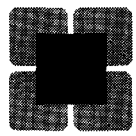

Noninfectious respiratory disease in pregnancy

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■ **BACKGROUND** Pregnancy increases the risk of many noninfectious respiratory conditions.

■ **OBJECTIVE** To review the clinical presentation and management of a variety of noninfectious respiratory conditions in pregnant women.

■ **SUMMARY** Asthma, aspiration pneumonia, venous air embolism, adult respiratory distress syndrome, pulmonary embolism, and deep venous thrombosis may have unique features in pregnant women.

■ **CONCLUSIONS** Evaluation and treatment of these diseases and conditions requires an understanding of the normal physiologic alterations that accompany pregnancy and an awareness of the risks of medication use during pregnancy and in the postpartum period.

■ INDEX TERMS: ASTHMA; DYSPNEA; PULMONARY EMBOLISM; RESPIRATORY DISTRESS SYNDROME, ADULT; PNEUMONIA, ASPIRATION; EMBOLISM, AIR; EMBOLISM, AMNIOTIC FLUID; PREGNANCY ■ CLEVE CLIN J MED 1993; 60:233–244

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MANY OF THE respiratory complaints in pregnant women that are not infection-related are due to normal physiologic alterations that accompany pregnancy. In addition, pregnant women are predisposed or uniquely susceptible to certain diseases, such as deep venous thrombosis (DVT), pulmonary embolism, aspiration pneumonia, amniotic fluid embolism, and venous air embolism. Other diseases such as asthma, while not more common during pregnancy, may begin, improve, or worsen during pregnancy. All such diseases may have deleterious effects on both the mother and the fetus.

In this article, we review the clinical presentation and management of seven important respiratory problems that occur during pregnancy.

DYSPNEA AND PULMONARY MECHANICS IN PREGNANCY

The most common respiratory complaint in pregnancy is dyspnea, which occurs in approximately 60% to 70% of women with no prior history of heart or lung dis-

ease.[1,2] Dyspnea may begin as early as the first or second trimester, but it is most common near term. As the woman develops tolerance to this sensation, her perception of dyspnea is reduced. Most likely, the sensation of dyspnea occurs because increased circulating levels of progesterone effect an increase in sensitivity to carbon dioxide (CO_2), resulting in hyperventilation that is characterized by a rise in tidal volume but not respiratory frequency.[3] Unlike pathologic dyspnea, symptoms do not increase with exertion.

Blood gases

Because of this maternal hyperventilation, arterial blood-gas measurements during normal pregnancy usually show a compensated respiratory alkalosis, with pH between 7.40 and 7.47, and the partial pressure of arterial CO_2 ($PaCO_2$) between 25 and 32 mm Hg.[3,4] The partial pressure of arterial oxygen (PaO_2) may be as high as 106 mm Hg in early pregnancy, decreasing during pregnancy, but remaining at 100 mm Hg (or slightly higher) at term.[4]

It is important that blood-gas analysis be accompanied by calculation of the alveolar-arterial oxygen tension gradient, $P(A–a)O_2$, because on casual observation, with the usual decreased $PaCO_2$ of pregnancy, a "normal" PaO_2 can be seen in patients who have an abnormally increased $P(A–a)O_2$ gradient. Pregnancy is accompanied by a mild elevation in the $P(A–a)O_2$ gradient which is greater when the patient is lying supine than it is when the patient is sitting.[5] Since most acute lung diseases are accompanied by an increased $P(A–a)O_2$ gradient, the gradient should be assessed with the pregnant patient in the upright position and should be considered abnormal only if it exceeds 25 mm Hg.

Other changes

In addition to these alterations in maternal respiratory physiology that can be expected during pregnancy, an increase in minute ventilation may occur. A slight decrease in total lung capacity also may occur, and in the second half of pregnancy this may be accompanied by decreases in residual volume and functional residual capacity. Furthermore, especially in the first trimester, an increase in diffusing capacity may be seen.[6]

Although chest radiography is performed infrequently in pregnancy, the radiographic appearance in a normal pregnancy may falsely suggest mild congestive heart failure because of lung markings caused by the increase in capillary blood volume. Because of displacement by the enlarging uterus, the diaphragm may be elevated as much as 4 cm at term, and the subcostal angle may increase from approximately 68.5° to 103.5°.[7] Postpartum pleural effusions may be seen, although their significance is unclear. Hughson et al[8] reported that pleural effusions frequently occurred in the first 24 hours following delivery and that, in the absence of symptoms or signs of illness, no intervention was necessary. However, a subsequent prospective ultrasound study[9] of 50 women within 1 to 45 hours of delivery found only 1 patient with a pleural effusion, a patient who also had pulmonary edema.

