolic function. There is also a moderate increase in the size of the right chambers and the left atrium, progressive dilation of pulmonary, tricuspid and mitral valve annuli as well as some degree of pulmonary, tricuspid, and mitral regurgitation. If necessary, a pacemaker can be safely placed during pregnancy with a minimal amount of radiation exposure with appropriate abdominal shielding *(49)*.

In the CARPREG study (Cardiac Disease in Pregnancy), a prospective analysis of 617 pregnancies complicated by cardiac disease, four risk factors were associated with adverse pregnancy outcomes *(50)*. Maternal risk was directly proportionate to the number of risk factors a patient held. These risk factors include:

1) A history of heart failure, arrhythmia, stroke, or transient ischemic attack
2) Pre-pregnancy New York Heart Association class > II
3) Mitral valve area less than 2 cm^2, aortic valve area less than 1.5 cm^2, or peak left outflow gradient greater than 30 mmHg
4) Ejection fraction less than 40%

Having no risk factors yielded a risk rate of 5%. One risk factor increased the risk for complications to 27%. Greater than one risk factor lead to complication rates >75% *(50)*.

General Management

Management of the gravid patient with cardiogenic shock can be difficult. Adequate preload needs to be ensured, and having the patient in the left lateral decubitus position to ensure adequate venous return is extremely important. If shock persists despite adequate preload, then management options include inotropic support and maximizing reduction in afterload. Dobutamine is the drug of choice for inotropic support, but it should be reserved for situations where benefits outweigh the risks, since it has been shown in animal models to decrease placental blood flow *(51)*. The decision to use dobutamine and other drugs that may affect fetal well being should be individualized based on many factors including gestational age and viability and the maternal and fetal risk if the medication is withheld. Fetal monitoring with non-stress tests is strongly advised once fetal viability is achieved in critically ill gravidas. This is discussed in more detail in the chapter on fetal monitoring (Chapter 7). Afterload reduction with nitroprusside or nitroglycerin can be initiated if inotropic support does not correct the shock state. Nitroprusside can only be used for extremely brief periods of time because of the risk of cyanide and/or thiocyanate toxicity to the fetus. The dose and duration should be minimized, and the patient converted to oral hydralazine as soon as possible. Angiotensin converting enzyme (ACE) inhibitors are absolutely contraindicated as they cause oligohydraminios and anuric renal failure in the fetus exposed in utero. When the pregnant cardiac patient delivers, the goal should be to minimize pain, avoid valsalva (pushing) and limit the duration of the second stage of labor to minimize the tachycardia, hypertension, and increase in oxygen consumption associated with normal labor and delivery. This can be accomplished

by insertion of an early epidural for good pain control, followed by an assisted vaginal delivery in the left lateral decubitus position.

Cardiac Dysfunction Acquired During Pregnancy

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is an acquired cause of cardiac dysfunction that occurs with an incidence of 1/1,300–1/15,000 deliveries, with large variations across countries *(52, 53)*. Maternal mortality of patients with class III or IV heart failure is around 7% *(54)*. This acquired heart failure of pregnancy usually occurs during the last month of pregnancy or during the first 5–6 months post-partum. The etiology is not well understood, but a small series would indicate an autoimmune phenomenon *(55)*. In this series of 10 patients, 7 underwent endocardial biopsy with no evidence of viral infection by microscopy or polymerase chain reaction *(55)*. Circulating auto-antibodies to cardiac tissue were detected in all 10 patients *(55)*. Risk factors have been identified for development of peri-partum cardiomyopathy. These include the following: African-American race, older age, twin gestation, preeclampsia, long-term tocolysis, and post-partum hypertension*(53)*. In most patients, there are molecular inflammatory markers present, but these are non-specific *(56)*. Roughly 50% of patients will return to normal cardiac function without complications *(53)*. Persistence of dilated cardiomyopathy 6 months post-partum indicates irreversible cardiomyopathy and leads to worse long-term survival *(53)*. Contractile reserve can be assessed by a dobutamine stress echo for patients who return to normal function at rest and are contemplating a future pregnancy.

Aortic Dissection

Pregnant patients have an increased risk for aortic dissection, possibly secondary to the increased shear stress from elevated cardiac output *(57)*. Dissection tends to present in the last trimester as a tearing sensation around the scapula. Risk factors for dissection include hypertension, increased age, multiparity, trauma, Marfan's syndrome, Ehler-Danlos syndrome, coarctation of the aorta, and bicuspid aortic valve *(57)*. History and a widened mediastinum on chest X-ray should raise the suspicion for dissection. The diagnosis can be made with infused chest CT, transesophageal echocardiogram, or MRI. Control of blood pressure, management of pain, and assuring adequate blood flow to the uterus is paramount. Emergent consultation of cardiology, cardiothoracic, and vascular surgery should occur.

Critical Care Syndromes Specific to Pregnancy

Preeclampsia

Preeclampsia is a circulatory disorder unique to pregnancy, thought to result from abnormal placentation that occurs in 5–10% of pregnancies *(58)*. Though the etiology is uncertain, the presence of hypertension and proteinuria (but no longer edema) define this entity. In some cases both may not be present at initial diagnosis and the manifestations may be mild. It occurs usually after the 20th week of pregnancy, but may happen post-partum. Risk factors for the development of preeclampsia include chronic hypertension, pre-existing renal disease, diabetes,

Table 21.5 Medications for hypertension during pregnancy.

Hydralazine:	5 mg IV, every 20 min as necessary, up to 20 mg
Labetalol:	10–20 mg IV, maximum dose of 220 mg
Nifedipine:	10 mg oral
Nicardipine:	1 μg/kg/min or 1–3 mg/h IV. May first load with 10 mg over 5 min
Nitroprusside	Relative contra-indicated secondary to cyanide toxicity
ACEi	Absolute contra-indicated secondary to fetal nephrotoxicity
Diuretics	May be used in low doses (10 mg of Furosemide) if evidence of pulmonary edema
Fenoldopam	Category B drug, but has not been used in large studies of preeclampsia

multiple gestations, primiparity, thrombophilias including antiphospholipid antibody syndrome, and hydatidiform mole *(58)*.

The principles that guide the management of preeclampsia include early diagnosis, close medical observation, and timely delivery. In most cases of preeclampsia, delivery is curative. In cases of severe preeclampsia, impending eclampsia, multiorgan involvement, or gestational age greater than 34 weeks, immediate delivery is recommended *(59, 60)*. Conservative management involves close blood pressure control. A diastolic blood pressure of 110 mmHg or greater should be treated with the goal of maintaining a mean arterial pressure between 105 and 126 mmHg, with the diastolic between 90 and 105 mmHg. The goal of blood pressure management is to prevent the development of encephalopathy and lower the risk of cerebral hemorrhage. Table 21.5 lists the medications commonly used to treat blood pressure in pregnant patients *(30, 61)*. Pulmonary edema, an important complication of severe preeclampsia, is discussed in Chapter 22 on acute lung injury.

Recent work has shed some light on the etiology of preeclampsia. Levels of the circulating protein soluble fms-like tyrosine kinase (sFLT-1) are increased in the serum of pregnant women with preeclampsia, and levels of placental growth factor (PLGF) and vascular endothelial growth factor (VEGF) are reduced *(62)*. Levine et al. utilized archived serum samples from a prior study of preeclampsia patients to study levels of sFLT-1, PLGF, and VEGF in women who ultimately developed preeclampsia. They hypothesized that sFLT-1 levels would increase and PLGF and VEGF levels would decline prior to the clinical onset of disease *(63)*. The study demonstrated that sFlt-1 levels increased approximately 5 weeks before the onset of preeclampsia. PLGF levels were significantly lower in the women who later had preeclampsia beginning at 13–16 weeks of gestation, with the greatest decline occurring at the same time as the increase in sFLT-1 *(63)*.

The normal pregnant patient has falling levels of activated protein C, returning to normal levels at 6 weeks post-partum *(41)*. Preeclampsia is associated with a further drop in APC levels. There is a rationale for future study of utilizing APC (Drotrecogin alpha) in the management of preeclampsia, though such a study has not been performed. It should be kept in mind that APC is an anticoagulant and may increase the risk for maternal or placental bleeding *(41)*.

Eclampsia

The principal concern of physicians caring for patients with preeclampsia is the development of eclampsia, a syndrome characterized by convulsions and increased risk for death. The seizures of eclampsia are best controlled with magnesium but benzodiazepines or phenytoin can be used if magnesium has not succeeded or if

contra-indicated. A large study demonstrated that magnesium was superior for control and further prevention of eclamptic seizures *(64)*. Magnesium is routinely used by obstetricians as a prophylactic against the development of seizures in patients with severe preeclampsia. However, no study has convincingly demonstrated prophylactic magnesium to be superior to blood pressure control in preventing eclampsia *(61)*. However, magnesium and blood pressure control are superior to phenytoin in preventing eclampsia *(64–66)*. Magnesium should be given for a minimum of 24 h post delivery in any woman with eclampsia. Patients receiving magnesium should be closely monitored for signs and symptoms of toxicity and levels checked periodically.

HELLP Syndrome

An extremely fulminant complication of preeclampsia is the HELLP syndrome (*H*emolytic anemia, *E*levated *L*iver enzymes, *L*ow *P*latelets), which occurs in 0.3% of deliveries and 4–18.9% of patients with preeclampsia *(67)*. The HELLP syndrome is characterized by multi-organ system dysfunction arising from an unclear endothelial abnormality that results in secondary fibrin deposition and organ hypoperfusion. In up to 30% of patients who develop HELLP, the disease manifests 48 h post-partum. Maternal mortality ranges from 0 to 24%, with fetal mortality ranging from 8 to 60%. The diagnosis is made based on laboratory values that demonstrate dropping platelets and elevated liver transaminases in the setting of a consumptive microangiopathic hemolytic anemia *(67)*. Management is supportive and requires timely delivery of the fetus.

Pulmonary Embolism

Pregnancy increases the risk for deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE) *(47)*. DVT occurs in about 1–5/1,000 deliveries, with more DVTs occurring in the left leg compared to the right leg. PE is the leading cause of maternal death *(68)*. There seems to be a relatively high frequency of Factor V Leiden mutation in pregnant patients who develop DVT *(69)*. Any pregnant patient with unexplained events that could result from thrombophilia (fetal loss, DVT, PE) should be evaluated for this mutation as part of the hypercoagulability evaluation. Diagnosing DVT and PE in the pregnant population can be challenging, as they often have lower extremity edema and dyspnea. The threshold to initiate a workup for DVT/PE therefore should be low. Figure 21.2 outlines a strategy to assist the workup for suspected PE. Perfusion scanning results in radiation exposure well within the limits of permissible fetal exposure (500 mrem). Ventilation scanning adds little information in cases of normal perfusion scans and should be withheld in order to avoid further unnecessary radiation. Patients with an abnormal perfusion should have a ventilation scan to document the presence of mismatched or matched defects, which would help in making a more certain diagnosis. In any patient with cardiopulmonary disease, imaging with helical CT is appropriate. Multidetector row CT exposes the fetus to 0.02–0.03 rads. Evaluation of the lower extremities by venous Doppler ultrasound is not as certain as for the non-gravid patient during the last half of pregnancy. Isolated pelvic thrombi have been found on magnetic resonance venography soon prior to hospital discharge in 46% of asymptomatic high risk patients following cesarean sections, all of whom had negative compression proximal lower extremity ultrasounds *(70)*. Pelvic thrombi should be kept in mind in patients with suspected DVT with negative leg dopplers.

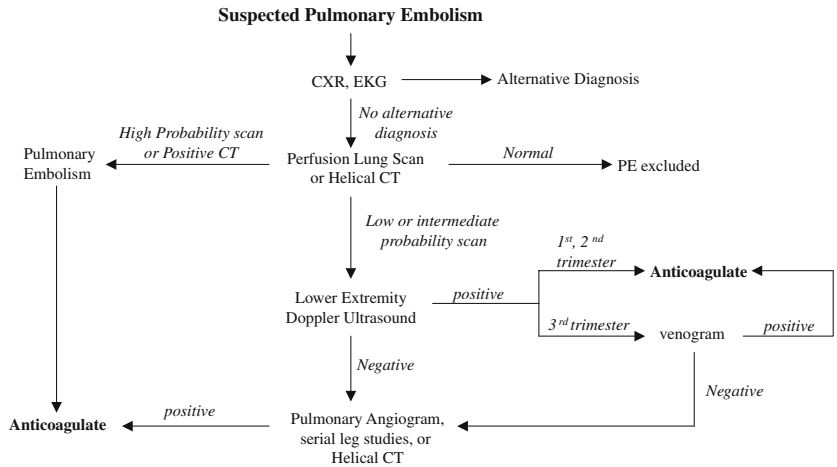


Figure 21.2 Suggested algorithm to evaluate suspected pulmonary embolism

The management of DVT and PE in the pregnant patient is quite different than the non-pregnant patient, as outlined in Table 21.6. Anticoagulation with heparin is the mainstay of therapy, as warfarin is contraindicated in pregnancy. An initial bolus of 80 units/kg of unfractionated heparin should be followed by a continuous infusion of 18 units/kg/h adjusted to achieve a goal aPTT of 1.5–2.3 times control. Some suggest that monitoring heparin levels via the anti-factor Xa assay for a level of 0.5–1.2 units/mL should be the goal of anticoagulation in pregnancy, as the gravid state increases the levels of factor VIII and fibrinogen, and these factors influence the effect on heparin in prolonging the aPTT [71]. No clinical data demonstrate superiority of outcome by either management strategy. Low molecular weight heparin (LMWH) has been shown to effectively treat DVT/PE, and LMWH usually requires no monitoring, potentially leading to a cost savings. Treatment with LMWH is weight based and inherently carries some limitations especially in pregnancy where dosing is initiated based on actual pregnancy weight but then frequently requires dose modification when levels of anti-Xa levels are checked periodically. We usually recommend checking anti-Xa levels once a month once the therapeutic dose is achieved. LMWH, like unfractionated heparin, does not cross the placenta *(72)*.

Thrombolytic therapy with streptokinase, urokinase, or tissue plasminogen activator can be performed, but there is increased risk of hemorrhage. There are

Table 21.6 Management of DVT/PE in pregnant versus non-pregnant patient.

Non-pregnant	Pregnant
Non-invasive leg studies helpful	Non-invasive leg studies not validated but routinely used
Thrombolytic therapy an option	Riskier, and contraindicated at term
IVC filters below the renal veins	IVC filters above the renal veins
Heparin, then warfarin	Heparin (unfractionated or low molecular weight) only
Monitor the PTT	Heparin and anti-Xa levels may be better monitor
Hypercoagulable state less common	Hypercoagulable state more common
Prophylactic Heparin is 5000 U sq BID	Higher doses recommended in second and third trimester

no clinical trials of their use in pregnant patients but many reports have described its use in pregnancy. As heparin is effective in treating DVT/PE and lowers the risk of subsequent events, thrombolytic therapy should only be considered in a patient with an unequivocal diagnosis of massive PE and hemodynamic compromise *(73, 74)*. In these patients, treatment should not be delayed because of pregnancy given the high mortality of PE in pregnancy. Thrombolytic agents are contraindicated 24 h before delivery and for 2 weeks post-partum.

If needed, an inferior vena cava filter (IVC filter) should be placed in the supra-renal position. An infra-renal location could obstruct the left ovarian vein, which empties into the left renal vein. An IVC filter increases the risk of recurrent DVT long-term. New temporary IVC filters have been utilized in this population, but the literature supporting their use is largely anecdotal or consisting of small series *(75)*.

Full anticoagulation with heparin does not significantly increase the risk for bleeding from vaginal delivery except for episiotomy hematoma *(76)*. However, spinal and epidural anesthesia are contraindicated owing to the increased risk of spinal cord hematoma and cord compression. Many experts recommend the use of unfractionated heparin close to term (at 36 weeks) and a planned induction around 39 weeks with close monitoring for anticoagulation. Full details of management and therapy of DVT and PE are discussed in Chapter 18 on venous thromboembolism in pregnancy.

Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) occurs in 1/8,000–1/80,000 pregnancies and accounts for 10% of all maternal deaths *(47, 77)*. The most important risk factors include maternal age and multiparity. Less well established risk factors include amniotomy, cesarean section, intrauterine fetal monitoring device, induction of labor, and term pregnancy in the presence of an intra-uterine device (IUD). While most cases occur during labor, AFE can happen during any trimester, usually in the setting of uterine manipulation or trauma.

The classic presentation of AFE is the sudden onset of severe dyspnea, tachypnea, tachycardia, cardiovascular collapse, and cyanosis, leading ultimately to seizures, pulmonary edema, and DIC *(47)*. If the patient is still pregnant with a viable gestation, urgent deliver of the fetus is advised. The diagnosis is made clinically. Aspiration of right heart catheter samples looking for epithelial cells has been suggested as a diagnostic maneuver but this finding is not sensitive, and surprisingly not specific (these cells have been found in males and in non-gravid women) *(78, 79)*. Bleeding from DIC occurs in up to 50% of patients who survive the first 60 min.

Treatment of AFE is supportive. The goal is to maximize oxygenation through mechanical ventilation with high oxygen concentrations using small tidal volumes. Cardiovascular support to stabilize the circulation should use inotropes and vasoactive agents to maximize cardiac output with the lowest possible left ventricular end diastolic pressure. Patients should be made comfortable with sedative medications. Bleeding complications of DIC should be managed with the help of a hematologist. The use of factor replacement or heparin is controversial.

Cardiopulmonary Arrest

The pregnant patient undergoing cardiopulmonary arrest represents a unique situation. Basic ACLS should be performed, ensuring an adequate airway, breathing, and the use of cardiopulmonary resuscitation (CPR). While the supine position is ideal for CPR, the pregnant patient has a gravid uterus pressing on the IVC impeding

venous return. Left lateral decubitus positioning does not allow adequate chest compressions. The use of the Cardiff Wedge in CPR of the pregnant patient has been proven to be beneficial *(80)*. This device allows the patient to be at a 20° angle, ensuring adequate support of the torso for CPR but also minimizing compression of the IVC. If the ICU does not have a Cardiff Wedge, then a backboard with rolled towels or pillows under one side approximating a 20° lift can suffice.

The pregnant patient can safely undergo direct current cardioversion, both synchronized and unsynchronized *(81, 82)*. Drugs such as lidocaine, procainamide, adenosine, and quinidine can be safely used in the gravid patient. Amiodarone should be avoided if possible secondary to the possible effects on fetal thyroid development *(81, 82)*.

It is possible for an emergent cesarean section to be performed during CPR *(83, 84)*.

Trauma

Trauma is a leading cause of mortality in pregnancy. Being pregnant does not increase the risk of maternal mortality associated with trauma, but does significantly affect the outcome of the pregnancy. Trauma is associated with an increased rate of fetal demise and fetal premature delivery, directly related to the severity of maternal trauma, hemodynamic disruption, and direct damage to the feto-placental unit. Fetal demise is increased in maternal shock, severe head injury, pelvic fractures, and hypoxemia.

The initial assessment team for a gravid trauma victim must recall the physiologic changes of pregnancy and broaden their differential considerations of injury. Furthermore, the stretch of the peritoneum by the gravid uterus as well as the stretch of the abdominal musculature can decrease maternal sensitivity to peritoneal disruption, leading to diminished peritoneal signs.

Summary

An understanding of the normal physiology of pregnancy is vital to adequately assess the pregnant patient. In most situations, providing adequate maternal circulation and oxygen delivery will ensure fetal well-being. While the pregnant patient can become critically ill from illnesses typical of the non-pregnant condition, the clinician must remain vigilant in assessing the patient for diseases unique to pregnancy, such as preeclampsia, eclampsia, and AFE. Though many drugs are safe to use in pregnancy, understanding the risk/benefit ratio of each drug in the pregnant patient is vital to provide safe and effective care. The core principles of "ABC" (Airway, Breathing, Circulation) that govern the management of non-pregnant patients apply to the care of the pregnant patient with only minor modifications. In all critically ill pregnant patients, a coordinated effort by intensivists, high-risk obstetricians, neonatologists, and anesthesiologists can provide the best possible outcome for the mother and the baby.

Clinical Pearls

- In normal pregnancy, the circulation is characterized by increased cardiac output, increased plasma volume, and decreased systemic vascular resistance.
- In normal pregnancy, the respiratory system and acid-base status is characterized by a baseline respiratory alkalosis with compensatory metabolic acidosis with decreased bicarbonate. Functional residual capacity is decreased. Minute ventilation is increased.

- The fetus is very sensitive to changes in oxygen delivery. Any degree of maternal hypoxemia should be immediately corrected.
- A pregnant patient in the ICU should always be in the left lateral decubitus position if possible.
- Hypovolemic shock should be immediately corrected with fluids and blood (if necessary). A search for hemorrhage from obstetrical and non-obstetrical causes should be undertaken.
- Septic shock should be managed with early goal directed therapy for a CVP of 10 mmHg and a central venous oxygen saturation of at least 70%. Inotropes should be used only after adequate fluid resuscitation. For continuing hypotension after CVP and ScVO2 goals have been met, vasopressor medications can be added.
- Pre-existing cardiac disease can worsen during pregnancy as the need for an increased cardiac output develops. Dilated cardiomyopathy of pregnancy is managed by ensuring adequate preload and minimizing afterload.
- Preeclampsia should be managed by delivery of the fetus if possible. Blood pressure control with expectant management for eclampsia and HELLP syndrome can be undertaken for the non-term pregnancy. Eclampsia seizures should be managed with magnesium and delivery of the fetus.
- PE should be managed with heparin. Thrombolytic therapy should be used when necessary. Diagnosis can be made with perfusion scanning, helical CT, or pulmonary angiogram.
- AFE is characterized by rapid hemodynamic and respiratory compromise in the appropriate setting. It is managed supportively.
- CPR can be performed using a Cardiff Wedge. Cardioversion is safe in pregnancy. Most anti-arrhythmia medications are safe to use.

