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96 THE LUNGS IN OBSTETRIC AND GYNECOLOGIC DISEASES

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INTRODUCTION

Both respiratory physiology and the respiratory tract's susceptibility to disease are uniquely altered in gynecologic and obstetric conditions, including normal pregnancy. This chapter summarizes normal physiologic alterations during pregnancy and considers pathologic diseases and disorders that arise during pregnancy. Airway disorders, infectious diseases, pulmonary vascular and embolic disorders, and acute lung injury are discussed. Finally, pleural and parenchymal diseases that arise as a consequence of gynecologic conditions are addressed.

PHYSIOLOGIC ALTERATIONS DURING NORMAL PREGNANCY

Profound alterations of respiratory function and cardiovascular physiology accompany normal pregnancy in healthy women; these conditions contribute to many of the disorders of the lungs during pregnancy. The adaptive changes during the gravid period are designed to support maternal and fetal well-being during the special stresses of fetal growth and parturition, but they may exacerbate some underlying disorders and confuse interpretation of laboratory and imaging studies used to assess many other common conditions.

ALTERATIONS IN RESPIRATORY PHYSIOLOGY

Upper airway, particularly nasal, mucosal edema is common in normal pregnancy. About 20% of gravid women complain of rhinitis symptoms, now attributed at least partially to placental growth hormone's effects on mucosal congestion.[1] The symptoms begin in the first trimester and persist throughout gestation. Many patients thought to have rhinitis of pregnancy may actually have other or coincident causes of rhinitis.[2] An important implication of nasal mucosal edema in pregnancy is that it predisposes to nosebleeds, including from nasal intubations, so an oral approach is favored if intubation is required at the time of delivery.

Chest wall configuration is also altered, partially due to a 50% increase in the average costal angle[3] and partially due to an increase in the circumference of the lower chest wall. Diaphragmatic position is elevated 4 to 5 cm, but excursion does not diminish.[3] Muscle strength, as measured by maximum transdiaphragmatic pressure, does not appear to be diminished from its usual mean value of about 95 cm H_2O,[4] allowing reserve for both the augmented minute ventilation of normal pregnancy and the stresses of delivery.

Important changes take place in lung function and lung volumes. The loss of lung volume resulting from elevation of the diaphragm is only partially offset by the increase in chest wall diameter, and therefore *functional residual capacity* (FRC) is diminished by about 18%, or 300 to 500 mL.[5] This reduction in FRC comprises an equal reduction in both the expiratory reserve volume and the residual volume.[3,5] The loss of FRC at term is made worse by recumbency, when diaphragm elevation is greatest because of the higher intra-abdominal pressure. Increased pulmonary blood volume in pregnancy may also serve to lower the FRC.[6] This reduction in FRC is associated clinically with increased uptake and elimination of inhalational anesthetics and with rapid desaturation during hypopnea, as a result of the loss of the oxygen reservoir function of end-expiratory lung volume.[7] Endotracheal intubation at term is thus substantially more hazardous than in nongravid patients.

Airway function is largely unchanged during pregnancy.[3] Airway resistance may actually decrease slightly. Routine measurements of air flow, such as the FEV_1 and flow rates at midexpiratory lung volume (forced expiratory flow between 25% and 75% of FVC, or $FEF_{25\%–75\%}$) are thus valuable in assessing dyspnea during pregnancy.

The most striking changes are in respiratory drive and minute ventilation. Central drive, as assessed by the inspiratory pressure measured 100 msec after airway occlusion at the onset of inspiration ($P_{0.1}$), is increased by 13 weeks and continues to increase to week 37 of gestation, returning to normal by 24 weeks after delivery.[4] These serial changes in respiratory drive appear to correlate with changes in serum progesterone levels.[4,8] Carbon dioxide production itself increases one third to one half by the last trimester, but this is more than made up for by the greatly augmented ventilation, so primary respiratory alkalosis with renal

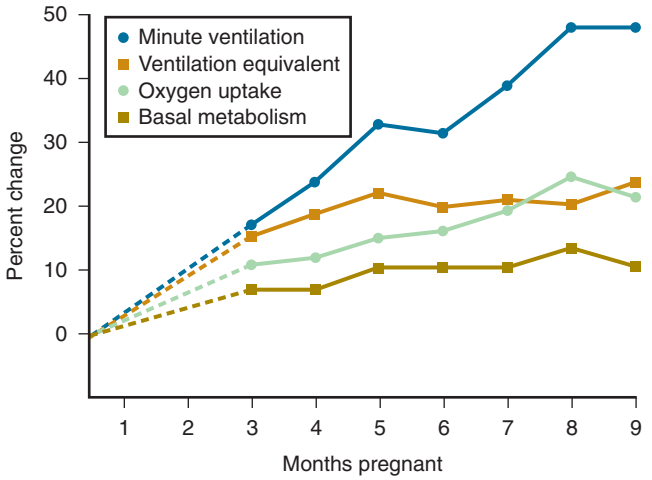

Figure 96-1 The physiology of pregnancy. The expected values for minute ventilation, the ventilatory equivalent for oxygen, oxygen uptake, and basal metabolism are shown at monthly intervals throughout pregnancy. (From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. *Anesthesiology* 26:381, 1965.)

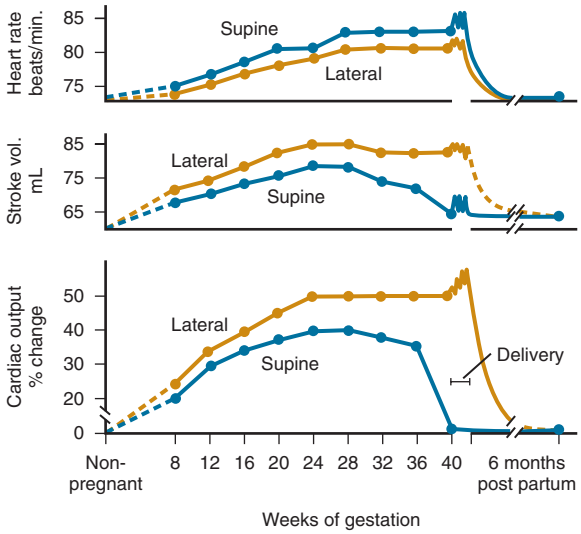

Figure 96-2 Changes in physiology in the supine position. Because the gravid uterus compromises venous return, there are characteristic changes in maternal heart rate, stroke volume, and cardiac output during pregnancy with the pregnant subject in the supine compared to the lateral position. (From Yanagihara N, von Leden H, Werner-Kukuk E: The physical parameters of cough: the larynx in a normal single cough. *Acta Otolaryngology* (Stockholm) 61:495–510, 1966.)

bicarbonate wasting as compensation is a normal finding.[9] Arterial blood gas measurements typically show the pH ranging from 7.40 to 7.47, with P_{CO_2} reaching as low as 28 to 32 mm Hg. P_{O_2} rises slightly as a result of the increase in alveolar ventilation.

Most of the increase in minute ventilation is due to a 30% to 35% increase in tidal volume. Respiratory rate is unchanged early and rises only about 10% later in pregnancy. Oxygen consumption increases 20% to 33% in pregnancy, owing to both maternal and fetal metabolic demands. Changes in some of these parameters are shown in Figure 96-1.

ALTERATIONS IN CARDIOVASCULAR PHYSIOLOGY

Adaptive cardiovascular changes are designed to support both maternal and fetal circulations but contribute to the risk for hydrostatic pulmonary edema; accordingly, cardiac disorders during pregnancy often present as respiratory failure. During normal pregnancy, maternal blood volume increases by about 2 L, or 40%.[10,11] Red blood cell mass increases as well, but only by 20% to 30%, accounting for the normal 10% to 12% decrease in hematocrit.[11,12] Plasma oncotic pressure also drops as intravascular volume expands, increasing the risk for pulmonary edema at lower intravascular hydrostatic pressures. During the 24 hours after parturition, oncotic pressure falls further because of blood loss and mobilization of extravascular fluid.