Fetal effects

In women with no pulmonary disease, the fetal umbilical vein blood gas typically has a PO_2 of 32 mm Hg and a PCO_2 of 50 mm Hg, suggesting that the fetus exists in a relative state of hypoxemia.[10] This low oxygen tension is compensated for by the high rate of maternal perfusion of the fetus, by the enhanced avidity of fetal hemoglobin for oxygen, by selective diversion of oxygenated blood to the most essential tissues (liver, heart, brain), and by a leftward shift of the maternal oxyhemoglobin dissociation curve.[10] These adaptations allow the fetus to tolerate changes in oxygen delivery, such as a reduction in maternal inspired oxygen, to as low as 15%.[10] However, the fetus is sensitive to large shifts in oxygen delivery, such as those caused by the hypoxemia and alkalosis that often accompany exacerbations of asthma; alterations such as these may contribute to the increased perinatal mortality and low birth weight seen in infants of mothers with poorly controlled asthma.[11–13]

ASTHMA IN PREGNANCY

Asthma is the most common obstructive lung disease affecting women of childbearing age, occurring in 0.4% to 1.3% of pregnant women.[13,14] In general, asthmatic women experience pregnancy with few ill effects, but at least one study has shown that these patients may have a higher frequency of hyperemesis, vaginal bleeding, and toxemia.[13] Asthma may worsen, improve, or remain unchanged during pregnancy. In a prospective study of 360 pregnancies in 330 pregnant asthmatic women, Gluck and Gluck found that the severity of asthma increased in 35% of patients during pregnancy,

TABLE 1
MEDICATIONS USED IN CONTROLLING ASTHMA

Agent	Route	FDA* pregnancy category†	Safety in breast feeding	Comments
Beta agonists				
Epinephrine	Inhalation Subcutaneous	C	Yes	Nonselective adrenergic agonist; side effects include anxiety, tremors, tachycardia, headache
Isoproterenol	Inhalation	C	Yes	
Isoetharine	Inhalation	C	Yes	
Terbutaline	Inhalation Oral Subcutaneous	B	Yes	Beta-2 selective agonist; side effects include nervousness, fatigue, dizziness, tinnitus, palpitations
Albuterol	Inhalation Oral	C	Yes	Beta-2 selective agonist; side effects include fine tremor, palpitations, nervousness
Metaproterenol	Inhalation Oral	C	Yes	
Pirbuterol	Inhalation	C	Yes	
Tornalate	Inhalation	C	Yes	
Xanthines				The xanthines have a narrow therapeutic window: monitor serum concentrations;‡ may exacerbate morning nausea; side effects include headache, dizziness, nervousness, insomnia, vomiting; multiple drug interactions; excreted in breast milk
Theophylline	Oral	C	Yes	
Aminophylline	Intravenous Oral Intravenous Rectal	C	Yes	
Corticosteroids				Both aerosol and systemic corticosteroids may increase response to beta adrenergics
Beclomethasone	Inhalation	Not classified	Yes	Inhaled corticosteroids only: Aerosols may replace or reduce oral corticosteroids; side effects include oral candidiasis, cough, throat irritation; side effects can be decreased with use of spacer and gargle
Triamcinolone	Inhalation	D	Yes	
Flunisolide	Inhalation	C	Yes	
Prednisone	Oral	Not classified	Yes	
Prednisolone	Oral	Not classified	Yes	Multiple side effects
Methylprednisolone	Intravenous	Not classified	Yes	
Hydrocortisone	Intravenous	Not classified	Yes	Excreted in breast milk
Cromolyn sodium	Inhalation	B	Yes	4- to 6-week trial recommended; effective in reducing exercise-induced asthma
Ipratropium bromide	Inhalation	B	Yes	Limited indications: more useful in chronic bronchitis and emphysema

*FDA, US Food and Drug Administration
†During pregnancy, severe bronchoconstriction is a greater danger to the mother and fetus than the drugs used to combat it (see *Table 2* for descriptions of the FDA pregnancy categories)
‡The serum concentration of the xanthines increases as much as 40% in the latter half of pregnancy; therefore, dosage and serum levels should be monitored closely

decreased in 28%, and remained unchanged in 33%.[15] Other investigators have shown an increase in both total asthma symptoms and severe asthma symptoms during weeks 29 to 36 of pregnancy, followed by improvement in symptoms during the final 4 weeks, with only a rare occurrence of symptoms during labor and delivery.[16] In addition, asthma often reverts to the pre-pregnancy course within 3 months of delivery, and the woman tends to experience a similar course of asthma during subsequent pregnancies.[15,16]