Example Cases

Case One

MK is a 24-year-old G_2P_1 with a healthy 36 week singleton gestation who presents to the emergency department complaining of increased shortness of breath and increasing lower extremity edema. Her respiratory complaints started 4 h ago. She notes the edema to have been increasing over the last 2 days, with the left leg being larger than the right. She has no other complaints. Her prior pregnancy was unremarkable. Vital signs in the emergency department revealed her to be afebrile, tachycardic at 110 beats/min, and tachypneic at 24 breaths/min. Her blood pressure was 100/60 mmHg and SaO2 by pulse oximetry was 92%. Neck exam revealed elevated jugular venous pressure. Cardiac exam was remarkable for tachycardia and the presence of an S_3. Pulmonary exam was unremarkable. Lower extremities were notable for pitting edema to the knee, with the circumference of the left leg being 3 cm greater than the right. Her CXR was negative for any acute process.

The clinical team was concerned that she may have had a PE. Supplemental oxygen was immediately administered to correct her hypoxemia and a perfusion scan was obtained. The results were read as low to intermediate probability. Doppler ultrasound of the lower extremities was negative for clot. An infused helical CT of the chest was obtained and revealed a large clot in the left main pulmonary artery. The patient was admitted to the hospital and begun on heparin therapy. Genetic analysis demonstrated the patient to be heterozygous for the Factor V Leiden mutation. She was discharged on LMWH and re-admitted at term for spontaneous labor. She was restarted on unfractionated heparin and

underwent an uneventful vaginal delivery. She completed a 9-month course of warfarin after delivery.

Case Two

RW is a 28-year-old G_4P_2 at 34 weeks with a singleton gestation who was the restrained driver in a rear-end motor vehicle accident. She has no complaints in the field but had an increased pulse at 110. She arrived via ambulance to the emergency room complaining of abdominal pain. Her vital signs showed her to be afebrile with a heart rate of 130 bpm, a blood pressure of 90/50 mmHg, and a respiratory rate of 30/min. Physical exam was remarkable for flat neck veins, tachycardia, clear lungs, and a tender abdomen with vaginal bleeding. Fetal heart rate was 100 bpm.

The patient was placed in the left lateral decubitus position and two large bore venous catheters were inserted to supplement the original small-bore intravenous line started in the field. Normal saline was infused wide open. The patient was typed and crossed and un-typed O negative blood was ordered. She was immediately sedated and intubated and an emergency caesarian section for fetal distress was performed in the trauma bay. Examination of the uterus revealed over two liters of clot and blood and the presence of a placental abruption. The infant had Apgar scores of 4 and 6 and was intubated and transferred to the NICU by the neonatology team. While the obstetrical team was sewing the wound, the patient suddenly became hypoxemic and her blood pressure fell to 60/30 mmHg with a heart rate of 150 bpm. Her oxygen was increased to 100% and the unmatched blood was infused. A clinical diagnosis of AFE was made and the patient was transferred to the intensive care unit for further management. Central access via the right internal jugular vein was obtained and fluids and blood were given until an adequate CVP was reached. Labs sent earlier revealed hemoglobin of 5 g/dL. The patient required inotropic and vasopressive support for the next 48 h, but could then be weaned from these medications. She required 5 units of packed red blood cells to achieve stable hemoglobin of 9 g/dL. On post-operative day number three, she was liberated from the ventilator.

Case Three

DL is a 19-year-old G_1P_0 at 28 weeks with a singleton gestation who presented to the emergency room with three days of fevers, chills, cough productive of dark sputum, and pleuritic chest pain. Her vital signs showed her to be febrile to 39^5 degrees centigrade, tachycardic at 110 bpm, tachypneic at 36/min, and a blood pressure of 85/30 mmHg. Her saturation on room air was 89%. Physical exam was remarkable for moderate respiratory distress with accessory muscle use, diminished breath sounds with egophony, dullness to percussion at the left base, warm bounding pulses, and she became progressively less alert. Fetal heart rate was 120. A CXR revealed a large left lower lobe infiltrate. An arterial blood gas revealed a pH 7.18, $PaCO_2 = 35$ mmHg, $PaO_2 = 55$ mmHg, and calculated $HCO_3 = 10$. Laboratory values indicated an anion gap of 20.

A diagnosis of septic shock was made. Blood, urine, and vaginal/cervical cultures were obtained. Broad-spectrum antibiotics were initiated. The patient was intubated for hypoxemic and ventilatory failure with 100% oxygen and 5 of PEEP. Her blood pressure dropped during the intubation to 65/30 mmHg and she was placed in the left lateral decubitus position. A right internal jugular venous introducer was inserted and a triple-lumen catheter was threaded through the device. Initial CVP was 1 mmHg. Normal saline was infused wide open to a goal of 10 mmHg. Mixed venous oxygen saturation was 64% once the goal CVP was

reached. Dobutamine at 5 μg/kg/min was initiated and titrated to a goal mixed venous saturation of 70%. The patient's blood pressure increased to 90/30 during this time, and urine output was maintained at a minimum of 30 cc/h. Fetal heart rate was 140–150 during the entire resuscitation time. The ventilator was adjusted by increasing the PEEP to allow a non-toxic FiO_2, and minute ventilation was adjusted to reach eucapnea. Blood cultures grew *S. pneumoniae* the subsequent day, sensitive to the antibiotics she was receiving. Three days later she was weaned off dobutamine, and she was successfully liberated from the ventilator that evening. She was transferred to the obstetrics ward the following day. The rest of her pregnancy was unremarkable and she had a normal spontaneous vaginal delivery.

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(6):1537–44.
2. Martin SR, Foley MR. Intensive care in obstetrics: an evidence-based review. Am J Obstet Gynecol 2006;195(3):673–89.
3. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ 2001;322(7294):1089–93; discussion 93–4.
4. Karnad DR, Guntupalli KK. Critical illness and pregnancy: review of a global problem. Crit Care Clin 2004;20(4):555–76, vii.
5. Afessa B, Green B, Delke I, Koch K. Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an ICU. Chest 2001;120(4):1271–7.
6. Mirghani HM, Hamed M, Ezimokhai M, Weerasinghe DS. Pregnancy-related admissions to the intensive care unit. Int J Obstet Anesth 2004;13(2):82–5.
7. Zeeman GG, Wendel GD, Jr., Cunningham FG. A blueprint for obstetric critical care. Am J Obstet Gynecol 2003;188(2):532–6.
8. Karnad DR, Lapsia V, Krishnana A, et al. Prognostic factors in obstetric patients admitted to an Indian intensive care unit. Crit Care Med 2004;32:1294–9.
9. Kilpatrick SJ, Matthay MA. Obstetric patients requiring critical care. A five-year review. Chest 1992;101(5):1407–12.
10. Scarpinato L. Critically ill obstetric patients: outcome and predictability utilizing the SAPS II score in a 314 bed community hospital. Chest 1995;108:184S.
11. Koch K, HD. R, Sanchez-Ramos L. Critically ill obstetrical patients: outcome and predictability. Crit Care Med 1988;16:A409.
12. el-Solh AA, Grant BJ. A comparison of severity of illness scoring systems for critically ill obstetric patients. Chest 1996;110(5):1299–304.
13. Belfort MA, Mares A, Saade G, Wen T, Rokey R. Two-dimensional echocardiography and Doppler ultrasound in managing obstetric patients. Obstet Gynecol 1997;90(3):326–30.
14. 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):884–92.
15. Lee W, Gonik B, Cotton DB. Urinary diagnostic indices in preeclampsia-associated oliguria: correlation with invasive hemodynamic monitoring. Am J Obstet Gynecol 1987;156(1):100–3.
16. Lorente L, Henry C, Martin MM, Jimenez A, Mora ML. Central venous catheter-related infection in a prospective and observational study of 2,595 catheters. Crit Care 2005;9(6):R631–5.
17. Connors AJ, Speroff T, Dawson N, Thomas C, Harrell FJ, Wagner D. The effectiveness of right heart catheterization in the initial care of critically ill patients: SUPPORT investigators. JAMA 1996;276:889–97.

18. Sandham J, Hull R, Brant R, et al. A randomized, controlled trial of the use of the pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348:5–14.
19. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. Obstet Gynecol 1980;55(6):701–4.
20. Finley BE. Acute coagulopathy in pregnancy. Med Clin North Am 1989;73(3):723–43.
21. Salihu HM, Bekan B, Aliyu MH, Rouse DJ, Kirby RS, Alexander GR. Perinatal mortality associated with abruptio placenta in singletons and multiples. Am J Obstet Gynecol 2005;193(1):198–203.
22. Hayashi RH. Hemorrhagic shock in obstetrics. Clin Perinatol 1986;13(4):755–63.
23. Suner S, Jagminas L, Peipert JF, Linakis J. Fatal spontaneous rupture of a gravid uterus: case report and literature review of uterine rupture. J Emerg Med 1996;14(2):181–5.
24. Toppenberg KS, Block WA, Jr. Uterine rupture: what family physicians need to know. Am Fam Physician 2002;66(5):823–8.
25. Guise JM, McDonagh MS, Osterweil P, Nygren P, Chan BK, Helfand M. Systematic review of the incidence and consequences of uterine rupture in women with previous caesarean section. BMJ 2004;329(7456):19–25.
26. Smith GC, Pell JP, Pasupathy D, Dobbie R. Factors predisposing to perinatal death related to uterine rupture during attempted vaginal birth after caesarean section: retrospective cohort study. BMJ 2004;329(7462):375.
27. Leung AS, Leung EK, Paul RH. Uterine rupture after previous cesarean delivery: maternal and fetal consequences. Am J Obstet Gynecol 1993;169(4):945–50.
28. Flamm BL, Goings JR, Liu Y, Wolde-Tsadik G. Elective repeat cesarean delivery versus trial of labor: a prospective multicenter study. Obstet Gynecol 1994;83(6):927–32.
29. Rouse DJ, Leindecker S, Landon M, et al. The MFMU Cesarean Registry: uterine atony after primary cesarean delivery. Am J Obstet Gynecol 2005;193(3 Pt 2):1056–60.
30. Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med 1995;152(2):427–55.
31. Levy M, Fink M, Marshall J, et al. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.
32. Gibbs RS. Severe infections in pregnancy. Med Clin North Am 1989;73(3):713–21.
33. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77.
34. Hollmen AI, Jouppila R, Albright GA, Jouppila P, Vierola H, Koivula A. Intervillous blood flow during caesarean section with prophylactic ephedrine and epidural anaesthesia. Acta Anaesthesiol Scand 1984;28(4):396–400.
35. Hollmen AI, Jouppila R, Jouppila P. Regional anaesthesia and uterine blood flow. Ann Chir Gynaecol 1984;73(3):149–52.
36. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus: DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study group. BMJ 1997;314:1512–5.
37. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359–67.
38. Hotchkiss R, Karl I. The pathophysiology and treatment of sepsis. N Engl J Med 2003;344:759–62.
39. Matthay MA. Severe sepsis: a new treatment with both anticoagulant and antiinflammatory properties. N Engl J Med 2001;344:759–62.
40. Bernard G, Vincent J, Laterre P, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
41. von Dadelszen P, Magee LA, Lee SK, et al. Activated protein C in normal human pregnancy and pregnancies complicated by severe preeclampsia: a therapeutic opportunity? Crit Care Med 2002;30(8):1883–92.
42. Medve L, Csitari IK, Molnar Z, Laszlo A. Recombinant human activated protein C treatment of septic shock syndrome in a patient at 18th week of gestation: a case report. Am J Obstet Gynecol 2005;193(3 Pt 1):864–5.

43. Mikaszewska-Sokolewicz M, Mayzner-Zawadzka E. Use of recombinant human activated protein C in treatment of severe sepsis in a pregnant patient with fully symptomatic ovarian hyperstimulation syndrome. Med Sci Monit 2005;11(6):CS27–32.
44. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med 1995;23(8):1430–9.
45. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. Crit Care Med 1995;23(7):1294–303.
46. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348(2):138–50.
47. Strek M, O'Connor M, Hall J. Critical Illness in Pregnancy. 2nd ed. New York: McGraw-Hill; 1998.
48. Ramsey PS, Ramin KD, Ramin SM. Cardiac disease in pregnancy. Am J Perinatol 2001;18(5):245–66.
49. Gowda R, Khan I, Mehta N, Vasavada B, Sacchi T. Cardiac arrhythmias in pregnancy: clinical and therapeutic considerations. Int J Cardiol 2003;88:129–33.
50. Siu S, Sermer M, Colman J, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515–21.
51. Fishburne JI, Meis PJ, Urban RB, et al. Vascular and uterine responses to dobutamine and dopamine in the gravid ewe. Am J Obstet Gynecol 1980;137(8):944–52.
52. Homans DC. Peripartum cardiomyopathy. N Engl J Med 1985;312(22):1432–7.
53. Abboud J, Murad Y, Chen-Scarabelli C, Saravolatz L, Scarabelli TM. Peripartum cardiomyopathy: A comprehensive review. Int J Cardiol 2007.
54. Sullivan JM, Ramanathan KB. Management of medical problems in pregnancy – severe cardiac disease. N Engl J Med 1985;313(5):304–9.
55. Lamparter S, Pankuweit S, Maisch B. Clinical and immunologic characteristics in peripartum cardiomyopathy. Int J Cardiol 2006.
56. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet 2006;368(9536): 687–93.
57. Mabie WC, Freire CM. Sudden chest pain and cardiac emergencies in the obstetric patient. Obstet Gynecol Clin North Am 1995;22(1):19–37.
58. Lindheimer MD, Katz AI. Preeclampsia: pathophysiology, diagnosis, and management. Annu Rev Med 1989;40:233–50.
59. Sibai BM, Frangieh AY. Management of severe preeclampsia. Curr Opin Obstet Gynecol 1996;8(2):110–3.
60. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. Br J Anaesth 1996;76(1):133–48.
61. Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med 1996;335(4):257–65.
62. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111(5):649–58.
63. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350(7):672–83.
64. Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev 2003(2): CD000025.
65. Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database Syst Rev 2003(4):CD000127.
66. Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev 2003(4):CD000128.
67. 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):436–45.

68. Chang J, Elam-Evans L, Berg C, et al. Pregnancy-related mortality surveillance: United States 1991–1999. MMWR Surveill Summ 2003;52:1–8.
69. Hirsch DR, Mikkola KM, Marks PW, et al. Pulmonary embolism and deep venous thrombosis during pregnancy or oral contraceptive use: prevalence of factor V Leiden. Am Heart J 1996;131(6):1145–8.
70. Barbour LA, Smith JM, Marlar RA. Heparin levels to guide thromboembolism prophylaxis during pregnancy. Am J Obstet Gynecol 1995;173(6):1869–73.
71. Rodger MA. Avruch LI. Howley HE. Olivier A. Walker MC. Pelvic magnetic resonance venography reveals high rate of pelvic vein thrombosis after cesarean section. Am J Obstet Gynecol 2006;194(2):436–7.
72. Shiach CR. Monitoring of low molecular weight heparin in pregnancy. Hematology 2003;8(1):47–52.
73. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 2001;119(1 Suppl):122S–31S.
74. Hirsh J, Dalen J, Guyatt G. The sixth (2000) ACCP guidelines for antithrombotic therapy for prevention and treatment of thrombosis. American College of Chest Physicians. Chest 2001;119(1 Suppl):1S–2S.
75. Clark SL, Blatter DD, Jackson GM. Placement of a temporary vena cava filter during labor. Am J Obstet Gynecol 2005;193(5):1746–7.
76. Dulitzki M, Pauzner R, Langevitz P, Pras M, Many A, Schiff E. Low-molecular-weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol 1996;87(3):380–3.
77. Masson RG. Amniotic fluid embolism. Clin Chest Med 1992;13(4):657–65.
78. Clark SL. Amniotic fluid embolism. Clin Perinatol 1986;13(4):801–11.
79. Giampaolo C, Schneider V, Kowalski BH, Bellaver LA. The cytologic diagnosis of amniotic fluid embolism: a critical reappraisal. Diagn Cytopathol 1987;3(2):126–8.
80. Rees GA, Willis BA. Resuscitation in late pregnancy. Anaesthesia 1988;43(5):347–9.
81. Joglar JA, Page RL. Antiarrhythmic drugs in pregnancy. Curr Opin Cardiol 2001;16(1):40–5.
82. Ferrero S, Colombo BM, Ragni N. Maternal arrhythmias during pregnancy. Arch Gynecol Obstet 2004;269(4):244–53.
83. DePace NL, Betesh JS, Kotler MN. 'Postmortem' cesarean section with recovery of both mother and offspring. JAMA 1982;248(8):971–3.
84. Mallampalli A, Guy E. Cardiac arrest in pregnancy and somatic support after brain death. Crit Care Med 2005;33(10 Suppl):S325–31.

22

Acute Lung Injury in Pregnancy

Nuala J. Meyer and Gregory A. Schmidt

Keywords: acute respiratory distress syndrome, acute lung injury, hypoxemia, pulmonary edema, mechanical ventilation

Introduction

Critical illness invariably elicits special trepidation and concern whenever a pregnant patient is involved. Not only must providers struggle to restore normal physiology to the mother, but they must do so whilst providing adequate circulation, oxygenation, and ventilation to the growing fetus. Few disease processes present as great a challenge to this delicate maternal-fetal balance as Acute Lung Injury (ALI) and its most severe form, the Acute Respiratory Distress Syndrome (ARDS). While the past decade has finally produced clinical trials demonstrating a reduced mortality when patients with ARDS are treated with careful ventilator strategies, investigational trials almost invariably exclude pregnant patients, leaving us to hypothesize how the application of various strategies will differ in a pregnant patient. In this chapter, we will review the definitions, clinical features, and epidemiology of ALI/ARDS in the pregnant patient, discuss the specific challenges that pregnancy imposes upon a patient with ALI, and present our therapeutic approach to the gravida with ALI.

Definition

The Acute Respiratory Distress Syndrome (ARDS) refers to the acute onset of refractory hypoxemia and radiographic findings suggestive of pulmonary edema, when heart failure is not the cause. The syndrome was first described in 1967 *(1)* and remained a clinical diagnosis based upon a constellation of clinical findings until 1994, when a conference of American and European clinician scientists published a consensus definition of both ARDS and its less severe form, ALI *(2)*. While both syndromes share the features of requiring an acute onset, bilateral radiographic infiltrates, and the absence of left atrial hypertension—if measured, a pulmonary artery occlusion pressure (P_{aop}) should be less than 18 mmHg—ARDS is present when the ratio of the partial pressure of arterial

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_22

oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) is less than 200. ALI is present when the first three conditions are met but the PaO_2/FiO_2 ratio is only less than 300. The syndrome has been reported to afflict children as young as 11, but is distinct from the respiratory distress syndrome or hyaline membrane disease of the newborn, which is most frequently encountered with premature neonates who have inadequate pulmonary surfactant *(3)*. Rather than representing specific disease processes unto themselves, ALI/ARDS seem to be final common pathways of lung injury following a variety of potential inciting events, including sepsis, pneumonia, aspiration, trauma, and blood transfusion.

Epidemiology

After years of struggling to estimate accurately the incidence of ALI and ARDS, researchers recently completed a large epidemiologic study in King County, Washington, which disclosed a crude incidence of ALI amongst adults at approximately 79 per 100,000 population *(4)*. Estimates of the incidence of ALI during pregnancy are far less certain. Surveying their own practices over several years, investigators in the United States reported maternal ARDS complicating from between 1 in 1,500 to 1 in 7,000 deliveries *(5–7)*, for an incidence of between 16 and 70 cases per 100,000 population. Because each study represented a single institution's experience, it remains controversial as to whether ALI/ARDS is more or less common during pregnancy than in the overall population. While rare, ALI/ARDS exerts a substantial toll, with reported maternal mortality ranging from 14 to 44% and fetal mortality 11 to 40% *(5–8)*. In addition, respiratory distress, along with bleeding complications, is a leading cause for maternal intensive care unit admission *(8–12)*. Intensivists and obstetricians are thus greatly invested in the care of pregnant patients with ALI.

Clinical Features

The course of ALI/ARDS is notoriously protean and heterogeneous, often progressing through various stages within an individual patient. Initially, during the acute or exudative phase, hallmarks include the rapid development of respiratory failure typified by cyanosis, arterial hypoxemia refractory to supplemental oxygen therapy, and marked tachypnea. Patients often require urgent intubation and mechanical ventilation. Extensive consolidation and collapse of airspaces is evident on the chest radiograph as marked pulmonary edema, which may be indistinguishable from cardiogenic edema due to increased pulmonary capillary hydrostatic pressure (Figure 22.1). As a result of the consolidation, lung compliance is greatly reduced, manifest as unusually high airway pressures on the ventilator despite normal or even low tidal volumes. Pathologically, the acute phase is characterized by diffuse alveolar damage, with alveolar septal thickening, hyaline membranes layering the alveolar surface, and interstitial edema widening the alveolar spaces. Pathologic damage has been visualized as early as several days following the onset of respiratory distress *(13)*.

