

## Pulmonary complications of pregnancy

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Although pregnancy is not a disease itself, a plethora of physiologic changes that occur during this period leave the woman more vulnerable to a variety of pulmonary disorders. Respiratory diseases are an important cause of morbidity and mortality in pregnant women. Some of these diseases are unique to this period, whereas others are pre-existing conditions that might worsen or exacerbate. Special concerns about the pregnant state alter or limit diagnostic procedures and therapies that would otherwise be used because the risks and benefits need to be balanced between the mother's health status and the fetal risks. The clinician should have a thorough understanding of the physiologic changes that occur in this period and be familiar with the best diagnostic and therapeutic options that are available. In this article, the pulmonary physiologic changes that occur during gestation are reviewed as well as the pulmonary diseases that are unique to this state and how pregnancy affects pre-existing lung disorders.

### Anatomic and physiologic changes during pregnancy that affect respiratory function

Because of increased estrogen levels, there is mucosal edema, hyperemia, mucus hypersecretion, capillary congestion, and increased fragility in the upper respiratory tract, most markedly during the third trimester of pregnancy [1]. This hormonally-mediated rhinitis affects 30% of pregnant women and is char-

acterized by nasal congestion and inflammation. Because of these changes, placement of endotracheal tubes, face-masks, and nasogastric tubes may be more difficult; smaller tubes and sufficient lubrication should be used to minimize trauma. The rhinitis does not correlate with a previous atopic history or with symptoms during previous pregnancies, usually is refractory to treatment, and disappears within 48 hours of delivery [2]. Epistaxis, sneezing, voice changes, and mouth breathing are frequent complaints in this period.

There are three important changes in the configuration of the thorax during pregnancy: (1) an increase in the circumference of the lower chest wall (with increases in anteroposterior and the transverse diameters); (2) elevation of the diaphragm (a cephalad displacement of approximately 4 cm to 5 cm); and (3) a 50% widening of the costal angle [2]. These changes peak around the 37th week of pregnancy and normalize within 6 months after delivery.

Pulmonary function is affected by changes of the airway, thoracic cage, and respiratory drive. There is a significant increase in minute ventilation as a result of a direct stimulatory effect of progesterone on central respiratory drive and an enhancement of the hypercapnic ventilatory drive (Fig. 1). Respiratory rate remains constant, and, therefore, tachypnea should be viewed as a possible incipient sign of cardiopulmonary disease.

The major changes in pulmonary function are a progressive decline in expiratory reserve volume and a decrement in residual volume of 7% to 22%, which result in a reduction of the functional residual capacity (FRC) by 10% to 25% close to term [3,4]. These changes are secondary to the enlargement of the abdominal contents with upward displacement of the diaphragm. The reduction in FRC causes closure

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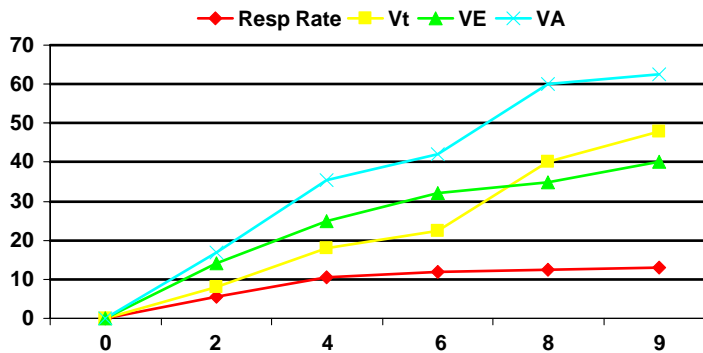


Fig. 1. Changes in the breathing pattern depicted on the y-axis as the % change from non-pregnant state. Gestational age (in months) shown on x-axis. Resp rate, respiratory rate/minute; VA, alveolar minute ventilation; VE, exhaled minute ventilation; Vt, tidal volume.

of small airways at the lung bases during normal tidal breathing which results in ventilation-perfusion mismatch and reduced gas exchange. Inspiratory capacity increases slightly. Total lung capacity decreases only minimally as the uterus enlarges. Overall, no significant change in peak flow rates, forced vital capacity, or forced expiratory volume in the first second ( $FEV_1$ ) is observed. The total pulmonary resistance is reduced by 50% as a result of a decrease in airway resistance. Lung compliance does not change, but total respiratory compliance is decreased at term as a result of a reduction in chest wall compliance. Despite the significant increase in intra-abdominal pressure that is due to the enlarging uterus, the maximal inspiratory and expiratory pressures, as well as maximum transdiaphragmatic pressure do not change significantly.