The enlarged intravascular volume of pregnancy is accommodated chiefly by venous capacitance vessels. Central venous pressure and pulmonary capillary occlusion ("wedge") pressure are unchanged, reflecting an increase in left ventricular compliance, as evidenced by the enlarged cardiac silhouette seen on chest radiograph. The increased left ventricular end-diastolic volume results in an augmented stroke volume (ejection fraction is little changed), but *systemic vascular resistance* (SVR) diminishes.[12,13] These changes account for the 30% to 45% increase in cardiac output reached by 25 to 32 weeks of gestation. After 5 weeks, heart rate increases as well,[14] but less so than stroke volume. Some of these changes, as well as the effects of supine versus lateral positioning, are depicted in Figure 96-2.

OBSTETRIC DISORDERS AND THE LUNGS

Gravid and newly postpartum patients may develop pregnancy-specific disorders but also continue to experience common disorders that arise outside of pregnancy; the natural history or frequency of coexisting disorders is sometimes altered by the gravid state. Even for diseases not altered by pregnancy, management requires special knowledge of the safety of therapies. Specific diseases are considered here with these principles in mind.

OBSTRUCTIVE AIRWAY DISEASE

Asthma

Asthma affects 4% to 8% of the general population and is the most common pulmonary disorder in pregnancy. The *Working Group on Asthma and Pregnancy of the National Asthma Education and Prevention Program* (NAEPP) estimated that 3.7% to 8.4% of pregnancies are complicated by asthma.[15] Maternal asthma increases the risk of preeclampsia, preterm birth, infants with low birth weight, intrauterine growth restriction or congenital malformations, and perinatal death.[16]

Studies examining the hormonal milieu have suggested that progesterone might diminish smooth muscle contractility in the lung, as it does in the uterus and gut. Juniper

and colleagues[17] performed serial measurements of bronchial reactivity to methacholine challenge in 16 women before and during pregnancy and found a decrease in airway hyperresponsiveness. Clinical and epidemiologic studies, however, have failed to provide convincing evidence of any consistent change in the natural history of asthma during pregnancy. Turner and coworkers,[18] for example, compiled the results of nine studies of asthma symptoms reported by pregnant women. Among them, 22% reported worsening, 29% reported improvement, and 49% reported no change. Other studies have reported similar figures, with about 23% to 42% worsening, 18% to 36% improving, and 40% exhibiting no change.[19,20] The differences reported in the natural history probably reflect differences in study populations, smoking history, ethnicity, or other variables.[21]

Fetal and maternal outcome for asthma and pregnancy have also been examined in a variety of studies since 1980. Adverse outcomes, including an increased incidence of preterm labor, low neonatal birth weight, increased perinatal mortality, preeclampsia, vaginal hemorrhage, chronic hypertension, and complicated labor, have been reported.[15,21] A large epidemiologic study from Sweden did confirm an association of asthma with perinatal mortality and low birth weight.[22] Nonetheless, adequate therapy tailored to disease severity is associated with good outcomes.[23] Therapy of asthma in pregnancy should be individualized according to severity of disease and frequency of symptoms, as outlined by the NAEPP.[15] Objective measurement of lung volumes and flow should be part of the regimen. Initial office spirometry is recommended, and home peak flow monitoring should be considered. For women who have asthma attacks during labor, fetal monitoring is considered essential by the NAEPP.

Therapy should be based on a step approach.[15] Mild intermittent asthma is best managed with inhaled short-acting β_2-agonists, for symptomatic relief. Asthma that causes more than occasional symptoms should be treated daily with anti-inflammatory therapy, with the preferred choice being inhaled corticosteroids. Budesonide is the best studied and hence preferred, although substantive safety data exist for beclomethasone as well. Alternative therapies include cromolyn, sustained-release theophylline, or a leukotriene antagonist.[15] Frequent need for short-acting β_2-agonists should prompt institution of, or an increase in, the use of anti-inflammatory agents to treat, rather than to mask, a deteriorating clinical course. Long-acting β-agonists should only be used concurrently with long-acting inhaled corticosteroids.[21] Finally, the addition of rapidly tapered courses of oral corticosteroids should be considered for those with acute severe asthma or patients with active symptoms who are already using inhaled steroids and β-agonists. Daily or alternate-day oral steroid administration (e.g., prednisone 40 mg/day) is sometimes required.[15] Extensive practice algorithms have been made available by the NAEPP Working Group on Asthma and Pregnancy.[15]

A large body of literature has examined the topic of possible teratogenicity of agents used in the pharmacotherapy of asthma in pregnancy. In general, the risks of poorly controlled asthma far outweigh the possible hazards of drug therapy. Both animal and human studies of β_2-agonists, administered either by inhalation or systemically, have indicated an acceptable safety profile for the fetus. They are also safe for use during lactation. Nonselective β-agonists, such as epinephrine, carry a risk of uterine vasoconstriction in animal models[25] and are probably best avoided. Acceptable β_2-agonists in pregnancy include metaproterenol, albuterol, pirbuterol, bitolterol, and terbutaline. Because the toxicology and pharmacology of the long-acting β-agonists salmeterol and formoterol are expected to be similar to shorter-acting β_2-agonists, these drugs have been recommended in patients with poor control on a combination of inhaled long-acting corticosteroids and short-acting β-agonists.[23,24] Limited data suggest that these drugs are safe in pregnancy.[26]

Theophylline also has a long history of use during pregnancy and is considered safe, but the therapeutic range in plasma should be lowered to 5 to 12 μg/mL because of diminished protein binding during pregnancy. Theophylline passes freely to the fetus, and newborns occasionally show signs of theophylline toxicity, particularly when maternal blood levels are high. Theophylline is also transmitted to breast milk, with a milk-to-serum ratio of about 0.70; but, in general, less than 1% of the maternal dose is transferred to the infant. Animal studies suggest that the leukotriene inhibitors montelukast and zafirlukast are safe in pregnancy, and they can be continued in patients who have previously responded.[25,27,28] Zileuton should be avoided because animal studies have raised questions about its safety in pregnancy.

Animal studies have shown an increased incidence of cleft palate with use of corticosteroids, and limited human data support this association, with an estimated excess risk of 0.2% to 0.3% when used in the first trimester.[15] Systemic corticosteroids have also been reported to cause intrauterine growth restriction, but of a relatively modest degree. Halogenated corticosteroids do not cross the placenta easily, and so fetal and neonatal adrenal suppression is not a major concern with these compounds.[15] Overall, risk-benefit considerations nonetheless favor their use in persistent severe asthma with exacerbations unresponsive to other measures. One study suggests that higher doses of inhaled corticosteroids (i.e., beclomethasone > 1000 mcg/day) may be associated with a small increased risk of congenital abnormalities, although the confounding effect of increased asthma severity cannot be excluded.[29] There are limited data to confirm the safety of newer inhaled costicosteroids.[26] Table 96-1 summarizes the U.S. *Food and Drug Administration* (FDA) safety classification for agents useful for the treatment of asthma in pregnancy.

Labor and delivery can be especially hazardous for asthmatic patients, partly because of the drugs commonly administered. Narcotics other than fentanyl release histamine, which may worsen bronchospasm. Lumbar epidural analgesia is generally preferred, but if general anesthesia is to be used, pretreatment with atropine or glycopyrrolate assists bronchodilation. Ketamine is the preferred anesthetic, although halogenated anesthetics at low concentrations may provide bronchodilation as well.[15] Preterm labor may be safely treated with nifedipine or magnesium sulfate. Oxytocin is the optimal labor induction agent and is useful for postpartum hemorrhage, but 15-methyl prostaglandin F_{2a}, methylergonovine, and ergonovine may cause bronchospasm and should be avoided if possible.