Severe and poorly controlled asthma has been associated with increased rates of such fetal complications as premature birth, stillbirth, low birth weight, and neurologic abnormalities.[13] A recent prospective study of 352 pregnant asthmatic women, who underwent serial spirometry at each monthly office visit and at times of symptom exacerbation, demonstrated a direct correlation between infant birth weight and the mean percent of predicted forced expiratory volume in 1 second (FEV_1) during pregnancy.[17] In addition, a lower mean maternal FEV_1 during pregnancy was associated with an increased incidence of low birth weight.[17] When asthma is closely managed during pregnancy, studies have demonstrated no increase in perinatal mortality compared with a control population, suggesting that with good control of asthmatic exacerbations in pregnancy, fetal outcome can be excellent.[18]

Although the symptom triad of dyspnea, cough, and wheezing is common, a nonproductive cough may be the most prominent presenting complaint in asthma. The following case history is typical.

Case 1: dyspnea, intractable cough

A 34-year-old white woman, 36 weeks pregnant with her first child, was evaluated because of complaints of dyspnea and intractable cough. Her pregnancy had been remarkable for complaints of dyspnea beginning in the first trimester and slowly improving as the pregnancy progressed. The cough began in approximately the 33rd week of pregnancy and was described as nonproductive, nonparoxysmal, unrelated to body position, but interfering with eating and sleeping. There were no complaints of postnasal drip, fever, chills, myalgias, arthralgias, or esophageal reflux. The cough increased with exertion and was associated with a tightness in the chest and shortness of breath. A shielded chest roentgenogram was interpreted as normal for this stage of pregnancy. Two weeks earlier she had started using an aerosol bronchodilator but experienced no improvement.

The patient underwent pulmonary function testing; the results were interpreted as normal for this stage of pregnancy. The bronchodilator was continued, but a regimen of theophylline and a tapering schedule of prednisone were also started. The patient took the medications as directed and experienced an improvement in her symptoms. At week 40 of pregnancy she was admitted to the hospital in active labor; she was given "stress doses" (in excess of the physiologic dose) of corticosteroids and underwent an uncomplicated vaginal delivery of a healthy infant. Two days postpartum, the cough spontaneously disappeared and did not recur.

Comment. This patient's complaints of dyspnea beginning in the first trimester and slowly improving as the pregnancy progressed are consistent with the dyspnea associated with normal pregnancy. Her subsequent complaints of chronic cough and increased shortness of breath associated with a tightness in her chest, exacerbated by exertion, suggest another etiology. Her symptoms—which worsened during the last few weeks of pregnancy, responded to antiasthmatic therapy, and disappeared soon after delivery—are consistent with a diagnosis of asthma. The normal pulmonary function test results do not exclude this diagnosis, and methacholine challenge testing could have confirmed the diagnosis.

Most of the agents for controlling asthma can be used safely in pregnant women when given in recommended dosages (*Table 1*). The dangers of inadequately controlled asthma are far greater than the small risks posed by pharmacotherapy. Nevertheless, common sense dictates that when medication is required, the minimum number of medications necessary to control symptoms should be used. Status asthmaticus (asthma not responsive to the usual sympathomimetic drugs), requires hospitalization, emergency treatment, and close monitoring for respiratory failure. Its management will not be discussed here.

Asthma management guidelines

Ideally, the management of asthma should begin prior to conception. A careful history should be performed to characterize the severity of a patient's asthma and to identify any recognizable precipitants of bronchospasm. Common precipitants include: allergens, exercise, infections, smoking, and cold weather. Chronic and intermittent medications

should be reviewed with the aim of optimizing dosage and frequency of administration. Aspirin and aspirin-containing medications should be avoided because of an association with bronchospasm in up to 25% of asthmatic patients.[19] Instruction in the early recognition of wheezing and the need for prompt intervention should be given. Influenza vaccination should be given in the autumn but should be delayed if possible until after the first trimester.[20] Immunotherapy, if started before pregnancy, should be continued, but it should not be started during pregnancy nor should doses be raised in large increments because of the risk of maternal anaphylaxis.[21] If the patient wishes to engage in safe but vigorous exercise, proper medication given prior to exertion will effectively block exercise-induced asthma. Swimming is customarily thought to be a good cardiovascular exercise and, because of the humid environment, is generally well tolerated.

TABLE 2
US FOOD AND DRUG ADMINISTRATION PREGNANCY CATEGORIES

Category A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in subsequent trimesters), and the possibility of fetal harm appears remote.
Category B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than decreased fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other effects) and there are no controlled studies in women, or studies in women and animals are not available. Drugs in this category should be given only if the potential benefit justifies the risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits for pregnant women may be acceptable despite the risk, as in life-threatening or serious diseases for which safer drugs cannot be used or are ineffective.
Category X	Studies in animals or humans have demonstrated fetal abnormalities, there is evidence of fetal risk based on human experience, or both, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Pulmonary function testing. Pulmonary function studies, which include vital capacity, FEV_1, and peak expiratory flow rate, should be performed early to provide a baseline and then repeated throughout pregnancy as warranted by disease activity. Patients can measure the course of their asthma with serial self-measurement of the peak expiratory flow rate.