Arterial blood gas analysis shows respiratory alkalosis that is due to an increase in minute ventilation, which is followed by compensatory renal bicarbonate excretion. Normal  $PaCO_2$  during pregnancy varies between 28 mm Hg and 32 mm Hg and plasma bicarbonate levels decrease to 18 to 21 mEq/L; this results in an arterial pH between 7.40 and 7.47. During the first trimester, the  $PaO_2$  averages 105 mm Hg to 107 mm Hg while sitting but decreases 5 mm Hg by the third trimester. Moving from the sitting to the supine position induces an average of 13 mm Hg decline in  $PaO_2$ . The alveolar to arterial oxygen tension difference while sitting increases from 14 mm Hg early in pregnancy to 20 mm Hg at term.

Dyspnea, which starts in the first or second trimesters, is reported by up to 70% of healthy pregnant women. It is secondary to the respiratory stimulation of progesterone, greater hypercapnic ventilatory response, and altered chest wall proprioceptors [5]. It is usually mild and tends to stabilize or decrease in

intensity close to term. Underlying heart or lung disease should be suspected when dyspnea worsens with time, interferes with daily activities, occurs at rest, is significant during exercise, or presents later in the course of gestation.

### Respiratory failure and the pregnant patient

Acute respiratory failure in pregnancy is an important cause of maternal and fetal morbidity and mortality. Numerous conditions have been associated with acute respiratory failure in pregnancy (Table 1). These entities usually are associated with a complicated pregnancy or parturition and the need for performing a cesarean section.

Critical illnesses that require admission to an ICU unit are uncommon during pregnancy and account for less than 1% of the ICU admissions [6,7]. The overall prevalence of obstetric patients that require critical care ranges from 1 to 9 in 1000 gestations [3]. The reported mortality rates have varied from 2% [6,8] to 20% [9,10]. By itself, pregnancy is not associated with a higher mortality than predicted for the severity of illness [11]. The most common reason for admission to the ICU is respiratory failure; it also is the most common factor that is associated with ICU mortality. Other common reasons for admission are preeclampsia/eclampsia, postcesarean section, and postpartum hemorrhage [6,8].

Many obstetric patients who receive mechanical ventilation require delivery because of their acute illness, although some women who began labor while receiving ventilation were able to deliver vaginally [12]. Common admission diagnoses include preeclampsia or eclampsia (44%), labor or preterm labor (14%), and pneumonia (12%). Ventilatory strategies

Table 1  
Differential diagnosis of pulmonary edema and acute lung injury in pregnancy

	Disorder	Features
Specific to pregnancy	Amniotic fluid emboli	Sudden onset hypotension, DIC
	Tocolytic pulmonary edema	Acute onset, rapid improvement
	Peripartum cardiomyopathy	Previously healthy, last month pregnancy up to 5 months postpartum
Not specific causes (increased risk in pregnancy)	Preeclampsia	Hypertension, proteinuria
	infections (Varicella, pyelonephritis, sepsis)	Fever, often misdiagnosed source
	Gastric aspiration (Mendelsson's syndrome)	Emesis, fever
	Thromboembolism	Leg edema, clear chest radiograph
	Air embolism	Post delivery, sudden collapse, murmur, seizures
	Pancreatitis	Abdominal pain, emesis
	Massive hemorrhage	Anemia, massive transfusions
Other causes	Drug abuse (cocaine)	Treated with bromocriptine
	Trauma	
	Ischemic heart disease	

in pregnancy should follow the same principles that are used in nonpregnant patients, although arterial blood gas goals are different. Normal PaCO<sub>2</sub> in the pregnant women is 28 mm Hg to 32 mm Hg; permissive hypercapnia may be hazardous to the fetus because it results in fetal respiratory acidosis that limits the ability of fetal hemoglobin to bind oxygen. There are insufficient data to support the use of bicarbonate to protect the fetus from the deleterious effects of hypercapnia. Although there are no studies that use low tidal volumes (V<sub>t</sub>) in treating pregnant patients who have acute respiratory distress syndrome (ARDS), the principles of lung protective ventilation apply, including low V<sub>t</sub> (6 mL/kg ideal body weight) and maintaining plateau pressures at less than 30 cm H<sub>2</sub>O. There are no studies that used the prone position during pregnancy [11]. Noninvasive positive pressure ventilation (NIPPV) has not been well studied in the pregnant population but the increased risks of aspiration and nasal mucosal irritation may limit its usefulness.