Table 96-1 Potential Fetal Risk of Drug Therapy in Pregnancy According to the FDA Classification for Safety in Pregnancy*

Drug	FDA Classification†
ASTHMA THERAPY	
Inhaled Bronchodilators	
Albuterol (salbutamol)	C
Terbutaline	C
Ipratropium	B
Salmeterol	C
Formoterol	C
Inhaled Corticosteroids	
Beclomethasone	C
Budesonide	B
Fluticasone	C
Leukotriene Antagonists	
Zafirlukast	B
Montelukast	B
Zileuton	C
Other Agents for Asthma	
Theophylline	C
Cromolyn	B
Systemic corticosteroids	B
ANTICOAGULANTS	
Heparin	C
Low-molecular-weight heparin	B
Warfarin	X
ANTIBIOTICS	
Penicillins	B
Cephalosporins	B
Macrolides	B/C
Quinolones	C
Clindamycin	B
Tetracyclines	D

*Although the U.S. Food and Drug Administration (FDA) classification provides an overview of fetal risk, it is being replaced by a narrative description of known drug effects. Detailed information should therefore be consulted for individual drugs. Classification of individual drugs may change as the literature evolves.

†Class B: Animal studies do not indicate a risk to the fetus, and there are no controlled human studies; *or* animal studies do show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Class C: Studies in animals have shown the drug to have teratogenic or embryocidal effects, but there are no controlled studies in women; *or* no studies are available in either animals or women. Class D: Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks. Class X: Studies in animals or humans have demonstrated fetal abnormalities, *or* there is evidence of fetal risk based on human experience, and the risk of the drug clearly outweighs any possible benefit. These drugs are contraindicated in pregnancy.

Cystic Fibrosis

Cystic fibrosis (CF), present in about 1 in 1500 whites and 1 in 17,000 blacks, is a common genetic disease. With improved therapy, median survival has now increased to 37 years.[30] Up to 4% of female CF patients between the ages of 17 and 37 may be pregnant at any time,[31] despite the frequent infertility of women due to delayed sexual development. Pregnancy in CF patients, as might be anticipated, has been associated with adverse fetal and maternal outcomes.[32,33] Several recent small case series have demonstrated good maternal and neonatal outcome in women with CF.[34-36] Premature delivery was more common in women with worse baseline FEV_1, and gestational diabetes was common. In a large U.S. review of 680 gravid women with CF enrolled in the U.S. Cystic Fibrosis Foundation National Patient Registry, from 1985 to 1997, survival was actually better in the gravid group than in the matched 3327 control patients with CF.[37] Women with CF who became pregnant had higher predicted percentages of FEV_1 and higher weights. Pregnancy was not clearly harmful in any subgroup, after severity adjustment for age, *Pseudomonas aeruginosa* colonization, pancreatic function, and FEV_1. In another case-control study, pregnancy had little effect on patients with stable CF, although poor outcomes were seen in those with severe disease.[38] As might be anticipated, most studies suggest that risk stratifies according to severity of illness.[33,38] Declines in pulmonary function tend to mirror severity-adjusted control subjects, and clearly CF patients require substantially more care and have more visits to physicians when pregnant than when not.[39] Prepregnancy counseling, particularly for women with more severe disease, is essential in limiting excessive maternal and fetal risk.

INFECTIOUS DISEASES

Bacterial Pneumonia

Pneumonia is a leading cause of maternal and fetal morbidity and mortality.[40-42] Maternal mortality from pneumonia in nonimmunocompromised hosts ranged from 0% to 4% in series published since 1980.[40-42] The reported incidence varies widely, from 0.4 to 2.7 per 1000 deliveries,[43] but may not be higher than that in the general population. One report, however, indicated that pneumonia may be increasing in incidence, with *human immunodeficiency virus* (HIV) infection and chronic disease the major risk factors.[40] Postpartum pneumonia may develop in the first 6 weeks after delivery and is more common after Cesarean section.[44]

Pregnancy increases the risk for major complications of pneumonia. In the series by Madinger and colleagues,[42] of 25 patients culled from 25,000 deliveries, 40% suffered major complications, including five intubations, two empyemas, one pneumothorax, and one pericardial tamponade. Similarly, in the series by Briggs and associates,[45] 7 of 34 patients required mechanical ventilation, and 2 died. The *Pneumonia Severity Index* (PSI)[46] used to identify severity of pneumonia for hospital admission does not appear to perform well in the obstetric population, underestimating the need for hospital admission.[47] Pneumonia increases the risk of preterm labor from 4% to 44%.[40-42] The small-for-gestational-age rate is as high as 12%,[40] and intrauterine and neonatal death rates have ranged from 1.9% to 12.0%.[41,42] In all series, underlying chronic illness in the mother has been a powerful predictor of adverse outcome in both fetus and mother.

Pneumonia in pregnancy is most commonly bacterial in origin; the microbiologic spectrum mirrors community-acquired pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* the most common organisms.[40-42] Other common organisms include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.* As in other community-acquired

pneumonias, the causative agent is identified in only about half of the cases. Unfortunately, the diagnosis of pneumonia is frequently delayed because of reluctance to obtain a chest radiograph; a posteroanterior radiograph performed with a grid and a peak voltage of 90 to 120 kV exposes the mother to 5 to 30 mrad but the fetus to 100 times less, or about 300 μrad.[48] A lateral chest radiograph produces greater maternal exposure (150 to 250 mrad) but is usually not required.[48] The hazard to both fetus and mother of delaying the diagnosis greatly exceeds the risk of this small radiation dose. Antibacterial therapy is similar to treatment in the nonpregnant patient, although tetracyclines, quinolones, and metronidazole should be avoided if possible.[48] Erythromycin, azithromycin, and β-lactam antibiotics are preferred because of their favorable safety profile (see Table 96-1).

Viral Pneumonia

Viral pneumonia remains a serious concern in pregnancy. In the influenza pandemic of 1918, the maternal rate of mortality from pneumonia was as high as 50%. In the epidemic of 1957, pregnant women accounted for 10% of fatalities, and about half of the women of childbearing age who died were pregnant.[49] Since then, the maternal mortality rate from influenza A and B pneumonia has been relatively low but still much higher than that in the general population. Because of this, the *Centers for Disease Control and Prevention* (CDC) recommends inactivated influenza vaccine in otherwise healthy women during the second and third trimesters of pregnancy.[50] Although influenza virus does cross the placenta, current opinion holds that it is not likely to be teratogenic to the fetus, despite isolated reports that link influenza with neural tube and other malformations. Amantadine has been used in pregnancy successfully, both as treatment and as prophylaxis, although there have been case reports of cardiovascular defects noted after first-trimester use; and there is considerable influenza viral resistance to the drug.

In the spring of 2009, a previously unrecognized strain of influenza A (H1N1) virus emerged and quickly spread around the world. Reports of clinical experiences with large numbers of hospitalized patients with H1N1 influenza in Australia-New Zealand and throughout the United States confirm that pregnancy confers a high risk of serious disease and appreciable mortality.[51,52] Early treatment of pregnant women and women up to 2 weeks postpartum with oseltamivir or zanamivir appears to be beneficial.[53] Pregnant women are also strongly urged to be vaccinated with the monovalent inactivated injectable H1N1 vaccine—not with the live attenuated vaccine.[54]

Varicella pneumonia, caused by a virus of the DNA herpesvirus group, has also been linked to particularly adverse outcomes during pregnancy. Haake and coworkers[55] report an increased incidence of pneumonitis in pregnant women with primary varicella infection and a 35% mortality rate in this group (over a time period dating back to 1964), compared with 10% in other adults. Data are conflicting, and not all prospective studies have confirmed an increased incidence or mortality in pregnancy.[48] Treatment with acyclovir does appear to reduce mortality in gravid patients and should be used as therapy for active disease.[56] Use of *varicella-zoster immune globulin* (VariZIG) should be considered within 96 hours for susceptible pregnant women who have been exposed to varicella. Administration of VariZIG reduces but does not abolish risk for fetal infection or congenital varicella syndrome, and it is effective in preventing complications of varicella in the mother. Patients should be evaluated similarly to other adults, and a decision made to administer the immune globulin on the basis of immune status, type of exposure, and health status. The currently licensed attenuated live vaccine against varicella is contraindicated in pregnancy.