Beta agonists. Inhaled beta agonists are probably the drugs of choice for managing occasional wheezing or exercise-induced asthma because of their efficacy, rapid onset of action, poor systemic absorption, and consequent low incidence of systemic side effects such as tachycardia, nervousness, and muscle tremor. Although some of the beta agonists (eg, albuterol, metaproterenol) have been associated with teratogenicity in animal studies (US Food and Drug Administration [FDA] Pregnancy Category C), there is no evidence of teratogenic effects in humans (*Table 2*).[22] Terbutaline is a relatively selective beta agonist and has been designated as FDA Pregnancy Category B.[22] Instruction in the proper use of the inhaler is necessary, and a chamber-like device fitted to the inhaler is available for those who have difficulty with proper technique. Beta agonists should be used cautiously near term because of an association with pulmonary edema in patients receiving both beta agonists and corticosteroids to treat premature labor.[23] In addition, beta agonists can interrupt the progress of labor and can contribute to postpartum uterine atony.[22,23]

Corticosteroids. Inhaled bronchodilators act to reverse bronchospasm but do nothing to relieve bronchial inflammation. Since bronchial inflammation is the principal lesion in asthma, patients who experience more than an occasional episode of bronchospasm are suitable candidates for corticosteroid therapy. The use of corticosteroids can result in a significant reduction in disease morbidity and mortality. A patient who requires repeated short courses of oral steroids, or who requires chronic steroid therapy, should probably receive an inhaled corticosteroid in an attempt to eliminate or decrease the dose of oral corticosteroids, or change to alternate-day dosing.

Human studies have not confirmed the increased risk of cleft palate seen in offspring of corticosteroid-treated animals,[24] and both inhaled beclomethasone and orally administered prednisone appear to be safe, even when given during the first trimester. Neonatal adrenal suppression has been seen only rarely, probably because of the rapid conversion of prednisone to its active form, prednisolone, in the mother and poor placental passage of prednisolone.[24,25] Additionally, the fetus may not be able to convert prednisone (which can cross the placenta) to prednisolone. Neonatal recovery from corticosteroid-induced adrenal suppression is rapid and does not appear to present a significant clinical risk.[25] Women who have received systemic or inhaled corticosteroids during pregnancy should be given hydrocortisone (100 mg intravenously or intramuscularly) upon admission in labor. This dose should be repeated every 8 hours until 24 hours after delivery; then, as in case 1 above, the patient should be returned to her previous corticosteroid regimen.[11]

Additional drugs. Patients whose asthma is inadequately controlled by bronchodilators and corticosteroids may require additional medications. Theophylline is a mild bronchodilator that can be given orally or parenterally and is available in extended-release forms. However, its therapeutic serum concentration is narrow (10 to 20 μg/mL), so it may be poorly tolerated. Serum levels should be kept in the lower therapeutic range and monitored frequently, because the volume of distribution may change in the latter half of pregnancy, which means that serum concentrations may increase by as much as 40% at term.[26] Levels above the therapeutic range may be associated with jitteriness, tachycardia, gagging, vomiting, or seizures.[27]

Theophylline is generally regarded as safe during pregnancy, although it does cross the placenta and results in fetal serum levels comparable to maternal serum levels.[27] Signs of toxicity may appear in neonates of mothers given theophylline, despite neonatal serum concentrations in the normal range.[27] Approximately 10% of the mother's dose of theophylline may be transmitted to the infant via the breast milk, occasionally leading to irritability and insomnia in the infant.[28]

Cromolyn sodium, though not specifically approved by the FDA for use in pregnancy, may be useful in preventing asthma exacerbations. It has been shown to prevent asthmatic reactions to antigen, exercise, cold air, hyperventilation, aspirin, and sulfur dioxide. Large intravenous doses of sodium cromoglycate in rats and rabbits do not have teratogenic effects,[23] and a study in 296 asthmatic women using recommended inhaled dosages of cromolyn sodium throughout pregnancy showed no increased risk of fetal malformations.[29] Because it is poorly absorbed after inhalation, the amount available for transfer across the placenta is probably insignificant, although this has not been specifically studied,[30] and notable side effects are limited to bronchial irritation caused by the dry powder.[28] When cromolyn is used, a 4- to 6-week trial of therapy is indicated because it may take from 2 to 4 weeks for the effects to become apparent. A single dose, administered 20 minutes before exercise, may prevent exercise-induced asthma.[28]

Case 2: potential complications of drug therapy

As mentioned above, most of the agents used to control asthma are safe during pregnancy; however, physicians need to be aware of the potential complications. An example follows.