Dead space fraction (V_D/V_T, calculated as the difference between the arterial partial pressure of carbon dioxide ($PaCO_2$) and the mean expired partial pressure of carbon dioxide (P_ECO_2) relative to the PaCO2: $V_D/V_T = PaCO_2–P_ECO_2/PaCO_2$) may be increased greatly. The clinician may thus observe a patient with extraordinary minute ventilation yet normal or near-normal $PaCO_2$. In the

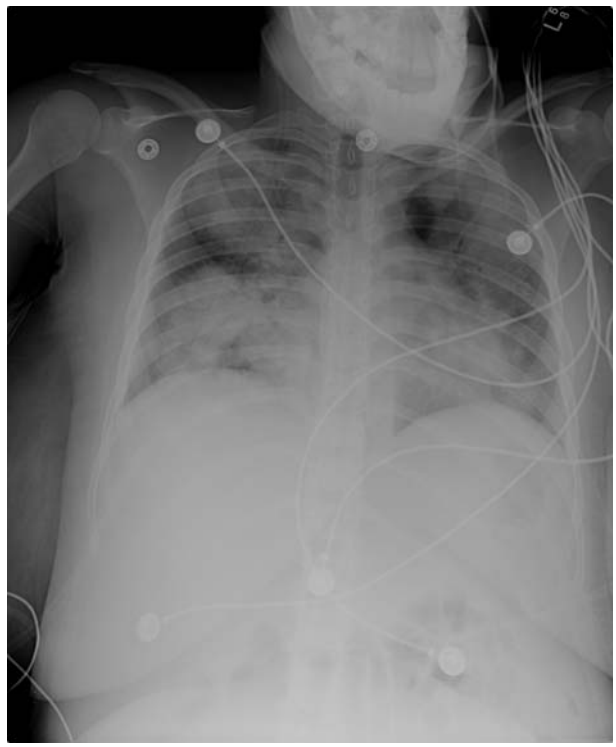


Figure 22.1 Chest radiograph of a young woman at 31 weeks' gestation with ARDS. She was intubated shortly after the film was taken

pregnant patient, the combination of an increased work of breathing, tachypnea, and a "normal" $PaCO_2$ (40 mmHg) must be recognized as impending respiratory failure, as the normal $PaCO_2$ during pregnancy is only 27–34 mmHg *(14)*.

While for some patients with ALI, the defect in alveolar permeability rapidly resolves, many patients progress into a subacute phase of ALI, with persistent clinical, radiographic, and physiologic findings for more than 7 days. Pathologically, this phase is distinguished by the formation of fibrosing alveolitis, whereby collagen and fibroblasts proliferate within the alveolar septae *(13)*. It is also marked by the loss of alveolar epithelial type I cells and their replacement by hardier alveolar type II cells, which are more resistant to injury. For the majority of patients, lung injury will resolve fully following the exudative phase, even when it persists longer than 10 days.

For the unlucky minority, however, the syndrome may progress to the "proliferative" phase, characterized clinically by persistent hypoxemia, low lung compliance, and high alveolar dead space fraction. Pathologic examination at this time reveals extensive pulmonary fibrosis with loss of normal, recognizable lung architecture *(15)*. Patients developing proliferative ARDS suffer persistent profound pulmonary limitations and may necessitate lung transplantation or succumb to the disease.

Etiology

Even at its first description, ALI/ARDS was recognized to be a final result, which could stem from a number of different initial insults. The original paper described 12 patients whose injuries varied from sepsis, viral pneumonia, aspiration,

pancreatitis, or trauma with accompanying massive blood transfusion *(1)*. Sepsis and pneumonia are the two clinical risk factors most frequently identified as precipitants of ALI/ARDS, with aspiration, massive blood transfusion, trauma, pancreatitis, pulmonary contusion, and near-drowning occurring less frequently *(4, 16, 17)*. Prospective studies of hospitalized patients with such "at risk" conditions report the development of ARDS in approximately 34%; the presence of multiple risk factors increases the likelihood of eventual ARDS *(16)*. The fact that it is actually the minority of patients with risk factors for the syndrome who go on to manifest ALI testifies to the marked heterogeneity of the disease, and to the possibility that host factors—environmental or genetic—play a major role in determining which patients develop the disease *(18)*.

In pregnancy, a number of unique precipitants of ALI/ARDS arise. Pregnant patients are of course subject to potential trauma, blood product transfusion, and infection, similar to the population at large. In addition, however, pregnant patients may develop ARDS as a complication of amniotic fluid embolism, tocolytic therapy, preeclampsia, or retained products of conception *(6, 19)*. Pregnant women are also more prone to specific infections which may blossom into ALI/ARDS; examples include chorioamnionitis or pyelonephritis causing sepsis *(5, 6, 19)*, or coccidioidomycosis pneumonia *(20)*. Other conditions may either be more common in pregnancy, or inflict a greater disease burden during pregnancy. Such is the case for aspiration associated with cesarean section (also called Mendelson's syndrome) *(21)*, massive transfusion due to disseminated intravascular coagulopathy (DIC), and viral pneumonias due to influenza or varicella. In each case, the pregnant patient may incur greater disability than is observed in the general population *(19, 22)*. This may reflect the increased "leakiness" of the vasculature in pregnancy due to decreased colloid oncotic pressure. As pregnancy progresses, a woman's circulating blood volume expands more than her red blood cell mass, resulting in not only a mild physiologic anemia, but also a decreased colloid oncotic pressure within the vasculature, contributing to a tendency to form extravascular edema. Clark and colleagues reported a 14% decrease in colloid oncotic pressure in the late third trimester relative to the non-pregnant state *(23)*. Pregnancy can thus be envisioned as a propensity for leaky blood vessels, which may predispose toward ALI or may worsen it once it has begun. As one author commented, "...a pregnant woman is a case of pulmonary edema waiting to happen." *(24)* Alternatively, changes in cellular immunity during pregnancy, including decreased helper T cells, depressed natural killer cell activity, and decreased cytotoxic activity, may contribute to the increased pathogenicity of viral and fungal organisms *(25)*. Table 22.1 enumerates many of the common risk factors for ALI/ARDS amongst pregnant women.

Pathogenesis

In the normal lung, the interface between inspired air and the bloodstream is governed by a semi-permeable barrier made up of respiratory epithelium and pulmonary capillary endothelium. In health, this barrier allows diffusion of gases—oxygen and carbon dioxide—into the airspace without allowing cells or protein to enter the alveolus. In cardiogenic edema, hydrostatic pressure within the pulmonary capillaries is greatly increased, and drives a protein-poor fluid into first the interstitium and then the alveolus. In non-cardiogenic edema, by contrast, the defect resides in the barrier itself. Both the endothelium, which is more

Table 22.1 Precipitants of ALI/ARDS in the pregnant population compared to the population at large.

Population at large	Pregnant patients: non-pregnancy related	Pregnant patients: pregnancy-specific
Sepsis	Sepsis • Pyelonephritis • *Listeria* bacteremia	Sepsis • Chorioamnionitis • Missed abortion
Pneumonia	Pneumonia • Varicella • Influenza • Coccidiomycosis	Pulmonary edema (high- vs. low-pressure) • Pre-eclampsia / eclampsia • Tocolytic therapy
Aspiration	Aspiration • ↑ with cesarean delivery or intubation	
Trauma	Trauma	
Disseminated intravascular coagulopathy (DIC)	DIC	DIC 2° retained products of conception
Massive transfusion	Massive transfusion 2° postpartum hemorrhage	
Air embolus	Air embolus	Amniotic fluid embolus
Pancreatitis		

permeable at baseline, and the traditionally impermeable epithelium are subjected to injury, which allows proteinaceous fluid to extrude into the alveolar airspace. In response to injury, respiratory epithelial type II cells proliferate on the alveolar surface but are functionally impaired, defective in their normal roles of surfactant production and fluid and ion transport *(26–28)*. As a result, edema is slow to resolve.

While ALI-induced damage to the epithelial–endothelial barrier is the result of deranged inflammation, the precise biological processes driving the condition are still under investigation. Leading theories as to how ALI/ARDS arises include activation of the complement cascade leading to neutrophilic inflammation, disordered intravascular coagulation and fibrinolyis, or biomechanical toxicities inflicted by mechanical ventilation and/or oxygen therapy *(26, 29)*. Indisputably, the shear stresses inflicted upon the lung by mechanical ventilation can result in ALI; one study found that 24% of patients without ALI at the initiation of mechanical ventilation nonetheless developed the syndrome over the first 5 days of ventilation *(30)*. Patients receiving larger tidal volumes from the ventilator—and thus, greater levels of shear stress at the alveolus—were especially at risk *(30)*. While there exists great interest in developing a biomarker or early molecular clue to detect ALI, no substance yet fulfills the desired criteria of being easy to measure, accurate, and clinically significant *(31)*.

Hypoxemia During Pregnancy: Risks and Protections

The severe hypoxemia of patients with ALI/ARDS is often alarming and quite difficult to reverse. Pregnant patients are uniquely susceptible to hypoxemia. As the pregnancy progresses, a mother's oxygen consumption increases by approximately

20% due to metabolic demands of the fetus and placenta *(14)*. Simultaneously, however, a mother's oxygen reserve is diminished, due to the pregnancy-related 20% decrement in functional residual capacity (FRC), which leaves less oxygen in the lungs *(32–34)*. Alveolar ventilation is also greatly increased, which results in rapid alterations in maternal blood gases when challenged with apnea, hypoventilation, or airway obstruction *(34)*. This diminished oxygen reserve and augmented alveolar ventilation result in the pregnant patient's dramatic vulnerability to hypoxemia in settings such as intubation or, once mechanical ventilation has been initiated, disruptions of positive end-expiratory pressure (PEEP). Intubation, suctioning, or other procedures for the gravida mandate an experienced operator attentive to these potential complications.

How do mother and baby avoid hypoxic consequences in light of this fragile oxygenation? Recall the components of arterial oxygen content (CaO_2) and oxygen delivery (Q_{O2}): arterial oxygen saturation, hemoglobin level, partial pressure of arterial oxygen, and cardiac output ($CaO_2 = 1.34 \times SaO_2\,[Hb] + (0.0031) \times PaO_2$; $Q_{O2} = Q_T \times CaO_2$). In the absence of stress or injury, pregnant women maintain normal oxygen delivery due largely to their compensatory increase in cardiac output, which peaks at almost 150% of non-pregnant values by the third trimester *(14, 23)*. This massive increase in cardiac output more than offsets the fall in oxygen content due to the physiologic anemia of pregnancy (Figure 22.2).

At the same time, the growing baby is shielded from the effects of hypoxemia by the nature of fetal hemoglobin, whose oxy-hemoglobin dissociation curve is shifted up and to the left, indicating that fetal hemoglobin is more avid for oxygen at every PaO_2 relative to adult hemoglobin. Fetal hemoglobin facilitates maximal uptake of oxygen from the placenta. The fetus maintains a circulating PO_2 level that would be

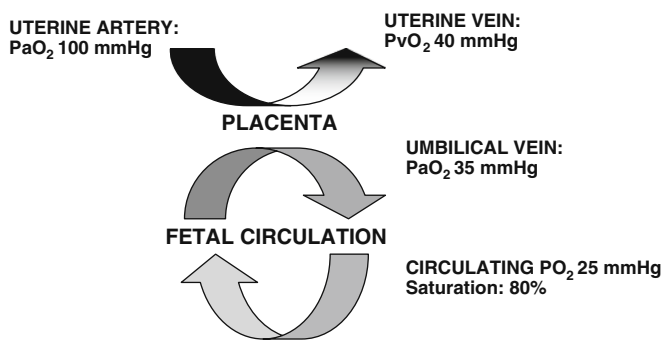


Figure 2 Normal maternal-fetal oxygen transfer. Despite the low oxygen tension (25 mmHg), the fetus remains 80% saturated. Adapted with permission from Lapinsky et al. Am J Resp Crit Care Med 1995 *(34)*

In normal pregnancy (maternal $SaO_2 = .95$, Hb = 11 g/dL, $PaO_2 = 90$ mmHg, $Q_T = 8.4$ L/min), oxygen content and delivery to the placenta are calculated as follows: Oxygen content = 1.34(.95)(11 g/dL) + 0.0031(90 mmHg) = 14.28 mL O_2/dL; Oxygen delivery = 14.28 mL O_2/dL * 8.4 L/min = 1,200 mL O_2/min

In the situation of maternal hypoxemia ($PaO_2 = 50$ mmHg, $SaO_2 = 0.80$), delivery to the placenta falls: Oxygen content = 1.34(.80)(11 g/dL) + 0.0031(50 mmHg) = 11.95 mL O_2/dL **(↓ 16%);** Oxygen delivery = 11.95 mL O_2/dL * 8.4 L/min = 1,120 mL O_2/min **(↓ 16%)**

Whereas if maternal cardiac output is reduced by 50% ($PaO_2 = 90$ mmHg but maternal Q_T = 4.2 L/min), delivery to the placenta is also halved: Oxygen content = 1.34(.95)(11 g/dL) + 0.0031(90 mmHg) = 14.28 mL O_2/dL **(unchanged);** Oxygen delivery = 14.28 mL O_2/dL * 4.2 L/min = 600 mL O_2/min **(↓ 50%)**

dangerously deoxygenated for an adult—25 mmHg—while remaining 80% saturated *(35)*. Further augmenting the properties of fetal hemoglobin, the fetus is aided by a relatively high hemoglobin concentration (15–16 g/dL) and a high cardiac output given the dual circulation through the patent ductus arteriosus *(35)*. Despite this astonishing ability to thrive in relatively hypoxic conditions, the fetus has little or no ability to defend against a drop in maternal cardiac output, the ultimate source for oxygen, as it has a very limited ability to shunt blood toward critical organs *(36, 37)*. Studies suggest that in the face of an acute disruption in uterine blood flow, a fetus can compensate for only 10 min before anoxic brain injury occurs *(38, 39)*. Figure 22.2 depicts the effect on oxygen delivery to the placenta when the fetus is challenged by maternal hypoxemia or maternal shock. As we will emphasize in the treatment recommendations for ALI/ARDS, careful attention to preservation of the maternal cardiac output is essential to ensure adequate oxygen delivery to the developing fetus, especially when the mother's oxygenation is impaired.

Differential Diagnosis

Variants of Pulmonary Edema

In all patients, one of the challenges of determining when a patient has ALI/ARDS is to distinguish "high-pressure" cardiogenic edema from "low-pressure" edema due to increased alveolar-capillary permeability. A diagnosis of ALI/ARDS is reserved for patients in whom airspace flooding is the result of exaggerated alveolocapillary permeability to both fluid and protein. In pregnancy, the distinction between high- and low-pressure pulmonary edema is even more problematic, and several disorders present variably, with features of both high and low pressure (Table 22.2).

Preeclampsia

Hemodynamic studies of women with preeclampsia have varied from reports of relative venoconstriction with low wedge pressure (P_{aop}; 4 mmHg) *(40)* to normal-to-high P_{aop} with normal cardiac index *(41, 42)*. Mabie reported that for a small subset of women presenting with preeclampsia and frank pulmonary edema, high P_{aop} (18 mmHg) and hyperdynamic cardiac function was the norm *(42)*. The expected fall in colloid oncotic pressure with pregnancy is exaggerated by preeclampsia, and coupled with an increase in hydrostatic pressure and pulmonary endothelial damage seen in preeclamptics, predisposes a woman toward excess extravascular fluid. This may explain why pulmonary edema may be seen so readily in preeclamptic patients with essentially normal hemodynamics, yet an expanded blood volume. Some patients with preeclampsia may manifest the full-blown syndrome of ALI/ARDS and may have persistent hypoxemia even after delivery, the definitive treatment for preeclampsia.

Tocolytic-Induced Pulmonary Edema

Tocolytic-induced pulmonary edema is another condition with features of both cardiogenic and increased-permeability edema. Despite widespread use of beta-agonists in the treatment of reactive airway disease, pulmonary edema is an uncommon consequence of therapy except in pregnant patients receiving beta-sympathomimetics for inhibition of preterm labor *(24)*. The incidence of this complication is difficult to assess, since the majority of studies are retrospective

Table 22.2 Differential diagnostic considerations for pregnant women with possible ALI.

Diagnosis	Diagnostic criteria	Therapeutic implications
Cardiogenic pulmonary edema	pCXR: Widened vascular pedicle width (>70 mm) Pra >8 cwp Echocardiographic abnormality	Diuresis Afterload reduction ± Inotrope therapy
Tocolytic-induced pulmonary edema	History of tocolytic use	Discontinue tocolytic therapy ± Diuresis
Pre-eclampsia with pulmonary edema	Appropriate clinical history and symptoms	Delivery May progress to ALI
Pulmonary embolism	DVT on Doppler ultrasonography Abnormal perfusion lung scan Filling defect on CT angiography	Anticoagulation ± vena caval interruption
Amniotic fluid embolism	Appropriate clinical history (active labor) ± left ventricular dysfunction ± DIC	May progress to ALI No specific therapy
Air embolism	Appropriate clinical history (portal for air entry)	May progress to ALI Cover & apply pressure to any exposed vessel Consider hyperbaric oxygen
Pneumocystis pneumonia	Stain of sputum or BAL fluid	Trimethoprim/sulfamethoxazole ± corticosteroids
Acute cryptogenic organizing pneumonia	Pathologic specimen (transbronchial or surgical lung biopsy)	Corticosteroids
Acute hypersensitivity pneumonitis	Appropriate clinical history (exposure)	Cessation of exposure ± Corticosteroids
Acute eosinophilic pneumonia	BAL fluid with >20% eosinophils	Corticosteroids
Diffuse alveolar hemorrhage	Appropriate comorbidity (vasculitis, connective tissue disease, or coagulopathy) Hemorrhagic BAL fluid Pathologic specimen if necessary	Treatment of underlying disease

and case-control design, but has been reported to vary between less than 1 to 10% of pregnant patients receiving tocolytic therapy *(43–45)*. While most reports implicate betamimetic drugs such as terbutaline or ritodrine, pulmonary edema has been reported with magnesium sulfate and calcium channel blockers used for tocolysis *(46, 47)*. Risk factors for the development of pulmonary edema include the use of multiple agents for tocolysis, intravenous fluid administration, multiple gestations, and the presence of maternal infection *(46)*. While tocolytic-induced pulmonary edema has been reported to blossom into ALI/ARDS *(24)*, in general the hypoxemia resolves quickly once the medication is withdrawn; progression to mechanical ventilation or maternal mortality is rare *(48, 49)*. Non-invasive positive pressure ventilation (NIPPV) has been successfully utilized in this condition *(50)*.

Cardiogenic Pulmonary Edema

Pulmonary edema in pregnancy may also arise as the manifestation of significant maternal cardiovascular disease. In a large retrospective review of their hospital's experience over 10 years, one group reported that cardiac disease was the cause for pulmonary edema in 25% of their observed cases *(51)*. Both valvular disease—mitral stenosis or regurgitation, and aortic stenosis or insufficiency—and left ventricular dysfunction may be previously diagnosed conditions or may be identified for the first time during pregnancy. Peripartum cardiomyopathy in particular may arise de novo late in pregnancy or in the early postpartum period, and may recur or worsen in a woman who undergoes subsequent pregnancies *(52)*. The mortality for women with peripartum cardiomyopathy may be as high as 15% despite recommended medical therapy *(53, 54)*. Evaluation with echocardiogram to exclude unrecognized structural heart disease and to quantify left ventricular function is thus recommended whenever a cardiogenic etiology of pulmonary edema is suspected or pulmonary edema fails to resolve in an expected time frame.

Ideally, the chest radiograph (CXR) should help to distinguish between cardiogenic pulmonary edema caused by increased hydrostatic pressure and non-cardiogenic edema. The hallmarks of cardiogenic edema include increased cardiac size, enlarged vascular pedicle width, a central and homogeneous distribution of edema, pleural effusions, and interstitial changes such as peribronchial cuffing or increased septal lines *(55)*. The CXR of increased permeability edema, in contrast, was described as having a normal vascular pedicle width and cardiac size, patchy or peripheral distribution of edema fluid, prominent air bronchograms, and no interstitial changes *(55)*. Such criteria are only modestly predictive of increased permeability edema in the best of circumstances *(56)*, and in pregnancy—during which the circulating volume is expanded, the thoracic cage diameter increases, and the lungs are prone to microatelectasis due to the expanding uterus—the CXR is often inadequate to determine accurately high- versus low-pressure edema. One study in non-pregnant critically ill patients found that on a portable frontal chest radiograph, a vascular pedicle width greater than 70 mm and a cardiothoracic ratio greater than 0.55 were 80% accurate in predicting that a patient's P_{aop} was greater than 18 mmHg *(57)*.

Computed tomography (CT) imaging of patients with ALI/ARDS reveals astonishing heterogeneity of lung involvement even when the airspaces on CXR appear homogeneously obscured. Often consolidation is somewhat gravity-dependent when viewed by CT, and serial CT following the application of PEEP demonstrates airspace recruitment and diminished atelectasis *(58, 59)*. Chest CTs may be used in pregnancy when an alternative diagnosis is in question. Fetal radiation exposure in multidetector CT of the chest ranges between 0.02 and 0.03 rad, with an acceptable exposure throughout the duration of pregnancy being 5 rads or less.

Embolic Disease: thrombus, air, fat, and amniotic fluid. Pulmonary thromboembolism (PE) is a leading cause of maternal death in the United States and United Kingdom *(60–62)*. While the incidence of PE appears to be decreasing over the past 10 years, a large US-based population study recently reported a rate of 47.9 per 100,000 woman-years *(63)*, and women who are post-partum and particularly post-cesarean delivery are at the highest risk *(62)*. The classic signs and symptoms of PE—tachycardia, tachypnea, dyspnea, pleuritic chest pain, and a sense of anxiety or apprehension—are neither specific to PE nor universally present, making PE difficult to distinguish from almost any cause of respiratory embarrassment *(64, 65)*. Classically, PE may be differentiated from ALI in that its attendant hypoxemia is more readily corrected with oxygen, because the

hypoxemia of PE is primarily due to ventilation-perfusion mismatch rather than shunt physiology. In addition, the chest radiograph of PE rarely demonstrates such dramatic 4-quadrant airspace opacities as are so characteristic of ALI/ARDS. Nonetheless, early ALI may have an underwhelming CXR and modest oxygen requirement, and additional tests—including venous Doppler to exclude deep venous occlusion, perfusion lung scan, or CT angiography—may be necessary to rule out PE. In addition, signs that are often ascribed to PE, such as right heart strain evident on electrocardiogram or echocardiogram, are frequently present in ALI, due to the severe hypoxemia causing global hypoxic pulmonary vasoconstriction. In general, we advocate a *consideration* of thromboembolic disease for all pregnant patients who reach an intensive care unit, if only to heighten the clinician's focus on the patient's clinical history and exam, and to give careful consideration to thrombotic prophylaxis in appropriate patients. PE is reviewed more thoroughly in Chapter 18.