Severe acute respiratory syndrome (SARS), due to a *novel coronavirus* (HuCoV-SARS), causes pneumonia and *acute respiratory distress syndrome* (ARDS), with respiratory failure in 15% of patients and a mortality rate of 8% to 30%.[57,58] Although data are limited, pregnant women appear to do worse than nonpregnant patients, with four of seven patients requiring ventilatory support in one series.[59] SARS infection adversely affects pregnancy, with miscarriage, fetal distress, and intrauterine death reported, presumably related to hypoxemia.

Fungal Pneumonias

Fungal pneumonias are uncommon in pregnancy. Although there is no evidence that blastomycosis and histoplasmosis are more severe during pregnancy, it does appear that coccidioidomycosis is more likely to disseminate in pregnancy.[60] In the southwestern United States, about 1 in 5000 pregnancies is complicated by *Coccidioides immitis* (see eFig. 37-7).[61] Dissemination is highly probable during the third trimester and has been related to both subtle impairment of cell-mediated immunity and a stimulatory effect of progesterone and 17-β-estradiols on fungal proliferation.[62] Amphotericin is the accepted therapy for disseminated coccidioidomycosis; azoles administered in the first trimester have been associated with branchial cleft abnormalities and should be used only after delivery.

Tuberculosis

Tuberculosis does not appear to be more common or severe in pregnancy. However, presentation may be atypical and disease is often extrapulmonary.[63] Diagnosis may be delayed by a reluctance to perform appropriate imaging studies. Pregnancy does not alter reactivity to tuberculin skin testing, and hence the test should be performed in the recommended groups during pregnancy. Interferon-γ-release assays are also an acceptable means of testing for tuberculous infection (see Chapter 35). Asymptomatic patients with positive skin tests should have their chest radiograph deferred until after 16 weeks of gestation. Symptomatic patients with positive skin tests merit chest radiographs regardless of gestational stage. Isoniazid, rifampin, and ethambutol have acceptable safety profiles in pregnancy and are part of the standard treatment regimens advised by the CDC and American Thoracic Society for pregnant women.[64] There is less collective experience with pyrazinamide, but this drug is recommended for use in pregnancy by the World Health Organization.[64] Worldwide data are accumulating, and pyrazinamide appears to be emerging as a drug that can be considered for treating multidrug-resistant tuberculosis and for HIV-infected women. Streptomycin, by contrast, is clearly associated with congenital deafness and is contraindicated during pregnancy.

PULMONARY EDEMA AND PULMONARY VASCULAR DISEASE

Gravid women are at special risk for pulmonary edema for a variety of reasons, including the hypervolemia and high cardiac output of pregnancy, the occasional need for tocolytic drugs that affect the vascular bed, and the unique vascular and endothelial disorders of pregnancy.

Among these effects, it is noteworthy that colloid osmotic pressure diminishes during pregnancy, although the effect on transcapillary pressure gradients is partially offset by a decrease in interstitial fluid colloid osmotic pressure (as explained in Chapter 6).[65] Etiologically, underlying cardiac disease, use of tocolytic drugs, fluid overload, and preeclampsia are the most common causes for acute pulmonary edema in pregnancy.[65]

Increased Pressure (Cardiogenic) Pulmonary Edema

The cardiovascular adaptations to pregnancy have already been summarized. Their effects on underlying cardiac disorders are predictable. Stenotic valvular lesions are particularly poorly tolerated.[66] Of these, mitral stenosis is the most common symptomatic valvular disease in pregnancy and frequently presents with pulmonary edema, not only during gestation but also immediately postpartum, because of the large shifts in intravascular volume associated with delivery. The gradient across a stenotic mitral valve is augmented by the increases in blood volume, cardiac output, and heart rate that take place during gestation and the puerperium. In aortic stenosis, the increase in cardiac output required for pregnancy worsens the gradient across the valve. As a compensatory mechanism, the left ventricular end-diastolic volume increases, but the low SVR impairs coronary artery filling during diastole and can precipitate ischemic syndromes. The reduction in SVR of pregnancy mitigates the consequences of mitral and aortic regurgitation and of the left-to-right intracardiac shunts of endocardial cushion defects but worsens the consequences of Eisenmenger syndrome and uncorrected tetralogy of Fallot. Depending on the cardiac disorder, perturbations induced by pregnancy can alter fractional shunts, induce hypoxemia, or precipitate pulmonary edema.

A special problem of pregnancy is peripartum cardiomyopathy, a disorder that develops in 1 of 1300 to 15,000 deliveries, may present with congestive heart failure, and is associated with a special propensity for both pulmonary and systemic embolization during the last month of pregnancy and for up to 5 months thereafter.[67] Standard therapy for heart failure, including β-blockers, diuretics, angiotensin-converting enzyme inhibitors and blockers, are usually effective, but sometimes implantable defibrillators and even left ventricular assist devices and heart transplantation are required.[67,68]

Tocolysis-Associated Pulmonary Edema

The use of drugs such as β_2-sympathomimetic agents to retard premature labor is uncommon in current obstetric practice but, in the past, was associated with a 0% to 4% incidence of pulmonary edema.[69] The etiology of this disorder is controversial and likely multifactorial in nature, related to myocardial effects, vascular permeability impairment, and fluid retention. It usually presents after at least 24 hours of β-adrenergic therapy, with relatively acute onset of dyspnea and pulmonary edema seen on chest radiographs. Simple discontinuation of β-adrenergic therapy often results in rapid improvement; whether diuretics need to be given is unresolved, but furosemide is usually administered. Pulmonary edema has also complicated tocolysis performed with calcium channel blockers.[70]

Pulmonary Edema Associated with Preeclampsia

About 2.9% of patients with preeclampsia or eclampsia develop pulmonary edema.[71] The spectrum of hemodynamic findings associated with pregnancy-induced hypertension and preeclampsia is wide but, in general, left ventricular preload is normal or low, afterload is high, and cardiac output is normal or low (Fig. 96-3). Systolic and diastolic function may also be impaired.[72] The pulmonary edema commonly first presents in the postpartum period,[71,72] reflecting fluid administration at delivery. Low colloid oncotic pressure and abnormal vascular permeability likely contribute as well. Hemodynamic monitoring of these patients is probably warranted if oliguria complicates the picture.

Pulmonary Embolism

Pulmonary embolism is a leading cause of maternal mortality,[73] accounting for 9% of 95 pregnancy-related deaths in a large health care delivery system in the United States between 2000 and 2006.[73] Even though the risk for venous thromboembolism in pregnant women is about five times as great as in age-matched and sex-matched nongravid controls, it is still relatively infrequent. A Danish population-based study of 63,000 deliveries found a cumulative incidence of 0.85 in 1000 deliveries from 1984 to 1994.[74] In this study, the incidence of detected venous thromboembolism increased to 1.23 in 1000 deliveries after the introduction of ultrasonography, demonstrating that its reported incidence may depend on the adequacy of diagnostic procedures employed. Other studies have reported rates of 0.6 to 2 per 1000 pregnancies.[75] The risk for thrombosis is increased in pregnancy, partly because of the increase in coagulation factors, particularly V, VIII, X, and von Willebrand factor antigen, and partly because of a marked fall in protein S.[76] Venous stasis, an important contributor to thrombosis, is caused by uterine compression of the inferior vena cava and the left iliac vein. Local trauma to pelvic veins at the time of delivery probably accounts for the peak incidence of thromboembolism in the postpartum period, especially after cesarean section. Specific risk factors for thromboembolism include previous thromboembolism during pregnancy or while taking oral contraceptives, prolonged bed rest, a complicated or cesarean delivery, age, thrombophilia, obesity, and smoking. The inherited defects include deficiencies of antithrombin, protein S, protein C, factor V Leiden, and prothrombin G20210A.[76] Antiphospholipid syndrome is an acquired thrombophilia. Previous thromboembolism or antithrombin deficiency warrant prophylactic heparin administration throughout pregnancy, now commonly accomplished with *low-molecular-weight heparins* (LMWHs) due to their safety and decreased risk of heparin-induced osteopenia and thrombocytopenia.