Case 2. A 22-year-old white woman, 32 weeks pregnant with her second child, presented in active labor. She had a history of asthma beginning in childhood and had experienced an increase in symptoms during both pregnancies. At the time of admission, she was asymptomatic on therapy consisting of an inhaled corticosteroid, an inhaled beta agonist, and oral theophylline. In an attempt to terminate the premature labor, the patient was placed on a continuous intravenous infusion of terbutaline. Systemic corticosteroids were administered with the intent of accelerating fetal lung maturity should delivery be unavoidable. Gradually, over the course of the next 72 hours, active uterine contractions ceased, and the corticosteroids and terbutaline infusion were discontinued.

Six hours later, the patient began complaining of dyspnea. At that time, her temperature was 38.5°C, pulse 130 beats per minute, respirations 32 per minute, blood pressure 90/58 mm Hg. Auscultation of the lungs revealed basilar crackles, but there was no jugular venous distension and no gallop was noted on cardiac examination. The patient's fluid balance over the prior 72 hours was reviewed, and a net positive balance of approximately 1.8 L was noted. An arterial blood gas obtained before placing the patient on oxygen disclosed the following: pH 7.49, P_{CO_2} 28, P_{O_2} 52, and bicarbonate (HCO_3) 25. A

shielded chest roentgenogram showed a normal heart size with diffuse bilateral alveolar-interstitial infiltrates. She was placed on oxygen; then, after cultures of sputum, blood, and urine were obtained, a regimen of intravenous antibiotics was begun. Progressive improvement in oxygenation occurred over the next several hours. By 24 hours, the patient no longer required supplemental oxygen. Culture results were all negative, and the antibiotics were discontinued. The patient was discharged the following day.

Comment. This patient had a clear history of asthma and was apparently on a good anti-asthmatic regimen that included an inhaled beta agonist. In an attempt to terminate labor, a regimen of an intravenous beta agonist and intravenous corticosteroids was started. A review of fluid balance indicated a net positive balance of 1.8 L. The patient's symptoms, physical findings, arterial blood gas values, and chest radiograph were consistent with a diagnosis of noncardiogenic pulmonary edema. Pulmonary edema has been associated with all tocolytic agents, and the combination of beta agonists and corticosteroids may increase the risk. Other risk factors include hypertension, diabetes, coronary and valvular heart disease, obstructive cardiomyopathy, multiple pregnancy, and amniotic fluid infection.[31] Beta-sympathomimetic agents appear to increase the permeability of the alveolar-capillary barrier, leading to increased lung water.[32] Impairment of free water clearance by corticosteroids may also contribute to fluid overload.[32] In high-risk patients, fluids should be restricted and oxygen saturation should be continuously monitored to identify impending hypoxemia as early as possible. Once present, noncardiogenic pulmonary edema is treated with diuretics and oxygen. Occasionally, patients may require intubation and invasive hemodynamic monitoring.

PULMONARY EMBOLISM

Predisposing factors

Factors predisposing to pulmonary embolism are common in pregnancy. They include venous stasis, immobilization, and a state of hypercoagulability. Therefore, it is not surprising that pulmonary embolism complicates approximately 1 in every 2,000 pregnancies, causing approximately one quarter to one half of all obstetric morbidity and mortality.[33] Emboli originate from sites of superficial and deep venous thrombosis, septic thrombophlebitis, or ovarian vein thrombosis. The highest risk of thrombophlebitis and pulmonary embolism occurs during the first 6 postpartum weeks, and the risk is particularly increased in the setting of preeclampsia or operative delivery, because of activation of the coagulation cascade during placental separation, and injury to the pelvic vessels.[34]

Symptoms and diagnosis

The symptoms of pulmonary embolism are not specific, and the diagnosis should be suspected when a patient presents with any of the following signs or symptoms: dyspnea, cough, pleuritic chest pain, panic, tachycardia, pleural friction rub, diaphoresis, cyanosis, hemoptysis, new gallop murmur, or accentuation of the second heart sound.