### Pulmonary complications due to pregnancy-specific conditions

#### *Amniotic fluid embolism*

Amniotic fluid embolism (AFE) is an enigmatic and often devastating obstetric syndrome that portends a mortality of 60% to 90% [13,14]. Because of its high case-fatality rate, AFE follows pulmonary thromboembolic disease (PTE) as the leading cause

of unexpected maternal deaths. Most survivors of this catastrophic complication suffer irreversible neurologic sequelae [14]. The incidence worldwide is between 1 in 8000 and 1 in 80,000 live births, whereas in the United States, it is approximately 1 in 20,000 to 30,000 deliveries [15]. A national registry for AFE was established in 1988. Among the first 46 cases in the AFE registry, 70% suffered AFE during labor (usually within minutes before delivery), 19% during cesarean section, and 11% during vaginal delivery. In this cohort, 61% of patients died and only 7 (15%) remained neurologically intact. Although 79% of the neonates survived, half suffered neurologic sequelae [14].

The pathophysiology of AFE is not understood completely [16–19]. Obstruction of the pulmonary vessels by fetal cells and debris is no longer believed to be the cause. Rather, the injury seems to be secondary to an intense inflammatory response to the presence of amniotic fluid in the circulation; this resulted in the term “anaphylactoid syndrome of pregnancy” [14]. Abruptio placentae was reported to occur in 50% of cases and fetal demise in 40% of cases before the clinical presentation [18]; this suggests that the disruption of the uteroplacental bed may be important in the pathogenesis of AFE.

As with other causes of severe anaphylaxis, there is damage to the endothelial-alveolar membrane that leads to a noncardiogenic, high-protein pulmonary edema. The ability of the lipid-rich particulate material in amniotic fluid to activate plasma complement may initiate a “leukostatic phase” which precipitates the acute lung injury syndrome [20]. Amniotic fluid

has antithrombin and thromboplastin-like effects and causes platelet aggregation, the release of platelet factors, and activation of complement and factor X directly, and thus initiates the coagulation cascade. Leukotrienes and other arachidonic acid metabolites are secreted by the human placenta and may play a role in amniotic fluid embolism [21,22].

The usual presentation is the sudden onset of cardiovascular collapse, dyspnea, severe hypoxemia, and seizures that are followed by a coagulopathy. AFE resembles anaphylactic or septic shock in its clinical course, laboratory abnormalities, and hemodynamic profile and usually occurs during labor or within 30 minutes of delivery. Most patients die within the first few hours [14,20,23].

Severe ventilation/perfusion mismatching and physiologic shunt result in profound and early hypoxemia. Approximately 50% of the deaths that are observed within the first hour after presentation are due to hypoxemia, whereas cardiogenic shock and bleeding account for the remaining deaths. Cardiovascular collapse is primarily the result of left ventricular (LV) dysfunction that is associated with a low cardiac output but only a small increase in pulmonary vascular resistance. Most patients who survive the first several hours develop noncardiogenic pulmonary edema, despite restoration of LV function [24]. Forty percent of patients develop disseminated intravascular coagulation (DIC) that can be associated with major hemorrhage [25,26].

The diagnosis of AFE should be suspected in any pregnant patient who develops profound shock and severe hypoxemic respiratory failure with bilateral pulmonary infiltrates during or immediately after labor. Recovering squames from a pulmonary artery catheter is no longer considered to be a specific indicator of AFE [23]. Other markers, such as the monoclonal antibody, TKAH-2, have been proposed as a means for a rapid diagnosis [27,28].

An unusual complication of abruption placentae can be confused with AFE but does not involve the entry of amniotic fluid into the maternal circulation. In these cases, there is the release of large amounts of placental thromboplastin and fibrinolytic activators into the circulation that may precipitate a syndrome of DIC and acute lung injury, which mimics AFE [18].

The treatment of AFE is mainly supportive; close attention should be paid to the early detection of ARDS and a coagulopathy. Mechanical ventilation should be instituted using lung protective strategies. Cardiogenic shock usually requires the use of inotropic and vasoactive agents; treatment of the coagulopathy requires the replacement of coagulation factors.

### *Tocolytic-induced pulmonary edema*

Acute pulmonary edema following the use of  $\beta$ -mimetic drugs for tocolysis has been reported in 6% to 15% of patients who receive these agents [29,30]. It also has been associated with the specific  $\beta_2$ -specific drugs, such as terbutaline, ritodrine, isoxsuprine, and albuterol, which are administered by oral, subcutaneous, or intravenous routes. The pathogenesis is probably multifactorial, including varying degrees of heart failure, pulmonary vasoconstriction, capillary leak syndrome, intravascular volume overload, and reduced serum oncotic pressure.