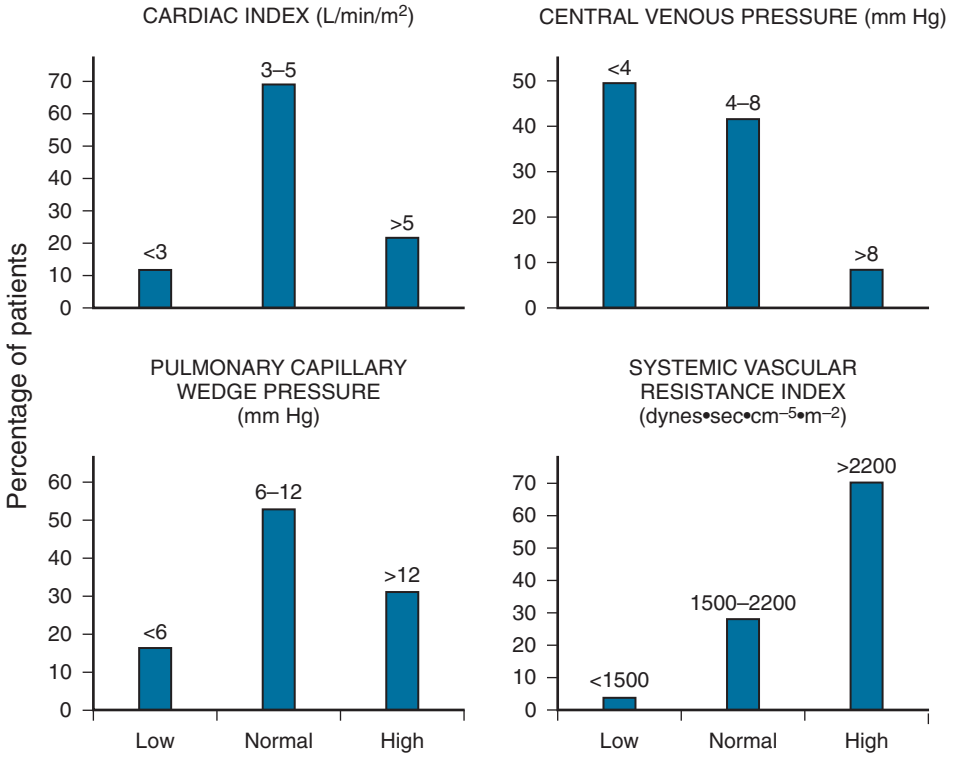

Figure 96-3 Pregnancy-induced hypertension. The spectrum of hemodynamic profiles is shown for 45 women with severe pregnancy-induced hypertension, one of the disorders sometimes complicated by pulmonary edema. Pulmonary edema in pregnancy-induced hypertension usually does not reflect simple volume overload. (From Cotton DB, Lee W, Huhta JC, et al: Hemodynamic profile of severe pregnancy-induced hypertension. *Am J Obstet Gynecol* 158:523–529, 1988.)

Clinical diagnosis of deep venous thrombosis during pregnancy and the puerperium is even more difficult than in the nonpregnant patient because of the peripheral edema associated with pregnancy and the asymmetrical compression of the left-sided common iliac vein by the gravid uterus. The initial diagnostic test should be duplex ultrasonography (combined real-time B-mode compression ultrasonography plus Doppler venous ultrasonography). In the patient with high clinical suspicion but a negative test, a repeat examination at 5 to 7 days may be valuable. When venous thrombosis of the lower extremity is documented, it is usually left sided, as it was in 84 of 96 (88%) cases reported by Chan and colleagues.[77]

The diagnosis of pulmonary embolism in pregnant women is relatively straightforward. Both ventilation-perfusion scanning and *computed tomography* (CT) pulmonary angiography can be performed during pregnancy in a modified fashion. Estimated fetal radiation exposure for a perfusion scan is about 0.011 to 0.022 cGy (11 to 22 mrad), and simply halving the perfusion dose is standard practice in pregnancy, without greatly impairing resolution.[78] There is no need for the ventilation portion of the study if perfusion is normal. CT pulmonary angiography is an acceptable imaging modality and is associated with similarly low radiation doses to the fetus (Fig. 96-4).[78,79] However, a risk to consider is the potential carcinogenic effect of radiation exposure to the mother's breasts,[78,80] although shielding can reduce exposure (see Fig. 96-4B). Pulmonary angiography, when performed by the brachial route, exposes the fetus to only about 0.050 cGy (50 mrad),[81] but this procedure has a limited role in pregnancy. Such levels of exposure are not believed to cause teratogenicity, which is associated with exposure of greater than 5 to 10 cGy (5 to 10 rad). However, an increased incidence of childhood leukemia has been documented with lower fetal radiation exposure, in the range of 1 to 5 cGy (1 to 5 rad). A comparison of lung scintigraphy and pulmonary CT angiography concluded that the former method was more accurate than the latter for diagnosing pulmonary embolism during pregnancy.[82] Ventilation-perfusion scanning in pregnancy, due to the patient's younger age and lack of comorbidity, is associated with a lower incidence of intermediate scans and higher rate of normal scans.[83] CT angiography may more often be technically suboptimal, due to the increased cardiac output in pregnancy.[84] *Magnetic resonance imaging* (MRI) with gadolinium contrast also has promise because it can image pelvic and lower extremity veins, as well as the pulmonary arteries, and it has little contrast-associated toxicity. Its widespread use will require increased availability of ultrafast scanners and more evaluation of its accuracy.

Venous thromboembolism in pregnancy is treated with heparin because warfarin crosses the placenta and causes nasal, ophthalmologic, and central nervous system abnormalities in the fetus. LMWH appears to be safe in pregnancy and, compared with unfractionated heparin, is associated with fewer adverse effects.[85,86] LMWH is preferred over unfractionated heparin in pregnancy, using a weight-adjusted dosing regimen.[87] Weight gain in pregnancy makes formulaic dosing less reliable, and some authors also