While less frequent than PE, amniotic fluid embolism (AFE) and air embolism are additional risks posed to the pregnant patient and may also present with profound respiratory distress, hypoxemia, and even shock. In one epidemiologic study from the United States, AFE was reported as a cause of maternal death with almost the same frequency as thromboembolic pulmonary embolism *(60)*. This may reflect the grave outcome historically reported in cases of AFE, wherein only 15% of mothers survived with an intact neurological status, and 61% of mothers and 21% of fetuses died *(66)*. The national registry of cases of amniotic fluid embolism, from which the preceding data was reported, has been criticized for potentially over-representing the most severe cases of AFE and failing to emphasize that milder cases may go unrecognized. Nonetheless, a separate population-based study of AFE found an incidence of one case per 21,000 deliveries and reported a sobering maternal mortality rate of 26% *(67)*. Both air embolism and AFE occur most commonly during labor and delivery—vaginal or cesarean—although air embolism may occur during sexual activity including oral sex, trauma, uterine rupture, or recreational diving *(68, 69)*. Echocardiographic studies suggest that air embolism is extremely common during cesarean delivery, with air bubbles being documented in up to 50%, although it is likely that the vast majority of these Doppler-documented bubbles result in no clinical symptoms *(68, 70, 71)*.

When embolized, both air and amniotic fluid may precipitate ALI/ARDS. Anecdotal wisdom maintains that the course of ARDS caused by these entities may resolve more rapidly than for ARDS triggered by the more common causes (e.g., sepsis or pneumonia); however, each entity may result in maternal fatality. Amniotic fluid embolism has been described to have two distinct clinical phases, with an initial period characterized by right heart strain, followed by overt pulmonary edema. This second phase may or may not be associated with left ventricular dysfunction, making the diagnosis of high- versus low-pressure pulmonary edema problematic *(72)*. In addition, AFE may be complicated by a consumptive coagulopathy (DIC) in up to 40% of cases *(66)*. Importantly, once ALI/ARDS develops in patients with either air or amniotic fluid embolism, treatment recommendations are largely unchanged from those to treat any pregnant patient with ALI (see below). In cases of air embolism that occur on the operating table while the uterus is exteriorized, anesthesiologists advocate immediate flooding of any exposed venous beds with saline and positioning the open wound below the heart *(68)*. For any embolism, positioning of the patient in a left lateral recumbent position may decrease the risk of paradoxical embolization and preserve venous return despite the enlarged uterus *(68)*. Hemodynamic and

neurologic consequences of air embolism may resolve more quickly with the administration of 100% oxygen or, for the fastest response, with hyperbaric oxygen to decrease the size of air bubbles, improve cerebral oxygenation, and decrease cerebral edema *(73)*.

Rare in Pregnancy: Mimics of ARDS

As in the general population, pregnant patients are at risk for conditions that may mimic ALI/ARDS, yet respond to different therapies (Table 22.2). Included among these are infections, idiopathic pneumonia syndromes, and alveolar hemorrhage. Pneumocystis pneumonia (PCP) caused by the fungus *Pneumocystis jirovecii* is the infection classically mistaken for ARDS, in that it causes a diffuse lung lesion and often severe hypoxemia. PCP is seen most commonly in patients with poorly-controlled HIV infection, although it is occasionally seen in solid organ transplant patients, especially those who have been receiving moderate to high doses of corticosteroids *(74)*. The diagnosis of PCP is commonly made by documenting the organism by silver staining or direct fluorescent antibody stain either in sputum or bronchoalveolar lavage (BAL) fluid. The infection typically responds well to therapy with trimethoprim/sulfamethoxazole plus corticosteroids for patients who are hypoxemic *(74)*.

Idiopathic pneumonia syndromes, including hypersensitivity pneumonitis (HP), acute eosinophilic pneumonia (AEP), or cryptogenic organizing pneumonia (COP) may also be mistaken for ALI clinically and radiographically. The diagnosis of HP often hinges on an appropriate clinical history, with symptoms occurring following an exposure to classic antigens such as birds, hay, or other organic agent *(75)*. Rarely, the agent driving hypersensitivity cannot be identified. Nonetheless, the prognosis for HP tends to be excellent with cessation of exposure and often the addition of corticosteroids *(76)*. The diagnosis is best made by surgical lung biopsy demonstrating non-necrotizing granulomata with possible bronchiolitis or interstitial inflammation, although a lymphocytic BAL fluid is suggestive in the context of an appropriate clinical history *(77)*.

Acute eosinophilic pneumonia is a rare disease which tends to afflict young, previously healthy individuals who present with acute fever, cough, dyspnea, myalgias, and chest pain *(75, 78)*. Hypoxemia is the rule, although unlike ALI, eosinophilia is present in BAL or pleural fluid. Peripheral eosinophilia, however, is rare. Acute eosinophilic pneumonia has been described in pregnancy, and in two cases appeared to be an allergic complication of fertility treatment with intramuscular progesterone *(79, 80)*. The prognosis for AEP, whether treated supportively or with corticosteroids, is excellent *(78)*.

Cryptogenic organizing pneumonia, which classically presents in a subacute, indolent fashion, occasionally manifests as sudden, explosive hypoxemia with dramatic pulmonary consolidation *(81)*. The diagnosis may be possible by transbronchial biopsy, although most cases of acute COP described in the literature relied upon surgical lung biopsy. The acute form is generally treated similarly to subacute COP with moderate to large doses of corticosteroids tapered over a course of weeks to months *(81)*.

Finally, diffuse alveolar hemorrhage (DAH), in which blood fills the airspaces, may present indistinguishably from ALI/ARDS. The syndrome results from inflammation and damage of the arterioles, capillaries, and venules of the pulmonary vasculature, often in the setting of a pulmonary vasculitis syndrome such as Wegener's granulomatosis, antiphospholipid syndrome, or antibasement membrane disease *(82)*. Coagulopathy may also precipitate the syndrome. Hemoptysis is

absent in up to a third of patients with DAH, thus DAH should be considered even in patients who do not cough up blood *(82)*. Whenever hemorrhage is suspected, early bronchoscopy should be performed to localize hemorrhage—in the event that massive hemorrhage may require an interventional vascular or surgical procedure—and to exclude airway trauma. In addition, early consideration should be given to biopsy if the underlying diagnosis is unknown, because many forms of vasculitis, while life-threatening if untreated, may respond rapidly to appropriate therapy *(82)*.

Management

Despite intense investigation for over 30 years, ALI research has yet to identify any specific pharmacologic therapy which benefits patients. Management thus appropriately focuses upon use of careful ventilator and volume strategies, as will be discussed below (Table 22.3). In addition, the gravid patient with ALI requires extra attention to oxygen delivery, body position, fetal monitoring, and collaboration with experienced maternal-fetal medicine specialists to determine the optimal time and route of delivery.

Monitoring

The admission of a gravida to the ICU mandates consultation with specialists from maternal-fetal medicine. Specific monitoring of the fetus is advisable once the pregnancy progresses to the point of potential fetal viability, although fetal heart rate (FHR) variability is a non-specific measure of fetal well-being and becomes

Table 22.3 Treatment recommendations for a gravida with ALI/ARDS.

Maintain adequate oxygen delivery
- Titrate to a **maternal PaO_2 of 70–90 mm Hg** or SaO_2 of 90–95%
- Use the least PEEP necessary to allow reduction in FiO_2 to below 0.6 expeditiously
- **Ensure adequate maternal cardiac output to provide adequate fetal oxygen delivery**; this may be assessed by documenting $ScvO_2$ >70%
- **Maintain maternal hemoglobin ≥10 g/dL**
- Consider **epidural anesthesia** in the event of contractions, uterine pain, or active labor

Maintain adequate perfusion
- Diurese while seeking the lowest filling pressures (P_{ra} 4 cwp) which allows adequate perfusion ($ScvO_2$ >70%)
- A central venous catheter is preferable to a PAC

Ventilator strategy
- Use a volume-controlled strategy using an initial V_T ≤6 mL/kg IBW
- Maintain plateau pressure ≤30 cwp through manipulating V_T and PEEP
- If hypercapnia results, it is tolerable up to a $PaCO_2$ of **60 mm Hg**

Ancillary considerations
- Position the patient in a **left lateral recumbent position**
- **Monitor the fetus** as appropriate by maternal-fetal medicine
- **Establish with maternal-fetal medicine a plan for delivery**, planned or emergent
- Sedation and analgesia to allow low-V_T ventilation is necessary, as in non-pregnant patients
- Paralysis is infrequently necessary once adequate sedation is ensured
- Liberation from mechanical ventilation should proceed via spontaneous breathing trials once the patient is awake, protecting her airway, and with FiO_2 ≤0.4 and PEEP ≤8 cm H_2O.

Recommendations in **bold** are specific to pregnancy.

reliable only at approximately 28 weeks *(83)*. While FHR is a sensitive test, and a reassuring tracing is highly predictive of a well-oxygenated fetus, many patterns are difficult to interpret. The most ominous FHR patterns may only be associated with a specificity for neonatal depression of 50–65% *(84)*. Neither fetal acidosis nor hypoxia is accurately predicted by FHR, so a non-reassuring pattern may be seen in the absence of fetal hypoxia *(83, 85)*. Internal FHR monitoring—which involves placement of a scalp electrode—is performed only upon women in labor whose membranes have ruptured *(85)*. Ancillary methods to assess fetal well-being, including non-stress testing (NST), ultrasound, biophysical profile, and umbilical artery Doppler velocimetry, may also be useful as determined by the obstetric team *(85)*. Collaboration between the intensive care and maternal-fetal services should include direct communication regarding monitoring, provision for planned or emergent birth or cesarean delivery, the presence of an anesthesiologist caring for pregnant patients, and the presence of neonatal specialists in the event of a birth. The obstetric team also provides vital communication to the patient and family members regarding any pregnancy complicated by illness.

Gravidas are especially sensitive to body position as they progress into the second trimester and beyond. Critical care of such patients should include attempts to avoid the standard supine position with head elevation, as this allows the enlarged uterus to press on and even compress the inferior vena cava, compromising preload. A left lateral recumbent or decubitus position is the preferred position and is especially important for hemodynamically unstable patients *(85)*. Such positioning may be accomplished with a wedge, as is used in the operating room, or with careful positioning of pillows. To preserve skin integrity, patients may also be positioned in a right lateral recumbent or decubitus position as their blood pressure and FHR monitoring permit.

Ventilator Strategy

The profound hypoxemia of ALI/ARDS almost invariably requires rapid intubation and mechanical ventilation in order to provide a high fraction of inspired oxygen, decrease oxygen consumption by assuming the work of breathing, and provide PEEP. Ventilator strategy for ARDS has been debated since the condition's description, but during the late 1990s a national network of centers invested in ALI research undertook a large randomized trial to actually compare different strategies and the result has shaped our management. The impetus for such a trial stemmed from the physiologic belief that the flooded lung of ALI in some ways represents a "baby lung," with a vastly reduced number of open or even partially open alveoli capable of participating in gas exchange. Following this reasoning, if a traditional tidal volume (V_T) was delivered to only the fraction of airspaces which were open to ventilation, these alveoli might sustain overdistension and become injured themselves. Prior to the clinical trial, a contrary and prevalent belief was instead that large tidal volumes (on the order of 12–15 mL/kg IBW) were necessary to recruit alveoli and improve oxygenation *(86)*.

A study from Brazil demonstrated that a ventilator strategy that sought to limit overdistension by a strict application of smaller tidal volumes and limited driving pressure dramatically decreased mortality in patients with ARDS, although the trial was criticized for being small, single-center, and for employing a tedious ventilator algorithm *(87)*. Subsequently, the US ARDS network group randomized 861 patients to initial tidal volumes of 6 versus 12 mL per kilogram of ideal

body weight (IBW), and found that the lower V_T group accrued a significant mortality benefit; 31% of the 6 mL/ kg group died, compared to 39% of the traditional group *(88)*. In addition to limiting V_T, the trial algorithm mandated that patients in the low V_T group have their plateau pressures maintained at or below 30 cm of water (cwp), whereas the traditional V_T group had their plateau pressure maintained below 50 cwp *(88)*. Plateau pressures were manipulated predominantly by lowering the set V_T. Of note, for all patients the initial V_T was determined by the patient's ideal, rather than actual, body weight. IBW is calculated based on the patient's height: 45.5 + 0.91 × (height in centimeters—152.4) for females. This point bears mention given the growing rate of obesity in the United States, as failure to use IBW would result in excessive tidal volumes for an overweight patient. Furthermore, when treating pregnant patients, there is no evidence to suggest that V_T should be adjusted due to the presence of the fetus. We advocate calculating the patient's IBW, setting the initial V_T at 6 mL/kg of this weight, and adjusting V_T accordingly to maintain the plateau pressure below 30 cwp. It is important to mention however that minute ventilation does increase significantly in normal pregnancy and may be 50% higher at term than the preconception V_T. This increase in minute ventilation is secondary to an increase in V_T with minimal contribution from the respiratory rate. The higher minute ventilation is thought to occur in part in response to increased metabolic demands and oxygen consumption of the fetus and the placenta and to effects of progesterone. For that reason, if the decision is to reduce V_T to 6 ml/kg in a pregnant patient, a compensatory increase in respiratory rate should be considered as long as intrinsic positive end expiratory pressure permits.

A necessary corollary of low V_T ventilation is that a portion of patients will develop hypercapnia. Low V_T ventilation institutes a relatively rapid, shallow breathing pattern, although there is little to be gained by driving the respiratory rate past 36 breaths per minute for this tends to leave little time for exhalation and may contribute to progressive dynamic hyperinflation (auto-PEEP). In non-pregnant patients with ALI, the strategy of permissive hypercapnia has been shown to be safe, even with PCO_2 values averaging 70 mmHg and as high as 140 mmHg *(89)*. One seminal trial allowed an average pH of 7.23 and did not administer sodium bicarbonate, even when the pH was as low as 7.02 *(89)*. Bicarbonate therapy is discouraged as a treatment for respiratory acidosis, iatrogenic or otherwise, as it is quickly converted to carbon dioxide and thus exerts an additional respiratory load on the patient. Furthermore, it is unclear whether bicarbonate adequately crosses the placenta to truly buffer a rising PCO_2 *(49)*. Among pregnant patients, the effect of hypercapnia remains controversial and poorly studied. In animal studies, maternal hypercarbia actually increased blood flow through the umbilical artery, although in one study uteroplacental blood flow initially rose until the maternal PCO_2 rose above 60 mmHg, from whence it began to fall *(90, 91)*. However, CO2 transfer across the placenta is dependent on a difference of 10 mmHg between the maternal and the umbilical veins which remains relatively constant across a wide range of CO2 tensions *(92, 93)*. Therefore, maternal hypercapnia may be quickly translated into fetal hypercapnia resulting in acidosis and a right shift of the oxyhemoglobin dissociation curve limiting the affinity to oxygen.

In addition to the effects of hypercapnia on the fetus, hypercapnia in the first hours of life may indicate an increased risk for intracranial hemorrhage and death *(94)*. Animal models also suggest that acidosis including respiratory acidosis may lead to retinopathy of the newborn *(95, 96)*.

Hypocapnia is to be avoided, primarily because it contributes to uterine artery constriction and as the attendant respiratory alkalosis causes a leftward shift of the maternal oxy-hemoglobin curve decreasing the release of oxygen in hypoxic tissue beds *(97–99)*. While maternal pH and PCO_2 are transmitted rapidly to the fetus, animals tolerate respiratory acidosis better than metabolic acidosis; despite 90 min of significant hypercapnia, animals were unchanged at delivery *(90)*. In pregnant humans, data are relatively scarce. One study induced experimental hypercapnia—average pH 7.18 and PCO_2 58 mmHg—in healthy women at term receiving anesthesia for labor, and found that compared to eucapneic controls, the babies of hypercapneic women had higher one-minute Apgar scores, higher umbilical vein PO_2, and faster onset of sustained respiration *(100)*. Case reports describe the successful application of permissive hypercapnia for ventilated pregnant women *(49, 101)*. Given the proven mortality benefit for the mother but the possible deleterious effects on the fetus, we thus advocate the practice of limited permissive hypercapnia (with a suggested PaCO2 <60 mmHg) when necessary to deliver low V_T ventilation for pregnant patients.

Non-invasive Positive Pressure Ventilation

Over the past 10 years, greater physician familiarity with non-invasive positive pressure ventilation (NIPPV) delivered by nasal or face mask has led to an increasingly broad application of this modality for various types of respiratory compromise. The best established indications for NIPPV are hypercapneic ventilatory failure (classically due to chronic obstructive pulmonary disease or asthma) or respiratory failure due to congestive heart failure *(102–104)*. Non-invasive ventilation is reserved for patients with a competent mental status agreeable to application of the tight-fitting mask, preserved ability to protect her airway, and a facial structure amenable to the mask. In patients with hypoxemic respiratory failure, including some with ALI, NIPPV effectively improved oxygenation *(105)*, and the avoidance of an endotracheal tube may result in a lower incidence of nosocomial pneumonia and infection *(105, 106)*. When patients truly have ARDS, however, NIPPV has a high rate of failure *(107, 108)*, which one might predict due to the limited pressures that can be delivered by a mask without causing skin necrosis.

Immunocompromised patients constitute one group who may especially benefit from NIPPV and avoidance of an endotracheal tube. Solid organ recipients and patients with HIV, hematologic malignancy, or receiving immunosuppressive medication all demonstrated reduced ICU mortality and reduced need for intubation when compared with conventional high-flow oxygen therapy *(109, 110)*. Clearly the early institution of NIPPV in an effort to avoid intubation is helpful to these patients. Nonetheless, once ARDS develops, invasive mechanical ventilation is often the only way to adequately oxygenate such patients.

In pregnancy, the largest reported use of NIPPV has been in non-emergent situations such as is the case in patients with obstructive sleep apnea *(104)* and chronic ventilatory failure due to neuromuscular disease *(106)*. Only case reports have been published on the use of NIPPV in emergency situations such as in pregnant patients with congestive heart failure *(111–113)*. Pregnant women are at an increased risk for aspiration secondary to delayed gastric emptying, a lower esophageal sphincter tone, and gastric displacement secondary to uterine enlargement. While there is a theoretical concern that NIPPV increases a tendency toward aspiration due to aerophagia, and this might be exacerbated in pregnancy, we have not found aspiration to complicate NIPPV in mentally competent adults, pregnant

or otherwise. In addition, there have been no studies done so far to evaluate the effect of positive pressure ventilation on uterine perfusion. We advocate a brief trial of NIPPV for patients with ALI who have no contraindication to mask ventilation and are hemodynamically stable. Both maternal and fetal monitoring should be performed in those situations and interventions decided upon accordingly. If oxygenation and respiratory effort do not improve dramatically within 30 min of applying NIPPV, or if fetal monitoring shows any evidence of acute distress, we favor intubation and mechanical ventilation.

Positive End-Expiratory Pressure (PEEP)

Having established that a volume-controlled strategy with initial V_T of 6 mL/kg IBW and maintenance of the plateau pressure below 30 cwp represents the standard of care for ALI/ARDS, the ARDS network was less successful in identifying an ideal level of PEEP. PEEP is viewed as essential to the ventilator management of ALI because it increases FRC and the number of alveoli able to participate in gas exchange. This may be especially important for pregnant patients, as pregnancy inflicts a 20% decrease in FRC *(34)* in health even before ALI further reduces it. The ARDS network randomized patients to strategies of either high PEEP (mean PEEP 13.2 cwp) or low PEEP (mean PEEP 8.3 cwp) *(114)*. No significant difference was noted between groups with respect to mortality, ventilator-free days, ICU length of stay, or freedom from organ failure *(114)*. Importantly, the high-PEEP group did not suffer more barotrauma—pneumothorax or air leaks—than the traditional PEEP group *(114)*. No study has been conducted on the effect of PEEP on pregnant patients, although it has been used successfully both via NIPPV and traditional endotracheal intubation and ventilation *(87, 112)*. While it is interesting to contemplate whether pregnant patients with ALI might benefit from additional PEEP relative to the general population, in an attempt to offset the pregnancy-related fall in FRC, there are no data to support this practice at this time. In addition, while PEEP is well-recognized to potentially diminish venous return and thus adversely affect cardiac output *(49)*, we find this is generally an issue only when the patient's intravascular volume is critically low. We advocate using enough PEEP to allow a reduction in FiO_2 below toxic levels (0.6) whilst maintaining maternal PaO_2 above 60 mmHg.

Disruptions in PEEP, even for very brief periods, are often associated with rapid alveolar derecruitment and acute desaturation. Routine ICU practices which briefly separate the patient from the ventilator such as suctioning or transport, during which a patient is often bag-ventilated, may incur a dramatic fall in oxygen saturation which may take hours of PEEP to reverse. Thus, once diagnostic samples have been obtained, we recommend that such interruptions be kept to a minimum and that bag ventilation for patients with ALI always be performed with a PEEP valve. In general, we practice rapid increases in PEEP when attempting to establish adequate saturation, and slow, stepwise reductions in PEEP once oxygenation has improved.

Oxygen Therapy

When setting the FiO_2 for the pregnant patient with ALI, we are again left without evidence to guide therapy. In non-pregnant patients, the ARDS network trials have demonstrated the safety of following relatively stringent oxygenation guidelines. The level of PEEP and FiO_2 were manipulated to attain only an arterial saturation

of 88% by pulse oximetry or a PaO_2 of 55 mmHg *(88, 114)*. Oxygen therapy has been administered in this conservative fashion due to the fact that oxygen itself can induce lung injury and that there is no evidence to suggest that a saturation of 95% is superior to one of 88%. Animal studies point to lung damage inflicted by reactive oxygen species *(115)*, while studies in non-survivors of ARDS have correlated pathologic severity of injury with the duration of oxygen therapy for patients receiving as little as 0.5 FiO_2 *(13)*. In normal subjects, physiologic studies have demonstrated a reduction in diffusion capacity following the inhalation of FiO_2 0.6 or greater for three or more days *(116)*. Controversy remains as to whether a true toxic threshold for oxygen exists, and it may be that injured lungs respond differently to enriched oxygen than do normal lungs.