Arterial blood gas testing may show a low PaO_2, but as many as 14% of patients with documented pulmonary emboli will have a PaO_2 >85 mm Hg on room air.[35] The $P(A–a)O_2$ gradient should be measured with the patient upright and should be considered abnormal if it exceeds 25 mm Hg. The chest radiograph may be normal but will usually show nonspecific changes, such as hemidiaphragm elevation, atelectasis, or pleural effusion. Oligemia and "Hampton's hump"—radiologic signs classically associated with pulmonary embolus or infarct—are rarely seen. The electrocardiogram may show evidence of right-ventricular strain, such as a right-axis deviation, right bundle branch block, or the $S_1Q_3T_3$ pattern (S wave in lead I, Q wave in lead III, inverted T wave in lead III).

Ventilation-perfusion scan. When a strong clinical suspicion of pulmonary embolism exists in a pregnant patient whose chest radiograph does not explain her symptoms, a ventilation-perfusion scan should be done. Leg vein studies including venography may be uninterpretable due to the significant incidence of false-positive and false-negative findings.[36] False-positive results often occur in the second and third trimesters because venous return is usually slowed by the enlarging uterus.[37] False-negative results may occur when a partially obstructed vein is evaluated using ultrasound techniques.[38] Fibrinogen-iodine 125 has a half-life of 60.2 days, and its use as a scanning agent is contraindicated in pregnancy because unbound iodine 125 can accumulate in the fetal thyroid gland.[36] It is also contraindicated during breast-feeding because it is excreted in breast milk.[38]

Lung scanning does carry the risk of fetal exposure to radiation, but no adverse fetal effects have been shown from such testing.[39] Even with the combination of ventilation-perfusion scanning and pulmonary angiography, the total radiation dose to the fetus is felt to be well below the lowest dose associated with an adverse effect.[39] Shielded chest radiography performed on a pregnant patient may expose the fetus to less than 1 mrad,[40] while fetal radiation exposure from lung scanning using technetium 99 has been estimated to range between 6 and 18 mrad.[40] The total fetal radiation dose absorbed during an entire pulmonary angiographic procedure has been estimated at between 50 and 405 mrad.[40] The overall risk of any adverse effect from exposure to 1 rad is estimated to be 0.1%, a risk that is thousands of times smaller than the risk of spontaneous abortion, malformation, or genetic disease.[40–42]

A normal lung perfusion scan virtually excludes the diagnosis of pulmonary embolism. A low- or intermediate-probability scan represents a 10% to 40% chance that the patient actually has had a pulmonary embolus, while a high-probability scan is associated with a 5% to 10% false-positive rate.[36] Because systemic anticoagulation carries some risk to both mother and fetus, pulmonary angiographic documentation should be considered in the absence of a normal perfusion scan.

Anticoagulation therapy

Once pulmonary embolism is documented, systemic anticoagulation is indicated, and heparin is the anticoagulant of choice. This agent is not only used as acute therapy, but also as maintenance therapy (rather than warfarin) because it does not have teratogenic effects, does not cross the placenta, and is not excreted in breast milk.[43,44] Warfarin use during the first trimester is associated with a characteristic embryopathy consisting of nasal hypoplasia, depression of the bridge of the nose, chondrodysplasia punctata, and a 30% incidence of developmental delay.[45] During the third trimester, warfarin therapy is associated with an increased incidence of fetal neurological abnormalities which may result in mental retardation.[46] Warfarin is also excreted in breast milk, although in quantities too low to affect neonatal coagulation.[46] Approximately 30% of pregnancies in which warfarin is used are associated with poor fetal outcome.[44–46]

To treat pulmonary embolism, heparin should be given intravenously for 10 to 14 days, and the activated partial thromboplastin time should be kept between 1.5 and 2.5 times the patient's control value. After this, subcutaneous heparin should be given at 12-hour intervals, with the dose adjusted to prolong the mid-interval (6-hour) activated partial thromboplastin time to 1.5 times the baseline value. Anticoagulant therapy should be continued throughout pregnancy, withdrawn during labor and delivery, restarted several hours postpartum, and continued for another 6 weeks. In a patient unable to use heparin, warfarin may be used after the first trimester, as long as the potential risks to the fetus are understood.[34,44] It should not be used near term; this avoids the possibility that the fetus will be in an anticoagulated state at delivery.

In patients with a history of thromboembolism, particularly if the thromboembolism occurred during pregnancy or within 6 months of conception, and in patients with significant risk factors (ie, preeclampsia, morbid obesity, or cardiac disease), there is an increased risk of recurrence during pregnancy. In patients with a history of thromboembolism occurring during pregnancy or within 6 months of conception, the use of subcutaneous "minidose" heparin is probably warranted, but recommendations for patients with other risk factors have not been clearly defined.[36]

ASPIRATION OF GASTRIC CONTENTS

Mendelson's syndrome (chemical pneumonitis) occurs following the aspiration of low-pH liquid stomach contents into the tracheobronchial tree. This syndrome is most likely to develop if aspirated material has a pH < 2.5, but some reports suggest that respiratory dysfunction can occur even if the pH of the aspirate is higher.[47,48]

Attempts at preventing aspiration have included the following: limitation of oral intake to essential medications once labor has begun; aspiration of stomach contents via a nasogastric tube; use of antacids and histamine receptor blockers; and use of regional anesthetics when possible.[49,50] Once aspiration has occurred, there is usually a delay of 6 to 8 hours before the occurrence of bronchospasm, tachycardia, tachypnea, and the appearance of a new radiographic infiltrate.