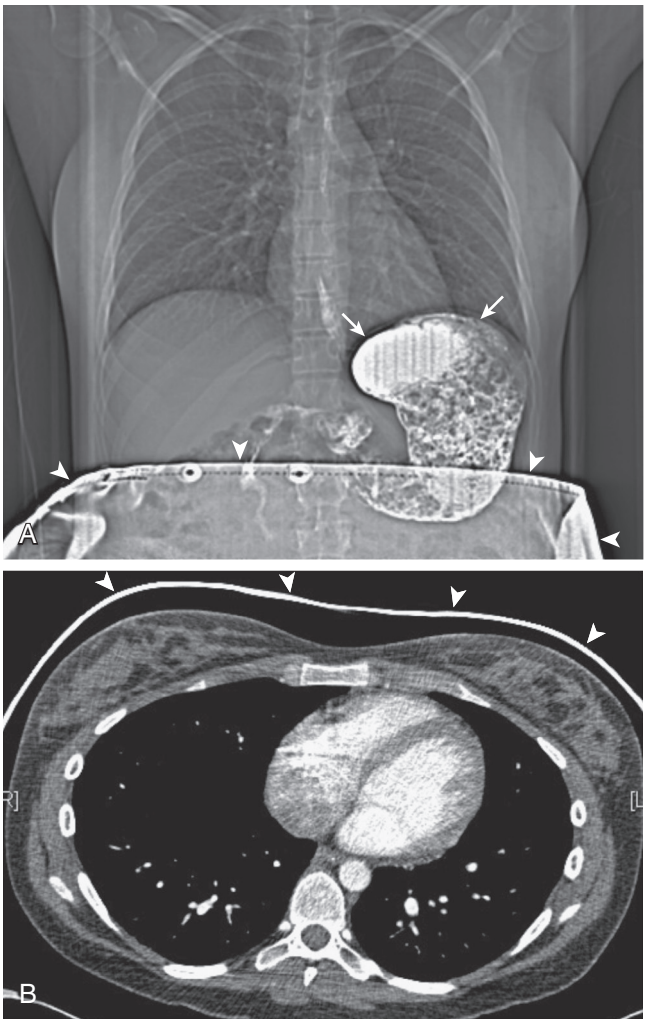

Figure 96-4 Dose-reduction methods for chest CT in the pregnant patient. A, Scout view before the CT acquisition shows an "internal barium shield" (*arrows*) created by having the patient swallow a dilute mixture of barium and water several minutes before CT scanning. The barium distributes within the stomach and proximal small bowel and attenuates internal maternal radiation that may otherwise expose the fetus. A lead apron (*arrowheads*) also reduces fetal radiation exposure. **B,** Axial chest CT pulmonary angiogram obtained with manual reduction of both the tube current and tube voltage shows excellent vascular opacification, providing high-quality assessment for pulmonary embolism and other thoracic disorders. A maternal breast shield (*arrowheads*) has also been placed; these shields selectively filter low-energy x-ray photons that would otherwise deposit preferentially in maternal breast tissue, significantly contributing to maternal breast radiation exposure. (Courtesy Michael Gotway, MD.)

advocate titrating the dose to achieve anti–factor X levels of 0.5 to 1.24 units/mL 4 hours after injection.[85,86] However, the lack of good data and lack of correlation of levels with efficacy or complications makes routine monitoring difficult to justify.[87] LMWH treatment is usually given for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months). LMWH should be held 24 hours before induction, cesarean section, or neuraxial anesthesia (for twice-daily dosing) or after a 50% dose the morning before delivery for daily dosing regimens.[87] Postpartum, warfarin can be given safely during lactation.

Thrombolytic therapy has been used successfully in life-threatening thromboembolism during pregnancy, with a complication rate similar to that in nonpregnant women.[88]

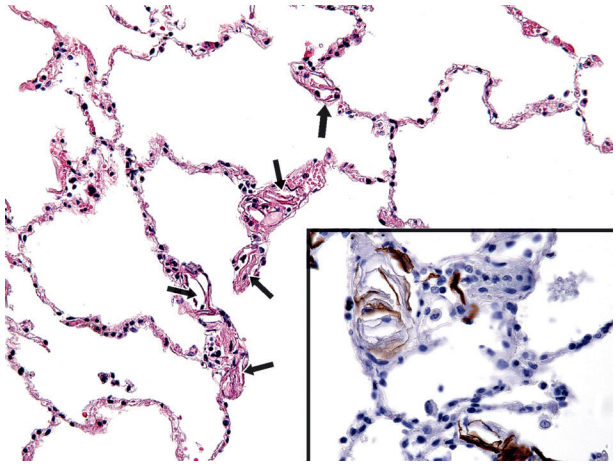

Figure 96-5 Amniotic fluid embolism. Interstitial pulmonary capillaries filled and expanded by eosinophilic fetal squamous cells (*arrows*) from a case of amniotic fluid embolism in a 39-year-old woman who succumbed within 4 hours of delivery. (H&E stain; original magnification ×200). *Insert:* High-molecular-weight keratin stain, CK5/6 staining the intravascular fetal squamous cells (shown by brown color)(original magnification ×400). (Courtesy Dr. Gerald Berry, Stanford University.)

Amniotic Fluid Embolism

Small amounts of amniotic fluid may enter the circulation during uncomplicated pregnancy but rarely cause the catastrophic syndrome of amniotic fluid embolism.[89] The reported incidence varies from 2 to 6 per 100,000 pregnancies, the variation being largely dependent on the method of case identification.[90] The onset is usually during labor and delivery or immediately after uterine manipulation, with development of severe dyspnea, hypoxemia, and then seizures and cardiovascular collapse or arrest. If the patient survives the initial insult, disseminated intravascular coagulation and ARDS usually supervene.[91] Risk factors include older maternal age, induction of labor, high parity, cesarean section, low uterine segment laceration, and meconium staining of amniotic fluid.[89-91] Abruptio placentae is present in 50% of cases, and fetal demise in 40%.[91] The maternal mortality rate has been as high as 86%,[92] but a more recent report suggests a mortality of 11% to 43%.[90] Overall, amniotic fluid embolism may account for 14% of all maternal deaths.[73]

In a U.S. registry of cases, 78% of the patients with amniotic fluid embolism had ruptured membranes, and several had just undergone intrauterine procedures,[93] clearly implicating traumatic opening of uterine vessels in the pathogenesis. The exact quantity or constituents of amniotic fluid required to initiate the syndrome is unknown. Pathologically, fetal squamous cells are found in the maternal pulmonary circulation at autopsy (Fig. 96-5) but, even in symptom-free patients, fetal cells may be aspirated from pulmonary artery catheters placed for other reasons.[94] Hemodynamically, the process is often biphasic, with pulmonary hypertension initially, followed by left ventricular failure.[95,96] These changes may be caused by leukotrienes and arachidonic acid metabolites, particularly prostaglandin F_{2a}, which appear in amniotic fluid during labor. An immunologic basis for some of the changes seems likely because women with male fetuses are more likely to acquire the disorder.[90] Clark and associates[93] seized on the similarities to anaphylaxis and suggested that the disorder be renamed

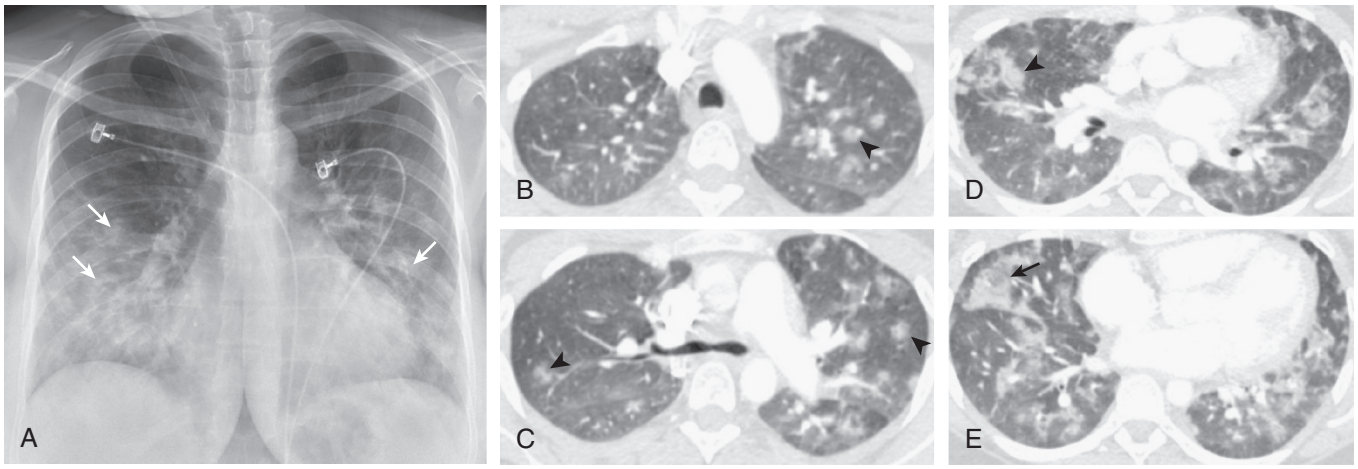

Figure 96-6 Amniotic fluid embolism. A, Frontal chest radiograph in a patient who developed shortness of breath and cardiovascular instability during delivery shows multifocal, poorly defined opacities (*arrows*) along the bronchovascular bundles, distributed in the mid and lower lungs bilaterally. **B–E,** Axial chest CT pulmonary angiogram obtained for pulmonary embolism evaluation, displayed in lung windows, shows multifocal nodular appearing ground-glass opacities (*arrowheads*), somewhat more confluent in the right middle lobe (*arrow*). No features to suggest increased pressure edema, such as pleural effusion or interlobular septal thickening, are present, and no pulmonary embolism was detected. The CT features are consistent with an acute lung injury pattern. (Courtesy Michael Gotway, MD.)