Management of maternal oxygenation is extremely complex, since almost all data regarding fetal oxygenation has been derived from animal studies, primarily on sheep. While the ovine model has many advantages, some important differences between humans and sheep leave unanswered questions about the safety of various levels of maternal hypoxemia. In sheep, when maternal circulating PaO_2 is reduced by 50%, the fetus demonstrates hemodynamic changes associated with critical hypoxemia and quickly develops metabolic acidosis *(117)*. On the other hand, the concurrent exchange of oxygen across the placenta limits the maximal attainable PO_2 in the fetus. As maternal PaO_2 increases, the difference between maternal and fetal oxygen tension also increases. In sheep, it was necessary to raise the maternal PaO_2 to over 2,000 mmHg via a hyperbaric chamber in order to raise fetal PaO_2 over 80 mmHg *(118)*. Given this relationship, there is little reason to advocate a supranormal PaO_2 for pregnant women with ARDS. A reasonable goal for maternal oxygenation is to maintain the PaO_2 between 70 and 90 mmHg. Because maternal oxygen consumption is greatly increased, especially during active labor when it essentially doubles, the mother may require high FiO_2 and/or PEEP in order to maintain 90% saturation. Epidural anesthesia is shown to decrease both the increment in minute ventilation and oxygen consumption associated with labor and therefore may improve maternal oxygenation. One case study correlated decrements in the patient's mixed venous oxygen saturation with her contractions, and demonstrated that successful epidural anesthesia obliterated these dips and treated her labor pains *(119)*.

Circulatory Management

While the pulmonary edema of ALI/ARDS is a result of increased alveolar-capillary permeability rather than excess hydrostatic pressure, traditional strategies to minimize edema formation are valid goals for patients with ALI. Past animal and human studies suggested that lowering the left atrial or P_{aop} in ALI resulted in less edema formation and improved outcomes such as extravascular lung water, days on the ventilator, and days in the ICU *(120–122)*. A retrospective study in patients with ARDS and a pulmonary artery catheter (PAC) found that patients who had an early reduction in P_{aop} had dramatically improved survival compared to patients whose P_{aop} was not lowered *(123)*. Recently, the US ARDS network completed a comparison of two volume strategies in patients with ALI. Once patients were hemodynamically stable and not requiring vasoactive medications, the volume conservative strategy aimed to reduce central venous pressure (CVP) to a goal of 4 cwp or P_{aop} to a goal of 8 cwp by the use of diuretics *(124)*. In the liberal volume group, the goals were 10–14 and 14–18 cwp for CVP and P_{aop}, respectively *(124)*. While mortality did not differ significantly between groups, patients in the volume conservative group spent an

average of two fewer days intubated and in the ICU, and did not manifest any excess shock or renal insufficiency *(124)*. Pregnant patients were again excluded from this trial, but we advocate applying its findings to gravidas, and seeking the lowest filling pressures which maintain adequate perfusion for mother and fetus. Given pregnant womens' increased renal blood flow, they may respond vigorously to very low doses of diuretic; doses should be titrated accordingly.

The second aim of this recent ARDS network trial compared the use of central venous catheters with PAC to guide fluid management, and found no advantage of PAC *(125)*. Complications were actually increased in the PAC group, leading to a recommendation that PAC not be routinely used in the management of ALI/ARDS *(125)*. This is the latest in a series of trials that have failed to demonstrate a benefit from the use of PAC *(126–130)*. Several studies found an excess of complications in groups receiving PAC *(125–128)*, which leads us to recommend against the use of PAC as well. Normal values for the central pressures (CVP and P_{aop}) of pregnant women near term have been reported and do not vary significantly from non-pregnant values *(23)*, reinforcing the principle that a central venous catheter can be helpful to guide therapy during pregnancy.

While we emphasize the importance of taking steps to minimize edemagenesis, we also must stress the importance of maintaining an adequate maternal cardiac output. Oxygen delivery, as we have previously stressed, is directly proportional to the cardiac output and thus one pivotal factor in treating pregnant patients with ALI/ARDS is careful attention to cardiac output. The central venous saturation ($ScvO_2$), which has been shown to correlate well with the mixed venous oxygen saturation (SvO_2) *(131, 132)*, can be helpful in determining the adequacy of cardiac output, as $ScvO_2$ tends to fall below 70% only when oxygen consumption significantly exceeds delivery. We encourage use of the $ScvO_2$ in pregnant patients with ALI as a way to optimize diuresis—and thus speed edema resolution—without sacrificing cardiac output.

Another consideration in treating the hypoxemia of a pregnant patient is to determine whether the patient will benefit from blood transfusion. In contrast to healthy non-anemic adults, in whom the augmentation of hemoglobin would have little effect on oxygenation, many pregnant women are anemic due their expanded circulating volume *(14)*. Because oxygen content (and thus oxygen delivery) is determined principally by the hemoglobin concentration and the arterial oxygen saturation, correcting anemia to a hemoglobin value greater than 10 g/dL can significantly impact maternal and fetal oxygen delivery. Whether this increment in oxygen carrying capacity outweighs the harmful effects of transfusion seen in unselected critically ill patients *(133)* is unknown.

Occasionally, vasoactive medications are necessary to maintain adequate perfusion in patients with ARDS. This is especially true for patients with septic shock. Vasoactive medications have not been well studied in pregnancy. All vasoconstrictive medications, especially those with alpha-adrenergic effects, are potentially dangerous to the fetus as they may cause uterine artery constriction *(35, 49)*. Vasoactive drugs are discussed in more detail in Chapter 21, "Critical Illness in Pregnancy." Whenever possible, it is advisable to avoid such medications. If they must be used, it is advisable to increase the intensity of fetal monitoring in conjunction with maternal-fetal specialists.

Experimental Therapy

As previously mentioned, no pharmacologic therapy has yet been shown to improve outcomes or mortality in ARDS. Among the many agents that have

been tested in ALI/ARDS, ketoconazole *(134)*, recombinant surfactant *(135, 136)*, prostaglandin E *(137)*, inhaled nitric oxide (iNO) *(138–141)*, and corticosteroids *(142–144)* have each failed to demonstrate an improved outcome. Inhaled nitric oxide and surfactant have improved oxygenation in the short term, but still failed to change the course of the disease *(136, 140, 145)*. We do not advocate routine use of any of these therapies in the treatment of ALI in pregnancy. Inhaled nitric oxide may have an experimental role in treating severe refractory hypoxemia and its use has been described in several published case reports of pregnant women *(146–150)*, although it has not been extensively investigated in pregnancy.

Prone positioning is another salvage therapy in ALI, which may improve oxygenation but has not demonstrated a sustained mortality benefit *(151, 152)*. In pregnant patients past the first trimester, a prone position is fraught with difficulty and it may impair adequate fetal monitoring. Left lateral recumbent position is the preferred position for such patients.

A number of experimental ventilator strategies, particularly high frequency oscillatory ventilation (HFOV) *(153)*, inverse ratio ventilation (IRV) *(154)*, and partial liquid ventilation (PLV) *(155)*, have received attention for their novelty and potential application in refractory ARDS, although none has been proven superior to the conventional strategy of low V_T, volume-controlled ventilation and none has been well studied in pregnant patients. Both IRV and HFOV may each may produce deleterious consequences—such as auto-PEEP or refractory hypercapnia—even when employed by experienced operators. We do not recommend routine use of these experimental therapies in pregnancy. Finally, extracorporeal gas exchange aimed at oxygenation or carbon dioxide removal (ECMO or $ECCO_2R$) has been tested in ARDS and not only failed to increase survival but was associated with high mortality and excess bleeding *(156, 157)*. At least one case report describes the application of ECMO/ $ECCO_2R$ in a pregnant patient with a good neonatal and maternal outcome *(158)*, but this can only be considered salvage therapy in a patient for whom conventional therapy is failing.

Timing of Delivery

Oxygen consumption is increased throughout pregnancy, and may double or even triple with the onset of active labor due to contractions and pain *(14, 34)*. For the pregnant patient with ALI, delivery may improve oxygenation, for the fetus receives a high blood flow and the fetoplacental unit increases maternal oxygen consumption. In addition, the physical removal of a near-term fetus should increase maternal FRC and allow more functional gas-exchanging units; lung volumes are estimated to return halfway to normal within the first 72 h following delivery *(14, 34)*. It is not clear how quickly maternal colloid oncotic pressure will normalize, but its resolution should also minimize edemagenesis. Case reports describe dramatic improvement following delivery *(5, 159)*, although certainly some women have succumbed to ARDS despite delivery *(6, 8)*. Cesarean delivery is more common in this situation, but mechanically ventilated women have successfully delivered vaginally *(159)*. The main arguments against delivery are the possibility of fetal immaturity and the fact that even with appropriate anesthesia, labor or cesarean will temporarily increase oxygen consumption. In one retrospective review of 10 patients with respiratory distress, delivery resulted in significant reduction in FiO_2 within 24 h, yet the duration of mechanical ventilation following delivery varied widely *(160)*. Furthermore, maternal mortality in that case series remained high at 33% *(160)*.

The decision to deliver cannot be codified by any clinical rule. Rather, a plan to deliver must be made by careful collaboration between intensive care, maternal-fetal, and perinatal services. In general, a stronger case can be made for delivery as the fetus approaches term, but this decision always necessitates multidisciplinary participation.

Outcomes

While the mortality amongst patients with ALI enrolled in large clinical trials such as the ARDS network studies continue to fall to as low as 26% *(124)*, epidemiological studies that include a broader patient population still report an in-hospital mortality of approximately 40% *(4)*. Information regarding the total number of pregnant patients with ALI/ARDS is lacking, which complicates accurate mortality estimation, but in several case series from individual institutions, maternal mortality ranged from 14 to 44% *(5–7, 160, 161)*. Perinatal mortality ranged from 11 to 40% *(5, 6, 8, 161)*. While respiratory failure was considered the likely cause of death in most early series of ARDS patients *(162)*, multisystem organ failure (MSOF) and sepsis seem to account for at least as many deaths as respiratory failure in more recent studies *(163, 164)*.

Increasingly we are recognizing that despite an improved survival for patients with ALI/ARDS, long-term sequelae are prevalent. Surprisingly, lung function returns nearly to normal within 6–12 months in the majority of survivors *(165)*. Diffusion capacity (D_LCO) may be the slowest index of pulmonary function to resolve, and in one study of survivors, D_LCO remained only 72% of predicted at 12 months. The greatest decrement was seen in patients' functional status. At 1 year, ALI survivors' 6-min walk distance remained significantly reduced, and patients attributed their functional decline to musculoskeletal problems as much as to dyspnea *(166)*. Interestingly, the strongest predictor of distance walked was the absence of corticosteroid therapy when ill with ALI, suggesting that corticosteroids may play a key role in these patients' functional limitation. In addition to neuromuscular deficits, survivors of ALI/ARDS also report a diminished health-related quality of life and higher rates of depression and post-traumatic stress disorder than other survivors of critical illness *(167–170)*. No information is available regarding the prevalence of these disorders following ALI in pregnancy. Our practice is to attempt to prepare patients and their families for a long recovery process through frank discussion and periodic follow-up in the pulmonary clinic during the first year. While many survivors—up to 70%—return to work within 6–12 months *(168)*, new mothers will need substantial support to care for themselves and their babies, especially during the critical early months following ALI.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, and Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319–23.
2. Bernard GR, Artigas AK, Brigham L, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, and Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818–24.

3. Long W, Zucker J, and Kraybill E. Symposium on synthetic surfactant. II: perspective and commentary. J Pediatr 1995;126(5 Pt 2): S1–5.
4. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, and Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353(16):1685–93.
5. Catanzarite V, Willms D, Wong D, Landers C, Cousins L, and Schrimmer D. Acute respiratory distress syndrome in pregnancy and the puerperium: causes, courses, and outcomes. Obstet Gynecol 2001;97(5 Pt 1):760–4.
6. Mabie WC, Barton JR, and Sibai BM. Adult respiratory distress syndrome in pregnancy. Am J Obstet Gynecol 1992;167(4 Pt 1):950–7.
7. Perry KG Jr, Martin RW, Blake PG, Roberts WE, and Martin JN Jr. Maternal mortality associated with adult respiratory distress syndrome. South Med J 1998;91(5):441–4.
8. Collop NA and Sahn SA. Critical illness in pregnancy. An analysis of 20 patients admitted to a medical intensive care unit. Chest 1993;103(5):1548–52.
9. Al-Suleiman SA, Qutub HO, Rahman J, and Rahman MS. Obstetric admissions to the intensive care unit: a 12-year review. Arch Gynecol Obstet 2006;274(1):4–8.
10. Mahutte NG, Murphy-Kaulbeck L, Le Q, Solomon J, Benjamin A, and Boyd ME. Obstetric admissions to the intensive care unit. Obstet Gynecol 1999;94(2):263–6.
11. Mirghani HM, Hamed M, Ezimokhai M, and Weerasinghe DS. Pregnancy-related admissions to the intensive care unit. Int J Obstet Anesth 2004;13(2):82–5.
12. Karnad DR and Guntupalli KK. Critical illness and pregnancy: review of a global problem. Crit Care Clin 2004;20(4):555–76, vii.
13. Pratt PC, Vollmer RT, Shelburne JD, and Crapo JD. Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. I. Light microscopy. Am J Pathol 1979;95(1):191–214.
14. Crapo RO. Normal cardiopulmonary physiology during pregnancy. Clin Obstet Gynecol 1996;39(1):3–16.
15. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, Spragg R, and Suter PM. The American-European Consensus Conference on ARDS, Part 2: ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Acute respiratory distress syndrome. Am J Respir Crit Care Med 1998;157(4 Pt 1):1332–47.
16. Pepe PE, Potkin RT, Reus DH, Hudson LD, and Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982;144(1):124–30.
17. Hudson LD, Milberg JA, Anardi D, and Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;151(2 Pt 1):293–301.
18. Meyer NJ and Garcia JG. Wading into the genomic pool to unravel acute lung injury genetics. Proc Am Thorac Soc 2007;4(1):69–76.
19. Cole DE, Taylor TL, McCullough DM, Shoff CT, and Derdak S. Acute respiratory distress syndrome in pregnancy. Crit Care Med 2005;33(10 Suppl):S269–78.
20. Caldwell JW, Arsura EL, Kilgore WB, Garcia AL, Reddy V, and Johnson RH. Coccidioidomycosis in pregnancy during an epidemic in California. Obstet Gynecol 2000;95(2):236–9.
21. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946;52:191–205.
22. Lim WS, Macfarlane JT, and Colthorpe CL. Pneumonia and pregnancy. Thorax 2001;56(5):398–405.
23. Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, Pivarnik J, Spillman T, DeVore GR, Phelan J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161(6 Pt 1):1439–42.
24. Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists. BJOG 2000;107(4):439–44.
25. Goodrum LA. Pneumonia in pregnancy. Semin Perinatol 1997;21(4):276–83.

26. Ware LB and Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334–49.
27. Matthay MA and Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 1990;142(6 Pt 1):1250–7.
28. Greene KE, Wright JR, Steinberg KP, Ruzinski JT, Caldwell E, Wong WB, Hull W, Whitsett JA, Akino T, Kuroki Y, Nagae H, Hudson LD, and Martin TR. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 1999;160(6):1843–50.
29. Rinaldo JE and Rogers RM. Adult respiratory-distress syndrome: changing concepts of lung injury and repair. N Engl J Med 1982;306(15):900–9.
30. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver L, Lymp JF, Afessa B, and Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004;32(9):1817–24.
31. Connelly KG and Repine JE. Markers for predicting the development of acute respiratory distress syndrome. Annu Rev Med 1997;48:429–45.
32. Cugell DW, Frank NR, Gaensler EA, and Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc 1953;67(5):568–97.
33. Baldwin GR, Moorthi DS, Whelton JA, and MacDonnell KF. New lung functions and pregnancy. Am J Obstet Gynecol 1977;127(3):235–9.
34. Elkus R and Popovich J Jr. Respiratory physiology in pregnancy. Clin Chest Med 1992;13(4):555–65.
35. Lapinsky SE, Kruczynski K, and Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med 1995;152(2):427–55.
36. Jensen A, Garnier Y, and Berger R. Dynamics of fetal circulatory responses to hypoxia and asphyxia. Eur J Obstet Gynecol Reprod Biol 1999;84(2):155–72.
37. Itskovitz J, LaGamma EF, and Rudolph AM. Effects of cord compression on fetal blood flow distribution and O2 delivery. Am J Physiol 1987;252(1 Pt 2):H100–9.
38. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. Am J Obstet Gynecol 1972;112(2):246–76.
39. Pasternak JF and Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. Pediatr Neurol 1998;18(5):391–8.
40. Wallenburg H. Hemodynamics in hypertensive pregnancy. In Rubin PC, editor. Hypertension in pregnancy, 1st ed. Elsevier, Amsterdam.1988;66–101.
41. Cotton DB, Lee W, Huhta JC, and Dorman KF. Hemodynamic profile of severe pregnancy-induced hypertension. Am J Obstet Gynecol 1988;158(3 Pt 1):523–9.
42. Mabie WC, Ratts TE, and Sibai BM. The central hemodynamics of severe preeclampsia. Am J Obstet Gynecol 1989;161(6 Pt 1):1443–8.
43. Elliott JP, Istwan NB, Rhea D, and Stanziano G. The occurrence of adverse events in women receiving continuous subcutaneous terbutaline therapy. Am J Obstet Gynecol 2004;191(4):1277–82.
44. Katz M, Robertson PA, and Creasy RK. Cardiovascular complications associated with terbutaline treatment for preterm labor. Am J Obstet Gynecol 1981;139(5):605–8.
45. Robertson PA, Herron M, Katz M, and Creasy RK. Maternal morbidity associated with isoxsuprine and terbutaline tocolysis. Eur J Obstet Gynecol Reprod Biol 1981;11(6):371–8.
46. Samol JM and Lambers DS. Magnesium sulfate tocolysis and pulmonary edema: the drug or the vehicle? Am J Obstet Gynecol 2005;192(5):1430–2.
47. Abbas OM, Nassar AH, Kanj NA, and Usta IM. Acute pulmonary edema during tocolytic therapy with nifedipine. Am J Obstet Gynecol 2006;195(4):e3–4.
48. DiFederico EM, Burlingame JM, Kilpatrick SJ, Harrison M, and Matthay MA. 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(4):925–33.

49. Bandi VD, Munnur U, and Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. Crit Care Clin 2004;20(4):577–607.
50. de La Chapelle A, Benoit S, Bouregba M, Durand-Reville M, and Raucoules-Aime M. The treatment of severe pulmonary edema induced by beta adrenergic agonist tocolytic therapy with continuous positive airway pressure delivered by face mask. Anesth Analg 2002;94(6):1593–4, table of contents.
51. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, and Colmorgen GH. Acute pulmonary edema in pregnancy. Obstet Gynecol 2003;101(3):511–5.
52. Sliwa K, Fett J, and Elkayam U. Peripartum cardiomyopathy. Lancet 2006;368(9536): 687–93.
53. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, and Ansari AA. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J 2006;27(4):441–6.
54. Fett JD, Christie LG, Carraway RD, and Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005;80(12):1602–6.
55. Milne EN, Pistolesi M, Miniati M, and Giuntini C. The radiologic distinction of cardiogenic and noncardiogenic edema. AJR Am J Roentgenol 1985;144(5):879–94.
56. Aberle DR, Wiener-Kronish JP, Webb WR, and Matthay MA. Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. Radiology 1988;168(1):73–9.
57. Ely EW, Smith AC, Chiles C, Aquino SL, Harle TS, Evans GW, and Haponik EF. Radiologic determination of intravascular volume status using portable, digital chest radiography: a prospective investigation in 100 patients. Crit Care Med 2001;29(8):1502–12.
58. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni D, et al. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 1988;69(6):824–32.
59. Zimmerman JE, Goodman LR, and Shahvari MB. Effect of mechanical ventilation and positive end-expiratory pressure (PEEP) on chest radiograph. AJR Am J Roentgenol 1979;133(5):811–5.
60. Berg CJ, Chang J, Callaghan WM, and Whitehead SJ. Pregnancy-related mortality in the United States, 1991–1997. Obstet Gynecol 2003;101(2):289–96.
61. MacKay AP, Berg CJ, Duran C, Chang J, and Rosenberg H. An assessment of pregnancy-related mortality in the United States. Paediatr Perinat Epidemiol 2005;19(3):206–14.
62. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999; 353(9160):1258–65.
63. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, and Melton LJ, 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005;143(10):697–706.
64. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263(20):2753–9.
65. Goldhaber SZ. Pulmonary embolism. Lancet 2004;363(9417):1295–305.
66. Clark SL, Hankins GD, Dudley DA, Dildy GA, and Porter TF. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995;172(4 Pt 1):1158–67;discussion 1167–9.
67. Gilbert WM and Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 1999;93(6):973–7.
68. Gei AF, Vadhera RB, and Hankins GD. Embolism during pregnancy: thrombus, air, and amniotic fluid. Anesthesiol Clin North America 2003;21(1):165–82.
69. Camporesi EM. Diving and pregnancy. Semin Perinatol 1996;20(4):292–302.
70. Malinow AM, Naulty JS, Hunt CO, Datta S, and Ostheimer GW. Precordial ultrasonic monitoring during cesarean delivery. Anesthesiology 1987;66(6):816–9.