Potential risk factors include multiple pregnancies, diabetes, preeclampsia, blood transfusions, silent cardiac disease, infections, simultaneous magnesium sulfate, and the use of corticosteroids for more than 48 hours [29,31–33]. Typically, pulmonary edema occurs during  $\beta$ -agonist use or within 24 hours after its discontinuation. Therapy includes immediate discontinuation of the drug and administration of oxygen, diuretics, and intravenous nitrates. Symptoms usually resolve within 24 hours. Recommendations for avoiding pulmonary edema that is associated with  $\beta$ -agonist agents are listed in Box 1.

### *Preeclampsia*

Pulmonary edema in the context of dysfunction of multiple organs occurs infrequently (~2.9%) during preeclampsia but is associated with a mortality rate of close to 10% [21,34]. The exact nature of the lung injury is unclear. The results of hemodynamic monitoring led to the conclusion that the most common cause of pulmonary edema in this setting is the

#### **Box 1. Recommendations when using $\beta$ -mimetic tocolytics**

- Use lowest possible perfusion rate
- Keep patient's heart rate at less than 120 beats/min
- Do not use for more than 48 hours
- Use one tocolytic agent; in particular avoid combinations, especially with  $\text{MgSO}_4$
- Monitor fluid balance closely, avoiding overload and keeping change of hematocrit less than 10%
- Avoid use in patients who have preeclampsia, pneumonia, or previous cardiac disease

administration of large volumes of fluid and consequent volume overload. It also was suggested that the underlying precipitating factor is a poorly-perfused fetoplacental unit with subsequent systemic activation of vascular endothelial cells [35].

### **Pulmonary complications due to conditions not specific to pregnancy**

#### *Pulmonary edema*

Pulmonary edema is an important cause of acute or subacute dyspnea during pregnancy. Its incidence in large series is 0.06% to 0.08% [32,36]. In a review of 62,917 consecutive pregnancies, half of the cases presented before delivery, 14% presented intrapartum, and 39% presented postpartum [32]. The mean gestational age at the time of diagnosis is between 26 and 32 weeks. Postpartum cases usually occur within the first week after delivery [36].

The cause of the pulmonary edema may be non-cardiogenic (ARDS) or hydrostatic (see Table 1). The most common causes include tocolytic agents, cardiac disease, fluid overload, and preeclampsia. Cardiogenic pulmonary edema was reported to be the most frequent cause [36]. The cardiogenic edema is most commonly due to the presence of previously undiagnosed structural heart disease [32] or from an idiopathic cardiomyopathy (usually in postpartum cases). Patients usually present with the classic symptoms of pulmonary edema. The most common radiographic finding is the presence of bilateral alveolar infiltrates, although unilateral pulmonary edema can occur [36]. Treatment of pulmonary edema includes diuretics, preload and afterload reduction, and ventilatory support. NIPPV, which is effective in nonpregnant cases, should be used with caution in pregnant women because they are more prone to aspirate and to have nasal mucosal inflammation.

#### *Peripartum cardiomyopathy*

A cardiomyopathy affects otherwise healthy young woman at a rate of 1 in 3000 to 1 in 15,000 pregnancies [37,38]. Women who are considered to be at particular risk are older than 30 years of age, obese, African American, and multiparous. Cardiomyopathy accounts for 4% of all maternal deaths in the United States; peripartum cardiomyopathy has a 25% to 50% mortality rate and nearly half of the deaths occur during the first 3 months postpartum [39]. Survivors who do not respond to medical treatment may require cardiac transplant.

Mild forms of peripartum cardiomyopathy may be underdiagnosed [40]. Early diagnosis and treatment are critical because this may affect the patient's long-term prognosis [41]. The diagnostic criteria for peripartum cardiomyopathy were established by Demakis and Rahimtoola [38] in 1971 and include: (1) onset of heart failure in the last month of pregnancy or within 5 months of delivery; (2) absence of a determinable cause for the cardiac failure, and (3) absence of demonstrable heart disease before the last month of pregnancy.

Cardiomegaly on the chest radiograph is observed in almost all patients. The cause of the disease remains obscure; however, current evidence suggests a viral, autoimmune, or idiopathic myocarditis [41].

The treatment for this cardiomyopathy is similar to the management of other nonischemic dilated cardiomyopathies except that special considerations must be given to the fetus.  $\beta$ -blockers and angiotensin-converting enzyme inhibitors are contraindicated in pregnancy. Digoxin can be used safely. In severe cases, intravenous inotropic agents should be considered (dobutamine, milrinone).