anaphylactoid syndrome of pregnancy. A small study did not demonstrate evidence of mast cell degranulation but suggested a role for complement activation.[97]

On imaging studies, affected patients usually develop bilateral parenchymal opacities consistent with pulmonary edema associated with increased permeability lung injury (Fig. 96-6). Treatment consists of supportive care for the associated disseminated intravascular coagulation and left ventricular and respiratory failure. The fetus should be promptly delivered. In cases of maternal demise, emergency postmortem or periresuscitative cesarean section is warranted, as it is in other instances of cardiopulmonary resuscitation in pregnancy.[98]

Arteriovenous Malformations

Pulmonary arteriovenous malformations may expand during pregnancy because of hormonal changes, the increase in blood volume, and venous distensibility.[99] This increases the likelihood of bleeding, with life-threatening complications in about 1% of pregnant women with hereditary hemorrhagic telangiectasia.[100,100a] Embolization and surgical management have been utilized successfully during pregnancy.

Air Embolism

Occasionally, venous air embolism can happen during pregnancy, presumably through the subplacental venous sinuses.[101] This disorder has been clearly documented during labor and delivery, during cesarean sections and abortions, in patients with placenta previa, and in those engaging in orogenital sex during pregnancy or the early puerperium.

ACUTE LUNG INJURY IN PREGNANCY

Aspiration Pneumonitis

Since Mendelson's[102] original report of 66 cases of gastric aspiration in 44,016 deliveries between 1932 and 1945 (an incidence of 0.15%), aspiration has continued to be a major cause of maternal morbidity and mortality. Increased intra-abdominal pressure due to the gravid uterus, the inhibitory effect of progesterone on the tone of the esophageal sphincter, and the assumption of the supine position for delivery all contribute. Eating during or just before labor increases the volume of emesis.[103] Aspiration of gastric contents with pH 2.5 or lower is known to cause chemical pneumonitis and increased permeability edema. Both in Mendelson's original report and today, about two thirds of cases of aspiration take place in the delivery suite. Emergency endotracheal intubation of patients with obstetric crises is particularly difficult,[104] and intubation in the delivery suite fails at a rate eight times that in the general surgical population.[105] To minimize the chance of acid aspiration at intubation, oral administration of histamine-2 blockers with antacids before intubation,[106] in conjunction with a formal airway assessment, is desirable. Identified risk factors in intubation include a high Mallampati class indicating poor visibility of the posterior pharynx, a short neck, protruding maxillary incisors, and a receding mandible.[107]

Acute Respiratory Distress Syndrome

ARDS is more common in pregnancy than in the general population, with an incidence of 1/6000 deliveries.[108] In one obstetric intensive care unit, ARDS was the leading cause of maternal death during a 6-year period.[109] The three most common nonobstetric causes are pneumonia, sepsis, and aspiration. The 2009 influenza A (H1N1) epidemic resulted in a significant increase in the incidence of ARDS in pregnancy, generating numerous publications on the epidemiologic and management issues. Australian investigators described a series of pregnant women treated with extracorporeal membrane oxygenation with reasonable outcome.[110] Common obstetric causes of ARDS include chorioamnionitis, amniotic fluid embolism (see Fig. 96-6), and trophoblastic embolism.[111] Ventilator management is unaltered in pregnancy and, although pregnancy was an exclusion criterion in the ARDS Network studies, the clear benefit in nonpregnant patients supports the use of

low-volume ventilatory strategies in pregnant patients, with tidal volume (6 mL/kg) based on the patient's ideal weight.[111,112] The prognosis also appears to be similar to the nonpregnant patient,[113] although ARDS outcome is dependent on the underlying etiology.

OTHER RESPIRATORY DISEASES IN PREGNANCY

Obstructive Sleep Apnea

Pregnancy may be complicated by *obstructive sleep apnea* (OSA), potentially adversely affecting both mother and fetus.[114] Although upper airway edema may potentiate obstructive events, apnea and hypopnea are uncommon in pregnancy because of the respiratory stimulatory effect of progesterone.[115] OSA usually develops in obese patients, precipitated by the airway mucosal edema and vascular congestion that accompany pregnancy. OSA is associated with preeclampsia and gestational diabetes.[115,116] Nocturnal hypoxemia may produce poor fetal growth, although snoring alone is not associated with fetal risk.[117] Pregnant women with documented obstructive sleep apnea are at increased risk of developing preeclampsia and preterm birth.[118] Treatment with nasal continuous positive airway pressure is safe and effective for women with documented significant OSA.[115]

Interstitial Lung Disease

Interstitial lung disease is usually seen in patients older than those in their childbearing years.[119] When interstitial disease exists in pregnant women, the reduced diffusing capacity may cause difficulty in meeting the increased oxygen consumption requirements of pregnancy. Associated pulmonary hypertension, regardless of its causes, carries significant risks because cardiac output increases during pregnancy. Few data exist on the management and outcome in these patients, but restrictive lung disease appears reasonably well tolerated in pregnancy.[120,120a] Lymphangioleiomyomatosis and systemic lupus erythematosus may worsen as a result of pregnancy.[119] Some drug therapy used for interstitial lung disease may be acceptable during pregnancy (e.g., prednisone, azathioprine), but other therapy (e.g., cyclophosphamide, rituximab, mycophenolate mofetil) is usually avoided.[119]

Pleural Disease

Pleural effusions may accompany obstetric complications such as preeclampsia and choriocarcinoma, but many women with normal pregnancies develop small, asymptomatic pleural effusions in the postpartum period.[121] They develop as a result of the increased blood volume and reduced colloid osmotic pressure in pregnancy, as well as from impaired lymphatic drainage due to repeated Valsalva maneuvers during labor. Moderate-size effusions or the presence of symptoms should prompt a full clinical evaluation. The Valsalva maneuvers of labor may also produce spontaneous pneumothorax and pneumomediastinum, particularly in patients with predisposing conditions such as asthma. This diagnosis should be considered in women who develop chest discomfort and dyspnea during, or immediately following, delivery.

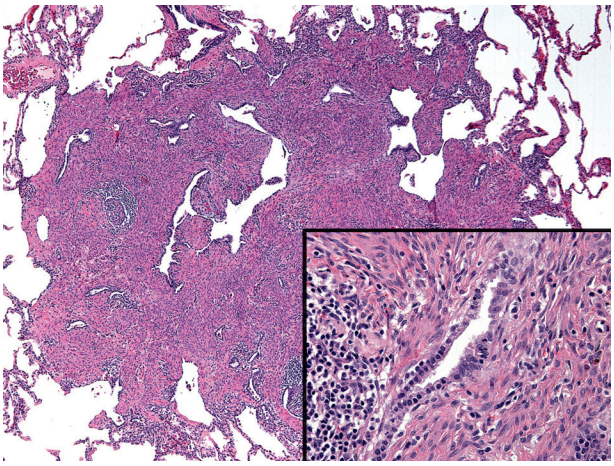

Figure 96-7 Pulmonary endometriosis. Wedge resection of right upper lobe subpleural nonencapsulated lesion in a 43-year-old woman with a history of pelvic endometriosis and recurrent pneumothoraces with menstrual cycles. (H&E stain; original magnification ×40). *Insert:* The discrete nodule is composed of endometrial stromal cells admixed with endometrial glands. (H&E; original magnification ×200.) (Courtesy Dr. Gerald Berry, Stanford University.)