Treatment is supportive, with oxygen and mechanical ventilation, if needed. Bronchodilators may be used to control bronchospasm, but an-

tibiotics are usually withheld until the patient develops signs of infection. Corticosteroids currently have no role in therapy.

AMNIOTIC FLUID EMBOLISM

More than 300 cases of amniotic fluid embolism have been reported in the literature. While infrequent, it is associated with a mortality rate as high as 80% and reportedly accounts for approximately 9% of all maternal deaths.[51,52] Although most episodes occur during labor (90%), amniotic fluid embolism can occur at any time throughout pregnancy and has been known to occur up to 48 hours postpartum.[51] The syndrome cannot be predicted, nor are there any known preventive measures.

Classically, patients present with sudden onset of dyspnea and hypotension, which may be followed within minutes by cardiac arrest. In patients who survive this initial insult, up to 70% will develop the adult respiratory distress syndrome (ARDS), up to 40% will develop some degree of consumptive coagulopathy, and most will show evidence of left-ventricular dysfunction or failure.[51,53,54] A bleeding diathesis (in 10% to 15% of patients) or generalized seizures (in 10% to 20% of patients) may presage the syndrome.[51,55] The differential diagnosis includes conventional causes of thromboembolic disease, toxemia of pregnancy, peripartum cardiomyopathy, Mendelson's syndrome, and fulminant pneumonia. The diagnosis must be made on the basis of clinical suspicion and supportive laboratory studies. The finding of squamous cells of presumed fetal origin in the sputum—or of squamous cells, hair, mucin, or other material of fetal origin in blood aspirated from the pulmonary circulation via a Swan-Ganz catheter—is suggestive but not diagnostic.[52,56,57]

Treatment is supportive and includes oxygen; mechanical ventilation with or without positive end-expiratory pressure (PEEP); hemodynamic resuscitation with fluids, directed toward treatment of left-ventricular dysfunction; vasopressors; and measures to combat the bleeding diathesis. A pulmonary artery catheter may be helpful in guiding hemodynamic management and in collecting pulmonary arterial blood for cytologic sampling.

VENOUS AIR EMBOLISM

Venous air embolism occurs in up to 1% of pregnancies, and maternal mortality associated with a clinically significant event may exceed 90%.[58] Usual risk factors include surgery, hemodialysis, intravenous infusions, and central venous catheter placement. During pregnancy, women are at increased risk of air embolism (1) via the venous sinuses of the uterus during normal labor; (2) during delivery of a placenta previa; and (3) as the result of criminal abortion (using air), orogenital sex, and insufflation of the vagina during gynecological procedures.[59] The consequences of venous air embolism depends on the amount and rate of air entry. As little as 100 mL has been reported to be fatal.[60]

Venous air circulates to the right side of the heart, where it may reach the arterial circulation via a patent foramen ovale or by passing through the pulmonary vascular bed. Once in the arterial circulation, air is diffusely distributed throughout the body and may result in a change in mentation, coma, seizure, or myocardial ischemia. Embolization of a large bolus of venous air to the right ventricle may result in mechanical obstruction to the forward flow of blood in the pulmonary artery outflow tract.[61] In addition, platelet aggregates tend to form on the bubbles, resulting in diffuse platelet microthrombi and thrombocytopenia.[61] In animal models, permeability-related pulmonary edema following venous air embolism has been related to leukocyte production and to the release of toxic oxygen metabolites.[62]

The presentation of venous air embolism is usually abrupt, with the sudden onset of all or several of the following: dyspnea, cough, wheezing, hypotension, tachycardia, diaphoresis, and substernal chest pain. An altered state of consciousness is common, and an evanescent "mill-wheel" or "water-wheel" murmur may be heard over the precordium. Paradoxical embolism may be evidenced by bubbles in the retinal arterioles, marble-like skin (air in superficial dermal vessels), and, possibly, stroke or myocardial infarction. Hypoxemia may be accompanied by metabolic acidosis, and chest radiography may occasionally demonstrate air in the right side of the heart or the main pulmonary artery. The electrocardiogram may show signs of right-heart strain, ischemia, or arrhythmia. The following case history is typical.