In contrast to peripartum cardiomyopathy, heart failure from underlying structural heart disease usually presents during the second trimester when hemodynamic changes are the greatest [42]. The most common cause of pulmonary edema that is due to structural heart disease continues to be rheumatic valvular heart disease, especially mitral stenosis. Up to 25% of women who have mitral stenosis present for the first time during pregnancy with pulmonary edema [43,44]. Stenotic valvular diseases are of major concern during gestation because the large fluctuations in volume and changes in cardiac output that are characteristic of pregnancy may be poorly tolerated in these setting. Congenital cardiac abnormalities (uncomplicated atrial septal defect, ventricular septal defect, patent ductus arteriosus) are increasing in prevalence and usually are well-tolerated during pregnancy unless pulmonary hypertension is present. The presence of pulmonary hypertension is associated with high maternal and fetal mortality as a result of the inability to increase cardiac output and respond to fluid shifts [3]. Hypertrophic obstructive cardiomyopathy and Marfan's syndrome can complicate pregnancy and close monitoring is recommended.

#### *Thromboembolic disease*

Embolic diseases are the primary cause of acute hemodynamic and respiratory collapse during gestation worldwide. This topic is covered in depth elsewhere in this issue. The pregnant state increases

the risk of venous thromboembolism (VTE) by several fold [42,46] and the incidence of VTE increases further after delivery [46]. This is attributed to the fact that during pregnancy several different mechanical, biochemical, and physiologic adaptations affect Virchow's triad and promote a prothrombotic state. For example, hypercoagulability and venous stasis increase the likelihood of developing VTE. In addition, thrombophilia is a common finding in approximately half of the women who develop VTE during pregnancy [45].

If the clinical suspicion of VTE is high, anticoagulation should be instituted before diagnostic testing is completed. The diagnostic work-up for VTE in the pregnant state is the same as for the nonpregnant patient. There usually is concern about exposing the fetus to radiation, but the doses are low (Table 2).

Acute therapy should be aimed at preserving adequate oxygenation and circulation and initiating anticoagulation with intravenous heparin (pregnancy category C). Heparin is not teratogenic and does not pose a bleeding risk to the fetus because it does not cross the placenta. Danaparoid is recommended [47]. Dextran, hirudin, and warfarin should be avoided [48–50].

#### Air embolism

Air embolism (AE) is an uncommon, but potentially fatal, event that occurs from the entry of air into the vasculature. AE accounts for approximately 1% of all maternal deaths [10], although its incidence is likely underestimated. This entity can occur with normal and complicated deliveries [51] and presents

as acute hemodynamic instability and neurologic symptoms. Precipitating factors include cesarean sections during which there is exteriorization of the uterus while the patient is in the Trendelenburg position; this creates a pressure gradient between the heart and the periphery. Sexual activity during pregnancy and puerperium, trauma, uterine rupture, and diving are other recognized risk factors [52–54].

Air enters the venous circulation through the subplacental myometrial veins, travels to the right side of the heart, and lodges within the pulmonary circulation. The acute effects of the air embolus depend on the rate and volume of air that is introduced. In vitro, the lungs are unable to filter microbubbles of air from the venous circulation when the entry of gas exceeds 0.30 mL/kg/minute [55]. It is estimated that 300 mL to 500 mL of gas that is introduced at a rate of 100 mL/second is fatal for humans [56,57]. This flow rate can be attained through a 14-gauge catheter with a pressure gradient of only 5 cm H<sub>2</sub>O [58].

After air is circulating in the venous system, it can cause injury by endothelial damage and mechanical obstruction [59]. Air affects the endothelial surface and produces increased capillary permeability, platelet aggregation, vasospasm, microthrombi, and coagulopathy. Bronchoconstriction and pulmonary edema follow the secondary activation of complement, inflammatory cells, and mediators, such as histamine and serotonin [60]. As a result of alveolar flooding and ventilation-perfusion mismatching, profound hypoxemia occurs. The physiologic dead space increases secondary to vascular occlusions and can be detected by an increase in PaCO<sub>2</sub> if ventilation is held constant. Hemodynamic compromise results from obstruction of the pulmonary outflow tract by air bubbles (or the froth of air-blood mixture) and "air lock" that decreases cardiac output, increases central venous pressure, and reduces pulmonary and systemic arterial pressures [57]. Smaller bubbles within the pulmonary arterioles can impede blood flow directly and result in vasoconstriction. A decreased preload may result in left-sided heart failure and electromechanical dissociation with cardiac arrest. Myocardial ischemia may occur secondary to hypoxia, right ventricular overload, and air emboli within the coronary arterial circulation.

Arterial embolization can result from direct passage of air into the arterial system, incomplete filtering of a large air embolus by the pulmonary capillaries, or paradoxical embolization through a right-to-left communication, such as a patent foramen ovale (present in 25%–30% of the normal population). This may result in damage to end-organs, such as the brain,

Table 2  
Fetal radiation exposure with different diagnostic procedures for VTE

Procedure	Fetal radiation (mrad)
Chest radiograph	50
Perfusion lung scan	18
Ventilation lung scan	3–20
Limited venography	<50
Radionuclide venography	205
Unilateral venography without abdomen shield	305
Bilateral venography without abdomen shield	610
Pulmonary angiogram by way of femoral route	405
Pulmonary angiogram by way of brachial route	6–18
Helical CT scan	4–130

spinal cord, heart, and skin [57,61], with possible secondary tissue damage from the release of inflammatory mediators and oxygen free radicals.