71. Lew TW, Tay DH, and Thomas E. Venous air embolism during cesarean section: more common than previously thought. Anesth Analg 1993;77(3):448–52.
72. Moore J and Baldisseri MR. Amniotic fluid embolism. Crit Care Med 2005;33 (10 Suppl):S279–85.
73. Mushkat Y, Luxman D, Nachum Z, David MP, and Melamed Y. Gas embolism complicating obstetric or gynecologic procedures. Case reports and review of the literature. Eur J Obstet Gynecol Reprod Biol 1995;63(1):97–103.
74. Thomas CF Jr and Limper AH. Pneumocystis pneumonia. N Engl J Med 2004;350(24):2487–98.
75. Schwarz MI and Albert RK. " Imitators" of the ARDS: implications for diagnosis and treatment. Chest 2004;125(4):1530–5.
76. Zacharisen MC, Schlueter DP, Kurup VP, and Fink JN. The long-term outcome in acute, subacute, and chronic forms of pigeon breeder's disease hypersensitivity pneumonitis. Ann Allergy Asthma Immunol 2002;88(2):175–82.
77. Jacobs RL, Andrews CP, and Coalson JJ. Hypersensitivity pneumonitis: beyond classic occupational disease-changing concepts of diagnosis and management. Ann Allergy Asthma Immunol 2005;95(2):115–28.
78. Philit F, Etienne-Mastroianni B, Parrot A, Guerin C, Robert D, and Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med 2002;166(9):1235–9.
79. Bouckaert Y, Robert F, Englert Y, De Backer D, De Vuyst P, and Delbaere A. Acute eosinophilic pneumonia associated with intramuscular administration of progesterone as luteal phase support after IVF: case report. Hum Reprod 2004;19(8):1806–10.
80. Losa Garcia JE, Mateos Rodriguez F, de la Calle B, Rodriguez Encinas A, Sanchez Sanchez R, and Perez Arellano JL. Acute eosinophilic pneumonia in a pregnant woman. Arch Bronconeumol 1997;33(6):306–8.
81. Nizami IY, Kissner DG, Visscher DW, and Dubaybo BA. Idiopathic bronchiolitis obliterans with organizing pneumonia. An acute and life-threatening syndrome. Chest 1995;108(1):271–7.
82. Schwarz MI and Brown KK. Small vessel vasculitis of the lung. Thorax 2000;55(6):502–10.
83. Schwartz N and Young BK. Intrapartum fetal monitoring today. J Perinat Med 2006;34(2):99–107.
84. Martin CB Jr. Electronic fetal monitoring: a brief summary of its development, problems and prospects. Eur J Obstet Gynecol Reprod Biol 1998;78(2):133–40.
85. Simpson KR. Critical illness during pregnancy: considerations for evaluation and treatment of the fetus as the second patient. Crit Care Nurs Q 2006;29(1):20–31.
86. Petty TL and Ashbaugh DG. The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management. Chest 1971;60(3):233–9.
87. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, and Carvalho CR. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–54.
88. 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(18):1301–8.
89. Hickling KG, Henderson SJ, and Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990;16(6):372–7.
90. Bruns PD, Bowes WA Jr, Drose VE, and Battaglia FC. Effect of respiratory acidosis on the rabbit fetus in utero. Am J Obstet Gynecol 1963;87:1074–80.
91. Walker AM, Oakes GK, Ehrenkranz R, McLaughlin M, and Chez RA. Effects of hypercapnia on uterine and umbilical circulations in conscious pregnant sheep. J Appl Physiol 1976;41(5 Pt. 1):727–33.

92. Campbell LA and Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med 2001;163(5):1051–4.
93. Stonestreet BS, Widness JA, and Berard DJ. Circulatory and metabolic effects of hypoxia in the hyperinsulinemic ovine fetus. Pediatr Res 1995;38(1):67–75.
94. Skouteli HN, Kuban KC, Leviton A, Brown ER, Krishnamoorthy KS, Pagano M, Allred EN, Sullivan KF, Baglivo JA, Huff KR, et al. Arterial blood gas derangements associated with death and intracranial hemorrhage in premature babies. J Perinatol 1988;8(4):336–41.
95. Holmes JM, Zhang S, Leske DA, and Lanier WL. Carbon dioxide-induced retinopathy in the neonatal rat. Curr Eye Res 1998;17(6):608–16.
96. Holmes JM, Zhang S, Leske DA, and Lanier WL. Metabolic acidosis-induced retinopathy in the neonatal rat. Invest Ophthalmol Vis Sci 1999;40(3):804–9.
97. Motoyama EK, Rivard G, Acheson F, and Cook CD. Adverse effect of maternal hyperventilation on the foetus. Lancet 1966;1(7432):286–8.
98. Morishima HO, Daniel SS, Adamsons K Jr, and James LS. 1965. Effects of positive pressure ventilation of the mother upon the acid-base state of the fetus. Am J Obstet Gynecol 1965;93:269–73.
99. Lumley J and Wood C. Effect of changes in maternal oxygen and carbon dioxide tensions on the fetus. Clin Anesth 1974;10(2):121–137.
100. Ivankovic AD, Elam JO, and Huffman J. Effect of maternal hypercarbia on the newborn infant. Am J Obstet Gynecol 1970;107(6):939–46.
101. Siddiqui AK, Gouda H, Multz AS, Steinberg H, and Kamholz SL. Ventilator strategy for status asthmaticus in pregnancy: a case-based review. J Asthma 2005;42(3):159–62.
102. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333(13):817–22.
103. Bersten AD, Holt AW, Vedig AE, Skowronski GA, and Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. N Engl J Med 1991;325(26):1825–30.
104. Peter JV, Moran JL, Phillips-Hughes J, Graham P, and Bersten AD. Effect of noninvasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. Lancet 2006;367(9517):1155–63.
105. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, Gasparetto A, and Meduri GU. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 1998;339(7):429–35.
106. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, Lemaire F, and Brochard L. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 2000;284(18):2361–7.
107. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti M, Passariello M, and Meduri GU. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 2001;27(11):1718–28.
108. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, and Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 2003;168(12):1438–44.
109. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, Gasparetto A, and Meduri GU. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA 2000;283(2):235–41.
110. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, and Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;344(7):481–7.

111. Guilleminault C, Kreutzer M, and Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004;5(1):43–51.
112. Hutter DA, Berkowitz R, Davis SE 3rd, and Ashtyani H. Application of continuous positive airway pressure in hypoxemic acute respiratory failure associated with diastolic dysfunction in pregnancy. Congest Heart Fail 2006;12(3):174–5.
113. Reddy R, Evans E, Khoo O, and Allen MB. Pregnancy in kyphoscoliosis: benefit of non-invasive ventilatory support. J Obstet Gynaecol 2005;25(3):267–8.
114. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, and Thompson BT. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351(4):327–36.
115. Mantell LL, Horowitz S, Davis JM, and Kazzaz JA. Hyperoxia-induced cell death in the lung – the correlation of apoptosis, necrosis, and inflammation. Ann N Y Acad Sci 1999;887:171–80.
116. Kapanci Y, Tosco R, Eggermann J, and Gould VE. Oxygen pneumonitis in man., Light- and electron-microscopic morphometric studies. Chest 1972;62(2):162–9.
117. Cohn HE, Sacks EJ, Heymann MA, and Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 1974;120(6):817–24.
118. Heymann MA, Rudolph AM, Nies AS, and Melmon KL. Bradykinin production associated with oxygenation of the fetal lamb. Circ Res 1969;25(5):521–34.
119. Ackerman WE 3rd, Molnar JM, and Juneja MM. Beneficial effect of epidural anesthesia on oxygen consumption in a parturient with adult respiratory distress syndrome. South Med J 1993;86(3):361–4.
120. Prewitt RM, McCarthy J and Wood LD. Treatment of acute low pressure pulmonary edema in dogs: relative effects of hydrostatic and oncotic pressure, nitroprusside, and positive end-expiratory pressure. J Clin Invest 1981;67(2):409–18.
121. Matthay MA, and Broaddus VC. Fluid and hemodynamic management in acute lung injury. Semin Respir Crit Care Med 1994;15:271–88.
122. Mitchell JP, Schuller D, Calandrino FS, and Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 1992;145(5):990–8.
123. Humphrey H, Hall J, Sznajder I, Silverstein M, and Wood L. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. Chest 1990;97(5):1176–80.
124. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, and Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564–75.
125. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, Connors AF Jr, Hite RD, and Harabin AL. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J =Med 2006;354(21):2213–24.
126. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, and Miller LW. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294(13):1625–33.
127. Rhodes A, Cusack RJ, Newman PJ, Grounds RM, and Bennett ED. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. Intensive Care Med 2002;28(3):256–64.
128. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, and Jacka M. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348(1):5–14.
129. Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, Boulain T, Lefort Y, Fartoukh M, Baud F, Boyer A, Brochard L, and Teboul JL. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2003;290(20):2713–20.

130. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, and Rowan K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366(9484):472–7.
131. Pestana D and Garcia-de-Lorenzo A. Calculated versus measured oxygen consumption during aortic surgery: reliability of the Fick method. Anesth Analg 1994; 78(2):253–6.
132. Reinhart K, Kuhn HJ, Hartog C, and Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 2004;30(8):1572–8.
133. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, and Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340(6):409–17.
134. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. The ARDS Network. JAMA 2000; 283(15):1995–2002.
135. Spragg RG, Lewis JF, Wurst W, Hafner D, Baughman RP, Wewers MD, and Marsh JJ. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. Am J Respir Crit Care Med 2003;167(11):1562–6.
136. Spragg RG, Lewis JF, Walmrath HD, Johannigman J, Bellingan G, Laterre PF, Witte MC, Richards GA, Rippin G, Rathgeb F, Hafner D, Taut FJ, and Seeger W. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 2004;351(9):884–92.
137. Bone RC, Slotman G, Maunder R, Silverman H, Hyers TM, Kerstein MD, and Ursprung JJ. Randomized double-blind, multicenter study of prostaglandin E1 in patients with the adult respiratory distress syndrome. Prostaglandin E1 Study Group. Chest 1989;96(1):114–9.
138. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K Jr, Hyers TM, and Papadakos P. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26(1):15–23.
139. Troncy E, Collet JP, Shapiro S, Guimond JG, Blair L, Ducruet T, Francoeur M, Charbonneau M, and Blaise G. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. Am J Respir Crit Care Med 1998;157(5 Pt 1):1483–8.
140. Michael JR, Barton RG, Saffle JR, Mone M, Markewitz BA, Hillier K, Elstad MR, Campbell EJ, Troyer BE, Whatley RE, Liou TG, Samuelson WM, Carveth HJ, Hinson DM, Morris SE, Davis BL, and Day RW. Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. Am J Respir Crit Care Med 1998;157(5 Pt 1):1372–80.
141. Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GJ, Davis K Jr, Kelly KM, Smith TC, and Small RJ. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291(13):1603–9.
142. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, and Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317(11):653–8.
143. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, and Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 1988;138(1):62–8.
144. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, and Ancukiewicz M. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354(16):1671–84.
145. Rossain RK. Falke J, Lopez F, Slama K, Pison U, and Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328(6):399–405.
146. Bose D, Yentis SM, and Fauvel NJ. Caesarean section in a parturient with respiratory failure caused by cystic fibrosis. Anaesthesia 1997;52(6):578–82.

147. Goodwin TM, Gherman RB, Hameed A, and Elkayam U. Favorable response of Eisenmenger syndrome to inhaled nitric oxide during pregnancy. Am J Obstet Gynecol 1999;180(1 Pt 1):64–7.
148. Lam GK, Stafford RE, Thorp J, Moise KJ Jr, and Cairns BA. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. Obstet Gynecol 2001;98(5 Pt 2):895–8.
149. Lust KM, Boots RJ, Dooris M, and Wilson J. Management of labor in Eisenmenger syndrome with inhaled nitric oxide. Am J Obstet Gynecol 1999;181(2):419–23.
150. Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, and Krivosic-Horber R. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. Can J Anaesth 2001;48(6):584–7.
151. Gattinoni L, Pelosi P, Crotti S, and Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151(6):1807–14.
152. Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, and Gattinoni L. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 1998;157(2):387–93.
153. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, and Granton J. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166(6):801–8.
154. Huang CC, Shih MJ, Tsai YH, Chang YC, Tsao TC and Hsu KH. Effects of inverse ratio ventilation versus positive end-expiratory pressure on gas exchange and gastric intramucosal PCO(2) and pH under constant mean airway pressure in acute respiratory distress syndrome. Anesthesiology 2001;95(5):1182–8.
155. Hirschl RB, Croce M, Gore D, Wiedemann H, Davis K, Zwischenberger J, and Bartlett RH. Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;165(6):781–7.
156. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC 2nd, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, and Miller RG Jr. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242(20):2193–6.
157. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, Dean NC, Thomas F, East TD, Pace NL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149(2 Pt 1):295–305.
158. Cunningham JA, Devine PC, and Jelic S. Extracorporeal membrane oxygenation in pregnancy. Obstet Gynecol 2006;108(3 Pt 2):792–5.
159. Sosin D, Krasnow J, Moawad A, and Hall JB. Successful spontaneous vaginal delivery during mechanical ventilatory support for the adult respiratory distress syndrome. Obstet Gynecol 1986;68(3 Suppl):19S–23S.
160. Tomlinson MW, Caruthers TJ, Whitty JE, and Gonik B. Does delivery improve maternal condition in the respiratory-compromised gravida? Obstet Gynecol 1998;91(1):108–11.
161. Jenkins TM, Troiano NH, Graves CR, Baird SM, and Boehm FH. Mechanical ventilation in an obstetric population: characteristics and delivery rates. Am J Obstet Gynecol 2003;188(2):549–52.
162. Fowler AA, Hamman RF, Zerbe GO, Benson KN, and Hyers TM. Adult respiratory distress syndrome. Prognosis after onset. Am Rev Respir Dis 1985;132(3):472–8.
163. Suchyta MR, Clemmer TP, Elliott CG, Orme JF Jr., and Weaver LK. The adult respiratory distress syndrome. A report of survival and modifying factors. Chest 1992;101(4):1074–9.
164. Montgomery AB, Stager MA, Carrico CJ, and Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132(3):485–9.

165. McHugh LG, Milberg JA, Whitcomb Me, Schoene RB, Maunder RJ, and Hudson LD. Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1994;150(1):90–4.
166. Herridge MS, Cheung AM, Tansey Mc, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer Cd, Mehta S, Stewart TE, Barr A, Cook D, and Slutsky AS. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348(8):683–93.
167. Weinert CR, Gross CR, Kangas JR, Bury CL, and Marinelli WA. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med 1997;156(4 Pt 1):1120–8.
168. Lee CM and Hudson LD. Long-term outcomes after ARDS. Semin Respir Crit Care Med 2001;22(3):327–36.
169. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, and Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 1999;281(4):354–60.
170. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, Lenhart A, Heyduck M, Polasek J, Meier M, Preuss U, Bullinger M, Schuffel W, and Peter K. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 1998;26(4):651–9.

23

Airway Management and Mechanical Ventilation in Pregnancy

Uma Munnur, Venkata DP Bandi, and Michael A. Gropper

Keywords: Pregnancy, airway, cesarean section, difficult intubation, mechanical ventilation, maternal mortality, airway devices

Introduction

Anesthesia-related maternal mortality rates have improved in the United States, but it still remains a prominent cause of maternal mortality. Anesthesia is the seventh leading cause of maternal mortality in the United States with the top six causes being embolism, hypertensive disorders, hemorrhage, infection, cardiomyopathy, and cerebrovascular accident *(1)*. General anesthesia is more likely to be associated with maternal mortality than regional anesthesia in the obstetric patient for the following reasons: (1) airway management tends to be more difficult in pregnant patients due to altered anatomy and physiology; (2) general anesthesia is chosen in emergency surgeries when there is no time for adequate preoperative evaluation and aspiration prophylaxis; (3) conversion of regional anesthetic to general anesthesia for inadequate block, hemorrhage, etc., with the patient not in the optimal position for intubation; and (4) increased usage of regional anesthesia in obstetrics with minimal exposure of trainees to general anesthesia for cesarean sections, resulting in decreased airway management skills for training and maintenance in the obstetric patient.

Several factors tend to evoke apprehension in even the most competent anesthesiologist when dealing with the airway in a pregnant woman. The most important reasons being pregnancy-related altered anatomy and physiology impacting anesthetic management, the urgent nature of the obstetric practice leading to limited time for adequate anesthetic preparation, and the potential risk of impacting both mother and fetus *(2)*. Failed tracheal intubation is well documented in the obstetric population, with an incidence eight times that of general surgical patients *(3)*.

G. Bourjeily, K. Rosene-Montella (eds.), *Pulmonary Problems in Pregnancy*, Respiratory Medicine,
DOI 10.1007/978-1-59745-445-2_23

Anatomic and Physiological Changes During Pregnancy

Management of the parturient's airway necessitates a thorough knowledge of the anatomic and physiologic demands placed on the mother due to the growing fetus. Such changes have a tremendous impact on the safe anesthetic management of the parturient.

Capillary engorgement of the mucosa throughout the respiratory tract causes swelling of the nasal and oral pharynx, larynx, and trachea *(4, 5)*. Elevated estrogen levels and increase in blood volume associated with pregnancy may also contribute to the mucosal edema *(6)*. These changes may be markedly accentuated by a mild upper respiratory tract infection, fluid overload, preeclampsia, oxytocin infusion, or prolonged strenuous second stage of labor *(7–9)*.

The progesterone-mediated smooth muscle relaxant effect on the gastrointestinal mucosa along with the anatomical changes secondary to the gravid uterus places the parturient at risk for both regurgitation and pulmonary aspiration. Lower esophageal sphincter tone is decreased allowing gastric reflux and heartburn during pregnancy *(10)*. Therefore, the parturient is prone to silent regurgitation, active vomiting, and aspiration during general anesthesia or impaired consciousness *(11)*. Studies have shown that gastric emptying is slowed and mean gastric volume increases during labor *(12, 13)*. All parturients undergoing an anesthetic for cesarean section are considered at risk for pulmonary aspiration and should receive aspiration prophylaxis preoperatively.

As the uterus enlarges, it impinges on the diaphragm, reducing the functional residual capacity. In addition, there is increased oxygen consumption and minute ventilation to meet the demands of the growing feto-maternal unit. As a result, apnea in the pregnant patient results in a more rapid onset of hypoxia, hypercarbia, and acidosis than in non-pregnant patient *(14)*.

A parturient may gain 10 kg or more during pregnancy. This weight gain results from the increasing size of the uterus and fetus, increased volumes of blood and interstitial fluid, and deposition of fat. There is also a significant increase in breast size during pregnancy. Increased weight gain during pregnancy and large breast size can cause difficulty with intubation. Manipulation of the upper airway in a parturient requires special attention. Placement of oral/nasal airways, suctioning, and careless laryngoscopy can result in airway trauma and bleeding. Manipulation of the nasal airway can lead to brisk epistaxis. Smaller size endotracheal tubes are recommended in parturients due to the mucosal swelling, which also decreases the area of the glottic opening. Breast engorgement can hinder laryngoscopy, and so proper positioning is necessary along with the availability of a short-handled blade. Therefore positioning with blankets or use of a ramp under the shoulders can minimize the hazards of difficult laryngoscopy. (Table 23.1)

Table 23.1 Anatomic and physiological factors affecting obstetric airway management.

Upper airway edema	Decreased FRC
Breast enlargement	Increased oxygen consumption
Excessive weight gain	Increased risk of aspiration
Cephalad displacement of diaphragm	Preeclampsia

Airway Assessment

Most airway catastrophes occur when airway difficulty is not recognized prior to induction of anesthesia. The timely evaluation of the parturient's airway in the non-emergent setting is tremendously helpful in avoiding airway problems. Eighty-seven percent of emergency or urgent cesarean deliveries can be anticipated by regular preoperative evaluation of patients who are admitted to labor and delivery suite *(15)*. There are a few simple preoperative bedside tests that can be performed within a few seconds to evaluate the airway in a pregnant patient in the same manner as a non-pregnant patient. These tests include mouth opening, thyromental distance, Mallampati class, atlanto-occipital extension, and ability to protrude the mandible. No single test can reliably predict a difficult airway. A combination of these tests is essential to facilitate the management of the airway and to reduce the likelihood of adverse outcomes related to the airway. Predicting difficult airway enables the anesthesia practitioner to implement appropriate care and thus avoid major airway catastrophes. Every parturient that needs an operative delivery should have a preanesthetic evaluation that emphasizes the airway examination as outlined by the American Society of Anesthesiologists (ASA) Practice Guidelines in 2003 *(16)*.

Preeclampsia and Airway-Related Changes

Preeclampsia is a multisystem disorder affecting approximately 8% of pregnancies. It is a pregnancy-associated disease occurring after 20 weeks gestation and is characterized by hypertension, proteinuria, and edema. The cause still remains unknown but the understanding of pathophysiology has greatly increased *(17–20)*.

Women with preeclampsia have an increased risk of upper airway narrowing from pharyngolaryngeal edema. Reduced plasma proteins due to proteinuria and marked fluid retention, (especially in the head and neck region), increase the size of the tongue making it less mobile, causing more difficult identification of landmarks in preeclamptic parturients. In severe preeclampsia, edema of the face and neck should alert the anesthesiologist to the possibility of difficult intubation, whereas edema of the tongue may herald imminent airway compromise *(4, 7, 21–23)*.

Preeclampsia accompanied by soft tissue edema and coagulopathy complicates repeated attempts at direct laryngoscopy causing laceration and bleeding in the upper airway *(24)*. Marked upper airway edema and swelling of the tongue and soft tissues can be severe enough to cause total airway obstruction *(25)*. Laryngeal edema can develop very rapidly in a preeclamptic patient without any warning signs such as facial edema, enlarged tongue, voice change or stridor; therefore, caution should be exercised even during extubation *(26)*. Dysphonia due to uvular edema has also been reported *(27)*. Upper respiratory infection can further compromise the edematous airway in preeclampsia *(7)*.

Morbid Obesity in Pregnancy and Airway

Morbid obesity in pregnancy is a growing problem and has a significant impact on maternal morbidity and mortality. It is associated with an increased risk for diabetes, hypertension, and preeclampsia *(28, 29)*. A recent study has shown that there is increased risk of post partum hemorrhage, cesarean section for

cephalo-pelvic disproportion, and gestational diabetes in morbidly obese parturients when compared with non-obese parturients *(30)*. Obese women are at risk for airway complications, cardiopulmonary dysfunction, perioperative morbidity and mortality, and also pose technical challenges *(31)*.