Case history

A 23-year-old black woman with no previous medical history and an uncomplicated first pregnancy presented to the labor and delivery suite in active

TABLE 3
DIAGNOSTIC CRITERIA
FOR ADULT RESPIRATORY DISTRESS SYNDROME*

Appropriate precipitating event present
Diffuse, bilateral radiographic infiltrates
Partial pressure of arterial oxygen <50 with fraction of inspired oxygen> 0.6
Pulmonary capillary wedge pressure <12 mm Hg
Shunt >30%
Total respiratory compliance reduced (<50 mL/cm)

*Adapted from Hansen-Flaschen J, Fishman AP. Adult respiratory distress syndrome: clinical features and pathogenesis. In: Fishman AP, editor. Pulmonary diseases and disorders. 2nd ed. New York: McGraw-Hill, 1988:2201.

TABLE 4
CAUSES OF ARDS* ASSOCIATED WITH PREGNANCY

Abruptio placentae	Eclampsia
Air embolism	Fat embolism
Amniotic fluid embolism	Hemorrhagic shock
Aspiration	Overwhelming pneumonia
Blood transfusion	Seizures
Dead fetus syndrome	Septic abortion
Drug overdose	Septicemia

*Adult respiratory distress syndrome

labor at 39 weeks of gestation. After a long and vigorous labor, vaginal delivery of a normal healthy fetus occurred uneventfully. During delivery of the placenta, however, the patient complained of feeling faint, dizzy, and short of breath, and screamed that she was going to die. She was noted to be tachypneic, tachycardiac, and diaphoretic. Within 2 to 3 minutes her systolic blood pressure dropped to 50 mm Hg, and she became unconscious. Physical examination revealed an elevated jugular venous pressure, inspiratory and expiratory wheezing, an S_3 gallop, and a mill-wheel murmur over the precordium. An arterial blood gas sample revealed the following: pH 7.23, P_{CO_2} 31, P_{O_2} 41, and HCO_3 19. An electrocardiogram demonstrated right-axis deviation and ischemic changes in the precordial leads.

The patient was intubated, was given 100% O_2, and was placed in the left lateral decubitus position. Her blood pressure improved in response to intravenous dopamine. A chest roentgenogram obtained at this time revealed mild cardiomegaly and pulmonary vascular congestion, but no infiltrates or effusions. Because of persistent hypoxemia, a flow-directed pulmonary artery catheter was inserted. A repeat roentgenogram, obtained routinely after Swan-Ganz insertion, revealed diffuse interstitial alveolar infiltrates. Initial measurements obtained via the pulmonary artery catheter showed normal cardiac filling pressures. Although there was no clinical evidence, an initial coagulation screen suggested low-grade disseminated intravascular coagulation. Over the ensuing 24 hours, the patient woke up, her blood pressure became normal, the coagulopathy corrected, and her oxygenation improved. On the second hospital day, she was extubated. She experienced a complete recovery and was discharged on the fourth hospital day.

Comment. As in this patient, treatment is directed towards prompt reduction of mechanical obstruction and efforts to encourage reabsorption of the embolus. The left lateral decubitus position minimizes obstruction to the right-ventricular outflow tract, and the administration of 100% O_2 promotes removal of nitrogen from the air bubble, resulting in a more rapid absorption of the embolus. Anticoagulation may minimize the formation of fibrin microemboli,[63] and mechanical ventilation may be necessary if profound hypoxemia or permeability-related pulmonary edema occurs. Recompression in a hyperbaric chamber can be lifesaving.

ADULT RESPIRATORY DISTRESS SYNDROME

In the pregnant patient, ARDS (*Table 3*) can be associated with many of the factors that complicate pregnancy and delivery (*Table 4*). The alveolar-capillary membrane, either directly or through mediators delivered by the pulmonary vasculature, becomes damaged, resulting in increased vascular permeability and noncardiogenic pulmonary edema. Most patients require mechanical ventilation for adequate oxygenation. Despite sophisticated intensive care guided by the use of pulmonary artery catheters, the mortality from ARDS continues to exceed 50%, a figure that has remained fairly constant over the last 20 years.[64]

SUMMARY

Pregnancy increases the risk of many noninfectious respiratory conditions. Most, including asthma, aspiration pneumonia, venous air em-

bolism, ARDS, pulmonary embolism, and DVT, are also observed in nonpregnant women. Amniotic fluid embolism, however, is a condition unique to pregnancy and must be included in the differential diagnosis of acute respiratory failure. The evaluation and treatment of these diseases and conditions requires an understanding of the normal physiologic alterations that accompany pregnancy and an awareness of the risks and safety of medication use during pregnancy and in the postpartum period.

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