Signs of air embolism include tachypnea, tachycardia, mottled skin, blanching of arteriole nail beds, and pallor of mucous membranes (Liebermeister's sign if the tongue becomes pale) [42]. A Mill-wheel murmur reflects air in the pulmonic valve and massive quantities of air in the circulation [62]. Cardiovascular collapse, respiratory arrest, and neurologic sequelae may ensue.

AE should be suspected when acute cardiorespiratory failure or neurologic symptoms develop during or after delivery. The differential diagnosis includes PTE, acute myocardial infarction, or cerebrovascular accident. Confirming the diagnosis of air embolism is difficult because air may be absorbed rapidly from the circulation while diagnostic tests are being arranged [63,64]. Occasionally, air bubbles can be seen on fundoscopic examination [62]. Echocardiography can detect up to 50% of AE episodes following cesarean sections [62]. The most sensitive procedure for diagnosis and monitoring of AE is transesophageal echocardiography (TEE). TEE can visualize as little as 0.2 mL of injected air within the right heart [65]. Another sensitive monitor for early detection of venous air embolism is a sharp decline in the end-tidal carbon dioxide concentration; this usually is accompanied by a decrease in oxygen saturation that results from significant ventilation/perfusion mismatch. [62,65]. This finding is nonspecific because it can be seen with PTE, massive blood loss, circulatory arrest, or disconnection from the anesthesia circuit.

The primary goals of treatment are identification of the source of air entry, prevention of further air embolization, removal of embolized gas, and restoration of the circulation. Supportive care (eg, the use of mechanical ventilation, vasopressors, and volume resuscitation) is the cornerstone of management [13]. To prevent further embolization, it may be helpful to keep the surgical site below the level of the heart and to flood the surgical field with normal saline to cover open venous sinuses. Although it is recommended to place the patient in Trendelenburg and the left lateral decubitus position, there is a paucity of evidence to supporting this [56,66]. In the operating room, aspiration of air from the right atrium can be attempted through a central venous catheter if it already is in place [56,57].

The only definite therapy for AE is the administration of hyperbaric oxygen (HBO); this should be instituted rapidly when there is continued evidence of cardiopulmonary compromise or neurologic defi-

cits. HBO reduces air bubble size according to Boyle's law, accelerates nitrogen resorption, and increases the oxygen content of arterial blood to the hypoxic brain. This may ameliorate cerebral edema and reduce ischemia. The benefits of HBO have been documented, even if the therapy is delayed up to 30 hours [67].

#### *Acute respiratory distress syndrome*

The incidence of ARDS in the pregnant population is low (0.2%–0.3%) but the mortality ranges between 30% and 60% [68,69]. Numerous conditions have been implicated in the development of ARDS in pregnancy. The most common obstetric causes are choriamnionitis and amniotic fluid embolism, whereas the most common nonobstetric causes are pneumonia, sepsis, and aspiration [21]. Other precipitating entities for ARDS in pregnancy include blood transfusion reactions, DIC, obstetric hemorrhage, acute fatty liver of pregnancy, and eclampsia or preeclampsia. These usually do not occur in isolation and almost invariably are associated with complicated parturition and the need for cesarean section.

Three major interactions between ARDS and pregnancy should be considered: (1) the effect of impaired maternal oxygenation on fetal distress; (2) the influence of ARDS treatments on the fetal status; and (3) the possibility that ARDS or maternal complications could trigger preterm labor. The dependence of fetal oxygenation on maternal cardiac output places important limitations before the delivery of the baby. For example, diuresis and high positive airway pressures may decrease blood flow to the uterus by diminishing cardiac output, whereas vasopressors may shunt flow away from the uterus.

Treatment is largely supportive and includes mechanical ventilation, hemodynamic support, nutrition, and prophylaxis against thromboembolism [9]. Maternal mortality rates are minimally affected by the duration of intubation; therefore, prolonged mechanical ventilation is justified for mothers who have ARDS [68]. In the patient who requires antepartum intubation for ARDS, early delivery often is required for maternal or fetal indications. Exceptions include an early gestational age or the presence of pyelonephritis or varicella pneumonia as the cause of respiratory compromise [68,70]. The use of sedatives, hypnotics, anxiolytics, and paralyzing agents in an intubated mother result in reduced fetal activity because these drugs are transferred to the fetus [71]. Because abrupt fetal deterioration is common during the course of ARDS, careful fetal monitoring and individualized risk benefit need to be considered [72,73].