The airway of the obese parturient can be very unpredictable. There is not only an increased risk of difficult intubation, but also increased difficulty in maintaining adequate mask ventilation in morbidly obese parturients. In the supine position, breasts and chest wall soft tissue can hinder chest wall excursion and decrease compliance. Hood et al. showed that difficult intubation was encountered more frequently in morbidly obese parturients (>130 kg) *(28)*. Morbidly obese parturients are at an increased risk for anesthesia-related morbidity and mortality during cesarean section and in particular, increased risk of failed intubation and gastric aspiration during procedures requiring general anesthesia *(32, 33)*. A review of anesthesia-related maternal mortality from Michigan showed that obesity was one of the major risk factors for maternal mortality *(32)*. Recently, two of the six deaths from the Confidential Enquiries into Maternal Deaths in the United Kingdom were obese parturients *(34)*. The obstetric closed claims files indicate that damaging events related to the respiratory system were significantly more common among obese (32%) than non-obese (7%) parturients. Death was also more common among the obese parturients. There is an increasing need to be cautious and to have emergency algorithms and equipment readily available when caring for these obese parturients *(35)*.

Pregnancy is a state of high metabolic and physiologic demand as mentioned earlier, but obese pregnant women are at double the risk. Anesthesia for both elective and emergency situations should be planned in advance with a difficult airway cart readily available. If possible, regional anesthesia with a good block should be the goal for cesarean section. General anesthesia should be avoided due to difficulty with endotracheal intubation and rapid oxygen desaturation during induction.

Aspiration of Gastric Contents

Aspiration-related deaths commonly occur from difficult/failed intubation or esophageal intubation *(1)*. Patients at greatest risk for aspiration are obese parturients who have eaten after the onset of labor or within 6–8 h of delivery. After 28 weeks of gestation, all appropriate precautions should be taken to prevent aspiration. The technique of rapid sequence induction (RSI) with cricoid pressure and endotracheal intubation (Selleck's maneuver) was introduced in obstetric anesthesia practice to protect the airway from pulmonary aspiration. Improper application of cricoid pressure can lead to problems with difficulty during intubation. Once intubation fails, the chances of not being able to ventilate increase markedly. Aspiration of gastric contents remains a clear risk during induction of general anesthesia and this risk is higher when difficulty is experienced while intubating the trachea. One should be mindful that with mask ventilation, there is a risk of gastric distension, along with an inherent danger of aspiration of stomach contents.

The parturient is particularly vulnerable to pulmonary aspiration due to the gastrointestinal changes, hormonal changes, parenteral analgesics, or induction agents during general anesthesia. Obesity and late pregnancy predispose to hiatus hernia, which make regurgitation of gastric contents more likely to occur *(34)*. Aspiration can also occur during a high spinal or epidural block when the patient

cannot cough or clear her secretions in the airway effectively. All precautions should be taken to prevent aspiration, as it is a significant precipitator for ARDS *(36)*.

Obstetricians' Role in Management of Airway

A collegial and collaborative approach between obstetricians and anesthesiologists facilitates optimal patient care. According to the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, the obstetric care team should be alert to the presence of risk factors that place the parturient at increased risk for complications from general anesthesia *(37)*. When such risk factors are identified, the anesthesiologist should be alerted. Consideration should be given for an early placement of a functioning epidural during labor in these patients.

Incidence of Failed Intubation

Failed intubation in the general surgical population is 1 in 2,330 *(38)*. The incidence of failed intubation is approximately eight times higher in the obstetric population compared to non-obstetric patients, where the estimated incidence is found to be 1 in 280 *(39)*. Furthermore, the incidence of fatal failed intubation is 13 times higher in the obstetric population *(40)*.

Anesthesia and Maternal Mortality

According to the 2003 report of anesthesia-related maternal mortality in the United States by Hawkins, anesthetic causes are the seventh leading cause for maternal mortality. Most maternal deaths that are caused by complications of anesthesia occurred during general anesthesia *(1)*. Anesthesia-related maternal mortality rates in the United States and the United Kingdom have proved to be similar.

Since the 1950s, the United Kingdom has published reports on the Confidential Enquiries into Maternal Deaths every triennium (3 years). These reports are published regularly to provide detailed information on all maternal deaths occurring during the triennium, and therefore serve as a measure for obstetric anesthesia care. The reports have provided more comprehensive information regarding maternal mortality than in any country in the world. Since the early 1980s, there has been a dramatic reduction in anesthesia-related maternal deaths. Increased use of regional anesthesia, aspiration prophylaxis, and improvement in airway training probably contributed to this reduction *(41)*. In the latest triennium from 2000–2002, six deaths were ascribed directly to the conduct of anesthesia. All six deaths were associated with general anesthesia. When general anesthesia is required for emergency cesarean sections, there is some concern now over the lack of experience by some anesthesia practitioners and their confidence in providing it *(34)*.

Cesarean Section: Recognized Difficult Airway

Regional Anesthesia

Under normal circumstances, anesthesia practitioners have adequate time to evaluate parturients posted for a cesarean section and administer aspiration

prophylaxis. If a difficult airway is suspected, one can proceed with either regional or general anesthesia. The advantage of regional anesthesia is that manipulation of the difficult airway can be avoided. The incidence of serious airway complications associated with multiple intubation attempts in patients with difficult airways generally outweighs the risks of regional anesthesia. If regional anesthesia is not contraindicated and there is adequate time, it is a favorable option. Nevertheless, one should realize that the use of regional anesthesia in patients with a recognized difficult airway does not solve the problem of the airway. The danger of regional anesthesia in a patient with known or suspected difficult airway is that failure of regional anesthesia could result in a precipitous induction of general anesthesia under suboptimal conditions. The difficult airway cart should always be readily available even during regional anesthesia as there is a possibility of conversion to general anesthesia. The anesthesia practitioner should be prepared both mentally and technically to administer general anesthesia.

Awake Intubation

If the plan is to proceed with general anesthesia for cesarean section and difficult airway is suspected, awake intubation is always a safe option. Successful awake endotracheal intubation requires proper preparation of the patient. The critical step is psychological preparation of the patient. The patient, who knows what is going to happen, is typically more receptive and cooperative. Topical anesthesia and judicious use of intravenous sedation aid in a successful awake intubation. It should be noted that expertise is needed to perform a fiberoptic bronchoscopy quickly and safely. Although awake intubation is generally safe, airway reflexes are blunted and caution should be taken to prevent vomiting and aspiration.

It is very common for anesthesia practitioners to avoid awake tracheal intubation during cesarean section. Some of the reasons being lack of skill in awake intubation, time constraints, and also a desire not to subject the patient to unnecessary discomfort. Awake intubations should be taught during the training period whenever a difficult airway is suspected. Only then, can anesthesia practitioners develop confidence in intubating pregnant patients awake.

Acute Fetal Distress

At times, the pregnant patient can present with acute fetal distress without any preanesthetic evaluation. Such a situation often necessitates emergency cesarean delivery under general anesthesia with rapid-sequence induction. It is crucial to evaluate the mother's airway prior to induction even in cases of fetal distress, as this can be done when the patient is moving from the stretcher to the operating room table. If a difficult airway is suspected, the mother's life takes priority over the fetus (who is dependent on maternal oxygenation), and maternal airway should be secured awake even at the expense of fetal well-being *(14)*. Even if intubation is not possible, every effort should be made to maintain adequate ventilation to prevent hypoxemia. If failure to intubate leads to loss of a healthy mother, it will be a devastating experience for all those involved.

Cesarean Section: Unrecognized Difficult Airway

At times general anesthesia is chosen due to the emergency nature of the cesarean section or in situations where regional anesthesia is contraindicated. In spite of the urgency, the head position should be optimized for tracheal intubation by aligning oral, pharyngeal, and laryngeal axes. Time should always be taken for proper positioning of the head prior to induction. After the initial failed attempts, the management goals remain oxygenation, airway protection, and prompt delivery of the baby. Request help early and try to ventilate the patient until spontaneous ventilation returns.

If surgery needs to proceed after initial failed attempts, mask ventilation with either one- or two-person effort should be initiated immediately. Mask ventilation is continued with cricoid pressure until the patient can protect her airway. The goal should remain "oxygenation without aspiration."

If mask ventilation is not possible, the laryngeal mask airway (LMA) should be placed immediately. In 2003, practice guidelines for management of the difficult airway were updated. According to these new guidelines, LMA is the tool of choice in a "cannot-ventilate, cannot-intubate" (CVCI) situation *(16)*. If the LMA fails, we need to proceed with emergency pathway. Combitube, transtracheal jet ventilation, or surgical airways are the reasonable options at this juncture.

A thorough working knowledge of devices available for the management of the difficult airway and recommended rescue strategies is essential in avoiding airway complications. Using airway equipment for the first time during failed intubation is a recipe for disaster.

Airway Devices

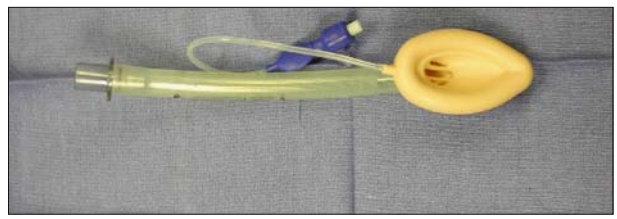
Laryngeal Mask Airway (LMA) (see Figure 1), Intubating LMA (see Figure 2), Proseal LMA (PLMA) (see Figure 3), and combitube (see Figure 4) are supraglottic airway devices and can be successfully used if there is no airway obstruction at or below the glottis. The laryngeal tube has also been used in a failed intubation scenario. Unfortunately, these devices do not provide reliable protection from gastric aspiration when compared to translaryngeal intubation.

Laryngeal Mask Airway

The LMA is now a recognized part of the ASA Difficult Airway Algorithm and should be a part of every obstetric anesthesiologist's armamentarium for managing difficult airways. LMA has been found to be a life-saving device in obstetric patients undergoing emergency cesarean section that could not be ventilated or intubated by conventional techniques. Han and colleagues reported the successful use of the LMA as a ventilatory device in 1,060 of 1,067 patients undergoing elective cesarean sections *(42)*.

A survey was conducted in Germany evaluating the availability of specialized airway equipment in obstetric units in the department of anesthesia. In this survey, LMAs were available in 91% of the obstetric departments, in accordance with figures from the United Kingdom (91.4%). According to the same survey, 72% of anesthesiologists favored the LMA as the first treatment option in

(CVCI) situations *(43)*. In a survey from the United Kingdom, 71.8% of obstetric anesthesiologists advocated use of LMA in CVCI situations. Eight anesthesiologists stated that LMA was found to be a lifesaver *(44)*. The most common alternative ventilation device in Irish national survey of the obstetric units was also the LMA *(45)*.

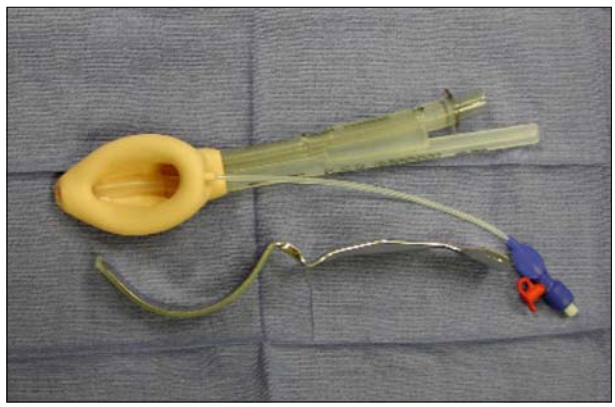


Classic LMA

Intubating LMA

Proseal-LMA (PLMA)

Proseal-LMA (PLMA) is a modification of the classic LMA and provides a better seal and better airway protection than LMA. It has a second lumen to place the orogastric tube to vent the regurgitated esophageal contents. The PLMA has been successfully used in parturients after failed intubation during RSI and in postoperative respiratory support *(46–48)*. The PLMA has been recently used in two failed obstetric intubation scenarios *(49)*. It has also been used during sessions of electroconvulsive therapy in a parturient at 20–22 weeks gestation with a known difficult airway *(50)*.



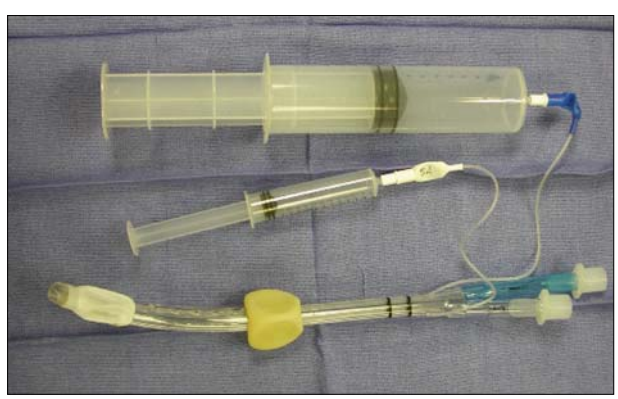
LMA Proseal

Intubating Laryngeal Mask Airway (ILMA)

The ILMA has been designed to increase the success rate of intubation through the LMA. The ILMA has been used in the management of unanticipated difficult intubation. The difference between a classic LMA and ILMA is that the ILMA has a rigid shaft. This shaft acts as an insertion tool for the endotracheal tube for atraumatic intubation when the mask aperture is in alignment with the glottic opening. ILMA has been used even in parturients after attempts at failed intubation *(51, 52)*.

Combitube

The Combitube is another airway device that can be used when mask ventilation and intubation have failed. It is a double lumen disposable tube with an esophageal and tracheal lumen and with two cuffs (esophageal and pharyngeal cuff). Combitube can be placed easily, rapidly, and without any preparation. It can be placed blindly or through direct laryngoscopy. Ventilation is possible when Combitube is placed either in the trachea or esophagus. When properly positioned, it allows ventilation and protects against regurgitation. It also allows subsequent



Combitube

attempts at intubation after deflating the pharyngeal cuff while the inflated esophageal cuff maintains airway protection. Combitube has also been successfully used in a failed intubation during cesarean section *(53)*. It is worth trying to place a Combitube if available, in a failed intubation scenario, before attempting a surgical airway.

Mechanical Ventilation in Pregnancy

Obstetric admissions to intensive care units (ICU) are uncommon and comprise less than 1% of ICU admissions *(54, 55)*. There are no objective data available regarding mechanical ventilation in pregnancy. The only data available consists of case reports and small case series *(56, 57)*. Management principles are an extrapolation of the general mechanical ventilation principles used routinely in the ICU, while being mindful of various cardiopulmonary changes associated with pregnancy.

The indications for mechanical ventilation are the same as in general ICU population consisting of one of the two categories.

1. Hypoxemic respiratory failure
2. Hypercapnic respiratory failure

There are two main ventilatory strategies: positive pressure and negative pressure ventilation. Positive pressure ventilation is the predominant mode of ventilatory support used in the ICU.

Initiating positive pressure ventilation could lead to a reduction in preload due to decreased venous return, possibly reduced afterload, and a reduction in cardiac output along with reduced splanchnic blood flow. Lower limits of normal oxygen saturation coupled with anemia could lead to reduction in oxygen delivery and affect fetal well-being.

Non-invasive positive pressure ventilation via a tightly fitting facemask is a well-utilized ventilatory and oxygenating modality in the general ICU population. It should be used only in those patients with an adequate respiratory drive, and who can tolerate a tight fitting facemask. It is particularly well suited for those patients with chest wall deformities, chronic neuromuscular problems, and muscle fatigue. There are a few case reports of its use in pregnancy and also during labor *(58–61)*. Poor airway, propensity for upper airway edema, and aspiration make its routine use less than optimal for obstetric patients *(62)*. In appropriately screened pregnant women with ARDS and a good airway, a short trial of NIPPV can be attempted in a closely monitored environment. In pregnant patients with respiratory failure, mechanical ventilation is predominantly delivered via an endotracheal tube utilizing positive pressure ventilation. There are two primary ways to deliver tidal volume. Volume control uses tidal volume and pressure control uses inspiratory pressure as the controller variable *(63)*.

Volume Control Type

It guarantees the tidal volume and minute ventilation even in situations of fluctuations in airway resistance and sudden changes in lung compliance. It is known to reduce lung atelectasis. The main disadvantages of this ventilatory mode are fixed inspiratory time, fixed inspiratory flow rates, predilection for barotrauma,

volutrauma, and somewhat higher work of breathing, depending on the type of ventilator triggering used.

Pressure Control Type

In this mode the inspiratory pressure is held constant leading to higher mean airway pressure, better V/Q matching, and slightly less work of breathing. The minute ventilation and tidal volume depend on compliance, airway resistance, and auto PEEP and hence, minute ventilation is not guaranteed. It takes slightly longer time to deliver a given tidal volume in pressure control ventilation compared to volume control. Table 23.2 outlines the main features of volume and pressure control.

Dual Control Ventilators

More and more ventilators are available where one can use both pressure and volume controls in the same breath. In these dual modes, once the given set of breath requirements are not met, the breath delivery changes to the alternate mode either in the same breath, or over the next few breaths. The reader can find an excellent discussion on dual control modes in this referenced article *(64)*.

Modes of Mechanical Ventilation

Controlled Mechanical Ventilation

In this mode the patient makes no effort and the work of breathing is done entirely by the mechanical ventilator. The set mandatory breaths guarantee patient's minute ventilation. No ventilator assist is given to respiratory efforts between the set breaths. This mode is rarely used, but may be appropriate when patient is on neuromuscular blockade or during general anesthesia *(63)*.

Assist Control Mode (A/C)

In A/C mode the clinician sets a minimal rate and tidal volume. The patient can trigger the ventilator at a higher rate than that is set, but the clinician determined tidal volume (or pressure) is delivered with each breath. This is an excellent initiating mode for a patient that has just been intubated. The work of breathing in this mode is low. Respiratory alkalosis and reduced cardiac output (especially in a hypovolemic patient) are its main drawbacks. In general, A/C has the lowest patient work of breathing demand.

Table 23.2 Features of volume and pressure control ventilation.

	Pressure control	Volume control
Pressure	Set variable	Dependent
Tidal volume (Vt)	Dependent	Set variable
Minute ventilation	Not guaranteed	Guaranteed
Flow profile	Decelerating	Constant or decelerating
Changes in airway resistance	Affect Vt to a greater degree	Minimal effect
Changes in compliance	Affect Vt to a greater degree	Minimal effect

Synchronized Intermittent Mandatory Ventilation (SIMV)

In this mode the ventilator attempts to deliver the mandatory breaths in synchrony with the patient's inspiratory efforts. Ventilator delivers a mandatory breath (volume or pressure) at a scheduled time when no inspiratory effort is detected. If the patient's ventilatory requirements are greater than the backup rate, the patient can take spontaneous breaths at a tidal volume of her choice. In this mode the patient is assured the set backup minute ventilation. This mode is primarily used in conjunction with pressure support (PS), where a pressure support level is set that assists with breaths that occur between the controlled breaths. Without the addition of PS, this mode is non-responsive to increasing ventilatory needs during periods of stress, where patient's work of breathing increases.

Pressure Support Ventilation

This mode can be used with PEEP, without a backup rate and is known as CPAP with PS. It can also be used along with a backup rate in SIMV and is known as SIMV with PS. It is a patient-triggered, pressure-limited, flow-cycled mode. In this mode the ventilator senses a patient's spontaneous inspiratory effort and triggers a demand valve and gas flow is immediately delivered. This flow rate decreases once the set pressure support level is reached. The tidal volume delivered with a pressure support breath depends on duration of the inspiratory effort, duration of the breath, airway resistance, and pulmonary compliance. The inspiratory time and tidal volume are variable and depend on the patient's respiratory drive. In the pressure support mode, the patient has control over respiratory rate, inspiratory flow, I-to-E ratio, tidal volume, and minute ventilation. This is the best mode for patient ventilator synchrony and was shown to reduce sedation requirements and work of breathing. This mode can also be used for weaning purposes. One should be sure of the patient's respiratory drive when using the CPAP with pressure support mode. On occasion, especially in patients with severe airway obstruction, it could lead to dyssynchrony.

Continuous Positive Airway Pressure (CPAP)

Continuous Positive Airway Pressure (CPAP) is a spontaneous breathing mode with no mandatory breaths. A set pressure is provided throughout the breathing cycle to maintain positive airway pressure. Theoretically, both alveolar collapse and the work of breathing are reduced. The rate and tidal volume are set by the patient's respiratory drive.

PEEP

PEEP is a mode of oxygenation and not a mode of ventilation. PEEP improves oxygenation by improving the V/Q, increasing functional residual capacity and recruiting collapsed alveoli. PEEP can help reduce FiO_2 to non-toxic levels. However, PEEP will increase intrathoracic pressure and has the potential to decrease cardiac output via reduction in venous return. PEEP reduces splanchnic and renal blood flow, and increases intracranial pressure.

Goals of mechanical ventilation are preservation of organ function and providing opportunity for the primary inciting events to resolve.

Oxygenation Goal

In the ICU, the normal goal is to maintain an oxygen saturation of 90–94% in most circumstances, utilizing the lowest possible FiO_2 to reduce oxygen toxicity. However, in pregnancy, oxygen saturation should be maintained slightly higher (>95%) to prevent hypoxia to the fetus. Although fetal hemoglobin will extract oxygen

from maternal hemoglobin, if oxygen delivery to the placenta is compromised, the fetus may become hypoxic, so a margin of safety must be maintained.