GYNECOLOGIC DISORDERS AND THE LUNGS

CATAMENIAL PNEUMOTHORAX

Lillington and colleagues[122] introduced in 1972 the term *catamenial pneumothorax* to describe the already reported phenomenon of spontaneous pneumothorax within 24 to 72 hours after onset of menses. It appears to account for about 2.8% to 5.6% of spontaneous pneumothoraces in women,[123,124] most often affecting women in the third or fourth decade of life. About 30% to 60% of cases are attributable to thoracic endometriosis, as judged by inspection at thoracotomy (Fig. 96-7)[125]; other cases have a more obscure etiology, however, so a number of theories have been advanced. The first theory is that, during menstruation, the absence of the normal cervical mucus plug permits an open connection between ambient air and the abdominal cavity through the uterus and fallopian tubes.[124] Air can move transdiaphragmatically through right-sided diaphragmatic fenestrations into the pleural space, as it sometimes does during abdominal laparoscopy,[126] accounting for the condition's right-sided predominance.[124] A second theory is that high levels of prostaglandin F_{2a} during menstruation cause bronchospasm with attendant air trapping and pneumothorax, but wheezing is not a common symptom of this disorder. A third theory is that pleural blebs or bullae are more susceptible to rupture during menstruation because of hormonal changes,[124,125] but visceral pleural leaks are rarely found at surgery (see also Chapter 81 for a full discussion).

For cases of endometriosis-associated pneumothorax, a trial of gonadotropin-releasing hormones is warranted if the phenomenon is repetitive but not life-threatening. Oral contraceptives, other progestational agents, and tubal

ligation have also been used with some success. For cases not clearly associated with systemic endometriosis, thoracoscopy during menstruation serves to define the etiology and can be used to achieve pleurodesis.[126]

ENDOMETRIOSIS

Endometriosis probably affects about 10% of women, shows no clear ethnic differences in prevalence, and is most commonly diagnosed at 30 to 34 years of age.[127] Although pelvic pain, dysmenorrhea, and infertility are its predominant manifestations, atypical locations, including diaphragmatic, pleural, and endobronchial sites, have been documented. As described previously, endometriosis can result in recurrent catamenial pneumothorax, which is its most common thoracic presentation (see Fig. 96-7). In one review of 110 cases with thoracic endometriosis, catamenial pneumothorax was the presenting symptom in 73% of cases, followed by hemothorax in 14% and hemoptysis in 7%.[127] It also has been associated with right-sided pleural pain, pleuritic effusions, and hemothorax. Inspection at thoracotomy or thoracoscopy typically reveals blue-brown nodules on the pleural surface, sometimes in a "gunshot" distribution.[128] The absence of known pelvic endometriosis does not exclude the diagnosis because only 20% to 70% of patients have associated pelvic disease. The diagnosis is suspected on clinical grounds because neither CT nor endoscopy is specific.[129] Rarely, the endometriosis deposits are found in lung parenchyma, accounting for the catamenial hemoptysis. Most pleural and diaphragmatic disease is thought to arise from transdiaphragmatic spread from retrograde menses, even when abdominal disease is not evident. Massive ascites is sometimes related, although only 27 cases have been reported.[130] Pneumothoraces may be attributed to cyclical sloughing of tissue on key surfaces, such as the visceral pleura,[131] or to air trapping from airway involvement or compression.[122] Pulmonary parenchymal disease may be embolic in origin, as is presumed to be in the case of central nervous system endometriosis. The diagnosis can be established only by biopsy showing the characteristic ectopic endometrial glands in involved sites. Medical therapy consists of progestational agents or gonadotropin-releasing hormones; surgical approaches include excision, local laser ablation, or pleurodesis.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM) is a rare disorder that afflicts predominantly premenopausal women.[132,133] The most common presenting event is a pneumothorax, reported in 86.5% of patients in the National Heart, Lung, and Blood Institute registry.[132] It is fundamentally a disorder of smooth muscle proliferation that results in functional obstruction of vessels, lymphatics, and airways. (See Chapter 69 for a complete discussion of LAM.) Involvement of pulmonary vascular structures is responsible for the hemoptysis, whereas lymphatic obstruction accounts for the chylous effusions. Mediastinal and retroperitoneal lymphatic proliferation may be a feature of the disease as well. LAM is also associated with renal angiomyolipomas, another hamartomatous disorder, and with tuberous sclerosis. Conventional therapy has included oophorectomy or progestational agents, mainly medroxyprogesterone acetate. Lung transplantation has been performed in more than 60 patients with this disorder, but it has clearly recurred in some of them. Sirolimus, in a trial in patients with angiomyolipomas and tuberous sclerosis complex or LAM, showed ameliorative effects on lung function and volume of angiomyolipomas, presumably by suppressing signaling pathways involved in products of the defective genes.[134] LAM is now included in the group of perivascular epithelioid cell tumors, whose molecular pathology is being elucidated, opening the possibility of targeted therapy.[135]

TROPHOBLASTIC EMBOLIZATION

Trophoblastic embolism is a rare complication of hydatidiform mole, an abnormal type of pregnancy in which nonviable fertilized tissue grows in the uterus. In one series, only 2.6% of 189 patients with hydatidiform mole had an embolic event, so most episodes of respiratory distress in such patients are not caused by embolic events but, rather, pulmonary edema, anemia, or another complicating event.[136] Embolization, when it happens, is most common at the time of evacuation of the mole. Chorionic neoplasms that arise during gestation are suggested by a large discrepancy between gestational date and uterine size and should be evaluated by transvaginal ultrasonography.[137]

OVARIAN HYPERSTIMULATION SYNDROME

The use of exogenous gonadotrophins to stimulate ovulation for in vitro fertilization has been associated with pulmonary complications.[138] This ovarian hyperstimulation syndrome usually manifests with ovarian cysts, bilateral pleural effusions, ascites, and intravascular volume depletion. Hypovolemic shock, renal failure, and ARDS may result. Pulmonary embolism and upper limb or superior venal caval thrombosis may result from the hypercoagulable state induced by estrogens and intravascular volume depletion. The mechanism of the effusions is unclear but is likely related to increased permeability due to release of vasoactive mediators, of which vascular endothelial growth factor appears to be the most important.[139] Evidence points to mutations in the follicle-stimulating hormone receptor as etiologic in at least some cases.[140] Treatment is supportive and involves maintaining intravascular volume, thoracentesis when required for respiratory compromise from abundant pleural effusion(s), and thromboprophylaxis.

Key Points

- Normal pregnancy is associated with profound alterations in respiratory and cardiovascular physiology, which—although designed for maternal and fetal well-being—may exacerbate underlying cardiopulmonary conditions or cause new ones.
- Major physiologic perturbations found in normal pregnancies include (1) an increase in central drive to breathe, with resulting changes in P_{CO_2} (28 to 32 mm Hg) and pH (7.40 to 7.47); and (2) an increase in both

maternal blood volume, of about 2 L (40%), and cardiac output, after 25 to 32 weeks of gestation, of 30% to 45%.

- The most common pulmonary disorder of pregnancy is asthma, but the effects of pregnancy on asthma are variable: it worsens, improves, or remains unchanged in roughly one third of afflicted women.
- The risks of poorly controlled asthma for both mother and fetus during pregnancy far outweigh the risks of drug therapy. Some standard drugs are safer than others (see Table 96-1) and should be selected whenever possible.
- Cystic fibrosis and infectious pneumonias have all been linked with adverse fetal and maternal outcomes, the risk of which depends largely on the severity of the complicating disorder. Prepregnancy counseling and avoidance of certain antimicrobial drugs (as noted in Table 96-1) are strongly recommended.
- Pulmonary edema may develop during pregnancy in women with underlying heart disease, especially valvular stenosis, cardiomyopathy, and preeclampsia. Because the causative mechanisms differ, so does specific therapy.
- Pulmonary embolism is a leading cause of maternal mortality. When indicated during pregnancy, low-molecular-weight heparins are safe for both treatment and prevention; warfarin is contraindicated. Ventilation-perfusion imaging, CT pulmonary angiography, and magnetic resonance imaging can be used as needed.

Complete reference list available at *ExpertConsult*.

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