### *Aspiration pneumonitis*

In 1946, Curtis Mendelsson described a series of obstetric patients who aspirated gastric contents while in the delivery room or shortly thereafter. Since that time, Mendelsson's syndrome has been a recognized cause of maternal complications that are associated with respiratory failure. Some investigators reported gastric aspiration as the most frequent respiratory complication that causes ARDS during delivery and postpartum [21]. Factors that predispose to aspiration in pregnant women include elevation of intra-abdominal pressure, a delay in gastric emptying, and decreased gastroesophageal sphincter tone as the result of progesterone. Abdominal palpation and the effects of analgesia and anesthesia in labor and delivery are contributory factors [3,74]. Women who deliver by cesarean section are at higher risk for aspiration than those who deliver vaginally [75].

Chemical pneumonitis is seen in the first 24 to 72 hours, especially if the pH of the aspirated fluid is less than 2.4. Resolution occurs over 4 to 5 days unless secondary superinfection occurs. Severe chemical pneumonitis results in ARDS and treatment is mainly supportive. Prophylactic antibiotics and corticosteroids are not recommended [3]. Antibiotics should be used only if a bacterial infection is suspected [76].

### *Pneumonia*

Pneumonia is the third leading cause of death in pregnant women [77]. The incidence and mortality rates of pneumonia in pregnancy are not different from those in nonpregnant adults. Despite the fact that most pregnant women who have community-acquired pneumonia are treated successfully, pneumonia is the most frequent cause of fatal nonobstetric infection during pregnancy and the puerperium [10,74] and is associated with frequent complications [10,42,78]. In addition to these maternal consequences, pneumonia increases the risk of preterm delivery and low birth weight infants.

Frequently, clinicians are concerned that the physiologic and immunologic changes that occur during pregnancy may compromise the mother's ability to respond to infections. Changes in the immune system during pregnancy predominantly are alterations in cell-mediated immunity; these include decreased natural killer cell activity, decreased number of circulating helper T cells, and a decreased lymphocyte proliferative and cytotoxic response [78]. Blockage of maternal recognition of fetal major histocompatibility antigens by trophoblastic substances may contribute. Proges-

terone, cortisol,  $\alpha$ -fetoprotein, and human chorionic gonadotropin also may inhibit cell-mediated immune response and increase the risk for viral and fungal infections [74]. Established risk factors for pneumonia during pregnancy include anemia, asthma, antepartum corticosteroids, and the use of tocolytics to induce labor. Diagnosis does not differ from the nonpregnant population but initial misdiagnosis in pregnant women is seen in 10% to 20% of cases [79]. A posteroanterior chest radiograph is safe and necessary, whereas a lateral chest radiograph usually is not required. The organisms that are responsible for community-acquired pneumonias in pregnant patients are similar to those in the nonpregnant host.

The most important viral pneumonias are caused by influenza and varicella. Therefore, the polyvalent influenza vaccine should be administered to all pregnant women. Type A influenza pneumonia is associated with significant (60%) mortality, especially during the third trimester and it can be transmitted to the fetus. The occurrence of maternal varicella during the pregnancy is rare (0.7/1000) because more than 90% of women are immunized. Intrauterine infections occur in 8.7% to 26% of subjects [74], exclusively during the first 20 weeks of gestation. Varicella virus has been associated with a higher mortality during gestation; the incidence and severity seems to be higher during the third trimester [80]. Risk factors for the development of pneumonia in pregnant women who have varicella zoster virus infection include a current smoking history or the presence of more than 100 skin lesions [81]. Hospital admission should be considered for women who have varicella pneumonia, especially if they have significant comorbid disease, because of the associated high maternal and fetal morbidity and mortality [82].

The most serious fungal threat to the pregnant patient is coccidioidomycosis because of a high risk of dissemination and mortality if the disease is acquired during the third trimester.

When choosing an antimicrobial agent, the physician should be aware of the unique pharmacologic considerations of pregnancy. Penicillin, macrolides, and cephalosporins are safe and can be used for treating bacterial community-acquired pneumonia. Quinolones, tetracyclines, chloramphenicol, and sulfa compounds are contraindicated because of fetal toxicity. Newer neuraminidase inhibitors are preferred over amantadine for influenza. Intravenous acyclovir should be used for treatment of varicella infection. Amphotericin B has been used to treat coccidioidomycosis.