Ventilation Goal

In adults, especially in cases of ARDS and obstructive lung disease, achieving normocapnea, leads to more volutrauma, biotrauma, and atelectrauma. The current goals of ventilation are permissive hypercapnea and maintaining the pH between 7.25 and 7.35. This is accomplished predominantly by the use of small tidal volumes. It is not unusual to allow a $PaCO_2$ of 60 mmHg or higher in non-pregnant patients. In pregnancy there is no clear-cut data on the role of permissive hypercapnea. There is a 10 mmHg PaCO2 gradient between maternal and the fetal circulation with fetus being higher *(65)*, and a normal maternal PaCO2 range of 27–34 mmHg. There are a few short-term animal experiments evaluating effects of hypercapnia on uteroplacental blood flow. There were no long-term studies and moreover the hypercapnia was induced rapidly without providing time for changes in the compensatory mechanisms to bring the pH towards more normal levels. On the contrary, Walker, in an unanesthetized sheep model, found no significant changes in uterine blood flow even when the maternal $PaCO_2$ reached 60 mmHg *(66)*. Above 60 mmHg $PaCO_2$, he noted increased uterine vascular resistance, resulting in decreased uterine blood flow. There is no human data regarding the effect of permissive hypoventilation on uteroplacental and umbilical blood flow. Human extrapolation of animal data may not be valid due to multiple reasons. The permissive hypoventilation as applied to patients with ARDS is not a sudden change in minute ventilation, but a gradual change while monitoring the patient *(67)*. The ARDS net protocol provides guidance with regards to the rapidity of CO_2 accumulation and the pH change *(68)*. Sodium bicarbonate infusions can be given to compensate for severe acidosis without causing maternal alkalosis. It is not clear how quickly bicarbonate transfer occurs through the maternal fetal circulation to correct fetal acidosis making this option less than optimal. There are no published studies investigating the use of low tidal volumes in the treatment of pregnant patients with acute lung injury and ARDS. The proven efficacy of low tidal volume strategy in non-pregnant patients with ARDS provides strong support for its universal use *(65)*. In managing the ARDS patients, we routinely use small tidal volumes, permissive hypoventilation (up to $PaCO_2$ of 60 mmHg) while closely monitoring the fetal status with biophysical profile. Doppler studies of uterine artery blood flow could be considered for further fetal monitoring, but no data exists to guide its use.

Respiratory Physiology Issues in Pregnancy

During pregnancy, minute ventilation increases by 50%, mostly due to increase in tidal volume without any significant change in respiratory rate. The increase in net ventilation is due to changes in maternal, placenta, and fetal oxygen requirements and CO_2 production. The increased placental production of progesterone affects the maternal set point for CO_2, resulting in mild compensated respiratory alkalosis. Respiratory muscle function and respiratory compliance are unaffected by pregnancy *(69)*. Chest wall compliance is however decreased because of the enlarging uterus. Functional residual capacity, expiratory reserve volume, and residual volume decrease by 4–20%. Inspiratory capacity increases by 5–10% with overall no change in the vital capacity or total lung capacity *(70)*. Mean inspiratory flow remains unchanged, whereas ventilatory drive and tidal volume increase, resulting

in an increase in minute ventilation and alveolar ventilation. This increased minute ventilation leads to a reduction in $PaCO_2$ by 7–10 mmHg *(71)*. Serum bicarbonate level is reduced to 18–21 mEq/L due to enhanced bicarbonate excretion by the maternal kidneys to maintain an arterial pH between 7.4 and 7.45. The hypocarbia leads to an increase in PaO2 to 100–105 mmHg. The data on maternal hyperventilation and its effect on the fetus and uteroplacental circulation are controversial. Many believe that maternal hyperventilation causes reduction in uteroplacental blood flow due to uteroplacental vasoconstriction leading to fetal hypoxia, acidosis, and neonatal depression *(72–75)*. There are few reports, which note that maternal hyperventilation does not lead to fetal cerebral ischemia *(76)*.

Ventilator Setup: Choose

Control Variable:
Volume control vs. Pressure control

Mode of Ventilation:
A/C, SIMV, SIMV with PS, CPAP with PS

Rate:
Sufficient to maintain pH in the range of 7.35–7.4

Tidal volume:
Keep plateau pressure less than 30 cm H_2O
ARDS Net vT = 8→6 mL/Kg of predicted body weight
Predicted body weight = [45.5 + 2.3 (height in inches—60)] *(66)*

(predicted body weight is based on non-pregnant data for the lack of a better predictor)

Flow:
Adequate to satisfy patient's demands

Flow profile:
Square wave—for obstructive lung disease and high minute ventilation
Decelerating—for all others for better patient comfort

PEEP:
Use the lowest PEEP that provides the best oxygenation
Lowest PEEP that provides the Best compliance

I:E ratio
At least 1:2.5 or better
In Obstructive lung disease > 1:4 if possible

Monitor auto-PEEP
Especially in situations with
High minute ventilation and Obstructive lung disease

Monitor Respiratory mechanics
Helps in trouble shooting at a later time

Calculations Important for Respiratory Monitoring

Static compliance = tidal volume/(plateau pressure-PEEP)
Dynamic compliance = tidal volume/(peak pressure-PEEP)
Airway resistance = (peak pressure-plateau pressure)/flow in L/sec

Measurement of peak inspiratory pressure, plateau pressure, airway resistance along with auto-PEEP help in trouble shooting ventilator alarms. Figure 23.1 outlines an algorithmic approach for acute deterioration in a ventilated patient *(77)*.

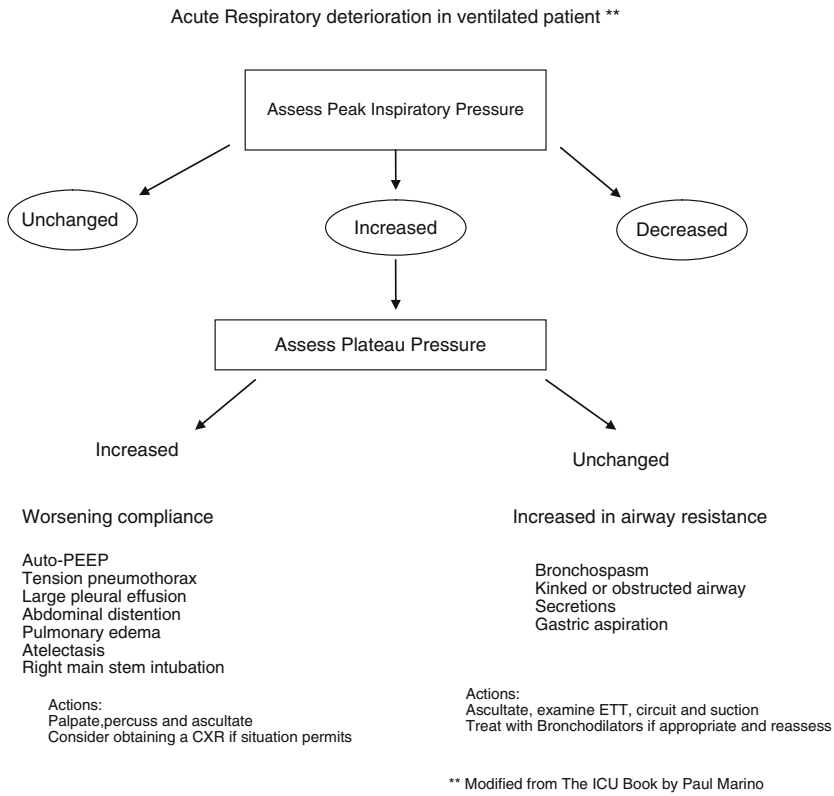


Figure 23.1 Assessment algorithm for acute respiratory deterioration in an intubated patient-Modified from *(77)*

Weaning

Guidelines for weaning from mechanical ventilation are similar to the general ICU population. The foremost being the resolution of the initial indication for intubation and mechanical ventilation, patient has adequate mentation, and can maintain oxygenation and ventilation after extubation. Daily awakening and spontaneous breathing trials are the most effective mode of liberation from mechanical ventilation. The following general parameters are helpful in assessment for extubation. One would like to guarantee post extubation oxygen saturation greater than 95% with supplemental oxygen in pregnant women.

Weaning Parameters

O2 sat of 92% while receiving FiO2 of 0.4 or less
PO2/FiO2 ratio >250
Shunt fraction (QS/QT) less than 20%
Respiratory rate <30 breaths/min
Tidal volume >10 mL/kg
Negative inspiratory force of >–20 cm of water
Minute ventilation <10 L/min
Dead space/tidal volume ratio <0.6
Rapid shallow breathing index (RSBI) of <105.

Conclusion

The inability to maintain a patent airway after attempts at failed intubation remains a major concern of anesthesia-related maternal morbidity and mortality and is also a significant source of malpractice claims in obstetrics *(21, 78)*. Teamwork between an anesthesiologist and an obstetrician is absolutely essential for the safety of both the mother and baby. Invariably, it seems that airway emergencies have a way of occurring at the worst time possible, especially during nighttime when there is reduced staffing. The overall decline in the use of general anesthesia in obstetric practice has implications for both training and skill maintenance in airway management in obstetric patients.

When dealing with a difficult airway in a parturient, it is mandatory to have a good working knowledge of alternative airway devices and rescue strategies if conventional attempts at securing an airway fail. It is therefore essential that a plan for airway emergencies be developed and understood by all members of the team caring for the patient. This plan may vary from institution to institution, depending on the available personnel and equipment. Knowledge of airway management has greatly increased in the last decade with various new tools and techniques but many anesthesia practitioners fail to keep their skills up to date. These skills can only be gained with positive attitude toward learning and should be the goal to enhance safe airway management. In our institution, a difficult airway cart is placed outside the operating rooms where cesarean sections are performed. Every operating room is equipped with various size LMAs and combitube. The trainees gain experience with airway equipment during their difficult airway rotation in all elective cases.

Management of respiratory failure in pregnancy is similar to management in non-pregnant women, keeping in mind the normal physiologic changes that occur in the parturient. Protective mechanical ventilation using smaller tidal volumes, elevation of the head of the bed to prevent ventilator associated pneumonia, and routine use of sedation holidays and weaning trials will minimize complications due to mechanical ventilation.

References

1. Hawkins JL. Anesthesia-related maternal mortality. Clin Obstet Gynecol 2003;46(3): 679–687.
2. Lewin SB, Cheek TG, Deutschman CS. Airway management in the obstetric patient. Crit Care Clin 2000;16(3):505–513.
3. Hawthorne L, Wilson R, Lyons G, Dresner M. Failed intubation revisited: 17-yr experience in a teaching maternity unit. Br J Anaesth 1996;76(5):680–684.
4. Jouppila R, Jouppila P, Hollmen A. Laryngeal oedema as an obstetric anaesthesia complication: case reports. Acta Anaesthesiol Scand 1980;24(2):97–98.
5. Kuczkowski KM, Reisner LS, Benumof JL. Airway problems and new solutions for the obstetric patient. J Clin Anesth 2003;15(7):552–563.
6. Norwitz ER, Robinson JN, Malone FD. Pregnancy-induced physiologic alterations. In: Dildy GA, Belfort MA, Saade GR, Phelan JP, Hankins GD, Clark SL, editors. Critical Care Obstetrics. 4th ed. Malden, MA: Blackwell Science; 2004 p. 19–42.
7. Seager SJ, Macdonald R. Laryngeal oedema and pre-eclampsia. Anaesthesia 1980;35(4):360–362.
8. Brimacombe J. Acute pharyngolaryngeal oedema and pre-eclamptic toxaemia. Anaesth Intensive Care 1992;20(1):97–98.

9. Brock-Utne JG, Downing JW, Seedat F. Laryngeal oedema associated with pre-eclamptic toxaemia. Anaesthesia 1977;32(6):556–558.
10. O'Sullivan G, Scrutton M. NPO during labor. Is there any scientific validation? Anesthesiol Clin North America 2003;21(1):87–98.
11. Cohen SE. The aspiration syndrome. Clin Obstet Gynaecol 1982;9(2):235–254.
12. Carp H, Jayaram A, Stoll M. Ultrasound examination of the stomach contents of parturients. Anesth Analg 1992;74(5):683–687.
13. Cheek TG, Gutsche BB. Pulmonary aspiration of gastric contents. In: Hughes SC, Levinson G, Rosen MA, editors. Shnider and Levinson's Anesthesia for Obstetrics. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002 p. 391–405.
14. Johnson MD, Ostheimer GW. Airway management in obstetric patients. Semin Anesth 1992; XI(1):1–12.
15. Morgan BM, Magni V, Goroszenuik T. Anesthesia for emergency cesarean section. Br J Obstet Gynaecol 1990;97:420–424.
16. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003;98(5):1269–1277.
17. Levine RJ, Lam C, Qian C et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 2006;355(10):992–1005.
18. Venkatesha S, Toporsian M, Lam C et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 2006;12(6):642–649.
19. Lam C, Lim KH, Karumanchi SA. Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. Hypertension 2005;46(5):1077–1085.
20. Levine RJ, Maynard SE, Qian C et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350(7):672–683.
21. Ezri T, Szmuk P, Evron S, Geva D, Hagay Z, Katz J. Difficult airway in obstetric anesthesia: a review. Obstet Gynecol Surv 2001;56(10):631–641.
22. Heller PJ, Scheider EP, Marx GF. Pharyngolaryngeal edema as a presenting symptom in preeclampsia. Obstet Gynecol 1983;62(4):523–525.
23. Pritchard JA. Severe preeclampsia with pharyngolaryngeal edema. Obstet Gynecol 1984;64(1):146–147.
24. Rasmussen GE, Malinow AM. Toward reducing maternal mortality: the problem airway in obstetrics. Int Anesthesiol Clin 1994;32(2):83–101.
25. Ramanathan J, Bennett K. Pre-eclampsia: fluids, drugs, and anesthetic management. Anesthesiol Clin North America 2003;21(1):145–163.
26. Rocke DA, Scoones GP. Rapidly progressive laryngeal oedema associated with pregnancy-aggravated hypertension. Anaesthesia 1992;47(2):141–143.
27. Perlow JH, Kirz DS. Severe preeclampsia presenting as dysphonia secondary to uvular edema. A case report. J Reprod Med 1990;35(11):1059–1062.
28. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. Anesthesiology 1993;79(6):1210–1218.
29. Kaiser PS, Kirby RS. Obesity as a risk factor for cesarean in a low-risk population. Obstet Gynecol 2001;97(1):39–43.
30. Pathi A, Esen U, Hildreth A. A comparison of complications of pregnancy and delivery in morbidly obese and non-obese women. J Obstet Gynaecol 2006;26(6):527–530.
31. Saravanakumar K, Rao SG, Cooper GM. The challenges of obesity and obstetric anaesthesia. Curr Opin Obstet Gynecol 2006;18(6):631–635.
32. Endler GC, Mariona FG, Sokol RJ, Stevenson LB. Anesthesia-related maternal mortality in Michigan, 1972 to 1984. Am J Obstet Gynecol 1988;159(1):187–193.
33. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth 2000; 85(1):91–108.
34. Cooper GM, McClure JH. Maternal deaths from anaesthesia. An extract from Why Mothers Die 2000–2002, the Confidential Enquiries into Maternal Deaths in the United Kingdom: Chapter 9: Anaesthesia. Br J Anaesth 2005;94(4):417–423.

35. Chadwick HS. Obstetric anesthesia closed claims update II. Anesthesiol Newsl 1999;63:1–6.
36. Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. Crit Care Clin 2004;20(4):577–607.
37. Anesthesia for emergency deliveries. ACOG committee opinion: committee on obstetrics: maternal and fetal medicine. Number 104 – March 1992. Int J Gynaecol Obstet 1992;39(2):148.
38. Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. Anaesthesia 1987;42(5):487–490.
39. Lyons G. Failed intubation. Six years' experience in a teaching maternity unit. Anaesthesia 1985;40(8):759–762.
40. Glassenberg R. General anesthesia and maternal mortality. Semin Perinatol 1991;15(5):386–396.
41. Bucklin BA. Gerard W. Ostheimer "what's new in obstetric anesthesia" lecture. Anesthesiology 2006;104(4):865–871.
42. Han TH, Brimacombe J, Lee EJ, Yang HS. The laryngeal mask airway is effective (and probably safe) in selected healthy parturients for elective Cesarean section: a prospective study of 1067 cases. Can J Anaesth 2001;48(11):1117–1121.
43. Stamer UM, Messerschmidt A, Wulf H, Hoeft A. Equipment for the difficult airway in obstetric units in Germany. J Clin Anesth 2000;12(2):151–156.
44. Gataure PS, Hughes JA. The laryngeal mask airway in obstetrical anaesthesia. Can J Anaesth 1995;42(2):130–133.
45. Niazi A, Cummins E, Walsh K. Difficult airway equipment in obstetric units in the republic of Ireland: results of a national survey. Eur J Anaesthesiol 2004;21(11): 861–863.
46. Awan R, Nolan JP, Cook TM. Use of a ProSeal laryngeal mask airway for airway maintenance during emergency Caesarean section after failed tracheal intubation. Br J Anaesth 2004;92(1):144–146.
47. Keller C, Brimacombe J, Lirk P, Puhringer F. Failed obstetric tracheal intubation and postoperative respiratory support with the ProSeal laryngeal mask airway. Anesth Analg 2004;98(5):1467–1470, table.
48. Cook TM, Brooks TS, Van der WJ, Clarke M. The Proseal LMA is a useful rescue device during failed rapid sequence intubation: two additional cases. Can J Anaesth 2005;52(6):630–633.
49. Sharma B, Sahai C, Sood J, Kumra VP. The ProSeal laryngeal mask airway in two failed obstetric tracheal intubation scenarios. Int J Obstet Anesth 2006;15(4):338–339.
50. Bullingham A. Use of the ProSeal laryngeal mask airway for airway maintenance during emergency Caesarean section after failed intubation. Br J Anaesth 2004;92(6):903.
51. Minville V, N'guyen L, Coustet B, Fourcade O, Samii K. Difficult airway in obstetric using Ilma-Fastrach. Anesth Analg 2004;99(6):1873.
52. Gonzalez GG, Marenco de la Fuente ML, Bertomeu CM. Fastrach mask to resolve a difficult airway during emergency cesarean section. Rev Esp Anestesiol Reanim 2005; 52(1):56–57.
53. Wissler RN. The esophageal-tracheal Combitube. Anesthesiol Rev 1993;20(4):147–152.
54. Munnur U, Karnad DR, Bandi VD et al. Critically ill obstetric patients in an American and an Indian public hospital: comparison of case-mix, organ dysfunction, intensive care requirements, and outcomes. Intensive Care Med 2005;31(8):1087–1094.
55. Hazelgrove JF, Price C, Pappachan VJ, Smith GB. Multicenter study of obstetric admissions to 14 intensive care units in southern England. Crit Care Med 2001;29(4):770–775.
56. Jenkins TM, Troiano NH, Graves CR, Baird SM, Boehm FH. Mechanical ventilation in an obstetric population: characteristics and delivery rates. Am J Obstet Gynecol 2003;188(2):549–552.
57. Ben LD, Daouas N, Ben JK, Slama A, Jegham H. Maternal emergencies requiring controlled ventilation: epidemiology and prognosis. J Gynecol Obstet Biol Reprod (Paris) 2002;31(3):256–260.

58. Reddy R, Evans E, Khoo O, Allen MB. Pregnancy in kyphoscoliosis: benefit of non-invasive ventilatory support. J Obstet Gynaecol 2005;25(3):267–268.
59. Diaz-Lobato S, Gomez Mendieta MA, Moreno Garcia MS, Mayoralas-Alises S, Arpa Gutierrez FJ. Two full-term pregnancies in a patient with mitochondrial myopathy and chronic ventilatory insufficiency. Respiration 2005;72(6):654–656.
60. Warren J, Sharma SK. Ventilatory support using bilevel positive airway pressure during neuraxial blockade in a patient with severe respiratory compromise. Anesth Analg 2006;102(3):910–911.
61. Kahler CM, Hogl B, Habeler R et al. Management of respiratory deterioration in a pregnant patient with severe kyphoscoliosis by non-invasive positive pressure ventilation. Wien Klin Wochenschr 2002;114(19–20):874–877.
62. Cole DE, Taylor TL, McCullough DM, Shoff CT, Derdak S. Acute respiratory distress syndrome in pregnancy. Crit Care Med 2005;33(10 Suppl):S269–S278.
63. Hess D, Kacmarek R. Essentials of Mechanical Ventilation. First ed. McGraw-Hill: 1996.
64. Hess D, Branson R. New modes of ventilation. In: Hill N, Levy M, editors. Ventilator Management Strategies for Critical Care. New York: Marcel Dekker, Inc; 2001 p. 171–211.
65. Campbell LA, Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med 2001;163(5):1051–1054.
66. Walker AM, Oakes GK, Ehrenkranz R, McLaughlin M, Chez RA. Effects of hypercapnia on uterine and umbilical circulations in conscious pregnant sheep. J Appl Physiol 1976;41(5 Pt. 1):727–733.
67. ARDS Net. ARMA protocol. ARDS Net 2007;2-14-2007. Ref Type: Electronic Citation.
68. 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(18):1301–1308.
69. Contreras G, Gutierrez M, Beroiza T et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144(4):837–841.
70. Baldwin GR, Moorthi DS, Whelton JA, MacDonnell KF. New lung functions and pregnancy. Am J Obstet Gynecol 1977;127(3):235–239.
71. Crapo RO. Normal cardiopulmonary physiology during pregnancy. Clin Obstet Gynecol 1996;39(1):3–16.
72. Morishima HO, Daniel SS, Adamsons K, Jr., James LS. Effects of positive pressure ventilation of the mother upon the acid-base state of the fetus. Am J Obstet Gynecol 1965;93:269–273.
73. Motoyama EK, Rivard G, Acheson F, Cook CD. Adverse effect of maternal hyperventilation on the fetus. Lancet 1966;1(7432):286–288.
74. Lumley J, Wood C. Effect of changes in maternal oxygen and carbon dioxide tensions on the fetus. Clin Anesth 1974;10(2):121–137.
75. Behrman RE, Parer JT, Novy MJ. Acute maternal respiratory alkalosis (hyperventilation) in the pregnant rhesus monkey. Pediatr Res 1967;1(5):354–363.
76. Bruce DA. Effects of hyperventilation on cerebral blood flow and metabolism. Clin Perinatol 1984;11(3):673–680.
77. Marino P. Principles of mechanical ventilation. In: Marino P, editor. The ICU Book. Second ed. Baltimore, MD: Williams & Wilkins; 1997 p. 421–433.
78. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: a closed claims analysis. Anesthesiology 1990;72(5):828–833.

Index

D