Many myths surround the outcome and treatment of tuberculosis (TB) during pregnancy. If proper and



adequate chemotherapy is given to pregnant women who have TB, their outcome is not significantly different than nonpregnant women who have TB. Neither the disease nor chemotherapy is threatening to the mother or newborn; however, the ominous combination of HIV, TB, and pregnancy poses a new challenge [83].

#### *HIV-related pulmonary complications*

Women and children are becoming the fastest growing group of persons who are newly infected with HIV. With longer survival after HIV infection, more infected women are becoming pregnant. Pulmonary disease is one of the most common presenting conditions of an AIDS-defining illness. *Pneumocystis carinii* pneumonia and TB are the most common disorders that herald the onset of AIDS [84,85]. Except for minor modifications that are related mainly to potential fetal effects, the diagnostic work-up and management are similar to in the nonpregnant patient.

#### *Asthma*

Asthma is the most frequent respiratory disorder that complicates pregnancy (0.4%–to 7% of all pregnancies) and its prevalence is increasing [86–88]. Only 10% or less of pregnant, asthmatic women experiences an acute exacerbation during their pregnancy. Previous studies showed that asthma control may improve in one third of patients, worsen in one third of patients, or remain the same in approximately one third of patients [86,89]. Recent studies showed a significant association between asthma and adverse outcomes. A major difference between the populations studied was the degree of asthma control and the intensity of treatment and surveillance [90,91].

Perinatal outcome is compromised if the pregnancy is complicated by chronic medication-dependent asthma. The extent is variable but correlates with disease severity as extrapolated from medication requirements. Adverse infant outcomes that have been described in pregnant, asthmatic patients include preterm delivery, increased infant hospital length of stay, low birth weight and small-for-gestational-age babies, and congenital abnormalities. Adverse effects for the mother include preeclampsia, placenta previa, cesarean delivery, and increased maternal hospital stay [92,93].

Uncontrolled asthma was shown to increase the rate of uterine hemorrhage and hyperemesis gravidarum. [91]. In a recently published retrospective chart

audit, an increased incidence of oligohydramnios, intrauterine growth restriction, and meconium-stained amniotic fluid in women who had asthma was found; smoking was not correlated with increased adverse outcomes [94]. Schatz et al [90] found that intrauterine growth retardation was related directly to lung function as measured by FEV<sub>1</sub>.

The control of rhinitis seems to have a significant concordance with asthma control during pregnancy; this relationship may have clinical and mechanistic significance. No statistical relationships were found between gestational asthma and maternal demographic factors, panic-fear score, smoking, maternal weight, infant birth weight, or infant sex [95]. Asthma severity often is consistent among successive pregnancies in individual women, which allows prediction of the course of the disease in subsequent gestations [89].

The National Institutes of Health Working Group on Asthma and Pregnancy established criteria for diagnosis and treatment of the pregnant woman in 1993 [88]. The goals of therapy include prevention and early treatment of exacerbations to reduce the risk of fetal and maternal hypoxemia. Patient education before conception and during pregnancy is crucial; pregnant women are commonly afraid to take their usual medications and physicians are more reluctant to add any medication during this period. It should be emphasized that hypoxemia has significant deleterious effects and is the most dangerous factor in poor fetal outcome; drugs that are used to control asthma have proven to be safe during gestation. The most common errors that lead to adverse outcome are underestimation of asthma severity and undertreatment of exacerbations [88]. Because physical examination and chest radiographs are poor measures of disease severity, close monitoring of serial FEV<sub>1</sub> measurements or peak flow rates are extremely helpful to help recognize deterioration. Most drugs that are used to treat asthma are safe during pregnancy, including oral corticosteroids. Inhaled corticosteroid therapy is the cornerstone of asthma control; its use has been shown to significantly decrease the likelihood of exacerbations [96] and to reduce readmission rates by 55% [87]. Budesonide has been studied extensively and is labeled class B by the United States Food and Drug Administration (FDA) [97]. Although beclomethasone and the other inhaled corticosteroids are labeled class C, they are considered to be safe to use and should be continued if needed.

Leukotriene moderators (montelukast and zafirlukast) have been classified as FDA category B but have been less well-studied than inhaled corticosteroids. Cromolyn sodium and nedocromil sodium seem

to be less effective than inhaled steroids in reducing symptoms but can be used safely during pregnancy for mild, persistent asthma. Theophylline can be used as a second-line drug when control is not achieved with inhaled steroids for moderate asthma control; maternal plasma levels should be kept less than 12 µg/mL to avoid fetal toxicity. Neonatal tachycardia, jitteriness, and vomiting are associated with high maternal plasma levels [88]. When severe asthma is not controlled or acute exacerbations occur, systemic corticosteroids should be instituted. Early consultation with a specialist should be done if symptoms persist so that therapy can be optimized.

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